

HIV Manual 2001

Integrated Treatment Centre
Special Preventive Programmes
Department of Health
Hong Kong

SPP

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**Integrated Treatment Centre
Special Preventive Programmes
Department of Health
Hong Kong**

ISBN 962-8135-08-2

Published in January 2002

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PREFACE

HIV Manual 2001 replaces the *AIDS Manual for Doctors and Dentists* published in 1995. (formerly *Information on AIDS for Doctors and Dentists, 1987 and 1992*) More than a simple update, the new manual has been extensively rewritten, based on a series of clinical protocols of the Integrated Treatment Centre of the Special Preventive Programmes, Department of Health. The changes between the two editions attest to the dramatic turn of events since 1996 when the very potent protease inhibitor was made available in Hong Kong. Highly active antiretroviral therapy as we know it today controls HIV and transforms it into a manageable disease. The outlook of HIV medicine thus took on a most positive note with decreased mortality and morbidity. Attention since then has become focussed on long term management issues.

This manual makes no pretensions to a textbook on the subject but does aim at giving medical practitioners in Hong Kong a synopsis of HIV medicine as it is today and in the local context. Algorithms of management are included wherever appropriate to assure convenience of use. As such, this manual should serve as a handy reference in that unexpected encounter with problems related to HIV, which are becoming less uncommon nowadays. To this end, a palm version of the manual is under preparation. (watch out: www.aids.gov.hk)

In the new manual, a shift towards HIV-specific treatment issues should be evident, commensurate with the modern paradigm of HIV management in which the proper use of antiretrovirals cannot be overemphasized. However, for various reasons, opportunistic infections and malignancies continue to be important, especially in the newly diagnosed and in the way effective antiretrovirals have impacted on their manifestations and management.

Until a cure of HIV is found, the pace of HIV medicine will continue to be rapid. Although this manual covers mainly the basic tenets of HIV medicine rather than its more controversial aspects, part if not all of the material will easily become outdated as new developments unearth. For this reason, a 'soft copy' of this manual is also housed in the web, which is updated on an as-needed basis. Regardless, all physicians are advised to keep abreast with the more significant developments in this area. We owe it to our patients.

We acknowledge the input of all clinicians currently working or have worked with us at the Integrated Treatment Centre (and the HIV clinics before it), the encouragement of the high-spirited nursing team of Special Preventive Programmes, without which, this Manual would remain an unfulfilled dream.

The editors

FOREWORD

Dr CH Leong, *OBE, JP*
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The first case of AIDS was identified in Hong Kong In 1985. Through the years of cooperation between Government, health care professionals, voluntary agencies, volunteers and the society in the battle against AIDS, the devastation of this pandemic in Hong Kong can be said at best to be "contained". Up to the end of June of 2001, we have 1,636 HIV positive reported cases and 524 cases of AIDS — figures much below prediction. Yet there is no cause for complacency.

The discovery of the "cocktail" treatment has brought on hopes, but also renewed problems. Yes, HIV carriers could have their full-blown symptoms delayed, gaining years of useful quality living and symptom-free life. Furthermore, if discovered early in pregnancy, it can markedly lower the chances of intra-utero transmission from HIV+ mothers to fetus. Regrettably, it is a very expensive treatment regime that has to be maintained life-long. The limitation on the spending of public money to match the treatment needs may well be round the corner. Furthermore, it is still early to postulate how effective the "cocktail" treatment will be on a long-term basis. As it is, there are reports that "breakthrough" has occurred, the virus simply fails to respond after an initial enthusiastic success of the "cocktail" drugs. The other worry is that whilst the "cocktail" treatment does not cure the disease, it has given many the wrong message that HIV/AIDS is no more deadly. Evidences exist that in some places, a second wave of AIDS epidemic is being witnessed because people are now taking on a laissez-faire attitude on prevention.

The fact remains that before a vaccine is discovered to induce immunity against AIDS; before a treatment is identified to cure the disease, the only way to minimize the devastation of AIDS is by prevention and proper education, caring for those infected and anti-discrimination to the victims of the disease.

Whilst it must be the responsibility of Government and the society at large to bring these issues forward to the very best, the medical and dental professions must play our parts and take on the challenge with conviction and special effort. After all, we are the professions that are in the know to give the most appropriate education. We are the professionals that the public would place their trust on how the horror of the infection could be prevented and how such prevention must be abided. We are the professions that have the knowledge of administering treatment and control the symptoms of the disease, and at the same time act as an advocate for facilities and funding for treating the victims. Finally, we are,

and should be, the professions to demonstrate that any form of discrimination against people living with HIV/AIDS and their families and friends are ill-founded and may even carry harmful backlash to the society.

To act effectively, doctors and dentists must be equipped with the right knowledge and up-to-date tools. This **HIV Manual 2001**, the fourth manual published by the Department of Health, Special Administrative Region Government, and the three manuals before, are exactly for such purpose. The Department, and in particular the authors, deserve the highest commendation in putting forward this publication that all doctors and dentists are advised to thoroughly read and digest, as we have an on-going role in the war against AIDS.

The job of the medical and dental professions is no easy task — for whilst HIV/AIDS is not just a medical problem and it is even more than an ethical, moral, legal and social problem together; yet the medical and dental professions must demonstrate our leadership role and rise to the challenge.

August 2001

FOREWORD

Dr the Honourable Lo Wing Lok
President, Hong Kong Medical Association
Member, The Legislative Council of Hong Kong SAR

I write to recommend the **HIV Manual 2001** to all medical and dental practitioners. As a student on communicable diseases and a user of the *AIDS Manual for Doctors and Dentists* (1995), I welcome this much-awaited update. True to its title, **HIV Manual 2001** provides doctors and dentists with handy reference, and readily applicable protocols and algorithms to assist them in their day-to-day management of patients with HIV infection.

Since the last manual was published, HIV/AIDS has become a manageable disease. For HIV infected persons who have the benefit of receiving treatment early, surviving the infection has become the rule rather than the exception. The new manual adequately reflected on the tremendous progress in antiretroviral therapy by expanding its coverage on the subject.

HIV Manual 2001 is the work of the leading HIV/AIDS experts in Hong Kong. It was written in such a manner that readers would feel as if they were sitting with the experts in their clinical sessions, to learn directly on how to do it. It would also help readers to understand the current HIV/AIDS situation in Hong Kong.

The manual is a modern era publication. A hand-held computer version and electronic updates will be made available through Internet. This is definitely an asset to readers of a publication on such a rapidly developing subject as HIV/AIDS.

I congratulate the editors, contributors, and the management team for their effort and achievement.

August 2001

HOW TO USE HIV MANUAL 2001

The **HIV Manual 2001** is meant to be a handy reference for busy medical practitioners who look after HIV/AIDS patients either regularly or are involved in their diagnosis and/or management from time to time. It would also be of use to public health physicians working on HIV prevention and policy development.

The Manual is organized in chapters plus an appendix. The general information about the infection, its epidemiology, pathogenesis and diagnosis are in **Chapter One** and **Two**. Therapeutic prevention, a new concept that incorporates the use of antiretrovirals in specific settings, is covered in **Chapter Three**. Specific HIV treatment, involving the use of highly active antiretroviral therapy (HAART) is discussed in conjunction with disease monitoring (**Chapter Four**). **Chapter Five** deals with opportunistic infections commonly associated with HIV/AIDS in Hong Kong, both in contexts of their prevention and their treatment. **Chapter Six** is devoted to neoplasms in HIV diseases, including the management of Kaposi's sarcoma, lymphoma and the screening of cervical neoplasia in women. The last chapter (**Chapter Seven**) provides information on HIV in selected clinical settings. There are two areas, one dealing with syndromes – skin diseases, diarrhea and wasting, and the other focussing on the settings of traveling, pregnancy and the childhood.

In order that the Manual can be of a manageable size, some details of HIV/AIDS have been deliberately omitted. For example, readers are advised to consult medical texts or one of the websites on HIV medicine for a comprehensive overview of clinical HIV/AIDS. Public health prevention of HIV infection falls outside the scope of our Manual. Over the years, a broad range of guidelines and information papers have been developed by the Government, largely through the Advisory Council on AIDS and its committees. Readers are asked to consult the designated AIDS webpage (Virtual AIDS Office) at www.aids.gov.hk or ask for copies of these documents from the Advisory Council on AIDS Secretariat. A list of these documents is in the **appendix**. Also included in the Appendix are: the HIV/AIDS report form, and three commonly used guidance papers, which touch upon (a) the classification of HIV/AIDS and the surveillance definition of AIDS in Hong Kong, (b) the ethical consideration in the case of an HIV infected health care worker, and (c) the infection control practice for preventing HIV infection in the health care setting.

Finally, there are always specific questions that cannot be answered straightaway by our **HIV Manual 2001**. Please seek advice from the local reference sources, a list of which is given in the Appendix.

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HIV – FROM EPIDEMIOLOGY TO DIAGNOSIS

1.1 EPIDEMIOLOGY OF HIV INFECTION IN HONG KONG

There are three major routes for HIV (human immunodeficiency virus) transmission – sexual contacts, exposure to contaminated blood or blood products, and perinatally from an infected mother to the child. The importance of each of these factors varies from one country to another. Other less common routes of transmission, for example, occupational exposure in health care settings, during transplantation, can be included in the category of blood exposure.

Globally, sexual transmission is the major mode of HIV spread. The risk of infection varies with the form of sexual activity, being higher with anal intercourse in the passive partner (0.1-0.3%) and lower in the active partner of vaginal sex (0.03-0.09%).¹ More recently, oral sex has also been linked with the transmission of the virus.² The exposure of contaminated blood refers largely to the sharing of needles in injecting drug users. Mother-to-child infection has resulted from extensive heterosexual transmission. With the advent of universal antenatal HIV testing and antiretroviral prophylaxis, perinatal infection has declined, particularly in western countries. On a global scale, HIV transmission in health care setting is rare.

In Hong Kong, the first cases of HIV infection and AIDS were diagnosed in 1984 and 1985 respectively. This chapter outlines the epidemiological situation as revealed by the results of the surveillance program maintained by Special Preventive Programmes, Department of Health.

I. HIV/AIDS surveillance in Hong Kong

The HIV/AIDS surveillance system comprises the following programs: (a) HIV/AIDS reporting, (b) seroprevalence studies, (c) STD surveillance and (d) behavioral surveillance and other research activities. Surveillance activities are undertaken through the Surveillance Office of the Special Preventive Programmes. Results are published in the Hong Kong STD/AIDS Update, a quarterly surveillance report of Special Preventive Programmes and Social Hygiene Service. Both the publication and the summary tables can be viewed and downloaded from the Virtual AIDS Office at www.aids.gov.hk.

The HIV/AIDS reporting programme is a dual mechanism involving the voluntary reporting of newly diagnosed HIV and AIDS cases by attending physicians using the DH2293 form (Appendix) and by laboratories providing confirmatory tests in the public service. Seroprevalence studies are conducted on selected communities. Methodologies such as

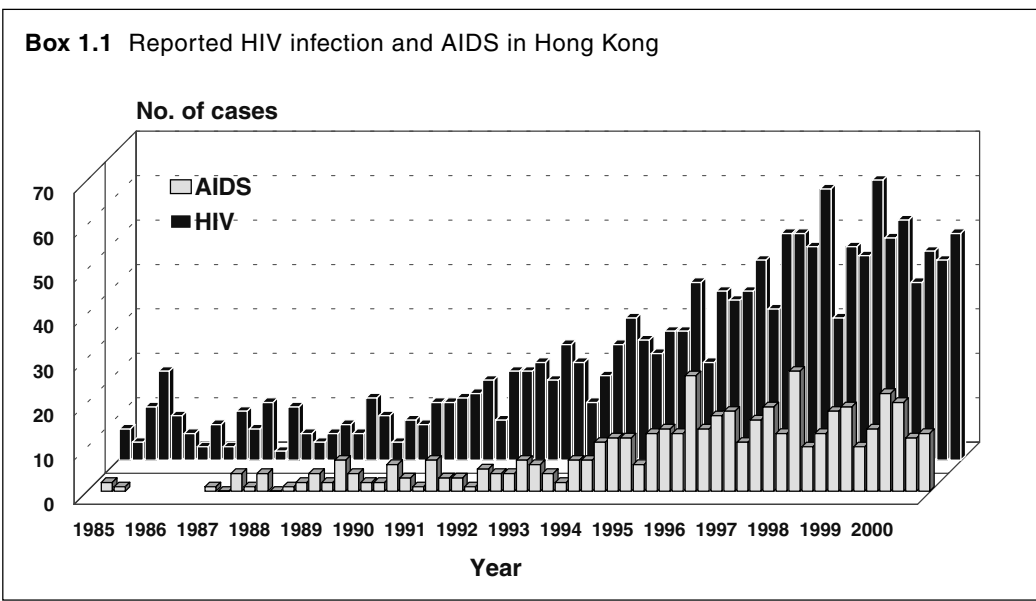
unlinked anonymous screening³ have been applied to enhance our understanding of the HIV situation. STD surveillance is a separate system coordinated in conjunction with the Social Hygiene Service. Finally, behavioral surveillance is a rather new concept in HIV epidemiology. Since 1994, Special Preventive Programmes has been experimenting on a pilot behavioral surveillance mechanism in collaboration with Department of Microbiology, The University of Hong Kong.⁴

II. Routes of HIV transmission

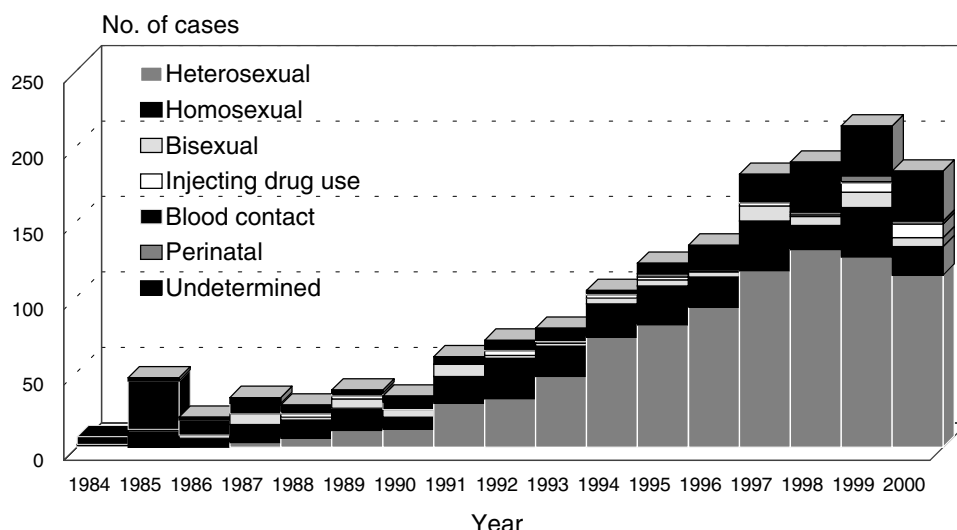
As of the end of the year 2000, a cumulative total of 1542 HIV infections have been reported. On a yearly basis, about two hundred cases are notified under the voluntary reporting mechanism to the Department of Health (Box 1.1). Through an analysis of the available epidemiological information, it was estimated that in 1999, the HIV prevalence in Hong Kong ranged between 2000 and 3000 (Revised projection of HIV infection and AIDS cases in Hong Kong by Dr James Chin, www.aids.gov.hk), a figure supported by results of seroprevalence studies. Sexual transmission has so far been accounting for a majority of the known cases.

II.A The central role of sexual transmission

Over the years, sexual transmission has remained the single most important route of HIV spread in Hong Kong (Box 1.2). Not surprisingly, the HIV prevalence is highest in the age



Box 1.2 Exposure categories of reported HIV infections in Hong Kong



25 to 34. From the reported figures, there has been a notable change from a predominantly homosexual to a heterosexual infection. Between 1985 and 1990, less than 30% of the reported sexually-acquired infections were heterosexuals. In 2000, this percentage has risen to 82%. These figures must be interpreted with care because of the different denominators involved. The importance of homosexually acquired infection should however not be ignored. Assuming that one-tenth of men in Hong Kong are homosexuals, the HIV prevalence in homosexual men is at least three to five times that of heterosexual men. In parallel there's been a narrowing of the male-to-female ratio from 8:1 in 1992 to about 3:1 in 1998 and beyond.⁵

The Government Social Hygiene Clinic, which looks after a significant fraction of local STD patients, is an important source of HIV reports. Diagnosis of HIV infection in STD patients reflects, to a certain extent, the HIV rate in those who have practiced high-risk sexual behavior. So far, clients of Social Hygiene Clinic have accounted for about 16% of all known cases of HIV. However, the prevalence of HIV in STD patients remained at a low level of 0.4% in year 2000. On the other hand, commercial sex is often considered to be another marker of possible high-risk behaviors. There is no reliable figure for the HIV rates in commercial sex workers in Hong Kong. Condom use is one of the behavioral markers regularly monitored in STD patients. The proportion that always or frequently used condom for commercial sex was less than 30% in the last two years. The condom usage rate varies significantly from one community group to another, but has remained relatively stable over years in the same community.⁶

II.B The potential risk of injecting drug use

Overseas observations have confirmed the propensity for rapid HIV spread to occur in the drug-taking communities once the virus gets into this very population. Hong Kong has so far been spared of this daunting phenomenon. Less than 5% of the reported infections in 2000 were attributable to injecting drug use. Cumulatively it is 2%.

There are indications that HIV rates in drug users are rising. Unlinked anonymous screening of methadone users revealed a yearly positive rate of less than 0.1% up 1997, rising gradually to 0.27% in 2000. The number of reported cases has also risen from not more than 3 per year before 1998, to 6 in 1999 and 9 in 2000.

Behavioral surveillance has provided further insights into the potential risk of HIV spread in the drug-taking communities. The injection rates, for example, had varied with the locations of the surveys, being highest at 80% in those before admission to an inpatient drug treatment center, and lowest at 20% in new registrants of methadone clinics.⁶ The average needle-sharing rate was higher in street addicts, followed by methadone users and then those opted for inpatient treatment (20%, 10% and 5% respectively for the last years). There has however not been any significant change in the behaviors of drug users surveyed. One recent study suggested that risk-taking behaviors generally fell after registering for methadone maintenance (data of Special Preventive Programmes, Department of Health).

II.C Contaminated blood and blood products – the historical past?

A total of 63 hemophilia patients and 4 transfusion recipients had contracted HIV before 1985 as a result of the use of contaminated blood product before blood screening and safer alternatives became available. Over the years about a quarter of the hemophiliacs have been tested positive for HIV. While the risk of transfusion has become a subject of the historical past, we were again reminded of the remote chance of infection from blood collected during the window period, when a patient actually got infected in 1997. There is no absolute safety despite the implementation of donor deferral, donor screening for HIV antibody and the introduction of Nucleic Acid Test (NAT) by the Hong Kong Red Cross Blood Transfusion Service. An infinitesimal residual risk of infection remains.

II.D Mother-to-child transmission: cause for concern

A study coordinated by Special Preventive Programmes had identified a total of 41 incidents of HIV positive pregnancies between 1992 and 1999. As of the end of the year 2000

reports of 12 cases of mother-to-child infections have been received, accounting for less than 1% of the cumulative total of reported HIV cases. A significant proportion of the reported infections were diagnosed only after the birth of the infected children. The Advisory Council on AIDS had proposed the strategy of universal antenatal HIV testing in Hong Kong,⁷ a move which may affect the profile of the infections in Hong Kong.

III. The setting of HIV diagnosis

HIV infection may present in one of the following settings: firstly, in the process of receiving voluntary counseling and testing (VCT) because of the perceived HIV risk, while one is still asymptomatic; secondly, undergoing an HIV test when seeking treatment for a condition that shares the same risk factor, for example sexually transmitted disease (STD) or drug addiction; thirdly, in the workup when one presents with a clinical complication.

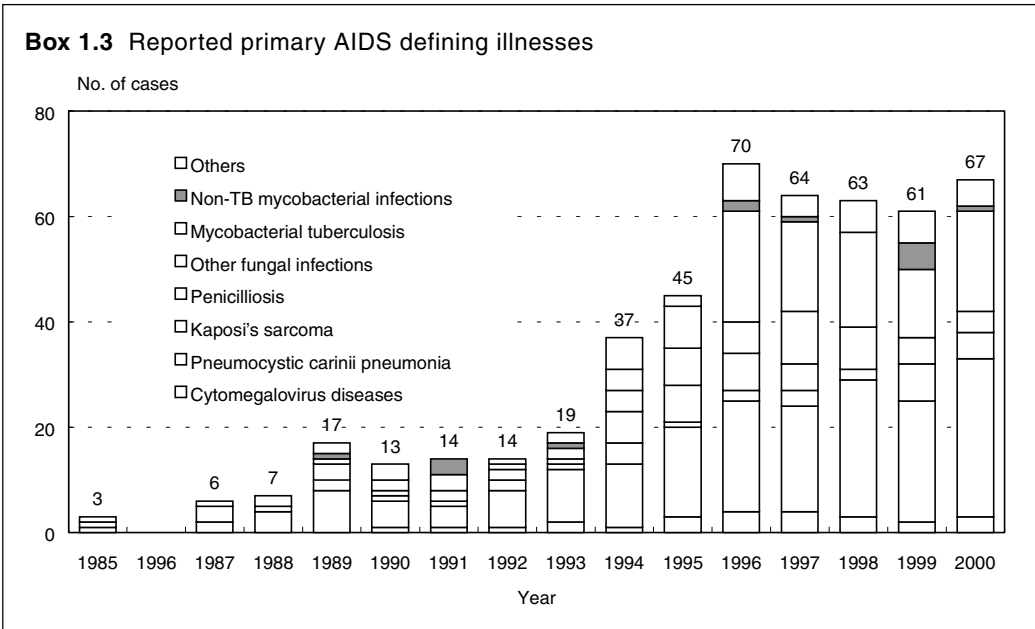
Over the years, a significant proportion of the HIV positive cases presented only after one had progressed to AIDS. Overall, about a third of the HIV infections were detected within three months of the corresponding AIDS diagnosis.⁸ Only 15% were reported from an AIDS service where VCT was offered, and another 15% from the Government's STD service, both considered as the avenues for early diagnosis.

Pneumocystis carinii pneumonia (PCP) remains the single most important ADI (AIDS defining illness) over the years. In the year 2000, PCP accounted for 45% of all ADIs, followed by tuberculosis. *Penicillium marneffe* is a unique infection occurring in South East Asia, including Hong Kong. Penicilliosis has been included as one of the ADIs in the definition established by the Scientific Committee on AIDS.⁹ Between 2 to 7 cases were reported annually. Box 1.3 shows the distribution of the major AIDS defining illnesses in Hong Kong. The access to antiretroviral therapy is gradually changing the landscape of AIDS with the number of reported AIDS reaching a plateau since 1997.

IV. Determinants of HIV spread in Hong Kong

What would the future patterns of HIV infection in Hong Kong be like? Two questions are proposed to help us predict the future. Firstly, are new infections happening? Secondly, are there societal forces that would affect the practice of risk behaviors in Hong Kong?

The determination of incidences is the key to understanding the occurrence of new infections. For HIV infection there is the intrinsic problem in assessing new infections because of (a) the absence of reliable laboratory tests for incidence testing, and (b) the difficulty in characterizing the onset of infection clinically. In evaluating all newly reported



HIV cases in the past ten plus years, it is evident however that the age has remained relatively constant at 32 to 36. The absence of age cohort effect testifies to the occurrence of new infections here in Hong Kong.

Knowingly, one's practice of risk behaviors exposes him/her to HIV infection. On the population scale, these behaviors are influenced by societal forces which either predispose individuals to or protect them from the virus. Human mobility is one such driving force. As a city in the Pearl River Delta region, there are ten times more people coming in and out of Hong Kong than the number of residents themselves. The human interaction in Hong Kong and the neighboring cities is far more complex than can be imagined. Cross-border commercial sex, drug trafficking and the practice of illicit drug are but some of the determinants of possible HIV spread. A quantification of the HIV risk of human mobility is an impossible task. On the other hand, a supportive environment is extremely important in ensuring the consistent practice of safer behaviors. Condom promotion, harm reduction in drug users, favorable legal framework, access to HIV testing and care are the building blocks of a supportive environment. So far, the network of methadone clinics, currently serving some 7000 drug users daily, has been providing a "safety net" to guard against HIV spread in the drug-taking communities. Regular methadone users are less frequent injectors and have a lower tendency to share needles.¹⁰ It must be noted however that the delicate equilibrium in methadone users, now with a low HIV rate, may be tipped once HIV is introduced.

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1.2 PATHOGENESIS AND DIAGNOSIS OF HIV INFECTION

I. HIV as a retrovirus

1.A Classification of the HIV virus

The human immunodeficiency virus (HIV) is an enveloped RNA virus belonging to the lentivirus subfamily of retroviruses. HIV-1 is the predominant strain of the current pandemic. HIV-2, in distinction from HIV-1, is identified mainly in West Africa, and is closely related to simian immunodeficiency virus (SIV). The clinical manifestations of HIV-2 are similar to those of HIV-1 but progression is typically slower. The Retroviridae is classified into three subfamilies:

- (a) Oncovirinae: examples are HTLV-I and HTLV-II, STLV-1 (Simian T Lymphocytic Virus type 1). They are associated with lymphoma or leukemia
- (b) Lentiviridae: HIV-1, HIV-2, SIV (Simian Immunodeficiency Virus)
- (c) Spumavirinae: this group of virus is found in animals and no disease association has been established

HIV was identified as the causative agent of the acquired immunodeficiency syndrome (AIDS) in 1983-84, by three different laboratories and named initially as:

- (a) Human T-lymphocytic virus type III (HTLV-III) by the National Cancer Institute¹
- (b) Lymphadenopathy-associated virus (LAV) by the Pasteur Institute,^{2,3} and
- (c) AIDS-related virus (ARV) by the University of California, San Francisco⁴

HIV-1 itself is mainly divided into the M (main) and O (outlier) groups. In addition, there are 10 subtypes or clades of group M: A, B, C, D, E, F, G, H, and J, some of which are actually recombinants of other forms. *Gag* and *env* sequences form the basis for classification. HIV subtyping may allow tracking of the epidemic to a certain extent (Box 1.4). In 1998, a new isolate that defied classification into either M or O group was designated group N for new or non-M, non-O. The predominant clade of HIV in Hong Kong is not known.

1.B Structure and function

As a retrovirus, HIV codes for reverse transcriptase, and is thus able to produce DNA from its native RNA. The mature virion is composed of a central core surrounded by a spherical lipid envelope that it acquires by budding from the surface of an infected cell. The core

Box 1.4 Global distribution of HIV-1 Group M subtypes and Group O⁵

Region	Highest prevalence	Moderate to low prevalence
North America	B	
South America	B	F
West Africa	A	
Central Africa	A	C, D, E, F, G, H, O
East Africa	A	D
South Africa	C	B
South Asia	C	B
Southeast Asia	E	B
Australia	B	
Western Europe	B	A, C, D, E, F, G, J
Eastern Europe	B	A, C, D, F, G

contains reverse transcriptase, integrase and protease in association with two strands of RNA.

HIV has a long genome with at least 9 genes. They are:

- 2 regulatory genes: *tat*, *rev*
- 4 accessory genes: *vif*, *vpu*, *vpr*, *nef*
- 3 structural genes:
 - gag* (inner core polypeptides):– p17, p24, p7, p9
 - pol* (viral enzymes): enzymes – reverse transcriptase, protease, integrase
 - env* (envelop proteins) – gp 120, gp 41

1.C The HIV life cycle

On entry, the HIV virus takes over the CD4 bearing cells for its own reproduction:⁶

- Free virus and possibly virus-infected cells enter the body during initial infection
- Virus envelope glycoprotein (gp120) attaches avidly to CD4 receptors, with the aid of a coreceptor, CCR-5 or CXCR4 (HIV strains that utilize CCR5 are termed R5 viruses and those that utilize CXCR4 are termed X4 viruses)
- The envelope fuses with the native cell plasma membrane
- The inner core is removed, freeing the retroviral RNA
- Using its *reverse transcriptase*, the HIV initiates viral DNA synthesis, using its own RNA as template

-
- (f) Once synthesized, the proviral DNA enters the nuclear cytoplasm and is integrated into the host cell's DNA by an enzyme called the ***integrase***
 - (g) Retroviral synthesis is begun, directed by the cell's infected DNA
 - (h) New viral particles are produced by budding at the cell membrane
 - (i) Mature viral cores are produced through action of viral ***protease*** after budding
 - (j) The complete virus is extruded into the bloodstream

Understanding the life cycle facilitates the development of drugs against HIV replication. For example, nucleoside reverse transcriptase inhibitors have been in use since 1987. In recent years, nonnucleoside reverse transcriptase inhibitors and protease inhibitors have also been developed. Possible candidates in the near future are the nucleotide reverse transcriptase inhibitors, integrase inhibitors and fusion inhibitors.

II. Pathogenesis

II.A Establishment of infection

On entry into a susceptible host through the mucosal route or blood stream, HIV transmission occurs by free virus entry or cell-to-cell transfer. The lymphoid organs have been implicated in the initial establishment of infection. Replication occurs in the infected cells in lymph nodes followed by systemic dissemination, which may result in systemic symptoms.

II.B Host immune response

The infected individual does mount specific immune responses against the HIV, as evidenced by the following phenomena:

- (a) Neutralizing antibody response – Antibodies are developed. Yet only those that can effectively activate complement can neutralize the antigen. There is evidence that this response is evaded by HIV with its enormous rate of mutations
- (b) Cytotoxic T lymphocyte (CTL) response – HIV-specific CD8+ cytotoxic T lymphocyte is developed early in the course of HIV infection. This is mediated through a MHC restricted mechanism. However, as the disease progresses, CTL is diminished. Interestingly, successful suppression of viral load by antiretroviral therapy is also followed by diminished CTL. One goal of current vaccine trials is to augment this response

II.C Immune destruction

As the disease progresses, the immune system is rendered progressively ineffective. As CD4 T lymphocytes (helper cells) are depleted by HIV infection, an overall lessening of immune function results. Thus HIV infection of CD4 cells destroys the very cells required to control the retrovirus.

The precise mechanisms whereby CD4 cells are depleted remain controversial. Some possibilities⁷ are:

- (a) Filling of all CD4 receptor sites – Not only do cells lose their function as a result, they become targets of immune surveillance by reason of the attached gp120
- (b) Syncytia formation – infected CD4 cells fuse with other uninfected cells to form giant multinucleated cells. Syncytium-inducing variants generally emerge in the course of infection and predate rapid decline in CD4 count
- (c) Apoptosis – also called programmed cell death, apoptosis may result from the cross-linking of CD4 by gp120-antigp120 immune complexes. Thus CD4 may be lost without direct infection by the virus
- (d) Autoimmunity – It has been shown that mice immunized with lymphocytes from another mouse strain develop antibodies against gp120. No HIV prior exposure was necessary.⁸ The corollary of this finding is that exposure to gp120 may also induce immunity against some component of the CD4 cell
- (e) Cellular transfer of HIV – by macrophages as antigen-presenting cells

The destruction of CD4 lymphocytes is staggering. In a war of attrition between CD4 cells and HIV, the half lives of CD4 cells and HIV are 1 to 2 days and <6 hours respectively.⁹ A tenuous balance is maintained in the beginning of the infection. As time goes on, the number of CD4 cells progressively decreases. When the count falls below 200/uL, the likelihood of developing opportunistic infections significantly increases.

II.D The roles of monocytes and macrophages

Monocytes and macrophages are the scavengers of the immune system. HIV infection of these cells occurs either by attachment of the CD4 receptor or by macrophage phagocytosis of whole HIV. The monocyte-macrophage is relatively resistant to the cytopathic effects of the virus. Once within the macrophage, HIV remains undetectable by the body's immune surveillance system and may replicate freely. Thus the macrophage may serve as a reservoir for HIV.

III. Diagnosis of HIV infection

III.A The HIV antibody test

HIV antibody detection is still the gold standard for diagnosis of HIV infection. The standard means of testing is to perform screening using the extremely sensitive but relatively less specific enzyme-linked immunosorbent assay (ELISA) test. In persons with positive ELISA, a confirmatory Western blot should be performed, which is the approach adopted in Hong Kong. The western blot is more time consuming and labor-intensive but is extremely specific. As an alternative, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization recommended 2 to 3 ELISA/rapid tests for HIV diagnosis in resource limited settings, depending on the HIV prevalence of the community and symptomatology of the patient.

Serum antibody appears most commonly 1-3 months after infection. This period between HIV inoculation and the detection of antibody is termed "window period". With modern technology, the window period can be shorter than one month. In most circumstances, a negative HIV antibody test at three months after a suspected exposure can safely exclude infection if no further risk exposure has occurred.

In Hong Kong, HIV screening is available in both private and public health services. Western blot confirmation is offered by the Government Virus Laboratory to other laboratories in case of a positive screening result.

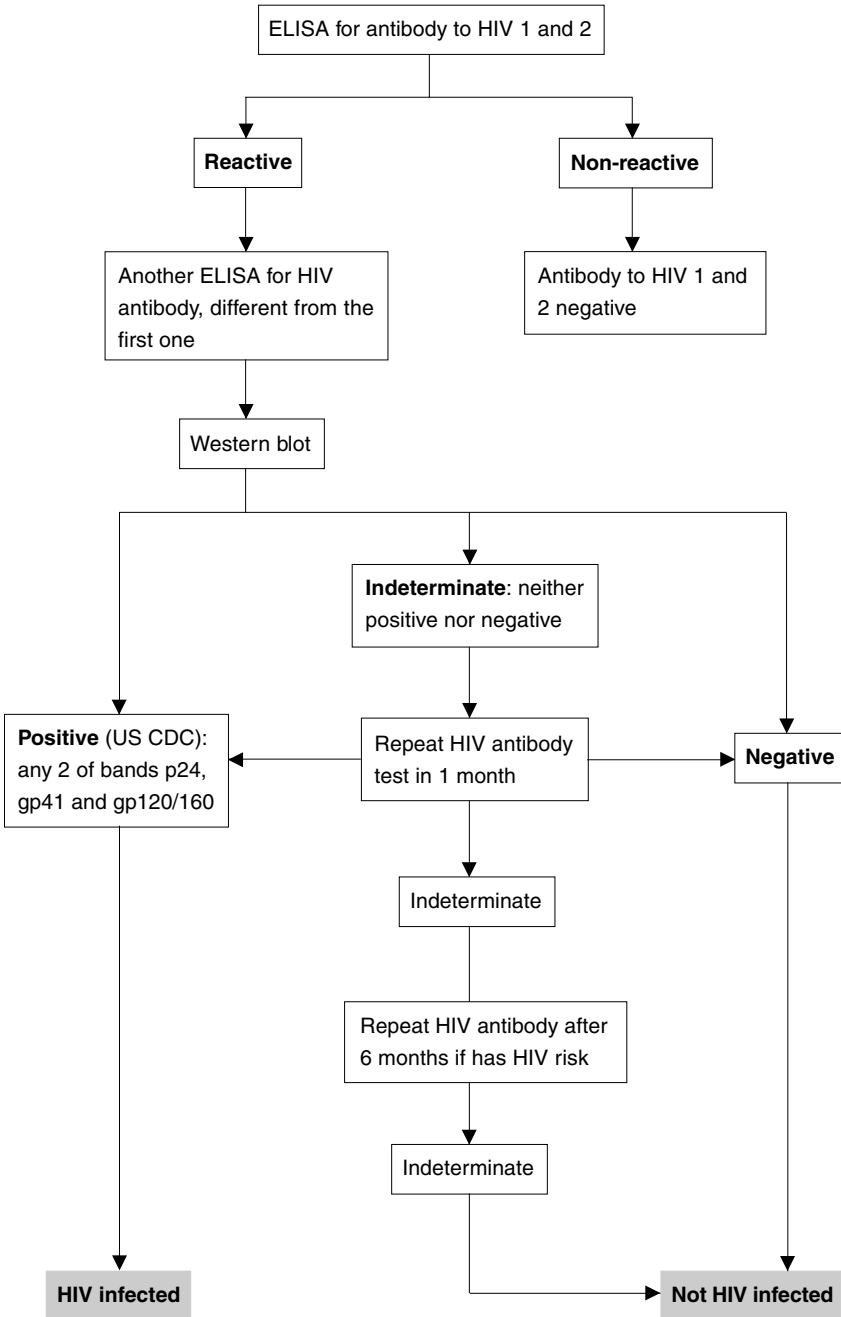
III.B Detection of virus

Detection of virus or its marker is clinically important, especially in:

- (a) diagnosis during acute HIV infection;
- (b) diagnosis of infants of HIV-infected mothers, who will continue to have maternal HIV antibody up to 18 months of age; and
- (c) monitoring the progress of disease.

Tests include viral culture, p24 assay, proviral DNA, and plasma HIV-RNA by PCR or bDNA (the viral load). Of these, only plasma HIV-RNA load is available as a standard assay in the public service. As a diagnostic tool, the test is sensitive but not specific, especially if the pretest probability is low.¹⁰ Nevertheless it will be useful in forming an early working diagnosis in primary HIV infection. Experts in HIV medicine should be consulted before requesting a test and in interpreting such result(s).

Algorithm 1.2 Laboratory diagnosis of HIV infection for adults (protocol of Virus Unit, Department of Health*)



*Modification may be needed by individual laboratory, based on the same principles

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THE FRAMEWORK OF CLINICAL HIV MANAGEMENT

2. THE FRAMEWORK OF CLINICAL HIV MANAGEMENT

HIV infected individuals suffer from the chronic complications of virus-induced immunodeficiency. The prevention and treatment of these complications lay the foundation of what is now referred as "HIV medicine". The practice of HIV medicine has, however, undergone changes over the years, and it varies from one place to another. Clearly, the clinical symptomatology of HIV/AIDS touches almost all possible medical disciplines. While HIV/AIDS could ideally be 'practised' by all medical practitioners, this has not happened because of the growing complexity of the subject, intensive research underlining new treatment strategy, and the dynamism of the disease unmatched by other clinical conditions. HIV/AIDS poses yet another challenge by exposing the medical profession to areas which some may not feel at ease with – risk behaviors, sexuality, marginalised communities, and the ever-ending ethical debates on the prevention and control of the infections.

This chapter deals with the system for providing clinical HIV management. While the general principles of good clinical practice apply equally to HIV medicine, characteristic features have emerged because of the specific needs of the local community, the uniqueness of Hong Kong's health care system, and the historical path of expertise development. A model of clinical care is presented which illustrates the practice adopted at the Integrated Treatment Centre (ITC), the base of the authors of this Manual.

I. Development of HIV care

1.A Historical perspectives

The historical path of discoveries in HIV/AIDS reflects on how HIV medicine has developed over the years. AIDS was perceived as a clinical syndrome in 1981. The isolation of HIV, its causative agent, was not made until 1982/1983, followed by the availability of diagnostic tests in 1985. In the early to mid-eighties, monitoring with CD4 and the diagnosis and treatment of opportunistic infections were the mainstay of HIV medicine. AIDS specialists in those days were either respiratory physicians (who managed *Pneumocystis carinii* pneumonia, PCP), other medical specialists, experts in intensive care or clinical infectious diseases. AIDS was the focus of HIV medicine, which was, naturally, part and parcel of acute medicine. Counselling played an important role in helping the young AIDS patients who were suffering from the stigmatizing fatal disease.

The effectiveness of prophylaxis against opportunistic infection like PCP alerted the medical profession that HIV/AIDS could be managed as a chronic illness. This belief was reinforced

in the late eighties by the short-term efficacy demonstrated by antiretroviral monotherapy. Hospice care flourished, in response to the needs of young AIDS patients who were going through a long and painful course of a chronic debilitating disease, with bouts of deterioration in its progressively downhill course to death. Concurrently, primary care had emerged as a model for managing HIV/AIDS during the early stages of the infection, when intensive counselling, health maintenance, CD4 monitoring and PCP prophylaxis (with or without antiretroviral monotherapy) were the pillars of HIV medicine. Community-based models were set up to bring HIV/AIDS patients closer to their homes and neighbourhood.

Between late-eighties and mid-nineties, there was a gradual shift from hospital-based to out-patient based services for HIV/AIDS patients.¹ Other non-hospital services like home care and residential facilities were set up, which all carried a very strong identity of being linked with the community.^{2,3} Hospital admissions had decreased even before combination antiretroviral treatment became available in developed countries.⁴ There was also the movement towards the setting-up of comprehensive dedicated HIV clinical services, especially in places where HIV/AIDS patients concentrate.⁵

Since the mid-nineties, the advent of highly active antiretroviral therapy (HAART) and the application of viral load testing have brought new challenges to HIV clinical services providers. The complexity of HIV treatment has grown, as a result of the availability of new regimens, the concerns about adherence, conduction of clinical trials on experimental treatments, introduction of salvage therapy and the need to correlate with resistance patterns.

1.B HIV treatment models and expertise development

There is no single model on clinical HIV management which can be universally applied in countries around the world. The historical development described above does highlight the key objectives of a clinical HIV management system – providing for the prevention and treatment of opportunistic complications, monitoring HIV disease, and optimizing treatment of HIV infection. Knowingly, the ultimate goal of an effective clinical HIV management system is to enable one to lead a normal life. In this connection, the following principles are essential:

- (a) *access* to the clinical care;
- (b) *continuity* of care;
- (c) effective mobilization of *community* resources;
- (d) adaptation of *professional expertise*; and
- (e) *integration* with the local health care infrastructure.

In the past there were debates on whether HIV/AIDS constitute a "primary care disease".⁶ A subsequent study revealed that AIDS patients under care of experienced doctors had a better outcome.⁷ Such observations testify to the notion that specialist care is desirable in managing HIV infection. Box 2.1 gives a good summary of the expectations of an HIV specialist, adapted from the clinical guidelines of New York State Department of Health.⁸ It must be noted, however, that HIV specialists can be ID (clinical infectious diseases) physicians, clinical immunologists, other clinical specialists or primary care physicians. The definition of a specialist is therefore gauged by the breadth of knowledge, skills and experience in HIV treatment.

On the other hand, primary care doctors and other medical practitioners not specializing in HIV treatment do have their general roles in HIV prevention and care in their practice. This includes the diagnosis of HIV/AIDS, and the promotion of risk reduction for preventing HIV infection. They may also facilitate the coordination of services for infected clients, and support their family in the long-term care of the disease.

In the last couples of years, there were efforts to better define the core competency of HIV specialists. Organizations have been established to promote the setting of standards in HIV medicine, for example, American Academy of HIV Medicine, HIV Medicine Association, International AIDS Society. Experience, commitment and currency of knowledgebase (in keeping updated on the fast-moving field) are the major components to HIV expertise. There is the tendency to disregard the original specialty of practising

Box 2.1 Expectations of an HIV specialist

- Latest information about HIV disease and treatments
- State-of-art diagnostic techniques
- Immune system monitoring
- Strategies to promote adherence
- Management of opportunistic infection and diseases
- Expertise in the management of HIV-infected patients suffering from common comorbid conditions
- Access and referral to clinical trials
- Post-exposure prophylaxis protocols and infection control issues
- Care coordination
- Patient education

**Excerpted from reference 8*

HIV specialist on one hand, and the move towards integration with such specialty as Clinical Infectious Disease to systematize training on the other.⁹

II. HIV medicine in Hong Kong

II.A HIV service provision

The development of clinical HIV programs in Hong Kong follows closely that of developed countries. In the public sector, there are two main HIV services that take care of a majority of adult patients – the Special Medical Service of the Hospital Authority's Queen Elizabeth Hospital, and the HIV clinical service of Special Preventive Programmes, Department of Health. In mid-2001, it is estimated that there are over 800 active adult cases in the two services. Other services involved in HIV care are: the Infectious Disease Division of Princess Margaret Hospital, Department of Paediatrics of Queen Mary Hospital.

The Special Medical Service is a hospital-based dedicated HIV service based at Queen Elizabeth Hospital. The HIV Clinical Service of the Department of Health is an out-patient based programme operating from the Integrated Treatment Centre (ITC). The model of care is described in the following section.

II.B The ITC model

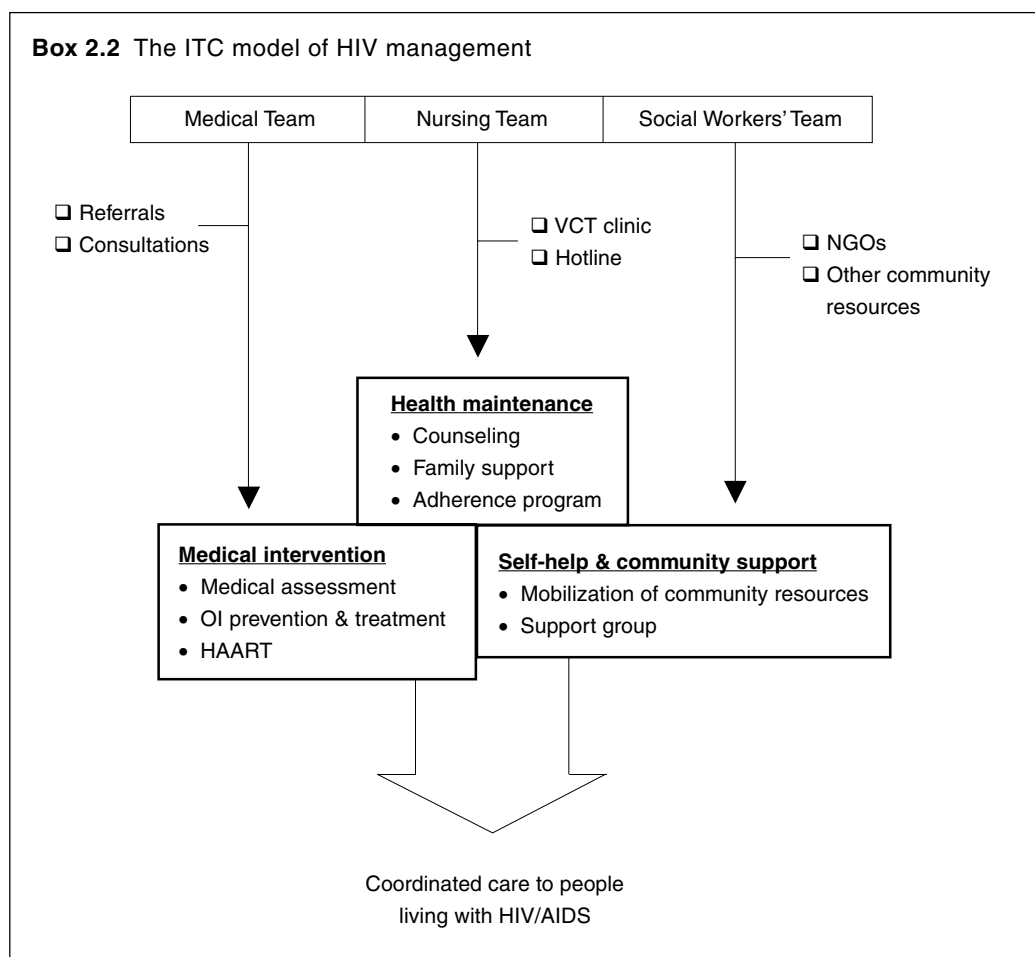
The mission of the ITC's HIV Clinical Service is to provide quality HIV/AIDS treatment through a systematic and integrated approach. The ITC model is founded on the following principles:

- (a) science-based protocol establishment;
- (b) commitment to continuous professional development;
- (c) community involvement in resource mobilization and care delivery; and
- (d) integration with clinical activities and professional development in the disciplines of infectious diseases, immunology, dermatology, STD treatment, infection control.

Three sets of activities are undertaken through the ITC programme: firstly, medical intervention; secondly, health maintenance, and thirdly, self-help and community support. A team of medical doctors, nurses and social workers are responsible for the delivery of activities in this model. The components, inter-relationship and external linkages of the three activities are illustrated in Box 2.2.

Medical intervention refers to the range of clinical activities designed to control symptoms and diseases arising from HIV infection, and to minimize their occurrence through the

Box 2.2 The ITC model of HIV management



adoption of appropriate therapeutic measures targeting the virus or the immune system. These measures include (a) monitoring – immunologic, virologic and physical health assessment; (b) prevention and management of opportunistic infections and neoplasms, and (c) HAART. The activities are delivered by trained physicians with experience in HIV/AIDS management. Through consultations and referrals, there is exchange of expertise in HIV medicine and other medical specialties.

Health maintenance is a set of activities organized to promote health in HIV infected individuals and their families. Counseling is provided to patients and families by nurses specialized in HIV care. With the use of HAART, special programs are conducted to promote adherence to the complex regimens. The nursing team works closely with the VCT (voluntary counseling and testing) clinic and the AIDS Hotline, which are the important channels for promoting HIV testing, and enhancing access of infected persons to quality care.

Self-help and community support are activities coordinated by social workers for the purpose of helping each client lead a normal life. This is done through mobilization of community resources and the conduction of support groups. Currently an editorial board composing of people living with HIV/AIDS is actively involved in the publication of a newsletter for networking the very community. Liaison with other non-governmental organizations is made to enable the establishment of support network for people living with the infection.

II.C Clinical governance

Quality is both a vision and an attribute in health care. The Institute of Medicine has defined quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge".¹⁰ In pursuing the goal of quality in HIV medicine, clinical governance, defined as corporate *accountability for clinical performance*,¹¹ has been adopted by ITC as the all-encompassing concept for constructing the quality framework.

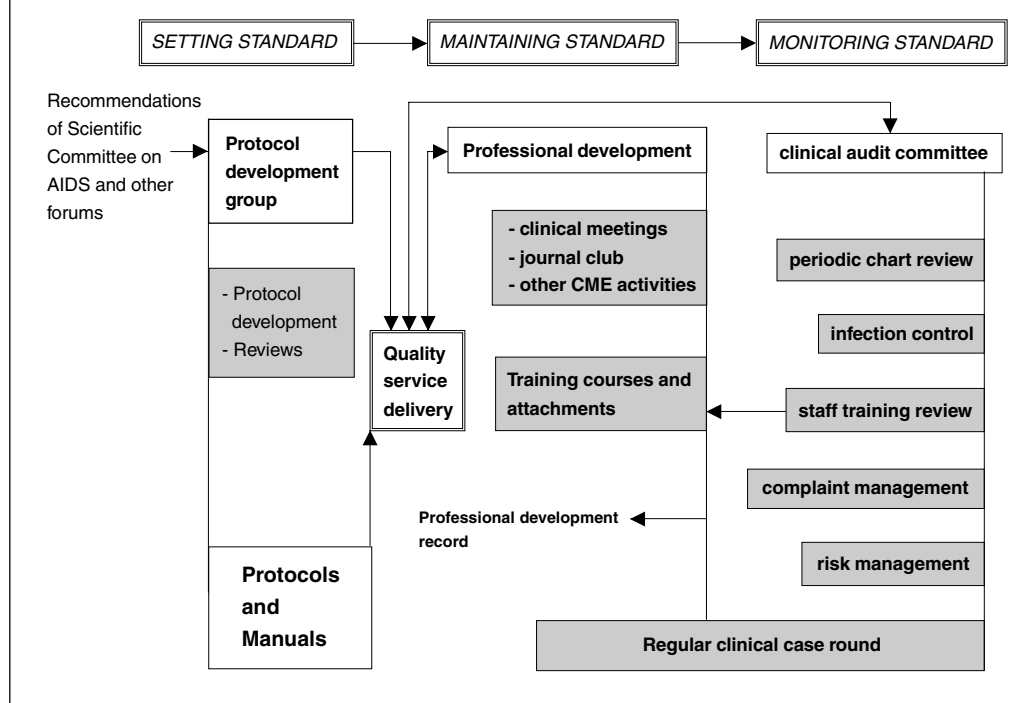
The framework of clinical governance can be considered as a continuum involving setting standards, delivering standards and monitoring standards.¹² (Box 2.3) This forms the backbone of five spheres of activities in the ITC model: (a) infection control, (b) evidence-based medicine, (c) risk and complaint management, (d) training and staff development, and (e) clinical audit. These activities and the framework are illustrated in Box 2.4.

III. Interface of clinical and public health medicine

While clinical medicine addresses the needs of individual patient, public health provides a broad perspective in linking the disease's impacts and response to the society. For HIV/

Box 2.3 The continuum of clinical governance	
Setting standards	<ul style="list-style-type: none">• Linkage with the Scientific Committee on AIDS• Protocol development mechanism
Maintaining standards	<ul style="list-style-type: none">• Journal meetings• Clinical meetings• Clinical case rounds• Case conference
Monitoring standards	<ul style="list-style-type: none">• Periodic chart review• Risk management• Complaint management• Infection control committee

Box 2.4 The framework of clinical governance at ITC



AIDS, clinical HIV medicine is intricately associated with its public health dimensions. These dimensions cover prevention, surveillance and control of disease spread. This section deals with the public health dimensions of HIV medicine.

III.A Prevention of HIV infection

The HIV clinical service plays a unique role in preventing the occurrence of HIV infection. In Hong Kong, the ITC program is affiliated with the **voluntary counseling and testing (VCT)** service, thus opening up the channel for accessing people practicing risk behaviors. Whereas HIV testing enables early diagnosis to be made in the confidential setting, counseling addresses risk behaviors with the purpose of minimizing the chance of contracting the virus.

Therapeutic prevention is another means of reducing HIV transmission through the use of antiretrovirals. This is now a regular clinical activity in two specific settings: (a) antenatal care, and occupational exposure in health professionals. Since 1 September 2001, universal antenatal HIV testing has become implemented as a regular health program in

Hong Kong. The use of antiretroviral agents plays an important role in preventing the virus from being transmitted from an infected mother to her baby. The management of postexposure prophylaxis is, on the other hand, packaged as one component of an infection control program. The two activities are discussed in more details in Chapter 3.

III.B HIV/AIDS surveillance

Disease Surveillance is a public health activity that consolidates the knowledgebase on the pattern of the disease in question. The conduction of effective HIV/AIDS surveillance requires the input of clinicians working on HIV medicine. Currently voluntary reporting is managed by the Special Preventive Programmes' Surveillance Office, which works closely with clinical HIV services in Hong Kong. This is a confidential system, the database of which does not contain personal identifiable information. Because of the relatively small number of patients, the Surveillance Office is cautious in its dissemination of the analyzed surveillance information, ensuring that the identity of reported cases is protected.

The HIV/AIDS situation as revealed by the surveillance mechanism is detailed in Chapter 2.

III.C Control of HIV infection

Conventional means of controlling infectious diseases requires the identification of the infected individuals, followed by measures to prevent secondary infections. Theoretically, this does not apply to HIV/AIDS because (a) the infections are limited to the settings of high risk behaviors, (b) of the asymptomatic property of the infections, and (c) of the unfeasibility of controlling a chronic condition with long incubation period and low infectivity.

Scientific advances have reversed some of the past perceptions of HIV. It is now generally agreed that an early diagnosis, appropriate antiretroviral treatment and risk-reduction counseling are supplemental means of minimizing the chance of secondary infections. A new strategy has emerged that emphasized on increasing the number of infected individuals who are aware of their status, and the use of the clinical setting for prevention.¹³ A good clinical service addressing the needs of an HIV infected person is in fact an effective means of minimizing the spread of the infections beyond.

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THERAPEUTIC PREVENTION OF HIV INFECTION

3.1 MANAGEMENT OF ACCIDENTAL PERCUTANEOUS EXPOSURE TO HIV

Percutaneous or mucosal exposure to HIV-contaminated blood or body fluids in health care setting is a rare but recognized mode of HIV transmission. It has been estimated that the average risk of infection after percutaneous exposure is 0.3%¹ whereas that of mucosal membrane exposure is about 0.09%.² As of end of December 1999, 102 definite and 217 possible occupationally acquired HIV (OAI) infections had been reported globally.³ Amongst these OAI, nurses and doctors were the most frequently implicated health care workers (HCW). Nevertheless, although OAI occurs, it accounts for just a fraction of the known HIV infections in HCW and therefore plays an infinitesimal role in the global HIV epidemic.

Attempts have been made to prevent HIV infection by the percutaneous route through administration of antiretroviral chemoprophylaxis, before or after exposure. Evidence of its effectiveness is available in both animal and human studies. In chimpanzees receiving nevirapine, HIV-1 challenge did not result in infection.⁴ In another animal model, antiretroviral drug given after simian immunodeficiency virus (SIV) exposure prevented virus transmission.⁵ In humans, a case-control study of health care workers who sustained mainly percutaneous injury also found efficacy of zidovudine in protecting against seroconversion.⁶

Despite the small absolute risk of infection, occupational exposure to HIV in health care setting could pose a significant psychological burden to the injured. Post-exposure management offers a unique chance for therapeutic prevention of HIV infection. Humane counseling, professional advice, together with appropriate treatment shall aim at minimizing psychosocial as well as physical morbidity consequent to the exposure. Currently, management of potential exposure to HIV has been one major focus of the scope of Accident & Emergency Departments and HIV care units in Hong Kong. Exposure to known HIV-infected patients is rare and a handful of post-exposure prophylaxis has been prescribed over the last years. There was no known incident of seroconversion upon accidental exposure in health care setting locally.

Primary prevention of occupational exposure to blood or body fluids is crucial. Adherence to standard infection control practice minimizes the occurrence of injury. Some 'accidents' are avoidable. Universal precautions protect HCW from blood-borne diseases beyond HIV, irrespective of the HIV status (whether known or unknown) of those involved.

The management of an incident of occupational exposure involves proper risk assessment, counseling tailored to the need of individual client, and the prescription of antiretroviral drugs to prevent HIV transmission if the risk is substantial. These are discussed in the following sections. An algorithm is provided at the end of the Chapter.

I. Risk assessment of exposure

HIV transmission can potentially occur in the event of a significant exposure to body fluids/tissues (e.g. blood, cerebrospinal fluid) which may harbor infectious blood-borne viruses from an HIV/AIDS patient. Risk assessment is the most important component of post-exposure management and should be commenced as soon as possible after exposure. The risk of transmission depends on (i) type and extent of exposure, and (ii) HIV status and stage of the source. In assessing the exposure, multiple factors need to be considered:

- (a) time lag between the incident of exposure and clinical consultation;
- (b) nature of exposure, i.e. (breached) skin, mucosal or percutaneous;
- (c) type of contact specimen;
- (d) severity of injury;
- (e) amount of blood/body fluids transferred to the injured;
- (f) device involved in injury; and
- (g) protective measures during the exposure.

Some factors of the accident itself are associated with a higher potential of seroconversion after percutaneous exposure to HIV-infected blood:⁶

- (a) injury with a device visibly contaminated with the patient's blood;
- (b) a procedure that involved a needle directly placed in a vein or artery;
- (c) deep injury; and
- (d) exposure to source patients with AIDS or high plasma viral burden.

No matter how extensive the exposure is, HIV transmission may only happen if the source is HIV infected. For known infected source, his/her stage of disease has bearing on the risk of transmission. It is, however, not uncommon that HIV status of the source is unknown or cannot be ascertained. In this case, the likelihood of HIV infection in the source shall be assessed by clues such as (a) HIV-related illnesses, e.g. *Pneumocystis carinii* pneumonia, oral thrush, (b) HIV-related risk behaviors, e.g. unprotected sex, multiple sex partners, needle-sharing for drug injection, and (c) HIV prevalence of the community group which the source belongs to. Re-evaluation of the exposed person should be considered if there is additional information after the first assessment, e.g. HIV status of source.⁷

II. Counseling and health advice

Counseling and psychological support is another crucial component of post-exposure management. This is often provided by the nursing as well as medical staff. The assessment and the determination of the risk of HIV transmission would provide a good case-by-case base for further counseling. A variety of areas need to be covered, including: general risk of infection after percutaneous or mucosal exposure, assessment of the specific exposure,

usefulness and limitations of PEP, necessary investigations, necessary precautions, arrangement of follow-up care and others.

In counseling for HIV antibody testing, one might need to explore if the injured is already at risk of HIV infection before injury. Any previous HIV antibody testing and its results should be inquired. This is particularly relevant if PEP has to be prescribed. For infected individuals, the antiretroviral prophylaxis (regimen similar to antiretroviral therapy) will actually be treatment of the disease. A thorough assessment and plan would be a must for optimizing antiretroviral therapy for any infected patient.

All cases with potential risk of infection have to be warned about HIV seroconversion illness, for which they should seek medical consultations. This typically occurs 2-6 weeks after exposure. (see Chapter 4.5) Classical symptoms are fever, skin rash, sore throat, swollen lymph glands especially on neck, and ulcers in mouth/genitalia. Sometimes, it can just be non-specific symptoms such as fever, headache or malaise. Also, there was report of delayed HIV seroconversion (8 to 9.5 months after exposure) in a health care worker who contracted both HIV and HCV after a needle-stick injury.⁸ Thus, symptoms suggestive of acute HIV infection should not be discarded lightly especially in the case of delayed presentation.

Similarly, the injured should be advised to take precautions while pending outcome of the exposure, if risk of HIV infection exists. For example, he/she should practice safer sex and not donate organ, blood and semen. Female should avoid pregnancy.

III. Blood investigations

A baseline HIV antibody test is needed for most of the injured. Its result serves as a reference for interpreting subsequent testing results, in case there is seroconversion after the exposure. Also, it can exclude an underlying HIV infection. One option is to test for HIV antibody only when subsequent follow-up blood samples are tested antibody positive. However, a baseline antibody test must be performed immediately if underlying HIV infection is suspected when an injured is put on PEP. In such circumstance, baseline blood investigations of complete blood picture (CBP), renal/liver function tests (R/LFT) and sugar (if protease inhibitor given) should be performed concurrently. Creatinine kinase and amylase are optional. Baseline investigations for viral hepatitis B and C shall also be pursued as appropriate for the injured.

In some cases, testing of source patient for HIV antibody might assist in the management of the injured. This should however be done after clear explanation of the rationale to the source and consent obtained. Confidentiality should be upheld throughout.

Follow-up investigations depend on whether the injured has been put on PEP. For those who are not on HIV PEP, they can be followed up 3-6 months after the initial assessment and consultation. For those on PEP, clinical and biochemical (CBP, R/LFT, amylase, CPK, sugar (if protease inhibitor is prescribed)) monitoring for drug tolerance at week 0,2,4, and third month should be considered.

Follow-up HIV antibody test shall be performed at month 6. A test earlier at month 3 is optional. An additional month 12 testing may be considered case-by-case for high infection risk cases who have taken PEP, for fear of the possibility of delayed seroconversion. HIV antibody testing and HIV RNA are performed for cases presenting with suspected seroconversion illness. Plasma shall be stored for resistance testing in such case.

IV. Post-exposure prophylaxis

IV.A The scientific evidence

Pathogenically, there is time lag between HIV exposure, viral seeding, replication and systemic infection. Antiretrovirals may theoretically be able to intervene by inhibiting viral replication after exposure. Both animal and human studies have provided evidence for the efficacy of PEP. From animal studies, it has been demonstrated that size of the inoculum, timing and duration of PEP affects chance of infection. Success of post-exposure prophylaxis (PEP) depends on its early initiation. PEP initiated at 72 hours after exposure in animal models was often ineffective. A retrospective case-control study on health care workers revealed that after controlling for other factors, there was a 81% (95% confidence interval, 48-94%) reduction in risk of infection with the use of zidovudine (AZT) after percutaneous exposure.⁶ The efficacy of abbreviated postpartum regimens initiated after childbirth in reducing mother-to-child HIV transmission also provides support to the principle of PEP. Nevertheless, PEP is definitely not fool-proof, and failure of antiretroviral prophylaxis has been reported in both animal and human studies.

Given the small absolute risk of HIV transmission even with significant exposure to HIV-contaminated blood or body fluids, the prescription of PEP depends on a balance of risks and benefits, which should be explained clearly to the injured. Potential drawbacks of PEP include: toxicity of antiretrovirals, unknown long term effects in HIV positive and negative people, uncertain level of effectiveness, development of resistance, and unknown impacts to the course of disease if seroconversion occurs. Potential benefits of PEP are: reduction of the chance of infection for injury with significant risk.

IV.B The recommended regimens

Though only zidovudine has been demonstrated to be effective in clinical studies, combination antiretroviral PEP is now recommended (based on data from treatment of HIV-infected patients) for its greater suppression of viral replication, broader coverage of resistance strains, and thus the theoretical advantage of more effective prevention of HIV transmission. When indicated, PEP should be initiated as soon as possible.

The US CDC recommended a basic 2-drug regimen of AZT (200 mg tid or 300 mg bid) and 3TC (150 mg bid) for cases with risk of infection.⁹ The tablet of Combivir (AZT 300 mg +3TC 150 mg) can be considered and given bid. A protease inhibitor (PI) such as indinavir (800 mg Q8H) or nelfinavir (750 mg tid) is added in an expanded 3-drug regimen if there is higher risk for transmission.⁹ However, UK authority generally favored a 3-drug PI-containing (indinavir, followed by nelfinavir) regimen for all exposures where PEP is indicated.¹⁰ There is insufficient evidence to support whether the US differentiated 2-drug/3-drug approach or the UK blanket 3-drug approach is superior. Decision should be made on a case-by-case basis, balancing against such factors as assessed risk, anticipated PEP efficacy and potential toxicity and tolerance for the injured.

The PEP regimen might need to be modified accordingly if resistance is known or suspected in source HIV strains. Suspicion is usually based on (a) failure of treatment in source, (b) prevalence of primary resistance in the locality, or (c) documented resistance by resistance assays. Evaluation of the treatment history and efficacy of the current regimen in the source patient is a must.

Lately, the US CDC suggested that nucleoside reverse transcriptase inhibitor other than AZT and 3TC could be considered, e.g. stavudine (d4T), didanosine (ddI).⁷ Other drugs such as efavirenz or abacavir can be the alternative for the third drug in the expanded regimen. However, the limited experience of using these alternative drugs for PEP shall be taken into account when choosing the regimen. The use of nevirapine to spare PI has caused severe morbidity and even deaths, which is thus contraindicated in PEP.¹¹

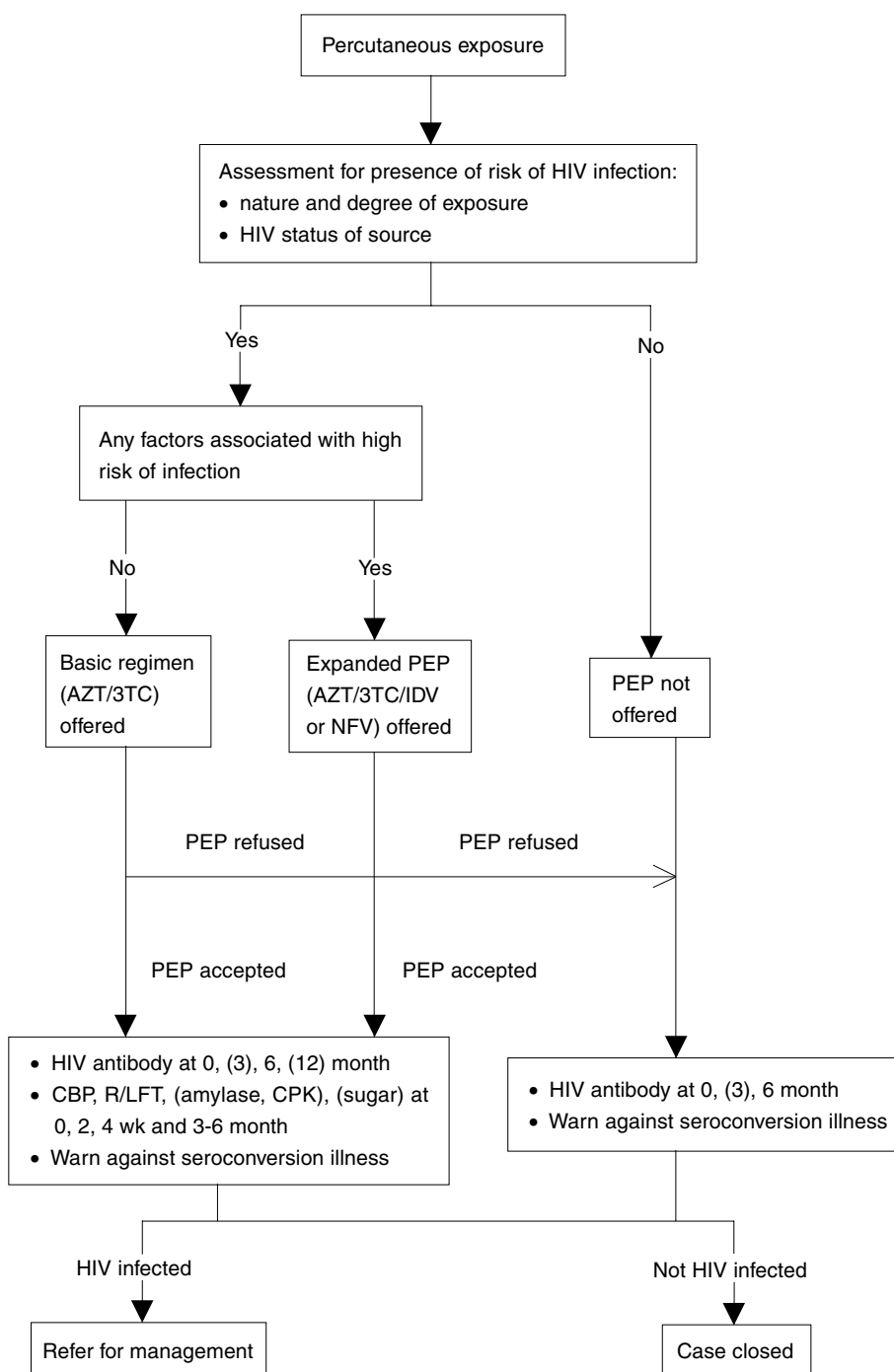
The dosage of common antiretrovirals and the potential side effects are in Box 3.1. Potential interactions of antiretrovirals with drugs that the injured is taking should be borne in mind. Special considerations are needed for those who are pregnant. For example, efavirenz is contraindicated because of its teratogenicity and indinavir should be avoided in late pregnancy for hyperbilirubinemia in newborn.

Box 3.1 Common antiretroviral preparations for post-exposure prophylaxis

Drug	Dosage	Potential side effects
Zidovudine (ZDV, AZT)	200 mg tid/300 mg bid	Anemia, neutropenia, gastrointestinal upset, myalgia/ myositis
Lamivudine (3TC)	150 mg bid	GI upset, pancreatitis
Zidovudine + lamivudine (Combivir)	1 tablet bid	Anemia, neutropenia, gastrointestinal upset, myalgia/ myositis, pancreatitis
Indinavir (IDV, Crixivan)	800 mg q8h, empty stomach	nausea, vomiting, renal stone, unconjugated hyperbilirubinemia
Nelfinavir (NFV, Viracept)	750 mg tid/1250 bid with food	Diarrhea, rash

The optimal duration of PEP is unknown but a complete course is normally 4 weeks. This is prescribed in no less than 2 separate visits. Many HCWs who took PEP experienced one or more symptoms and a substantial proportion could not complete the course.^{12,13} Pretreatment counseling of all potential side effects might hopefully improve compliance of PEP. Besides blood investigations, toxicity should be evaluated clinically and managed accordingly. The best efforts should be made to have the exposed person complete the 4-week course if PEP is indicated. For PEP prescribed for unknown source who is subsequently found HIV negative, the PEP should be stopped.

Algorithm 3.1 Management of accidental percutaneous exposure to HIV



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3.2 NON-OCCUPATIONAL EXPOSURE – SEX AND INTRAVENOUS DRUG USE

The average **risk of HIV transmission** associated with receptive anal intercourse (0.8% to 3.2%) or receptive vaginal intercourse (0.05% to 0.15%) with an HIV-infected partner is similar to that with puncture by an HIV-contaminated needle. The risk of insertive vaginal intercourse is lower (0.03% to 0.09%). The risks associated with insertive anal intercourse and oral sex are unknown.¹ In addition to the mode of exposure, the per-contact risk of HIV transmission also varies significantly according to the stage of disease, viral load, mode of contact, virulence of HIV strain, and co-morbid factors (e.g. genital ulcerative disease, bleeding, trauma).

While the average risk in shared injecting drug use is estimated to be between 0.67% and 1%, this can vary widely, depending, among other factors, on the size of the needle and syringe, and the sequence of sharing.²

I. Rationale of postexposure prophylaxis other than percutaneous contact

It has been shown in a case-controlled study that ZDV prophylaxis alone reduced the risk of HIV transmission by 81%.³ In this study, exposure occurred mainly by the percutaneous route. As a result, the use of ZDV as postexposure prophylaxis (PEP) is now routinely recommended in percutaneous exposure to HIV, especially in health care workers.⁴ Nevertheless, the utility of PEP in this context is still subject to debate. Isolated case reports have documented both success (after transfusion)⁵ and failure (after needlestick).⁶

The recommendation on ZDV PEP is not extended to routinely cover sexual contact and shared injecting drug use because of the following concerns on efficacy and public health implications:

I.A Efficacy of PEP for non-occupational injuries

The mechanism of infection via a percutaneous needle stick is not identical to that via sexual contact or shared injecting drug use (IDU). In sexual contact, HIV is transmitted through mucosa; in shared IDU, local defenses are bypassed as the injection is intended to be intravenous.

The time limit of prophylactic treatment should be noted, as this is often less well-defined than a case of occupational exposure. In animal studies where HIV was inoculated intravenously, the efficacy of PEP decreases rapidly with time after exposure. Treatment initiated after 8 hours is much less likely to be effective, and after 72 hours useless.^{7,8} These studies essentially impose a **time limit** of 72 hours after which PEP should not be considered at all.

The use of a potent and usually more toxic drug combination does not automatically translate into efficacy since the viral load in the initial stage of HIV infection is small. In fact, up to one third of health care workers could not tolerate postexposure treatment with ZDV alone.⁹ In another trial of PEP after mostly sexual contact, only 78% completed a 4-week regimen of double NRTI therapy.¹⁰ Long term toxicity of antiretrovirals in HIV-negative individuals is still unknown.

There are hitherto limited data to validate that routine PEP after IDU or sex is useful. In particular, the assessment of HIV risk is currently not standardized. To date there is no consensus as to the optimal regimen and criteria for PEP after sex and shared IDU.

1.B Public health implications

The application of PEP cannot be undertaken lightly without addressing the possible impacts on public health in terms of alteration of sexual behavior, prevalence of drug resistant virus, cost-effectiveness, and service delivery.

All in all, the use of PEP on exposure through sexual and shared injecting drug use is based on theoretical considerations only, there having been no systematic study to address its efficacy. At the moment, decision on PEP will have to balance drug toxicity in an HIV-negative individual against a variable risk of infection and the unknown efficacy of PEP. Until this balance is properly addressed, routine PEP after sexual and IDU contact is hardly convincing.

Nevertheless, the assessment for PEP after at-risk contact does provide a good opportunity for risk-reduction counseling.

II. Management on potential exposure to HIV via sex or IDU

The steps of assessment, behavioral modification, consideration for post-exposure chemoprophylaxis and followup are considered in the management of a case of potential exposure through sex or drug injection. (algorithm at the end of the Chapter) There is a

difference from the management of primary HIV infection when infection has presumably occurred (Chapter 4.5).

II.A Assessment

The following assessment shall be made on presentation:

- (a) The type and time of contact
- (b) Risk factors for HIV in the source – examination for concurrent STD is indicated
- (c) Practice of High risk behavior
- (d) Likelihood of repeat exposure

All clients shall receive baseline testing for HIV. Syphilis screening and hepatitis B and C serology may also be indicated.

II.B Behavior modification

It is almost certain that as a public health tool, PEP as we know it today has a cost-effectiveness ratio inferior to that of intensive risk-reduction counseling. Counseling is given on safer sex and the danger of needle-sharing, with a view to modifying high risk behaviors.

II.C Postexposure chemoprophylaxis

Due to the theoretical basis of chemoprophylaxis in this situation, this should be considered in the exceptional case where there is a high risk of transmission, no contraindication to the use of antiretrovirals and only if the client understands and accepts the risks involved.

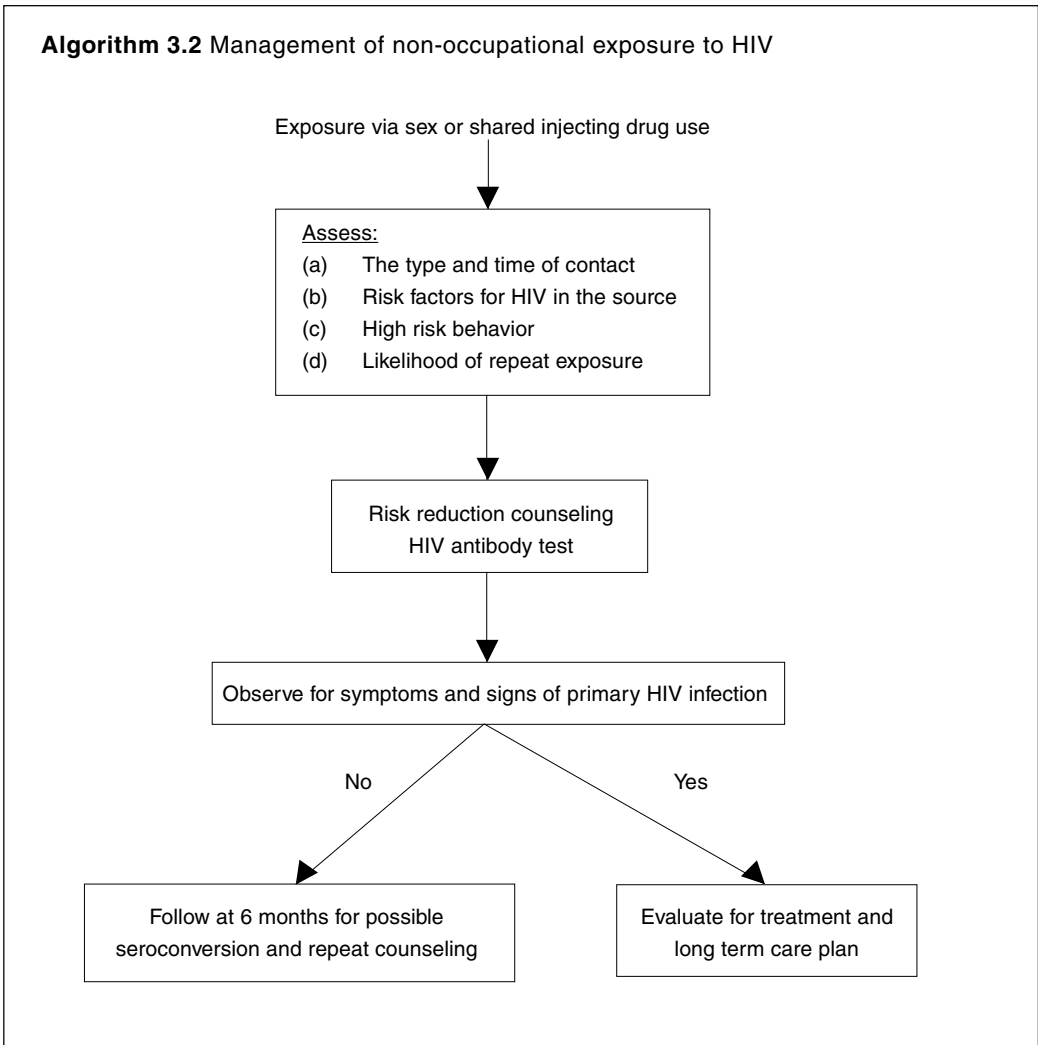
Were PEP to be used after exposure via sex and injecting drug use, the regimens would logically follow those in the percutaneous setting.¹¹ (refer to Chapter 3.1) Four weeks of zidovudine (ZDV), and lamivudine (3TC), with or without indinavir (IDV) would be the preferred choice. Alternatives are stavudine (d4T), didanosine (ddI) and nelfinavir (NFV). There is no consensus as to the number and kind of drugs that should be used.¹² However, it is noted that AZT is the only drug shown to be effective after percutaneous exposure in the health care setting. Non-nucleoside reverse transcriptase inhibitors (NNRTI) should normally not be used for this indication because of its low genetic barrier and its toxicity.¹³

It is emphasized that chemoprophylaxis in situations other than percutaneous contact should not be the rule. It should not be prescribed lightly without a thorough assessment

and discussion with the patient who is likely to be in great anxiety and distress. As far as possible, treatment should form part of a clinical trial to derive the best information for the benefit of the index and other clients.

II.D Followup

Explanation should be given to clients of the symptoms and signs of primary HIV infection.¹⁴ Occurrence of such will prompt an evaluation, on a case-by-case basis, of the possibility of HIV antigen or viral load testing. Treatment of primary HIV infection itself is also fraught with controversy. Repeat testing for HIV antibody will be done for all the others to test for seroconversion. This provides a second opportunity of risk-reduction counseling.



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HIV THERAPY

4.1 MONITORING OF HIV DISEASE

On establishment of infection, HIV replicates at a frantic rate, producing over 10 billion virions a day.¹ There is an associated decline of CD4 count, although its mechanism remains controversial.^{2,3} Four successive stages of disease have traditionally been identified. Essentially these constitute a spectrum of disease manifestations, or lack thereof, that correspond to the degree of immune system damage:

- (a) Primary HIV infection
- (b) Asymptomatic HIV infection
- (c) Chronic symptomatic infection
- (d) AIDS

I. Clinical profile of HIV infection

In Hong Kong, HIV patients most commonly present in the following circumstances:

- (a) Sexually transmitted disease clinics;
- (b) Emergency room admissions with AIDS-defining conditions such as tuberculosis and *Pneumocystis carinii* pneumonia; and
- (c) voluntary testing at the Counseling clinic of the Department of Health through the AIDS Hotline, or the client's family doctor in the private sector.

These presentations reflect a continuum from asymptomatic carriage to advanced AIDS, with a number of intermediate stages. These have been referred to as AIDS prodrome, pre-AIDS, or AIDS-related complex (ARC). These non-specific terms are less commonly used today. The classification system proposed overseas and locally also provides a guide for disease monitoring.

1.A Evolution of the CDC and Hong Kong classification and surveillance definitions

As early as 1982, the US Centers for Disease Control and Prevention (CDC) developed a case definition of AIDS.⁴ The diagnosis was based on the presence of diseases moderately indicative of underlying cellular immunodeficiency in a person without recognized cause (e.g. neoplastic disease and immunosuppressive therapy).

In 1984, the term ARC was coined to describe the symptoms of immunodeficiency that were being recognized with increased frequency in persons at risk for AIDS. They were

unexplained generalized lymphadenopathy, idiopathic thrombocytopenia, oral candidiasis, herpes zoster infection, and a constitutional wasting syndrome. This is now referred to as symptomatic HIV infection.

In 1984-85, serological testing became available to identify HIV-infected persons. In 1986,⁵ the CDC defined a classification system to accommodate the increased number of clinical manifestations that had become associated with chronic HIV infection. This new system classified HIV infection into acute infection, asymptomatic infection, persistent generalized lymphadenopathy, and certain other categories.

In 1987, the CDC expanded its definition of AIDS in order to track more effectively the morbidity associated with HIV infection. This was revised and further expanded in 1993.⁶ Progression of disease is indicated by opportunistic conditions that belong to the next category. The CD4 count provides another dimension of staging. Hong Kong has mostly been following the CDC classification,⁷ (Box 4.1) but adopted the following modifications: (1) disseminated penicilliosis is added as one AIDS-defining condition, (2) pulmonary or cervical lymph node tuberculosis included only if CD4 <200/ul, (3) a CD4 <200/ul without any AIDS-defining condition is not counted as AIDS.⁸

It must be noted that the listing of the complications and the definition of immunodeficiency by CD4 count offer one means of surveillance rather than clinical monitoring, though they are often used in comparing the characteristics of cohorts. The AIDS-defining conditions are not equal. Pulmonary tuberculosis and Kaposi's sarcoma may occur at CD4 count higher than 200/ul; PCP occurs with a CD4 count below 200/ul; and conditions like CMV retinitis, cerebral toxoplasmosis and disseminated MAC do not usually manifest until the count is below 50/ul.

1.B Other classifications

The Walter Reed (WR) staging system of HIV infection⁹ classifies patients on the basis of CD4 counts, skin-test responsiveness, lymphadenopathy, oral candidiasis and opportunistic infections. It has limitations with respect to predictive value.

World Health Organization (WHO) has also developed a case definition for AIDS that can be used in developing countries where sophisticated diagnostic technologies are not available.

Box 4.1 Classification for HIV infection and surveillance case definitions for AIDS in adults and adolescents

CD4 categories	(A) Asymptomatic, acute (primary) HIV or PGL	(B) symptomatic, not (A) or (C) conditions	(C) AIDS-indicator conditions
(1) $\geq 500/\text{ul}$	A1	B1	C1
(2) 200-499/ ul	A2	B2	C2
(3) $< 200/\text{ul}$	A3	B3	C3*

Category A Asymptomatic HIV infection
Persistent generalized lymphadenopathy
Acute HIV infection with accompanying illness or history of acute HIV infection

**Category B
(includes but
not limited to)** Bacillary angiomatosis
Candidiasis, oropharyngeal (thrush)
Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
Hairy leukoplakia, oral
Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
Idiopathic thrombocytopenia
Listeriosis
Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
Peripheral neuropathy

**Category C
AIDS indicator
conditions** Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, primary, of brain
***Mycobacterium tuberculosis*; extrapulmonary or pulmonary/cervical lymph node (only if $\text{CD4} < 200/\text{ul}$)
Pneumonia, recurrent
**Penicilliosis, disseminated
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

*A low CD4 alone is not an AIDS defining condition in Hong Kong for surveillance purpose

**AIDS defining conditions adopted in Hong Kong
(see text for explanation)

1.C Clinical manifestations

The clinical conditions that arise from immune deficiency are highly variable. But in general the CD4 count determines what opportunistic diseases may occur. The B conditions as described are seen even if the CD4 is above 200/ul. On the other hand, the AIDS-defining diseases generally do not occur until the CD4 drops below 200/ul.

During the chronic phase of HIV disease, the patient generally remains well (clinically latent) for a few years before symptoms or signs manifest. This is usually predated by a progressive fall in CD4 level. Clinical presentation depends on which organ/system is involved and the stage of the disease.

Opportunistic infections from a variety of agents e.g. *Pneumocystis carinii* pneumonia (PCP) as well as tuberculosis, are the most frequent **AIDS-defining conditions** in Hong Kong. Malignancies e.g. Kaposi's sarcoma, primary CNS lymphoma, or conditions directly related to HIV e.g. AIDS dementia complex are sometimes seen. In general, relatively minor diseases precede major life-threatening AIDS-defining illnesses. Classical examples of **pre-AIDS illnesses** are mucocutaneous conditions such as *herpes zoster*, oral thrush and oral hairy leukoplakia which all predict faster disease progression. Overall, the respiratory system, GI system and CNS are common sites of complications in HIV/AIDS.

In the pre-HAART era, survival after the onset of AIDS was numbered. Today, with the aid of potent antiretroviral agents, the viral load may be suppressed, CD4 may rise and survival considerably increases.

II. Assessment of a newly diagnosed HIV+ individual

The purpose of assessment is three-fold:

- (a) Determination of disease stage and treatment strategy – this is done by history, physical and laboratory tests (Boxes 4.2 and 4.3).
- (b) Education about risk reduction and lifestyle management – this involves the consideration of pregnancy, condom use, accommodation at work, disclosure (or not) of status.
- (c) Addressing issues unique to special groups – the needs of, for example, women, hemophiliacs, drug users and other marginalised communities should be noted.

Box 4.2 The essentials of history-taking and physical examination in a newly diagnosed HIV-infected individual

History

- **Past conditions** symptomatic of HIV infection, e.g. zoster, thrush, vaginal candidiasis, oral hairy leukoplakia, etc
- **Past opportunistic and associated conditions** like *Pneumocystis carinii* pneumonia, cryptococcal meningitis, TB, other STDs, etc
- **Current conditions and symptoms** – fever, night sweats, weight loss, oral discomfort, visual changes, headaches, diarrhea, lymphadenopathy, dermatologic conditions, respiratory symptoms, neurologic symptoms, etc
- **Social history** – past and present drug use, needle-sharing, practice of safer sex, current and past sex partners, diet, household pets, employment, current living situation, etc
- **Previous immunizations**

Physical Examination

- Weight, temperature, skin, oropharynx, fundi, lymph nodes, lungs, abdominal organs, genitalia, and the nervous system
- Tuberculin test (to test for exposure to TB)
- Pap smear for women (to rule out cervical dysplasia)
- STD screening

Box 4.3 Baseline investigations of a newly diagnosed HIV-seropositive individual

Investigation	Reason
<i>Immunology</i> T-lymphocyte subsets	Prognostic marker; initiation of antiretroviral or prophylaxis
<i>Microbiology</i> Syphilis serology (VDRL/TPHA/FTA) <i>Toxoplasma</i> serology	Latent disease Previous exposure; risk of future disease
<i>Biochemistry</i> RFT (renal function test) LFT (liver function test)	Baseline; drug therapy Abnormal liver disease; drug therapy
<i>Hematology</i> Full blood count	HIV-related hematologic abnormalities/ drug therapy
<i>Radiology</i> Chest	Occult disease/baseline

III. Viral and immune prognostic factors of HIV infection

HIV disease progresses to AIDS after a median of 11 years. However, the rate of progression is very variable. At one extreme, there are long term survivors who are free of clinical AIDS after 20 years.¹⁰ At the other, there are those who manifest AIDS and die within 2 to 3 years. Factors have been identified that influence the rate of disease progression.

Both viral and immune factors are important. For example, it has been found in studies of long term non-progressors that HIV disease is favorably associated with the NSI phenotype, homozygous CCR5Δ32 deletion,¹¹ and defective *nef* in HIV genotype.¹² Indices of immune function may also predict disease: tumor necrosis factor-α,¹³ CD38 count and anti-HIV specific CTL response.¹⁴ The two most commonly used parameters for disease monitoring are the CD4 lymphocyte count and viral load.

III.A The CD4 lymphocyte count

CD4 count is often measured by flow cytometry which uses specific monoclonal antibodies to determine the percentage of lymphocytes bearing the CD4 glycoprotein. The absolute CD4 count is calculated by multiplying this percentage and the total lymphocyte count. The CD4 count is widely variable, depending also on factors other than HIV (Box 4.4). To a certain extent, this variability may be countered by using the CD4 percentage instead.

Box 4.4 Factors known to influence CD4 lymphocyte count*	
Factor	Effect on CD4 count
Diurnal variation	Lower in AM; higher in PM
Splenectomy	Increased absolute CD4 count; does not imply improved immune function
Age	Decreased absolute CD4 count with age
Acute infections (tuberculosis, herpesvirus infections, bacterial sepsis, respiratory infections, others)	Most studies document a decreased CD4 lymphocyte count, percent, or CD4/CD8 ratio
Other factors (major surgery, exercise, malnutrition, smoking)	Most have been associated with a decreased CD4 count or percent
Ethnicity	Chinese may have a lower normal range of CD4 count ¹⁵
*Adapted from: Johnson SC, Kuritzikes DR. Monitoring therapy with plasma HIV RNA and CD4 counts. HIV Advances in Research and Therapy. 1997; 7(3): 13-18.	

A significant change is usually refers to one more than 30% for absolute count, or 3% for CD4 percentage. Comparison is preferably made between CD4 counts obtained from blood drawn at the same time of the day.

III.B Viral load

The search for a marker of disease progression began with the identification of β 2-microglobulin and p24 as prognostic markers. Then in the landmark study of Multicenter AIDS Cohort Study (MACS), a low baseline CD4 count and high viral load were found to predict time to AIDS.¹⁶ This study also established the role of the viral set point as a most clinically useful parameter. To date, "multiple analyses in over 5000 patients who participated in approximately 18 trials with viral load monitoring showed a statistically significant dose-response type association between decreases in plasma viremia and improved clinical outcome based on standard endpoints of new AIDS-defining diagnoses and survival".¹⁷ Viral load is deemed a valid surrogate marker of clinical progression and should be closely followed during therapy.

Measurement of viral load – Cell free HIV-RNA in plasma is best measured by the branched DNA technique – bDNA (Chiron) or reverse transcription polymerase chain reaction – RT-PCR (Roche). Nucleic acid sequence based amplification – NASBA (Organon) is not available in Hong Kong. At this stage of development, viral load testing is not an exact test yet, having a significant intratest variability of up to 0.3-0.5 log. Furthermore viral load results obtained by bDNA and PCR may not correlate with each other. Neither do results obtained with conventional and more sensitive versions of the same testing method. Factors affecting viral load measurements are in Box 4.5.

Viral load as tested by other techniques such as quantitative cell culture or plasma culture is also useful but expensive. Ultrasensitive cell culture techniques that stimulate CD4 lymphocytes into production of HIV allow HIV to be isolated even in those individuals with undetectable viral load. Their clinical utility is however uncertain.

Utility of viral load – Regular viral load monitoring provides useful information on the rate of disease progression. This, together with CD4 enumeration every three to four months is advisable for assessing individual patient even if definitive treatment is unavailable. Indications for viral load testing are in Box 4.6.

To minimize the intrinsic variability of viral load tests, repeat measurement is indicated when the decision to initiate or change treatment is to be based on the results. Serial measurements are best made with the same methodology (bDNA or PCR) and with the same version of test. A change is deemed significant only if it is more than 0.5 log.

Box 4.5 Factors known to influence viral load measurements

Factor	Effect on viral load measurement
Selected aspects of specimen handling (delay in processing, freeze/thaw, etc)	Variable effects, but handling of specimens should be consistent
Intrinsic variability of assays	0.1-0.2 log standard deviation
Immunizations, including influenza vaccine, pneumococcal vaccine, hepatitis B vaccine, and presumably other vaccines	Viral load may increase for 2 to 4 weeks after immunization
Tuberculosis, herpesvirus infections, and presumably many other infections	Increased viral load for 2 to 4 weeks after infection
Sex	Women may have lower viral load Viral load may decrease during ovulation

**Adapted from: Johnson SC, Kuritzikes DR. Monitoring therapy with plasma HIV RNA and CD4 counts. HIV Advances in Research and Therapy. 1997; 7(3): 13-18.*

Box 4.6 Indications and use of plasma HIV RNA testing*

Clinical indication	Information	Use
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis**
Initial evaluation of newly diagnosed HIV infection	Baseline viral load "set point"	Decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	Decision to start therapy
2-8 weeks after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 months after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4 cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

** From: DHHS. Guidelines for the use of antiretroviral agents in HIV infected adults and adolescents. <http://www.hivatis.org> May 5 1999.*

*** Diagnosis of HIV infection made by HIV RNA testing should be confirmed by standard methods such as Western blot serology performed 2-4 weeks, 3 and 6 months after the initial indeterminate or negative test as appropriate.*

The most sensitive assay of viral load test is recommended, in recognition of the fact that the nadir of viral load suppression correlates with the durability of response. This is particularly important in managing patients on antiretroviral therapy.

III.C Discordant CD4 and viral load

An incompletely suppressed viral load may still be associated with a rising CD4 count, especially with protease inhibitor (PI). Nevertheless, this response is usually less with non-responders than partial responders.¹⁸ Several hypotheses have been postulated to explain this discordance:

- (a) Continuing moderate control even after rebound from a viral load nadir
- (b) Diminution of viral replication kinetics, intrinsic pathogenicity, or infectivity of drug-resistant strains
- (c) Potential benefits of PI unrelated to anti-HIV activity
- (d) Reduced viral fitness
- (e) Altered cellular/tissue tropism
- (f) Inhibition of T cell apoptosis

It is not uncommon that a discordant CD4 and viral load response should occur following treatment with PI. It should not be regarded as invalid. Clinical benefit may derive from continued therapy. In this connection, it cannot be overemphasized that viral load and CD4 count are surrogate markers of clinical outcome at their best. They are not the disease itself. Clinical manifestations of disease remain the overriding guide to treatment.

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4.2 ANTIRETROVIRAL AGENTS

Understanding of the HIV life cycle has enabled the systematic quest for drugs active against HIV. Three classes of more than 10 drugs are now available for clinical use in Hong Kong. New classes are also being investigated overseas. Since the debut of protease inhibitors, combination therapy of three or more drug components has become the standard of therapy. Monotherapy is limited to the unique situation of preventing perinatal transmission in a pregnant mother where therapy is otherwise not indicated or not available. At the current state of development, these drugs will have to be used life-long and very often concurrent with treatment against opportunistic infections. Thus it is important that the prescribing physician become very familiar with the adverse effects and drug interaction profile of the antiretrovirals (ARV) he prescribes.

I. Overview of the three classes of antiretrovirals

Most antiretrovirals are available in Hong Kong (see Box 4.7). However, availability does not guarantee treatment success. Based on their mechanisms of anti-HIV activity, they can be divided into three classes.

1.A Nucleoside reverse transcriptase inhibitors (NRTI)

The first antiretroviral agents developed were members of the family of nucleoside analogs called dideoxynucleosides. On conversion into active triphosphates by cellular kinases, they exert their pharmacological effects through competitive inhibition of the viral reverse transcriptase, acting as chain terminators in the formation of viral DNA. There are 6 NRTI currently available in Hong Kong (year 2001): zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC), stavudine (d4T) lamivudine (3TC), and abacavir (ABC).

1.B Non-nucleoside reverse transcriptase inhibitors (NNRTI)

NNRTI has specific activity against HIV-1 reverse transcriptase. Its activity against HIV-2 is believed to be limited. It binds non-competitively to a pocket near the active site of reverse transcriptase and induces a conformational change to inactivate the enzyme. Currently only nevirapine (NVP) and efavirenz (EFV) but not delavirdine (DLV) are available in Hong Kong. Despite its great potency, NNRTI suffers from one major drawback: a low genetic barrier whereby a single mutation confers high level and cross class resistance.

Box 4.7 Features of major antiretrovirals in Hong Kong

Drug	Dose	Major adverse effects	Remarks
<i>NNRTI</i>			
Zidovudine (AZT, ZDV, Retrovir)	200 mg tid, 250 mg bid, 300 mg bid	Anemia, myopathy	Crosses the blood-brain barrier; proven to alleviate AIDS Dementia Complex, reduce occupational and mother-to-child transmission; contraindicated with d4T.
Didanosine (ddl, Videx); ddl EC (Videx EC)	If <60 kg: ddl 125 mg bid or ddl EC 250 mg qd If ≥60 kg, ddl 250 mg bid or ddl EC 400 mg qd	Pancreatitis; peripheral neuropathy	To be taken on empty stomach; ddl, but not ddl EC, should not be taken together with indinavir
Zalcitabine (ddC, HIVID)	0.75 mg tid	Oral ulcers, peripheral neuropathy; pancreatitis	Falling out of favor because of suboptimal potency, tid administration and overlapping resistance with ddl
Stavudine (d4T, Zerit)	40 mg bid; 30 mg bid (BW<60Kg)	Peripheral neuropathy	Contraindicated with AZT and ddC
Lamivudine (3TC, Epivir)	150 mg bid	Peripheral neuropathy	Single mutation, M184V, confers high level resistance
Abacavir (ABC)	300 mg bid	Hypersensitivity syndrome	Potent; crosses the blood-brain barrier; hypersensitivity reaction may be subtle with vague discomfort – do not rechallenge
<i>NNRTI</i>			
Nevirapine (NVP, Viramune)	200 mg bid	Rash, deranged liver function	Dose escalation for autoinduction – 200 mg qd in the first 2 weeks followed by bid; single mutations may confer high level resistance to the whole class, especially when used together with AZT; proven to reduce MTCT; blood-brain crosses barrier and placenta; monitor liver function tests; hepatotoxicity precludes use in postexposure prophylaxis
Efavirenz (EFV, Stocrin, Sustiva)	600 mg nocte; 200 mg am and 400 mg nocte	Rash, CNS symptoms of insomnia, disorientation, nightmares, etc	Take drug at bed time to avoid CNS symptoms; rapid emergence of resistance to all NNRTIs if nonadherent; contraindicated in pregnancy
<i>PI</i>			
Hard gel Saquinavir (SQV-HGC, Invirase) Soft Gel saquinavir (SQV-SGC, Fortovase)	600 mg tid (Invirase) 1200 mg tid (Fortovase)	Nausea, vomiting, diarrhea, lipodystrophy	Food increases bioavailability; Invirase has such poor bioavailability that it does not constitute HAART unless given with a pharmacokinetic enhancer like RTV; Fortovase has high pill burden. SQV is antagonistic to IDV in vitro
Ritonavir (RTV, Norvir)	600 mg bid	Nausea, vomiting, lipodystrophy, circumoral paresthesia, taste disturbance	Poor tolerability; more commonly used as pharmacokinetic enhancer in reduced dosage; strongest inhibitor of P450; poor palatability with liquid formulation; beware disulfiram reaction with metronidazole because formulation contains alcohol
Indinavir (IDV, Crixivan)	800 mg q8h; (800 mg + RTV 100 to 200 mg)q12h	Nausea, hyperbilirubinemia, nephrolithiasis, nephropathy, lipodystrophy, alopecia	To be taken on empty stomach; bid dosing with food permissible when RTV is given as enhancer; requires ≥1.5 liter of water per day to avoid crystallization in kidney
Nelfinavir (NFV, Viracept)	750 mg tid, 1250 mg bid	Diarrhea, lipodystrophy	May be less potent than other PIs
Lopinavir/ritonavir (Kaletra)	Each tablet contains lopinavir 133 mg and RTV 33 mg; Given 3 tablets bid; 4 tablets bid if given with EFV or NVP	Diarrhea, lipodystrophy	Potent; achieves high blood concentration; no specific primary mutations identified

I.C Protease inhibitors (PI)

The availability of PI since 1996 dramatically changed the outlook of HIV medicine. Never before had it been imaginable that the progress of immune deficiency could be halted, let alone reversed. A PI works by inhibiting the viral protease which is responsible for the final packaging of a viable HIV virion. Its incapacitation by specific inhibitors results in non-infective viral particles. Unlike NNRTI, the PI is endowed with a high genetic barrier, requiring more than a few mutations before significant resistance develops. The most commonly used PIs in Hong Kong include hard gel (SQV-HGC) and soft gel saquinavir (SQV-SGC), ritonavir (RTV), indinavir (IDV), nelfinavir (NFV), and the combination lopinavir/ritonavir (LPV/r or Kaletra).

II. The nucleoside reverse transcriptase inhibitor (NRTI)

In the construction of a highly active antiretroviral regimen (HAART), usually two NRTIs are chosen as the backbone upon which a PI or NNRTI is added. Recent advances in HIV medicine have allowed deeper insight into the toxicity and resistance profile of NRTIs. Hydroxyurea potentiates NRTIs, especially ddI. Nevertheless, enthusiasm for its use waned following reports of death due to pancreatitis.

II.A Adverse effects

Mitochondrial toxicity – mitochondrial DNA is replicated by DNA polymerase-gamma whose function is inhibited by NRTI. The resulting mitochondrial dysfunction will therefore manifest as a downregulation of oxidative phosphorylation. Thus fatal lactic acidosis with an increased ratios of lactate/pyruvate and beta-hydroxybutyrate/acetoacetate may occur.¹ It is also possibly the underlying mechanism of the various NRTI toxicities,² such as neuropathy of ddC and myopathy of AZT.³ Although controversial, it has been argued that lipodystrophy also originated from mitochondrial toxicity.^{4,5}

Lipodystrophy (LDS) is not unique to protease inhibitors. All NRTIs, especially d4T, have been associated with this syndrome. Currently the pathogenesis and treatment of LDS are actively researched areas.

II.B Resistance

Two major mechanisms are plausible. One is **reduced affinity** of the mutated reverse transcriptase for the nucleotide analogue, as occurs with M184V (3TC) and L74V (ddI)

mutations. Another is **pyrophosphorolysis**, as demonstrated with AZT where zidovudine monophosphate is removed from a chain-terminated transcript. Either way, NRTI-specific mutations in viral RT have been identified which are associated with both in vitro and in vivo resistance. In general, these mutations result in accelerated progression of disease unless appropriate changes in antiretrovirals are made. Interpretation of mutated genotypes is difficult and should usually be done with expert consultation.

Except lamivudine which requires only one mutation, i.e. M184V, to result in high level resistance, other members of the group require more than one mutation for significant resistance. Relatively little is known about interactions between mutations, which are extremely complex. For example, the M184V mutation classically associated with 3TC partially reverses resistance to AZT. The surprising finding that prolonged exposure to d4T results in classical AZT-specific mutations⁶ without prior AZT experience challenges the very concept of drug-specific mutations. At present, the database of mutations is not complete, adding to the difficulty of interpreting genotypes.

Resistance may occur through mechanisms other than those related to mutations. For example, cellular resistance to d4T may happen by reduced phosphorylation in patients previously exposed to AZT, although this is controversial.^{7,8} AZT-resistant reverse transcriptase may also be biochemically cross-resistant to d4T.⁹ In certain sanctuary sites, distribution of some ARV is limited.

III. The non-nucleoside reverse transcriptase inhibitor (NNRTI)

Nevirapine (NVP) and efavirenz (EFV) are the 2 most commonly used NNRTI in Hong Kong. As a rule, their use is limited to HIV-1 infection. They are potent but prone to resistance if used suboptimally. Their toxicity and resistance profiles are different from other ARV. However, the assertion that NNRTI will not cause lipodystrophy is controversial. While NVP is likely to be less potent than EFV,¹⁰ it is the only proven NNRTI in prevention against mother-to-child transmission.¹¹

III.A Adverse effects

Both NVP and EFV may cause rash, and even Stevens-Johnson syndrome in the case of NVP. Chinese¹² and women¹³ are more susceptible. Most patients with rash may be treated through the event, but those with constitutional symptoms, vesicular eruptions or mucous membrane involvement, will need to have the drug stopped. In order to avoid rash and adjust to autoinduction, a dose escalation schedule of NVP is employed. In the first two

weeks, it is dosed 200 mg qd, after which it is then given 200 mg bid. NVP can also be associated with severe hepatitis, requiring frequent monitoring of liver function tests at least in the first few months of therapy.

EFV may cause CNS symptoms, especially in the first few weeks, in the form of depersonalization, nightmares or dizziness. For this reason, it is usually dosed at bedtime. It is classified as category C by FDA for use in pregnancy because of teratogenicity in monkeys. Most authorities would avoid EFV in pregnant women or in those who are planning to conceive.

Due to the fact that they induce cytochrome P-450 and, in particular, the CYP3A4 isoform, NVP and EFV may interact with concurrently administered drugs. Significantly, they may reduce the concentration of protease inhibitors, necessitating dose adjustments to be made. Another NNRTI, delavirdine, is an inhibitor of the enzyme. It will therefore increase the concentration of concurrent PIs.

III.B Resistance

The current generation of NNRTIs has limited potency against HIV-2. Furthermore, high level and cross resistance may emerge with even one mutation, generally in the region corresponding to the binding site. Efavirenz is particularly prone to induce K103N which is highly cross resistant to other members of the group. For this reason, there has been suggestion that NVP (which more often causes the less cross-resistant Y181C/I) should be used ahead of EFV. This is controversial and likely to be of limited benefit.¹⁴ For example, consideration has to be given to the limited availability of resistance testing, the probably inferior potency of NVP compared to EFV, and the fact that K103N is more prone to occur with NVP if it is used together with AZT.

An interesting phenomenon of NNRTI-dependent stimulation of HIV replication has also been described in which certain mutations, e.g. M230L, will result in enhanced growth of the virus.¹⁵ If true, then prolonged use of NNRTI might not be appropriate in the face of virologic failure.

Development is under way for the second generation of NNRTIs with a different resistance profile. Until then, use of an NNRTI in anything other than a fully suppressive regimen will be counterproductive by wiping out an entire class of drugs for future use. The only exception is in the case of prevention against perinatal infection in a locality where antiretrovirals are not the standard of care, or when the mother presents late in pregnancy preventing use of the standard prophylactic regimen.

IV. Protease inhibitors (PI)

The advent of PI dramatically changed the fate of people living with HIV/AIDS. For the first time since the onset of the epidemic, prolongation of life and promotion of health had become realistic goals of HIV therapy. This is testified by the decreasing morbidity and mortality attributed to AIDS in countries where this group of drugs is included in combination therapy.^{16,17}

The use of PI against HIV is now extended to other occasions such as postexposure prophylaxis. Current evidence also suggests that PI-containing HAART in antenatal women decreases the risk of perinatal transmission to less than 2%.¹⁸

IV.A Adverse effects

Significant **drug interactions** may occur by reason of their inhibition of cytochrome P-450, especially the CYP3A4 isoform. This may result in undue toxicity of concomitant medications such as amiodarone, astemizole, cisapride, ergotamine, flecanide, midazolam, pimozide, quinidine, terfenadine, and triazolam. As a result these drugs are contraindicated.

Conversely, other drugs that act on CYP3A4 might also affect the metabolism of PIs. For example, rifamycins induce the enzyme and decrease the concentration of most PIs. NNRTIs such as NVP and EFV inhibit the enzyme and require dosage adjustments of PIs.

Lipodystrophy (LDS) was first reported with use of PI^{19,20} but is now recognized to be a complication of NRTI as well. A case definition has yet to be achieved. In general, LDS has the following components occurring singly or in various combinations:

- (a) Lipoatrophy affecting the face and extremities,
- (b) Lipohypertrophy affecting visceral abdominal fat, neck (the buffalo hump) and breasts,
- (c) Hypercholesterolemia and hypertriglyceridemia,
- (d) Insulin resistance and occasionally diabetes mellitus.

In one local study, LDS occurs in 20% of patients after 8 months on an IDV-containing regimen.²¹ Theories of pathogenesis abound, ranging from mitochondrial toxicity, immune reconstitution,²² polycystic ovary²³ to lipoprotein receptor homology with PI.²⁴ None is proven. Despite the apparent 'Cushingoid' features, the adrenal axis is intact in the large majority of cases. Attempts of treatment are being made with resistance exercise training, growth hormone²⁵ and insulin sensitizers such as metformin²⁶ and troglitazone.²⁷ But efficacy, if any, is limited to selected aspects of the syndrome.

Switching a PI-containing regimen to a PI-sparing regimen sometimes results in alleviation of the syndrome, especially its metabolic aspects. Potential loss of disease control is the main weakness of such a strategy.

In the long run, the elevated cholesterol may be detrimental to HIV infected patients as well as in HIV seronegative individuals.²⁸ Most authorities recommend treatment according to protocols in HIV-negative individuals. However, drugs that interact or have overlapping toxicity with ARV should be avoided.

In hemophiliacs, PI may cause an increase in the ***requirement of anti-hemophilic factor***.

Gastrointestinal side effects are common with PI and are frequent reasons for nonadherence. Some side effects are more common with certain drugs, e.g. nausea and vomiting (RTV and IDV), diarrhea (NFV). PI also occasionally results in elevated transaminases.

Individual PI may be associated with ***unique side effects*** such as nephrolithiasis, hyperbilirubinemia, cracked lips and in-grown toe nails²⁹ with IDV, circumoral paresthesia and taste disturbance with RTV.

IV.B Resistance

PI is classically described as drugs having a high genetic barrier to resistance, meaning that full resistance will not happen unless a certain number of mutations have developed. This however should not be used as pretext to suboptimal therapy. Despite its high potency, any PI given as monotherapy will encounter resistance that is ultimately cross class. Cross resistance is particularly common among RTV, IDV and SQV. Although limited evidence suggests that viral isolates resistant to nelfinavir may retain susceptibility to other PIs, cross resistance eventually develops after prolonged use in the presence of a high viral load.

V. New drugs and new classes

Primarily because of cross resistance, it is not difficult for a patient to develop resistance to all known ARV. New drugs and preferably new classes of drugs are urgently needed to combat resistance. Another line of development is to improve on pharmacokinetics in the direction of simplified dosing, reducing drug interactions and increasing bioavailability.

In the first category, nucleotide analogs, fusion inhibitors and integrase inhibitors are hopeful candidates, as are immunologic modifiers such as interleukin-2. In the second, once a day PI and bioavailable prodrugs of existing PI (e.g. amprenavir) are being developed.

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4.3 ANTIRETROVIRAL THERAPY – ITS PRINCIPLES, INITIATION AND EVALUATION

I. Rationale of antiretroviral therapy

HIV causes progressive damage to the immune system of the infected person, largely through destruction of CD4+ T lymphocytes. The CD4 loss is probably driven by the rapid viral replication and clearance.¹ As many as 10^{10} virions are produced and cleared every day. The half-life of circulating virions is estimated to be 1-2 hours.²

Antiretroviral therapy inhibits HIV replication through interrupting the life cycle of the virus. Advances in the development of potent antiretroviral agents against HIV have led to the concept of highly active antiretroviral therapy (HAART). This literally means using very potent antiretroviral regimen to control HIV disease. In practical terms, therapy is HAART if sustained suppression of viral load to undetectability is achieved.

As a result of significant viral suppression by HAART, the immune damage is halted or even reversed, when immune capability is reconstituted. The virologic and immunologic benefits have translated into lowered morbidity and mortality associated with HIV/AIDS. Prognosis of patients improves remarkably with HAART. Nevertheless, the regimens available today cannot eradicate HIV. There is residual viral replication even in patients who have achieved an undetectable viral load by the most sensitive assay currently available. Replication competent virus also exists in latently infected resting CD4 lymphocytes,^{3,4} ready to rekindle HIV mediated damage on interruption of therapy. The virus is also recoverable in the semen of some patients with undetectable plasma viral load and transmission of HIV can occur⁵ from these patients.

II. Goals of therapy

To date, HAART comprising two nucleoside analogue reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI) is the regimen with the most abundant data on its beneficial virologic, immunologic and clinical effects. In clinical practice, the goals of HAART are three-fold:

- (a) suppression of viral replication to undetectable levels for as long as possible;
- (b) immune reconstitution as manifested principally by a rise of CD4 count; and
- (c) reduction of morbidity and mortality.

II.A Durable suppression of viral load

While durable suppression of viral load is most desirable, partial suppression can also be beneficial in immunologic and clinical terms. The extent of viral suppression is monitored by measuring the HIV RNA level in the plasma, often by methods of reverse transcription polymerase chain reaction (RT-PCR) or branched DNA (bDNA). Very often, patients on HAART can attain suppression of their plasma viral load to below the limit of quantitation (undetectable level). A lower nadir of viral level after treatment initiation correlates with a longer duration of response.⁶

II.B Immune reconstitution

In general, immune reconstitution follows the use of HAART and successful suppression of viral load. There is a biphasic increase of CD4 T lymphocytes, where the first rapid wave of increase is represented by mainly memory (CD45RO+) cells, followed a few months later by the addition of naïve (CD45RA+) cells. Proliferative lymphocyte responses to recall antigens and mitogens are also increased over time. There is reduced T cell activation due to reduced viral replication and the T cell receptor repertoire is partly restored. However, immune response specific to HIV antigens remain weak.

Clinically immune reconstitution is evidenced by the spontaneous remission or improvement of opportunistic infections, e.g. microsporidiosis, and Kaposi's sarcoma. Growing evidence suggests that primary or even secondary prophylaxis for some opportunistic infections can be safely stopped if there is good immune recovery. However, there were also reports of unmasking or exacerbation of HIV-related complications, e.g. CMV retinitis,⁷ MAI lymphadenitis,⁸ upon immune reconstitution.

II.C Reduction of morbidity and mortality

In the mid-1990s, the increasing trend of morbidity and mortality reversed itself in countries where HAART was available.⁹ At the clinical level, immune recovery not only leads to prolonged life expectancy but control of many otherwise crippling opportunistic diseases, e.g. cryptosporidiosis, microsporidiosis, Kaposi's sarcoma, oral hairy leukoplakia, esophageal candidiasis, and progressive multifocal leukoencephalopathy (PML).

III. Timing of therapy in established infection

The first antiretroviral regimen carries the best chance of success. Its timing is therefore crucial. While antiretroviral therapy is indicated in patients with AIDS, significant

symptomatic HIV disease, low CD4 count or high viral load, a **universal** cut-off threshold of CD4 or viral load for consideration of treatment does not exist for patients with asymptomatic disease. Overseas authorities, e.g. US, UK, Canada, have established guidelines with different cut-off values. Even the same guideline differs rapidly according to time. As one example, the current treatment guidelines from the US suggest consideration of treatment when the CD4 count drops below 350/ul or a viral load above 55,000/ml by PCR. There are pros and cons for early vs. late initiation of ART.¹⁰

Potential **benefits** of early treatment are (a) control of viral replication and mutation, (b) prevention of progressive immunodeficiency; potential maintenance or reconstitution of a normal immune system, (c) delayed AIDS progression and prolonged life, (d) decreased risk of selection of resistant virus, (e) decreased risk of drug toxicity, and (f) possibly decreased risk of viral transmission.

Potential **risks** of early treatment are (a) reduced quality of life from toxicity and inconvenience of drug intake, (b) earlier development of drug resistance, (c) limitation of future drug choices due to the early development of drug resistance, (d) unknown long-term toxicity of ART, (e) unknown duration of effectiveness of current ART, and (f) transmission of drug resistant virus. Some authorities have also noted that in a patient with an otherwise good host immune response against HIV, suppression of viral replication by HAART would remove the viral stimulus and weaken this immune response.¹¹

In Hong Kong, this issue is further complicated by the finding that healthy adult Chinese¹² and HIV-infected Chinese¹³ may have a lower natural CD4 level than Caucasians. Hence the cut-off CD4 values recommended for starting ART in some western countries may be overaggressive in Chinese.

IV. Choice of antiretrovirals

Once the decision to initiate treatment is made, an appropriate regimen is concocted after evaluating the following:

- (a) The maximal potency consistent with tolerance.
- (b) The genetic barrier of the regimen, which influences the likelihood of resistance.
- (c) Toxicity profile of a regimen and its impact on the patient with his/her unique medical history. Overlapping toxicity of neuropathy is the reason why it is not advisable to combine ddl and ddC.
- (d) The possibility of primary drug resistance – This is quickly becoming a problem in developed countries as more virus is getting transmitted from patients who have been treated.¹⁴ Where primary drug resistance is common, it may be useful to determine the resistance before starting treatment, although the absence of resistance still does not guarantee success as resistant viruses may have been

overgrown by wild type virus.

- (e) Pharmacodynamic and pharmacokinetic interaction – certain combinations of drugs are contraindicated, e.g. AZT + d4T; rifampicin + hard gel SQV.
- (f) Food restrictions, pill burden and frequency of administration, and their estimated impact on a patient's adherence.
- (g) The existence of a plausible salvage therapy on failure of the first regimen – This salvage therapy should not only work virologically but be acceptable to patients. For example, failure of AZT/3TC/NVP is theoretically salvageable by d4T/ddI/IDV. However IDV and ddI are not to be taken together as the antacid of ddI will hinder absorption of IDV. This means that the patient will have to take his medications on an empty stomach five times a day! An alternative combination of d4T/ddI/NFV is less daunting but still requires careful spacing with ddI taken on an empty stomach and NFV with food.

Patient factors count if a first regimen is to become the only regimen that will ever be needed. Pros and cons of all reasonable options should be clearly explained to the patient before embarking on this lifelong commitment. Some patients might benefit from a trial of mock pills to see how their lifestyle would adapt. Encourage questions and dispel myths. After treatment is started, heed to and deal with complaints. Monitor toxicity as appropriate. Many clinics run drug adherence programs where adherence is monitored by either pill counting or MEMScap, an electronic device that registers the number of times a bottle is opened. There is no perfect tool in this regard. Even drug level monitoring only gives a snapshot of the adherence around the time blood level is checked.

In ways more than one, drug adherence reflects the quality of a clinical service. It takes very good rapport and mutual trust before adherence can be monitored correctly, let alone enforced.

IV.A PI-containing regimen

The inclusion of a protease inhibitor in HAART has documented benefits for patients with advanced HIV disease. Indeed, a regimen of PI added to a backbone of two NRTIs has become the *de facto* standard by which other regimens are compared. However, all PIs are not equal in terms of potency or adverse effects. For example, it is believed that nelfinavir is more tolerable but less potent than other PIs. Furthermore, regimens containing NRTI and the poorly absorbed hard gel saquinavir as the only PI do not count as HAART. Recently double-PI based regimens are proving themselves. Most of these combinations use ritonavir as a pharmacokinetic enhancer. By inhibiting the cytochrome P450 enzyme, the dose and frequency of the other PI can be reduced. More popular combinations are RTV100-200 mg/IDV 800 mg bid, RTV 400 mg/IDV400 mg bid, and RTV400 mg/SQV400 mg bid. In fact, lopinavir is coformulated with RTV as Kaletra, and is not available alone.

IV.B NNRTI-containing regimen

In the INCAS study,¹⁵ the regimen of AZT, ddI and NVP demonstrated its superiority over a double-nucleoside regimen. The Atlantic trial¹⁶ and COMBINE study¹⁷ further suggested that as a component of 2 NRTI-based HAART, NVP was equivalent to IDV and NFV respectively. Another prospective trial showed that an efavirenz-based HAART actually surpassed an IDV-containing regimen.¹⁸ Thus was established the potency and durability of a regimen composed of two NRTIs and one NNRTI. However, it has to be remembered that NNRTI has a low genetic barrier, with one mutation being sufficient to generate a high level of cross-class resistance. Furthermore, its immunologic and clinical benefits are less well demonstrated as with PI. For all these shortcomings, an NNRTI-based regimen is gaining popularity because it is dosed less frequently and more tolerable to take.

IV.C Alternative first line agents

In limited circumstances where there is strong patient preference or unique drug interaction profile to avoid, the following may be used.

Triple NRTI – This generally refers to the combination AZT/3TC/ABC. Studies have been done demonstrating an acceptable potency, but durability is doubtful. This regimen is probably inferior to NNRTI- or PI-based regimens, especially in patients with a low CD4 count and high viral load. However, this regimen does have the advantages of saving at least two classes of antiretrovirals for future use in case of failure, a low pill burden (two pills a day for the coformulation pill, Trizivir), and avoidance of many significant drug interactions.

Hydroxyurea(HU)-based treatment – The addition of HU to NRTIs, especially ddI, results in enhanced potency at the expense of suppression of lymphocyte count. Toxicity is also increased. Fatalities due to pancreatitis have dampened a lot of enthusiasm over HU.

IV.D Intensification and consolidation

While in the majority of cases, the viral load will promptly become undetectable upon initiation of standard HAART, a small number of patients may still manifest a low level of viral load. It is important to exclude nonadherence, primary resistance and pharmacokinetic interactions. If these are comfortably excluded, some experts recommend '**intensifying**' the treatment with one additional drug. Both doctors and patients should understand that this approach is not standard practice and should be undertaken by experts in HIV medicine. An ideal intensifying agent will be one that is

- (a) well tolerated;
- (b) free of side effects;

- (c) free of complex drug interactions; and
- (d) with a high genetic barrier to resistance.

Potentially useful intensifying agents are: hydroxyurea, abacavir, or an additional PI as a pharmacokinetic enhancer such as ritonavir. Alternatively one may switch to a more potent protease inhibitor.

A prerequisite for the success of intensification is the absence of drug resistance, as otherwise this will have become sequential monotherapy. For maximum assurance, extra-frequent and rapidly reported viral loads, probably together with resistance testing would be needed to ensure that no resistance has arisen when a regimen is being intensified. The advantages and disadvantages of treatment intensification are summarized (Box 4.8).

The other end of the spectrum is a group of patients who have been able to maintain an undetectable viral load with the use of suboptimal therapy such as 2 NRTIs. It is controversial if this should be '**consolidated**' with an additional agent or change to HAART. Factors to consider are:²⁰

- (a) Available future options and their genetic barrier to resistance
- (b) Duration of therapy and hence the likelihood of resistance
- (c) Likelihood of tolerance and adherence to more complicated regimens
- (d) Availability of ultrasensitive assays
- (e) Patient's own preference

In all likelihood, these patients will eventually fail and require adequate HAART for control. But until then, the patient is benefiting from disease control by a simpler regimen. The choice between adding an extra agent and changing to new drugs is also controversial.

Box 4.8 Potential advantages and disadvantages of antiretroviral intensification¹⁹

Advantages

- Avoid premature switching, because lack of sufficient potency of a regimen does not necessarily imply drug resistance
- Allow preservation of drugs that remain potentially useful
- Avoid initial use of additional drugs in patients who may not need them

Disadvantages

- May exacerbate resistance, because inadequate virologic response could reflect emergence of drug-resistant variants
- May aggravate problems with adherence in poorly adherent patients
- May complicate drug-drug interactions and increase their frequency

V. Treatment evaluation

V.A Clinical, immunologic and virologic criteria

The disease status of a patient shall be worked up with respect to his/her clinical conditions, CD4 count and plasma viral load. Clinical manifestations, especially the so-called B symptoms (refer to Chapter 4.1), would indicate treatment regardless of CD4 count and viral load. However, in the absence of clinical indicators, there is no universal guideline for defining the absolute values of CD4 and plasma viral load that should trigger treatment in Hong Kong. Those recommended by the US i.e. 350/ul and 55,000 copies/ml of CD4 and viral load, may conveniently be taken as thresholds beyond which treatment at least should be contemplated. In general, because of the multiple factors affecting CD4 count and viral load, they should be repeated before any treatment-related decision based on these values should be made.

Immediate response to treatment is assessed by viral load. Effective treatment should decrease the viral load by at least 2 logs within 8 weeks and render the viral load undetectable within 6 months. Failure to do such should prompt an immediate attempt to exclude non-compliance, unfavorable drug interaction, drug malabsorption and superimposed infections or vaccination.

The current standard of care demands at least pre- and post-treatment CD4 and viral load for the purpose of monitoring. In addition, it is essential to monitor for the clinical progression of disease, features of immune reconstitution, and adverse effects of drugs. Followup laboratory studies of complete blood count, liver and renal function tests are indicated most of the time. Signs and symptoms of lipodystrophy should also be looked for.

V.B Resistance testing

It is not necessarily true that the viral population in the treatment-naïve consists solely of wild type. Patients who contracted the infection recently and in countries where antiretrovirals were available have a higher chance of harboring primary resistance. This may or may not be detectable by resistance testing, as wild type virus tends to overgrow the original resistant species with time.

Aside from its possible role prior to treatment, resistance testing may conceivably be employed where decrease in viral load is suboptimal following initiation of treatment. This would facilitate the decision on intensification. Alternatively, in a patient who has rebounds of viral load after initial suppression, resistance testing may be able to differentiate drug failure due to resistance from malabsorption and nonadherence, as well as guide the formulation of alternative, salvage therapy.

There are two ways of assessing drug resistance. The **genotypic resistance assays** detect specific mutations. They are based on PCR technologies and can generally detect mutations in plasma samples with more than 1000 copies/ml of HIV RNA. Species constituting 20% or more of amplified product can usually be detected. Either point mutation or gene sequencing is used in the assay.

Phenotypic assays measure the 50% or 90% inhibitory concentrations of a drug against the virus in vitro. More rapid assays of phenotype are now available abroad that are based on recombinant DNA technology. A comparison among the tests are presented as follows (Box 4.9).

Currently, available resistance assays have not been independently validated. They are expensive and interpretation is difficult. Nevertheless it is believed that immense utility will result after further refinement of these tests. Two recent studies suggested they are useful in enhancing the virologic response of salvage therapy (VIRADAPT²¹ and GART²²). No data however exist to support routine testing before there is treatment failure.

Box 4.9 Comparison among assays of drug resistance

Type of assay	For and against
Sequencing assays <ul style="list-style-type: none">Chain termination assays (e.g. Perkin-Elmer, Visible Genetics)Microchip assays (e.g. Affymetrix)	<i>For:</i> scans the complete sequence of the amplified gene, and so can detect unanticipated or undiscovered mutations <i>Against:</i> magnitude of data that must be interpreted
Point mutation assays <ul style="list-style-type: none">Differential hybridization assays (Chiron)Line probe assays (Innogenetics)	<i>For:</i> detects minority species and mixtures; simplicity of performance and interpretation <i>Against:</i> detects only what is looked for
Phenotypic assays <ul style="list-style-type: none">Virco's AntivirogramVirologic's Phenosense	<i>For:</i> rapid, high throughput, automated assays now in development <i>Against:</i> both are 'in-house' assays, so all samples have to be analyzed at a single site. Phenotyping is more expensive than genotyping

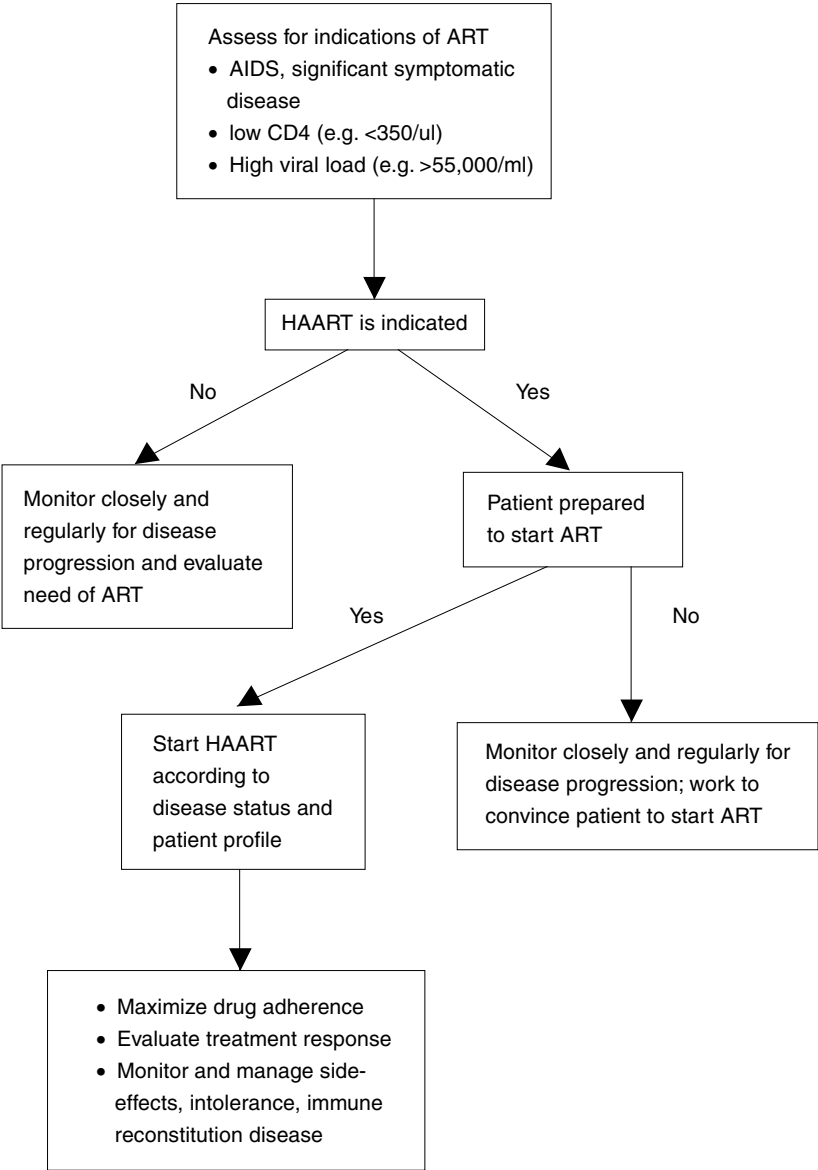
It is almost certain that resistance testing will assume a bigger role in the near future, when tests are validated and interpretation of data can be made with confidence. Currently, resistance testing is more useful for identifying drugs that will not be optimally active. It does not necessarily predict response.²³ In clinical practice for now, resistance testing is employed only after case-by-case evaluation.

V.C Therapeutic drug monitoring

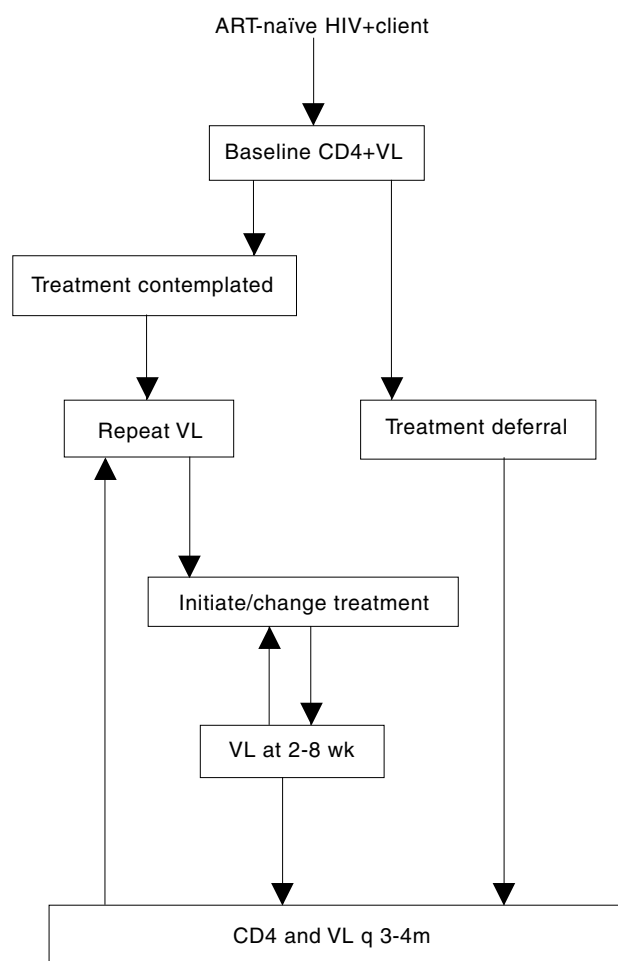
Evidence is accumulating that therapeutic drug monitoring (TDM) will be useful in the monitoring of patients on ART. In the VIRADAPT study, it was found that there was a negative correlation between drug concentration and viral load.²⁴ This should not be surprising. Studies are now being done on the use of TDM with or without resistance testing in salvage therapy.

In addition, TDM may be useful in assessing adherence and identifying drug malabsorption. Drug interaction affecting levels of antiretrovirals can also be investigated by TDM. However, not all antiretrovirals are amenable to measurement. The nucleoside RTI works intracellularly and is less easily measured. Its intracellular half life also differs markedly from its plasma counterpart.

Algorithm 4.3-A Initiating antiretroviral therapy for treatment-naïve patients with established HIV infection.



Algorithm 4.3-B Followup of clients on treatment with viral load (VL) and CD4



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4.4 ALTERNATIVE ANTIRETROVIRAL THERAPY FOR TREATMENT FAILURE

The advent of highly active antiretroviral therapy (HAART) has improved the disease course of most of HIV/AIDS patients who responded well to the treatment, in terms of reduced morbidity and mortality. Nevertheless the long term durability of HAART is still unclear. In some patients, HAART may not be potent enough to fully suppress viral replication. In most patients, the rigid adherence required for long term control is difficult. In all patients, the goal of HIV eradication is still beyond reach. The inability of drugs to penetrate some sanctuary sites, e.g. central nervous system, and the presence of latently infected CD4 cells¹ explain why.

I. Why does HAART fail?

The basic tenet of antiretroviral treatment is one of complete suppression of viral replication. This theoretically will forestall the development of resistance as well as damage to the immune system. In this environment, immune recovery follows.

Yet, current treatment now known as HAART may not be that potent. With very sensitive assays, very low level viral replication is still detectable in most patients.^{2,3} The long term implication of such ultralow level of viral replication on development of resistance is unknown, but is potential cause for concern. Furthermore, it is increasingly recognized that occasional 'viral blips' of usually less than 1000 copies/ml occur in some patients despite otherwise good virologic control.⁴ Its significance is unclear.

All in all, control of viral replication with HAART as we know it today is a precarious affair. Inadequate HAART for whatever reasons will quickly lead to failure. The reasons for inadequate treatment may be:

- (a) Suboptimal 'HAART' – The antiretrovirals are not identical. Drugs differ in potency, genetic barrier for resistance, prevalence of primary resistance, and toxicity. Antagonism also exists between some drugs
- (b) Inadequate delivery – nonadherence, malabsorption, vomiting, pharmacokinetic interaction
- (c) Excessive metabolism – individual variation, pharmacokinetic interaction

On a clinical level, it is known that response to HAART is often poorer in patients with AIDS or advanced disease, the antiretroviral-experienced, those with a high baseline viral load and suboptimal drug adherence. In addition, treatment efficacy is usually higher in

clinical trials where supervision is more intense. Between 60% and 90% of patients were driven to below level of detection for their viral load in clinical trials. However, in real life, the corresponding proportion is only 50-60%.⁵

II. When is failure present?

II.A Definition of failure

Treatment failure may be virologic (persistent detection or rebound of plasma HIV-1 RNA), immunologic (falling CD4) or clinical (progression to new ADI). There is no consensus on the precise definition of treatment failure although some criteria have been proposed. According to the US Department of Health and Human Service guidelines,⁶ criteria that should lead to consideration of new therapy are:

- (a) Less than a 0.5-0.75 \log_{10} reduction in plasma HIV RNA by 4 weeks following initiation of therapy, or less than one \log_{10} reduction by 8 weeks
- (b) Failure to suppress plasma HIV RNA to undetectable levels within 4-6 months of initiating therapy
- (c) Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance
- (d) Any reproducible significant increase (defined as 3-fold or greater) from the nadir of plasma HIV RNA which is not attributable to intercurrent infection, vaccination, or test methodology
- (e) Persistently declining CD4 cell counts as measured on at least two separate occasions
- (f) Clinical deterioration (differentiate from immune reconstitution disease)

Nevertheless, the virologic and clinical profiles might be discordant. Despite virologic rebound from undetectable level, there could be little disease progression,⁷ at least in the short term. In some individuals, CD4 count may also remain stable in the presence of virologic rebound,⁸ but it is likely that the CD4 will eventually decline and clinical deterioration ensue.

II.B The role of resistance

Not all failures are due to drug resistance. Yet its occurrence is highly associated with failure to salvage therapy^{9,10} and carries a poor prognostic significance.¹¹ When resistance is suspected as the cause of failure, alternative treatment is usually indicated.

The success of a new regimen after failure is highly dependent on prior experience of antiretrovirals. Before a new regimen is concocted, the possibility of cross-resistance

between old and new drugs should be considered. Cross-class resistance is almost the rule for NNRTIs while it is less of a problem with NRTIs. Sequencing of PIs is fraught with conflicting data but it is generally agreed that cross resistance will eventually follow if any PI is used long enough in the presence of a high viral load.¹²

Clinically, patients who have been heavily treated with different antiretroviral agents of all classes, in particular with prolonged incompletely suppressive therapy, are likely to harbor multi-drug resistant strains. In some, a viable regimen is impossible. They might benefit from enrolment in clinical trials of experimental therapies.

III. Devising new therapy after failure

The decision whether to change therapy depends on several considerations:

- (a) The degree of failure
- (b) How well the patient is doing and the risk of disease progression
- (c) Reasons for failure
- (d) Drug combinations that the patient is on
- (e) Options left for this change and also subsequently

III.A Timing of therapy change after failure

In the case of detectable viral load while on ***suboptimal therapy***, it is still justifiable to maintain current treatment if (a) the viral load is low (e.g. <10,000 copies/ml), (b) patient is doing well immunologically and clinically, (c) the chance of developing cross resistance to the future drugs and thus hampering its efficacy is low, and (d) patient does not favor swapping to HAART. The best example is double-nucleoside regimen. The rationale is one of preserving viable treatment options for the future.

For patients on ***protease inhibitors***, it is relatively more appropriate to change earlier upon viral rebound in order to avoid the development of multiple and high level drug resistance.¹³

In general, the likelihood of success for ***second hit*** is greater than that for genuine salvage therapy when there is insufficient option to compose a HAART. Thus one may want to change earlier for second line therapy compared with salvage purpose.

For patients with treatment failure due to drug resistance arising from ***non-compliance***, the decision to change therapy should be made more cautiously and only after a strategy is devised to improve adherence to the new regimen.

III.B Choice of new therapy after first failure

In the case of treatment failure due to resistance, the patient should ideally be switched to new drugs that do not have cross-resistance to previously failed drugs. At least, all drugs should be changed. In this regard, the use of drug resistance test is gaining acceptance.^{14,15} Studies have shown that the additional use of resistance testing, besides clinical judgement and viral load, for choosing alternative therapy gives a better virologic outcome.¹⁶ Yet, resistance testing may be good at excluding potential drug candidates but not at ruling in suitable drugs.¹⁷

Instead of changing all the drugs in a failing regimen, the approach of keeping some current drugs and change/intensify with some drugs, e.g. abacavir, hydroxyurea, or a pharmacokinetic enhancer is being studied. This may work when switch is done very early when high level drug resistance has not developed. Until more definitive data are available, this approach should be regarded as experimental. The recommended scheme of switching drugs after first failure is as in Box 4.10.

III.C Salvage therapy

This is usually taken to mean therapy for patients who have failed at least two regimens of HAART. In this situation, the chance of success is much smaller and no definite recommendations can be made. In principle, the use of new drugs and especially new classes of drugs would still be able to control viral replication. But the current antiretroviral armamentarium is limited. Before a salvage therapy is devised, the following have to be determined:

- (a) The reasonable goal of treatment – undetectable viral load may no longer be an option.
- (b) The reasonable chance of success – a new regimen may not necessarily work better. In many cases, even partial suppression of viral load confers clinical benefit.¹⁸
- (c) The tolerance – an effective salvage regimen may be too toxic for the patient to take on a long term basis.

Box 4.10 Change of therapy after first treatment failure

Present regimen	To switch to
1NRTI	2 new NRTI+1PI/NNRTI
2NRTI	2 new NRTI+1PI/NNRTI
NRTI+1 to 2 PI	2 new NRTI+2 new PI, 2 new NRTI+1NNRTI, 1 to 2 new NRTI+1PI+1NNRTI
2NRTI+1NNRTI	2 new NRTI+1 to 2 PI

With the above in mind, following are some of the options when no viable HAART can be constructed:

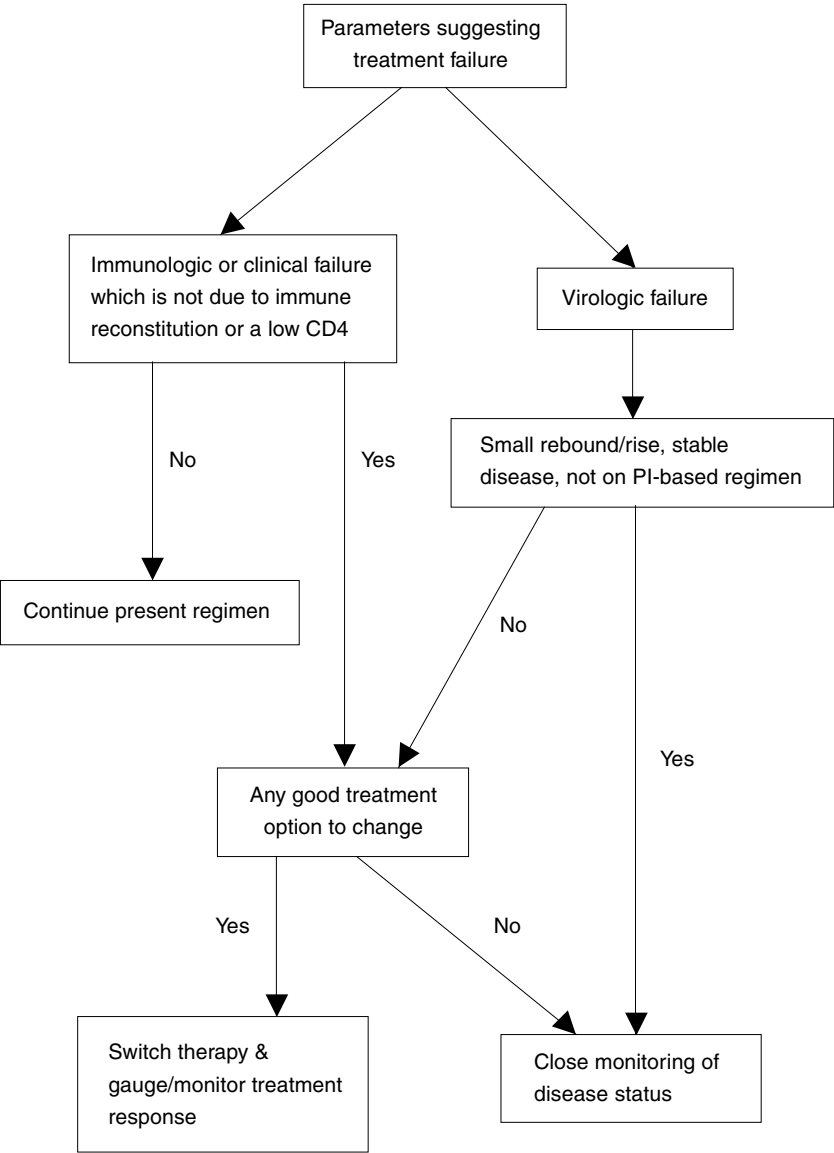
Maintenance of the failing regimen is reasonable when no good option is available for change and the existing regimen is (a) partially suppressing the viral load which could be an independent predictor of risk of opportunistic infections,¹⁹ (b) the viral strains kept by the current drugs may be less fit or inhibited by concomitant drugs, e.g. the M184V mutation of 3TC delays the emergence of AZT resistance, or (c) CD4 is rising despite virologic failure. This especially applies to end-stage disease.

Mega-HAART comprising more than 4 drugs has been tried for patients with experience to many drugs. Such regimens usually include at least 2 PI, 1 to 2 NNRTI, several NRTI and perhaps hydroxyurea. Some would include foscarnet.²⁰ Patient motivation is important. Success relies on the possibility that there is still partial response to some of the drugs being used. Mega-HAART is difficult in terms of adherence, side effects, and potential drug interactions. In some patients, however, it can attain virologic control at least in the short term.

Structured treatment interruption (STI) is being studied intensively. As one strategy for salvage therapy, however, the results are not promising. It was hoped that by STI, the wild type would overgrow resistant virus and respond to ordinary therapy. However, only a transient virologic response was achieved in most cases. Lost CD4 count during STI may not be recoverable.²¹

Enrolment into clinical trials is probably the only way of obtaining new drugs and treatment otherwise unavailable. However, as experimental therapies, the balance between benefits and risks has to be carefully addressed.

Algorithm 4.4 Approach to treatment failure



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4.5 MANAGEMENT OF PRIMARY HIV INFECTION

HIV infection has long been known to cause chronic disease. The acute phase of the infection is often ignored until recent years when the pathogenesis of the infection began to unfold. Primary HIV infection represents the earliest interaction between the immune system and the virus after the latter is introduced to the human body. Primary infection is characterized by active viral replication, bursts of viremia, precipitous fall of CD4 cell count, and the development of cytotoxic T cell (CTL) responses. Symptoms classically occur 2-6 weeks after exposure and last for 1-2 weeks.¹ Severe and prolonged symptoms are associated with a more rapid progression.

Primary HIV infection offers an opportunity to establish rapport for planning future treatment strategies, discuss rationales of antiretroviral treatment and explore means of preventing HIV spread. There is not yet a standard regimen to treat people with primary HIV infection. The decision is often complicated by

- (a) difficulty in making timely diagnosis and implementing intervention;
- (b) insufficient evidence of treatment effects; and
- (c) unknown long term implications of therapy.

A systematic approach is desirable in managing a suspected case of primary HIV infection.

I. Terminology

Terminology is confusing in the subject of primary HIV infection. The term ***primary HIV infection*** is often used as an all-encompassing name describing the early phase of the disease process after virus inoculation. Technically it is defined as the process of HIV replication prior to the development of HIV antibody.² ***Acute HIV infection*** is used interchangeably with primary HIV infection.

Acute seroconversion syndrome, acute retroviral syndrome, and acute retroviral seroconversion syndrome are descriptions of cases of primary HIV infection presenting symptomatically as mononucleosis-like illness, coinciding with the development of HIV antibody. The commonest symptomatology includes fever, adenopathy, pharyngitis and rash.¹

II. Diagnosis of primary HIV infection

A diagnosis of primary infection should be considered in clients who (a) have a recent history of high risk exposure and (b) present with symptoms of a mononucleosis-like illness. Other occasions are (c) clients who voluntarily suggest a diagnosis of primary HIV infection and (d) specific referral from other institutions.

When primary HIV infection is suspected, a detailed history must be obtained to include clinical symptomatology and the time sequence from exposure to the time of consultation. A presumptive and/or a working diagnosis can be made, the former to guide further investigation and the latter to assist the process of decision making for implementing therapeutic intervention.

A **presumptive diagnosis** of primary HIV infection is made if one (a) is symptomatic and (b) has a clear history of exposure not more than 12 weeks ago. In these circumstances, blood tests should be arranged for (a) HIV antibody, (b) HIV RNA and (c) CD4 count. HIV p24 antigen can be an alternative for HIV RNA if the latter is unavailable. The laboratory should be alerted of the urgency of the situation so that HIV antibody and HIV RNA could be assayed as soon as is practicable.

A **working diagnosis** of primary HIV infection is made if, in addition to the criteria for presumptive diagnosis, one tests positive for plasma HIV RNA (or p24 antigen) and negative (or indeterminate) for HIV antibody. Another supportive evidence would be a low CD4 level.

For a patient with a presumptive working diagnosis of primary HIV infection, advice should be made on the following about treatment:

- (a) There have been researches on the use of antiretroviral agents in primary HIV infection, but so far scientific evidence for their effectiveness as a general clinical measure is limited.
- (b) Such treatment involves the use of multiple drugs on an indefinite basis.
- (c) It is unlikely that treatment of primary infection, even if effective, would eradicate the virus from the body.
- (d) The possible theoretical benefits of treatment are the preservation of the immune reserve and a lowering of the baseline viral load.

The client should be advised to return for a repeat blood test for HIV antibody to confirm the diagnosis, at three and six months after exposure. The subsequent plan of management would be the same as that for those with established infection.

III. Medical treatment of primary HIV infection

III.A The pros and cons of medical treatment

The benefits of antiretroviral therapy in primary infection have been extensively studied, though there are limited scientific data to date in support of their clinical effectiveness. The main considerations are the likelihood of preserving one's immune system, decreasing the severity of acute disease, suppressing the initial burst of viral replication, lowering the viral setpoint and thereby improving prognosis. The principle of treating primary HIV infection has been highlighted by an NIH Panel,³ and the rationales summarized in the draft guidelines published thereafter.⁴

There are theoretical advantages and drawbacks for treatment primary HIV infection. There is active viral replication, high viral load and thus a higher potential of transmission to others during the acute phase HIV infection. Intervention at this stage could theoretically reduce the infection risk of subsequent exposure. This can be done through modifying high risk behavior. As a chronic illness, this would also be the right moment to engage clients for the purpose of developing long term treatment plan on an individual basis. The drawbacks of antiretroviral treatment in primary infection are (a) lack of evidence for clinical benefit, (b) drug toxicity, (c) need for taking the medicines indefinitely and (d) the uncertainty of long term implications.

III.B Treatment Regimens

Highly active antiretroviral therapy (HAART) using two nucleoside reverse transcriptase inhibitors (NRTI) and another potent agent e.g. protease inhibitor (PI) is the commonest regimen in situations where antiretroviral therapy is considered. The combination is often similar to those for established infections.

IV. Other considerations in primary HIV infection

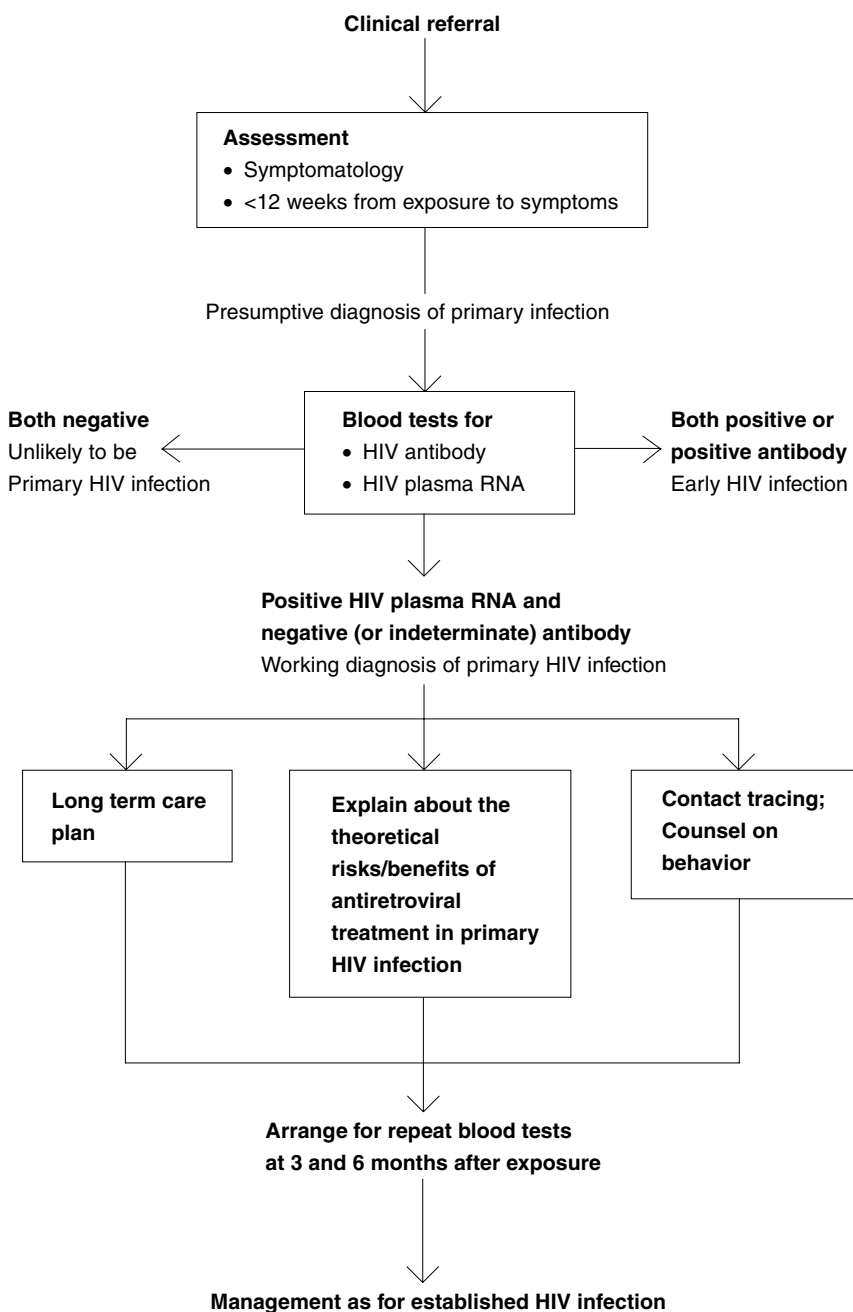
Primary HIV infection can be a sensational issue because of the often unique setting surrounding a diagnosis, relative insufficiency in treatment experiences, and the urge to do the best for a patient without delay. Clinicians should be aware that there may be a wide gap between the expectation of the client and the current understanding in the management of primary HIV infection. The following principles are proposed in addressing primary infection:

- (a) A high index of suspicion should be cultivated in identifying and diagnosing primary HIV infection.
- (b) The patient should be engaged in the development of long-term care plan, and to prevent subsequent spread through behavioral modification. The theoretical advantages, potential risks, and the underlying uncertainty associated with primary HIV infection should be made known to the patient concerned. Combination antiretroviral therapy is not a routine in the case of primary HIV infection.

Finally, both the diagnosis and the therapy (if provided) of primary HIV infection are complex issues demanding good clinical skills. It is never a straight-forward business, and clinicians must also beware of the following situations:

- (a) Results of both HIV tests and plasma viral RNA could be difficult to interpret. False positive results in HIV RNA may confound the picture of primary HIV infection.⁵ The results should be interpreted with care and in context of the clinical presentation.
- (b) Management-wise, primary HIV infection must be distinguished from two other conditions: Firstly, Early HIV disease denotes recent infection, and is defined as HIV antibody positivity with previous documentation of a negative HIV test about 6 to 12 months ago. It normally represents the period from seroconversion to 6 months following HIV transmission. Secondly, post-exposure prophylaxis refers to the management of cases before infection is established. Although the use of antiretroviral treatment may be indicated in either situation, the rationales and hence followup protocol will be very different from that in primary HIV infection.
- (c) The diagnosis of primary HIV infection implies the detection of a recent incident of high risk exposure. This provides therefore also a window of opportunity to investigate recent contacts of the index client, encouraging them to be counseled and HIV tested if appropriate.

Algorithm 4.5 Management of primary HIV infection



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PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS

5.1 *PNEUMOCYSTIS CARINII* PNEUMONIA

Pneumocystis carinii pneumonia (PCP) occurs in the immunocompromised patients and is a common occurrence in those with AIDS. In the Multicenter AIDS Cohort Study,¹ the risk of PCP was greatly increased in HIV patients with CD4 counts of less than 200/uL,² thrush or unexplained fever >2 weeks. PCP is the most common AIDS-defining disease in Hong Kong,³ typically occurring in those who are unaware of their HIV infection. Breakthrough or relapsed PCP is relatively uncommon.

I. Prevention

Pneumocystis carinii is acquired by inhalation. Both reactivation and exogenous reinfection may occur with HIV infection. Although there is some evidence that person-to-person spread may occur among the immunocompromised, the usefulness of respiratory isolation of PCP patients is unclear.

I.A Standard primary chemoprophylaxis

Studies have documented the high efficacy of trimethoprim-sulfamethoxazole (TMP-SMZ or Septrin), dapsone and pentamidine in the primary prophylaxis of PCP. In fact, effective PCP prophylaxis alone, in the absence of HAART, delays the onset of AIDS by 6-12 months.⁴ Direct head to head comparisons among these agents have also been performed. In general, they asserted the superiority of Septrin. For instance, ACTG 081⁵ showed that, when the CD4 was 100-200/uL, Septrin (DS, 960 mg bid), dapsone (50 mg bid) and pentamidine (300 mg q4wk) had similar efficacy in the primary prevention of PCP. However, when CD4 was below 100/mm³, aerosolized pentamidine was less effective. Also failures occurred more often with dapsone 50 mg qd than 50 mg bid.

Thus, **Septtrin** is the drug of choice and should be started when the CD4 count falls below 200/uL or there is oral thrush. Various dosages have been proven effective: one single strength, SS (480 mg; 80 mg TMP) tablet a day; two SS every other day;⁶ or one double-strength, DS (960 mg; 160 mg TMP) tablet 3 times a week (Mon, Wed, Fri). The two latter dosages are also effective against toxoplasmosis. Concurrent folinic acid is not necessary, contrary to previous guidelines.

Despite its efficacy, between 20% and 50% of patients with AIDS have to discontinue Septrin prophylaxis or therapy. Toxicity most commonly in the form of cutaneous

hypersensitivity is due to the accumulation of metabolites as a result of a deficient glutathione system in HIV-infected patients.⁷ Most adverse effects can be managed with supportive care. However, discontinuation of Septrin is necessary when there is severe rash with mucosal involvement, drug-induced hypotension, or anaphylaxis. There are different approaches to desensitizing or rechallenging persons. In general, they involve gradual escalation of Septrin elixir (Box 5.1). Alternatively, a rapid desensitization schedule where 12 increasing doses are administered at 30-min intervals has also been described.⁸ No comparative studies have been done on these regimens. Once desensitization is achieved, interruption of therapy should be avoided and daily rather than thrice weekly Septrin should theoretically be used.

Aerosolized **pentamidine** and dapsone are better tolerated than Septrin but less effective. They do not have the additional advantage of protecting from toxoplasmosis. The jet nebulizer, Respigard II, is the standard for aerosolization of pentamidine. Other forms of administration (eg ultrasonic, metered dose inhaler) have not been adequately evaluated. It should be noted that aerosolized pentamidine may not be adequately delivered in those with chronic obstructive pulmonary disease. Furthermore, it offers no systemic protection. Bronchospasm as a complication of treatment can be severe and should be promptly

Box 5.1 Protocol of outpatient Septrin desensitization (of Integrated Treatment Centre, Department of Health, Hong Kong)

Day	Time	Dose	Bottle	Amount
1	8:00	10 ug	A	0.1 ml
	12:00	25 ug	A	0.25 ml
	16:00	50 ug	A	0.5 ml
	20:00	100 ug	A	1 ml
	23:00	250 ug	A	2.5 ml
2	8:00	50 ug	A	5 ml
	12:00	1 mg	A	10 ml
	16:00	2 mg	A	20 ml
	20:00	4 mg	B	0.4 ml
	23:00	8 mg	B	0.8 ml
3	8:00	15 mg	B	1.5 ml
	12:00	30 mg	B	3 ml
	16:00	50 mg	B	5 ml
	20:00	100 mg	B	10 ml
	23:00	200 mg	B	20 ml
4	8:00	One SS Septrin		

Bottle A: 100 ug/ml
Bottle B: 10 mg/ml

N.B.

- Desensitization is contraindicated in those with a history of life-threatening reaction to Septrin e.g. Steven-Johnson Syndrome
- Abort regimen on any sign of reaction

treated with inhaled beta-agonists. For the same reason, pretreatment with such is indicated in those with a history of bronchospasm to pentamidine.

Dapsone as prophylaxis should preferably be given 100 mg per day. Other dosages investigated include 50 mg qd and 100 mg twice a week. There is additional protection against toxoplasmosis if daily dapsone at 50 mg is combined with weekly pyrimethamine at 50 mg and folinic acid.⁹ The efficacy of dapsone (50 mg bid) is higher than that of aerosolized pentamidine when the CD4 count is below 100/mm³. Nevertheless, its incompatibility with G6PD deficiency has made many reluctant to use this otherwise very useful drug. In most cases of sulfa allergy, dapsone may still be safely used. It is essential that a G-6-PD screen be done before dapsone, primaquine or pyrimethamine is given.

In patients with a CD4 <100/mm³ and **positive anti-toxoplasma IgG serology**, Septrin confers added protection against toxoplasmosis. Dapsone combined with pyrimethamine is the alternative.

I.B Alternative chemoprophylaxis with atovaquone

Atovaquone 1500 mg qd has been compared with dapsone 100 mg qd in those who could not tolerate Septrin.¹⁰ It demonstrated no difference in efficacy whether the drugs were used as primary or secondary prophylaxis. Nevertheless, atovaquone was better tolerated. The potential advantage of atovaquone in preventing toxoplasmosis, however, could not be proven and remained theoretical. Atovaquone is currently not available in Hong Kong.

I.C Discontinuation of primary prophylaxis

Consensus has been developed that 1° prophylaxis may be discontinued after successful use of HAART, when the CD4 count has risen above 200/ul in the absence of detectable viral load.¹¹ This follows the results of several clinical trials to this effect.^{12,13} The corollary is that it has to be reinitiated if the CD4 drops below 200/mm³ again (confirmed by repeat testing).

II. Diagnosis of PCP

II.A Clinical features

The cardinal manifestation of PCP is an insidious onset of dry cough and fever. Weight loss and exertional dyspnea are relatively late features. Physical findings are notoriously

nonspecific – tachypnea, tachycardia, and cyanosis, although a low pulse oximetry reading with exercise-induced desaturation is suggestive if corroborated by other clues. Rales can be detected in 30-40% of cases.

Chest radiology classically shows interstitial infiltrates that begin in the perihilar areas and spread to the lower and later upper lung fields. An alveolar pattern with air bronchograms may develop as the disease progresses. Lactate dehydrogenase (LDH) that originates in the lung is elevated. Elevated LDH has a diagnostic sensitivity of 78% and specificity of 74%. Gallium accumulates in activated macrophages, but pulmonary uptake is not specific for PCP.

Breakthrough PCP that occurs during aerosolized pentamidine prophylaxis tends to have atypical presentations: upper lobe infiltrates, pneumothorax, or extrapulmonary infection. The sensitivity of bronchoalveolar lavage is also lower. Vigilance on the part of the clinician is therefore necessary for early diagnosis. Site-directed and/or upper lobe lavage may increase diagnostic yield.

II.B Diagnostic tools

A pathologic diagnosis should be obtained wherever possible, especially when adjunctive steroid is used together with empiric treatment. This is because infections like tuberculosis or systemic mycosis may temporarily improve with steroids, thus misleading clinical judgement and delaying diagnosis. Diagnosis is usually achieved by identification of *Pneumocystis* cysts in respiratory secretions through Gomori's methenamine silver staining. The diagnostic yield increases with the invasiveness of obtaining the specimen. Induced sputum has a variable sensitivity between 74% to 83%;¹⁴ bronchoalveolar lavage (BAL) alone has a sensitivity in excess of 95%. When combined with BAL, transbronchial biopsy (TBB) has a sensitivity of almost 100%. However, it is best avoided for fear of pneumothorax and pulmonary hemorrhage. If available, immunochemical stains with monoclonal antibody, and nested PCR also substantially increase the diagnostic yield. Empiric therapy does not usually interfere with diagnosis as large numbers of *Pneumocystis* cysts remain for weeks to months after therapy.

II.C Assessment and prognostic factors

An alveolar-arterial oxygen gradient, $P(A-a)O_2 > 35$ mmHg (4.6 kPa), LDH > 500 IU/dL, and relapsed PCP are poor prognostic factors. The $P(A-a)O_2$ could be computed with the simplified formula: $150 - 1.25(PaCO_2) - PaO_2$, in mmHg. A $P(A-a)O_2 > 35$ mmHg (4.6 kPa), or room-air $PaO_2 < 70$ mmHg (9.3 kPa) defines **severe PCP** and indicates use of adjunctive steroid. A diffusing capacity, DLCO, yields essentially the same information

and is usually not necessary. It has been found that experience of the caretakers also influences prognosis.

III. Treatment of PCP

Empiric treatment of *Pneumocystis* is justifiable, but should not detract from the need to confirm the diagnosis by identification of the organism. This often requires an aggressive approach to the collection of proper specimens. Sputum by induction or BAL has a high diagnostic yield. More difficult cases may require transbronchial biopsy.

III.A Septrin

Intravenous Septrin is the drug of choice for the therapy of PCP. Oral therapy at a lower dosage (12-15 mg/kg/day; TMP component), or of a shorter duration (2 weeks vs 3 weeks) is justifiable only in mild episodes. Folinic acid should be avoided lest it compromises the action of Septrin.¹⁵ As opposed to HIV negative patients where treatment for 14 days is adequate, treatment is generally given for 21 days in AIDS patients. It is also prudent to wait at least 7 days before concluding that therapy has failed.

III.B Steroid

Clinical studies have demonstrated that adjunctive steroid therapy initiated within 72 hours in patients with PCP who have moderate to severe hypoxemia significantly reduced the risk of transfer to the intensive care unit, intubation and death.¹⁶ Skin rashes also appear to occur less frequently in Septrin recipients when steroid is given.¹⁷ The steroid may be given orally or intravenously. One regimen that proved successful was the use of prednisone (or prednisolone)

- 40 mg bid for 5 days
- 40 mg qd for 5 days
- 20 mg qd in the remaining days of therapy
- (No concomitant H₂ blocker is necessary)

It must be cautioned that the use of steroids in AIDS could have detrimental effects in the presence of Kaposi's sarcoma, tuberculosis and some fungal infections.

III.C Intravenous pentamidine

Compared to Septrin, intravenous pentamidine yields inferior results in term of survival rates.¹⁸ Furthermore, it is fraught with complications e.g. hypoglycemia, hyperglycemia,

hypotension, nephrotoxicity, and neutropenia. Substitution of pentamidine in case of Septrin failure is often ineffective; neither does it increase the efficacy of Septrin when given in combination. Nevertheless, in severe PCP, it is the second line agent to use in the event of Septrin intolerance. Inhaled pentamidine is not acceptable as treatment of PCP owing to a high rate of relapse.¹⁹

III.D Alternative agents (Box 5.2)

All alternative agents are inferior to Septrin in terms of therapeutic success but may be more tolerable. Their role is therefore limited to mild-to-moderate episodes of PCP, with the possible exception of trimetrexate. In combination with folinic acid, intravenous trimetrexate may be used for severe PCP that has failed Septrin and pentamidine.

III.E Breakthrough PCP and treatment failure

Breakthrough PCP in patients receiving prophylaxis can occur. Although it makes sense to switch to another agent for treatment, there are no data to support this approach. Treatment should therefore be based on the same consideration as for PCP in other circumstances.

Box 5.2 Alternative treatment of PCP

For mild to moderate PCP

Trimethoprim(TMP)-dapsone – in one small study,²⁰ TMP-dapsone was as effective as Septrin and had fewer adverse events. Dapsone alone is not effective. TMP-dapsone is especially valuable in the event of sulfa allergy

Clindamycin-primaquine – neither alone is effective against PCP. In a study²¹ of mild to moderate PCP, this combination however yielded comparable rates of response and intolerance as Septrin.

Atovaquone – In a multicenter trial,²² use of atovaquone in mild-to-moderate PCP, as compared against Septrin, was associated with lower rates of clinical efficacy and survival but better tolerated. Therapeutic success correlated with plasma concentrations. The new liquid formulation of atovaquone allows it to be given twice a day only (not available in Hong Kong).

For severe PCP

Trimetrexate – trimetrexate (in combination with folinic acid) is inferior to Septin. Its role is limited to patients who have failed or are intolerant to both Septrin and pentamidine.

In **treatment failure**, regimens may be switched. However, there are little data to guide management at this stage; neither is there in vitro susceptibility testing. Failure of Septrin or intravenous pentamidine should be dealt with on a case by case basis. In general, there is no benefit obtained by switching to one another, although it would be logical to switch to Septrin if it was not the agent that failed. Combination treatment adds to toxicity and is usually no more effective. Genotypic study of PCP resistance is being explored. Mutations in the dihydropteroate synthetase (DHPS) gene have been reported in patients who broke through Septrin prophylaxis.²³ Nevertheless, genotyping is still in its infancy and correlation with outcome is not possible at the moment. It is noted that supportive care with mechanical ventilation may be equally important, if not more, for survival of patients.

Trimetrexate as treatment of PCP is based on limited data. It requires parenteral therapy and is poorly tolerated. In general its use cannot be recommended. It may be considered in severe PCP where both Setprin and pentamidine either fail or cannot be tolerated. It is important to note that a temporary deterioration of PCP is not uncommon in the initial days following therapy. This should not be mistaken for treatment failure. Nevertheless, the clinician should still be on the alert of superimposed opportunistic infections.

IV. Maintenance treatment (secondary prophylaxis)

Without maintenance treatment, more than 60% of PCP recur by 1 year, irrespective of CD4 count.²⁴ In this context, Septrin^{25,26} is superior to monthly aerosolized pentamidine to achieve prevention. Upon successful treatment of PCP, lifelong treatment with Septrin should be initiated, at 2 SS qd, or 2 SS tiw. Although Septrin at 1 SS qd or 2 SS qod (every other day) has not been adequately evaluated for 2° prophylaxis, these dosages are commonly used. Dapsone 50 mg bid, monthly aerosolized pentamidine, and daily Septrin after desensitization are the alternatives.

Data are accumulating that maintenance may be discontinued when there is adequate immunologic response to HAART.

A table listing regimens for prevention and treatment of PCP is in Box 5.3.

V. G6PD deficiency

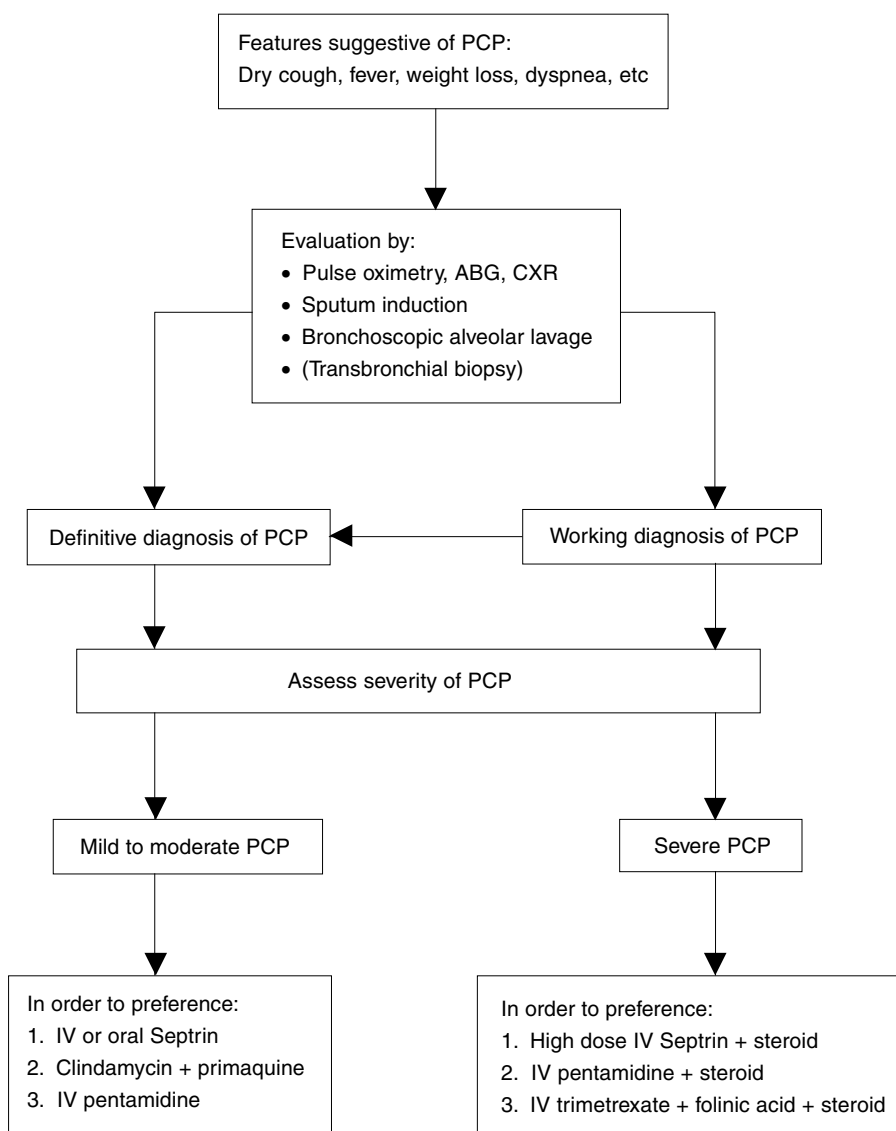
A G6PD screen is usually incorporated in the baseline work up of all HIV-infected patients. This is because dapsone, primaquine and pyrimethamine may precipitate hemolysis in those who are G6PD deficient, especially those who are homozygous B-. There having been no systematic study of the predominant G6PD variants in Hong Kong, it is prudent

Box 5.3 Regimens for prophylaxis and treatment of PCP

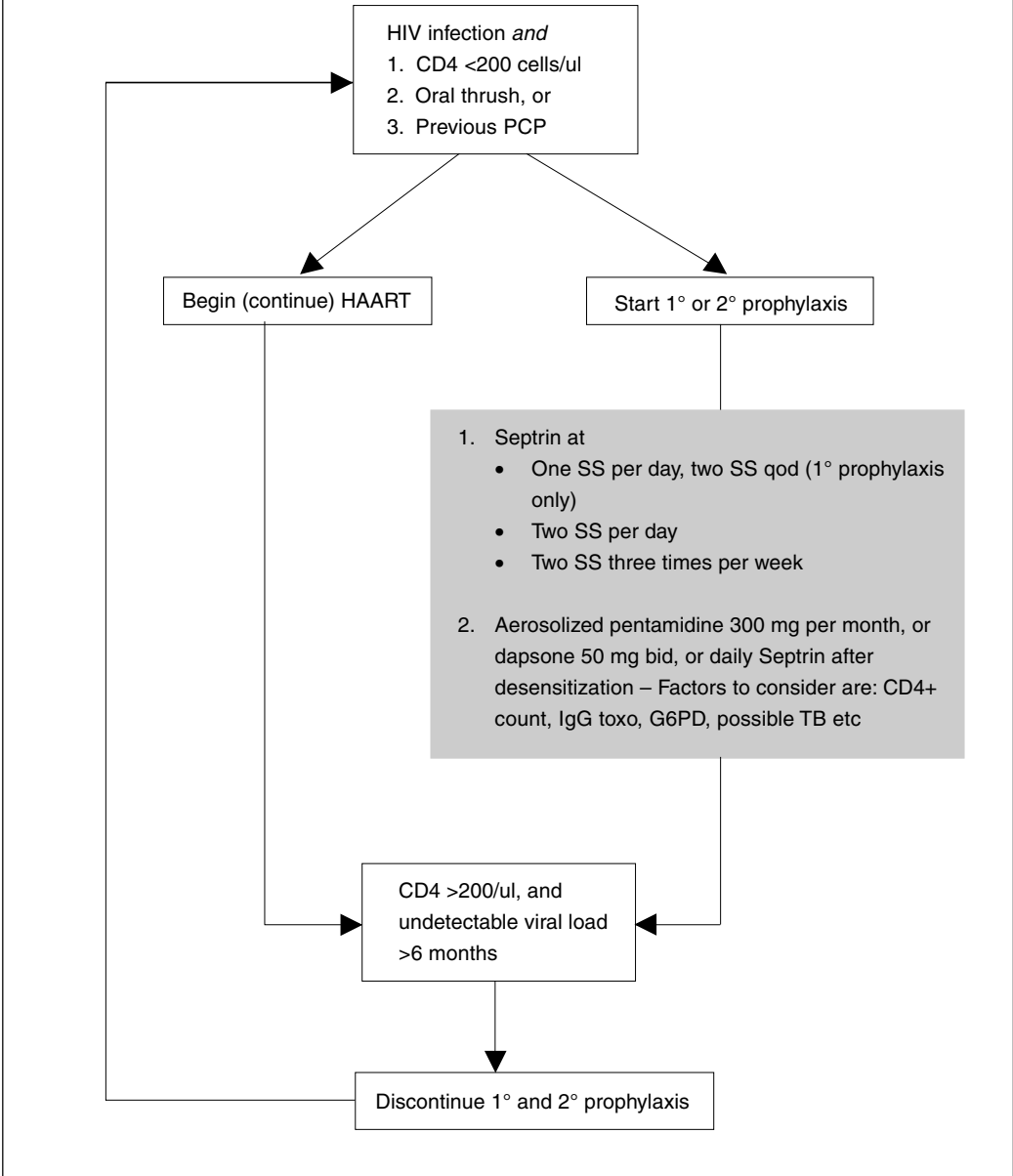
Regimen	Dosage	Major adverse reactions	Remarks
Prophylaxis of PCP			
TMP-SMX (Septrin)	One SS qd, Two SS qod (1° prophylaxis only) Two SS qd Two SS tiw (3 consecutive days or M,W,F)	GI – nausea, vomiting, diarrhea Rash – maculopapular, exfoliative dermatitis, Stevens-Johnson, TEN Myelosuppression – thrombocytopenia, megaloblastic anemia, neutropenia	Desensitization is usually successful; prevents toxoplasmosis; folate reduces megaloblastic changes; folic acid may increase failure
Dapsone	50 mg bid, 100 mg qd	Hemolysis, methemoglobinemia, 'sulfone syndrome' (fever, rash, hepatic injury)	Rule out G6PD deficiency; dapsone alone is not effective against PCP
Aerosolized pentamidine	300 mg q 4wk	bronchospasm	Use Respigard II; beware atypical breakthrough PCP
Dapsone + pyrimethamine	50 mg qd + 50 mg qwk	Hemolysis, methemoglobinemia	Add folic acid; rule out G6PD deficiency; regimen also prevents toxoplasmosis
Atovaquone	1500 mg-suspension qd	GI intolerance	take drug with food; new liquid form has better bioavailability, not available in HK
Treatment – severe PCP			
IV TMP-SMX (Septrin)	15-20 mg/kg/d, in 3-4 doses	See above	
IV pentamidine	4 mg/kg/d	Pancreatitis, hypo- and hyperglycemia, electrolyte disturbance, nephrotoxicity, hypotension, neutropenia, thrombocytopenia	
Trimetrexate+folinic acid	45 mg/M ² /d + 80 mg/M ² /d (in 4 doses)	Myelosuppression, nephrotoxicity, hepatotoxicity	Avoid in pregnancy; watch LFT, CBP, RFT
PLUS Oral prednisolone	40 mg bidX5d, 40 mg qdX5d, 20mg qd for rest	Aggravation of other infections and Kaposi's	Rule out other pathogens; confirm PCP; IV steroid may be substituted
Treatment – mild-to-moderate PCP			
Low dose po TMP-SMX	12-15 mg/kg/d	See above	
Trimethoprim+dapsone	12-15 mg/kg/d + 100 mg qd	TMP – Rash, hyperkalemia Dapsone – see above	Mutually increase blood levels; trimethoprim is not available in HK
Clindamycin+ primaquine	600 mg IV q6h (or 300-450 po q6h) + 15 mg base qd	Rash, hemolytic anemia, methemoglobinemia	Rule out G6PD deficiency; monitor methemoglobin; avoid primaquine in pregnancy
Atovaquone	750 mg bid to tid	GI intolerance	take drug with food; new liquid form has better bioavailability, not available in HK

**All regimens for treatment should be given for 21 days. Shorter duration of therapy is admissible only in mild PCP*

Algorithm 5.1A Diagnosis and treatment of PCP



Algorithm 5.1B Prophylaxis for PCP



to avoid these drugs in those who are G6PD deficient. On the other hand, low dose Septrin may still be used as it rarely precipitates hemolysis. However, close monitoring is necessary.

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5.2 TUBERCULOSIS IN HIV INFECTION

The HIV epidemic has significantly increased TB infections in many parts of the world, especially sub-Saharan Africa. Southeast Asia also has a long history of high TB endemicity. During the years 1989 through 1991, Southeast Asia had the highest notification rate of TB in the world at 146 per 100,000, and the second highest annual risk of TB infection (ARTI) at 1 to 2%. In comparison, the ARTI in Sub-Saharan Africa was 1.5 to 2.5%.¹ The corresponding estimate of Hong Kong was 0.9%.²

Clinically, *Mycobacterium tuberculosis* (mTB) spreads by the airborne route and causes mainly pulmonary disease. Although it infects both HIV-positive and negative individuals, HIV increases the risk of active TB by 25 to 30-fold. Conversely, active TB is associated with an increased risk of developing opportunistic infections.³ A transient decrease in CD4 count and a 5 to 160-fold rise in viral load have been demonstrated with TB. HIV-infected persons with TB tend to, however, have fewer acid-fast bacilli in their sputum and less pulmonary cavitation, especially with increasing immunosuppression. On an individual level, HIV-infected persons with TB are less infectious than their HIV-negative counterparts. However, this is more than compensated by the fact that HIV infection enhances the very development of active TB.

In Hong Kong, both extrapulmonary TB (at any CD4 count) and pulmonary TB (in those with a CD4 count below 200/ul) are AIDS-defining conditions for surveillance purpose (refer to Chapter 4.1). As of Jun 98, there had been 125 cases of coinfection of TB and HIV. Eighty-four percent had TB as the primary AIDS-defining disease; 3 had primary INH mono-resistance, and 1 had multi-drug resistant TB. These co-infections account for a small minority of the annual TB notification which now stands at about 100 per 100,000.⁴

I. Manifestations of TB in HIV

There are three scenarios that TB may manifest in the course of HIV infection:

- (a) reactivation of latent mTB being the most common mechanism,
- (b) progressive primary TB, and
- (c) exogenous reinfection with a different strain.

The frequency of extrapulmonary TB, with or without concurrent pulmonary TB, is high, ranging from 40% to 80% and increasing with immunosuppression. Extrapulmonary TB takes the form of lymphadenitis, bacteremia, disseminated disease, pleural or pericardial disease. CNS involvement is common, occurring in 5% to 10% of cases in the form of

meningitis and tuberculomas. Although urine cultures are frequently positive in disseminated disease, localized renal TB is rare.⁵

II. Diagnosis of TB

Diagnosis of TB in HIV positive patients demands a high index of suspicion because of often atypical clinical features. A full medical evaluation for TB begins with a history and physical examination. Workup is then guided by the symptomatology but should always include a chest radiograph and sputum examination to identify a pulmonary component. In addition, gastric aspiration, BACTEC™ culture for bacteremia, abdominal sonogram or CT, bone marrow biopsy, lumbar puncture and urine cultures may be indicated for a definitive diagnosis.

With the suspicion of infectious TB, the physician should also assess the need to admit the patient for respiratory isolation. This can be discontinued when there is clinical and radiological response to treatment, and after 3 consecutive negative smears (collected on different days) have been obtained.

At times it is necessary to initiate empiric treatment notwithstanding. Nevertheless it remains important to pursue culture and identification of the organism in view of the atypical presentation and complex clinical scenarios in the context of HIV infection. Initial clinical response is encouraging but not an indication to halt investigation.

II.A Smear and culture

The gold standard of diagnosing TB is culture of the organism. Incidentally it is also more sensitive than the AFB smear, requiring only 10-100 viable organisms to become positive. On the other hand, a sputum sample must contain 5000-10 000 bacilli/ml to yield a positive AFB smear.⁶

To expedite the diagnosis of TB and determination of its susceptibility, the use of BACTEC™ is recommended in situations where culture confirmation and sensitivity pattern are important in the clinical management. The radiometric liquid BACTEC™ system reduces average detection time to 10-14 days. Susceptibility results to commonly used drugs should follow in another 4-7 days. In contrast, one review in the US found it took 18.5 (for smear positive cultures) to 27.5 days (for smear negative cultures) before culture results are reported with solid media.⁷ In Hong Kong it may take 6 to 10 weeks, especially for negative results.⁸

It must, however, be emphasized that direct sputum smear plays a most important role in allowing highly infectious cases to be promptly identified. Together with clinical assessment, chest X-ray and other simple diagnostic tests, sputum smear often allows treatment to be started without waiting for culture results.

II.B Tuberculin skin test (TST)

Because of the implementation of universal BCG vaccination in newborns in Hong Kong, the tuberculin skin test (TST) is not routinely employed to aid diagnosis as its reliability may fall in the event of prior vaccination. This might have been overcautious as it was estimated that BCG's effect on TST should wane significantly in ten years' time.⁹

A positive TST will not be able to differentiate latent from active TB infection. A single positive test should therefore be interpreted with care in the local setting where there is a high prevalence of infection. Nevertheless, a conversion to positive from a previous negative result, in a clinical picture compatible with active TB infection, will still be suggestive of the diagnosis.

II.C DNA probes

DNA probes that rapidly and specifically identify acid fast growth are available in some labs. They hybridize with mycobacterial ribosomal RNA and are able to identify *M. tuberculosis*, *M. bovis*, *M. avium intracellulare*, etc. Although these probes are currently of insufficient sensitivity to be used directly on clinical specimens, they provide valuable clues to the choice of initial anti-mycobacterial drugs after identification of AFB. The practical use of other newer rapid diagnostic methods on a service basis is either limited to special circumstances or of uncertain value.^{10,11} These include immunoassays for antigens or antibodies, and detection of tuberculostearic acid and mycolic acid. Recently, a nucleic acid amplification test by Gen-Probe was approved for clinical use in the US.¹²

II.D Rapidity of diagnosis

The success of TB treatment and prevention of secondary spread hinges firstly on the speed of diagnosis, which in turn depends on a high index of suspicion. Secondly, an adequate number of appropriately collected specimens are crucial for examination. Thirdly, rapid tests for identity and sensitivity have become available in selected laboratories and may be useful in specific circumstances.

III. Management of TB in HIV

If a patient suspected of TB is in critical condition, it is justifiable to start empiric therapy for TB. However, the physician should be ready to modify therapy according to culture and sensitivity results, as well as the clinical response.

III.A Anti-TB treatment and directly observed treatment (DOT)

If supervised properly, standard anti-TB regimens are as effective in HIV positive as in negative patients. The British¹³ and American¹⁴ Thoracic Societies, as well as the US CDC,¹⁵ recommend the 'short' course 6-month treatment in HIV-related TB. However, some studies showed higher relapse rates with this regimen compared to longer ones. Apparently this 6-month regimen gives good results with TB that is pan-susceptible and that responds promptly to treatment. Modification of drugs and prolongation will be necessary in the event of resistance, drug interaction, CNS disease (and possibly joint and bone TB), or unsatisfactory clinical response.

In TB treatment the emphasis is on supervision. The occurrence of MDR TB (resistant to isoniazid and rifampin), as well as outbreaks of TB has been linked to non-compliance. For this reason, DOT (directly observed therapy) is deemed the standard of care, especially with patients who are unable to cooperate. DOT could be provided daily or intermittently (two to three times a week). In Hong Kong the endemicity of TB in Hong Kong has helped establish an infrastructure of expertise on DOT, through the network of chest clinics in the public service. It is to the client's advantage that this be fully utilized, especially in the face of drug resistance and doubtful compliance. Where DOT is not utilized, pill counts and possibly urine tests for RIF/RFB should be done regularly.

III.B First line anti-TB drugs

Isoniazid (INH) is the most potent bactericidal drug that acts on metabolically active bacilli. Rifampin (RIF) is also bactericidal with an additional potent sterilizing effect on the so-called 'persisters'. Together they form the cornerstone of anti-tuberculosis treatment. Without a rifamycin, an anti-TB regimen comprising INH, pyrazinamide (PZA) and streptomycin (SM) is not as effective and its duration will have to be prolonged to beyond 9 months. This has been studied only in HIV-negative patients, though.¹⁶ It is only prudent that in HIV-related TB, ethambutol (EMB) should be added in the initial phase.¹⁷

III.C The standard anti-TB regimen

In HIV infection, the standard regimen is one containing INH and a rifamycin for at least 6 months. PZA and EMB/SM are added in initial phase. At the end of 2 months, response should be thoroughly assessed. Delayed culture conversion and resolution of signs and symptoms call for evaluation of drug resistance, malabsorption, interaction. Consideration is given to prolongation and/or drug substitution. For extrapulmonary TB, including bone and joint TB, a minimum of 9 months is required. For CNS involvement, treatment is prolonged to 12 months. The dosage of first line anti-TB drugs is in Box 5.4.

III.D Monitoring of TB treatment

Reactions to anti-TB drugs are more common with HIV positive individuals in whom life threatening adverse events may occur (Box 5.5). Careful clinical monitoring is called for. Pretreatment assessment by liver function tests, HBsAg status¹⁸ and visual acuity (with EMB) is indicated. Pyridoxine supplementation is necessary with INH to prevent peripheral neuropathy. Desensitization and/or rechallenge in the event of sensitivity or toxicity are complicated and are best dealt with by an expert in this field.

Box 5.4 Dosage of first line ant-TB drugs*

Drug	Daily dose	tiw dose
INH	5 (300 mg)	15 (900 mg)
RIF	10 (600 mg)	10 (600 mg)
RFB	5 (300 mg)	Unknown
PZA	15-30 (2.0 g)	50-70 (2.5 g)
EMB	15-25 (1600 mg)	25-30 (2000 mg)
SM	15 (1 g)	25-30 (1.5 g)

**Dosage of common antituberculosis drugs in mg/kg, maximum dose in ()*

Box 5.5 Adverse reactions to the main antituberculosis drugs

Isoniazid	Hepatitis, cutaneous hypersensitivity, peripheral neuropathy
Rifampin	Hepatitis, cutaneous reactions, gastrointestinal reactions, thrombocytopenic purpura, febrile reactions, 'flu' syndrome
Rifabutin	Skin discoloration, uveitis, arthralgia, leukopenia
Pyrazinamide	Anorexia, nausea, flushing, hepatitis, arthralgia, hyperuricemia, cutaneous hypersensitivity
Ethambutol	Retrobulbar neuritis, arthralgia

Aside from adverse reactions to anti-TB drugs, the patient should also be monitored for drug compliance and for possible treatment failure with frequent clinical examinations, visual tests, blood count, liver function tests, chest radiography, urine tests for rifamycin, or abdominal sonogram depending on the drugs used. In CNS TB, repeat CT scan and/or LP may be indicated to document resolution.

III.E Paradoxical reaction

After initial clinical improvement, paradoxical worsening of disease develops in up to 36% of patients treated with concurrent anti-tuberculosis and potent anti-retroviral therapy (ART), about 2 weeks after the initiation of ART. The reaction is characterized by fever, worsening chest infiltrates on radiography, and peripheral and mediastinal lymphadenopathy.¹⁹ In contrast, the paradoxical reaction occurs in only 7% of those not treated with antiretrovirals. Such reactions, albeit florid at times, never revert a patient from smear- or culture-negative status to positivity. Furthermore the paradoxical reaction is a diagnosis of exclusion. The physician needs to rule out other possibilities such as drug fever, treatment failure, drug resistance, and other opportunistic infections. Almost invariably a paradoxical reaction is associated with a concurrent drop of viral load and a temporal relationship with ART in HIV-infected persons. At times systemic steroids might be needed for control of the paradoxical reaction.

III.F Non-rifamycin TB treatment

The optimum TB treatment is one containing a rifamycin. A non-rifamycin anti-TB regimen is called for when:

- (a) ART incompatible with RFB and RIF is needed for control HIV, or
- (b) there is primary rifampin resistance (N.B. only one third of rifampin-resistant TB remains susceptible to RFB).

A non-rifamycin regimen, if chosen, should ideally include an injectable agent such as streptomycin, amikacin and kanamycin. There is some evidence in support of a 9-month non-rifamycin regimen that contains an injectable agent. However, since the level of primary resistance to streptomycin is relatively high in Hong Kong, this must be excluded if streptomycin is employed. Without a rifamycin and an injectable, the duration of treatment may have to be extended to 18 months. Expert advice need to be sought on the optimum therapy especially if sensitivity results are not favorable or available.

IV. Drug-drug interaction in concurrent TB and HIV treatment

IV.A Cytochrome P450

Since RIF strongly induces the CYP 3A component of cytochrome P450, it increases clearance of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Conversely many PIs and NNRTIs are either inhibitors or inducers of the enzyme, thus affecting the level of rifamycins. The concurrent use of RIF with NNRTI or PI will have to be carefully monitored, if not contraindicated. Similarly, RIF reduces the concentration of fluconazole and itraconazole, and ketoconazole can inhibit the absorption of RIF.

IV.B Rifampin-containing regimen

In the presence of PI or NNRTI, rifampin is generally avoided because of complex drug interactions. On a theoretical basis, a limited number of PI and NNRTI may be attempted with RIF (Box 5.6). In this situation, it is important that adverse effects be very carefully monitored. RIF is contraindicated with delavirdine, amprenavir, indinavir, nelfinavir, and hard-gel saquinavir (except in combination with RTV). In practice, the use of a RIF-based regimen in HIV-related TB is restricted to where (a) the ART does not contain a PI or NNRTI, e.g. the AZT/3TC/ABC combination, and (b) rarely, antiretrovirals are not indicated yet.

IV.C Rifabutin-containing regimen

Rifabutin (RFB), another rifamycin, has substantially less activity as an enzyme inducer. Its efficacy against mTB has been fairly well established in a few comparison trials against RIF.^{20,21} RFB in reduced dosage can be used together with nelfinavir (NFV) indinavir (IDV), soft-gel saquinavir (SGC-SQV), amprenavir (APV), and ritonavir (RTV). Normal-dose RFB (300 mg qd) may be used with soft-gel saquinavir (SGC-SQV) and nevirapine (NVP). With efavirenz (EFV), RFB will have to be increased to 450 mg qd. The role of another rifamycin,

Box 5.6 Dosage adjustment of RIF in combination with some ART (in mg) ²²				
	NVP	EFV	RTV/SQV combination	RTV
RIF in mg	600 qd+ 200 bid	600 qd+ 600 qd	600 qd+ 400/400 bid	600 qd+ 600 bid

rifapentine, is limited owing to its stronger capability of enzyme induction than RFB. Dosage modification of RFB in the company of ART is as follows (Box 5.7).

Box 5.7 Dosage adjustment of RFB in combination with ART (in mg)

	NVP	EFV	SGC-SQV	APV	IDV	NFV	RTV
RFB qd in mg	300 qd+	450 qd+	300 qd+	150 qd+	150 qd+	150 qd+	Daily RFB
Daily regimen	200 bid	600 qd	1200 tid	1200 bid	1000 q8h, or 1200 q8h	750 tid, or 1000 tid, or 1250 bid	contra- indicated; 150 mg biw - tiw +600 bid

The following ART are generally contraindicated with RFB

- delavirdine
- Hard gel saquinavir (Invirase) alone, without ritonavir
- Dual PI, or PI/NNRTI combination (data insufficient)

When RFB is used with PIs and NNRTIs, a staggered initiation of treatment is justifiable in some patients where ART is not started until after the initial phase of anti-TB treatment is over. This enhances tolerance and adherence to treatment. It is noted that the recommended dosage adjustment is not perfect, and variability among individuals is expected. Therefore the physician should remain watchful against undue adverse effects due to RFB (e.g. uveitis, skin discoloration) or reduced potency of PI when they are given in combination.

IV.D Washout period for switching therapy

For those who are already on RIF and who are about to be switched to RFB so that a PI may be used, a washout period of 2 to 3 weeks is recommended after the discontinuation of RIF. In the meantime, RFB in full dosage i.e. 300 mg per day is given until the PI is started. Dosage of both RFB and ART may need to be adjusted.

Conversely if a PI is to be discontinued so that RIF can be started (in general, this is not recommended), 2 to 3 days of washout are allowed. The RIF is then started at half dose and increased to full dose after a week.

V. Resistant TB

Patients with drug resistant TB should be dealt with carefully. Although individual situations vary, the following are the major **principles** in management of resistant TB:

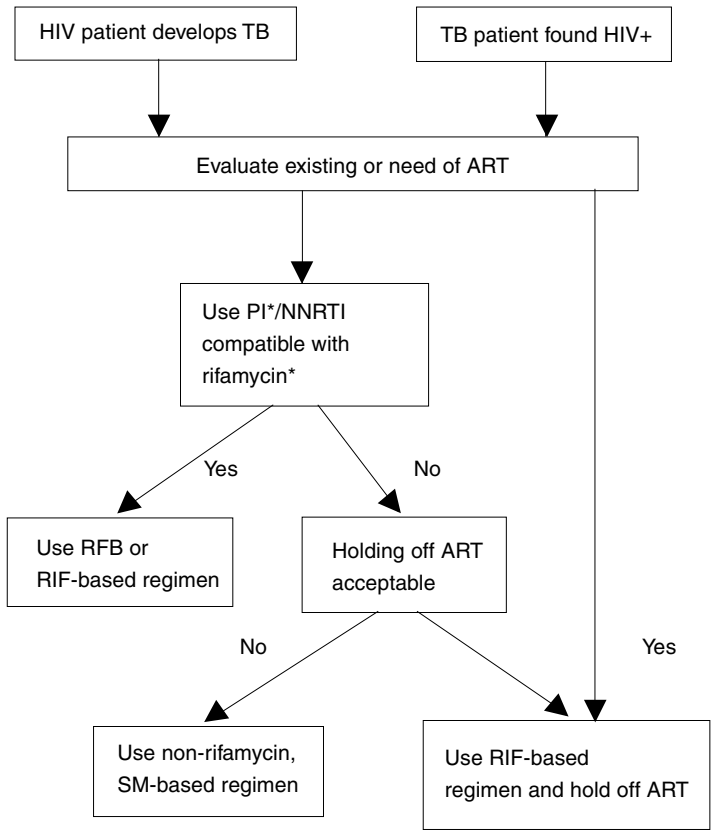
- (a) DOT is mandatory
- (b) A single drug is never added to a failing regimen
- (c) The drug regimen should include at least 24 drugs that are active in vitro

The following are examples of regimens for managing **monoresistant TB**:

- SM resistance – Use standard regimen
- INH resistance – RIF/RFB+PZA+EMB+SM for 2 m, then RIF/RFB+PZA+EMB for 10 months
- RIF resistance – Uncommon; watch out for MDR TB; use INH+PZA+EMB for 3-4 m, then INH+PZA+EMB for a total duration of 18 m; or 12 m after negative culture
- PZA resistance – sensitivity result may not be reliable; also watch out for *M. bovis* (naturally resistant); use RIF+INH+EMB for 2 m, then RIF+INH for 7 m

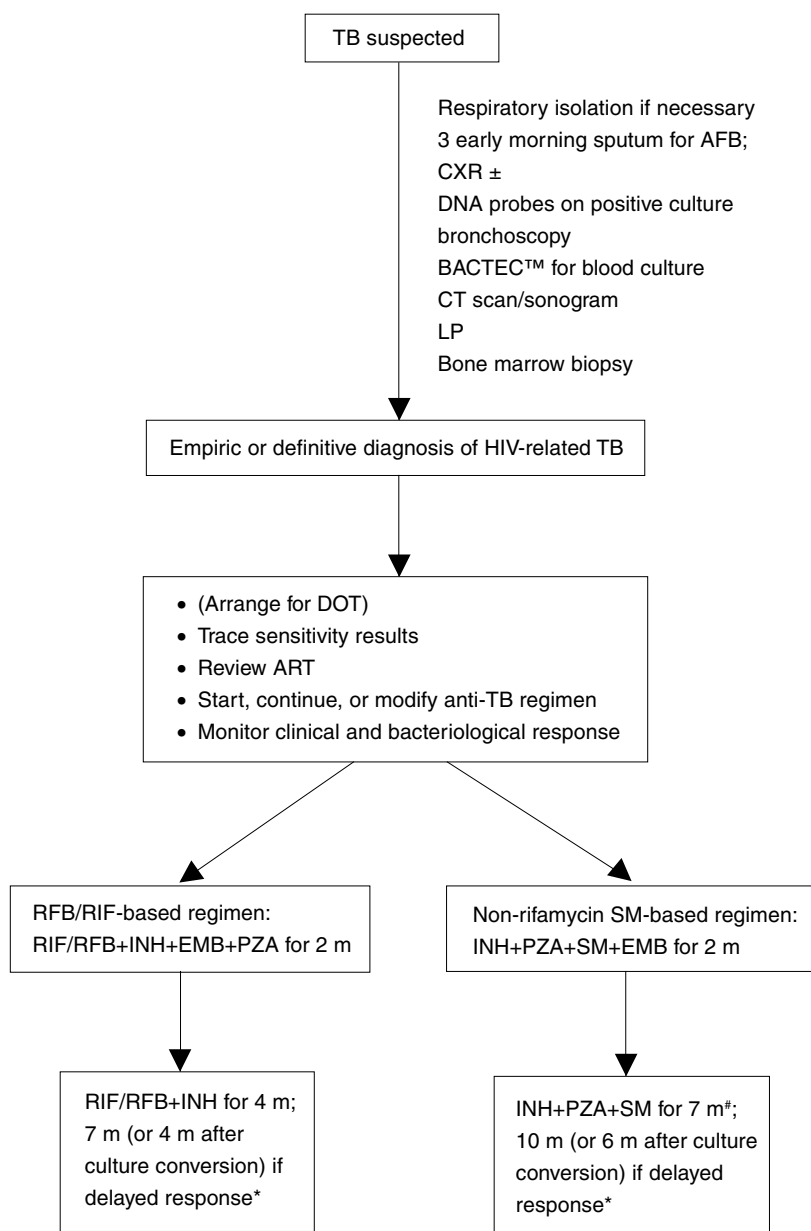
Multidrug resistant TB refer to those resistant to INH and RIF. Management is highly individualised and requires considerable expertise.

Algorithm 5.2A Management of concurrent ART and anti-TB treatment



**compatible PI and NNRTI are EFV, NVP, IDV, APV, and NFV;
RTV+SQV and SGC-SQV are theoretically also compatible
Delavirdine is contraindicated with RIF and RFB.*

Algorithm 5.2B Management of TB in HIV infection



**response is delayed when assessment at the end of the 2-month initial phase shows (a) lack of culture conversion, or (b) lack of resolution or progression of signs and symptoms of TB.*

#resistance to SM should be excluded; alternative non-SM 18-month regimen may have to be considered.

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5.3 ISONIAZID PROPHYLAXIS AGAINST TUBERCULOSIS

As T4 lymphocytes become depleted in HIV infection, the patients are put at risk of reactivation, reinfection and primary infection with TB. The chance of active TB in HIV increases from 5-10% over a person's lifetime to 8% per year.¹ It has also been shown that active TB upregulates HIV replication in vivo, probably by inducing macrophages to produce TNF-alpha, IL-1, and IL-6.²

In view of the high chance of developing TB in the lifetime of an HIV infected person, prevention has become an important strategy to reduce mortality and morbidity of TB in HIV/AIDS. Prevention can be considered from the perspectives of minimizing exposure, and reduction of active disease following tuberculosis infections. The treatment of latent TB infection offers an opportunity to minimize the harm carried by TB/HIV coinfection.

I. Rationale of using isoniazid (INH) to prevent active TB

INH is cheap and bactericidal against both extracellular and intracellular bacilli. In latent TB infection, the bacterial burden is small, allowing the possibility of monotherapy. Prior to the HIV epidemic, it had been shown in Alaska³ and Europe that INH monotherapy reduced active TB by 54-93%. The benefit increased with the duration of treatment up to 12 months. This protective effect lasted at least 19 years.

I.A Recommendations in the US

As early as 1990, the US CDC recommended IPT for 12 months in all HIV-infected persons with a positive tuberculin skin test (TST) as well as those who had recently been exposed to active TB.⁴ These recommendations were not widely adopted in Hong Kong because of the following concerns:

- (a) The data had largely been derived from studies of HIV-negative individuals
- (b) TB is endemic in Hong Kong, and the annual risk of TB infection is likely to be higher than low-prevalence areas
- (c) Primary INH resistance is relatively high at 6%
- (d) Universal BCG vaccination at birth and BCG revaccination among tuberculin-negative schoolchildren in Hong Kong might confound TST results

1.B New data on isoniazid preventive therapy (IPT) in HIV infection

In recent years, large randomized controlled trials in Haiti^{5,6} and some Sub-Saharan African countries^{7,8} have been completed, effectively addressing many of these concerns, as well as providing guidance on the proper use and limitations of IPT. In summary these studies showed that:

- (a) IPT for 6 to 12 months significantly reduced the risk of active TB in those who were TST positive.
- (b) Subjects with a CD4 count of over 200/ul derived greater benefit from INH.
- (c) The efficacy of multi-drug regimens using pyrazinamide (PZA) and rifampin (RIF) was similar to INH.
- (d) In one study, the efficacy of preventive therapy (PT) was time-limited, probably because of the high background incidence of TB.
- (e) There was no significant reduction on mortality.
- (f) In those who were anergic, IPT or its equivalents did not confer any benefit.

It has to be noted also that:

- (a) Two units of PPD-RT 23 (the formulation used in Hong Kong) were used in at least two of these studies.
- (b) BCG scars were present in 47% of subjects in Haiti, 75% in Kenya, and 80% in Zambia.
- (c) The cutoff value used in TST was 5 mm in all.
- (d) Compared to Hong Kong, these countries have greater incidence and prevalence of TB and probably have a higher rate of primary INH monoresistance.
- (e) There was no association between the booster phenomenon and BCG scar in the study in Uganda.⁹

In view of the research findings, it is apparent that IPT or its equivalents should potentially be useful in Hong Kong as it is in Africa or US in reducing the incidence of active TB in HIV-infected individuals, at least in the short term. In a policy statement, WHO and UNAIDS expressed that 'there can therefore no longer be any doubt that treatment of PPD+ [HIV infected] individuals living in a setting with a high prevalence of TB with isoniazid will reduce the risk of developing active TB in the short term to around 40%', and 'IPT should be part of the package of care available to PLWH [people living with HIV/AIDS]'.¹⁰

It must be noted that the efficacy of IPT is never 100%. Re-infection is also a genuine possibility with the passage of time. Therefore it is necessary to maintain a high index of suspicion of TB whenever the clinical presentation is compatible, regardless of whether IPT has been given.

II. Use and interpretation of TST

II.A TST interpretation

TST is a tool for detecting latent and active TB. Its cutoff value depends on the purpose of testing and the population tested. In relation to the use of IPT in HIV infection, the cutoff value of 5 mm is recommended as IPT initiated according to this interpretation had led to significant protection from active TB, in places with or without a high incidence of TB and with or without routine BCG vaccination. According to this interpretation, approximately 17% of the local HIV infected population will test positive.¹¹

A positive TST indicates active or latent TB. New conversion to TST positivity from a prior negative reading denotes a boosted phenomenon, new TB infection, or improvement of cell mediated immune function. Regardless, active TB should be ruled out.

Since most trials of IPT have involved only adults, and the possibility exists that false positive TST could result from BCG given in infancy and/or in primary school in children, regular TST followed by IPT when indicated should be limited to HIV-infected adults at present, until more information is available for the proper interpretation of TST in BCG-vaccinated children.

II.B Administration of TST

In Hong Kong, all adult HIV positive patients who have not been treated for active TB or received preventive therapy should be screened with tuberculin sensitivity test using 2 units of PPD-RT23. PPD is injected intradermally on the volar aspect of the forearm and the transverse diameter of induration read 48 to 72 hours later. A reading of 5 mm or above is considered positive. Testing with anergy panel is no longer appropriate as no benefit can be demonstrated with IPT in those who are anergic.¹² If TST is positive, active TB has to be ruled out by CXR and by noting compatible signs and symptoms. Sputum smears for AFB and mycobacterial cultures may be necessary.

III. Standard and alternative drug regimens

III.A The standard regimen

Although various combinations of anti-TB drugs have been shown to work in preventive therapy, isoniazid remains the standard to compare with. The level of primary INH resistance in Hong Kong is not significantly different from that in the US, and there is no reason why IPT should not be as effective in this locality.

In the Bethel study,⁶ no additional benefit can be derived from isoniazid given for more than 12 months. Besides the same level of benefit extended to individuals 70% compliant with treatment. As preventive therapy, it is therefore recommended that isoniazid should be given for at least 9 months. In practice, **a minimum of 270 doses taken within 12 months** will indicate sufficient treatment. To enhance adherence, detailed counseling on the rationale of IPT should be given.

Currently there exist no data regarding the use of continuous or intermittent courses of IPT. Theoretically such treatment might be useful in an endemic population, but the balance against added toxicity, bacterial resistance and cost is unknown.

III.B Indications and contraindications

The criteria for initiating IPT are:

- (a) TST positive, with
- (b) No evidence of active TB; and
- (c) Low suspicion of infection with INH or multi-resistant TB (consider alternative regimens); and
- (d) The absence of contraindication to isoniazid (consider alternative regimens)

The contraindications to IPT are:

- (a) Previous treatment of TB or preventive therapy (IPT may be repeated in those who are recent household contacts of infectious TB patients)
- (b) Previous INH adverse reaction (alternative regimens to be considered)

Seropositive individuals who have had close household contact with active TB should be worked up for possible active TB, regardless of the results of a PPD test. Most authorities would agree to IPT in such circumstance, but it should be evaluated on a case-by-case basis, especially in regard to the extent of exposure. IPT is not indicated after treatment of TB, as treatment theoretically should have eliminated latent TB as well.

III.C Adverse effects of IPT

INH as preventive therapy has an acceptable safety record.¹³ Two major adverse effects are peripheral neuropathy and hepatitis.

To prevent **peripheral neuropathy**, concomitant pyridoxine at 25-50 mg qd is advisable for prevention. Although it is probable that INH-induced **hepatitis** is rarer than originally thought, it is still necessary to watch out for signs and symptoms of hepatitis and monitor with liver function tests.

III.D Alternative preventive therapy

PT with drugs other than INH have a role in circumstances where infection with INH resistant TB is suspected, prolonged therapy is inappropriate, or there is contraindication to INH. Regimens that have been evaluated include:

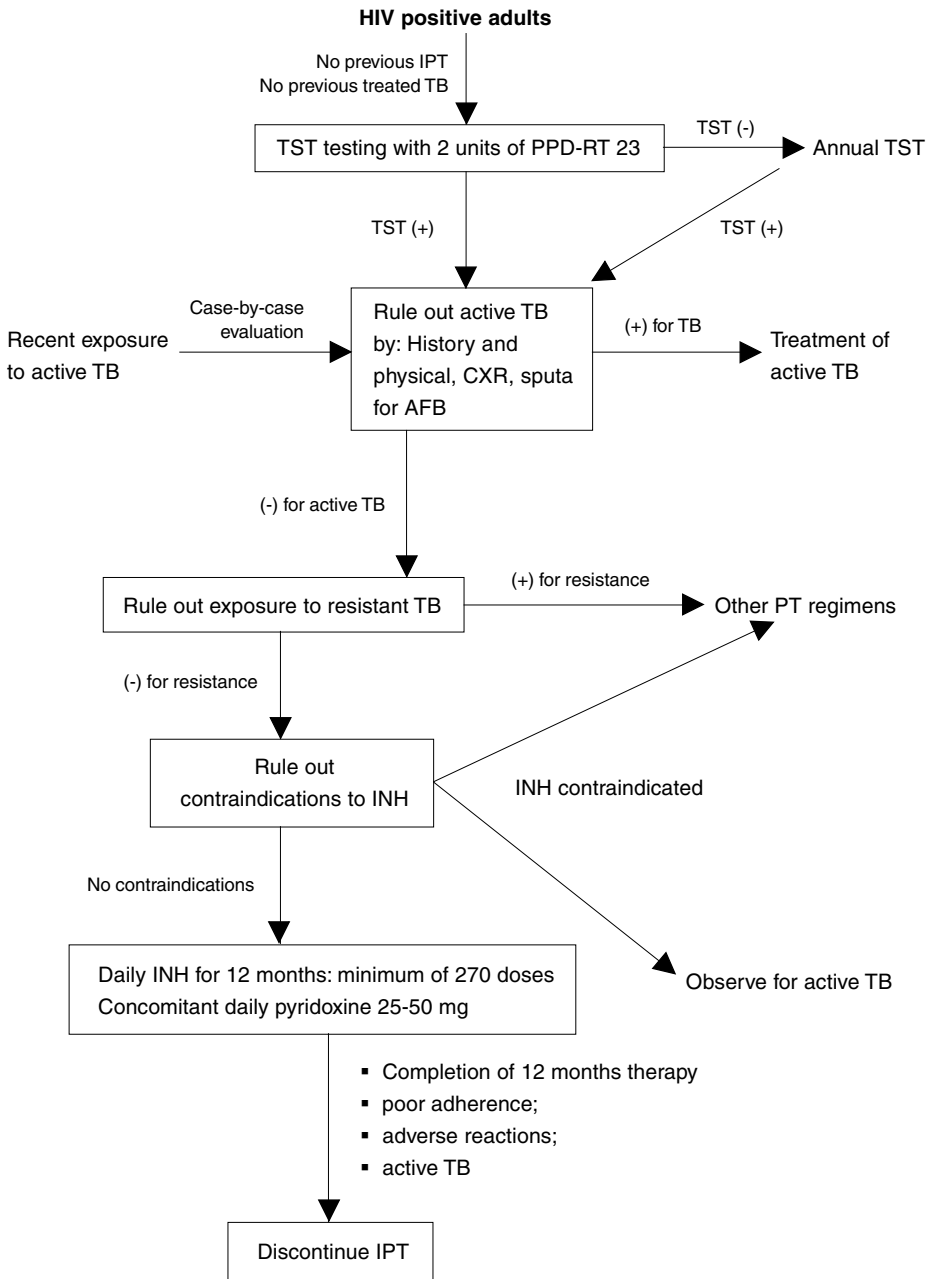
- (a) Rifampin (RIF) 600 mg + pyrazinamide (PZA) 20 mg/kg qd for two months (equivalent to 12 months of INH 300 mg qd)¹⁴
- (b) RIF 450-600 mg + PZA 1500-2500 mg twice weekly for 2 months (equivalent to 6 months of twice weekly INH at 600-800 mg)⁶
- (c) RIF 600 mg + PZA 3500 mg twice a week for three months (equivalent to 6 months of twice weekly INH at 900 mg)⁸
- (d) INH 300 mg + RIF 600 mg qd for 3 months (may be equivalent to 6 months of INH at 300 mg qd)¹⁵

In general these alternative regimens are comparable in efficacy. The disadvantages are increased cost, pill burden and potential drug-drug interaction. None of these regimens have been tested in HIV-negative individuals. For those on protease inhibitors or nonnucleoside reverse transcriptase inhibitors, rifabutin may be considered in place of RIF to avoid drug interaction. Reports of fatal liver injuries associated with the 2-month RIF-PZA regimen in the treatment of latent TB in HIV negative individuals had prompted CDC and American Thoracic Society to revise their previous recommendations. It was proposed that the 9-month INH regimen is preferred while the 2-month RIF-PZA regimen should be used with caution, especially those with pre-existing liver diseases or alcoholism.¹⁶

III.E The case of multi-drug resistant TB

It is not known what is the best regimen for preventive therapy in those who are close contacts of infectious ***multi-drug (INH and RIF) resistant TB***. Some authorities recommend pyrazinamide + ethambutol or a quinolone (levofloxacin or ofloxacin) for 12 months.¹⁷

Algorithm 5.3 Use of Isoniazid preventive therapy in HIV infection



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5.4 *PENICILLIUM MARNEFFEI* INFECTION

I. Epidemiology of *Penicillium marneffe* infection

Penicillium marneffe is a dimorphic fungus that can cause systemic mycosis in human beings. While it can also affect immunocompetent persons, it is most frequently found in immunocompromised hosts, e.g. HIV-infected patients. As a result of the HIV epidemic, its prevalence has increased substantially in the past few years.¹

The distribution of *Penicillium* infection in the world varies remarkably. Thailand probably has the largest disease burden reported, contributed by its HIV explosion a few years back. Other endemic places in Asia include southern China, Hong Kong, Vietnam and Taiwan. The infection does not occur in Western countries per se, reported cases of which had history of travel to endemic places.

P. marneffe infection is a significant opportunistic infection in HIV-infected patients in endemic areas. It is the third most common opportunistic infections in Thailand, after tuberculosis and cryptococcosis.²

Disseminated *P. marneffe* infection is classified as an AIDS-defining illness (ADI) in Hong Kong.³ Its occurrence in AIDS patients has increased in recent years, with some 10% having penicilliosis as the primary ADI.⁴ It ranks behind only *Pneumocystis carinii* pneumonia and tuberculosis.

II. Clinical presentations and investigations

II.A Clinical presentation

Common presenting symptoms and signs of *P. marneffe* infection are fever, anemia, weight loss, and skin lesions – classically generalized skin papules with central umbilication.¹ Cervical/generalized lymphadenopathy and hepatomegaly are also common in our local patients. Most of them have a very low CD4 count, at a median of 34/ul. Thus penicilliosis should be suspected when an advanced HIV/AIDS patient presents with compatible features.

II.B Diagnosis

It has been shown that patients who were diagnosed and treated usually responded. On the contrary, people who were not diagnosed early or were treated late often died.⁵ Definitive diagnosis of *Penicillium* infection is made from culture of blood, bone marrow aspirate or other tissue specimens. Bone marrow biopsy gives a high yield. Skin biopsy and/or fine needle aspiration biopsy of lymph node are useful when lesions are present. Nevertheless, presumptive diagnosis can be made from microscopic examination, to assist prompt initiation of therapy in a compatible clinical setting.

Besides microbiological and histological investigations, there are serological ones. Detection of circulating galactomannan by Pastorex Aspergillus, a latex agglutination test, can be used to aid the diagnosis of penicilliosis.⁶ An ELISA-based test for detecting anti-Mp1p (a purified recombinant antigenic mannoprotein of *P. marneffe*) antibody can also be done.⁷ Ancillary investigations of complete blood count may detect anemia whereas liver function test may show raised alkaline phosphatase.

III. Treatment and maintenance with anti-fungal drugs

III.A Antifungals

Delay in treatment of penicilliosis should be avoided as this is associated with high morbidity and mortality. Amphotericin B of 0.5-0.8 mg/ kg/day should be given for 2-4 weeks, followed by itraconazole 200 mg bid for a total treatment period of 3 months. For patients with good treatment response, which is often the case, life-long maintenance with itraconazole 200 mg qd is recommended to minimize relapse of the disease.⁸

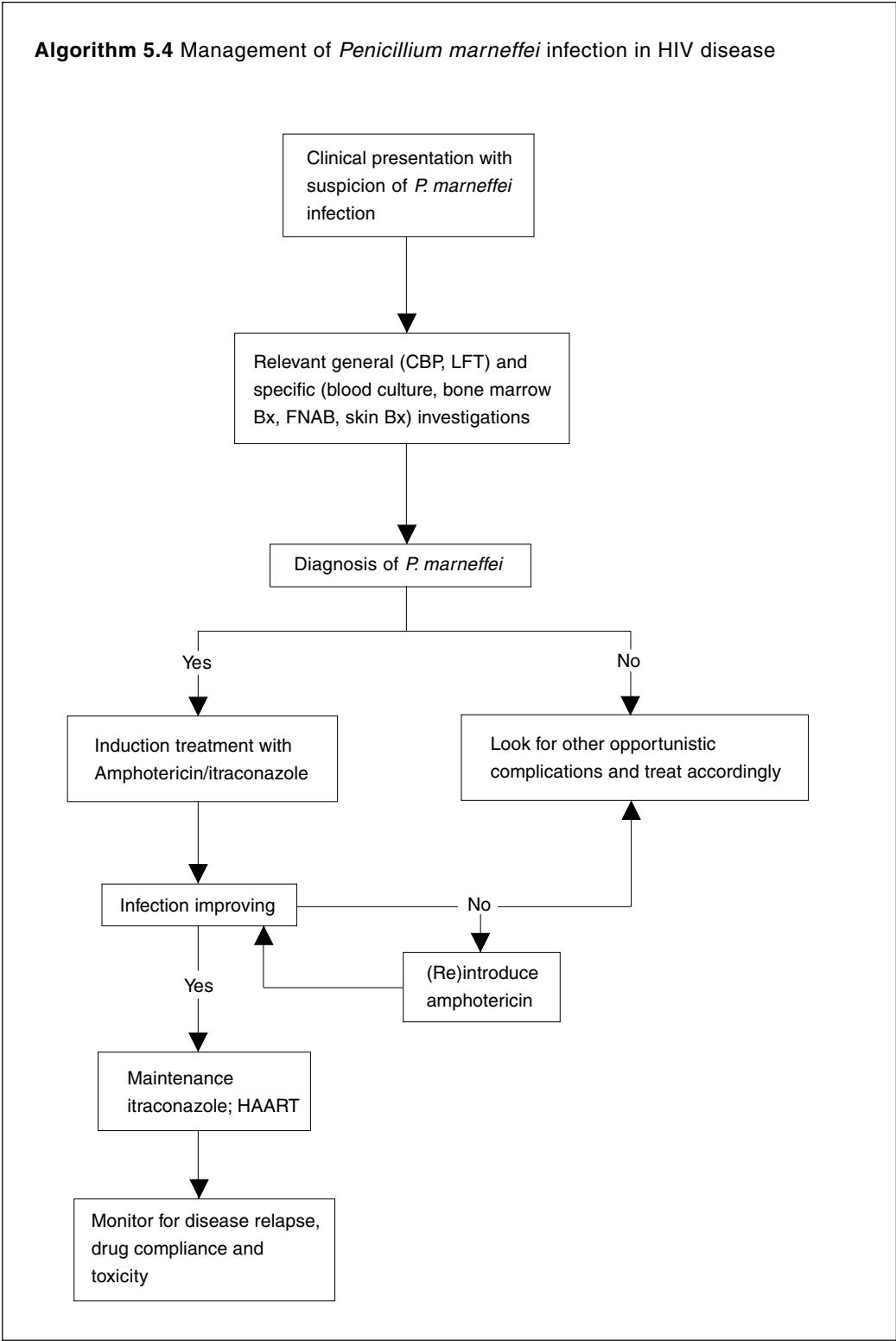
For mild to moderate cases, Amphotericin B may be omitted and itraconazole given from the start, as the efficacy may be equivalent.⁹ Fluconazole is not effective for treating *P. marneffe* both in vitro and clinically.

Treatment response should be monitored according to symptoms, signs and laboratory markers. The presenting signs and symptoms should improve shortly with effective treatment. Blood parameters, e.g. anemia and deranged liver function test shall improve gradually. Sterilization of blood should be confirmed with repeat of blood culture if it was positive beforehand.

III.B The impact of HAART

The patient should be evaluated for initiation or change of antiretroviral therapy. Drug compliance cannot be overemphasized. Unlike other common opportunistic infections internationally, no data are available regarding the impact of HAART on the incidence and relapse of *P. marneffei* infection and thus no recommendation is currently available in the literature. However, limited clinical experience suggested that maintenance therapy could probably be withheld in patients with no evidence of disease activity who had good CD4 and virologic response to HAART. Primary prophylaxis is not recommended for *P. marneffei* infection.

Algorithm 5.4 Management of *Penicillium marneffei* infection in HIV disease



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5.5 CMV RETINITIS AND OTHER DISEASES

I. Epidemiology and clinical course

Cytomegalovirus (CMV) disease is a common and potentially debilitating condition, occurring in 21-44% of AIDS patients in western countries before the era of highly active antiretroviral therapy (HAART). The most frequent presentation is retinitis which accounted for 75-85% of the diseases¹ while gastrointestinal (colitis, esophagitis), respiratory (pneumonitis), and neurological (encephalitis, polyradiculopathy) diseases can also occur. However, similar to most opportunistic infections occurring in HIV-infected patients, the incidence of CMV retinitis has come down after the institution of HAART.

Floaters, loss of visual fields, and blurring of vision are the commonest presentations of CMV retinitis, which mostly occur in patients with CD4 count <50-100/ul.² Without CMV-specific treatment the retinitis invariably progresses and it can lead to blindness.³ Blindness can result from macular involvement or retinal detachment that is caused by extensive peripheral retinitis.⁴

There have been reports of CMV retinitis presenting soon after the initiation of HAART, which may be due to the unmasking of subclinical CMV retinal infection by a HAART-induced immune inflammatory response.⁵ In addition, sight-threatening immune recovery vitritis has been described in HAART responders with inactive CMV retinitis.⁶

In Hong Kong, CMV diseases, primarily retinitis, contributed to some 5-6% of the primary AIDS-defining illnesses (ADI) and was the commonest subsequent ADI.⁷

II. Diagnosis of CMV retinitis

II.A High index of suspicion

Owing to the potential serious impact on vision, prompt diagnosis followed by treatment is essential, especially for patients with near macular involvement of the retinitis. Diagnosis of CMV diagnosis is a clinical one. Health care providers should be on the alert for symptoms and signs of CMV retinitis, more so if the patient has visual complaints or the CD4 count is <50-100/ul.

Primary prophylaxis against CMV is currently unavailable. All HIV-infected patients shall learn about the symptoms of CMV retinitis during their early visits and the need to inform

their health care providers should such symptoms arise. They are to be reminded again if their CD4 count falls below 50-100/ul. In this case, regular indirect ophthalmoscopy by an ophthalmologist shall be considered.⁸ Also, it is necessary to look out for "precipitation" of CMV retinitis after initiation of HAART in advanced HIV disease patients.

II.B Differential diagnosis

When CMV retinitis is suspected, urgent referral for ophthalmologist assessment and confirmation is warranted before initiating anti-CMV treatment. The objective is to primarily establish a baseline to monitor treatment and to exclude conditions such as herpetic retinal necrosis, toxoplasma retinochoroiditis, cryptococcal choroiditis, large cell lymphoma, candidiasis, syphilitic uveitis and *Pneumocystis carinii* choroiditis.

III. Treatment of CMV retinitis

Despite the threats associated with CMV disease, several effective drugs are available for its treatment and prevention of relapse. Also, the advent of HAART has modified the management (besides its natural history) of CMV disease in HIV-infected patients.

III.A Treatment goal

The objectives of managing CMV retinitis are to minimize its potential morbidity, mortality and impact to the quality of life (especially blindness/impaired vision) of the patient. This could be achieved through early diagnosis, timely treatment, appropriate maintenance therapy and monitoring for relapse of the disease.

III.B Treatment modalities

The benefit of drug treatment of CMV retinitis has to be balanced against its side effects and tolerance of patient. Standard treatment starts with induction therapy of anti-CMV drugs to halt progression and induce resolution of the retinitis. It aims at preserving vision and preventing complication of retinitis, in particular retinal detachment. Maintenance therapy generally follows to prevent further retinal necrosis, which can occur in 2-6 weeks if therapy is stopped.⁹

Based on the managing principles, care of each patient should be tailored according to his/her specific needs. Treatment regimen shall be discussed with the patient and chosen according to characteristics of the retinitis, patient's work and living conditions, family

support, concomitant drugs, and contraindications to each potential drug. The features of various anti-CMV drugs are listed (see Box 5.8). In general, **IV ganciclovir**, **IV foscarnet** and **IV cidofovir** are all appropriate initial choices for induction and maintenance therapy. However, cidofovir is a more convenient first line drug as it requires only weekly induction, followed by bi-weekly maintenance administration. This obviates the need of having long-term intravenous access as is the case with IV ganciclovir or foscarnet. If IV foscarnet is used for maintenance, the patient should have access to an infusion pump to avoid dangerous electrolyte disturbance.

Oral ganciclovir alone should not be used for induction treatment. However, it can be considered for maintenance therapy when other options are not feasible. And it should be considered only for cases with peripheral retinitis under regular ophthalmologic supervision. Those with single eyes should not rely on oral ganciclovir. The concern is the poor bioavailability of oral ganciclovir.

Treatment response to the anti-CMV drugs should be assessed by the ophthalmologist. A course of 2- to 3-week induction treatment shall be given until satisfactory response is noted. Maintenance therapy follows. Close monitoring for relapse of retinitis or involvement of the fellow eye (if not yet affected) by the ophthalmologist is a must. The sequelae of retinitis and impact on work and daily living activities of the patient shall be assessed. It is useful to maintain good communication with the ophthalmologist for joint management of patients with CMV retinitis. The nursing team can definitely help in clinical care, health counseling and psychological support of the patient. Medical social worker comes in for mobilization of community resources.

Ganciclovir implant is a useful alternative for those who cannot tolerate systemic treatment. By releasing a high local concentration of ganciclovir, it controls CMV retinitis with little toxicity. The drawbacks are:

- (a) Implantation may be complicated by retinal detachment, vitreous hemorrhage or infection,
- (b) The implant has a finite life of 6-8 months, requiring regular replacement, and
- (c) It offers no systemic protection against CMV.

III.C Relapsing/refractory retinitis

Prior to the era of HAART, almost all patients had relapse of CMV retinitis despite long term suppressive therapy. Others might have disease refractory to initial CMV treatment. Management of relapsing or refractory retinitis is difficult and should be individualized according to initial/previous response to therapy, concomitant medical conditions, characteristics of retinitis, immunologic and virologic status, and expertise of specialized treatment available. Adherence to maintenance therapy should be reassessed for relapsed cases.

Box 5.8 Commonly used anti-CMV drugs

Drug	Induction regimen	Maintenance regimen	Administration	Monitoring	Side effects	Precautions & contraindications
Cidofovir	5 mg/kg/wk	5 mg/kg every 2 weeks	cidofovir is given in 1 hour infusion; give 2 gram probenecid 3 hours before and 1 gram 2 and 8 hrs after cidofovir; give 1 liter NS before cidofovir	CBP with differential counts, serum creatinine and urine for protein within 2 days before cidofovir	nephrotoxicity, neutropenia, probenecid S/E (rash, fever, nausea, headache)	avoid nephrotoxic drugs; off cidofovir if 3+ proteinuria or creatinine rise by 44 umol/L
IV Ganciclovir	5 mg/kg q12 hours	5 mg/kg /day	infusion in one hour	wkly CBP, R/LFT for induction, 2-monthly for maintenance	neutropenia, thrombocytopenia, phlebitis	-
Foscarnet	90 mg/kg q12 hours	90-120 mg/kg/day, adjust with renal impairment	Controlled infusion using <24 mg/ml (undiluted) via central venous access or <12 mg/ml (diluted in 5% dextrose or saline) via peripheral line; infuse 0.5-1 liter of normal saline together with foscarnet	wkly CBP, R/LFT for induction, 2-monthly for maintenance	nephrotoxicity, hypocalcemia, hypomagnesaemia, penile ulcer, anemia	Avoid nephrotoxic drugs
Oral ganciclovir	avoid	one gram tid	with meals	same as IV ganciclovir	same as IV ganciclovir	-

For relapse while on IV ganciclovir or foscarnet maintenance, re-induce with the maintenance drug or switch to the other drug has similar efficacy.¹⁰ Re-induction with cidofovir is also effective for relapse on maintenance with IV ganciclovir, IV foscarnet or cidofovir maintenance.

Refractory disease during initial treatment or upon relapse with monotherapy requires combination therapy. Combination of IV ganciclovir and foscarnet has been shown to be superior to using either alone in treating relapse.⁹ In vitro data suggests synergistic inhibition of CMV when cidofovir is combined with ganciclovir or foscarnet.⁹ Ganciclovir ocular implant or intravitreal ganciclovir/foscarnet injection can be considered if expertise for such treatment is available. Either of these two treatments can be given alone or in supplementation to IV therapy.

III.D Discontinuation of maintenance therapy

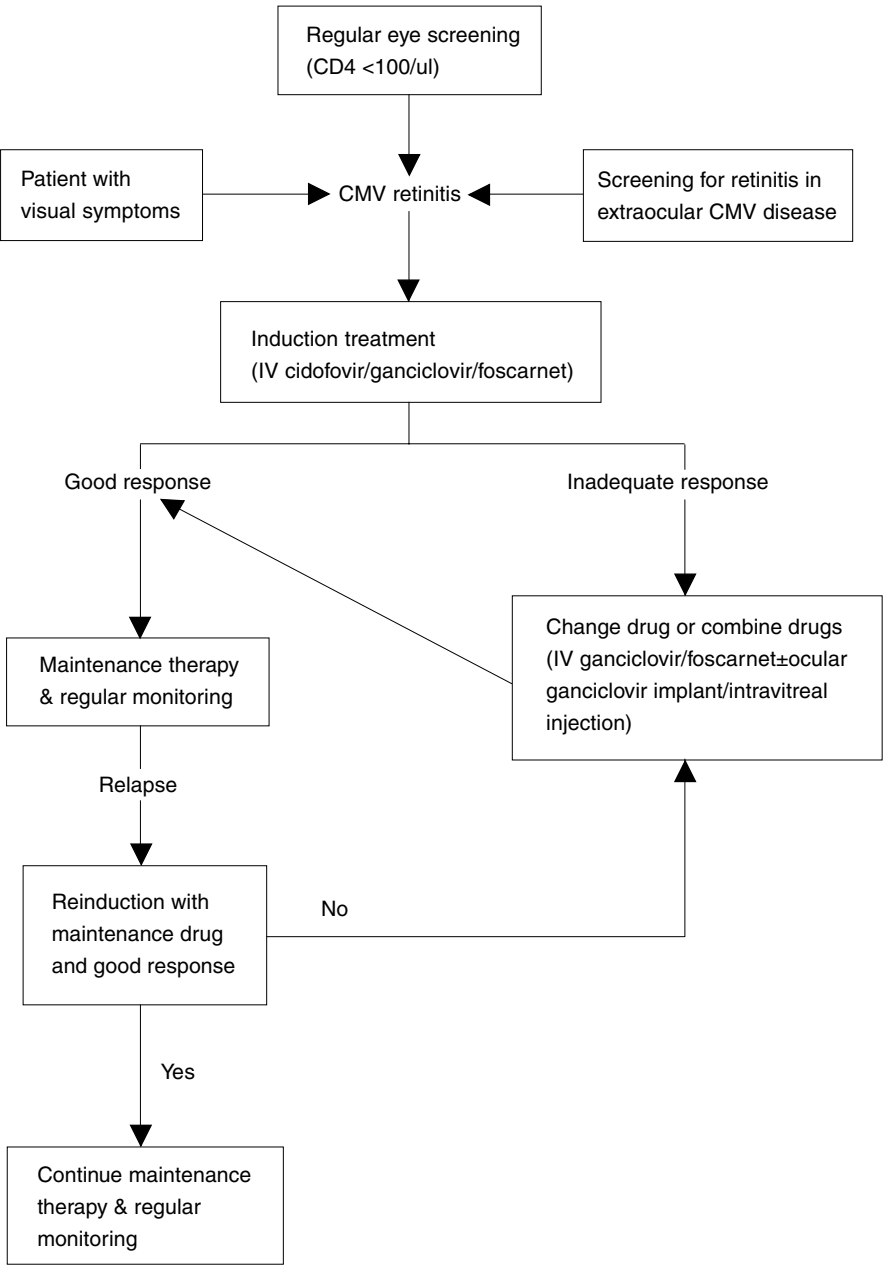
Evidence is strong that maintenance therapy can be stopped in patients who responded to HAART with good CD4 response (>100/ul).^{11,12} Withdrawal of maintenance therapy may thus be considered if all of the following criteria are met: (a) CD4 count >100-150/ul for 3-6 months, (a) vision adequate in contralateral eye, (c) undetectable plasma viral load for >3-6 months, (d) patient can attend regular ophthalmic examination.⁷ Of course, the CD4 and plasma viral load of the patients should be regularly monitored too. Risks and benefits of withdrawing secondary prophylaxis need to be explained to the patient. Some doctors may prefer a higher threshold of CD4, e.g. >200/ul for > 6 months, and an adequate vision (after treatment) of both eyes before withdrawing maintenance therapy.

IV. Other CMV diseases

CMV diseases of gastrointestinal tract, respiratory tract and central nervous system are to be suspected when clinical presentation is suggestive. Definitive diagnosis of end-organ CMV diseases is evidenced by the presence of CMV inclusion bodies and/or tissue damage in biopsy specimens. In these circumstances the risk of CMV retinitis is high and ophthalmologic assessment is indicated even when there are no visual symptoms.

Induction treatment with IV ganciclovir or foscarnet for 3-6 weeks is often indicated. A combination of the two drugs may be considered for CMV encephalitis or polyradiculopathy and in patients who have received prior anti-CMV therapy.¹³ Maintenance therapy is generally not necessary for non-retinal CMV diseases unless there is relapse.

Algorithm 5.5 Management of CMV retinitis



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5.6 MYCOBACTERIUM AVIUM-INTRACELLULARE COMPLEX (MAC) INFECTION

Mycobacterium avium-intracellulare complex (MAC) comprises two species, *Mycobacterium avium* and *Mycobacterium intracellulare*. They are environmental saprophytes found in soil, water and food. MAC causes four diseases:

- (a) **Disseminated MAC (dMAC)** occurs almost exclusively in AIDS. It is characterized by bacteremia, intracellular infection of numerous other tissues and a high total bacterial burden. Symptoms are persistent fever, night sweats, weight loss and diarrhea.
- (b) **"Reactivation" or "unmasked" MAC** is a new entity described after the advent of HAART for HIV infection. It is believed that HAART-induced immunologic improvement restores immunity to mycobacterial antigens and causes disease in those with subclinical infection. Localized lymphadenitis, sometimes with caseous discharge, is the most commonly described manifestation.¹
- (c) **Pulmonary MAC** is uncommon, found in immunocompetent individuals with underlying lung disease. HIV-infected patients develop MAC pneumonitis very rarely.
- (d) **MAC cervical lymphadenitis** occurs in the immunocompetent at 2 to 4 years of age.

On acquisition of MAC by an HIV-infected patient, a steady increase in the total bacterial burden occurs while the CD4 count drops. Progressively, colonization proceeds through localized infection to disseminated infection when blood culture turns positive.² Therefore although colonization of the respiratory and GI tracts is common in the early stage and predictive of disseminated MAC, it not diagnostic of such. Disseminated MAC, when properly diagnosed, is an independent predictor of mortality.

I. Chemoprophylaxis

Unlike chemoprophylaxis, avoidance of exposure is not practical as a prophylactic measure in HIV-infected persons. The US Public Health Service recommends a CD4 count of 50/uL as the threshold for chemoprophylaxis against MAC.

Prior to initiation of chemoprophylaxis, a clinical examination and a BACTEC blood culture are preferably performed to rule out subclinical MAC infection. Sputum and stool examination for AFB are not necessary.

I.A Monotherapy for prophylaxis

Rifabutin (RFB) has been shown to reduce the development of disseminated MAC infection by 55% over placebo. Other studies also established the efficacy of clarithromycin (CLR) and azithromycin (AZM) monotherapy (Box 5.9).

I.B Combination therapy for prophylaxis

A prospective, randomized, double-blind controlled trial⁷ has evaluated the efficacy of rifabutin + clarithromycin, and their respective monotherapy. It was found that the relative risk for MAC bacteremia was 0.56 for clarithromycin compared with rifabutin, and 0.43 for the combination compared with rifabutin. The difference between the combination and clarithromycin alone was not significant. This might be due to the fact that rifabutin lowered the concentration of clarithromycin. Furthermore, the combination was not well tolerated (8.5% developed uveitis) and there was no difference in survival (Box 5.10).

A similar trial⁸ evaluated azithromycin and rifabutin as chemoprophylaxis. The combination of both agents resulted in a lower level of MAC bacteremia than rifabutin alone (8.3 vs 23.3%) or azithromycin alone (8.3 vs 13.9%). Pairwise comparisons reported a relative risk for an MAC event of 0.53 for azithromycin compared with rifabutin, and 0.28 for the combination compared with rifabutin. However, the combination was not well tolerated. Furthermore, there was no difference in survival (Box 5.10).

Box 5.9 Summary of data from 3 randomized, double-blind, placebo-controlled studies investigating the efficacy of rifabutin, clarithromycin or azithromycin monotherapy in the prevention of disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection in patients with AIDS

Study	n	Median CD4	Followup (days)	Drug [n](mg)	Pt with DMAC (%)	RR in DMAC	RR in mortality (%)
Nightingale et al ³	1146	59	202	RFB [566] 300 qd	8.5 vs 17.6	55	26 ⁴
Pierce et al ⁵	682	30	270	CLR [333] 500 bid	5.7 vs 15.9	69	28
Oldfield et al ⁶	182	44	360	AZM [85] 1200 qwk	10.6 vs 26.9	59	ns*

RR = risk reduction; ns = not significant

*Although a survival benefit was shown only in RFB and CLR monotherapy, a similar benefit in the case of AZM was likely if the number of subjects in the study was larger or followup longer.

Box 5.10 Summary of data from comparative studies evaluating the efficacy of single agent therapy with that of combination therapy in the prevention of disseminated *Mycobacterium avium-intracellulare* complex (MAC) in patients with AIDS

Drug (mg)	n	Median CD4	Pt with dMAC (%)	Death (%)	Discontinuation (%)	Resistance in breakthrough(%)
ACTG 196/CPCRA 009⁶						
CLR 500 bid	398	27	9.0	42	15.8	29
RFB 450 qd, then 300 qd	391	30	15.1	43.0	18.2	2
CLR 500 bid + RFB 450 qd, then 300 qd	389	28	6.7	46.0	30.8	27
CCTG/MOPPS Study⁷						
AZM 1200 qwk	23	36	13.9	37.2	8.1	11
RFB 300 qd	223	38	23.3	38.1	8.1	0
AZM 1200 qwk + RFB 300 qd	218	45	8.3	37.2	9.2	0

1.C The preferred chemoprophylactic regimen

Either weekly azithromycin or twice daily clarithromycin is suited for the role of a chemoprophylactic agent. Rifabutin (300 mg qd) is best reserved for second line use when these two drugs are contraindicated or poorly tolerated. This strategy is in line with the recommendations of the US Public Health Service. The relative merits of the three agents are tabulated in Box 5.11. Azithromycin is often the preferred choice for its convenience, lower cost and fewer interactions with concomitant antiretroviral therapy. The dose of 1000 mg rather than 1200 mg per week has been employed in Hong Kong where azithromycin comes in 250-mg capsule formulation. Hitherto there has been no reported breakthrough disseminated MAC infection on this regimen after more than two years of use in HIV disease.

Although the addition of rifabutin to azithromycin confers added efficacy, it is poorly tolerated. Furthermore, the combination of rifabutin and clarithromycin has not proven superior to clarithromycin alone. Therefore, combination therapy cannot be recommended for routine chemoprophylaxis at the moment.

Box 5.11 Comparison of agents used for primary prophylaxis against MAC

	Clarithromycin	Azithromycin	Rifabutin
Efficacy	Good; 69% reduction	Good; 59% reduction	Good; 55% reduction
Drug interaction with PI and NNRTI	moderate	least	significant
Additional protection	Bacterial chest infections and giardiasis ³	Bacterial pneumonia, PCP, sinusitis ⁶	Probably mTB
Resistance in breakthrough	Significant	Less	Least
Adverse events	GI, taste perversion	GI	Uveitis, GI, thrombocytopenia, neutropenia
Convenience	Bid	Q week	Q day
Cost	Expensive	Less expensive	expensive

It must be noted that chemoprophylaxis has to be preceded by exclusion of disseminated MAC. This is accomplished by a careful clinical assessment and a BACTEC blood culture for mycobacteria. If rifabutin is considered, it is also important to rule out tuberculosis as there is extensive cross resistance with rifampin in the treatment of mTB.

If HAART has only been started recently, it is not unreasonable to wait 6 months before primary chemoprophylaxis against disseminated MAC is given. This allows time for the unmasking of subclinical MAC infection when MAC treatment rather than prophylaxis is more appropriately indicated.

1.D Resistance and breakthrough infection

The studies described above provided data on the emergence of resistance in breakthrough infection. Breakthroughs in those on clarithromycin, alone or in combination with rifabutin, seemed to be associated with a high rate of clarithromycin resistance. Azithromycin had less while rifabutin was associated with the least resistance. The development of clarithromycin resistance was also more likely if preventive therapy had been initiated at a lower CD4 count e.g. <20/mm³.⁹

II. Diagnosis

Disseminated MAC should be suspected when a patient with a CD4 count <100/uL presents with fever, night sweats, diarrhea, and/or weight loss. Patients often have intraabdominal lymphadenopathy, hepatosplenomegaly, anemia and an elevated alkaline phosphatase. Diagnosis is pursued by culturing in BACTEC blood, bone marrow, lymph node aspirate, liver or spleen tissues, followed by DNA probe if available.

As pulmonary MAC is rare in AIDS, AFB in a sputum smear and/or positive mycobacterial sputum culture should prompt one to consider pulmonary TB rather than MAC pneumonitis. Speciation by DNA probe is done on positive culture expeditiously if available. Similarly, recovery of MAC from stool, duodenal biopsies or aspirates should be correlated with the clinical picture as its presence might merely reflect colonization.

Finally, MAC isolation in sputum and/or stool alone is **not** disseminated MAC infection. MAC treatment is not indicated without symptoms. The role of prophylaxis in this situation is undefined.

III. Treatment of disseminated MAC

Combination treatment is the mainstay of therapy for disseminated MAC, involving the use of macrolides, rifabutin and ethambutol.

Macrolides – Clarithromycin monotherapy significantly reduced levels of MAC bacteraemia and led to clinical improvement at a dose of 500 mg twice daily. However, 46% developed in vitro resistance that was associated with a recrudescence of clinical symptoms and increase in bacteremia. Higher doses caused gastrointestinal side effects and poorer survival.¹⁰ Similarly, azithromycin (600 mg once daily) was effective in reducing MAC bacteraemia.¹¹ However, in a head-to-head comparison with clarithromycin, azithromycin was inferior (both drugs used in combination with ethambutol).¹² Clofazimine should probably not be used at all to treat MAC as it has been associated with reduced survival.¹³

Rifabutin (bactericidal) and **ethambutol** (bacteristatic) are also active against MAC. When combinations of either with a macrolide are used for treatment, not only are they clinically active,¹⁴ but the risk of resistance is reduced.^{15,16} ACTG 223¹⁷ compared three treatment regimens for disseminated MAC: clarithromycin + ethambutol, clarithromycin + rifabutin, and clarithromycin + ethambutol + rifabutin. It was shown that the 3-drug treatment had better clinical and bacteriologic outcomes, there being more bacteriologic clearance, increased patient survival and less resistance to clarithromycin. By inference, the addition of rifabutin to azithromycin + ethambutol may also be useful, as rifabutin does not reduce

azithromycin levels as it does clarithromycin. Nevertheless, any increased efficacy of a 3-drug regimen should be balanced against their relative intolerability.

Others – Amikacin and a quinolone (e.g. ciprofloxacin or levofloxacin) may be used for salvage therapy as they are active *in vitro*.

III.A Preferred regimen for the treatment of disseminated MAC

The role of resistance testing in designing an effective MAC treatment regimen is limited. Although clarithromycin resistance is known to be associated with poor outcome of treatment, resistance to other agents is less well studied. The extent of cross-resistance among the macrolides has not been fully evaluated either. Furthermore, even without demonstrable *in vitro* resistance, the bacteriologic response to all MAC regimens is 60 odd percent at its best. Thus the clinical progress is the best guide a physician has at the moment.

In a patient without prior chemoprophylaxis, the current standard treatment of dMAC is clarithromycin 500 mg bid (azithromycin 500 to 600 mg qd is the alternative) and ethambutol 15 mg/kg qd. If the CD4 count is very low (say below 20/mm³), and there is no contraindication, attempts are made to add rifabutin 300-450 mg qd. In principle, treatment is life long.

In the event of breakthrough infection, it is prudent that treatment regimens should take into account the chemoprophylactic agent previously used (see below).

III.B Treatment failure

Clinical improvement is anticipated within 4 to 6 weeks, which correlates with a decrease in mycobacteraemia. Sterilisation of blood cultures may take up to 12 weeks. If there is a good clinical response, regular monitoring of blood cultures is optional. In contrast, if no response is evident after 4 to 8 weeks, the patient should be reevaluated.¹⁸

By reason of a high bacterial load, MAC rapidly acquires resistance when treated with single drugs. Active disease therefore has to be treated with at least two drugs at all times. When a regimen is failing, at least two new drugs must be added or substituted. A salvage regimen is concocted from a limited armamentarium after a case-by-case evaluation. Amikacin or a quinolone (levofloxacin or ciprofloxacin), in addition to the first line drugs, may be considered.

HAART should have already been or is about to be started in a patient with such low CD4 count. Although interaction exists between the macrolides on the one hand, and protease inhibitors and NNRTIs on the other, no adjustment in dosage is necessary. This is in contrast to rifabutin which may be combined only with certain PIs and NNRTIs.

III.C Breakthrough infection

In the event that infection breaks through during primary prophylaxis, a thorough assessment has to be made regarding adherence, drug malabsorption and possible drug resistance.

- (a) Breakthrough with rifabutin prophylaxis – A macrolide and ethambutol shall be used. Rifabutin may be continued.
- (b) Breakthrough with azithromycin prophylaxis – Rifabutin and clarithromycin shall be used, or at least two drugs out of rifabutin, ethambutol, amikacin, and a quinolone.
- (c) Breakthrough with clarithromycin prophylaxis – At least two drugs shall be used, out of rifabutin, ethambutol, amikacin, and a quinolone. The continued use of CLR is not justified since resistance associated with a breakthrough is common.

The role of drug resistance testing, even if available, is unclear in guiding the design of salvage therapy.

IV. The influence of HAART

Highly active antiretroviral therapy (HAART) has significant impacts both on the manifestations and treatment of dMAC infection.

IV.A Unmasking of dMAC

HAART-induced immunologic improvement may be associated with the unmasking of subclinical MAC infection. Typically it occurs within 3 months of initiating HAART. Localized rather than disseminated MAC is more common.¹ For this reason, it is reasonable to delay primary prophylaxis in a patient about to be started on HAART, lest subclinical infection be inappropriately treated with one drug only. In practice one may indefinitely withhold prophylaxis if the CD4 count rises above 100/mm³ and the viral load becomes undetectable. However, if this is not achieved in 6 months, prophylaxis should be started.

IV.B Concomitant HAART

The concurrent use of HAART should be evaluated for either initiation or modification. Rifabutin is not "compatible" with the hard gel formulation of saquinavir, and delavirdine (not available in Hong Kong). Dose adjustment is indicated when combined with most other protease inhibitors(PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI)¹⁹ (Box 5.12). New data will continue to update the appropriate dose adjustments.

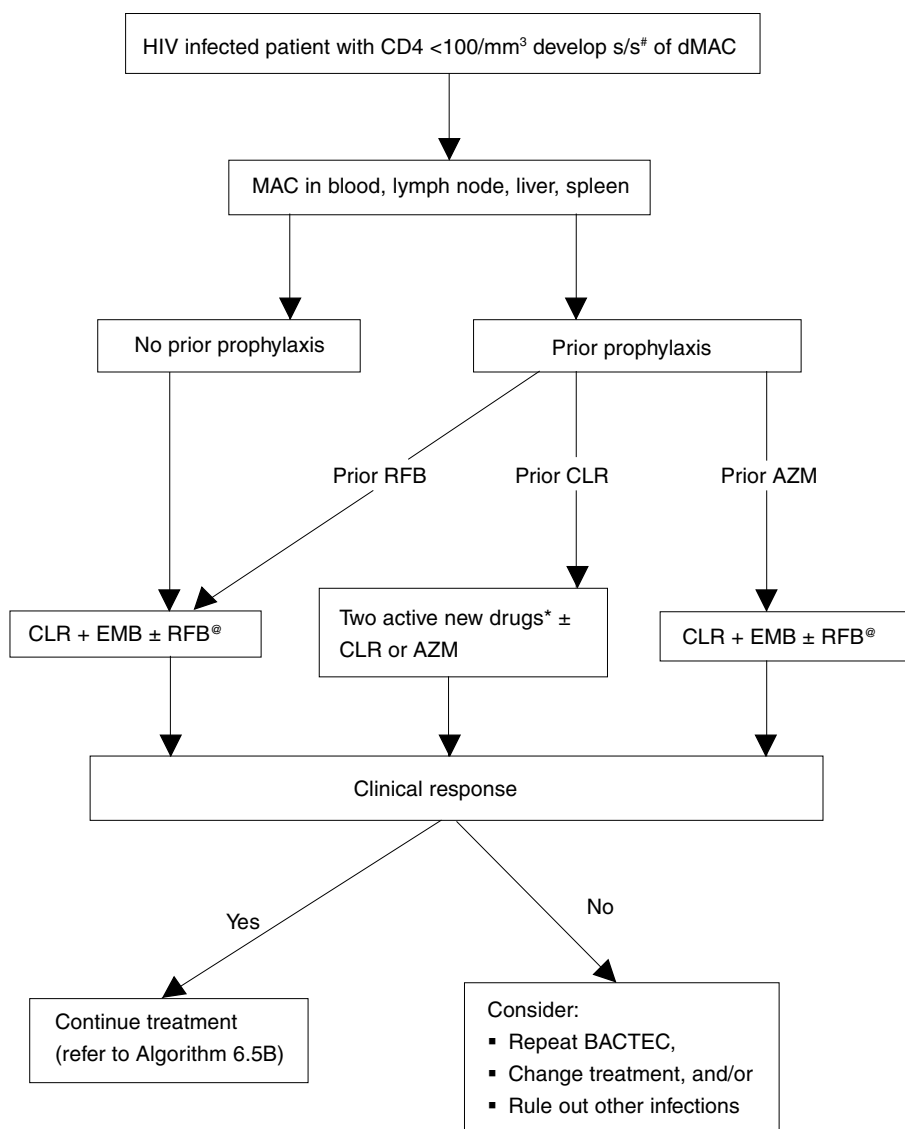
IV.C Stopping prophylaxis

Evidence is accumulating that discontinuation of primary MAC prophylaxis is justifiable upon good response to HAART, e.g. after CD4 count reaches and stabilizes at above 100/mm³ for more than 3 months,²⁰ and in the presence of an undetectable viral load.²¹ Primary prophylaxis should be re-introduced if CD4 count decreases to below 50/mm³.²¹

Prior to the era of HAART patients with disseminated MAC received life-long maintenance therapy. Yet, both ACTG 223 and the Canadian Randomized MAC Treatment Trial have demonstrated the favorable effect of potent ART on the treatment of disseminated MAC. The risk of MAC recurrence appears to be small after 12 months of MAC treatment if HAART has led to a sustained response of CD4 to >100/mm³ for at least six months, and patient is asymptomatic of MAC disease.²¹ It is not unreasonable to consider discontinuation of secondary prophylaxis in such patients but to reintroduce if CD4 falls below 100/uL.²¹

Box 5.12 Dosage of RFB in combination with ART (in mg)							
	NVP	EFV	RTV	SGC-SQV	APV	IDV	NFV
<i>RFB</i>	<i>300 qd +</i>	<i>450 qd +</i>	<i>150 2-3X</i>	<i>150 2-3X</i>	<i>150 qd +</i>	<i>150 qd +</i>	<i>150 qd+</i>
			<i>per wk +</i>	<i>per wk +</i>			
Daily ART regimen (in mg)	200 bid	600 qd	600 bd	1200 tds	1200 bid	1000 q8h, or 1200 q8h	750 tds, or 1000 tds, or 1250 bid
NVP = nevirapine; EFV = efavirenz; RTV = ritonavir; SGC-SQV = soft gel capsule of saquinavir, APV = amprenavir; IDV = indinavir; NFV = nelfinavir							

Algorithm 5.6A Diagnosis and treatment of dMAC infection

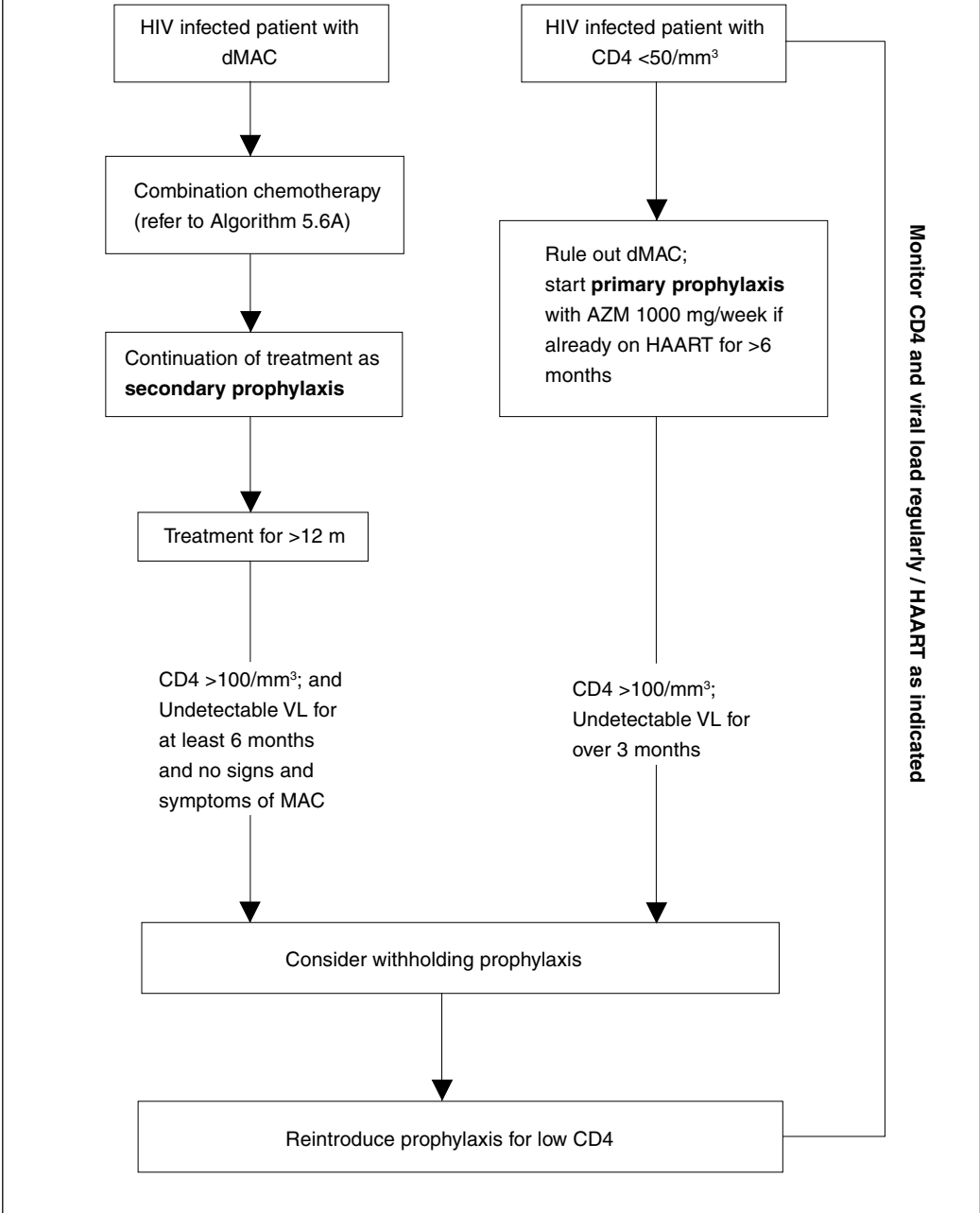


*weight loss, fever, fatigue, anemia, diarrhea

*Ethambutol, rifabutin, amikacin, a quinolone

®ritonavir, saquinavir and delavirdine are contraindicated for concomitant use; dose adjustment may be needed when used with other PIs and NNRTIs (Box 5.11)

Algorithm 5.6B Initiation of MAC chemoprophylaxis in HIV infection



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5.7 CRYPTOCOCCAL INFECTION

I. Epidemiology

Cryptococcus neoformans is a budding encapsulated solid yeast found ubiquitously in soil. There are four serotypes of *C. neoformans* divided into two groups: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gatti*. Clinical diseases seen in HIV/AIDS patients are mostly caused by *C. neoformans* var. *neoformans*, which is often serious and potentially life-threatening.

Though *C. neoformans* is also commonly found in pigeon feces, there is no evidence that exposure to pigeon droppings is associated with increased risk of cryptococcosis. It is believed that *C. neoformans* enters the human body via the respiratory tract. Elimination of *C. neoformans* is through cell-mediated immunity, with the participation of neutrophils, macrophages and cytotoxic T lymphocytes. In the face of immunodeficiency, control of the infection fails. The fungus may then disseminate to the central nervous system or other organs. However, the exact mechanism of dissemination remains unclear.

Cryptococcosis in HIV positive patients may manifest as symptomatic or asymptomatic pneumonia but the commonest presentation is meningitis. Overseas data showed that some 6-10% of AIDS patients would develop cryptococcal meningitis.^{1,2} In 3022 AIDS patients with extrapulmonary cryptococcosis, 80% had meningitis and their median survival was only 8.4 months.³ Cryptococcal meningitis has been the second commonest fungal primary AIDS-defining illness in Hong Kong, occurring in some 6% of the AIDS patients. Moreover, it was the most frequent neurological presentation of AIDS, developing at a median CD4 count of 43/uL.⁴

II. Clinical manifestations

Clinical presentation of cryptococcal meningitis can be subtle, with non-specific features of fever, malaise, mild headache and, sometimes, nausea and vomiting. Neck stiffness is an infrequent sign. Severe cases can have encephalopathic features such as personality change and confusion, which also carry a worsened prognosis.⁵ Dissemination of the infection is common in AIDS patients to e.g. liver and lymph nodes. Skin lesions resemble that of molluscum contagiosum.

Though cryptococcal meningitis carries a sinister prognosis and occurs mostly in patients with low CD4 count, routine antifungal prophylaxis for its prevention is not recommended. This is because of the lack of survival benefit with primary prophylaxis, potential for development of resistance, possibility of drug interactions and cost.⁶

II.A Diagnosis

Preliminary diagnosis of cryptococcal infection is made by identification of the **yeast** in a compatible clinical setting. Definitive diagnosis is confirmed by the **culture** of specimens, often the cerebrospinal fluid (CSF) or blood.

Serum cryptococcal antigen (CRAG) is an accurate and sensitive predictor of cryptococcal meningitis in advanced patients with fever. It has been shown that 98% of patients with culture-proven cryptococcal meningitis has a positive serum CRAG.² A positive titer >1:8 should be taken as a presumptive diagnosis of cryptococcal meningitis. Blood culture may also be positive in case of systemic infection.

Lumbar puncture for CSF examination is indicated when the clinical picture suggests cryptococcal meningitis. Before that CT scan must be performed to rule out space-occupying lesion, especially when there are focal neurological signs or encephalopathic changes suggestive of raised intracranial pressure. Opening pressure of CSF is to be recorded as this is of prognostic significance. Encapsulated yeast in the CSF is looked for with the Indian ink stain. CRAG and fungal culture results of CSF are useful for confirming the diagnosis subsequently.

CSF examination is important for both diagnosis and for predicting prognosis of cryptococcal meningitis. Unlike HIV negative patients, cryptococcal meningitis in AIDS patients can have normal protein/sugar and no pleocytosis in up to half of the cases.⁷ In one study, Indian ink stain of CSF revealed the organisms in 75% of the HIV-infected patients while fungal culture was positive in 85%.⁸ CRAG in CSF is also useful for diagnosis. Several CSF parameters are associated with poor prognosis: a raised opening pressure, low white blood cell count, high antigen titer and more organisms.²

II.B Treatment of cryptococcal meningitis

The primary objectives of treating cryptococcal meningitis are relief of symptoms and signs, control of infection, decrease in early mortality, prevention of relapse and maintenance of patient's quality of life. Prompt treatment is especially important for patients with severe meningitis and poor prognostic factors. Treatment aims at bringing down the fungal burden in the CSF or blood to the point of sterile cultures.

Amphotericin B and **fluconazole** are the two drugs found to be most effective in treating AIDS-related cryptococcal meningitis.⁵ Flucytosine adds to the marrow toxicity of amphotericin B and such combination may not be well tolerated, especially in advanced disease.

High-dose amphotericin B, with or without 5-flucytosine, followed by fluconazole is the standard induction treatment for acute cryptococcal meningitis. Though the duration of intravenous amphotericin B induction treatment is arbitrary, it is generally given at dose of 0.5-0.7 mg/kg/day for 2 weeks, followed by consolidation therapy of fluconazole 200 mg bid for 8 weeks if response to treatment is good. The dose of fluconazole can then be halved to maintenance dose of 200 mg daily after 10 weeks of standard therapy with amphotericin B and fluconazole. It is customary to give amphotericin B for a longer period if response to treatment is unsatisfactory, say up to a total dose of 1000 mg. If necessary, itraconazole can be employed as the alternative for consolidation and maintenance therapy but it is presumably less effective than fluconazole.

For very mild disease with normal mental state, some authorities suggested that amphotericin B might be omitted and fluconazole given alone. Evidence for this approach is generally not adequate.

Response to acute antifungal treatment should be monitored against clinical, biochemical and microbiological parameters. Toxicity of drugs should also be monitored. For example, fluconazole inhibits cytochrome P450 hepatic enzymes, increasing levels of drugs such as rifabutin, terfenadine and cisapride. As a result, the risk of uveitis from rifabutin and cardiac arrhythmia from terfenadine and cisapride will be increased with concomitant fluconazole.

Complete blood picture, renal and liver function tests are done at intervals no less than twice per week during amphotericin B therapy. The treatment response is best gauged by clinical assessment and CSF findings. Therefore examination of CSF has to be repeated after 2-4 weeks of therapy. While serum CRAG should not be used to monitor progress and response of the infection, CSF CRAG titer can be useful for such purpose. The median time for sterilizing CSF is about 2 weeks for amphotericin B and more than 4 weeks for fluconazole.⁵ Likewise blood culture should be repeated to ensure sterilization if it was positive before treatment.

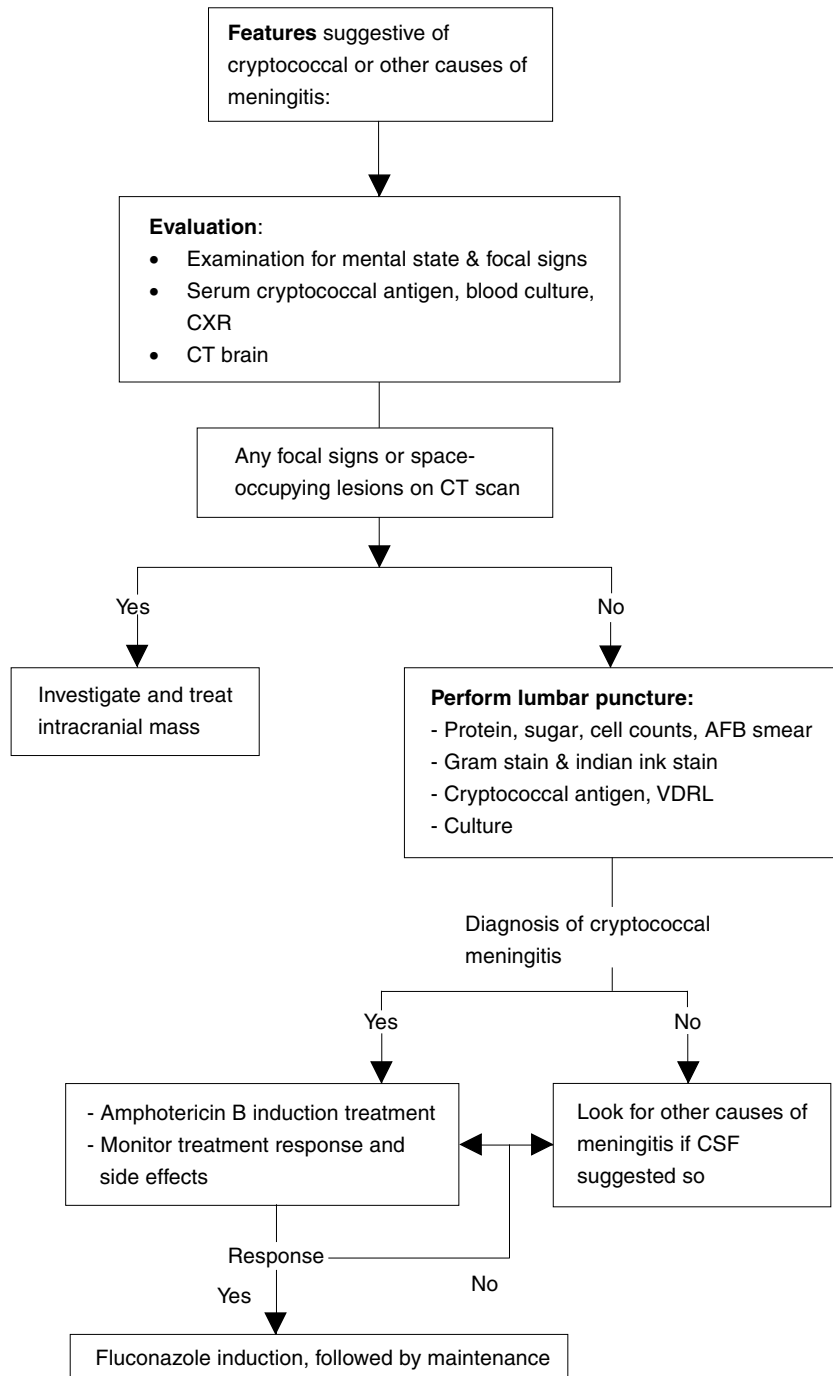
II.C Maintenance treatment

Chronic suppressive treatment for life is required after induction treatment of cryptococcal meningitis as relapse rates of 50-60%⁹ and shortened survival have been found for patients

not receiving such maintenance. Life-long suppressive therapy with fluconazole is thus indicated after acute treatment, which may be substituted by itraconazole if fluconazole is not tolerated. A higher than usual (1.5-2 times) dose of fluconazole might be needed for consolidation and maintenance in some difficult cases. Despite maintenance, relapse should be watched out for, especially in patients with persistent severe immunosuppression.

The impact of immune reconstitution in AIDS-related cryptococcal meningitis is unclear. Experience of discontinuing maintenance in this situation has been minimal and no recommendation can be made. Suffice to recap that cryptococcal meningitis can definitely be fatal, either at around time of acute diagnosis or for chronic refractory cases. Extreme caution has to be exercised and adequate treatment given for all cases to ensure control of the infection.

Algorithm 5.7 Management of cryptococcosis



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5.8 CANDIDIASIS

Candida organisms are ubiquitous in nature and can be isolated from soil, hospital environments and food. In HIV-positive patients, colonization in oral cavity and other mucosal surfaces is common, especially with *C. albicans*, at rates that increase with decreasing CD4 counts. Other underlying causes of candida disease in HIV infection¹ are decreased salivary flow and antimycotic factors such as IgA, lysozyme, lactoperoxidase and lactoferrin. Candidiasis is also associated with the use of oral contraceptives, chemotherapeutic regimens, corticosteroids and immune suppression related to pregnancy and diabetes. In HIV infection, these conditions may aggravate or precipitate candidiasis.

Mucosal candidiasis is common in HIV/AIDS. The incidence of oral candidiasis in HIV infection varies from 7 to 93%, depending on diagnostic criteria and study methods. In a review of local HIV-infected women, the prevalence of oral candidiasis was 9% and vaginal candidiasis 28%.² In another study of HIV-infected women, vulvovaginitis was the first as well as the commonest HIV-associated clinical condition.³ In the revised 1993 CDC case definition⁴ from which the Hong Kong Scientific Committee on AIDS adapted its own classification,⁵ vaginal candidiasis that was persistent, frequent or poorly responsive to therapy, as well as oral candidiasis, became a designated HIV-associated category B condition.

On the other hand, esophageal candidiasis is an AIDS-defining condition. It often occurs with a CD4 <200/ul and in conjunction with oral candidiasis.

Disseminated candidiasis is rare in AIDS. This is due to adequate neutrophil function in most HIV+ individuals. Candidemia usually occurs with other risk factors: neutropenia, parenteral nutrition, abdominal surgery, broad spectrum antibiotics, or corticosteroid use.

I. Antifungal therapy

The mainstay of treatment of candidiasis is the application of antifungals. Although a standard for antifungal sensitivity testing against *Candida* has been defined, its use in the clinical setting is still very limited. This implies that in the event of failure, treatment is usually changed without clear objective criteria. In general the options are increasing the dosage, changing to a new drug, or using combinations of drugs.

Since oral and vaginal candidiasis can occur in the presence of a relatively high CD4 count, the impact of highly active antiretroviral therapy (HAART) on their occurrence may

be less than that on esophageal candidiasis. Nevertheless, a higher CD4 count and a more competent CD4 repertoire should theoretically contribute to a more rapid cure with antifungals and possibly less resistance.

1.A The antifungals

Readily available antifungals in Hong Kong are nystatin suspension 10⁵u/ml, nystatin pessary, clotrimazole (Gyne-lotremin) pessary, talsutin pessary, tioconazole (Gyno-trosyd) pessary, ketoconazole, itraconazole, fluconazole and amphotericin B (IV and lozenge). The ***local agents*** are best used as first line agents for oral and vaginal candidiasis. ***Systemic therapy***, e.g. fluconazole, is reserved for second line therapy, advanced AIDS and esophageal candidiasis. Randomised trials have been conducted comparing all these agents but their optimal sequential use is still unknown. Among the systemic azoles, efficacy is highest with fluconazole and itraconazole solution. Ketoconazole is inferior, probably because of impaired absorption in advanced AIDS.⁶ The relative inefficacy of clotrimazole troches and nystatin suspension is partially offset by their low cost.

Despite years of use, resistance to amphotericin B is still rare. However the widespread use of systemic azoles in recent years has led to the emergence of primary and secondary resistance, especially in advanced AIDS.⁷

1.B Prophylaxis against candidiasis

Except in the case of maintenance therapy with esophageal candidiasis, prolonged primary prophylaxis is not advised, "because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant *Candida* organisms to develop, the possibility of drug interactions, and the cost of prophylaxis".⁸

1.C Drug interaction

While the systemic azoles could potentiate the hypoglycemic effect of sulfonylureas, their metabolism is increased by rifampicin, isoniazid and phenytoin. Ketoconazole and itraconazole are contraindicated with cisapride, terfenadine and astemizole for fear of ventricular arrhythmia. There is interaction with protease inhibitor but this is probably clinically insignificant. Fluconazole may increase the level of rifabutin leading to uveitis.

I.D Teratogenicity

Craniofacial and skeletal abnormalities have been reported following prolonged *in utero* exposure to fluconazole. Itraconazole is embryotoxic in animal systems. Consequently systemic azoles are contraindicated in pregnancy.

II. Oral candidiasis

Oral candidiasis is an independent prognostic factor of disease progression⁹ and *Pneumocystis carinii* pneumonia (PCP). Its presence is an indication for PCP prophylaxis.

II.A Clinical features

The symptoms of oral thrush are burning pain, altered taste sensation, and difficulty with swallowing. However, most patients are asymptomatic. There are 3 forms of disease on examination:

- (a) ***Pseudomembranous candidiasis*** is characterized by the presence of white or creamy plaques on the oral mucosa.
- (b) ***Erythematous candidiasis*** appears as a flat red lesion on the hard or soft palate, or the dorsal surface of the tongue resulting in a patchy depapillated surface.
- (c) ***Angular cheilitis*** appears as cracking, fissuring, or erythema at the corner of the mouth.

II.B Diagnosis

C. albicans is a common commensal of the skin and mucosal surface. Its identification therefore does not equate disease. Diagnosis of candidiasis is usually made on the grounds of clinical symptoms and physical examination. In atypical cases, microscopic examination of a KOH smear helps in making the differential diagnosis by showing hyphae and blastospores. Culture is not routinely indicated.

The major differential diagnoses of oral candidiasis are oral hairy leukoplakia and possibly Kaposi' sarcoma.

II.C Recurrences

There are 2 patterns of recurrences: those with the same strain of *C. albicans*, and those with a new species of *Candida* such as *C. (Torulopsis). glabrata*, *C. parapsilosis* and *C. krusei*. Species other than *C. albicans* are inherently less susceptible to therapy, and arise mainly with low CD4 count after repeated or prolonged antifungal treatment.

II.D Treatment

The following are the **first line** treatments:

- (a) Clotrimazole pessary qid for 7-10 days
- (b) Nystatin oral suspension 5 ml swish and swallow qid to 5x/day for 7-10 days
- (c) Systemic fluconazole (100 mg qd for 7-10 days or till thrush resolves; some authorities recommend a loading dose of 200 mg on Day 1) may be used in the event of low CD4 or recurrent disease.

With **treatment failure**, diagnosis is preferably documented by microscopy or culture and then managed by:

- (a) Increasing the fluconazole dosage, up to 800 mg per day,
- (b) IV amphotericin B \pm flucytosine, or
- (c) Combinations of treatment

III. Esophageal candidiasis

III.A Diagnosis

In a similar fashion to oral thrush, esophageal candidiasis may be presumptively diagnosed when typical symptoms occur in the presence of oral candidiasis. Typical symptoms are esophageal pain, odynophagia, mid-epigastric abdominal pain and fever. Upper endoscopy is warranted on treatment failure to identify adherent, whitish mucosal plaques and superficial mucosal ulcerations, and to differentiate from such lesions as (i) herpetic esophagitis, (ii) CMV esophagitis, (iii) aphthous ulceration, (iv) AZT- and ddC-induced ulceration, and (v) idiopathic or HIV esophagitis.

III.B Therapy

Systemic therapy is necessary for esophageal candidiasis in the form of fluconazole 200-400 mg qd for 2-3 weeks. An alternative is itraconazole 100-200 mg bid. Long term

suppressive therapy (secondary prophylaxis) with fluconazole 100-200 mg qd or itraconazole 200 mg qd is advisable.

Failure of symptoms to respond in 1 week should be followed by upper endoscopy to document the diagnosis, after which IV amphotericin B 0.3-0.5 mg/kg/day with or without flucytosine may be considered.

IV. Vaginal candidiasis

IV.A Clinical features

Patients may be asymptomatic or may complain of perivaginal pruritus or dysuria. A gynaecologic examination typically shows erythematous labia, shallow, linear ulcerations on the introitus and/or satellite papules beyond the main area of erythema. *Candida* discharge is classically thick and adherent.

IV.B Diagnosis

Diagnosis is often made clinically and treatment begun empirically. With atypical presentation or treatment failure, a KOH smear, a Gram stain or culture for vaginal candidiasis may be performed. The following table is useful to help distinguish vaginal thrush from trichomoniasis and bacterial vaginosis, the major differential diagnoses (Box 5.13).¹⁰

IV.C Treatment

The following specific treatments, in no particular order, are used as first line (adapted from Chan LY. Candidiasis. In: Handbook of Dermatology and Venereology 2nd ed. Hong Kong: Social Hygiene Service, Department of Health, 1997):

- (a) Clotrimazole 100 mg pessary at bedtime for 7 days
- (b) One nystatin pessary (10⁵u) at bedtime, for 14 days
- (c) Two isoconazole (Gyno-Travogen) vaginal tablets for once
- (d) One talsutin vaginal tablet nocte for 7-14 days

Aggravating factors such as diabetes, corticosteroid and contraceptive use should be ruled out or controlled as far as possible.

Recurrent infection can be a major problem. On ruling out other causes of chronic vaginitis, one may re-treat with the above regimens but with a longer duration.¹¹ Alternatively

Box 5.13 Differential diagnosis of vaginal candidiasis

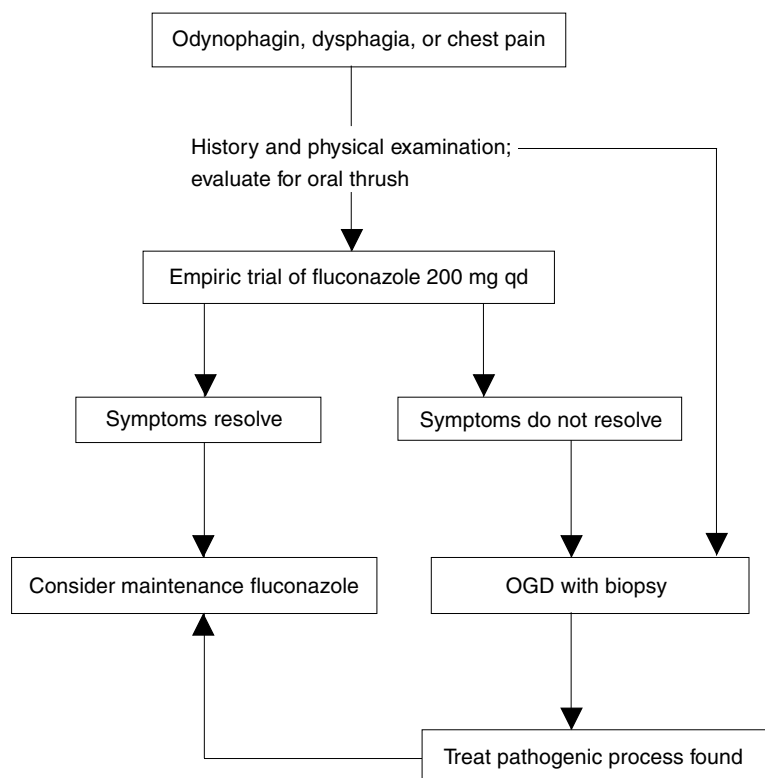
	Trichomoniasis	Candidiasis	Bacterial vaginosis
Sexual transmission	yes	very rarely	often
Symptoms			
Relation to menses	often postmenstrual	often postmenstrual	none
Vulvar irritation	mild to marked	mild to marked	absent to mild
Dysuria	internal and external	external	
Odor	sometimes	absent	fishy, amine-like
Signs			
labial erythema	variable	variable	no
Satellite lesions	no	yes	no
Vaginal tenderness	yes	yes	no
Adnexal tenderness	occasionally	no	no
Discharge			
Consistency	Frothy	Sometimes curdy	Homogenous, frothy
Color	yellow-green 25%	white	gray, white
Adherent to vaginal walls	no	yes	yes
pH	>4.7	<4.5	>4.7

one may consider the following oral regimens:

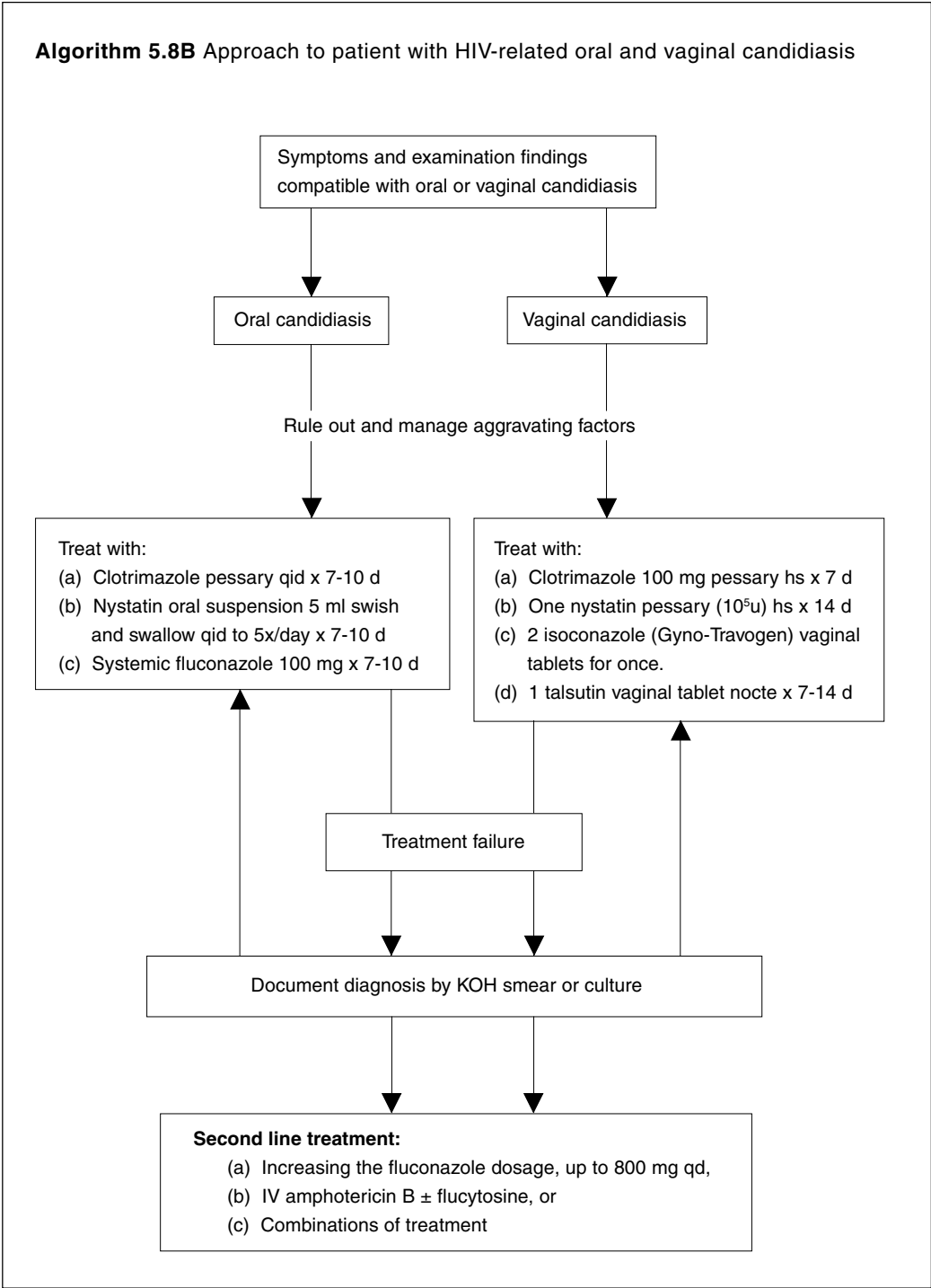
- (a) Single-dose fluconazole 150 mg (as effective as 7 days of intravaginal clotrimazole)¹²
- (b) Itraconazole 200 mg bid for 1 day (limited clinical data)
- (c) Itraconazole 200 mg qd for 3 days (limited clinical data)

Suppressive therapy with daily or weekly fluconazole is generally not advisable but may be considered in exceptional cases such as recurrent vulvovaginal candidiasis (RVVC), defined as 4 or more episodes of symptomatic vaginal candidiasis annually. The diagnosis should be confirmed by culture before such treatment. The sexual partner should also be examined for balanitis. The need for such maintenance treatment is reevaluated after 6 months.

Algorithm 5.8A Approach to patient with HIV-related esophageal disease



Algorithm 5.8B Approach to patient with HIV-related oral and vaginal candidiasis



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5.9 HERPES SIMPLEX AND ZOSTER

I. Herpes simplex and zoster viruses

Herpes simplex virus (HSV) is a DNA virus, belonging to the family Herpesviridae. Sequence homology between HSV types 1 and 2 is about 50%. Serologic assays of antibody are able to differentiate between the two by using type specific antigens, such as the gG1 and gG2 proteins. Infection with HSV involves the mucocutaneous surfaces and may extend to the central nervous system or viscera. Upon primary infection, the virus establishes latency in neuronal cells of ganglia. Especially in the first year after infection, reactivation is frequent. The mechanism of reactivation may be through alteration in viral proteins that are responsible for maintaining latency. UV light, trauma, immunosuppression and stress have been cited as factors causing reactivation. As cell-mediated immunity is essential to the containment of infection, it is understandable why HSV infection is particularly important in HIV disease.

Varicella-zoster virus (VZV) is also a herpesvirus. As such it shares structural characteristics with HSV. Furthermore, they cause similar histopathologic features, e.g. intranuclear inclusions and multinucleated giant cells. VZV causes two major syndromes: varicella (chickenpox) and zoster (shingles).

II. The relationship between HSV and HIV

In HIV disease, HSV infections carry important implications:

- (a) There is a 2 to 3 times increase in the risk of HIV acquisition in those with genital herpes. It has been demonstrated that HIV was consistently found in herpetic ulcers.¹ Concomitant HSV infection also upregulates HIV replication.
- (b) Patients with HIV may have more frequent, severe and prolonged episodes of recurrences of genital herpes. There is a higher rate of subclinical shedding of HSV in those seropositive for HIV, and especially in those with a low CD4 count.² HSV actually defines AIDS in the case of chronic ulcers of more than one month duration, bronchitis, pneumonitis or oesophagitis.³
- (c) Primary herpes serves as an indicator of high risk sexual behavior.

III. Epidemiology and risk of transmission of HSV

Traditionally, HSV-1 has been associated with orolabial herpes and HSV-2 with genital herpes. Although the distinction is not as clear nowadays, HSV-2 still remains largely a sexually transmitted disease. Its prevalence starts to increase during adolescence, and is higher in attendees of STD clinics, male homosexuals and women. In overseas studies, more than 80% of homosexual HIV infected patients have antibody to HSV-2, reflecting their shared route of transmission. As expected, this prevalence is higher than that in patients infected with HIV by other routes.

In Hong Kong, the seroprevalence of HSV-1 rises rapidly with age (Box 5.14), so much so that between 80% to 90% are positive by the age of 24. As for HSV-2 seroprevalence, data from the Government Virus Unit in 1995 showed that it was less prevalent than in overseas countries such as the US but the pattern was similar.⁴ Compared to two decades ago, the prevalence had risen across different subgroups of the population⁵ (Box 5.15, Box 5.16). In

Box 5.14 Seroprevalence of HSV-1 in general population in Hong Kong in 1995 (unpublished data, Dr. J. Lo, Government Virus Unit)

Age group	HSV-1 Ab+ (%)	
	male	female
0-4	37.5	25.6
5-14	57.5	47.2
15-24	88.6	81.2
25-59	94.9	89.7
>=60	100	100

Box 5.15 HSV-2 seroprevalence in the general population

Patient group	Age	HSV-2 antibody (1977)	HSV-2 antibody (1995)
Male	15-24	0%	5.7%
	25-29	0%	12.8%
	>=60	n/a	22.2%
Female	12-24	10.8%	6.2%
	25-59	6.7%	17.9%
	>=60	n/a	18.9%

n/a - not available

Box 5.16 HSV-2 seroprevalence in various population groups in 1995

Patient group	Age	HSV-2 antibody
General population		
Male	15-59	9.5%
Female	15-59	12.7%
STD clinic attendees		
Male	15-65	24.3%
Female	15-79	35.5%
Sex workers	14-71	77.5%
IVDU	14-63	26.7%
Antenatal women⁸	13-39	10.2%

prospective studies of HSV-2 discordant couples, the transmission rate is higher from man to woman and probably to those who are HSV-1 negative. The average annual rate of transmission is 12%.^{6,7}

IV. Clinical spectrum of HSV – genital herpes and others

The hallmark of HSV infection is the development of painful vesicles at a mucocutaneous site. The vesicles ulcerate and then heal by re-epithelialisation. HSV-1 commonly causes orolabial lesions while HSV-2 infects primarily the genital and perianal regions. Clinical manifestations depend on the site of inoculation, degree of immunosuppression, subtype of HSV and whether the infection is the first episode or a reactivation.

First episode herpes is divided into primary (absence of antibody to HSV-1 and HSV-2), and nonprimary first episode herpes (serologic evidence of past HSV infection). The incubation period of primary infection ranges from 2 to 14 days (median 7 days). Nonprimary first episode herpes is usually milder and shorter in duration. There are no systemic symptoms and the lesions resolve in about a week's time.

IV.A Genital herpes

If symptomatic, genital herpes presents as small painful papules in the genitalia that evolve into fluid-filled vesicles. Tender inguinal lymphadenopathy and systemic symptoms such as fever, headache, malaise, myalgias and meningismus are common in primary infection. These vesicles ulcerate rapidly and heal by crusting and re-epithelialisation. New lesion

formation during the course of infection is also common. In women, primary genital infection frequently results in **cervicitis**, thus partially explaining the high frequency of perinatal transmission when herpes is acquired late in pregnancy.

IV.B HSV pharyngitis

HSV pharyngitis is not uncommon in those with primary genital herpes probably because of orogenital contact. Ulcers are seen in the pharynx which are covered by a white exudate. These are accompanied by tender cervical lymphadenopathy, and a vesicular eruption on the lips, tongue and buccal mucosa. It is said to occur more frequently in those with HIV infection. HSV-1 gingivostomatitis and pharyngitis usually occur alone without genital involvement after transmission by kissing or other intimate contact. It reactivates in the form of herpes labialis.

IV.C HSV proctitis

Proctitis may be caused by either HSV-1 or HSV-2 after rectal sex. Primary infection presents with systemic symptoms and autonomic neuropathy such as urinary detention and impotence. Local symptoms include rectal pain, tenesmus and discharge. Reactivations are usually asymptomatic. Reactivation of HSV in sacral ganglia may also involve the perianal region in people with no history of rectal sex. HSV proctitis can be severe in HIV disease.

IV.D HSV eye infections

HSV keratitis is characterised by dendritic corneal ulcerations. It probably is a result of autoinoculation. Recurrences are common. Progressive scarring ultimately results in blindness. In disseminated HSV, chorioretinitis may also occur. Either HSV or varicella zoster virus may cause an acute retinal necrosis syndrome which is difficult to treat.

IV.E Recurrent disease and complications

Upon initial genital infection, the herpesvirus lie dormant in sacral ganglia. Reactivation follows unidentified stimuli. Immune suppression increases the rate and severity of reactivation. HSV-2 also tends to reactivate more commonly than HSV-1. Nevertheless, the pattern of reactivation has no relationship with that in the source partner. Symptoms of recurrent disease are less severe than first episode disease. In general, systemic

symptoms are absent and lesions are confined to the genitalia. Prodromal symptoms of tingling sensation or pain are common before a recurrence.

In HIV infection, defective cell mediated immunity increases the chance of complications. Recurrences and subclinical shedding of virus become more common. Furthermore, the following may occur in either primary infection or reactivation:

- (a) A persistent mucocutaneous form of genital herpes with extensive involvement of the genital and perianal area
- (b) Disseminated herpes
- (c) HSV oesophagitis manifesting as odynophagia and retrosternal pain; definitive diagnosis requires endoscopically obtained biopsy in order to differentiate from CMV and candida infections
- (d) HSV encephalitis and meningitis
- (e) HSV pneumonitis

V. Clinical spectrum of VZV in HIV disease

Varicella is a common childhood infection in Hong Kong. Most adults and adolescents with HIV infection are already infected with the virus. Thus the major manifestations are those related to zoster. During primary varicella infection, VZV enters cutaneous endings of sensory nerves and migrates to dorsal root ganglia where it establishes latency in a similar fashion to HSV. Reactivation in the form of zoster occurs at all ages in the immunocompetent, but is more common after 50 and in the immunocompromised. HIV disease predisposes towards zoster that is more severe, extensive, and common.

Typical zoster presents as a painful maculopapular eruption distributed along a dermatome. Radicular pain may precede the rash by 48 to 72 h. The lesions evolve over a few days to vesicles and pustules. Resolution by crusting and re-epithelialisation may be followed by scarring. There is no evidence that postherpetic neuralgia is more common in HIV disease.

Recurrent zoster is exceedingly rare in the immunocompetent but is not uncommon in HIV disease.⁹ HIV-associated zoster can also be unusually severe, involving more than one dermatome.¹⁰ Both recurrent and **multidermatomal zoster** are category B conditions in the staging of HIV disease, and usually predate AIDS by a few years.¹¹ In general, zoster occurs at an earlier age than the immunocompetent, reflecting the younger HIV-infected age group.

Chronic disseminated zoster may present as verrucous or ulcerative lesions. A less common presentation is a persistent localized form of zoster. Both forms are typically resistant to treatment with acyclovir.

Zoster involving the ophthalmic branch of the trigeminal nerve (**zoster ophthalmicus**) may result in keratitis and uveitis and may be more common in HIV disease.¹² VZV can also cause **acute retinal necrosis** which carries a poor prognosis and which mandates aggressive antiviral treatment.

Apart from cutaneous dissemination, **visceral dissemination** may also occur, resulting in life threatening infections of the liver, lungs and CNS.

VI. Diagnostics

VI.A Diagnosis of HSV infections

Genital herpes is but one differential diagnosis of the so-called genital ulcer adenopathy syndrome. The others are syphilis, chancroid, lymphogranuloma venereum (LGV) and donovanosis. In addition, giant idiopathic aphthous genital ulcers may rarely occur in HIV disease.¹³ Among them, herpes is the most common in Hong Kong. Diagnosis by serology is unreliable as current commercial tests do not distinguish well between HSV-1 and HSV-2 antibodies, and positive serology may merely indicate past infection.

The **Tzanck smear** is positive in about 50% of cases of genital herpes. The smear is obtained by scraping the base of a vesicle with a scalpel. The material is then fixed in alcohol and stained with Wright or Giemsa stain. Multinucleated giant cells will be seen as with other herpesvirus infections. **Viral culture** in tissue is positive in up to 80% of cases, depending on the stage of disease. Alternatively, isolation may be achieved by direct immunofluorescence study with monoclonal antibodies (**DFA**) on sample from the active lesions. The **PCR assay** is highly sensitive and specific for HSV in clinical specimens. Detection of HSV DNA in CSF is particularly helpful in the early diagnosis of HSV encephalitis. A dark ground examination (DGE) should also be performed if syphilis is suspected.

HSV infections in sites other than genitalia may require special procedures for diagnosis, e.g. sigmoidoscopy in proctitis, upper endoscopy in oesophagitis, and lumbar puncture or brain biopsy in CNS infections.

VI.B Diagnosis of herpes zoster

Typical zoster is diagnosed clinically. Atypical or disseminated forms of zoster may require laboratory confirmation by viral culture, Tzanck smear or DFA. PCR may be utilized for the diagnosis of CNS infection or pneumonitis.

VII. Management of HSV infection

Prompt recognition of infection allows antivirals to be started early. They help control the symptoms and signs of herpes episodes and reduce viral shedding. In typical presentations, treatment should not be delayed by waiting for laboratory confirmation. Patient-initiated treatment upon first sign of recurrence is effective.

VII.A The first line antivirals

Drugs against HSV and varicella-zoster (VZV) infections act by inhibiting viral DNA polymerase. Acyclovir is the standard to compare with. Other commonly used drugs are valacyclovir and famciclovir (Box 5.17). Ganciclovir is also effective but, without added efficacy, is too toxic for routine use. Acyclovir is available in three formulations – topical, oral and intravenous.

Topical acyclovir – 5% acyclovir ointment is available for topical application. It achieves negligible systemic levels but does reduce slightly the duration of symptoms in primary genital infection. Topical acyclovir has now fallen out of favour because it (a) does not work in reactivations, (b) does not alleviate systemic symptoms, (c) has to be applied 6 times a day, and (d) care must be taken to avoid autoinoculation.

Oral acyclovir – This is the treatment of choice in most situations. In first episode genital herpes, acyclovir is given 200 mg 5X/d or 400 mg tid for 7-10 days. In recurrent disease,

Box 5.17 Commonly used antivirals against HSV and VZV

	Acyclovir	Valacyclovir	Famciclovir
Nature	Nucleoside analog	L-valyl ester of acyclovir	Analog of penciclovir
Formulation	Topical, oral, IV	Oral	Oral, topical
Oral bioavailability	20%	Good, with in vivo conversion to acyclovir	Good, with in vivo conversion to penciclovir
TK-dependent	Yes	Yes	Yes
Active form	Acyclovir triphosphate	Acyclovir triphosphate	Penciclovir triphosphate
Major adverse effects	Crystalluria with high dose; impaired renal function	TTP/HUS* with high dose (8g/d)	

*thrombocytopenic purpura/haemolytic uraemic syndrome

acyclovir is given 200 mg 5X/d or 400 mg tid for 5 days. For achieving suppression of disease recurrence, acyclovir 400 mg bid or 800 mg qd is effective.

The standard US CDC recommended treatment of genital herpes is listed in Box 5.18.¹⁴ However, in HIV disease, herpes may be more severe and may respond less well to treatment. Therefore both the duration and dose will need to be increased if response is unsatisfactory. The clinician also has to bear in mind the emergence of resistance.

Intravenous acyclovir – this is used for serious infections such as disseminated infection, pneumonitis, hepatitis or CNS infections. Alternatively, it may be considered in suspected resistance and in patients with poor absorption or drug compliance. The standard recommended dose is 5-10 mg/kg IV q8h for 5-7 d or until clinical resolution is attained. The higher end of the range, i.e. 10 mg/kg, is mandatory for CNS infections as CSF level is usually only 30-50% of that in plasma.

VII.B Antiviral resistance

Acyclovir, valacyclovir, famciclovir and ganciclovir require viral thymidine kinase (TK) for antiviral action. The most common mechanism of HSV resistance is mediated through altered substrate specificity of the enzyme. Resistance is rare in immunocompetent hosts, but in HIV disease, about 5% of HSV infections are resistant to acyclovir. Cross resistance to the other first line drugs is the rule. Both foscarnet and vidarabine are active against acyclovir-resistant HSV in vitro since phosphorylation of vidarabine dose not depend on

Box 5.18 Standard doses of antivirals against HSV according to indication			
Indication	Acyclovir	Valacyclovir	Famciclovir
First episode	400 mg tid X 7-10 d	1 g bid X 7-10 d	250 mg tid X 7-10 d
Genital herpes*	200 mg 5X/d X 7-10 d		
Recurrent episode	400 mg tid X 5 d 200 mg 5X/d X 5 d 800 mg bid X 5 d	500 mg bid X 5 d	125 mg bid X 5 d
Daily suppressive therapy	400 mg bid	250 mg bid 500 mg qd 1000 mg qd – for >10 recurrences a year	250 mg qd
* treatment may be extended if healing is incomplete after 10 days of therapy; higher doses of acyclovir at 400 mg 5X/d are generally used for first episode HSV proctitis, gingivostomatitis, and pharyngitis			

viral TK and foscarnet dose not even require phosphorylation for activity. However, in a comparative trial in AIDS patients, foscarnet was shown to be superior to vidarabine.¹⁵ Thus IV foscarnet at 40 mg/kg tid is the preferred treatment modality. IV cidofovir, cidofovir gel or high-dose, continuous-infusion acyclovir may also be considered.

VII.C Prevention

It is important to educate the patient on the use of barrier contraceptives and the knowledge that shedding of virus is often subclinical. Sex should be abstained when there are recognisable recurrences. The use of condom reduces but does not eliminate the risk of infection as some genital lesions may not be covered by the condom. The use of **daily suppressive therapy** in frequent relapsers (>6 recurrences per year) is beneficial not only for symptomatic improvement but also in reduction of virus shedding.¹⁶ In this way, transmission of both HSV and HIV may be reduced. Breakthrough recurrences do not necessarily represent drug resistance. Higher doses of suppressive therapy may be attempted.

VIII. Management of zoster

Acute management of zoster lesions involves pain management with analgesics, local treatment and specific antivirals.

VIII.A Antivirals

In general higher doses of antivirals are required for zoster than HSV infections and should be started within 72 hours of rash onset. Antivirals reduce shedding of viruses and duration of disease. They may also reduce the risk of postherpetic neuralgia. Acyclovir, valacyclovir and famciclovir are the preferred first line drugs. Treatment is continued for 7-10 days or until lesions have crusted. Although no comparative trials have been done among them, it is suspected that acyclovir may be inferior because of its relatively poor bioavailability. The comparative doses of the commonly used antivirals against zoster are listed in Box 5.19.

Box 5.19 Doses of antivirals against zoster			
Indication	Acyclovir	Valacyclovir	Famciclovir
Localized zoster	800 mg 5X/d	1 g tid	500 mg tid
Disseminated zoster	IV 10 mg/kg q8h		

Most HIV infected patients with localized zoster require only oral treatment as an outpatient. However, cutaneous dissemination and visceral involvement require in-hospital intravenous acyclovir for treatment.

VIII.B Steroid

The use of steroid to reduce postherpetic neuralgia is controversial even in immunocompetent persons.^{17,18} The risks of immunosuppression and varicella dissemination do not justify their use in HIV infected patients.

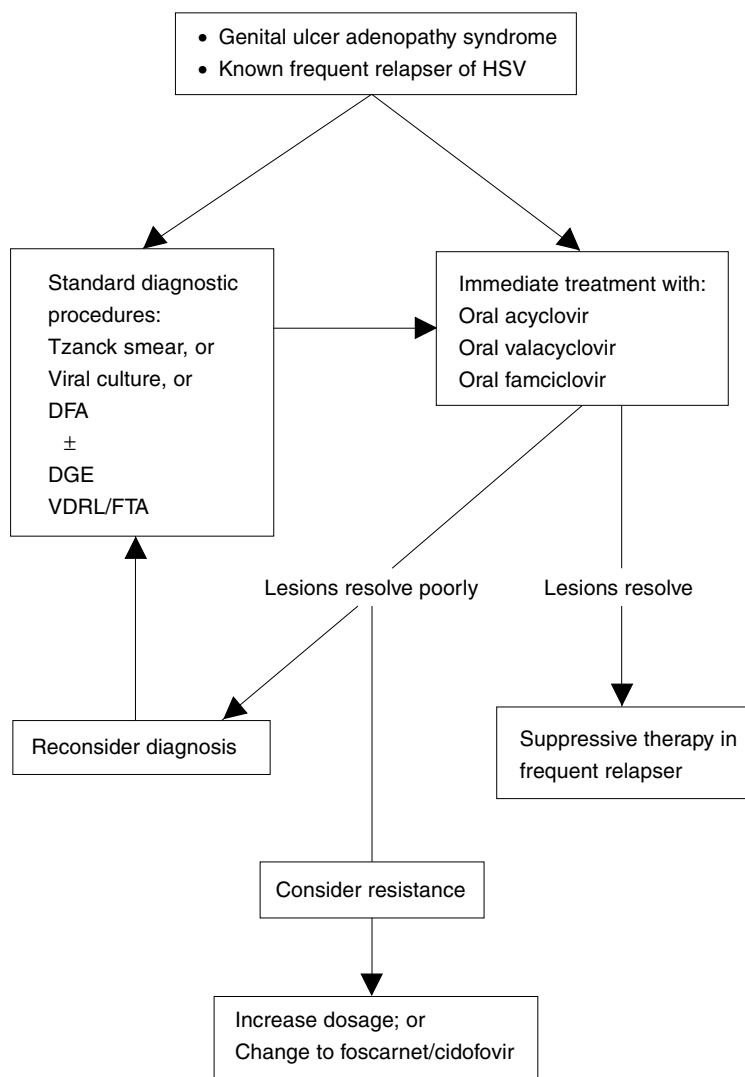
VIII.C Acyclovir resistant zoster

Resistant zoster generally presents as persistent lesions refractory to treatment. The mechanism is usually one of deficient or altered thymidine kinase. Cross resistance among the first line antivirals is expected. In this case, IV foscarnet at 40 mg/kg tid may be effective.

VIII.D Varicella

Most patients have been infected by varicella prior to HIV. In the rare occurrence of varicella in an HIV infected person, IV acyclovir treatment should be considered as visceral dissemination is not uncommon in the immunocompromised. Susceptible patients without history of chickenpox and antibody should be given varicella-zoster immune globulin (VZIG) as prophylaxis within 96 hours of exposure. Note that VZIG is ineffective as treatment. As a live attenuated vaccine, the varicella vaccine is contraindicated in HIV patients.

Algorithm 5.9 Management of herpes genitalia in HIV disease



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5.10 SYPHILIS AND HIV INFECTION

I. Epidemiology and clinical course of syphilis

Syphilis is caused by the spirochaetates *Treponema pallidum*. It is an obligate human pathogen. Nearly all cases of venereal syphilis are acquired by direct sexual contact with lesions of an individual who has active primary or secondary syphilis. Transmission of syphilis occurs in approximately one half of such contacts. Syphilis can also be transmitted vertically from infected mother to her baby.

I.A Epidemiology

In the US, rates of syphilis declined rapidly during the late 1940s. However, in the late 1980s and early 1990s, syphilis re-emerged and concentrated in the urban and rural regions of southern US.¹ In Hong Kong, a parallel trend could be delineated. The number of new cases of syphilis recorded by the Hong Kong Government Social Hygiene Service (GSHS) reached its trough of 310 cases in the year of 1990 but went up to 1110 in 1999.² The rise was more marked among those with primary or secondary syphilis. Point prevalence study at a local HIV clinic revealed that 40 out of 493 patients (8%) had evidence of past history of syphilis. (Integrated Treatment Centre, unpublished data)

I.B Natural course of infection

After an incubation period that ranges from 9 to 90 days, a local sore (chancre) usually develops at the site (usually the genital region) of entry of the treponeme. There may also be painless enlargement of the regional lymph nodes. This stage of disease is called primary syphilis. After a further 1-6 months, the generalised signs of secondary syphilis may appear. These include a variety of skin and mucosal lesions, generalised lymphadenopathy, fever, and visceral involvement including the central nervous system (30-40%).³ Left untreated, spontaneous resolution of the physical findings of primary and secondary syphilis is almost the rule. During the following 2-4 years, relapses of clinical disease of secondary syphilis may occur in ¼ of the cases.

Afterwards, in about 30% of the cases, the disease appears to burn out, reverting to seronegativity towards tests with non-treponemal antigens (VDRL). Apparently a

spontaneous cure has been achieved. In another 30%, no sign develops but serological reaction to tests with both non-treponemal and treponemal antigens remains positive throughout life.^{3,4}

Symptomatic late syphilis follows in the remaining 40% of untreated patients who have latent diseases. About 1/3 develop tertiary gummata, slightly more than 1/3 develop cardiovascular syphilis and less than 1/3 will develop neurosyphilis with central nervous system involvement. There are four well-established clinical types of neurosyphilis – meningovascular syphilis, general paralysis of insane, tabes dorsalis and CNS gumma^{3,4} Asymptomatic neurosyphilis is increasingly recognised in recent years and could well be the fifth type. Owing to the widespread use of antibiotics, symptomatic late syphilis is not common nowadays.

Up to 30-50% HIV infected people having clinical latent syphilis have abnormal cerebrospinal fluid (CSF) findings⁵⁻⁷ that are consistent with neurosyphilis. A substantial proportion of cases develop early neurosyphilis within 6 months even after therapy⁸ which is rare in HIV negative patients.

II. Diagnosis of syphilis in HIV positive patients

II.A Serologic tests

Irrespective of symptoms, all HIV positive patients should have baseline VDRL screening performed and 3 months later, to cover the possibility of false negative result. Seroconversion generally takes about 4-6 weeks after exposure. In the case of a reactive VDRL, the diagnosis of syphilis should be confirmed by FTA-ABS or TPHA.

Syphilitic serology should always be ordered in various kinds of neurological presentation. In cases with negative VDRL but reactive FTA-ABS, TPHA has to be done to support the diagnosis of syphilis. If the FTA-ABS is the only test that is positive and the patient does not have any clinical symptom or signs suggesting syphilis, blood test for syphilitic serology should be repeated 6-12 weeks later. The role of enzyme immunoassay (EIA) testing has yet to be defined.

II.B Other diagnostic tests

When the clinical feature suggests syphilitic infection, investigations to confirm the diagnosis have to be performed. **Darkground microscopy** of serum obtained from mucocutaneous lesions (other than oral lesion) for treponemata should be performed if

such is present. Skin biopsy may rarely be performed on lesions when serology is indeterminate or inapplicable, which is more common in HIV infection. This could be in the form of a false negative syphilitic serology or persistent serofast state after treatment for syphilis.

Lumbar puncture (LP) with CSF analysis is recommended for syphilis of all stages other than primary syphilis (PS). As PS may overlap with secondary syphilis (SS), LP is desirable in case of doubt even for PS. Space-occupying lesion has to be excluded, e.g. by CT scan, before the lumbar puncture. CSF analysis including protein, sugar, cell count, VDRL (if it is available at the supporting laboratory), AFB, Indian ink, cryptococcal antigen, culture for the respective organisms and cytology should be done.

It has been reported that both false positive and false negative results of VDRL can happen in HIV infected people. The serological response i.e. decrease in VDRL titre after apparently adequate treatment could be delayed or flattened (serofast). However, in the vast majority of HIV infected individuals, the titre of VDRL still reliably reflects the disease activity and response to treatment even at low level of CD4 count.^{8,9} It has to be noted that the staging of HIV infection including the CD4 level is not predictive of development of neurosyphilis.

Serological and other investigations alone are not adequate for a comprehensive assessment of syphilis. Careful **history and physical examination** is necessary to determine the staging of syphilis that may affect the management plan. Furthermore, opportunistic infections, neoplastic diseases, HIV infection itself and drugs affecting the central/peripheral nervous system could be alternative explanations for symptoms and signs suggestive of neurosyphilis. One should always think of multiple pathologies in approaching an HIV infected person suspected to have neurosyphilis. Thorough investigations or even therapeutic trial should not be delayed.

III. Treatment and follow-up of syphilis

There are few data on the optimal treatment of syphilis in HIV disease, and there is consequently considerable disagreement among experts regarding therapeutic recommendations. The general treatment recommendations for Hong Kong are as shown in Box 5.20. The regimens adopted by the Social Hygiene Service are more aggressive than those recommended by CDC or WHO for HIV negative cases.^{1,10} In this set of recommendations, benzathine penicillin treatment which does not achieve adequate (or even detectable) levels in CSF is not advocated in any stage of syphilis.

Patients with symptoms or signs compatible with neurosyphilis or CSF abnormality, e.g. CSF pleocytosis, increase in protein with or without reactive VDRL (PCR for treponema

and rabbit inoculation are not commercially available locally) attributable to syphilitic infection, treatment as for neurosyphilis is recommended. For HIV-infected patients, benzyl penicillin (soluble penicillin) 16-24 mu ivi daily in 4-6 divided doses for 14-20 days is recommended¹¹ (A 14 day course of treatment is recommended in standard text for bacterial meningitis¹² and 20 days by GSHS for neurosyphilis without HIV infection).¹³ In HIV negative patients, the use of procaine penicillin G 2.4 mu imi daily with probenecid 500 mg qid for 20 days should be adequate but the data for its use in people with HIV infection are limited.

Because of reports of treatment failure, HIV-infected persons should be followed up regularly to monitor response or relapse.

Box 5.21 shows the different types of potential reactions in syphilitic patients receiving penicillin treatment. They can be allergic reactions (to major or minor determinant) to penicillin, Jarish-Herxheimer reaction and procaine reaction. Steroid cover with prednisolone 30 mg orally for 3 days before treatment to prevent Jarish-Herxheimer reaction

Box 5.20 Recommended treatment of syphilis by the Government Social Hygiene Service

	P.S., S.S., E.L.S.	L.L.S., Cardiovascular syphills	N.S., Ocular syphills
Procaine Penicillin	1.2 megaunit i.m.i.	1.2 megaunit i.m.i. + Probenecid 500 mg 4x/day	2.4 megaunit i.m.i. + Probenecid 500 mg 4x/day
No. of days	10	15	20
Alternative Treatment	<ul style="list-style-type: none"> • Doxycycline 100 mg 2x/day • Tetracycline 500 mg 4x/day • Erythromycin 500 mg 4x/day 	<ul style="list-style-type: none"> • Doxycycline 100 mg 2x/day • Tetracycline 500 mg 4x/day • Erythromycin 500 mg 4x/day 	<ul style="list-style-type: none"> • Doxycycline 100 mg 2x/day • Tetracycline 500 mg 4x/day • Erythromycin 500 mg 4x/day
No. of days	15	Procaine penicillin: 15 Alternate (oral) treatment: 28	28

P.S. = primary syphilis; S.S. = secondary syphilis; E.L.S. = early latent syphilis; L.L.S. = late latent syphilis; N.S. = neurosyphilis

NOTE :

1. Doxycycline and tetracycline should not be used during pregnancy or lactation.
2. Steroid cover with prednisolone 30mg daily is recommended to prevent Jarish Herxheimer reaction in the treatment of cardiovascular, neuro and ocular syphilis.
3. Baby delivered by woman with syphilis should be treated by procaine penicillin 50,000 unit/kg i.m.i. daily for 15 days if the mother had not been treated by penicillin regimen during her gestation.
4. Benzathine penicillin 2.4 megaunit i.m.i. weekly for 3 weeks is a less ideal treatment regimen for syphilis nowadays because the level achieved in the CSF is not good enough to prevent CNS involvement by *Treponema pallidum*.

Box 5.21 Reactions observed in patients receiving penicillin for treatment of syphilis

Jarish-Herxheimer reaction: It is manifested as fever, chill, arthralgia, headache, and is believed to be an endotoxin like reaction related to killed treponeme or released toxin. It is more common in secondary syphilis and is not an indication for discontinuation of treatment.¹ Management of this reaction is mainly supportive.

Procaine reaction: The manifestations consist of severe anxiety, agitation, feeling of doom, vertigo, tinnitus, visual and auditory hallucination. It is supposed to be mediated by brain microembolism secondary to inadvertent injection of crystals of procaine penicillin intravenously. Grand mal seizures have been reported. Treatment is supportive.

Penicillin reaction: The penicillin reaction associated with penicillin can be divided into toxic and allergic ones. The toxic adverse reaction is dose related, occurring in penicillin overdose or patients with renal impairment. Generalised seizure may occur. Allergic reactions are immunologically mediated and are reported in 10% people in US. There are 4 types of reactions: (a) type 1 reaction is characterised by urticaria, angioedema or anaphylaxis, and is IgE mediated, (b) type 2 reaction results in haemolytic anaemia and leukopaenia, (c) type 3 reaction is similar to serum sickness and is manifested by drug fever and vasculitis, and (d) morbilliform rash and toxic epidermal necrolysis are believed to be mediated by type 4 hypersensitivity reaction.

in HIV negative person may also be considered in person with HIV infection. Sometimes these reactions may not manifest until the end of the treatment course.

For patients known to be allergic to penicillin, they can be admitted to hospital for desensitisation before giving the full course of treatment with benzyl penicillin. An alternative is to give ceftriaxone 1-2 gm ivi daily for 14 to 20 days, although efficacy is unproven.⁵ Close observation is necessary as 10% of patients sensitive to penicillin may also be sensitive to cephalosporins as well. Treatment with oral tetracycline or erythromycin is not recommended in persons with HIV infection. Box 5.22 shows the protocol for desensitisation for patients with skin test positive for penicillin determinants (commercial skin test reagents including major and minor determinants are not readily available in Hong Kong, and this regime could be adopted for use in patients with a history of penicillin sensitivity with or without positive skin testing).

Similar to management of other STDs, counseling on safer sex and contact tracing are important parts of management for patients with syphilis. Screening for concomitant STDs should also be done.

Box 5.22 Oral desensitisation protocol for patients with a positive skin test¹⁴

Penicillin V Suspension dose[†]	Amount[§] (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

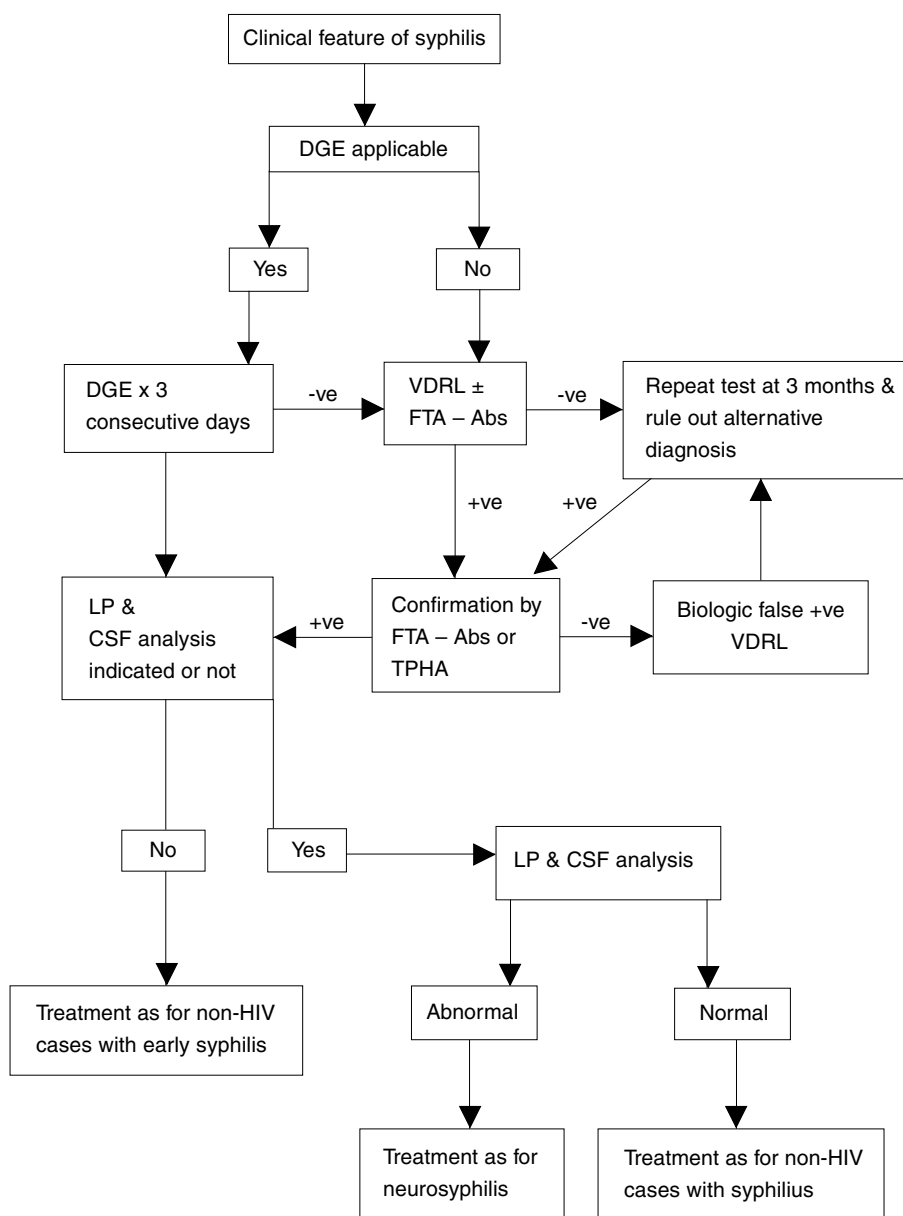
Observation period: 30 minutes before parenteral administration of penicillin.

[†]Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.

[§]The specific amount of drug was diluted in approximately 30 ml of water and then administered orally.

After treatment, syphilitic serology is done at 6 weeks, 3 months and 6 months and every 3 to 6 months interval thereafter as treatment failure is well documented.^{5,7} LP and CSF analysis at 6 to 12 weeks and 6 month (if the CSF has not yet been normalised) is necessary to monitor response or relapse to treatment for person with HIV and syphilis.

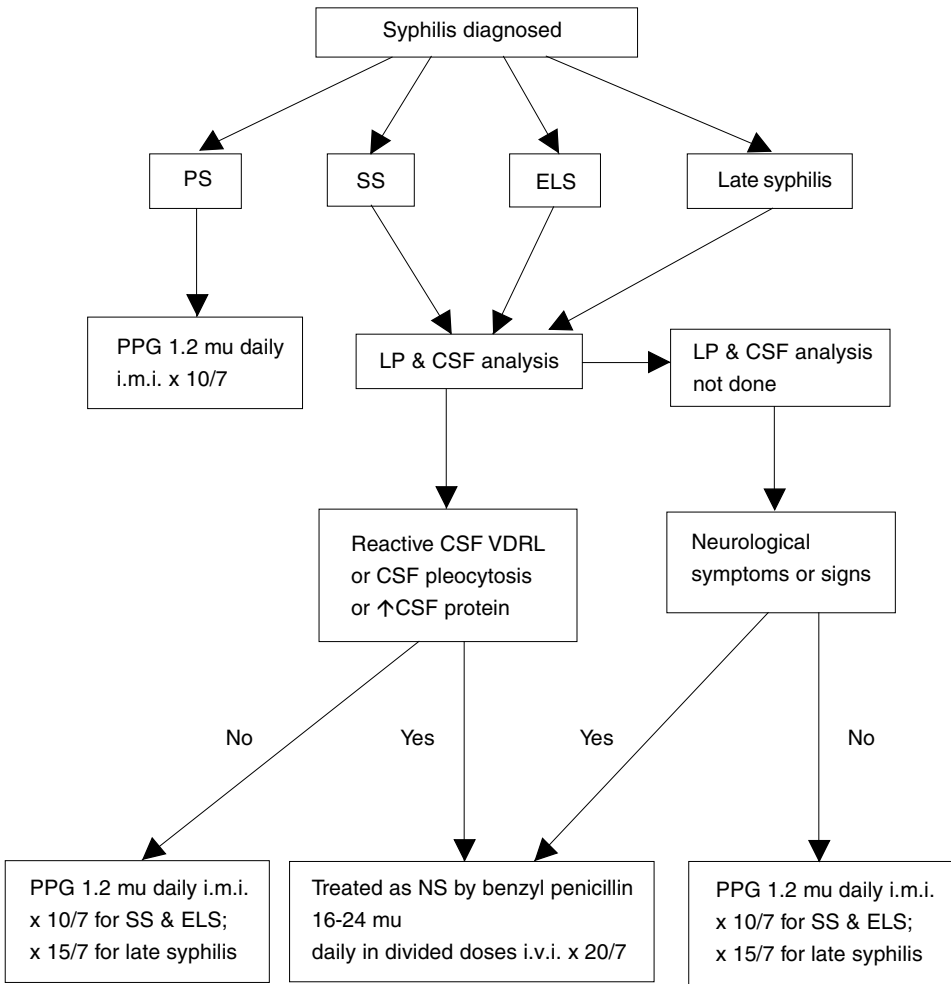
Algorithm 5.10A Diagnosis of syphilis



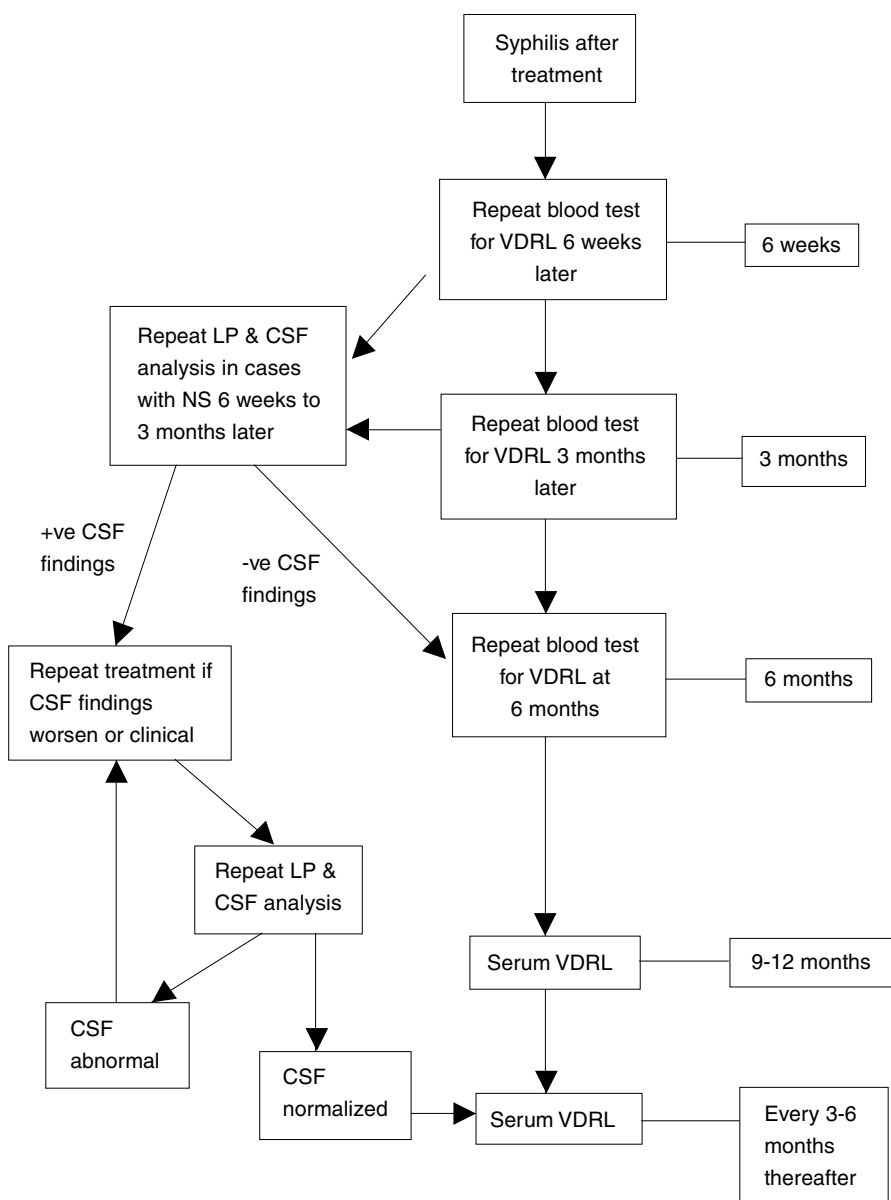
* unless the diagnosis of PS is very clear cut, LP is better to be performed.

For exceptional cases of uninterpretable syphilitic serology, other diagnostic modality like skin biopsy may be used to establish the diagnosis.

Algorithm 5.10B Treatment of syphilis



Algorithm 5.10C Follow up of syphilis



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5.11 TOXOPLASMOSIS

I. Clinical epidemiology of toxoplasma infection

Toxoplasma gondii (*T. gondii*) is a ubiquitous protozoan parasite of human and animals, especially cat. Toxoplasma infection is benign in immunocompetent hosts but serious in immunocompromised hosts and fetus.¹ Disease caused by infection with *T. gondii* is termed toxoplasmosis. Although pneumonitis² and chorioretinitis³ can also occur, the commonest manifestation in HIV-infected patients is encephalitis, almost always due to reactivation of a chronic (latent) infection. It has been found that about one-third of patients with HIV infection and latent *T. gondii* will develop toxoplasmosis in its natural disease course.⁴

Toxoplasmic encephalitis is the most frequent cause of focal intracranial lesions in patients with AIDS.⁵ Its prevalence, however, varies with the endemicity of latent toxoplasma infection in a locality. For example, it occurred in some 5% and 20% of AIDS patients in the US and France respectively.^{6,7} In Hong Kong, toxoplasmic encephalitis accounts for about 2% of the primary AIDS-defining illnesses. Patients develop toxoplasmic encephalitis often at a CD4 count of less than 100/uL.⁸

II. Diagnosis of toxoplasmic encephalitis

II.A Clinical features

Toxoplasmic encephalitis can present with a wide spectrum of clinical manifestations, including fever, reduced alertness, headache, focal neurological deficits and seizures. One should proceed to investigations when an advanced HIV-infected patient presents with symptoms or signs of central nervous system infection, especially focal neurologic features.

II.B Diagnosis

The relevant investigations can be divided into radiological, serological and histological ones. Radiological investigation is a must while serology may be helpful in some circumstances.

CT scan or MRI (if readily accessible) of the brain should be performed to detect mass lesions when the diagnosis is suspected. The classical appearance of toxoplasmic encephalitis in CT scan of the brain is multiple, contrast-enhancing (ring) mass lesions over basal ganglia and grey-white junction with edema effects. MRI scan is usually more sensitive than CT scan in picking up the multiple lesions, sometimes possible even without contrast. The presence of **IgG anti-toxoplasma** antibody supports the diagnosis and it should be repeated for previously seronegative patients. However, some 10-15% of patients with toxoplasmosis may have false negative serology which therefore is not sufficient to rule out the diagnosis. **Brain biopsy**, which is rarely done, may yield a definitive histopathological diagnosis of toxoplasmic encephalitis.

CD4 count should be repeated if no recent results are available. Fundi are to be examined for evidence of choroidoretinitis and ophthalmologist has to be consulted in case of doubt. Often the diagnosis can be made clinically by a treatment response to anti-toxoplasma therapy in a compatible setting: clinical, radiological and serological.

III. Primary prevention of toxoplasmosis

There are two levels of primary prevention of toxoplasmosis: (a) prevention of disease acquisition, and (b) prevention of clinical disease in latently infected individuals.

The route of contracting *T. gondii* is often via contacting infected animals or eating contaminated undercooked meats that harbor the pathogen. Measures should be taken to prevent acquisition of toxoplasma if the patient does not have it already. This minimizes the problem of subsequent reactivation of the infection and thus disease manifestations.

All HIV positive patients should have a baseline check for IgG antibody to *Toxoplasma*. For subjects who test negative, repeat screening might be performed yearly to look for seroconversion. Such practice is indicated especially if the patient's CD4 count is <100/uL and where septrin has not been used for prophylaxis, as the risk of developing toxoplasmic encephalitis is higher in these circumstances.

HIV/AIDS patients, in particular those who are anti-toxoplasma seronegative, should be advised to avoid exposure to *Toxoplasma*:⁹

- (a) All meat and eggs must be well-cooked before ingestion
- (b) Wash hands after handling uncooked meat, gardening or other contact with soil
- (c) Wash fruits and vegetables well before eating them
- (d) Avoid handling litter of cats
- (e) Avoid handling stray cats

Septtrin in dosage of 2 SS (single strength) or 1 DS (double strength) tablet daily should be used for PCP prophylaxis when indicated as it also protects against toxoplasmosis. The necessity of choosing another regimen for primary protection against toxoplasmosis (when CD4 <100/ul and anti-toxoplasma IgG positive) is controversial, but could be useful if one cannot tolerate septtrin. Nevertheless, the regimen of dapsone 50 mg/day + pyrimethamine 50 mg/week + folinic acid 25 mg/week can be considered for prophylaxis against both PCP and toxoplasmosis in such cases.

IV. Treatment of toxoplasmic encephalitis

IV.A Empiric treatment

Therapeutic trial or empiric anti-toxoplasmosis treatment is indicated when clinical findings and investigations results support or cannot rule out the diagnosis. Such circumstances include (a) brain mass in the presence of anti-toxoplasma seropositivity, and (b) multiple CNS mass lesions irrespective of serology results. Otherwise, brain biopsy should be considered though empiric therapy may still have to be given if brain biopsy cannot be done.

Steroid use should generally be avoided as, by reducing brain edema, it may lead to treatment response by itself and complicate the assessment of empiric anti-toxoplasma therapy. Some lymphoma mass (a valid differential diagnosis) may also shrink with steroid. If there are large mass lesions with the danger of herniation, one should proceed to open brain biopsy and decompression. Dexamethasone may also be given to reduce intracranial pressure in this life-saving situation.

IV.B Treatment regimen

Classical anti-toxoplasmosis treatment is oral pyrimethamine (100 mg D1, then 50-75 mg/day) plus sulfadiazine (4-6 g/day) for at least six weeks. Folinic acid 10-15 mg qd is needed. Clindamycin (300-450 mg qid) can be used in place of sulfadiazine. Studies have revealed that pyrimethamine plus sulfadiazine is superior to pyrimethamine plus clindamycin.⁸ However, sulfadiazine is not readily available in Hong Kong. During anti-toxoplasmosis treatment, side effects should be monitored – anemia, neutropenia, skin rash, diarrhea and pseudomembranous colitis.

Clinical response is observed in 74% of patients by day 7 of treatment and 91% by day 14.⁸ Radiological improvement occurs in 80-90% of the toxoplasmosis patients after 2-3 weeks of therapy.⁴ Follow-up CT scan/MRI should be performed about 2 weeks after

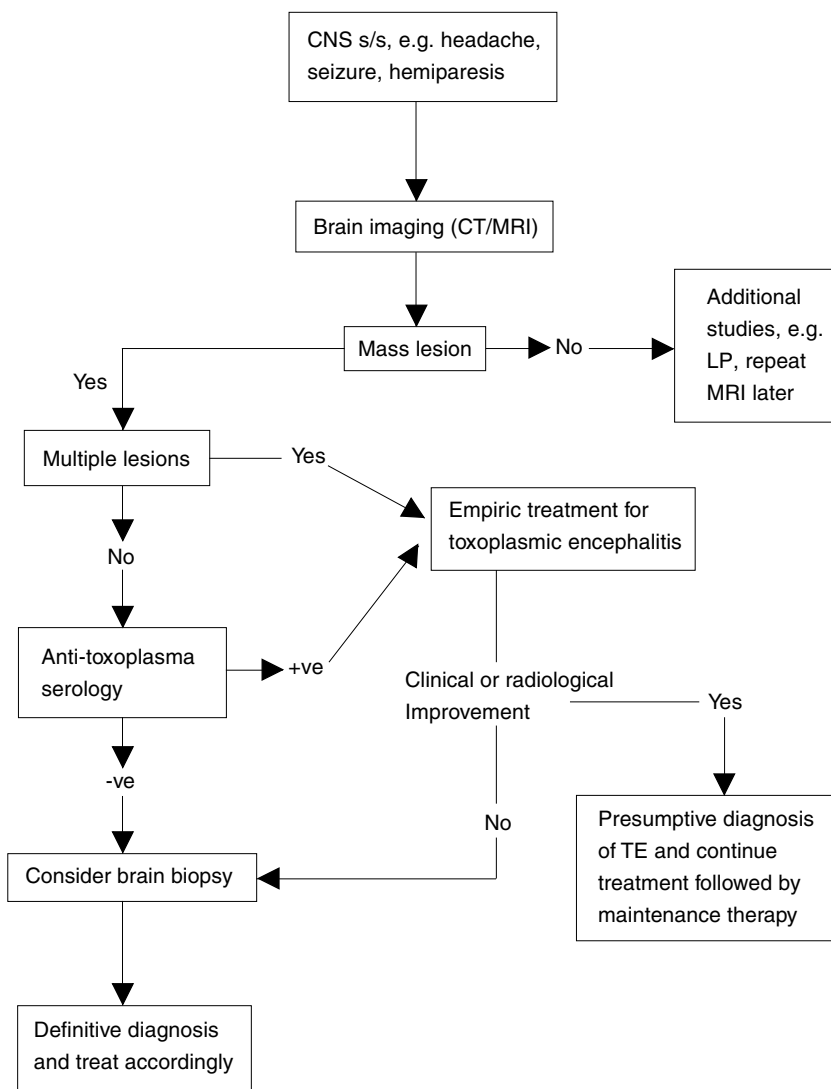
initiation of treatment to ascertain treatment response. Improvement after steroid should be interpreted with caution. If feasible, concomitant steroid is to be taken off early so as to allow better assessment of response to anti-toxoplasma therapy. Follow-up CT scan/MRI every 4-6 weeks is preferable till resolution of the mass lesions.

Patients with genuine toxoplasmosis rarely fail classical anti-toxoplasmosis treatment. If they do, limited data are available on the use of salvage therapy, e.g. azithromycin, clarithromycin, atovaquone, trimetrexate, doxycycline. It has to be remembered that patients who fail to respond to empiric anti-toxoplasmosis treatment may have an alternative or concurrent pathology, e.g. lymphoma, tuberculoma, or progressive multi-focal leucoencephalopathy. Stereotactic brain biopsy can help to derive a diagnosis and hopefully treatment.

IV.C Secondary prevention

After induction treatment, life-long suppressive (maintenance) therapy with drugs active against toxoplasma is indicated to prevent relapse. The usual regimen is half of the treatment dose of pyrimethamine and sulfadiazine/clindamycin. There is as yet insufficient evidence to provide definitive recommendation on the discontinuation of maintenance therapy in patients with good response to HAART.

Algorithm 5.11 Management of toxoplasmosis in HIV infection



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TUMORS IN HIV/AIDS

6.1 AIDS RELATED KAPOSI'S SARCOMA

Kaposi's Sarcoma (KS) is an important AIDS defining condition in patients infected with HIV. In the early 1980s, some 35% to 40% of all reported AIDS patients in the US presented first with KS,¹ particularly among homosexual men. The incidence had been declining in US and many other developed countries. In Hong Kong, KS accounted for 13% of AIDS defining disease between 1985 and 1994,² falling to about 4% in 1995 and 1996, while none was reported between 1998 and 2000.³

The recognition of KS in HIV negative homosexual men suggested a role for a sexually transmitted cofactor. The discovery of human herpes virus 8 (HHV-8) and its association with KS shed light on the pathogenesis of the condition.⁴

Histopathologically, KS is characterised by the proliferation of spindle cells with an abundance of vascular channels and inflammatory mononuclear cell infiltrations. The cellular origin of KS is likely to be the spindle cell, which is a mesenchymal progenitor cell of either lymphatic endothelial or monocyte-macrophage lineage. HHV-8 induces changes in the endothelial cells, making the latter susceptible to the effects of various cytokines. The spindle cells undergo transformation, and begin to produce autocrine and paracrine growth factors.

As tumorigenesis is related to systemic infection of both HHV-8 and HIV, KS is usually multifocal on presentation. The integument is the most common site of involvement followed by oral cavity, gastrointestinal tract and lung. There is no definitive therapy for KS. A plan of action shall be worked out following careful assessment of the clinical condition.

I. Assessment of Kaposi's sarcoma

Assessment of HIV related KS carries three main objectives, which are firstly, to confirm the diagnosis; secondly, evaluate the disease status; and thirdly, make assessment to facilitate future monitoring.

I.A Diagnosis of Kaposi's sarcoma

A clinical diagnosis of KS can be made when a patient presents with the characteristic violaceous skin macules, papules, plaques or nodules. As the lesions may vary in size, color and distribution, a biopsy is recommended to distinguish from other lesions, especially when treatment is contemplated.

It must be noted that KS may develop in the oral cavity, gastrointestinal tract, the lungs, and/or other visceral sites like liver, spleen, heart and bone marrow. Other investigations including endoscopy or radiology may therefore be indicated depending on the presentation. Lymphoedema is a frequent complication of HIV related KS.

1.B Evaluation of disease status

Staging is helpful not just for evaluation of a diagnosed case, but for comparison of information from different clinics. The AIDS Clinical Trials Group (ACTG) staging classification system can be used to guide management. Three groups of factors are considered in the system - tumor (T), immunity (I) and systemic illness (S).⁵ A patient can be classified into T₀ or T₁, I₀ or I₁ and S₀ or S₁ in accordance with the definitions given in Box 6.1.

1.C Disease monitoring

In the course of making diagnosis and staging, it is important to establish a baseline of the condition for future monitoring. This would entail counting the total number of lesions, delineating the sites of involvement, and taking the measurements of, say, 5 discrete

Box 6.1 ACTG staging classification for Kaposi's sarcoma⁶

	Good risk (₀) (all of the following)	Poor risk (₁) (any of the following)
Tumor (T)	Confined to skin and/or lymph nodes and /or minimal oral disease ^a	Tumour-associated oedema or ulceration and/or extensive oral KS, and/or gastrointestinal KS, and/or KS in other non-nodal viscera
Immune System (I)	CD4 cells ≥200/μl	CD4 cells <200 μl
Systemic Illness (S)	No history of OI or thrush No "B" symptoms Performance status ≥70 (Karnofsky)	History of OI and/or thrush and/or "B" symptoms present, and/or Performance status <70, and/or other HIV-related illness (e.g. neurologic disease, lymphoma)

^a Minimal oral disease is non-nodular KS confined to the palate.

^b "B" symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or persistent diarrhoea.

representative marker lesions for serial follow up of progression.⁶ Clinical photographs of the representative lesions shall be taken with scale in case the lesions could be difficult to follow with the above measures (e.g. bizarre shape, confluent lesions etc.). A careful documentation would be particularly useful for long term followup.

In subsequent followup, the assessment shall be repeated to determine the progress as a result of treatment or the natural course of the condition.

II. Treatment of Kaposi's sarcoma

After ascertaining the TIS staging and treatment goal of the patient, the physician should come with a decision on the therapeutic options for the patient. There is no definitive therapy for KS. There are four indications for treatment of KS: (a) life threatening complications e.g. extensive pulmonary involvement, (b) symptomatic disease e.g. bulky oral lesion, (c) cosmetic disability, (d) to prevent progression.

Treatment modalities can be categorised into 2 broad groups: local vs systemic. Choice of treatment is based largely on its indication. However, with the advent of highly active antiretroviral therapy (HAART), the therapeutic goals have been shifting from palliative care to long-term, durable remissions.⁷ There were anecdotal reports of tumour regression after HAART.^{8,9} Kaposi's sarcoma may be a good indication for starting HAART in HIV infected people.

II.A Local treatment

Cryotherapy is to be used for restricted lesions that are small. Intralesional vinblastine (0.01-0.02 mg/lesion with a reconstitution of 0.2 mg/ml preparation) is useful for lesions that are larger (>1 cm). Radiation (low dose, e.g. 400 rads q wk x 6 weeks) is useful for larger local lesions that cause symptoms (e.g. obstruction). Other local treatment modalities such as laser and electrocauterisation will be dependent on the availability and experience of the centre.¹⁰

II.B Systemic treatment

Systemic therapy is preferred for patients with widespread skin involvement (> 25 lesions), extensive cutaneous KS non-responsive to local treatment, extensive oedema and/or symptomatic visceral organ involvement (especially lung or GI involvement).

Options for systemic therapy are single agent chemotherapy, combination chemotherapy, and interferon-alfa. Etoposide 50 mg/day p.o. for 21 days q 4-5 wks or for 7 days q 2 wks can be tried on an outpatient basis.^{6,10} Paclitaxel 100 mg/m² infusion over 3 hours q 2 wks or 135 mg/m² q 3 wks is the other alternative.^{6,7,10} Bleomycin and liposomal doxorubicin can also be used but liposomal doxorubicin is not readily available in Hong Kong.

Combination chemotherapy can be adopted for good risk patients with curative intent or patients with severe systemic involvement. A commonly used combination comprises doxorubicin (Adriamycin), bleomycin and vincristine or vinblastine (ABV). However, recommendation of one treatment regimen over another is difficult because prospective large randomised comparative trial have not been performed while meta-analysis of various trials is not easy as there have been wide variations in both the methodology and subjects selected.^{6,7,10}

Interferon-alfa given at a dose by 36 mu daily for IFN- α 2a, or 30 mu daily per m² 3 times per week has been approved by FDA for treatment of KS.

Two other possible experimental modalities that are feasible in this locality are all-trans-retinoic acid (ATRA) and human chorionic gonadotropin (hCG). ATRA at a dose of 45 mg/m² p.o. daily for 12 wks, or hCG at 5000 iu S.C. daily or 10000 iu S.C. three times weekly can be tried.¹¹

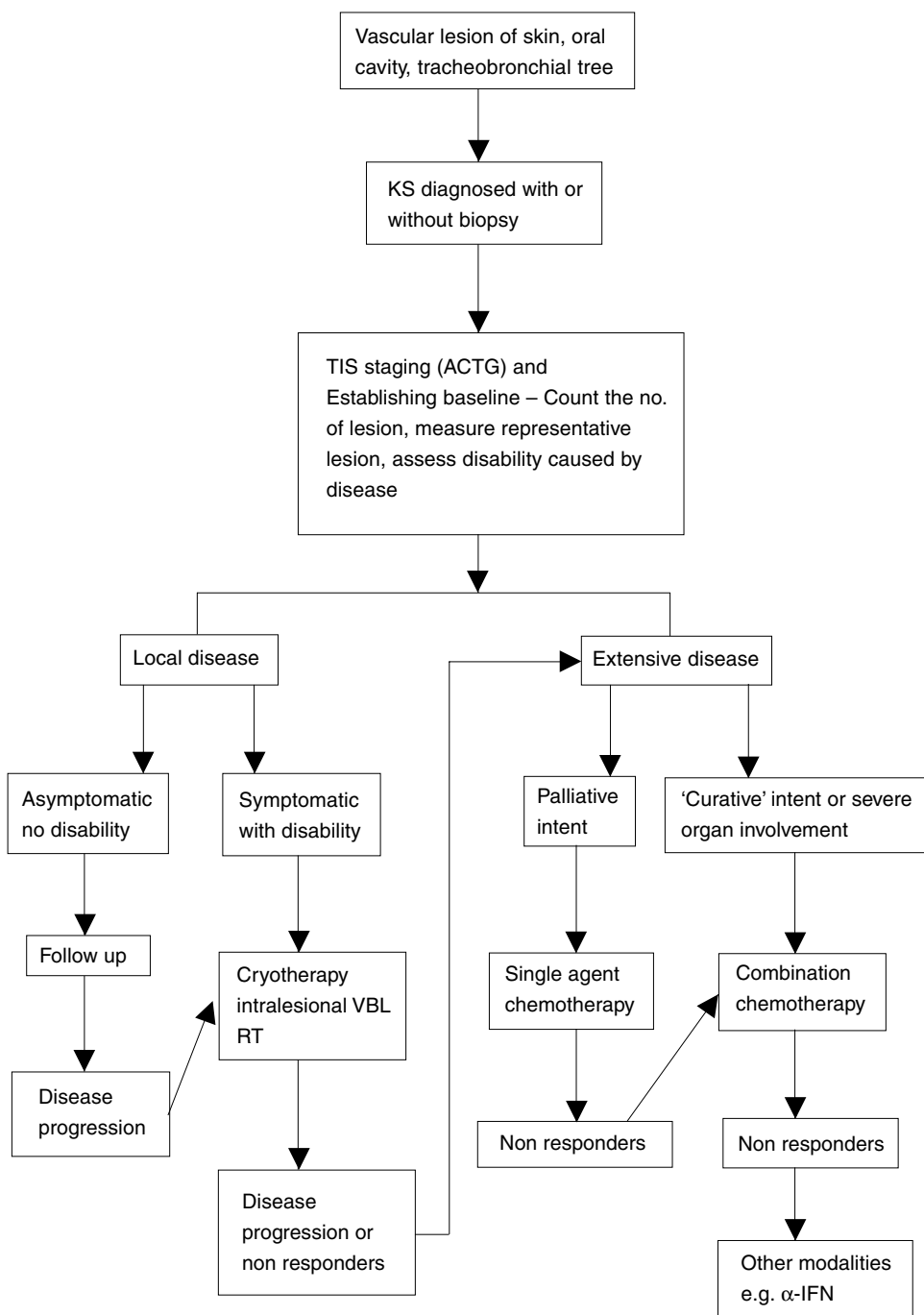
III. Other Considerations

The spectrum of adverse effects of agents for treatment of KS can overlap with anti-retroviral agents. Examples are: neutropaenia can be induced when IFN is used together with AZT; vincristine, paclitaxel, ddI, ddC, and d4T can cause peripheral neuropathy; VP-16 and IDV can cause nausea and vomiting.

Few AIDS-related KS patients die of the disease. Both over and under-treatment of KS are undesirable. Remember to treat the patient rather than the disease itself.

There are active researches in pathogenesis-based therapies. These include anti-angiogenic compounds, hormonal agents, and antiviral (either HIV Tat inhibitors or anti-HHV-8 agents) approaches.¹² Results of these researches may change the current recommendations on treatment for KS.

Algorithm 6.1 Management of AIDS related Kaposi's sarcoma



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6.2 MANAGEMENT OF HIV-ASSOCIATED LYMPHOMA

The immunodeficiency state in HIV infection predisposes one to the development of both opportunistic infections and neoplasms. In the latter case, lymphoma is usually a late manifestation. The incidence of different types of lymphoma including Hodgkin's disease, non-Hodgkin lymphoma (NHL) and T-cell lymphoma is increased in HIV infected individuals, though only immunoblastic and primary central nervous system (CNS) lymphoma are increased significantly. Three kinds of HIV-associated lymphoma are included as an AIDS-defining illness under the Centres for Disease Control (CDC) classification system – Burkitt's, immunoblastic and primary CNS lymphoma.¹ In Hong Kong, NHL has accounted for 2.2% (up to end of 2000) of all AIDS defining illnesses reported over the years.

Epidemiologically, all exposure categories appear to be at equal risk to the development of lymphoma. With the widespread use of highly active antiretroviral therapy (HAART), the incidence of primary CNS lymphoma is apparently declining due to improved immunity. However, the absolute number of reported NHL may paradoxically rise as life expectancy increases.

There are two main clinical types of HIV-associated lymphoma – systemic lymphoma arising in the periphery, and CNS lymphoma limited to the central nervous system. Large overseas studies suggested that systemic lymphoma was the commoner of the two.² The average CD4 cell count at which HIV-associated systemic lymphoma occurs is around 100 cells/mm³, compared to less than 50 in CNS lymphoma. The latter carries a worse prognosis. Between 12% to 16% of HIV infected individuals eventually die of lymphoma. Other unusual types of HIV-associated lymphoma are primary effusion lymphoma, Hodgkin's Disease and T-cell lymphoma.³

Pathologically, AIDS related lymphoma arises as a consequence of long-term stimulation⁴ and proliferation of lymphocytes due to HIV itself as well as to reactivation of prior EBV infection secondary to immunosuppression.⁵ Activation of *c-myc* and *bcl* oncogene is probably involved in the pathogenesis.⁶ Two-thirds of AIDS associated lymphoproliferative disorders are of high grade aggressive types including either B-immunoblastic or small cell non-cleaved lymphoma (either Burkitt or non-Burkitt subtype). The remaining third are intermediate grade diffuse large cell lymphoma.⁷

The algorithms for managing HIV-associated lymphoma are provided at the end of this chapter.

I. Diagnosis of lymphoma in HIV/AIDS

The main differential diagnoses of HIV-associated lymphoma are other causes of lymphadenopathy, notably Persistent Generalised Lymphadenopathy (PGL) and other infections. The characteristic features which might suggest lymphoma as opposed to reactive lymphadenopathy include rapidity of growth, asymmetry, extranodal involvement, and a relatively low CD4 cell count. Fluctuation of lymph node size over time is quite characteristic of PGL. Early diagnosis of lymphoma in patients with HIV infection can be difficult since reactive lymph node enlargement is quite common while extranodal involvement is not uncommon in the setting of HIV infection. For systemic lymphoma, extranodal diseases could occur in such sites as the liver, gastrointestinal tract, bone marrow, and rarely subcutaneous and soft tissues, presenting with corresponding symptomatology in the organ system. On the other hand, opportunistic infections like toxoplasmosis may mimic primary CNS lymphoma. It is important to note that tuberculosis (TB) can present as lymph node enlargement.

It is of prime importance not only to ascertain the diagnosis of lymphoma, but the histological typing and staging before initiation of treatment. A high index of clinical suspicion is crucial in making a diagnosis of HIV-related lymphoma promptly. Other investigations may be indicated to differentiate lymphoma from other lesions. Some examples are:

- (a) CT scan and MRI are performed in the case of a possible diagnosis of CNS lymphoma. This may however not be diagnostic. SPECT scan with Thallium 201 may be better able to differentiate between CNS lymphoma and toxoplasmosis.
- (b) Imaging could be useful in the diagnosis of extranodal involvement in systemic lymphoma, for example, in gastrointestinal diseases.

Investigations should then be followed by measures to obtain histological diagnosis. Though fine needle aspiration biopsy of lymph node may be helpful in the diagnosis of certain infections, it has not replaced conventional excisional biopsy. The latter is still preferred in the evaluation of lymphadenopathy if the suspicion of lymphoma is imminent.

II. Assessment of a case of lymphoma

Assessment of a case of lymphoma determines the prognosis and the plan of treatment. Several factors are associated with shortened survival in patients with AIDS related lymphoma. These include CD4 <100 cells/mm³, history of AIDS prior to the diagnosis of lymphoma, advanced stage, older age (greater than 35 years), poor performance status, primary CNS lymphoma, injecting drug use and elevated LDH level.

The histology and extent of disease provide guidance to treatment. Histologically, HIV-associated NHL is often aggressive and is of high or intermediate grade. Clonality measurement may be another factor for assessing prognosis, with a better survival for monoclonal versus polyclonal lymphoma.⁸ A staging work-up is suggested in Box 6.2, although it has small impact on treatment in patients with NHL. The Ann-Arbor staging system, originally derived for use in Hodgkin's disease, is commonly adopted (Box 6.3).

III. Treatment of HIV-associated lymphoma

In principle, high-grade lymphoma should be treated aggressively with curative intent. However, initial studies with aggressive regimens yielded dismal results with only a fraction of patients achieving complete remission and a high frequency of relapse and fatal opportunistic infections. The quality of life was severely undermined. Hence the planning of treatment needs to be guided by the clinical, virological and immune status of the

Box 6.2 Staging evaluation for non-Hodgkin's lymphoma⁹

Essential

1. Pathologic documentation by haematopathologist
2. Physical examination
3. Documentation of B symptoms
4. Laboratory
 - a. Complete blood counts
 - b. Liver function tests including LDH
 - c. Renal function tests
 - d. Uric acid
 - e. Calcium
 - f. Serum protein electrophoresis
 - g. Serum β_2 -microglobulin
5. Chest radiograph
6. CT scan of abdomen and pelvis
7. Bone marrow biopsy (bilateral trephine)
8. Lumbar puncture

Essential under certain circumstances

1. Chest CT scan
2. Head CT scan
3. Barium studies of gastrointestinal tract
4. Endoscopic examination
5. Cytologic examination of effusion
6. Gallium scan (planar or SPECT)
7. Stereotactic brain biopsy

Box 6.3 Ann Arbor staging system⁹

Stage I	Involvement in single lymph node region or single extralymphatic site
Stage II	Involvement of two or more lymph node regions on the same side of diaphragm Localised contiguous involvement of only one extralymphatic site and lymph node region (stage IIE)
Stage III	Involvement of lymph node regions on both sides of diaphragm; may include spleen
Stage IV	Disseminated involvement of one or more extralymphatic organs with or without lymph node involvement

patient, the histology and staging of the lymphoma, as well as the potential treatment complications. Oncologic consultation is recommended.

III.A Treatment of systemic lymphoma

At the outset of the AIDS epidemic in the early 1980s, the use of dose intensive therapy was considered for HIV-associated systemic lymphoma. The results were generally poor, which could be related to the toxicity of chemotherapy, and/or the poor immune status of patients treated. A modified form of chemotherapy using a lower dose has since replaced standard chemotherapy as the recommended form of therapy. Outcome is generally poor in those who fail the initial regimen. In practice the following regimens can be considered:

- (a) A low dose modified m-BACOD regimen with CNS prophylaxis (Box 6.4) could achieve complete remission in about 50% of patients with 70% complete responders remaining in continuous complete remission without relapse. Although the median survival was only 6.5 months, a median survival of 15 months was documented in those patients who attained complete remission.¹⁰ (reference for Box 6.4)¹¹
- (b) Alternative regimens include the CDE regimen involving the continuous infusion of cyclophosphamide, doxorubicin and etoposide given over 96 hours;¹² infusional dose adjusted EPOCH regimen consisting of etoposide, prednisone, vincristine (oncovin), cyclophosphamide, doxorubicin (hydroxodaunorubicin) together with intra-theal methotrexate and appropriate anti-retroviral therapy at the conclusion of EPOCH;¹³ an oral regimen consisting of CCNU, etoposide, cyclophosphamide, and procarbazine have also yielded good results.¹⁴

As CNS relapse is common, routine lumbar puncture with CSF cytological analysis and prophylaxis is recommended as long as it is not contraindicated on the results of CT or

Box 6.4 Low dose m-BACOD regimen¹¹

Bleomycin	4 mg/m ² , day 1, IV
Doxorubicin	25 mg/m ² , day 1, IV
Cyclophosphamide	30 mg/m ² , day 1, IV
Vincristine sulfate	1.4 mg/m ² , day 1, IV (not to exceed 2 mg)
Dexamethasone	3 mg/m ² , days 1-5, PO
Methotrexate (MTX)	500 mg/m ² , day 15, IV with folinic acid rescue, 25 mg PO q6h X 4, beginning 6 hours after completion of MTX
Cytosine arabinoside(Ara-C)	50 mg, intrathecal, days 1, 8, 21, 28, cycle 1
Helmet-field radiotherapy	4000cGy with known CNS involvement
Appropriate HAART	starting after chemotherapy
Total treatment	4-6 cycles, at 28-day intervals

MRI scan.¹⁵ As systemic lymphoma occurs rarely in conjunction with primary CNS lymphoma, extensive routine evaluation is unnecessary in most patients unless there is CSF seedling. In such instance, local treatment with radiotherapy is warranted. The benefit of combination chemotherapy followed by whole brain irradiation is not ascertained.

III.B Treatment of primary CNS lymphoma

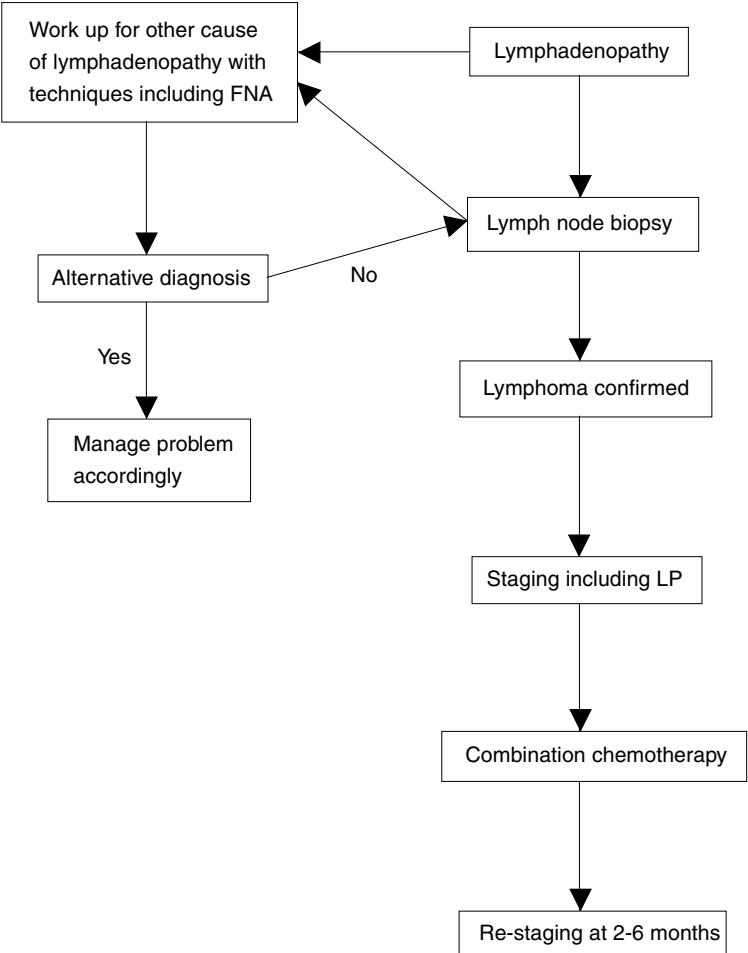
Whole brain irradiation is the treatment of choice for primary CNS lymphomas although the outlook is generally gloomy. Other alternatives are intrathecal ara-C or methotrexate, or combined chemotherapy and radiotherapy. A therapeutic trial of anti-toxoplasma treatment can be considered if histological diagnosis is not available.

III.C Other treatment issues

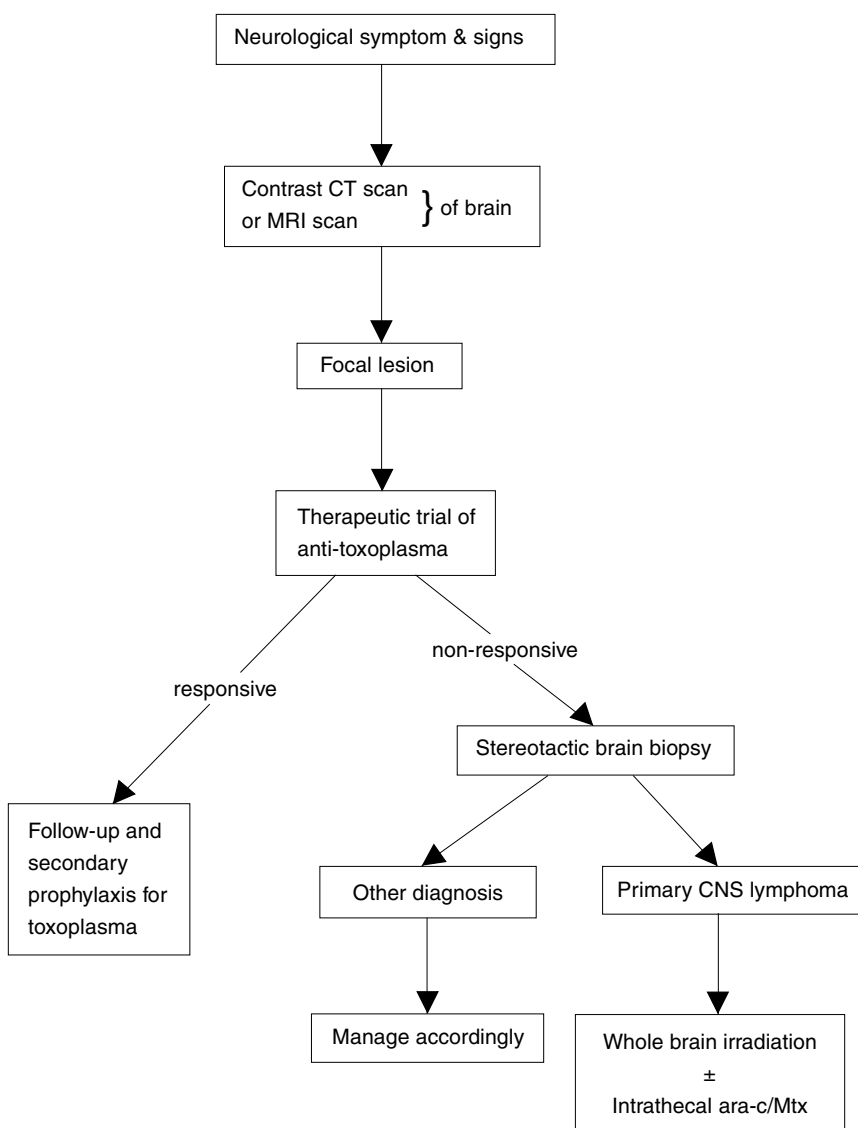
The prognosis of HIV-associated lymphoma is linked partly with the patients' immune status. The advent of highly active antiretroviral treatment (HAART) can probably be used safely but with caution in conjunction with multiple chemotherapy for lymphoma. The success of HAART in improving the immunological status as well as general well being of a patient is likely to make standard therapies more tolerable. This would favour approaches that involve dose-escalation rather than reduction in future.

One potentially fatal complication of chemotherapy is the development of neutropaenia. G-CSF can be used in HIV patients in conjunction with chemotherapy.

Algorithm 6.2A Management of suspected NHL other than primary CNS lymphoma



Algorithm 6.2B Managing a suspected case of primary CNS lymphoma



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6.3 SCREENING FOR CERVICAL NEOPLASIA

The pathogenesis of invasive cervical cancer is multifactorial. There are extensive epidemiological data linking human papillomavirus (HPV) infection with invasive carcinoma of cervix. Of the more than 30 different types of HPV that infect the anogenital tract, a majority of the cervical cancer worldwide is associated with HPV-16 and HPV-18.¹ HPV DNA can be detected in over 30% of such cancers. Histologically HPV-16 and HPV-18 are associated with invasive squamous cell carcinoma and adenocarcinoma of the cervix respectively. The two are now known human oncogenic viruses.

HIV infection, HPV and cervical pathology are related biologically and epidemiologically. Cervical dysplasia and invasive cervical cancer are more prevalent in HIV-positive versus negative women. On the other hand, HIV positive women have a higher rate of HPV infections which are strongly associated with the development of high-grade squamous intraepithelial lesions (SIL) and invasive cervical cancer.² Immune suppression is the factor predisposing HIV positive women to HPV infections. Cervical intraepithelial neoplasm is commoner in HIV infected women with a lower CD4 or who are at an advanced stage of the HIV disease.³

For surveillance purpose, invasive cervical cancer has been added to the list of AIDS-defining illnesses in the 1993 revised classification system recommended by the Centers for Disease Control and Prevention (CDC).⁴ This has also been adopted in Hong Kong. Cervical dysplasia, cervical carcinoma in situ are included as Category B conditions which are attributable to HIV infection or are indicative of the defective cell-mediated immunity.

The management of HIV infection in women involves the prevention of cervical cancer, as well as the early diagnosis and treatment of the cancer and related conditions.

I. Prevention of invasive cervical cancer

Invasive cervical cancer carries significant morbidity and mortality. There is increasing evidence of a causal relationship between HPV infection and cervical cancer, while SIL is the precursor of invasive cervical cancer. In light of the increased occurrence of cervical cancer in HIV infection, and the rising incidence of HIV in women, early detection and treatment of early lesions, for example, SIL, forms the main strategy of cervical screening. A single screening carries significant false negative while periodic regular screening is more effective and is therefore advocated.

Screening can be considered at two levels – screening for specific oncogenic HPV and the screening of early pathological lesions. The benefit of cervical screening in HIV infection is well-established, while that of HPV remains to be determined. Cervical screening helps distinguish between low grade SIL (LSIL) with mild dysplasia, from high grade SIL (HSIL). The risk of invasive cancer increases with the severity of dysplasia.⁵

1.A Cervical screening

After obtaining a complete history of previous cervical diseases, the HIV infected woman should undergo a comprehensive gynecological examination, including a pelvic examination and Pap smear as part of the initial evaluation.

The spatula is the standard device for obtaining specimen in a Pap smear. The additional use of endocervical brush may be considered when:

- (a) the transformation zone is high as in some postmenopausal women;
- (b) the anatomy of the cervix has been altered by previous treatment; and/or
- (c) endocervical lesion is suspected.

The quality of the smear may be undermined by poor technique, concurrent infections or bleeding. The Pap smear should be repeated in the case of an unsatisfactory specimen. Repeat smears should not be performed till 6-8 weeks have lapsed, to allow time for the scrapped surface to re-epithelialize. It must be noted that most cancers and precancerous lesions arise in the transformation zone. It is essential that the whole transformation zone be sampled in the examination.

A newer Pap smear technique using a liquid-based medium is currently being investigated. It has the advantage of sensitivity with the potential of simultaneous HPV testing. However, it is more expensive and does not eliminate false negatives.

In general Pap smear results can be reported using the Pap smear report format according to the Bethesda System:⁶

- (a) specimen adequacy
- (b) general categorization – within normal limits or with specific descriptive diagnosis
- (c) descriptive diagnosis – including benign cellular changes, reactive and reparative cellular change
- (d) epithelial cell abnormality –
 - atypical squamous cells of undetermined significance (ASCUS)

-
- LSIL, including HPV changes and mild dysplasia/CIN 1
 - HSIL, including moderate and severe dysplasia, CIN 2, CIN 3, carcinoma in situ
 - squamous cell carcinoma
 - glandular cell abnormalities
- (e) non-epithelial malignant neoplasm
- (f) hormonal evaluation (for vaginal smear only)

1.B The schedule of cervical screening

On a routine basis, pelvic examination and Pap smear should be performed on HIV infected women for the detection of invasive cervical cancer and SIL. This can be done in line with the recommendations published in the MMWR.^{7,8}

Pelvic examination and Pap smear are performed at first diagnosis of HIV infection and then every six months. After two normal examinations, it is then repeated every twelve months alongside careful vulvar, vaginal and anal inspections. There is no specific CD4 threshold under which the frequency of Pap smear would need to be increased, though this can be considered in cases of:⁶

- (a) previous abnormalities
- (b) HPV infection
- (c) Symptomatic HIV disease and/or deteriorating immune functions
- (d) Post-treatment for dysplasia

Colposcopic evaluation is indicated in the case of atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGCUS), LSIL and HSIL on any Pap smear.

II. Management of cervical lesions

The implementation of periodic cervical screening would lead to the diagnosis of occasional cases of lesions demanding medical attention. It would be useful to develop feasible protocols with gynecologists so that patients can be offered standard quality care. The following table (Box 6.5) summarizes the practice recommended by the Health Resources and Services Administration of the United States:⁶

Box 6.5 Recommended management of abnormal Pap smear

Pap smear result

Severe inflammation

Atypia, ASCUS

LSIL, CIN 1

HSIL, CIN 2 or 3, carcinoma in situ

Invasive carcinoma

Management

Evaluate for infection; repeat Pap smear if inadequate

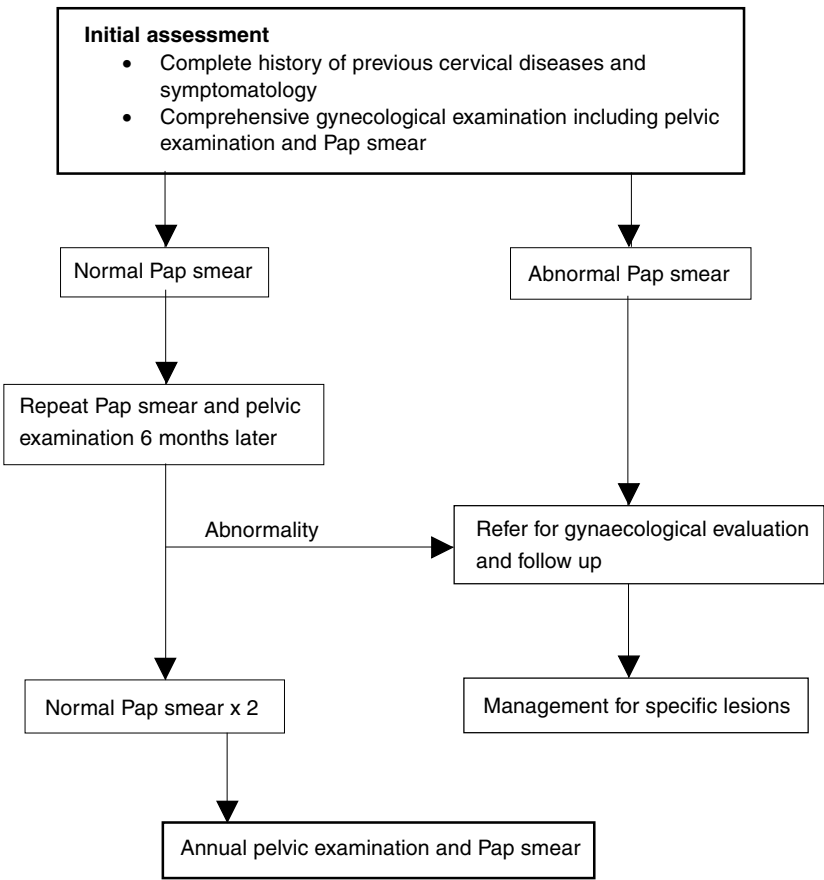
Colposcopy, biopsy if indicated; follow with Pap smear every 6 months

Colposcopy, biopsy if indicated; follow with Pap smear every 6 months; consider repeat colposcopy annually

Colposcopy, biopsy; treat with loop excision or conization

Colposcopy with biopsy or conization; treat with surgery or radiation

Algorithm 6.3 Cervical screening for HIV infected women



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HIV MANAGEMENT IN SELECTED CLINICAL SETTINGS

7.1 HIV-ASSOCIATED DIARRHEA

Diarrhea is experienced by over 50% of AIDS patients at some time during the course of their illness. It can be an important cause of morbidity and mortality in up to a quarter of all patients.¹

I. Etiology of diarrhea in HIV/AIDS

In 15-46% of HIV infected patients with diarrhea, no pathogen can be identified. In such circumstances, the symptomatology may be attributed to HIV itself – a condition termed HIV enteropathy. In some cases there is impaired epithelial barrier function. There is suggestion of the opening of the tight junctions between epithelial cells by HIV-stimulated cytokine release, leading to diarrhea by a leak flux mechanism. Other proposed mechanisms include bile acid malabsorption, dysregulation of the enteric immune system, local production of lymphokines and anatomic denervation.

I.A Infective causes of diarrhea

Diarrhea in HIV/AIDS patients is commonly infective in origin. A whole range of pathogens may give rise to diarrhea, including bacteria, virus, mycobacteria and parasites, involving the small and/or large bowel.² Classical pathogens in HIV/AIDS include *Cryptosporidia*, *Isospora belli*, *Microsporidia* and *Mycobacterium avium-intracellulare* (MAI). Systemic infections could occur when the pathogen disseminates from the gut, as in some cases of bacterial infections (MAI, *Salmonella*, *Shigella*, *Campylobacter*). Relapses are not uncommon after successful treatment, for example, in cytomegalovirus, MAI, *Salmonella*, *Shigella*, *Campylobacter*, *Cryptosporidia*, *Microsporidia* and *Cyclospora* infections.

I.B Non-infective causes of diarrhea

Non-infective causes must also be considered in the differential diagnosis: neoplastic involvement of the gut, drug reaction, lactose intolerance, and pancreatic insufficiency which may be a secondary effect of pentamidine or didanosine (ddI) therapy, and which could lead to malabsorption and steatorrhea.

Advance in HIV treatment is changing the profile of AIDS-associated diarrhea. Highly active antiretroviral therapy (HAART) is causing a reduction of opportunistic infections as

the cause of diarrhea. Chronic diarrhea, if occurs, is more likely to be a result of the side effects of antiretrovirals themselves. Nevertheless, diarrhea is still one common gastrointestinal symptom of HIV/AIDS, which is more common as immune deficiency progresses.

II. Workup on HIV associated diarrhea

In approaching an HIV/AIDS patient with diarrhea, it is important to consider three basic aims: detection of treatable causes, relief of symptoms, and the prevention of malabsorption. An algorithm is provided at the end of the chapter.

Overall, infection is still by far the commonest cause of diarrhea in HIV/AIDS, the diagnosis of which should be made promptly to facilitate effective treatment. Patients may present very similarly despite the variety of pathogens which might be the cause of the symptoms. A careful workup would help in assessing the severity, pinpointing the underlying cause, and making plan on management.

The diagnosis of HIV enteropathy is by exclusion, where there are histopathologic and functional abnormalities of the small bowel but the absence of pathogen or malignancies after investigations. Antiretroviral therapy may lead to a resolution of the diarrhea.

II.A Initial assessment of HIV-associated diarrhea

A careful food history, drug history, travel, and associated symptoms (e.g. nausea, vomiting, fever and other systemic upset), diet (e.g. lactose) could provide some hints to the underlying **cause**. Chronic diarrhea is defined as intermittent or continuous loose or watery stools for more than one month.

The initial assessment should determine the **degree of immune deficiency**. A low CD4 count and previous history of opportunistic infections are indications of a poor immune status. An evaluation of the degree of immunodeficiency is useful as it is a common factor behind some major bacterial causes of diarrhea. *Cryptosporidia*, *C. difficile*, *I. belli* and *Microsporidia* occur in the presence of a low CD4 of often less than 100/ul.

The assessment would also lead to the **anatomical site** of the pathology, that is, whether the diarrhea is a result of small bowel or large bowel disease. In this connection, the number and volume of bowel movements should be noted. Large volume or relatively infrequent or nocturnal diarrhea points to the small bowel. Frequent small volume bloody bowel movements with lower abdominal pain, urgency and rebound tenderness are features of large bowel problems.

II.B Determining the etiology of diarrhea

A working diagnosis could be formulated after a good history and physical examination. Generally speaking, chronic diarrhea and a low CD4 count of less than 200/ul, male homosexuality, and significant weight loss are factors deserving attention.³ Infective causes must be considered. Some additional hints of a bacterial etiology are as follows:

- (a) *C. difficile* is associated with antibiotic uses, notably clindamycin and penicillin.
- (b) *Cryptosporidia* may give a large volume diarrhea in the presence of immunodeficiency. It is however not distinguishable clinically from Isosporiasis and *Microsporidia*. Low grade fever may be experienced. The various *Microsporidia* account for up to 20% of the diarrhea in those with CD4 <50/ul, and as much as 60% in those with chronic diarrhea.
- (c) CMV infection may account for 20% of patients with AIDS. The clinical picture is typically one of fever and small-volume and occasionally bloody diarrhea with fecal leucocytes. Occasionally the disease is complicated by perforation or toxic megacolon.
- (d) MAI is often associated with significant systemic upset including fever, weight loss, night sweat and a generally catabolic state.

Although various viruses such as rotavirus, adenovirus, coronavirus, astrovirus and calicivirus have been implicated as causes of diarrhea in AIDS, most appear to be self-limiting and do not require treatment.

II.C Investigations

As in non-HIV diarrhea, stool **microscopy**, **microbiology** and **culture** can be the most important workup in determining the cause of the symptoms when infections are suspected. Commonly three sets of stool studies are sent to the laboratory because the shedding of microorganisms is often episodic.

If stool examination yields inconclusive results, **endoscopy with biopsy** is the next step. Patients who may benefit from endoscopy have not been well-characterized although those with weight loss and more severe diarrhea would likely benefit from the investigations. Approximately 50% of HIV infected patients in whom chronic diarrhea remains unexplained after multiple stool tests had a potential etiology identified by endoscopic examination.⁴ Specifically,

- (a) patients with classic small bowel diarrhea should undergo upper gastrointestinal tract endoscopy, with biopsy from the distal duodenum or proximal jejunum. Aspirates and cytologic brushings as well as biopsy samples placed directly in glutaraldehyde may be needed.
- (b) If the history suggests colorectal problem, lower endoscopy is indicated.

- (c) *C. difficile* can be difficult to diagnose. A *C. difficile* toxin assay should be considered as part of the workup for new-onset watery diarrhea, especially if there is associated fever, leukocytosis and cramp.
- (d) Histology could be useful for arriving at a definitive diagnosis. In CMV infection, the virus typically produces a colitis with the endoscopic appearance of punctate hemorrhages and ulceration, and the demonstration of intranuclear inclusion on biopsy.

If fever accompanies the diarrhea, **blood culture**, **chest radiograph** and **urinalysis** should also be performed.

If diarrhea persists for over 6 to 8 weeks, the diagnostic cycle should begin again, with stool tests and then endoscopic examination and biopsies.

III. Treatment of HIV associated diarrhea

There are two forms of treatment, specific therapy for identified etiology, and general treatment to relieve symptoms. HAART is another treatment option that works by improving the immunity.

III.A Pathogen-specific therapy

Generally, most infective causes of diarrhea are amenable to treatment. Treatment responses can sometimes be one means of confirming the original diagnosis. Standard treatment regimen for common infective causes of diarrhea are listed in Box 7.1. Metronidazole is the treatment for *C. difficile*. *Isospora belli* responds to trimethoprim-sulfamethoxazole. MAI responds to treatment with macrolide and ethambutol. The treatment of CMV colitis resembles that of retinitis.

On the other hand, pathogen-specific therapy for *Cryptosporidia* infection has so far yielded disappointing results. The most effective therapy is HAART. Immune reconstitution following potent antiretroviral therapy can induce cessation of diarrhea, weight gain, and complete remission of cryptosporidiosis. Usually the symptoms disappear once CD4 rises above 250/ul. There is no standard treatment for microsporidiosis. Albendazole may decrease the diarrhea but cannot clear the organisms for the stool.

Some pathogens cause diseases in the setting of low CD4 counts. Even if initial treatment is successful, relapse is common. This is the situation for CMV, MAI, cryptosporidiosis, microsporidia and Cyclospora infections.

Box 7.1 Pathogen-specific treatment⁵

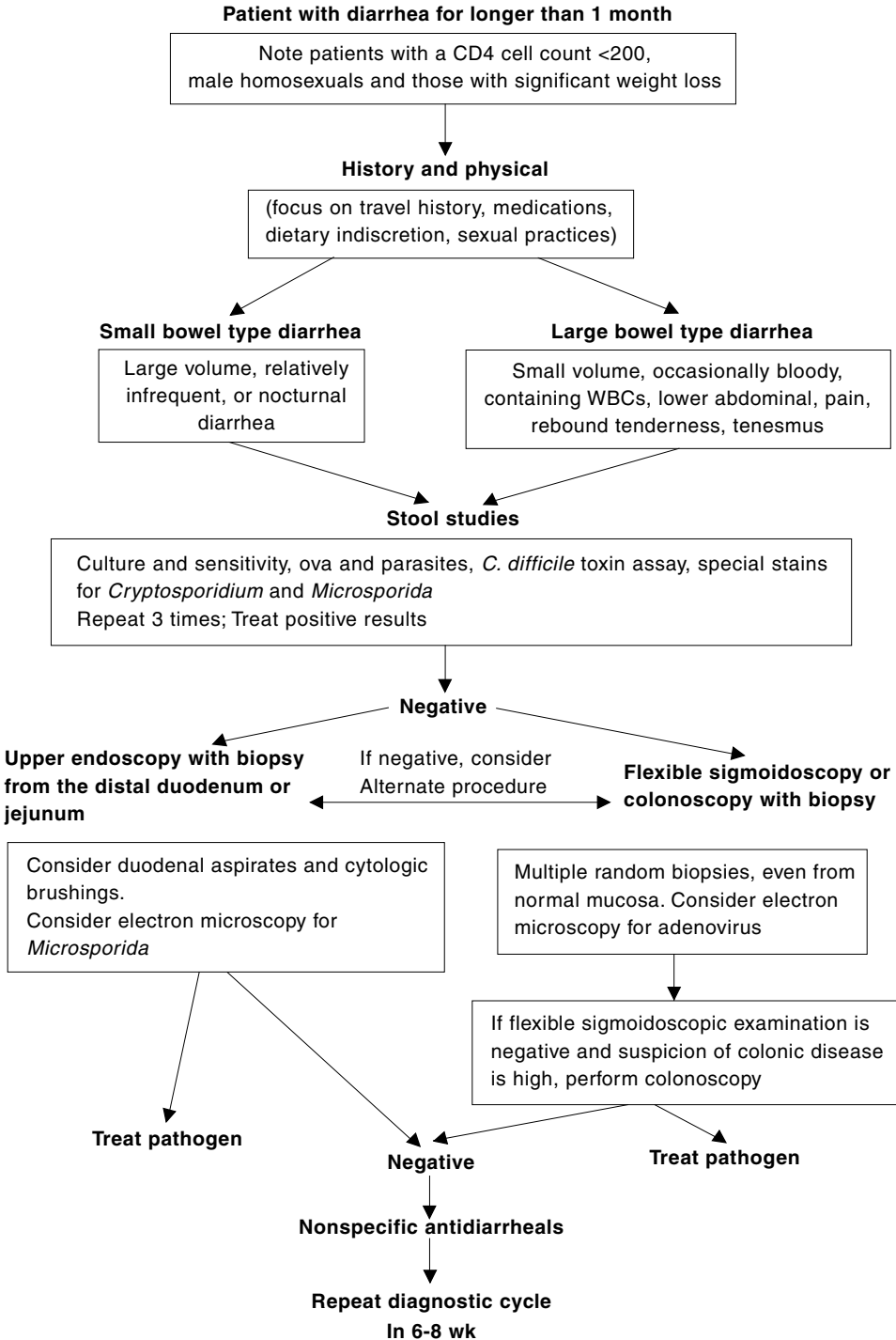
CMV colitis	Ganciclovir 5 mg/Kg IV every 12 hours for 14 days. If intolerant or unresponsive, use foscarnet 90 mg/Kg per day IV for 14 days
MAI infection	Rifabutin 300 mg po daily, plus ethambutol 400 mg po every 12 hours, and clarithromycin 500 mg po every 12 hours.
Salmonella / Shigella enterocolitis	Ciprofloxacin 500 mg po every 12 hours for 14 days
Campylobacter colitis	Erythromycin 500 mg po every 6 hours
Cryptosporidiosis	Paromomycin 500 mg po every 8 hours for 14 days. No proven effective therapy. Other possible treatment includes azithromycin and letrozol. Response generally poor for all treatment.
Microsporidiosis	Albendazole 400 mg po every 12 hours for 14 days. No proven effective therapy. Response generally poor and relapse is common.
Isosporiasis	Trimethoprim-sulfamethoxazole 160/800 mg po every 6 hours for 10 days, then twice daily for 21 days. Relapse common.

III.B Supportive treatment

Symptomatic management is the mainstay of the treatment in diarrhea, in particular when no treatable cause can be identified. A non-narcotic, narcotic, or antisecretory medicine can be used.

Chronic diarrhea may lead to malnutrition, which can jeopardize the quality and length of life. Dietary assessment and ensuring adequate intake is crucial. The use of nutritional supplements, vitamin and mineral replacements is important. Depending on the severity of malabsorption, enteral supplement and feeding would need to be considered. Total parenteral nutrition is indicated when enteral intake is contraindicated or for a limited but crucial period, for example, perioperatively.

Algorithm 7.1



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7.2 DERMATOLOGIC MANIFESTATIONS IN HIV DISEASE

The underlying immunodeficiency and immune dysregulation predispose HIV-infected patients to a variety of skin disorders. Recognition and management of skin diseases in HIV/AIDS patients are important in several aspects. In some patients, skin findings may be the earliest sign of HIV presentation and can thus alert one to an early HIV diagnosis and care. In more advanced diseases with systemic opportunistic infections, cutaneous manifestations may facilitate correct diagnosis and specific treatment. In general, skin complications tend to linger on in HIV-infected patients. This adds to the psychosocial impact of HIV disease. Appropriate management can hopefully ameliorate the distressing symptoms and alter disease course.

I. Presentations of skin diseases in HIV/AIDS

The frequency and distribution of dermatologic complications in HIV infection vary widely. This can be partially explained by the difference in study design, stage of HIV disease, observer bias, endemicity of complicating infections and time frame of the studies. A myriad of skin disorders has been implicated in HIV/AIDS patients; some of the conditions are more specifically associated with HIV/AIDS (Box 7.2). The pattern of dermatological disorders of the local patients with HIV infection is summarized in Box 7.3. (Ho KM & Ho TTY, unpublished data)

Presentation of a skin disease in HIV disease may either be typical or atypical. Some examples are:

- (a) Typical clinical presentation of a common skin disease – e.g. seborrhoeic dermatitis
- (b) Atypical presentation of a common skin disease – e.g. giant molluscum in an adult man
- (c) Typical presentation of an uncommon disease – e.g. Kaposi's sarcoma (KS)
- (d) Atypical presentation of an uncommon disease – e.g. extrapulmonary pneumocystosis involving the external auditory canal
- (e) Unique condition in HIV disease – e.g. lipodystrophy syndrome

A more systematic way of classifying skin manifestations in HIV disease is according to its aetiology or pathogenetic mechanisms (Box 7.4). This may be more useful in clinical management. Presentations, diagnoses, investigations and treatment of selected skin conditions in HIV disease are in Boxes 7.5 to 7.10. General principles are considered below.

Box 7.2 Cutaneous conditions in patients with HIV Infection¹ (according to disease occurrence and relationship to HIV infection)

Group 1: Conditions that are specific for HIV infection

Bacillary angiomatosis
Diffuse interstitial lymphocytosis syndrome
Kaposi sarcoma
Proximal white subungual onychomycosis

Group 2: Conditions that occur with an increased prevalence in patients with HIV infection

Infective

Bacterial:

Staphylococcus aureus infection
Syphilis

Fungal:

Dermatophyte infection – nails and skin
Systemic fungal infection – especially those with cutaneous or oral lesions
Cryptococcosis
Histoplasmosis

Viral:

Herpes simplex virus infection
Human papillomavirus infection
Molluscum contagiosum
Varicella-zoster virus infection – especially disseminated or more than 1 episode

Parasitic:

Scabies

Inflammatory

Acquired ichthyosis
Drug reactions
Eosinophilic folliculitis
Erythema elevatum diutinum
Granuloma annulare
Photo-induced and photoaggravated conditions
Porphyria cutanea tarda
Prurigo nodularis
Pruritus
Psoriasis vulgaris
Seborrheic dermatitis
Vitiligo

Proliferative or Neoplastic

Dermatofibromas (multiples)
Lymphomas – especially non-Hodgkins B-cell
Epithelial neoplasms (basal cell carcinoma and mucosal tumors)

Miscellaneous

Alopecia areata and alopecia universalis
Eyelash trichomegaly – acquired

Group 3: Conditions that coincidentally occur in patients with HIV infection

Autoimmune bullous disorders
Calciophylaxis
Granuloma inguinale
Kawasaki disease – adult onset
Lichen amyloidosis
Pityriasis rubra pilaris
Pyoderma gangrenosum
Reactive perforating dermatosis
Transient acantholytic dermatosis

Box 7.3 Cutaneous disorders in a cross sectional study of patients in an HIV clinic in Hong Kong (n = 186)

Cutaneous disorders#	No. of subjects affected	Prevalence
1. Fungal infections	89	47.8%
<i>Tinea pedis</i>	68	36.6%
<i>Onychomycosis</i>	58	31.2%
<i>Tinea cruris</i>	5	2.7%
<i>Tinea corporis</i>	1	0.5%
<i>Pityriasis versicolor</i>	2	1.1%
2. Eczema (all types)	49	26.3%
3. Seborrhoeic dermatitis	42	22.6%
4. Lipodystrophy	22	11.8%
5. Miscellaneous nail conditions	20	10.8%
<i>Melanonychia</i>	8	4.3%
<i>Nail dystrophy</i>	7	3.8%
<i>Chronic paronychia</i>	2	1.1%
<i>Subungual haematoma</i>	2	1.1%
<i>Ingrown toenail</i>	1	0.5%
6. Folliculitis	19	10.2%
Bacterial folliculitis	13	7.0%
Eosinophilic folliculitis	4	2.2%
<i>Pityrosporum folliculitis</i>	2	1.1%
7. Pruritic papular eruption	14	7.5%
8. Viral infections#	9	4.8%
<i>Common warts</i>	7	3.8%
<i>Post-herpetic neuralgia</i>	2	1.1%
<i>Molluscum contagiosum</i>	1	0.5%
9. Cheilitis / dry lips	11	5.9%
10. Hyperpigmentation	9	4.8%
<i>Melasma</i>	4	2.2%
<i>Easy suntan</i>	4	2.2%
<i>Generalized hyperpigmentation</i>	1	0.5%
11. Drug reaction	6	3.2%
12. Exaggerated insect bite reaction	4	2.2%
13. Xerosis	4	2.2%
14. Keratosis pilaris	3	1.6%
15. Kaposi's sarcoma	2	1.1%
16. Urticaria	2	1.1%
17. Vitiligo	2	1.1%

#An individual may have more than 1 dermatological condition, 175 (94%) had suffered one or more cutaneous disorder during their course of HIV infection, giving a total cumulative incidence of 528 dermatoses. 160 (86%) were found to have one or more cutaneous disorders at the time of the study.

Box 7.4 Classification of skin diseases in HIV infection according to aetiology

A. Infective	<i>Bacterial</i>	<ul style="list-style-type: none"> • bacterial folliculitis • boil • impetigo • skin abscess • syphilis (1° & 2°) • tuberculosis • atypical mycobacterium • bacillary angiomatosis
	<i>Fungal</i>	<ul style="list-style-type: none"> • dermatophytosis • pityriasis versicolor • candidiasis • cryptococcosis • penicilliosis
	<i>Viral</i>	<ul style="list-style-type: none"> • herpes zoster • herpes simplex • molluscum contagiosum • wart
	<i>Arthropod</i>	<ul style="list-style-type: none"> • scabies
B. Inflammatory		<ul style="list-style-type: none"> • cutaneous drug eruption • eosinophilic folliculitis • seborrhoeic dermatitis • psoriasis • atopic eczema • xerosis, ichthyosis and asteatotic dermatitis • pruritic papular eruption
C. Neoplastic		<ul style="list-style-type: none"> • Kaposi's sarcoma (KS) • Non-Hodgkin's lymphoma • Cloacogenic carcinoma
D. Miscellaneous		<ul style="list-style-type: none"> • Lipodystrophy syndrome • Conditions involving nails and hair

Box 7.5 Bacterial infections

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Boils, folliculitis, impetigo or related conditions	The primary skin lesion for boil and folliculitis is pustule; for impetigo it's weeping macule or small patch with peripheral fine scale. They are commonly caused by staphylococcus or streptococcus, or pseudomonas in other cases	Could include botryomycosis which presents with non descript papules or plaque surrounded by pustules on the trunk, neck or extremities related to staphylococcus	Clinical and swab for culture	Antibiotics, antiseptics, with or without surgical drainage	Recurrent bacterial infection is a feature of HIV infection in children
Tuberculosis & atypical Mycobacterium	Varying appearances – small papules and pustules that resemble folliculitis, eruption that resemble atopic dermatitis, localized cutaneous abscess, suppurative lymphadenitis, non-specific ulcerations, palmar and plantar hyperkeratoses, and sporotrichoid nodules all have been reported ⁴		Mainly by culture or histopathology supplemented by molecular diagnostic technique such as PCR	Similar to those with systemic involvement according to the type of mycobacteria isolated and the immune status of the individual	
Bacillary angiomatosis	The primary lesions are vascular papules or nodules (pyogenic granuloma – like) distributed over the face or upper trunk. It is an important differential diagnosis for KS		By histopathology with special stain (e.g. Warthin Starry stain)	May include macrolide (or azalides) antibiotics, doxycycline; ciprofloxacin, rifampicin and septrin also have activity against the causative organism (<i>Bartonella sp.</i>)	

Box 7.6 Fungal infection

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Superficial dermatophytosis	Annular lesion with active margin and central clearing in tinea corporis, faciale and cruris, and diffuse hyperkeratosis or vesiculation in tinea pedis	Tinea faciale mimicking erythema multiforme or seborrhoeic dermatitis, ⁵ and tinea pedis presented as keratoderma blenorrhagica like lesion has been reported	Microscopic examination or culture of scale/ nail/hair sample obtained	Common treatment used are topical imidazoles or, Whitfield ointment; oral drugs are griseofulvin, itraconazole or terbinafine	Dermatophytes can affect the body (tinea corporis), sole (tinea pedis), groin (tinea cruris), face (tinea faciale), scalp (tinea capitis) and nail (tinea unguium; onychomycosis)
Pityrosporum yeast	The classical lesion of pityriasis versicolor is hypopigmented macules with superficial fine powdery scale over upper trunk; <i>pityrosporum</i> folliculitis presents with itchy monomorphic folliculitis or follicular papules over upper back, chest or face		Clinical or microscopic examination of scale or histopathology	Topical or oral imidazoles (or triazole)	Apart from causing pityriasis versicolor, <i>pityrosporum</i> folliculitis, it is also related to seborrhoeic dermatitis
Penicilliosis	Typical lesions are umbilicated papules simulating molluscum contagiosum ⁶	Other presentation may include ecthyma, folliculitis, subcutaneous nodule and morbilliform rash	Histopathology and/ or culture of biopsy specimen	Amphotericin B or itraconazole	
Cryptococcus	Molluscum contagiosum like lesions	Other presentations can mimic HSV, cellulitis, KS or hypertrophic lesions like rhinophyma	Histopathology and/ or appropriate culture	Amphotericin B or fluconazole/itraconazole	

Box 7.7 Viral infection

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Varicella zoster	The primary skin lesion is vesicles arranged in crops, distributed along one or more dermatomes; can be recurrent	Persistent non-healing ulcers, warty molluscum-like nodular lesion, disseminated and generalized involvement of the body	Mainly clinical; viral culture, direct immunofluorescence study or histopathology may sometimes be required for confirmation	Systemic acyclovir	Though proven useful in general people, valaciclovir or famciclovir had not been tested extensively in immuno-compromised hosts
Molluscum contagiosum	The primary skin lesion is white or red papules or small nodules with or without umbilication	Large and multiple lesions on the face in adult, which can occur in HIV positive patients	Mainly clinical; histopathology may be required for confirmation in atypical cases	Curettage and iodination is commonly used in our locality; spontaneous resolution after HAART has been reported	

Box 7.8 Inflammatory dermatosis

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Psoriasis	Typical lesion is an erythematous well demarcated plaque with silvery scale distributed more on the extensor surface of the limbs and body; HIV-related psoriasis may develop in patients with mild pre-existing psoriasis that suddenly undergoes severe exacerbation once AIDS develops, or may erupt spontaneously at some point after HIV seroconversion		Usually by clinical and occasionally by histopathology	Composed of topical tar, salicylic acid, steroid, dithranol, calcipotriol, phototherapy (PUVA can theoretically depress the body immunological function), and systemic agents such as retinoid, methotrexate (that should also be used with caution in HIV patient)	
Seborrhoeic dermatitis	Typical lesion is poorly marginated scaly erythematous patches affecting glabella, nasolabial fold, external auditory canal, scalp, presternal area and occasionally the groin	Unusual sites such as the trunk and extremities may be affected in HIV patients. It can be extensive and resistant to conventional treatment	Clinical examination	As <i>pityrosporum</i> yeast is thought to play an important role in this papulosquamous disorder, treatment is by combination of topical imidazole and mild topical steroid	It is probably one of the commonest skin condition encountered in patient with HIV infection, occurring in 85% of the patients at some point of their disease

Box 7.8 Inflammatory dermatosis (Cont'd)

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Atopic dermatitis	May have recurrence of pre-existing atopic dermatitis, which have been in remission for some years, when they become immunological deficient; erythroderma has been reported; ⁵ typical skin rash is itchy poorly demarcated erythematous papulovesicular lesion with weeping, scale crust that have a characteristic distribution; there are also different protean minor manifestations		Clinical examination (strict criteria as proposed by Hannaffin or British Working Group should be used to qualify the diagnosis of atopic dermatitis)	Emollient, topical steroid, and occasionally phototherapy and short course of systemic steroid	
Xerosis, ichthyosis, and asteatotic dermatitis	Dry skin is very common in patient with HIV infection and is probably the commonest cause of pruritus; typically the skin is dry and flaky with or without excoriation marks; its aetiology is not certain		Mainly on clinical ground but it is very important to rule out other important dermatological conditions that can also present with pruritus	By proper skin care and liberal use of emollient	

Box 7.8 Inflammatory dermatosis (Cont'd)

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Pruritic papular eruption	Eosinophilic folliculitis is the better characterised entity and one of the most common pruritic dermatosis in patients with HIV infection; patients generally present with widespread excoriated follicular papules that involve the trunk, extremities, and head and neck; intact pustules are unusually seen. ⁷ It is important to exclude other conditions that may present with pruritus such as scabies, NHL or dermatitis herpetiformis		Clinical and histopathology	Oral isotretinoin, metronidazole, itraconazole or UVB have been reported with variable success	It was originally described as a specific entity that affected HIV infected individual of African black ethnic origin; however, it is now believed to be a result skin diseases of heterogeneous causes
Cutaneous drug reaction	Cutaneous drug eruptions are the most common manifestation of drug hypersensitivity; the incidence of drug reaction is higher in patient with HIV infection; septrin, anti-TB drugs and NNRTIs are the well reported culprits; morbilliform rash is probably the commonest type of drug rash; Stevens-Johnson syndrome and toxic epidermal necrolysis are also well known; penile ulceration associated with foscarnet, pentamidine associated skin ulceration, urticarial and lichenoid rash have also been described		Mainly by clinical assessment supplemented by histopathology and by exclusion	Withdrawal of culprit drug and supportive management is most important	

Box 7.9 Neoplastic diseases (refer to chapters 6.1 to 6.3)

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Kaposi's sarcoma	Typical lesions in KS are asymptomatic bluish/reddish macules, papulonodules or plaque on nearly any sites on the body		Clinical diagnosis confirmed by histopathology	Can be expectant, local destructive, local chemotherapeutic or radiotherapy or systemic chemotherapy dependent on the symptom and organ involvement; HAART may sometimes induce remission of KS	More common in homosexual men
Non-Hodgkin's lymphoma (NHL)	The B-cell types of NHL may occasionally present as fleshy skin papulonodules/plaques; the T-cell types may present as bizarre shaped patches, plaques or nodules with superficial scaling and inter/intra-lesional variation		Histopathology supplemented by immunohistochemical/molecular techniques	B-cell type NHL is mainly treated by systemic chemotherapy; T-cell type NHL can be treated by chemophototherapy, radiotherapy (including total body electron beam), interferon, and systemic chemotherapy	
Cloacogenic carcinoma (or related dystrophic conditions)	Lesions can present as wart like papules (bowenoid papulosis/vulval dystrophy) or squamous carcinoma like exophytic growth involving anogenital area		Histopathology or cytology in screening test; testing for HPV is undergoing active research	As for non-HIV infected person with similar conditions	It is related to HPV infection and the pathogenesis is probably quite similar as that for carcinoma of the cervix in female; the disease incidence is increased in HIV infected population

Box 7.10 Miscellaneous skin conditions

Disease	Typical presentation	Atypical presentation	Diagnosis	Treatment	Comments
Lipodystrophy	Peripheral fat loss (liopatrophy in face, limbs, and buttocks) and central fat accumulation (abdomen, breast, dorsocervical spine – buffalo hump) ⁸		Clinical; dual energy X-ray absorptiometry (DEXA) and CT scan of abdomen	No well-proven therapy; withdraw potential associated drug	Incidence and definition varied widely across different studies; may be related to protease inhibitor use, metabolic disturbance such as hyperglycaemia, hyperlipidaemia can occur
Conditions involving nail and hair					Proximal white subungual onychomycosis is thought to be highly suggestive of HIV infection; the incidence of candida and scytalidium (and other non-dermatophyte filamentous fungus) related onychomycosis is increased; yellow nail syndrome, nail ridging and opacity and Beau's line are well reported; melanonychia is associated with zidovudine treatment; hair abnormalities have been described in patients with HIV infection - these include telogen effluvium, premature graying, diffuse thinning, alteration of texture and alopecia areata
Miscellaneous dermatoses					Generalised hyperpigmentation is very common in patient with long standing HIV infection; porphyria cutanea tarda, granuloma annulare, pityriasis rubra pilaris, vasculitis have all been described in patients with HIV infection

Clinical courses of many skin diseases may be altered in concomitant HIV infection, especially when there is deterioration or improvement in immune status. In general, skin conditions in HIV infection can occur in unusual settings, can be unusually severe, can have bizarre clinical appearance, can run recurrent course, can be part of systemic opportunistic infections and can have abnormal response to conventional treatment.

1.A Unusual settings

HIV infection should be suspected when a cutaneous disease presents in unusual settings, e.g. multidermatomal herpes zoster occurring in a young healthy adult. Herpes zoster in immunocompromised patients tends to be more chronic, severe and involve more than one dermatome. Similarly, KS in a young individual is strongly indicative of HIV disease.

1.B Increased severity

Minor skin conditions may be unusually severe if they occur with HIV infection. One example is seborrhoeic dermatitis which is very common in HIV-infected people. It is characterised by thick, scaly plaques with inflammation. Involvement can be more extensive in HIV-infected patients. On the other hand, HIV infection may present as an acute exacerbation or onset of severe psoriasis. Likewise, skin infections such as folliculitis, furuncle, wart and superficial fungal infections may be extensive and recalcitrant.

1.C Bizarre presentations

Bizarre skin presentations may occur in HIV/AIDS. Molluscum contagiosum may involve extragenital sites, e.g. the face, which is otherwise uncommon in HIV negative adults. Herpes simplex infection may become disseminated due to poor host immunity. Scabies may be widespread and manifest as an erythematous papulosquamous eruption. Hypersensitivity reaction to drugs is more frequent and severe with concomitant HIV infection.² Drug eruption due to co-trimoxazole is a good example. Constitutional symptoms are often prominent and can precede the rash.

1.D As part of systemic diseases

Apart from local or systemic involvement of a skin disease, skin lesions in HIV-infected patients can also be part of a systemic opportunistic infection. Disseminated cryptococcal

infection can give rise to the typical skin-coloured papules with central umbilication, which resembles molluscum contagiosum. *Penicillium marneffe*i infection may present with erythematous maculopapular rash. Inflamed, tender nodules or ulcerating lesions are skin manifestations of systemic mycobacterial infection. Skin biopsies for histology and appropriate culture are indicated when diagnosis is uncertain, or when disseminated infections are suspected. Bacillary angiomatosis, a vascular proliferative process caused by *Bartonella henselae*, presents most commonly with multiple pyogenic granuloma like red skin papules/nodules. It may be mistaken as KS. Differentiation by biopsy and culture is prudent as it may cause visceral disease and death if untreated.

II. General principles of management

II.A Diagnosis

The unusual manifestations of skin diseases in HIV disease may make diagnosis by the naked eye unreliable. Nevertheless, one can avoid mistakes by following the basic principles of dermatology, where diagnosis begins with a careful inspection of the primary lesion, delineation of spread and secondary lesions, and exclusion of a systemic cause.

Skin biopsy is particularly useful in the setting of HIV disease, unless the diagnosis is obvious. Sometimes the patient may benefit from a therapeutic trial while waiting for the biopsy results. Regardless, it would be wrong to consider skin biopsy as the definitive method of diagnosis. The unusual clinical presentation of a dermatosis may also extend to its histological pattern. Despite the use of special stain and culture, immunohistochemical or molecular technique, the diagnosis may still be beyond reach.

II.B Treatment

A majority of the topical dermatologic treatment can be used in person with HIV infection. Systemic therapy, including phototherapy, should however be used with caution. Response to conventional treatment of skin diseases is sometimes inferior in HIV-infected individuals compared with negative ones. Higher doses of medication, multi-modality treatment, prolonged therapy or supplementary surgical procedures may be needed. Superficial folliculitis, eosinophilic folliculitis, seborrhoeic dermatitis and dermatophytosis are common examples in this regard. Because of the tendency to relapse, therapy may have to be maintained continuously.

In some cases the quality of life may be hampered due to the accompanying disfigurement, e.g. extensive cutaneous KS, or severe symptoms, e.g. intense pruritus due to eosinophilic

folliculitis. Although skin problems are usually not life-threatening, management of these conditions in HIV-infected patients should not be overlooked. Successful treatment can greatly improve the quality of life and provide patients with a sense of control over the most visible aspect of their HIV disease.

II.C HAART and skin disease

The advent of highly active antiretroviral therapy (HAART) has also benefited skin complications in terms of prognosis and outcomes. There were reports that as immune competence improved, the skin conditions either had better treatment response or even subsided spontaneously, e.g. Kaposi's sarcoma,³ molluscum contagiosum and psoriasis.

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7.3 AIDS WASTING SYNDROME

As a chronic debilitating disease, AIDS is commonly associated with progressive loss of weight. For this reason, AIDS is also called 'slim disease' in Africa. The ***AIDS wasting syndrome*** shares many features with the cachexia seen in cancer or sepsis. Nevertheless, the precise pathophysiology is only incompletely understood. This does not, however, undermine the significance of wasting. Studies have repeatedly documented that the existence and magnitude of weight loss predict morbidity and mortality.^{1,2} In one study, as little as 5% of weight loss over 4 months was associated with decreased survival.³

Though wasting is well-recognized in HIV/AIDS, its diagnosis and characterization as an AIDS-defining condition is not common. In many cases an underlying opportunistic infection may emerge as the cause of the symptomatology. In Hong Kong, there were only 2 cases of wasting presenting as the primary AIDS-defining illness in 200 consecutive (1%) AIDS cases.⁴

I. Definition

Patients with gross wasting are easily recognizable for their cachectic appearance. To objectively define this syndrome, most authorities have used the definition by the CDC adopted over a decade ago: involuntary weight loss of greater than 10% of baseline body weight, plus either chronic diarrhea (at least two loose stools per day for greater than or equal to 30 days), or chronic weakness and documented fever (for greater than or equal to 30 days, intermittent or constant), in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (e.g., cancer, tuberculosis, cryptosporidiosis, or other specific enteritis).^{5,6} As such, AIDS wasting also constitutes one of the AIDS-defining conditions for surveillance purpose.

It must be noted that inflexible adoption of this definition may lead to underdiagnosis and undertreatment, because (a) diarrhea and fever might be unrelated to the weight loss, (b) the baseline weight might be difficult to define, (c) early cases could be missed, and (d) wasting thus defined may be mimicked by lipodystrophy caused by highly active antiretroviral therapy, in which the loss is fat rather than lean body mass (LBM)*.

*Body weight (BW) = fat + lean body mass (LBM)

LBM = extracellular mass (EM) + body cell mass (BCM)

An alternative definition has been proposed,⁷ which excluded other systemic symptoms from the equation, addressed the significance of compartmentalizing body weight, and allowed syndrome recognition without knowledge of premorbid body weight. In this definition, HIV-associated wasting is said to occur if one or more of the following criteria are met:

- (a) 10% unintentional weight loss over 12 months
- (b) 7.5% unintentional weight loss over 6 months
- (c) 5% body cell mass (BCM) loss within 6 months
- (d) body mass index (BMI) $<20 \text{ kg/m}^2$
- (e) in men – BCM $<35\%$ body weight AND BMI (body mass index) $<27 \text{ kg/m}^2$
- (f) in women – BCM $<23\%$ body weight AND BMI $<27 \text{ kg/m}^2$

BCM is preferred to LBM for definition of wasting because LBM suffers from fluctuation due to hydration status.

II. Etiology

The causes of AIDS Wasting are complex and multifaceted. Decreased oral intake, malabsorption, hormonal factors, cytokine effects, hypermetabolism and inefficient use of energy (so-called futile metabolic cycles) combine in varying proportions to result in wasting. Studies in this area often generated conflicting results. The followings are some general observations relating to the pathophysiology in AIDS wasting.

- (a) Although BCM is depleted out of proportion to fat⁸ in both men and women with severe wasting, women with early wasting lose more of fat and less of BCM.⁹ This sexual difference may originate from the effect of hypogonadism or a generally higher content of fat in women. Indeed, men who started with a higher content of fat also lost more fat and less LBM.¹⁰
- (b) The resting energy expenditure (REE) increases early on¹¹ and has a tendency of further increasing with clinical progression. In the event of secondary infections, the REE does not significantly increase. In fact the total energy expenditure (TEE) decreases as a result of the decrease in volitional energy expenditure. However this is not sufficient to counteract the decrease in caloric intake which is so common in these situations.^{12,13}
- (c) There is no convincing evidence that wasting regresses or decreases in prevalence with HAART. However, clinicians should be aware of fat redistribution in HAART-treated individuals, which might invalidate anthropometric measurements.
- (d) As HIV disease progresses, secondary hypogonadism is commonly found.^{14,15} A low total testosterone is a good screening test in men. Although controversial, hypogonadism may be more of a cause than effect of wasting. In the MACS

cohort, a low testosterone level precedes wasting.¹⁶ Furthermore, testosterone supplements help reverse loss of LBM (see below). The effects on body mass occur at higher concentrations of testosterone than on impotence. Thus adequate sexual function does not rule out hypogonadism.

- (e) Increased levels of some cytokines in HIV disease have been associated with wasting. To varying extents, tumor necrosis factor (TNF or cachectin), interleukin-1 and interferon-alfa have been incriminated. The mechanism of action is not understood but attempts of treatment with cytokine inhibitors have been made.
- (f) Low levels of cholesterol and albumin, and high level of triglyceride are associated with wasting in AIDS. Hypertriglyceridemia is probably related to interferon-alfa and TNF. Its etiologic significance is unknown and is further compounded by its occurrence in patients successfully treated with HAART.
- (g) Alterations of protein and lipid metabolism are commonly found in AIDS patients, but studies have produced conflicting results. It is tempting to hypothesize that an anabolic block exists that prohibits accrual of lean body mass despite increased caloric intake. One possible mechanism is futile metabolic cycles in which there is uncontrolled cycling between triglyceride and fatty acid.
- (h) Along with a negative energy or nitrogen balance, deficiency of micronutrients is common in AIDS patients, including but not limited to vitamin B12, pyridoxine, zinc and selenium.

III. Clinical approach to weight loss in HIV disease

Rather than being obsessed with diagnosing a patient as AIDS-wasted or not, the clinician might approach weight loss as a clinical problem by itself. Proper and timely management is important because of its prognostic significance. Apart from being a harbinger of opportunistic infections and lymphoma, weight loss can also be a prominent feature of these conditions. Furthermore reversal of weight loss is associated with improved well being and function.

A rational approach to weight loss involves the following steps:

- (a) Identifying weight loss and characterizing changes in body composition
- (b) Looking for treatable causes
- (c) Treatment

III.A Identifying and characterizing weight change

Monitoring and charting the body weight of a patient in each and every visit is important. In more sophisticated clinics, bioimpedance analysis (BIA) or dual energy X-ray absorptiometry (DEXA) may also be employed.

- (a) **Body weight** – Simple and convenient to chart, crude body weight is nevertheless insensitive and cannot discriminate between changes in different compartments. Nevertheless, any change over 5% is likely to be real and deserves investigation into its causes.
- (b) **Anthropometry** – This is an operator-dependent method of measuring muscle mass and fat by skinfold thickness and various circumferences. This method lacks reliability and is difficult to standardize especially now that lipodystrophy is a common complication of therapy.
- (c) **DEXA** – This is a reliable and accurate technique of measuring LBM and fat, which can also be useful for documenting regional changes. DEXA is not routinely used because it is expensive and relatively cumbersome, requiring long scan times. Furthermore, it cannot differentiate the two components of LBM, i.e. BCM and extracellular water.
- (d) **BIA** – until the arrival of BIA, BCM was back calculated from measurements of total body potassium or nitrogen. This was tedious. The BIA machine is portable, inexpensive and its results highly reproducible. The concept is based on the human body as an ionic conductor. The level of resistance reflects its fat content while the reactance varies with the BCM. The BIA is quickly supplanting DEXA in the care of HIV infected patients.

III.B Looking for treatable causes

Reversible causes of weight loss must be explored. Patients who have active secondary infections usually show more rapid weight loss (e.g. more than 4 kg in less than 4 months). Slower weight loss results from gastrointestinal disease, such as malabsorption and diarrhea.¹⁷ In excluding concurrent opportunistic infections, a systematic approach begins with a meticulous history and physical examination, followed by appropriate investigations. The history should include an estimation of caloric intake. A nutritionist's assessment will be very helpful. The common causes of weight loss are as listed in Box 7.11. More often than not, they operate through more than one of the following mechanisms: hypermetabolism, malabsorption, decreased intake and hypogonadism.

IV. Treatment modalities

Several treatment modalities for wasting are available.

Box 7.11 Common causes of wasting in HIV/AIDS

Mechanisms	Causes
Hypermetabolism	<ul style="list-style-type: none">• <i>Mycobacterium avium</i> complex• Cytomegalovirus• <i>Pneumocystis carinii</i>• <i>Cryptococcus neoformans</i>• Malignancy (non-Hodgkin's lymphoma)
Malabsorption	<ul style="list-style-type: none">• Gastrointestinal pathogen (cryptosporidia, <i>Mycobacterium avium</i> complex, cytomegalovirus)• Malignancy (non-Hodgkin's lymphoma, Kaposi's sarcoma)• HIV enteropathy• Pancreatic insufficiency (?HIV-related or drug induced, e.g. ddl)• Small-bowel dysfunction• Medication-induced diarrhea (e.g., ddl, NFV)
Decreased oral intake	<ul style="list-style-type: none">• Oro-esophageal infections (<i>Candida albicans</i>, herpes simplex, cytomegalovirus, bacterial gingivo-stomatitis, chronic sinusitis)• Malignancy (non-Hodgkin's lymphoma, Kaposi's sarcoma)• Anorexia (medications, gastric motility disorder)• Neuropsychiatric abnormalities (depression, dementia, confusional states)• "Voluntary" (fear of making diarrhea worse, poor food preparation skills), etc
Hypogonadism	<ul style="list-style-type: none">• Testicular failure• Hypothalmo-pituitary disease• Hyperprolactinemia• Estrogen excess

IV.A Appetite stimulants

In the context of AIDS, the best studied appetite stimulant is **megestrol acetate** (Megace), a progestational agent. At 800 mg/day, patients gained an average of 3.5 kg, although most of the weight gained was fat.¹⁸ Megace has significant hormonal effects. Its glucocorticoid activity may aggravate diabetes and cause Cushing's syndrome. Abrupt withdrawal after long term use may precipitate adrenal insufficiency. As a progestational agent, it may cause further hypogonadism.

Corticosteroids and cyproheptadine are not useful in AIDS wasting. Dronabinol, a synthetic analog of cannabis, improves appetite and mood but does not result in significant weight gain. Its addition to megestrol does not result in additional weight gain either.

IV.B Anabolic agents

Testosterone supplementation – Frequently testosterone levels are decreased in AIDS wasting. Physiologic replacement in these patients with IM testosterone enanthate (300 mg q3wk for 6 months) resulted in significant increase in LBM (mean increase of 2 kg) and an improved quality of life, although there was no change in body weight.¹⁹ Additional LBM is accrued with extension of this protocol for another 6 months.²⁰ Transdermal testosterone at 5 mg per day has also been evaluated in a placebo-controlled trial. LBM increased moderately with treatment, but there was no significant difference from placebo. The low dose of testosterone that can be delivered by this expensive system probably is the major limiting factor.²¹

IM testosterone achieves very high levels after the first day of administration, which then stabilize in two weeks, the so-called roller coaster effect. Apart from its physiologic effects, testosterone increases the risks of prostate cancer, sleep apnea, and hepatotoxicity. Polycythemia is common. Thus it is important to monitor liver function, prostate size and prostate-specific antigen.

Currently testosterone is not indicated in women with wasting, although androgen deficiency and low testosterone levels are also common. Irregular menses, hirsutism and other virilizing effects are the major drawbacks. A low dose (150 µl/d) transdermal system has been evaluated in women. Weight gain was achieved but it was predominantly fat. There was no major masculinizing effect in this study.²²

Anabolic steroids – The oral oxandrolone²³ and IM nandrolone²⁴ are the two major anabolic steroids that have been studied. They are synthetic analogs of testosterone that supposedly have more anabolic than androgen effects. This is controversial as only one androgen receptor has been identified. But if true, the relative lack of virilizing side effects may be an advantage for use in women. It is unlikely that these steroids are more effective than testosterone. Experience with these anabolic agents is currently limited. Meanwhile they should be regarded as being able to share in all toxicity of testosterone. Adverse effects that have been reported include cardiomyopathy, hepatocellular carcinoma, tendon tears, psychiatric disorders, sudden death and hypercoagulability.

IV.C Growth hormone

It is possible that in AIDS wasting, there is relative growth hormone deficiency as suggested by a low serum insulin-like growth factor in the presence of high serum growth hormone concentrations. Subcutaneous recombinant human growth hormone (rhGH) at high dose (0.1 mg per kg per day for 12 wk; maximum 6 mg qd) successfully lost fat and accured weight and LBM.²⁵ Side effects included arthralgias, edema, myalgias, carpal tunnel syndrome and insulin resistance. Growth hormone may also be useful for lipodystrophy.

IV.D Progressive resistance exercise

Progressive resistance exercise (PRE) results in muscle hypertrophy and improved strength, at least in the short term. It may have a role in AIDS wasting provided the patient is up to the demands. Supervision is important. The effects of PRE may be synergistic with those of anabolic steroids.²⁶

IV.E Cytokine inhibition

Among the antagonists of TNF, thalidomide is the most promising. It has been shown to work in doses ranging from 100 to 400 mg qd with treatment duration up to 12 weeks. Body weight increases but it is unsure whether the weight gained is mainly LBM or fat. Major side effects are somnolence, rash and peripheral neuropathy. Because of its documented teratogenicity, thalidomide is contraindicated in women with any potential of child bearing. Patients should also be warned to keep their drugs in a safe and private place.

IV.F Nutritional supplementation

Nutritional supplementation is a logical treatment of negative caloric and nitrogen balance. In AIDS wasting, success of this strategy is limited to circumstances where restricted oral intake is the main cause of weight loss, such as with oral ulcers, anorexia or frequent vomiting. However, removal of the primary causes will be more effective.

Nutritional supplementation may be achieved by oral formula supplements or non-volitional feeding such as the percutaneous gastrostomy (PEG) or total parenteral nutrition. In AIDS wasting, efficacy is often short-lived, as if there is a lower set point to which the body autoregulates. Besides, whatever weight gained is mostly fat. Adequate nutritional intake is a necessary but not sufficient condition for reversal of wasting.

V. Management

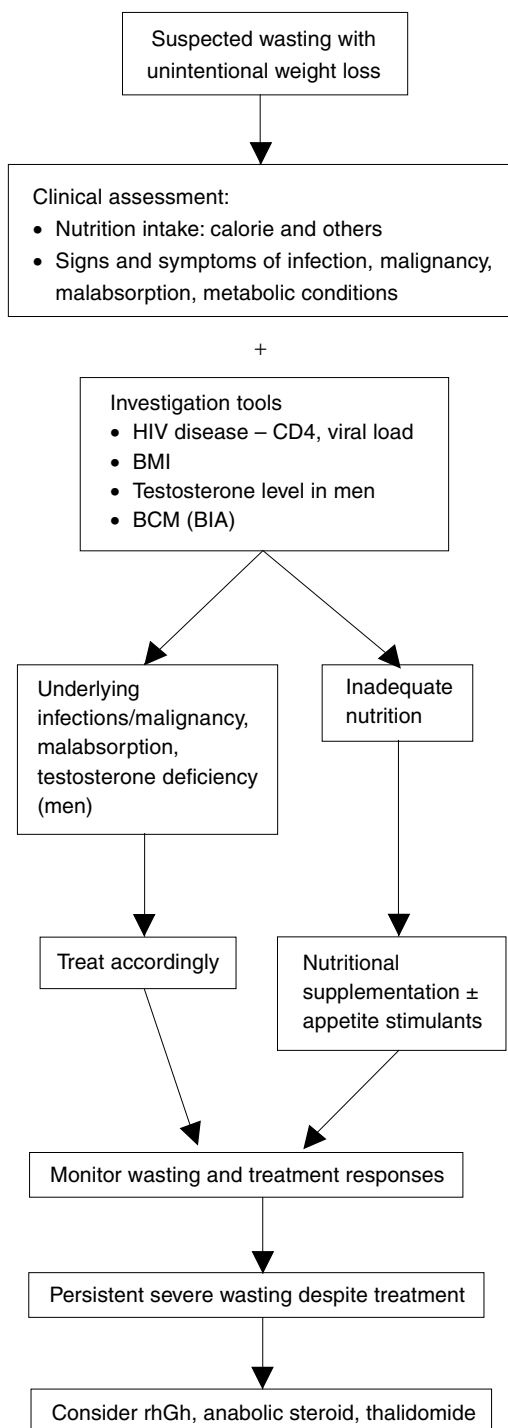
Knowledge of the relationship between weight loss and AIDS enables one to manage the problem in a logical manner.²⁷ This should begin with regular screening of body weight and BCM by BIA. Testosterone may be monitored annually and should be measured when abnormal loss in weight or BCM is noted. In this situation, a nutritional assessment is also undertaken, preferably with input by the nutritionist. The physician looks for direct precipitating causes of weight loss and treat accordingly.

Wasting-specific treatment is indicated should the BCM continues to fall. If the patient is male and hypogonadal, a therapeutic trial of testosterone supplementation at 200 mg per 2 weeks may be given for 4 weeks. Failure should prompt one to consider rhGH. The average dose is 6 mg qd. A typical course is 12 weeks. This may be extended in those with suboptimal response or restarted in those whose BCM declines after stopping treatment. Monitoring of adverse effects of testosterone and growth hormone are important.

On the other hand, for those whose weight loss is mainly due to decreased intake, nutritional supplementation with or without megace is considered. Response should be monitored in terms of both body weight and BCM. If increase in BCM is unsatisfactory, testosterone or rhGH might be added.

The use of transdermal testosterone in women or anabolic steroids is regarded as experimental. Thalidomide is not standard treatment and should only be used very carefully. The role of progressive resistance exercise in wasting is unclear. Patients should be aware of the balance of risks and benefits before treatment is initiated.

Algorithm 7.3 Management of wasting in patients with HIV/AIDS



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7.4 TRAVELING AND VACCINATION FOR HIV-INFECTED PATIENTS

Travel is nearly unavoidable in modern living but there can be associated health risks, particularly for immunocompromised hosts such as HIV/AIDS patients. One major concern is the risk of exposure to opportunistic and other pathogens that are not prevalent locally, as different places may have their own endemic infections not common in other places.¹

HIV infection leads to progressive depletion of one's immunity. This may enhance the individual's susceptibility to (a) secondary infections, (b) diseases and/or more severe diseases after secondary infections, (c) poorer response to treatment of the infection, and (d) chronicity and long-term sequelae of the infection.

Given the increased risk and complications arising from superimposed infections, it is natural that preventive measures should be taken as far as possible. Ways to minimize exposure to infections, e.g. food hygiene for food-borne diseases, are important but may not be feasible for all situations. Acquiring immunity through vaccination or passive immunization is a possible means for some specific diseases. Prophylactic anti-pathogen drugs, e.g. anti-malarial prophylaxis, is another useful measure.

I. Prevention of exposure to infections

A very common route of exposure to infections is via the gastrointestinal tract. To prevent enteric infections, patients should be advised to avoid foods and beverages that might be contaminated, particularly raw/undercooked foods, raw fruits and vegetables, tap water, ice made from tap water, unpasteurised milk and dairy products, and items sold by street vendors.²

Food and beverages that are generally safe include steaming-hot foods, fruits that are peeled by the traveler, bottled (especially carbonated) beverages, hot drinks, and water brought to a rolling boil for 1 minute. Personal hygiene, e.g. washing hands before eating is needed. Patients should avoid swimming in water that may be contaminated and avoid swallowing water during swimming. Cryptosporidiosis is one specific pathogen of caution with drinking contaminated water.

Animals can transmit diseases threatening health of HIV positive patients. Patients should avoid direct contact with soil that contains animal wastes. Use protective devices, e.g. shoes and clothing as appropriate and observe personal hygiene. Patients should also

avoid close contact with people with infectious air-borne diseases, e.g. tuberculosis, measles or chickenpox.

Apart from drugs, non-pharmacological methods, e.g. wearing long-sleeve clothes or using insect repellents to avoid mosquito bites can also be used for diseases such as malaria and yellow fever.

II. Health advice and interventions for travel

HIV-infected patients going for travel overseas, especially to developing countries, should have the trip planned well ahead if possible. They shall have disease assessment well before departure for necessary advice.³ The advice shall strike the balance between the risk of catching infection, availability and feasibility of prevention measures, and pros and cons of applying such measures in different settings.

In general, HIV/AIDS patients are advised to refrain from going to places with endemic diseases that are not preventable or the prevention means is contraindicated in HIV/AIDS patients, e.g. yellow fever vaccine. It is also important to check if there is restriction of entry for HIV/AIDS patients for the place that the patient intends to travel.

II.A Pre-travel

The latest HIV disease status of the patient has to be ascertained, especially in its immunologic aspect. Acute illness, if any, has to be treated before the travel. If possible, the travel should best happen after appropriate prophylaxis for opportunistic infections as well as antiretroviral therapy have been instituted for some time, and the patient has been tolerating the medications well. Prescription of new antivirals or prophylactics drugs for HIV opportunistic infections shortly before the scheduled time of travel should be avoided to obviate the chance of having to deal with side effects during travel.

The patients should be advised to carry adequate stock of drugs that they are on, with spare quantities for extra few days. The need of good compliance with their medications, the antiretrovirals in particular, must be emphasized. If the travel involves a change of time zone, advice should be given on how to shift the timing of drug taking accordingly (Box 7.12). If necessary, a note may be provided for the customs to certify which drugs the patients are taking. A medical summary would also be helpful as the patient might need to seek medical care for HIV-related illnesses during travel. It may be necessary to identify in advance HIV physicians in the place of travel. Advise the patient to contact his caring team as necessary should there be health problems during travel.

Box 7.12 An example of switch of antiretrovirals when travelling overseas

A patient on AZT 200 mg, 100 mg, 200 mg/day, 3TC 150 mg bid, and IDV 800 mg q8h traveled from Hong Kong (HK) to San Diego (SD) 23-09-98 to 1-10-98. Dosing regimen of ART was changed to, when convenient, according to time in San Diego after arrival and switched back to that in HK upon return. It may be necessary to gradually adjust the timing between doses when change from one place to other and vice versa

SD (time, date)	HK (time, date)	Dosing according to HK time	Dosing according to SD time	Remarks
	2pm, 23-09-98 DEPART from HK	2 IDV,1 AZT	2 IDV,2 AZT,1 3TC	
7am, 23-09-98	10pm, 23-09-98	2 IDV,2 AZT,1 3TC	2 IDV,2 AZT,1 3TC	
4pm, 23-09-98	7am, 24-09-98	2 IDV,2 AZT,1 3TC	2 IDV,1 AZT	
11pm, 23-09-98	2pm, 24-09-98 ARRIVAL in SD	2 IDV,1 AZT	2 IDV,2 AZT,1 3TC	Can switch to dosing regimen according to SD time
7am, 24-09-98	10pm, 24-09-98	2 IDV,2 AZT,1 3TC	2 IDV,2 AZT,1 3TC	
4pm, 24-09-98	7am, 25-09-98	2 IDV,2 AZT,1 3TC	2 IDV,1 AZT	

7am, 29-09-98	10pm, 29-09-98 DEPART from SD	2 IDV,2 AZT,1 3TC	2 IDV,2 AZT,1 3TC	
4pm, 29-09-98	7am, 30-09-98	2 IDV,2 AZT,1 3TC	2 IDV,1 AZT	
11pm, 29-09-98	2pm, 30-09-98	2 IDV,1 AZT	2 IDV,2 AZT,1 3TC	
7am, 30-09-98	10pm, 30-09-98	2 IDV,2 AZT,1 3TC	2 IDV,2 AZT,1 3TC	
4pm, 30-09-98	7am, 1-10-98 ARRIVAL in HK	2 IDV,2 AZT,1 3TC	2 IDV,1 AZT	Switch back to dosing regimen according to HK time

Note: The patient may follow dosing regimen according to time in HK for the whole journey if (a) it is a short stay or (b) for convenience.

The patient should be advised to consult the Port Health Office of the Department of Health (or other travel medicine clinic) for advice on vaccination and other precautionary measures for the place of travel, as in the case of an HIV negative individual. Together with the travel medicine doctor, an evaluation would help to see if the implicated vaccines

are safe for the patient. The Port Health Service of the Department of Health provides the yellow fever vaccine and prescriptions of malaria prophylaxis.

II.B Travel

The patients should follow the prevention measures (as depicted above) to avoid exposure to infections.

They might be issued a course of antibiotic for empiric treatment of traveler's diarrhea should it develop. A course of ciprofloxacin 500 mg BD for 7 days is the treatment of choice. However, medical advice should always be sought wherever possible, especially when the diarrheal disease is severe or does not improve with ciprofloxacin. Anti-motility agents can be prescribed with caution – it is contraindicated in diarrhea with high fever, blood in stool or persistent diarrhea despite treatment.

The traveling patient should take the same precautions, i.e. avoidance of unsafe sex, to prevent spreading HIV and contracting other sexually transmitted infections. For drug users, he/she has to avoid unsafe injection, including sharing of needles and other injection equipment. Although the same advice is usually given to the patient not on travel, it has to be reemphasized to those who are.⁴

II.C Post-travel

The patient is advised to seek medical advice if there is fever or other illnesses upon return from travel. An early follow-up shortly after the patient comes back is desirable. Investigations would be needed depending on the possible cause of illnesses related to the travel.

III. Vaccination

Vaccination is an important and effective means of protecting against infectious diseases. While vaccination is also useful for health maintenance of HIV-infected people, its use can be limited by possible toxicity and lower efficacy in HIV/AIDS patients. Apart from vaccination (active immunization), passive immunization can also render temporary protection to certain infections.

Vaccination in HIV/AIDS patients should be considered against many factors, including (a) danger of live vaccines in causing diseases in the infected, (b) risk of spread to other people, especially immunocompromised ones, after live vaccines, (c) uncertainty of immune

response and thus protection even after vaccination, especially for symptomatic patients,⁵ (d) risk of stimulating HIV replication,⁶ and (e) the applicability and indication of vaccines in different countries/places.

Generally speaking, inactivated and subunit vaccines are safe and can be used in HIV-infected patients. Live vaccines are contraindicated due to the risk of severe adverse reactions. For this reason, ***inactivated killed polio vaccines*** are used instead of the oral live polio vaccine. However, exceptions occur when the benefit outweighs the risk. For example, the ***measles*** vaccine can be administered to pediatric patients in the early stage of the disease. Because of impaired immunity, HIV-infected persons should not be presumed immune after vaccination.

Whenever possible, vaccinations that are indicated should be given early in the course of HIV disease for better immune response. Whether improved immunity from highly active antiretroviral therapy will enhance the immune response to vaccines is currently unknown. Because of differing epidemiology, overseas recommendations on vaccination in the HIV infected should not be adopted without due consideration of the unique local setting.

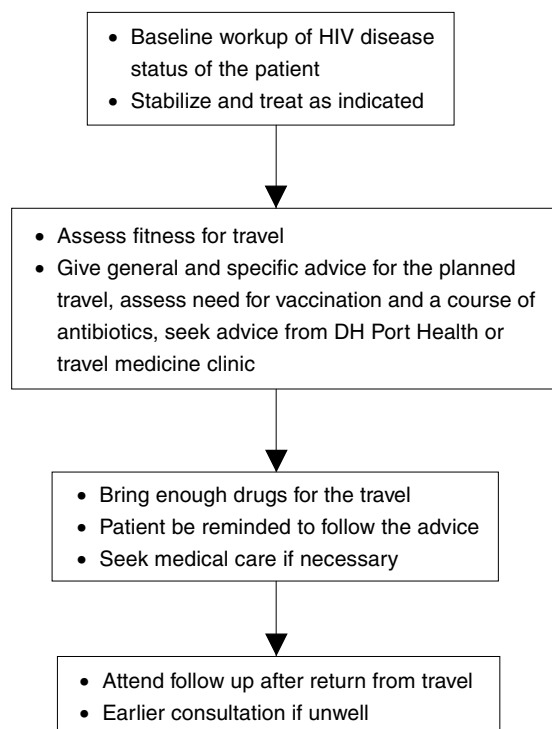
Unlike in the US, *Streptococcus pneumoniae* infection is relatively uncommon among HIV-infected patients in Hong Kong. The local strains may also be different from those covered by the commercially available ***pneumococcal vaccine***. Thus the US recommendation of giving pneumococcal vaccine for all HIV positive patients may not be applicable in Hong Kong.

HIV-infected patients have a higher chance of becoming chronic carriers after infection with ***hepatitis B virus*** (HBV) but they are not at increased risk of more severe disease. The overall risk shall however be considered in the context of the exposure risk and the universal hepatitis B vaccination programs implemented in Hong Kong. There is no evidence either that the risk of developing chronic liver complications is higher than in HIV negative counterparts. Whether this will be changed with the advent of HAART is unknown. HBV vaccination may be considered as an optional measure for personal protection.

A higher incidence of fulminant hepatitis A has been reported in chronic hepatitis C (HIV negative) patients.⁷ Increased mortality may conceivably happen in people with other forms of chronic liver disease. Implications of these findings in HIV/HCV co-infected patients are unclear. In general, justifications for ***hepatitis A*** vaccination should be based on risk factors such as traveling to endemic countries, rather than HIV status itself.

The live ***varicella-zoster*** vaccine is contraindicated in HIV-infected patients. They should also avoid contact with lesions of chickenpox or herpes zoster if they do not have a history of such. Varicella zoster immunoglobulin (VZIG) can be considered for high risk cases within 96 hours of exposure.

Algorithm 7.4 Health advice for an HIV-infected traveler



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7.5 MANAGEMENT OF HIV-POSITIVE PREGNANCY

I. Epidemiology of MTCT of HIV in Hong Kong

In Hong Kong, mother-to-child-transmission (MTCT) of HIV is the major source of pediatric infection. Although the relative proportion of MTCT among all local HIV infection is small, it is the single most important route by which a child is infected with HIV, now that all donated blood is screened. Furthermore, MTCT is unique in the sense that a window of opportunity exists whereby appropriate intervention will prevent against the disease.

A study identified 41 HIV-exposed pregnancies of 32 women between 1992 and 1999 in Hong Kong. Out of the 12 HIV-related pregnancies diagnosed before delivery, only 1 baby was infected. This contrasted with those whose diagnosis was made late after delivery, where 9 out of 14 (64.3%) were infected – a relative risk of 8. The importance of early diagnosis is therefore clearly evident. This can be achieved by the dual strategy of encouraging HIV testing in women in general, and the implementation of universal antenatal HIV testing in particular. Meanwhile, unlinked anonymous screening of cord blood attested to a low overall prevalence of 0.033% (1 in 3031) in 1998 and 0.032% (1 in 3125) in 1999.¹

II. Mechanisms and timing of transmission

Although the exact mechanism of MTCT is still being worked out, factors have been identified which are associated with the risk of transmission (Box 7.13). It has become obvious that transmission is possible during pregnancy, delivery and the postnatal period.

II.A Intrauterine infection

HIV may cause placental infection and subsequently intrauterine infection of fetus.^{2,3} This possibility is supported by the findings that some placental cells express CD4, and the fact that two peaks of HIV positivity can be detected in the infected neonate: 38% of the HIV infected infants tested positive with HIV DNA PCR within 48 hours of life and almost all the rest at 2 weeks.⁴

Box 7.13 Risk factors of MTCT of HIV

Antepartum factors

High maternal viral load
Low maternal CD4 count
Progression to AIDS
Vitamin A deficiency
Illicit drug use
Amniocentesis,
esp in 3rd trimester

Intrapartum factors

Cervicovaginal
HIV levels
Mode of delivery
Prolonged rupture of
membranes
Premature delivery
Vaginal laceration
Episiotomy
Invasive fetal monitoring
Instrumental delivery

Postpartum factors

Breast feeding
mastitis

Source: McGowan JP, Shah SS. Prevention of perinatal HIV transmission during pregnancy [review]. J Antimicrob Chemother 2000; 46:L 657-68

II.B Intrapartum infection

Transmission during parturition may result from exchange of body fluids, including blood and genital secretions of the mother. This explains why babies born to mothers with membranes ruptured for more than 4 hours prior to delivery had a higher risk of infection (25% vs. 14%).⁵ Ascending infection from the maternal genital tract may also be important as judged from the correlation between infection and the level of HIV in cervicovaginal fluids.⁶

II.C Postpartum infection

Breastfeeding is the medium of transmission in the postnatal period. It accounts for the higher rate of MTCT in developing countries. In one randomized trial carried out in Kenya,⁷ the rate of breast milk transmission was 16.2% at 24 months (36.7% in breastfeeding arm vs. 20.5% in control arm). Interestingly, the 2-year mortality of children is not different between the two groups, supporting the notion that breastfeeding should remain as an option in developing countries.⁸ In the latter circumstances, the risks of infectious gastroenteritis as a result of the poorer access to clean water and medical resources may outweigh those due to pediatric HIV infections. In developed countries where safe formula feeding is available, breastfeeding should be avoided in HIV infected women.

III. Interventions to reduce MTCT

Contrary to what the lay public believe, MTCT is not inevitable. The chance of infection is between 20% to 40%, depending on factors like breastfeeding, viral load in the mother, clinical status, and the CD4 count. The higher range of MTCT occurs in the breastfeeding population in developing countries. What must be remembered is that this risk is reducible by interventions.

In view of its complex nature, the Scientific Committee on AIDS has published clinical guidelines on the prevention of perinatal infection⁹ in the Hong Kong setting. The principles of management are listed in Box 7.14.

III.A Termination of pregnancy (TOP)

Knowing that more than 70% of newborns born without intervention are not infected, it is hard to, as a rule, justify TOP on the grounds of maternal HIV infection alone. Furthermore, since the majority of transmission takes place in later pregnancy or intrapartum, most aborted fetuses will be negative for HIV.

III.B Abstinence from breastfeeding

With access to clean water and an adequate medical infrastructure, the balance of risks in Hong Kong is clearly in favor of replacement feeding.

III.C Antiretrovirals

The identification of zidovudine (AZT or ZDV) monotherapy in 1994 as an effective means to reduce the rate of MTCT ushered in a new era of optimism and immense shift in public policy. In the randomized placebo-controlled trial known as AIDS Clinical Trials Group (ACTG) Protocol 076,¹⁰ a three-part regimen of AZT started as early as 14 weeks of pregnancy successfully reduced the rate of transmission by 68%, from 25.8% to 8.3%. This finding spearheaded a multitude of other studies on regimens that were simpler or more intensified. The efficacy of this diverse range of regimens provides us with alternatives to accommodate the myriad presentations of HIV-exposed pregnancies.

Box 7.14 Principles of management in prevention of perinatal transmission (Scientific Committee on AIDS, Apr 2001)

- 1 Universal testing of HIV antibody should be preformed for antenatal women in Hong Kong.
- 2 The prevention of mother-to-child transmission of HIV involves the administration of antiretroviral prophylaxis
 - 2.A The standard regimen comprises the use of zidouvidine (ZDV) beginning as early as 14 weeks or pregnancy, continuing through labour by intravenous administration, and followed by treatment of the newborn for 6 weeks.
 - 2.B Alternative antiretroviral prophylaxis should be administered in special circumstances where the standard regimen is considered not practicable.
 - 2.C When maternal HIV infection is not diagnosed until labour, the options of antiretroviral prophylaxis are:
 - 2.C.1.1 standard regimen of ZDV abbreviated to intrapartum and postpartum components only;
 - 2.C.1.2 Nevirapine (NVP) one dose to mother, and one dose to newborn at 48-72 h;
 - 2.C.1.3 ZDV/3TC intrapartum, and to newborn for 7 days, and;
 - 2.C.1.4 Abbreviated ZDV + nevirapine
 - 2.D In infants born to HIV-infected mothers who have not taken antiretroviral therapy, the recommended regimen is 6 weeks of ZDV as soon as possible
- 3 Clinical management should include that for the maternal HIV infection
 - 3.A A pregnant woman who is HIV positive shall receive the same standards of care established for HIV-infected nonpregnant patients. To best balance between benefits and risks to the foetus, mother and newborn, management should be assisted by a physician specialising in HIV medicine
 - 3.B A woman who is diagnosed HIV positive in the course of pregnancy should be counselled on the long term care plan, informed of the efficacy of prophylaxis against MTCT, and evaluated for antiretroviral treatment.
 - 3.C In mothers who become pregnant while receiving antiretroviral therapy, evaluation should be made of the treatment regarding antiretroviral potency, potential toxicity to the mother and foetus, and prophylactic efficacy against MTCT. The rationales of alteration or continuation of therapy should be fully explained to the mother to facilitate decision.
- 4 The mode of delivery and its management should be considered on the grounds of obstetric indications as well as HIV status
- 5 Paediatric management should be offered to reduce the risk of MTCT of HIV
- 6 Coordinated efforts should be made to strengthen our knowledge base regarding MTCT of HIV in Hong Kong

III.D Elective Cesarean Section (CS)

When performed prior to the onset of labor and rupture of membranes, an elective CS avoids most of the intrapartum factors associated with transmission. In one large prospective trial¹¹ and a meta-analysis of multiple observational trials,¹² elective CS reduced MTCT by 55-80%. However, for those who were already on the 3-part AZT regimen, elective CS did not significantly add to further reduction of transmission.

IV. Management of HIV in pregnancy

The availability of interventions to decrease MTCT should not distract the obstetrician from managing the pregnancy as a whole. The objectives of management are:

- (a) Prevention of MTCT
- (b) Health of the baby
- (c) Wellbeing of the mother
- (d) Preparation of the family for a newcomer and impacts of the HIV diagnosis

IV.A Preventing MTCT by antiretrovirals

Antiretroviral is now the standard in the prevention of MTCT. The best regimen is one that gives the best compromise between toxicity and efficacy.

Standard ZDV monotherapy – The 076 regimen is the standard to compare with. In the original study, the drug was administered 5 times per day, but in practice, it could be given two or three times a day to enhance compliance. (Box 7.15)

Box 7.15 The standard 076 AZT regimen

- *Antepartum* – ZDV 300 mg bid (or 200 mg tid) initiated at or after 14 wk
- *Intrapartum* – IV ZDV at loading dose of 2 mg/kg in hr, followed by 1 mg/kg till delivery
- *Postpartum* – ZDV syrup at 2 mg/kg q6h to newborn begun at 8-12 h for 6 wk (IV ZDV at 2 mg/kg q6h in those who could not tolerate oral intake; ZDV at 1.5 mg/kg IV or po q12h in preterm infants of <34 wk for the first 2 wk may be considered)

Although subjects of ACTG 076 were limited to those with CD4 counts above 200/ul, a subsequent trial, ACTG 185, confirmed that the efficacy of AZT extended to those with CD4 below 200/ul. Importantly, in this study subjects previously on AZT also derived benefit.¹³ The major concern of using monotherapy in this situation is the development of resistance. Apparently, the relatively brief use of AZT limits the development of high level resistance in the mother. However, in those who do develop resistance, the chance of transmission may be increased.¹⁴

Simplified AZT regimens – A CDC-sponsored trial in Thailand¹⁵ showed that a simplified regimen of AZT was still effective, reducing transmission by about 50%. This regimen comprised a prenatal AZT component commenced at 36 weeks and continued through labor orally. No neonatal AZT was given. Although the efficacy of this regimen cannot be compared directly with ACTG 076, it is widely believed that delayed and deintensified regimen will be inferior because of the existence of in utero transmission. In another Thai study, the rate of in utero transmission was higher (5.1% vs 1.6%)¹⁶ in women who received a regimen with shortened maternal treatment.

The efficacy of simplified regimens is highly significant to countries with poor access to antiretrovirals. These regimens also have a role in developed countries, where late presentation of pregnancy to antenatal care makes the full 076 regimen impracticable. In these circumstances, a study by the New York State Department of Health¹⁷ on abbreviated 076 regimens showed that AZT begun as late as 48 hours after birth would still be effective.

Alternative regimens – The randomized trial, HIVNET 012,¹⁸ showed that two doses of **nevirapine** (NVP), one to the mother at the onset of labor and another to the newborn between 48 to 72 hours, were able to achieve a 50% reduction of transmission compared to a simplified regimen of AZT. However, there was a relatively high incidence of resistance to NVP as a result of this regimen.¹⁹ Nevertheless, this study testified that AZT was not unique in its ability to reduce MTCT.

At least two studies have evaluated the combination of **AZT and lamivudine (3TC)**. In the PETRA study,²⁰ the combination started either at 36 weeks or at labor was more efficacious than placebo (8.6% and 10.8% respectively vs. 17.2%). However, if the drugs were given only intrapartum, they were no more effective than placebo. Apart from its implications in developing countries, this combination given as the 3-part or 2-part regimen provides us with an alternative in the scenario where the HIV-infected mother presents late in pregnancy or during labor.

In a French cohort study,²¹ 3TC was added to the standard AZT regimen at 32 weeks. A low transmission rate of 1.6% was achieved. Compared with historic controls, this represented a 5-fold reduction. Nevertheless, there was a high incidence of mutation

associated with 3TC (M184V), and mitochondrial toxicity in the newborn was noted. The relationship between this complication to AZT or 3TC exposure is highly controversial. Regardless, this trial does suggest that combination therapy might be superior to monotherapy.

On a theoretical basis, **NVP may be added to a 076 regimen** abbreviated for whatever reason to restore efficacy. Additive results are expected because they work through different mechanisms.²² As NVP is relatively ineffective against HIV-2, it should not be used when the epidemiologic background suggests maternal HIV-2 infection.

Regimens in late presentation – The above considerations provide the basis for the application of available options in situations where the pregnancy presents late, sometimes even after delivery. These options are:

- (a) Initiation of an abbreviated 076 regimen;
- (b) AZT + 3TC;
- (c) NVP in 2 doses; and
- (d) NVP + abbreviated 076 regimen.

Box 7.16 presents the details of these regimens, the dosages and the evidence on which they were based.

Highly active antiretroviral therapy (HAART) – HAART is generally taken to mean a 3 to 4 drug combination containing nucleoside reverse transcriptase inhibitors and protease inhibitors/nonnucleoside reverse transcriptase inhibitors. The goal of HAART is an undetectable viral load. Based on a number of observational studies,^{23,24} the risk of perinatal transmission with the use of HAART is estimated to be below 2%. Undetectability of virus commonly achieved by HAART should also avoid the emergence of resistance which is commonly reported in trials on NVP and AZT/3TC combination. The use of HAART is now the standard of care in adult HIV infection. For the prevention of MTCT alone, however, the use of HAART has to be balanced against added toxicities of drugs used in pregnancy, many of which are still unknown.

IV.B Preventing MTCT by cesarean section

It would be a disservice to the mother and baby if cesarean section is performed routinely without due balancing of its risks and benefits.²⁵ This is achieved after the following considerations:

- (a) Reduction of MTCT is only one of the many obstetric indications of surgery
- (b) The benefit of MTCT reduction is minimal when an adequate antiretroviral regimen is in use and especially when there is full suppression of viral load

Box 7.16 Antiretroviral prophylaxis against MTCT of HIV

Regimen	dosing	Evidence of efficacy (reference study)	Remarks
Standard 076 ZDV regimen	Antepartum – ZDV 300 mg bid (or 200 mg tid) initiated at or after 14 wk Intrapartum – IV ZDV at loading dose of 2 mg/kg in hr, followed by 1 mg/kg till delivery Postpartum – ZDV syrup at 2 mg/kg q6h to newborn begun at 8-12 h for 6 wk (IV ZDV at 2 mg/kg q6h in those who could not tolerate oral intake; ZDV at 1.5 mg/kg IV or po q12h in preterm infants of <34 wk for the first 2 wk may be considered)	Transmission rate was 7.6%; Placebo group was 22.6% (PACTG 076 ⁹)	No breastfeeding
AZT/3TC	3-part regimen: (ZDV 300 mg + 3TC 150 mg) bid from 36 wk to labor; (ZDV 300 mg + 3TC 150 mg) q3h during labor; (ZDV 4 mg/kg + 3TC 2 mg/kg) bid to newborn and (ZDV 300 mg + 3TC 150 mg) bid to mother for 7 d Modified 2-part regimen (in non breastfeeding women): Intrapartum – (ZDV 300mg-600 mg po + 3TC 150 mg) as loading dose, then ZDV 300 mg q3h + 3TC 150 mg q12h; Postpartum – (ZDV 4mg/kg + 3TC 2mg/kg) q12h to newborn for 7d	At 6 wk, transmission was 8.6% (3-part regimen), and 10.8% (without prenatal component); Placebo group was 17.2% (PETRA ¹⁹)	Breastfeeding; Intrapartum ZDV alone was ineffective;
Nevirapine	NVP 200 mg at the onset of labor; NVP 2 mg/kg to newborn at 48-72 h	Transmission rate was 13.1% at 14-16 wk Comparison arm (ZDV intrapartum and to newborn for 7 d) was 25.1% (HIVNET-012 ¹⁷)	Breastfeeding in 95% Rapid emergence of resistance in mother ¹⁸
Abbreviated ZDV 076 regimens	ZDV 076 regimen begun prenatally, intrapartum or in newborns	Transmission rates were 6.1% (prenatal), 10% (intrapartum) and 9.3% if ZDV initiated within 48h in newborn; Transmission rate without ZDV was 26.6% (observational study in New York State ¹⁶)	No breastfeeding
ZDV + nevirapine	Intrapartum – IV ZDV at loading dose of 2 mg/kg in hr, followed by 1 mg/kg till delivery + NVP 200 mg at the onset of labor; Postpartum – ZDV syrup at 2 mg/kg q6h to newborn begun at 8-12 h for 6 wk + NVP 2 mg/kg to newborn at 48-72 h	Unknown; based on extrapolation from existing data	

-
- (c) Emergency CS or CS after rupture of membranes and onset of labour probably have no benefit.
 - (d) HIV infected patients may have a higher incidence of morbidity following surgery.²⁶

In practice, elective cesarean section is often employed when:

- (a) The mother cannot tolerate antiretroviral prophylaxis.
- (b) The mother presents late in pregnancy so that no adequate prophylaxis can be given.
- (c) Failure of antiretrovirals to suppress viral load to a low level.
- (d) Obstetric complications.

IV.C Having a healthy baby

The prevention of MTCT does not necessarily equate a healthy baby. The health status of a newborn may suffer on several fronts:

- (a) ***Negative impacts of maternal HIV disease*** – HIV disease may confer a worsened pregnancy outcome.^{27,28} This may be mediated through associated risks such as drug use and poor access to antenatal care as well as the disease itself.
- (b) ***Fetal exposure to antiretrovirals*** – It must be remembered that two individuals are exposed to any drug used in pregnancy. While potent antiretrovirals may decrease MTCT and control maternal disease, the fetus may suffer adverse effects. Box 7.17 lists some of what is currently known of the adverse effects on the fetus or newborn.²⁹ Toxicity of antiretrovirals in pregnancy is a relatively uncharted area. Results of animal studies must be interpreted with caution as these often employed exceptionally high dosage, the outcomes of which do not necessarily hold true in humans. The HIV physician has to keep abreast with progress in this area and be on the alert for unexpected toxicity.
- (c) ***Expert pediatric care*** – The prevention of MTCT does not stop at delivery. Expert pediatric care has to be provided for optimal continuation and monitoring of antiretrovirals, establishment of HIV diagnosis, initiation of PCP prophylaxis, and the supervision of replacement feeding.

IV.D Maternal wellbeing

The quest for preventing the baby from HIV infection should not compromise the welfare of the mother. Potential conflicts of interest may occur in the following circumstances:

- (a) Continuation or initiation of antiretrovirals for maternal disease in the first trimester of pregnancy;

Box 7.17 Potential toxicity of antiretrovirals in pregnancy

(Adapted from: New York State Department of Health AIDS Institute. Clinical guidelines: Prevention of perinatal HIV transmission)

Drug	FDA Category*	Potential teratogenicity and carcinogenicity	Known adverse effects on newborn
AZT	C	Vaginal tumors in rodents; Good safety profile in human use ³⁰	Reversible anemia Mitochondrial toxicity ³¹ – controversial
ddl	B	The only nucleoside not toxic to early embryonic development in animals	
ddC	C		
d4T	C	Skeletal malformations in rats	
3TC	C		Mitochondrial toxicity – controversial
ABC	C	Anasarca and skeletal malformations in rodents	
NVP	C		Watch out for liver toxicity; possible development of resistance
EFV	C	Anencephaly and anophthalmia in monkeys; therefore avoid use in pregnancy	
NFV	B		Hyperbilirubinemia and hyperglycemia
IDV	C	Extra ribs in rodents	Hyperglycemia
RTV	B	Liver adenomas and carcinoma in mice; cryptorchidism in rodents	ditto
SQV	B		ditto
Kaletra	C	Delayed ossification in rats	ditto

*FDA defined pregnancy categories are: A = adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters); B = animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted; C – safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus; D = positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks; X – studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug on pregnant women clearly outweighs any possible benefits.

-
- (b) Use of antiretrovirals for prevention of MTCT in a mother whose disease does not require treatment yet; and
 - (c) The impacts of elective cesarean section on prematurity and maternal morbidity

The issue is complex and all pros and cons should be fully explained to the mother to allow her to make an informed decision. For example, the mother may wish to sacrifice a period of HIV control in the first trimester so that the fetus will not be exposed. In this regard, the doctor's duty is to provide her with the most up-to-date information on the delicate balance between maternal health, fetal toxicity, and efficacy of MTCT prevention.

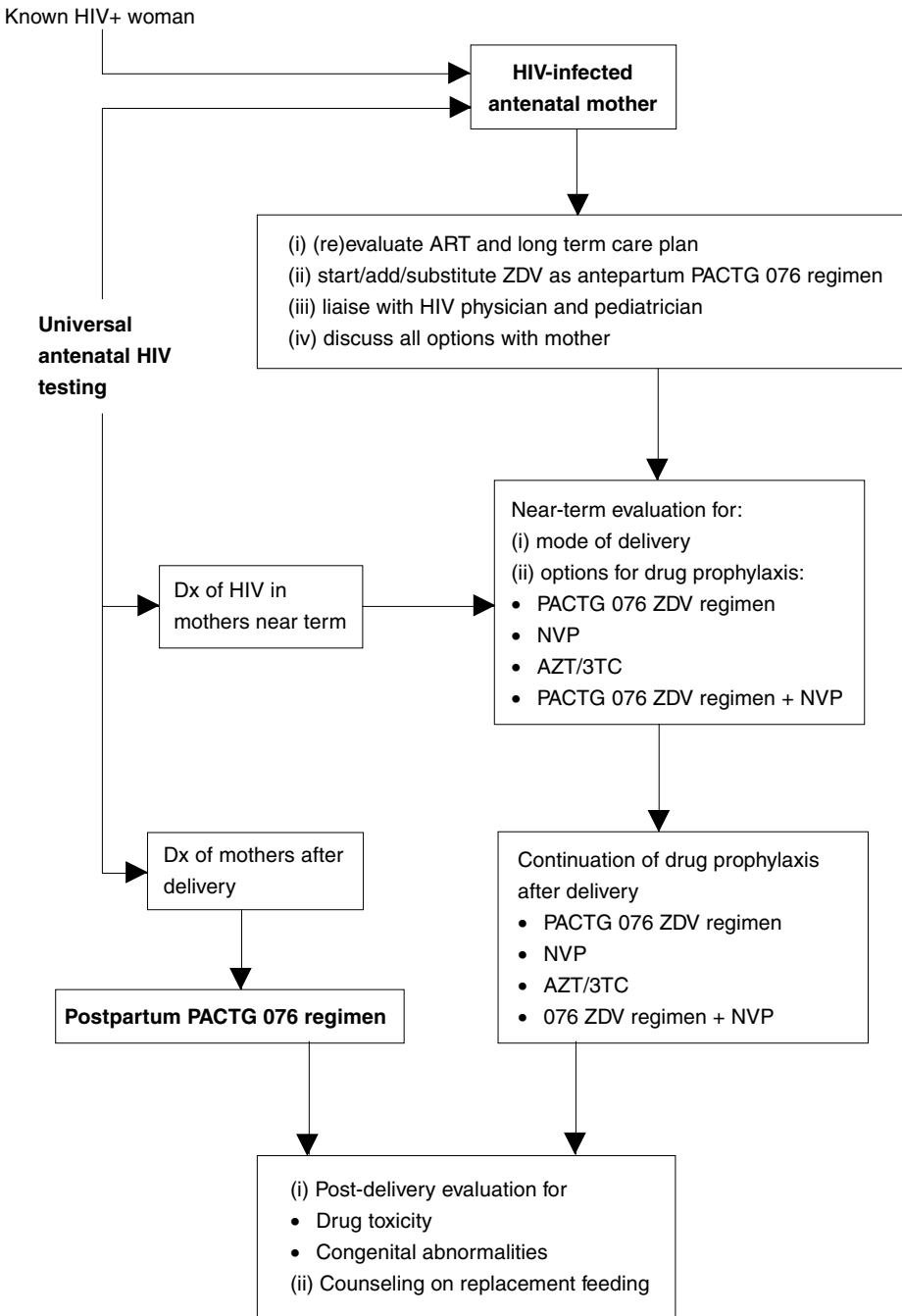
IV.E The social and psychological impacts

A diagnosis of maternal HIV infection carries enormous social and psychological implications, which arise largely as a result of the stigma attached to the infection. The health care provider is faced with the following challenges:

- (a) encouraging partner referral for HIV testing,
- (b) preparing the mother for the dual challenge of preventing transmission to the baby and taking care of her own health,
- (c) enlisting support from social or other service agencies where appropriate,
- (d) creating a supportive environment for the newborn baby, which poses a challenge also to the sick mother, and
- (e) the need to accomplish the above in a relatively short time.

Today, the science of HIV treatment and prevention against MTCT is sophisticated. To ensure that the best management is offered, negative psychosocial factors would have to be tackled. This may turn out to be the most difficult of all.

Algorithm 7.5 Management plan to prevent mother to child transmission of HIV



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7.6 PEDIATRIC HIV INFECTION

HIV infection in children can occur as a result of transfusion or mother-to-child infection. Since the introduction of blood screening for HIV antibody in the mid-80s, HIV infection through transfusion has become a rarity. Most pediatric infections in Hong Kong are now perinatally acquired.¹ To date, children accounts for a small proportion of the HIV (human immunodeficiency virus) infected population in Hong Kong. As of the end of the year 2000, 36 out of the 1542 reported (cumulative) cases of HIV infection were aged 15 or below. The majority (64%) contracted the virus through transfusion of blood or blood products before August 1985. A good proportion of the perinatally infected children are receiving care at one referral centre in Hong Kong.²

HIV infection progresses more rapidly in children infected perinatally than those infected at an older age. Among those infected perinatally, a evidence of *in utero* transmission generally predicts rapid progression: a positive PCR or p24 at birth, hepato-splenomegaly at birth and high viral loads after 1 month of life.³

Compared to adult infections, clinical studies on the management of HIV/AIDS in children are limited. The principles however follow closely that for adult infection. In 2001, the Scientific Committee on AIDS established a set of recommendations to assist clinicians in the management of HIV infection in children.⁴ This chapter should be read in conjunction with the document.

I. Diagnosis and classification

I.A Clinical features

HIV-infected children may present with nonspecific features such as failure to thrive, fever, chronic diarrhea, generalized lymphadenopathy, hepatosplenomegaly, or slowly responsive bacterial infections, e.g. otitis media and pneumonia. Neurologic involvement is common in advanced HIV disease, presenting as developmental delay, or encephalopathy. In a local series, five of the eight perinatally infected children were diagnosed only after a parent tested positive for the virus. The remaining three presented with an AIDS-defining illness.²

1.B Diagnostic tools

Diagnosis of HIV infection in infants is complicated by the transplacental transfer of maternal antibody that may persist for up to 18 months after birth. To facilitate early diagnosis, it is useful to consider virologic methods. Viral culture and DNA PCR assay are the tools for providing the definitive diagnosis in perinatally exposed babies. These tests are, however, not routinely available in clinical laboratories. The p24 antigen test is specific but not sufficiently sensitive to rule out a diagnosis of HIV infection. HIV RNA PCR assay is currently the recommended test in Hong Kong.

1.C Diagnosis of HIV infection in children⁵

For babies born to HIV infected women, it is recommended to perform HIV RNA PCR at 48 h, 1-2 months and then 3-6 months to rule out a diagnosis of HIV infection. It is noted that before 18 months of age, a positive HIV antibody test serves to identify those who are HIV exposed rather than infected.

A positive diagnosis is made if

- (a) there are two positive HIV RNA PCR results on separate blood samples (umbilical cord blood excluded); or
- (b) the HIV antibody test is positive at 18 months.

HIV infection can be excluded:

- (a) if there are two or more negative results on RNA PCR at ≥ 1 month, with one at ≥ 4 months; or
- (b) if the HIV antibody test is negative on two or more occasions at >6 months of age with an interval of ≥ 1 month between the tests, in the absence of clinical symptoms; or
- (c) definitely if the HIV antibody test is negative at 18 months in the absence of hypogammaglobulinemia, without clinical symptoms and with a negative virologic assay.

The same scheme can be applied or slightly modified if a child presents shortly after birth, symptomatically or otherwise. For older children, say, above the age of 18 months, the standard HIV antibody test can be used as a diagnostic tool.

II. Staging and monitoring of disease

Initial assessment of an HIV-infected child involves an evaluation to identify superimposed opportunistic diseases, establishment of developmental milestones, as well as virologic and immunologic measurements.

II.A Staging of disease

Clinical categorization is made on the grounds of symptomatic manifestations (categories A, B and C) as well as the immunologic stages (categories 1, 2 and 3) as shown in Boxes 7.18, 7.19 and 7.20. As CD4 count declines with age, the CD4 percent is more useful as a surrogate marker for staging and disease monitoring.

II.B Monitoring disease by viral load

Viral loads are useful prognostic markers.⁶ It should be noted that the values are often higher than adults and it takes longer to decline to the 'set point'. In very general terms, for those ≥ 30 months of age, the baseline viral load has similar predictive value as in adults, i.e. a vastly increased risk of disease progression when plasma HIV RNA exceeds 10,000-20,000/ml. However, interpretation of HIV RNA levels in younger children is difficult. A composite use of viral load and CD4 percent and especially their rate of change is advisable.

The ***intrinsic biologic variation*** of viral load is greater in young children. Only changes greater than fivefold (0.7 log) in those <2 years are considered significant. It has to be borne in mind that even without treatment, the HIV RNA level slowly declines, at 0.6 log per year in the first 12-24 months, and then 0.3 log per year until 4-5 years of age.

III. Treatment of pediatric HIV disease

III.A Caveats

The use of antiretroviral therapy in children is plagued with the paucity of pharmacokinetic studies and clinical trial data, especially in asymptomatic children. Furthermore, pediatric formulations are not available for every antiretroviral.

Nevertheless, clinical trials support the use of combination antiretroviral therapy in those with symptoms or evidence of immune suppression.^{8,9} By extrapolation of existing data in

Box 7.18 Pediatric human immunodeficiency virus (HIV) infection classification

(adapted from CDC 1994 revised classification system for HIV infection in children less than 13 years of age⁷ and Guidelines for the use of antiretroviral agents in pediatric HIV infection⁸)

Category N: not symptomatic	Category A: mildly symptomatic	Category B: moderately symptomatic	Category C: severely symptomatic
No signs or symptoms of HIV disease or only one of the conditions in category A	Two or more of the following conditions but none of those in B or C: <ul style="list-style-type: none"> • Lymphadenopathy (≥ 0.5cm at >2 sites; bilateral=1 site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent or persistent upper respiratory infection, sinusitis or otitis media 	Symptomatic conditions other than those in A or C, examples: <ul style="list-style-type: none"> • Anemia (<8g/dL), neutropenia ($<1 \times 10^9/L$), or thrombocytopenia ($<100 \times 10^9/L$) • Bacterial meningitis, pneumonia or sepsis (single episode) • Candidiasis, oropharyngeal persisting for >2 m in children >6 m • Cardiomyopathy • CMV infection with onset before 1 month of age • Diarrhea, recurrent or chronic • Hepatitis • HSV stomatitis, recurrent (>2 episodes in 1 year) • Herpes zoster involving >2 distinct episodes or more than one dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex • Nephropathy • Nocardiosis • Fever lasting >1 month • Toxoplasmosis with onset before 1 month of age • Varicella, disseminated 	Equivalence of "AIDS defining conditions"

Box 7.19 Category C diseases in pediatric human immunodeficiency virus (HIV) infection (*modified from CDC 1994 revised classification system for HIV infection in children less than 13 years of age*⁷ and *Guidelines for the use of antiretroviral agents in pediatric HIV infection*⁵)

- Serious bacterial infections, multiple or recurrent (i.e., any combination of ≥ 2 culture-confirmed infections within a 2-year period) of the following types: septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and in-dwelling catheter-related infections).
- Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhoea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen or lymph nodes)
- Encephalopathy (3 one of the following progressive findings present for ≥ 2 months in the absence of a concurrent illness other than HIV that could explain the findings):
 - a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard development scale or neuropsychological test;
 - b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerised tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age);
 - c) acquired symmetric motor deficit manifested by ≥ 2 of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Infection with HSV causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or oesophagitis for any duration in a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt) or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other or in addition to lungs or cervical or hilar lymph nodes)
- *Pneumocystis carinii* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicaemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings:
 - a) persistent weight loss $>10\%$ of baseline, or
 - b) downward crossing of at least one of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age, or
 - c) $<5^{\text{th}}$ percentile on weight-for-age chart on 2 consecutive measurements, ≥ 30 days apart) plus 1) chronic diarrhea (at least 2 loose stools/day for ≥ 30 days) or, 2) documented fever (for ≥ 30 days, intermittent or constant)
- Disseminated penicilliosis is a category C condition in the Hong Kong context.
- Pulmonary and cervical TB are designated category C when there is severe immune suppression. (immunologic category 3)

Box 7.20 1994 revised HIV pediatric classification system: immune categories based on age-specific CD4+ T-lymphocyte count and percentages^{5,7}

Immunologic category	Age of child		
	< 2 mo /ul (%)	1-5 yr /ul (%)	6-12 yr /ul (%)
Category 1. No suppression	≥1500 (≥25)	≥1000 (≥25)	≥500 (≥25)
Category 2. Moderate suppression	750-1499 (15-24)	500-999 (15-24)	200-499 (15-24)
Category 3. Severe suppression	<750 (<15)	<500 (<15)	<200 (<15)

adults, it is reasonable that such therapy should be as potent as possible, usually in the form of 2 nucleosides plus a protease inhibitor.

It is possible that mothers ignore their own health while providing excellent care to their HIV infected children. Therefore it should also be emphasized to the mother that the long term health of her child ultimately depend on that of her own.

III.B Multidisciplinary approach

The fact that perinatally infected children and infants are raised by at least one infected parent engenders complex medical and social problems. Therefore, management of pediatric HIV infection should be directed by a specialist in pediatric HIV infection with a multidisciplinary team approach that involves pediatricians, nurses, social workers, psychologists and nutritionists. The treatment team will initiate and monitor antiretroviral and prophylactic treatment, modify the vaccination schedule, assess developmental milestones, and help resolve psychosocial issues. Good liaison is maintained between the care teams of the HIV infected parent(s) and the child.

III.C Antiretroviral treatment

Indications of antiretroviral therapy⁵ – In principle, early highly active antiretroviral therapy (HAART) is beneficial in children with HIV/AIDS by virtue of preserving the immune function, diminishing viral dissemination, and a lowering the viral set point. However, the problems with adherence, resistance and tolerance should be considered and discussed with the care-giver before a decision is made. Generally speaking, HAART is indicated in the following situations:

-
- (a) Clinical disease (category A, B or C) irrespective of age;
 - (b) Immune suppression (category 2 or 3) irrespective of age;
 - (c) All children under the age of 1, irrespective of clinical, immunologic and virologic status – Though ideally this should be considered, definitive evidence on the therapeutic benefit of this approach is currently lacking. The problems of drug dosing, adherence and resistance shall be individually assessed.

For children at or above the age of one, two approaches can be considered. The clinician may choose to

- (a) initiate treatment promptly, or
- (b) defer until there is a high or rising viral load, rapidly decreasing CD4, and/or the development of clinical symptoms.

Preferred antiretroviral therapy – 2 nucleosides and a protease inhibitor (e.g. ritonavir syrup or nelfinavir powder) is the preferred choice. A nonnucleoside reverse transcriptase inhibitor (NNRTI), e.g. nevirapine may be substituted for a protease inhibitor¹⁰ in case of intolerance or difficulty in adherence or added to the regimen for added potency. Durability of response may be inferior with an NNRTI-based regimen. A regimen of efavirenz, nelfinavir and an NRTI is potent and an alternative¹¹ in older children.

It is important that the patient be **monitored** for virologic and immunologic response as well as clinical signs and symptoms. Adverse effects of drugs such as anemia and neutropenia should also be looked out for. It may not be realistic to aim at an undetectable viral load in all HIV infected children under treatment.

A change in therapy is considered if the viral load has risen by more than 0.5-0.7 log and is more than 4 logs (confirmed by repeat testing). Such change should involve at least two drugs of two classes.¹²

III.D Prophylaxis against opportunistic infections

The principles of primary and secondary prevention of opportunistic infections are largely the same as in adults. Noteworthy, however, are the following:¹³

- (a) **PCP prophylaxis**¹⁴ – Children perinatally exposed to HIV should be started on Septrin for prophylaxis beginning at 4-6 weeks, until HIV infection is excluded. For documented infection, prophylaxis after the first year shall be based on clinical and immunologic criteria.
- (b) **Toxoplasmosis, CMV and hepatitis C** – Infants born to HIV infected women who have serologic evidence of toxoplasma, CMV and hepatitis C should be evaluated for toxoplasmosis, CMV infection, and hepatitis C respectively.
- (c) **MAC** – prophylaxis with clarithromycin or azithromycin should be offered if the

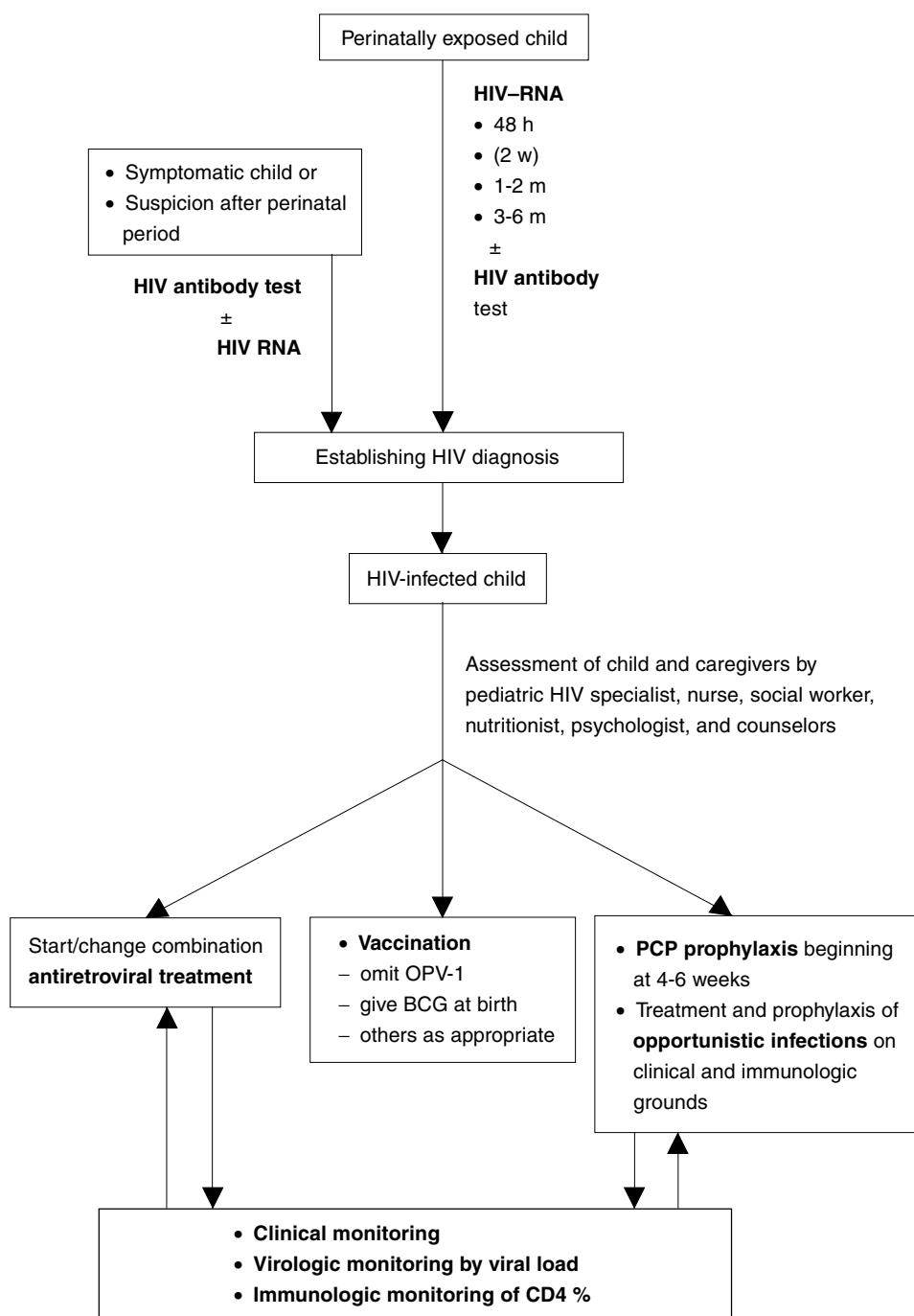
CD4 count is <50/ul in children aged ≥ 6 yr; <75/ul in children 2-6 yr; <500/ul in children 1-2 yr, and <750/ul in children <12 months. Rifabutin is not available in liquid formulation.

- (d) **Recurrent bacterial infections** – intravenous immunoglobulin (IVIG) may be considered in those with hypogammaglobulinemia or recurrent serious bacterial infections.
- (e) **Discontinuation of prophylaxis** – In some cases, immunologic improvement on HAART may allow discontinuation of prophylaxis in adults. However, relevant data in the pediatric population are not yet available.

III.E Vaccination

In general, vaccination for HIV infected children follows closely that for the healthy children with some modifications. Live vaccines are avoided in HIV-infected children as far as possible. IPV is substituted for OPV in those infected and their household members. OPV-1 is universally given in Hong Kong. This should be avoided in the known HIV infected infant. In those without immune suppression, the MMR and varicella vaccine may be given, as the benefits may outweigh the risks. In Hong Kong where TB is endemic, BCG is recommended at birth to those perinatally exposed to HIV.³

Algorithm 7.6 Management of HIV-infected children



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APPENDIX I

DH2293

APPENDIX I. DH2293

DEPARTMENT OF HEALTH HIV/AIDS Report Form

Please read the following instructions:

- This is a voluntary report form for reporting:
 - newly diagnosed HIV infection;
 - newly diagnosed AIDS;
 - change(s) of status of previously diagnosed HIV/AIDS cases
- Only sections (A), (C) & (D) need to be completed for reporting HIV infection.
- All sections, (A), (B), (C) & (D) have to be completed for reporting AIDS or updating information.
- All individual's information will be treated as strictly confidential and used in global analysis only.
- Please mark CONFIDENTIAL on the envelope and mail the completed form to:

Consultant Physician
Special Preventive Programmes
Department of Health
5/F Yaumatei Jockey Club Clinic
145 Battery Street, Yaumatei,
Kowloon.

Section (A) Reporting HIV Infection

Your reference code number: _____ (HK resident/non-resident*)
 Sex: M/F* Date of Birth: (dd/mm/yyyy) _____ or age (at last birthday) _____
 For female: Is she pregnant: Yes/No* (complete Box 1 if "Yes")
 Ethnicity: Chinese/non-Chinese* (Asian/Caucasian/Black/others, please specify _____)*
 Marital Status: married/widowed/separated/never married*
 Date of laboratory diagnosis in HK: (dd/mm/yyyy) _____ Western Blot Confirmation: Yes/No*
 Name of Laboratory: _____
 Previous HIV positive result outside Hong Kong: No/Yes*
 (specify place: _____; date: (dd/mm/yyyy) _____)
 Main route of transmission (please tick; if > 1, put down 1 & 2 in descending order of the two most likely routes)
 _____ sex: (_____ heterosexual/ _____ homosexual/ _____ bisexual)*
 _____ transfusion of blood – local/overseas* (specify date: _____)
 _____ haemophilia
 _____ injecting drug use
 _____ perinatal
 _____ others; specify _____
 _____ not known
 CD4 count per ul (if known): _____ date: (dd/mm/yyyy): _____
 HIV status of spouse, if any: unknown/positive/negative*

Box 1

Gravida _____ Para _____
 LMP (dd/mm/yyyy) _____
 Obstetric follow-up at:
 hospital/clinic _____
 Expected hospital/place of delivery:

 Current plan: Continue pregnancy/
 T.O.P.*

Section (B) Reporting AIDS

Is this an update of a previously reported HIV+ case: Yes/No*
 Date of diagnosis: (dd/mm/yyyy) _____
 AIDS defining illness(es):
 1. _____ clinical Dx/pathological Dx*
 2. _____ clinical Dx/pathological Dx*
 3. _____ clinical Dx/pathological Dx*
 CD4 count per ul (if known): _____ date: (dd/mm/yyyy): _____

Section (C):

Current status (please tick the right choice):
 _____ An outpatient
 _____ An inpatient (Hospital: _____)
 _____ Died (date: (dd/mm/yyyy) _____ cause of death: _____)
 _____ Left HK/defaulted follow-up (date last seen: (dd/mm/yyyy) _____)

Section (D)

Name of medical practitioner: _____ in private practice/public service*
 Correspondence Address: _____

Date: _____ Tel no: _____ Fax no: _____ E-mail: _____

**delete whichever inappropriate*

DH2293, revised August 2001

ALL INFORMATION WILL BE TREATED IN STRICT CONFIDENCE



APPENDIX II

PROFILE OF SPP

APPENDIX II. PROFILE OF SPP

SPP – DEPARTMENT OF HEALTH

Aims

The aims of Special Preventive Programmes (SPP) are to

1. expand the community's response to HIV/AIDS
2. support the development of evidence-based AIDS strategies
3. cultivate expertise in clinical and public health practice in HIV medicine and infectious diseases

Historical background

SPP began as a series of projects based in Queen Elizabeth Hospital to provide hepatitis B vaccination to health care workers in the early eighties. An AIDS Counselling Service was added to the portfolio in 1985, followed gradually by the incorporation of AIDS education activities and clinical services in the subsequent years. When the Government set up the Advisory Council on AIDS, SPP took up the role as its Secretariat. In 1991, The SPP was restructured to integrate its Viral Hepatitis Preventive Service and AIDS Unit, which were relocated to Yaumatei in 1994. In late 1996, SPP opened its Red Ribbon Centre to centralise its health promotion and HIV prevention activities. The Centre was designated an UNAIDS Collaborating Centre in 1998. In 1999, the Integrated Treatment Centre began operation, the latter focusing on the delivery of quality clinical services.

SPP is now made up of four programmes operating through three physical premises. The range of services is increasing, the nature of which evolving in response to the need of the community.

The four programmes of SPP

There are four virtual programmes with overlapping functions: (a) clinical programme, (b) HIV prevention and health promotion programme, (c) policy development programme and (d) research and epidemiology programme.

Clinical programme – Centering on HIV medicine, this is the programme that specializes in the delivery of direct services to people living with HIV/AIDS. The services form a continuum from hotlines, voluntary counselling and testing (VCT), medical treatment and consultation, nursing care, psychosocial support to referrals. The programme also includes the following clinical activities – dermatology, genitourinary medicine, hepatitis B vaccination for health care workers, infection control, and management of needlestick injuries.

HIV prevention and health promotion programme – This is the programme that addresses HIV prevention in the community setting. There are four main activity areas: communication and information, targeted prevention, promoting acceptance and capacity-building. While the main focus is HIV/AIDS, there is also involvement in viral hepatitis, STD and bloodborne infections in the health care setting. The characteristics of the programme are its collaborative approach, partnership with the community, and the provision of support to community-based initiatives.

Policy development programme – This is the programme that supports the functions of the Advisory Council on AIDS (ACA) and its committees, Scientific Working Group on Viral Hepatitis

Prevention, and Expert Panel on HIV and Health Care Workers. Programme staff are engaged in the vigorous review of scientific evidence on the subject matters, research, information dissemination, and the coordination among stakeholders.

Research and epidemiology programme – The programme is underpinned by surveillance and research activities. For surveillance, SPP maintains the voluntary HIV/AIDS reporting system, coordinates an HIV seroprevalence system, operates a behavioural surveillance mechanism, supports an STD (sexually transmitted disease) surveillance programme, and runs a series of registries and cohort studies. The programme also supports the collation of epidemiology information on viral hepatitis. There are research projects and participation in biomedical, clinical and public health research on HIV/AIDS, as well as the evaluation of programmes relating to HIV prevention, care and control.

Physical premises

There are three physical premises, located in Yaumatei, Wang Tau Hom and Kowloon Bay.

Yaumatei premise is the physical location for the ACA Secretariat, the SPP Office, and part of the clinical services and hotlines.

Wang Tau Hom premise houses the Red Ribbon Centre (incorporating the UNAIDS Collaborating Centre for Technical Support), and the Research Office. The Wang Tau Hom premise is a purpose-built HIV resource centre, the construction of which was supported by the AIDS Trust Fund. The Centre's facilities include an exhibition area, activity area, library, production room, audiovisual room, conference room and lecture room. The Centre's operation is supervised by the Red Ribbon Centre Management Advisory Committee appointed by the Director of Health.

Kowloon Bay premise houses the Integrated Treatment Centre, the main clinical unit of SPP. The premise is a purpose-built medical centre equipped with outpatient clinics, treatment and investigation facilities, and day services for patients with skin diseases, STD and HIV/AIDS.

SPP services, centres and offices

SPP discharges its responsibilities through a number of units (named services, centres or offices) run by designated professional staff.

HIV Clinical Service is the clinical unit based in Integrated Treatment Centre (Kowloon Bay premise) that provides clinical HIV services and consultations, counselling, coordinates support service and organises professional development activities. The Unit is run by doctors, nurses and medical social workers.

Infection Control Service is the unit that operates the Therapeutic Prevention Clinic for providing post-exposure management to health care workers, maintains a resource collection on infection control, and provides support to infection control initiatives of the Department of Health.

Hepatitis Vaccination Service provides hepatitis B vaccination to eligible health care workers, researches on the efficacy of hepatitis vaccinations and the epidemiology of viral hepatitis in Hong Kong.

Dermatology & GUM Service is the clinical unit that manages patients with skin diseases and STDs. The Service entails the provision of medical treatment, consultation, investigative procedures and minor surgical interventions.

Research Office is the focal point for coordinating HIV surveillance activities, generating surveillance reports, and collating hepatitis epidemiology information. The Office also provides support to research activities.

Red Ribbon Centre is both the physical premise as well as the operating base of SPP's HIV Prevention and Health Promotion Team. The mission of the Centre is *to facilitate and enhance the community's response to HIV/AIDS*. Team staff conduct programmes with the themes of

Collaborative Projects

SPP enters into collaborative arrangement with other agencies in the conduction of specially designed projects on HIV prevention and care. Some of these projects are as follows:

Hong Kong Community Charter on AIDS – In collaboration with Lions Clubs International District 303 Hong Kong & Macau, the Charter was launched in 1994 to promote the development of non-discriminatory workplace policy on AIDS. The Honourable Tung Chee Hwa, Chief Executive of HKSAR, is the patron of the project. So far 81 agencies have become signatories of the Charter. Now operating under an independent Executive Board, the Charter is evolving to become a community project to promote acceptance of people living with HIV/AIDS.

Youth Funding Scheme on AIDS – The "Youth Action on AIDS" Funding Scheme celebrated its 10th anniversary in 2001. Through technical and financial support, the Scheme encourages young people to develop AIDS awareness initiatives for their peers. As an affiliated project of the AIDS Prevention and Care Committee of the Advisory Council on AIDS, the Scheme is maintained by SPP with the support of a task force with representatives from youth organizations, government departments and the community.

Media Campaigns – SPP collaborates with the Government Information Service in the development of the government's AIDS awareness campaigns. The production of these campaigns is advised by the AIDS Prevention and Care Committee.

Phoenix Project – In collaboration with the methadone clinics and the Society for the Aid and Rehabilitation of Drug Abusers (SARDA), the Phoenix project was initiated in 2000 to outreach drug users through the participation of a group of ex-drug users. Using the vicinity of the methadone clinics as the base, the outreach volunteers deliver harm reduction messages to drug users on the street.

SPACE Courses – In collaboration with the University of Hong Kong's School of Professional and Continuing Education (SPACE), training courses on HIV/AIDS, sexually transmitted diseases (STD) and other infectious diseases are organized for health care workers and people working on HIV prevention and care.

Lions-RRC Fellowship – Beginning 1999, SPP has been managing a fellowship scheme to support Mainland AIDS workers to undertake short attachment in Hong Kong. The Scheme is funded by Lions Clubs International District 303 Hong Kong and Macau and supervised by the Red Ribbon Centre Management Advisory Committee.

communication and information, capacity-building, targeted prevention and the promotion of acceptance of people living with HIV/AIDS. These programmes are delivered in the form of resource development efforts, centre-based and community-based activities in the settings of individuals and communities.

UNAIDS Collaborating Centre for Technical Support – The Collaborating Centre provides the framework for interfacing the Mainland's AIDS programmes, and developing regional and international collaboration. The Centre specializes in resource networking, operates the UNAIDS Hong Kong Ambassador Scheme (Miss Miriam Yeung being the first ambassador) and the organization of workshops for Mainland AIDS workers. Mrs Betty Tung is the Patron of the Centre.

AIDS Counselling Service – Through an interactive voice response telephone system, AIDS messages can be accessed through the designated AIDS Hotline 27802211. The Hotline is also the contact point for accessing AIDS counseling and voluntary HIV testing, which is a free and anonymous service.

ACA Secretariat – The Secretariat is the focus for coordinating activities of the Advisory Council on AIDS and its three committees. It provides administrative and professional support to these forums, the latter through evaluation, review, research and the preparation of strategy papers, guidelines and position papers.

SPP Office – This is the head office of the SPP that takes care of all administrative activities including human resource management, planning and resource management.

Service Hours and Correspondence

Premises/Services	Correspondence	Service hours
Integrated Treatment Centre	8-9/F Kowloon Bay Health Centre, 9 Kai Yan Street, Kowloon Bay, Kowloon, Hong Kong Enquiry: Tel: (852) 2116 2888 Fax: (852) 2117 0809	Monday to Friday: 9am-1pm, 2pm-5pm Saturday: 9am-1pm
Red Ribbon Centre	2/F 200 Junction Road East, Wang Tau Hom, Kowloon, Hong Kong Enquiry: Tel: (852) 2304 6268 Fax: (852) 2338 0534	Monday to Friday: 10am-1pm, 2pm-6pm Saturday: 9am-12 noon
Advisory Council on AIDS Secretariat	5/F Yaumatei Jockey Club Clinic, 145 Battery Street, Yaumatei, Kowloon, Hong Kong Enquiry: Tel: (852) 2304 6100 Fax: (852) 2337 0897	Monday to Friday: 9am-1pm, 2pm-5pm Saturday: 9am-1pm
SPP Office	5/F Yaumatei Jockey Club Clinic, 145 Battery Street, Yaumatei, Kowloon, Hong Kong Enquiry: Tel: (852) 2780 8622 Fax: (852) 2780 9580	Monday to Friday: 9am-1pm, 2pm-5pm Saturday: 9am-1pm
AIDS Counselling Service	Tel: (852) 2780 2211	24-hour hotline (interactive voice response system) Counsellor's service Monday - Friday: 8am-8pm

Regular publications

SPP functions as the editorial office for the following publications that are issued on a regular basis:

ACA Newsfile (English) – a monthly newsletter of the ACA Secretariat for members of the Advisory Council on AIDS and its committees, on subjects relating to AIDS policy development in Hong Kong.

AIDS Newsletter (Chinese) – a four-monthly newsletter of Red Ribbon Centre for youth, schools and community groups interested in any aspect of HIV prevention and care.

The Node (bilingual) – a four-monthly publication of the UNAIDS Collaborating Centre for Technical Support, which covers activities of the Centre, news and information of regional interest.

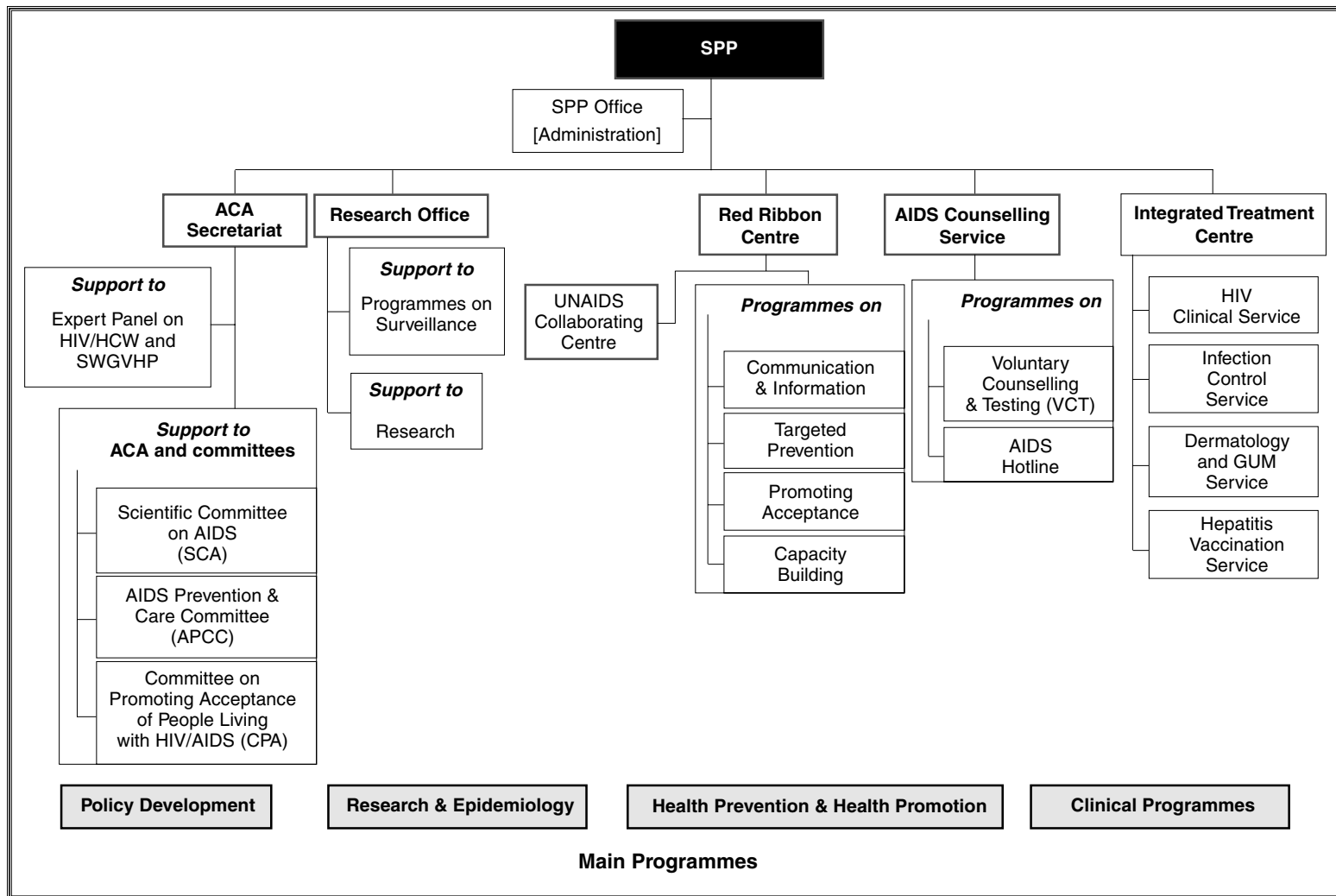
Hong Kong STD/AIDS Update (English) – a quarterly surveillance report of the Research Office that covers epidemiological information on STD and HIV/AIDS in Hong Kong.

Red Ribbon (Chinese) – a half-yearly publication of HIV Clinical Service, featuring articles and information of interest to people living with HIV/AIDS.

Networking Voice (Chinese) – a 4-monthly publication of the Task Force of Youth of the AIDS Prevention and Care Committee for networking youth workers, focusing on the subject of HIV/AIDS.

Communication in the Cyberspace

SPP communicates with health professionals and the community through the internet. In 1997 a website was launched to pool useful HIV/AIDS information for easy access of anyone interested in the HIV situation and programmes in Hong Kong. Named "Virtual AIDS Office", the website www.aids.gov.hk has recorded a total of over 50 000 visitors in 2000. The site can also be reached through the home pages of Red Ribbon Centre www.rrc-hk.com and Advisory Council on AIDS www.aca-hk.com. SPP is now working on the development of a new internet project to deliver HIV prevention messages and to promote acceptance of people living with HIV/AIDS in Hong Kong.





APPENDIX III

LIST OF LOCAL DOCUMENTS

APPENDIX III. LIST OF LOCAL DOCUMENTS

Practice Manuals

HIV Manual 2001 (formerly <i>AIDS Manual for Doctors and Dentists 1995 and Information on AIDS for Doctors and Dentists 1987, 1992</i>)	DH Special Preventive Programmes	E	2001
HIV and AIDS for Primary Care Doctors – An Information Booklet (first published in 1993, revised 1995)	DH AIDS Unit	E	1997
Manual for Nurses (Formerly <i>Information on AIDS for Nurses 1988, 1993</i>) 護理人員愛滋病手冊	DH AIDS Unit 衛生署愛滋病服務組	E C	1997 1998
Manual on HIV/AIDS for Social Welfare Personnel	ACA AIDS Services Development Committee	E	1995
Manual on HIV/AIDS for Social Welfare Personnel - A Synopsis 社會福利工作人員愛滋病手冊 - 撮要	ACA AIDS Services Development Committee 香港愛滋病顧問委員會轄下 愛滋病服務發展委員會	E C	1995
Manual on Counselling for HIV infection and AIDS 愛滋病毒感染及愛滋病輔導工作指南	DH AIDS Unit 衛生署愛滋病服務組	E C	1999

HIV Management and Clinical Guidelines

Guidelines on Management of HIV Infection in Children	ACA Scientific Committee on AIDS	E	1995
Consensus Statement on Principles of Antiretroviral Therapy for HIV Infection in Hong Kong (formerly <i>Consensus Statement on Antiretroviral Therapy for HIV Infection in Hong Kong, 1997</i>)	ACA Scientific Committee on AIDS	E	1998
Prevention & Management of Tuberculosis in HIV Infected Patients in Hong Kong an Information Paper	ACA Scientific Committee on AIDS	E	1995
A Review of Services provided to People with HIV/AIDS in Hong Kong	ACA AIDS Services Development Committee	E	1994
Principle of STD Management	DH Social Hygiene Service & AIDS Unit	E	1998
Recommended Clinical Guidelines on the Prevention of Perinatal HIV Transmission	ACA Scientific Committee on AIDS	E	2001
Recommendations on the Treatment of Latent TB Infection in HIV-positive Persons in Hong Kong	ACA Scientific Committee on AIDS	E	2001
Recommendations on the Management of HIV Infection in Infants and Children	ACA Scientific Committee on AIDS	E	2001

Infection Control Series

Prevention of Transmission of HIV in Health Care Setting – Guidelines and Practices (initially formulated by ACA in 1990, first edition by Scientific Working Group on AIDS 1992)	ACA Scientific Committee on AIDS	E	1995
Guideline on Infection Control Practice in dental Clinics	DH Infection Control Committee	E	1993
The Basic Protocol, Infection Control Guideline for Dentist	DH	E	1999
Guidelines on Infection Control Practice in Clinics and Maternity Home	DH	E	1993
Guidelines on Infection Control Practice in Outpatient Clinics	DH	E	1999
Procedure for Management of Needlestick Injury or Mucosal Contact with Blood Body Fluids – Recommended Guidelines for Hepatitis B, C & HIV Prevention (first published 1992, revised 1995) 對被利器刺傷或經黏膜與血液 / 體液接觸後的處理方法	ACA Scientific Committee on AIDS, & DH Scientific Working Group on Viral Hepatitis Prevention 愛滋病顧問局轄下愛滋病科學委員會	E C	1997 with amendment in 2000
Precautions for Handling and Disposal of Dead Bodies (first published 1994, revised 1997) 處理屍體所需的預防措施	Department of Health, Hospital Authority, Urban Service Department & Regional Service Department 衛生署, 醫院管理局, 市政署及區域市政署	E C	1999
Guidelines on the Prevention of Blood-Borne Diseases in Schools (first published 1994, formerly <i>Prevention of blood-borne diseases in schools, 1987</i>) 血液傳染病在校內的預防指引	Education Department & DH 衛生署及教育署	E C	2001

Surveillance, Epidemiology and HIV Testing

HIV Antibody Testing: Recommended Measures to Generate Quality Result	ACA Scientific Working Group on AIDS	E	1994
Classification System for HIV Infection and Surveillance Case Definition for AIDS in Adolescents and Adults in Hong Kong	ACA Scientific Committee on AIDS	E	1995
Unlinked Anonymous Screening for HIV Surveillance in Hong Kong 1990-1996	ACA Scientific Committee on AIDS	E	1997

Proceedings of Workshop on HIV Surveillance and Epidemiology in the Pearl River Delta Region 11-12 Dec 1999 Macau	HKU Centre of Infection	E C	2000
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Guidelines on Consent for HIV Testing	DH	E	1993
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Recommended Guidelines for Undertaking Unlinked Anonymous Screening for Public Health Surveillance of HIV Infection in Hong Kong	ACA Scientific Working Group on AIDS	E	1993
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Blood and Blood Products Safety

Proposed Revised Specification for Clotting Factor Concentrates	ACA Scientific Working Group on AIDS	E	1993
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The Choice of Safe Clotting Factor Concentrates for Treatment of Haemophilia in Hong Kong: Recommended Guidelines	ACA Scientific Committee on AIDS	E	1994
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Report of the Study Group on HIV Infection of Haemophiliacs through Blood Products in Hong Kong	The Study Group on HIV Infection of Haemophiliacs	E	1993
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Strategy and Position Papers

Strategies for AIDS Prevention, Care & Control in Hong Kong (an executive Summary) 香港防治愛滋病策略 - 撮要	Advisory Council on AIDS 愛滋病顧問委員會	E C	1994
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Strategies for AIDS Prevention, Care & Control in Hong Kong	Advisory Council on AIDS	E	1994
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An Overview of the HIV/AIDS Situation and the Programmes on Its Prevention, Care and Control in Hong Kong 香港愛滋病 / 愛滋病毒感染現況概覽	ACA 愛滋病顧問局	E C	1997
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HIV Prevention in Hong Kong Strategy Series 香港愛滋病預防工作策略系列	ACA 愛滋病顧問局		
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Recommended Strategy for HIV Prevention in MSM in HK 香港的男同性性接觸者社群 - 預防愛滋病毒病感染建議策略	ACA Committee on Education and Publicity on AIDS 愛滋病教育及宣傳委員會	E C	1998
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HIV Prevention in Mobile Population – Principles of Strategy 流動人口的愛滋病毒病預防計劃 - 策略原則	ACA Committee on Education and Publicity on AIDS 愛滋病教育及宣傳委員會	E	1998
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HIV Prevention and Care in Youth – Principles of Strategy 青少年的愛滋病毒預防及關懷 - 策略原則	ACA AIDS Prevention and Care Committee 愛滋病預防及護理委員會	E C	2000
HIV Prevention in Drug Users – Principles of Strategy	ACA AIDS Prevention and Care Committee	E C	2001
HIV/AIDS Programme Review Series			
Internal Assessment Report – A Review of the HIV/AIDS Situation and the Programmes on Its Prevention, Care and Control in Hong Kong	ACA	E	1998
Moving Ahead Together – Expanding Hong Kong's Response to AIDS 齊邁向前 積極回應	ACA	E C	1998
AIDS Strategy for Hong Kong 1999-2001 香港愛滋病策略一九九九至二零零一	ACA 愛滋病顧問局	E C	1999
The First Decade of AIDS in Hong Kong – a Collection of Essays	ACA	E	1999
HIV Infection & The Health Care Workers Recommended Guidelines	ACA	E	1994
Setting the Agenda of Promoting Acceptance of People Living with HIV/AIDS in Hong Kong 為促進社會接納愛滋病患者而制訂工作計劃 - 策略原則	ACA Committee on Promoting Acceptance of People Living with HIV/AIDS 愛滋病顧問局轄下接納愛滋病患者促進委員會	E C	2001
The Government's Involvement in Promoting Public Awareness on AIDS in Hong Kong – A Position Paper	ACA	E	2001
AIDS and the Law: The Hong Kong Experience	ACA	E	1997
Key: E English C Chinese ACA Advisory Council on AIDS DH Department of Health HKU The University of Hong Kong "AIDS Unit" and "Special Preventive Programmes" are used interchangeably			



APPENDIX IV

SELECTED GUIDELINES

- (A) Classification system for HIV infection and surveillance case definition for AIDS in adolescents and adults in Hong Kong. Scientific Committee on AIDS, 1995**
- (B) HIV infection and the health care workers – recommended guidelines. Advisory Council on AIDS, 1994**
- (C) Prevention of transmission of HIV in health care settings – guidelines and practices. Scientific Committee on AIDS, 1995**

APPENDIX IV. SELECTED GUIDELINES

(A) Classification System for HIV Infection and Surveillance Case Definition for AIDS in Adolescents and Adults in Hong Kong

**Scientific Committee of the Advisory Council on AIDS Hong Kong
July 1995**

Classification System for HIV Infection and Surveillance Case Definition for AIDS in Adolescents and Adults in Hong Kong is prepared by the Scientific Committee on AIDS, one of the three committees of the Governor-appointed Advisory Council on AIDS. The paper contains information on (1) the background of developing and adopting an official system for HIV classification and AIDS surveillance in Hong Kong; (2) the system adopted which was a modified version from the 1993 CDC Classification system due to local needs; and (3) the local HIV/AIDS reporting system. The situation will be kept under review by the Committee, taking into consideration local as well as international development in this area.

Scientific Committee on AIDS
July 1995

Scientific Committee on AIDS 1995/96

Chairman: Prof. NG Mun-hon, Department of Microbiology, HKU

Members: Dr. W K LAM, Department of Medicine, University of Hong Kong
Dr. Y L LAU, Department of Paediatrics, University of Hong Kong
Dr. Homer TSO, Advisory Council on AIDS
Dr. Joseph LAU, Centre for Clinical Trials & Epidemiological Research, Chinese University of Hong Kong
Dr. Susan LEONG, JP, Hong Kong Red Cross Blood Transfusion Service
Dr. J B HOLLINRAKE, MBE, SARDA
Dr. C F LAI, Hong Kong Medical Association
Dr. Philip S L TANG, Hong Kong Dental Association
Dr. T W WONG, Department of Community & Family Medicine, Chinese University of Hong Kong
Ms. K Y WAH, Hong Kong College of Nursing
Dr. Patrick LI, Hospital Authority
Ms. Patricia CHENG, Hospital Authority
Dr. K B CHAN, Correctional Services Department
Dr. C M TAM, Tuberculosis & Chest Services, Department of Health
Dr. Brian JONES, Immunology Section, Queen Mary Hospital
Dr. K K LO, Social Hygiene Service, Department of Health
Dr. W L LIM, Virus Unit, Department of Health
Dr. W P MAK, Institute of Pathology, Department of Health
Dr. W M CHAN, JP, Department of Health
Dr. S S LEE, Special Preventive Programme, Department of Health
Dr. Thomas TSANG, Department of Health

Secretaries: Dr. L C KWAN, Special Preventive Programme, Department of Health
Mr. S Y YAU, Advisory Council on AIDS

Classification System for HIV Infection and Surveillance Case Definition for AIDS in Adolescents and Adults in Hong Kong

Background

AIDS represents the late stage of HIV infection with profound immunosuppression and the occurrence of unusual opportunistic infections and tumours. The first AIDS Surveillance Definition was developed by the US Centers for Disease Control and Prevention (CDC) before HIV was discovered. The definition emphasized on clinical diseases related to a then unknown agent. With advances in knowledge of HIV, the 1987 Surveillance Definition required evidence of HIV infection (or lack of evidence of other causes of immune suppression) and a diagnosis of at least one of the specified diseases that was moderately to highly indicative of cellular immune dysfunction. Twenty-three diseases were listed and labelled as AIDS defining conditions.

In 1993, CDC revised the classification system for HIV infection and AIDS Surveillance Definition for Adolescents and Adults. Both clinical parameters and CD4 counts were used in the new classification system. As for surveillance definition a CD4 level of less than 200/uL had become a criterion for AIDS, and that three other diseases were included as AIDS-defining conditions – recurrent pneumonia, any site of mycobacterium tuberculosis and invasive cervical cancer.

In Hong Kong, the Scientific Committee of the Advisory Council on AIDS recommended adoption of a slightly modified (from CDC 1993) classification system for HIV infection and a clinical approach to AIDS surveillance definition. The local classification system and AIDS surveillance system should however be kept under periodic review and revision made when appropriate, taken into consideration the international and local development in this area, as well as changes in local disease pattern.

Classification for HIV infection in Adolescents & Adults in Hong Kong

CD4+ T-cell categories	Clinical categories		
	(A) Asymptomatic, acute (primary) HIV or PGL	(B) Symptomatic, not (A) or (C) conditions	(C)* AIDS-indicator conditions
(1) $\geq 500/\mu\text{L}$	A1	B1	C1
(2) 200-499/ μL	A2	B2	C2
(3) $< 200/\mu\text{L}$	A3	B3	C3

I. CD4+ T-Lymphocyte Categories

The lowest accurate, but not necessarily the most recent, CD4 count should be used for classification.

II. Clinical Categories

Category A

- * Asymptomatic HIV infection
- * Persistent generalized lymphadenopathy
- * Acute (primary) HIV infection

Category B

Conditions attributed to HIV infection /indicative of defect in cell-mediated immunity or whose clinical course or management is complicated by HIV infection. It includes the conditions listed below which are however not exhaustive :

- * Bacillary angiomatosis
- * Oropharyngeal candidiasis
- * Vulvovaginal candidiasis (persistent, recurrent or refractory)
- * Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- * Constitutional symptoms
- * Oral hairy leukoplakia
- * Herpes zoster (>1 episode or >1 dermatome)
- * Idiopathic thrombocytopenic purpura
- * Listeriosis
- * Pelvic inflammatory disease
- * Peripheral neuropathy

Category C

- * Candidiasis of bronchi, trachea, or lungs
- * Candidiasis, esophageal
- * Cervical cancer, invasive
- * Coccidioidomycosis, disseminated or extrapulmonary
- * Cryptococcosis, extrapulmonary
- * Cryptosporidiosis, chronic intestinal
- * Cytomegalovirus retinitis
- * Cytomegalovirus disease (other than liver, spleen or nodes)
- * Encephalopathy, HIV-related
- * Herpes simplex, chronic ulcer, bronchitis, pneumonitis or esophagitis
- * Histoplasmosis, disseminated or extrapulmonary
- * Isosporiasis, chronic intestinal
- * Kaposi's sarcoma
- * Lymphoma, Burkitt's
- * Lymphoma, immunoblastic
- * Lymphoma, primary of brain
- * Mycobacterium avium complex or kansasii, disseminated or extrapulmonary
- * Mycobacterium tuberculosis, extrapulmonary or pulmonary/cervical lymph node (only if CD4 <200/uL)*
- * Mycobacterium, other species, disseminated or extrapulmonary
- * Penicilliosis, disseminated*
- * Pneumocystis carinii pneumonia

- * Pneumonia, recurrent
- * Progressive multifocal leukoencephalopathy
- * Salmonella septicemia, recurrent
- * Toxoplasmosis of brain
- * Wasting syndrome due to HIV

*Modification of the CDC 1993 Classification system : – (1) Penicilliosis has been added and (2) pulmonary or cervical lymph node tuberculosis included only if CD4 < 200/ul.

AIDS Surveillance Definition for Adolescents & Adults in Hong Kong

For surveillance purpose, AIDS is defined only if a patient develops one or more of the conditions listed under category C in the classification system described in section 2.

Reporting of HIV/AIDS

HIV/AIDS is not a statutory notifiable disease in Hong Kong but a voluntary reporting system has been adopted since 1985. Medical and dental practitioners are urged to report HIV infection and AIDS cases to the Department of Health using the form DH 2293. In addition, in order to enhance the detection and understanding of any new or changing diseases arising from HIV infection, practitioners shall also report unusual complications or presentations (which are not known AIDS-defining illnesses) occurring in HIV-infected patients.

(B) HIV Infection and the Health Care Workers – Recommended Guidelines

Advisory Council on AIDS
Hong Kong
Published in April 1994

(1) Background

- 1.1 AIDS (Acquired Immunodeficiency Syndrome) is caused by a retrovirus named HIV, the human immunodeficiency virus. The syndrome, characterised by development of complications like opportunistic infections or tumours, was first described in 1981 in the USA. The human race is now hard hit by the pandemic. An estimated total of 15 million people worldwide have already been infected so far.
- 1.2 HIV is transmitted largely through three routes: (a) sexual contact with an HIV-infected person, (b) exposure to contaminated blood and needles, and (c) perinatally from an infected mother to her baby. Worldwide over three-quarters of the infection have been contracted through sex, and largely heterosexual contacts.
- 1.3 HIV infection has been reported to occur in health care settings by exposure to contaminated blood through cutaneous injuries or mucous membranes. The estimated risk of contracting the virus after such injuries or exposure to infected blood is 0.4%.
- 1.4 The chance of HIV transmission from an infected health care worker to his / her client is much lower. The CDC (Centers for Diseases Control) in Atlanta has reported that six patients of an HIV-positive dentist in Florida were infected since 1990. There is still controversy as to how the transmission has occurred but this is the only case documented so far. In other 'look-back' studies of over 15000 clients of 32 HIV infected health care workers, including dentists and surgeons, none was found to have caught the virus.
- 1.5 Taken the extremely low risk of HIV transmission in the health care setting, universal precaution in handling blood and other body fluids was generally advocated as the most effective measure in further minimising the chance of infection. HIV has been isolated from blood, semen, saliva, tears, urine, vaginal secretion, cerebrospinal fluid, synovial fluid, breast milk and amniotic fluid of infected individuals. However only blood, blood products, semen, vaginal secretion and breast milk have been linked to HIV transmission.

(2) General principles

- 2.1 The most effective means of preventing HIV transmission in health care setting is through adherence to universal precautions, thereby decreasing the risk of direct exposure to blood and/or body fluids.
- 2.2 Voluntary instead of mandatory HIV testing is the best way of encouraging people (including health care workers) at risk of infection to seek counselling and appropriate treatment.
- 2.3 Health care workers should consider receiving counselling and HIV antibody testing if they have reason to suspect that they have been infected.
- 2.4 Health care workers are generally not required to disclose their HIV status to their patients or employers. Disclosure, if any, should be made on a need-to-know basis and with consent of the worker. Maintaining confidentiality is one way to prevent interference with individual privacy. It is also essential in encouraging the health care workers (either infected or at risk of infection) to receive proper counselling and management.
- 2.5 Currently there is no justification for restricting practice of health care workers on the basis of the HIV status alone. Restriction or modification, if any, should be determined on a case-by-case basis.

(3) Guidelines

3.1 Enforcement of infection control

The best way of preventing blood-borne diseases is to treat all blood (and certain body fluids) as potentially infectious. Universal precautionary measures should be adopted when handling blood, amniotic fluid, pericardial fluid, pleural fluid, peritoneal fluid, synovial fluid, cerebrospinal fluid, semen and vaginal secretion. The risk of HIV transmission from faeces, saliva, nasal secretion, sputum, sweat, tears, urine and vomitus without overt blood staining is extremely low, and good simple hygienic measures should be sufficient.

Sound infection control practice with appropriate quality assurance should be implemented at all levels, taking into consideration factors unique to individual setting.

(a) Infection control committee

Rapid advancement in medicine and technology has meant that it is essential to keep updated on issues relating to infection control practice. Infection control committees should efficiently serve the functions of developing, promulgating and updating infection control policies in each institution and for each clinical specialty.

(b) Written infection control guidelines

Written infection control guidelines on universal blood/body fluid precaution should be developed and periodically updated in all health care settings – by infection control committees or equivalents for institutions/government departments and by professional bodies for health care professionals in private and solo practice.

(c) Infection control training

The subject of infection control should be made an integral part of undergraduate, pre-registration or pre-employment training for all health care workers who may come into contact with blood/body fluids. Similarly regular courses tailored to the infection control needs of individual specialties, should be organised by professional bodies, universities/polytechnics as well as relevant government departments. It should be made known that those who fail to use appropriate infection control techniques to protect patients may be subject to charges of professional misconduct by the relevant governing body.

3.2 HIV counselling & related services for health care workers

Information and counselling should be made easily available for health care workers who may have been exposed to HIV through risk behaviour, exposure to contaminated blood/blood products or occupational accidents. The importance of voluntary, confidential and anonymous counselling and HIV testing should be underlined.

3.3 Rights & responsibilities of HIV infected health care worker

3.3.1 Confidentiality

In general, health care workers are not required to disclose their HIV status to their employers or clients. HIV infection and AIDS are not notifiable diseases by law in Hong Kong, and reporting is on a voluntary basis. There are, however, occasions where the HIV status has to be made known on a need-to-know basis, and this will normally be with the consent of the infected worker. For example, doctors or specialists involved in evaluating an infected health care worker may need to know his HIV status. In exceptional circumstances, breach of confidentiality may be warranted, for instance when an HIV infected health care worker refuses to observe the restrictions and patients have been put at risk.

3.3.2 Right to work

The status and rights of an HIV infected health care worker as an employee should be safeguarded. If work restriction is required, employers should make arrangement for alternative work, with provision for retraining and redeployment.

3.3.3 Ethical issues

An HIV infected health care worker should seek appropriate counselling and to act upon it when given. It is unethical if one fails to do so as patients are put at risk. The attending doctor of an HIV-infected health care worker should seek the advice of the expert panel formed by the Director of Health on the areas of management and possible need for job modification. The doctor who has counselled an HIV infected colleague on job modification and who is aware that the advice is not being followed and patients are put at risk, has a duty to inform the Medical/Dental Council for appropriate action.

3.3.4 Source of advice

Referral to the expert panel should be made by the health care worker's attending physician. Formed by the Director of Health, the panel shall decide on whether job modification, limitation or restriction is warranted. A case-by-case evaluation would be undertaken considering multiple factors that can influence risk and work performance.

3.4 Responding to the public

The issue of HIV transmission in health care setting has caused much public concern despite the minimal risk incurred. Focusing on health care setting in fact deflects the society from proper attention to the major transmission routes through sex and drug abuse. The health care profession has the duty of constantly reassuring the public, and to educate the clients on how HIV can and cannot be contracted. More importantly, the public looks on the health care profession as an example of how AIDS should be dealt with. By adhering to the guidelines for prevention of HIV infection in the health care setting, public fear can be allayed.

Remarks

- Advice to be sought from the Expert Panel should be addressed to:

The Secretary
Expert Panel on HIV Infected Health Care Workers
c/o Department of Health
21/F, Wu Chung House
213, Queen's Road East, Wanchai
Hong Kong.
Tel: 2780 4390 Consultant (Special Preventive Programme)

- Copies of the guideline could be obtained from the
Advisory Council on AIDS Secretariat
5/F, 145 Battery Street, Yaumatei, Kowloon, Hong Kong
Tel: 2304 6100

(C) Prevention of Transmission of HIV in Health Care Settings Guidelines and Practices

First edition by
Scientific Working Group on AIDS in 1992

Second edition by
Scientific Committee of the Advisory Council on AIDS
Hong Kong
July 1995

Prevention of Transmission of HIV in Health Care Settings – Guidelines and Practices was first prepared by the Scientific Working Group on AIDS in 1992. It was revised in July 1995 by the Scientific Committee on AIDS, one of the three committees of the Governor-appointed Advisory Council on AIDS. The revision was made owing to the new development of infection control practices in the past few years. The situation will be kept under review by the Committee, taking into consideration local as well as international development in this area.

Scientific Committee on AIDS
July 1995

Scientific Committee on AIDS 1995/96

Chairman: Prof. NG Mun-hon, Department of Microbiology, HKU

Members: Dr. W K LAM, Department of Medicine, University of Hong Kong
Dr. Y L LAU, Department of Paediatrics, University of Hong Kong
Dr. Homer TSO, Advisory Council on AIDS
Dr. Joseph LAU, Centre for Clinical Trials & Epidemiological Research, Chinese University of Hong Kong
Dr. Susan LEONG, JP, Hong Kong Red Cross Blood Transfusion Service
Dr. J B HOLLINRAKE, MBE, SARDA
Dr. C F LAI, Hong Kong Medical Association
Dr. Philip S L TANG, Hong Kong Dental Association
Dr. T W WONG, Department of Community & Family Medicine, Chinese University of Hong Kong
Ms. K Y WAH, Hong Kong College of Nursing
Dr. Patrick LI, Hospital Authority
Ms. Patricia CHENG, Hospital Authority
Dr. K B CHAN, Correctional Services Department
Dr. C M TAM, Tuberculosis & Chest Services, Department of Health
Dr. Brian JONES, Immunology Section, Queen Mary Hospital
Dr. K K LO, Social Hygiene Service, Department of Health
Dr. W L LIM, Virus Unit, Department of Health
Dr. W P MAK, Institute of Pathology, Department of Health
Dr. W M CHAN, JP, Department of Health
Dr. S S LEE, Special Preventive Programme, Department of Health
Dr. Thomas TSANG, Department of Health

Secretaries: Dr. L C KWAN, Special Preventive Programme, Department of Health
Mr. S Y YAU, Advisory Council on AIDS

Background

1. Acquired Immune Deficiency Syndrome (AIDS) is caused by a human RNA retrovirus known as the human immunodeficiency virus (HIV). The virus appears to cause chronic and probably life long infection. A person may have a mild, "flu-like" illness within the first few weeks after the initial infection and then be asymptomatic for years. The HIV causes a progressive destruction of the body's immune function, predisposing an individual to a variety of infections, malignancies and neuropsychiatric abnormalities. A diagnosis of AIDS is made when an HIV infected individual develops diseases associated with severe immune deficiency.
2. HIV is transmitted through sexual contacts, exposure to infected blood or blood components, and perinatally from an infected mother to neonate. HIV has been isolated from blood, semen, saliva, tears, urine, vaginal secretion, cerebrospinal fluid, synovial fluid, breast milk and amniotic fluid. However, only blood and blood products, semen, vaginal secretion and breast milk have been linked to the transmission of HIV.
3. Based on the information available, transmission of HIV can and does occur in health care settings. Transmission of HIV from infected patients to health care workers has been documented after parenteral or mucous membrane exposure to blood. However, this risk is low (<0.5%) and can be minimized through adherence to routine infection control measures. Patient to patient transmission through invasive equipment or through HIV infected blood, blood products, organs, tissues or semen may also occur but can be prevented by proper sterilization of instruments and through donor screening, routine testing of donated blood for HIV antibody and heat or chemical treatment of factor VIII or IX to inactivate HIV. The risk of transmission from an infected health care worker to patients is estimated to be extremely low. To date, there has been only one documented incident of HIV transmission from a health care workers to patients. Restriction of practice depending on types of procedure, techniques, skills and medical conditions of the infected health care worker should further minimize the risk.

Guidelines and Practices Relating to HIV in Health Care Settings

4. The prevalence of HIV infection appears to be low in Hong Kong (<0.1%). Because it is often impossible to know when an individual has been infected with HIV or other blood-borne pathogens, and in light of the high prevalence of hepatitis B virus infection in the community, guidelines and practices that reduce health care workers' exposure to blood and body fluids of **all** patients should be developed. Appropriate work practices, including protective barriers to prevent parenteral, mucous membrane and non-intact skin exposure to blood and certain body fluids (amniotic fluid, pericardial fluid, pleural fluid, peritoneal fluid, synovial fluid, cerebrospinal fluid, semen and vaginal secretion) of all patients, should be adopted. The risk of HIV transmission from faeces, nasal secretion, sputum, sweat, tears, saliva, urine and vomitus without overt blood staining is extremely low or non-existent. As all available evidence indicates that percutaneous injury with sharps is the most common mode of blood-borne pathogen transmission in health care settings, all sharps and potential sharps should be handled with extreme care.
5. Health care workers who consider themselves at increased risk of HIV infection should arrange confidential testing. Those who are infected must seek appropriate medical advice to ensure they pose no risk to patients.
6. When performing invasive procedures, higher risk of blood-borne pathogens transmission is expected. Health care workers must be protected from mucocutaneous exposure to the patient's blood and the patient must be protected from intraoperative wound contamination. The use of special precautionary measures based on the nature of surgical procedures is justifiable.

7. The following recommendations outline work practices and barrier techniques that should be adopted in in-patient and out-patient settings, including Accident and Emergency Department and ambulatory care settings. The recommendations are based on current available information. Infection Control Committees of all health care institutions are urged to familiarize themselves with these recommendations and adapt them in light of local circumstances and requirements. The adopted precautions should then be widely disseminated to all health care workers.

Precautions for General Care

8. (a) **Protective Barriers**

(i) **Gloves**

Gloves should be worn for direct contact with blood and body fluids, as well as contact with mucous membrane and non-intact skin of all patients. They should also be worn when handling contaminated items or surfaces.

When performing phlebotomy procedures, there may be a possibility of contamination with blood. If there is a likelihood of hand contamination with blood, the wearing of gloves is advisable.

If gloves are worn, they should be changed after contact with each patient and before administering care to another patient, whenever torn and when a needle-stick or other injury occurs.

General purpose utility gloves such as rubber household gloves may be used for housekeeping chores involving potential blood contact, as well as for instrument cleaning and decontamination procedures. Utility gloves should be decontaminated and reused if still in satisfactory condition.

(ii) **Masks and Protective Eyewears**

Masks and protective eyewears or face shields should be worn when the splashing of blood and body fluids is anticipated.

(iii) **Gowns and Aprons**

Gowns or aprons should be worn during procedures that are likely to cause the spattering or splashing of blood and body fluids.

(b) **Hands**

All skin defects should be covered with waterproof dressing.

Hands must be washed after examining patients or touching potentially contaminated articles and before taking care of another patients.

Hands and other skin surfaces should be washed with soap and water immediately and thoroughly if contaminated with blood or other body fluids.

(c) **Rooms**

A single room may be indicated for a patient with profuse bleeding that is likely to cause environmental contamination, or when patient hygiene is poor, for example, when a patient contaminates the environment with blood, secretion or excretion.

Individuals with known HIV infection often suffer from other infectious diseases such as tuberculosis. Patients complicated with such contagious infections should be placed on isolation precautions as recommended by the Infection Control Committee of individual hospital.

(d) **Sharps**

Precautions should be taken to prevent injuries caused by needles, scalpels and other sharp instruments or devices during procedures, when cleaning instruments, during disposal of used needles and handling sharp instruments after procedures.

USED NEEDLES SHOULD NOT BE RECAPPED. If recapping of needles is necessary, a 'scoop' technique or a needle recapping device should be used.

All used sharps should be placed in a puncture-resistant sharps box which should be located in the area where it is used. Do not overfill the sharps box.

Used sharps boxes should be placed in a red plastic bag and disposed of as medical waste.

(e) **Specimens**

All patients' specimens should be placed in sturdy leak-proof containers with secure lids to prevent leaking during transport. Care should be taken when collecting and handling specimens to avoid contamination of the outside of the containers and the laboratory request slips accompanying the specimens. When the primary container is subject to leakage, or the specimen is to be transported between institutions, a secondary leakproof container such as a zip lock clear plastic bag should be used. Request slips should be placed outside the secondary container.

(f) **Accidental Exposure to Blood or Body Fluids**

In case of penetrating injury or mucocutaneous exposure to blood and body fluids, the injured or exposed areas should be washed with copious amount of running water. Minor penetrating injuries should be encouraged to bleed.

All incidents of exposure to blood or body fluids, either parenteral or mucous membrane exposures, should be reported. Appropriate serologic testing, medical evaluation and follow up should be performed in accordance with institutional policy for hepatitis B. Advice could be sought from the AIDS Unit of the Department of Health, the individual hospital's Infection Control Unit, Staff clinic or Accident & Emergency Department.

(g) **Decontamination of Articles and Environment**

All equipment to be used should be disinfected in accordance with hospital disinfectant policy.

HIV is sensitive to heat. Studies showed that it is inactivated by moist heat at 60°C in 30 minutes. It is also inactivated rapidly after exposure to commonly used chemical disinfectants at concentrations much lower than those used in routine hospital practice. Depending on the amount of blood and mucus present on the surface to be cleaned and disinfected, a solution of sodium hypochlorite (household bleach) in concentration ranging from 1,000 ppm (1:50 dilution) to 10,000 ppm (1:5 dilution) available chlorine is effective.

Thorough cleansing before disinfection or sterilization is an important part of all decontamination procedures. Heating is the most effective method of disinfection. For heat sensitive items, immersion in 1,000 ppm hypochlorite solution for at least 10 minutes should be effective. For metal devices which might be corroded by repeated exposure to hypochlorite solution, 2% glutaraldehyde for 10 minutes is recommended.

Spills of blood and body fluids should be cleaned up as soon as possible. They should be removed with disposable absorbent material held in a gloved hand. The spill site should then be wiped down with paper towel soaked in 10,000 ppm hypochlorite solution. This should be rinsed off to reduce the risk of surface damage, particularly if used on metal surface.

No special precautions are necessary for dishes, drinking glasses and eating utensils. Individuals with known or suspected HIV infections should have their meals served with ordinary eating utensils. These can be cleaned together with those used by other patients in accordance with the institutional policy. There is no need to use disposable items.

Environmental surfaces such as wall, floor and other surfaces have not been associated with the transmission of HIV. Common housekeeping procedures are adequate for cleaning environmental surfaces.

(h) **Laundry**

All used linen should be bagged at the location where it is used. Linen should not be sorted or rinsed in patient care areas. There is no need to use disposable linen for HIV infected patients.

Linen soiled with blood or body fluids should be disinfected with 1,000 ppm hypochlorite solution for 30 minutes and then bagged and sent to the laundry. Alternatively, untreated soiled linen can be placed in alginated bags for treatment in the laundry.

Linen should be washed with detergent in hot water. The temperature of the items in the machine should be maintained at over 80°C for at least 10 minutes.

(i) **Waste Disposal**

Wastes should be disposed of in accordance with the established institutional policy. Medical wastes should be discarded into red plastic bags with minimal handling. They should be sent for incineration or stored in a designated location to be collected by USD/RSD staff.

Blood, excretion and secretion may be carefully poured down a drain connected to the sewer system.

Precautions for Invasive Procedures

9. Invasive procedures are those diagnostic or therapeutic procedures that involve surgical entry into tissues, body cavities or organs, or repair of major traumatic injuries. As it is recognized that the risk of accidental exposure to blood and body fluids during these procedures cannot be reduced to zero under current technology, depending on the types of operation, the length of operation, blood loss and the requirement of irrigations, special precautionary measures may be required. In general, when performing "exposure-prone" procedures, or procedures which are predicted to last longer than 3 hours, and result in blood loss greater than 300 ml, in addition to the procedures adopted routinely to prevent cross-infection, the following barrier protection should be used:

- (a) The surgical team should wear two pairs of gloves.
- (b) Protective eyewear should be worn to avoid conjunctival contamination.
- (c) A disposable plastic apron should be worn by the scrubbed team under their gowns and by other staff in the theatre.

Precautions for Dialysis

10. (a) Patients with suspected or known HIV infection who required haemodialysis or peritoneal dialysis can be dialysed in any hospital-based or free standing dialysing unit that uses standard infection control precautions. A single room is preferable for HIV infected patients undergoing haemodialysis.

- (b) Haemodialysis machines should be disinfected with 500-750 ppm hypochlorite solution for 30-40 min. or 4% formalin overnight.

Precautions for Endoscopy

- 11. (a) All endoscopists must wear gloves, gown, mask and protected eyewear.
- (b) All procedures should be performed in rooms with adequate ventilation. For bronchoscopy, as far as practicable, the rooms should have negative pressure with ≥ 6 air changes per hour.
- (c) Use totally immersible endoscopes as far as possible.
- (d) The endoscope should be cleaned and disinfected at the beginning of the first procedure of the day and after each procedure.
- (e) In between cases, after thorough cleaning which should include irrigating and brushing of channels, the endoscope and all internal channels should be soaked in 2% glutaraldehyde for at least 5 min. (at least 30 min. for bronchoscopy).
- (f) After the glutaraldehyde soak, the channels should be rinsed with sterile water followed by wiping the insertion tube with 70% alcohol.
- (g) Use autoclavable biopsy forceps and cytology brushes. A separate pair of biopsy forceps and cytology brush should be used for each patient. Do not use a needle to remove biopsy material from biopsy forceps.

Precautions for Dental Surgery

- 12. Blood, blood contaminated saliva and gingival fluids from all patients should be considered infective and appropriate barriers should be used during dental procedures in all health care settings. Procedures adopted routinely for all practices must be adequate to prevent cross-infection.

Please refer to documents on prevention of cross infections in dental settings promulgated by the Hong Kong Dental Association or the Department of Health.

Precautions in Clinical Laboratories

- 13. (a) Blood, serum, unfixed tissues and tissues fluids from all patients should be considered potentially infective. Minimal risk of HIV transmission is presented by urine, saliva and faeces without overt blood staining, though they may contain other pathogens.
- (b) Laboratory access should be restricted to authorized staff only.
- (c) Eating, drinking, smoking and the application of cosmetics should be prohibited in the laboratory.
- (d) Laboratory coats, gloves or other protective clothing should be worn to prevent contamination of exposed skin and soiling of clothing. Protective clothing should be changed if visibly contaminated with the blood or body fluids, and should always be removed before leaving the laboratory.

- (e) Care should be taken when opening specimen containers to prevent splashing or spattering. Routine procedures with blood and body fluids can be performed on an open bench. However, processing of specimens which are likely to create splash should be carried out with gloved hands in a biological safety cabinet. Alternatively, laboratory personnel should wear protective barriers including gloves, masks, protective eyewear to prevent the contamination of skin or mucous membrane.
- (f) Centrifuges with sealed buckets, safety cups or sealed heads should be used to prevent the escape of liquids or aerosols.
- (g) Mechanical pipetting devices must be used for the manipulation of all liquids in the laboratory. Mouth pipetting must not be allowed.
- (h) Laboratory and quality control reagents containing or derived from blood or blood products should be considered potentially contaminated.
- (i) Needles and syringes should be used only when necessary and in a situation in which there is no alternatives. The use of plastic pipettes should be encouraged. Care should be taken to prevent injuries caused by needles, scalpels, glass slides and other sharp or breakable instruments or devices. Needles should not be recapped or manipulated by hand. Disposable needles and other sharp items should be placed in a puncture-resistant sharp box for disposal after use. These containers should be located as close as practical to areas where they will be used.
- (j) Laboratory work surfaces should be decontaminated with 1,000 ppm hypochlorite solution on a daily basis and following spillage of blood or body fluids. For large spills of cultured or concentrated infectious agents, the contaminated area should be first flooded with 10,000 ppm hypochlorite solution before cleaning, and then wiped down with disposable towels in a gloved hand.
- (k) Automated machines should have designs to avoid splashing or be adequately screened. There should be a closed system from specimen presentation to safe discharge of effluent, and should accept periodic disinfection readily.
- (l) As far as possible, equipment should be decontaminated before they are sent for mechanical or electrical servicing.
- (m) Tissue or serum specimens to be stored should be clearly and permanently labelled as potentially hazardous.
- (n) Infective waste from the laboratory should be autoclaved before disposal or sent for incineration.

Precautions for Autopsy and Disposal of Dead Bodies

14. See the guidelines 'Precautions for handling and disposal of dead bodies'.



APPENDIX V

USEFUL SOURCES OF REFERENCES

APPENDIX V. USEFUL SOURCES OF REFERENCES

Agencies working on HIV/AIDS in Hong Kong

	Tel.	Fax	Webpage / email	Address
Advisory Council on AIDS Secretariat	2780 8622	2337 0897	www.aca-hk.com / aca@health.gcn.gov.hk	5/F Yaumatei Jockey Club Clinic, 145 Battery Street, Kowloon

Department of Health Special Preventive Programmes			Virtual AIDS Office at www.aids.gov.hk	
Head Office	2780 8622	2780 9580	aids@health.gcn.gov.hk	5/F Yaumatei Jockey Club Clinic, 145 Battery Street, Kowloon

AIDS Counseling Service

(A) AIDS Hotlines

24-hour computerized recorded messages in English, Cantonese, Putonghua 2780 2211 www.27802211.com

24-hour computerized recorded messages in Tagalog, Thai and Vietnamese 2359 9112

Telephone counseling 2780 2211
Service operated by nurse counselors
(Mon - Fri: 8 am to 8 pm)

<i>(B) Voluntary Counseling and Testing Service</i>	2780 2211	Appointment by phone
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Integrated Treatment Centre aidsclinic@health.gcn.gov.hk

<i>(A) HIV Clinical Service</i>	2116 2898	2117 0809	8-9/F Kowloon Bay Health Centre, 9 Kai Yan Street, Kowloon Bay, Kowloon, Hong Kong
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<i>(B) Therapeutic Prevention Clinic for post exposure management</i>	2116 2929	2117 0812
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Red Ribbon Centre			www.rrc-hk.com /	
(A) <u>AIDS Resource Centre</u>	2304 6268	2338 0534	rrc@health.gcn.gov.hk	2/F 200 Junction Road East, Wang Tau Hom, Kowloon, Hong Kong
(B) <u>Dr Sex Hotline</u>	2337 2121			
24-hour computerized recorded messages in English, Cantonese, Putonghua				
(C) <u>UNAIDS Collaborating Centre for Technical Support</u>	2304 6268	2338 0534		
Queen Elizabeth Hospital Special Medical Service	2958 6571	2783 7415	6/F Ambulatory Care Center, Queen Elizabeth Hospital 30 Gascoigne Road, Kowloon, Hong Kong	
Public Health Laboratory Centre (Virus Unit)	2319 8387	2776 2553	382 Nam Cheong Street, Shek Kip Mei, Kowloon	
(A) HIV antibody test				
(B) Confirmatory test				
(C) Viral load assay				
Sai Ying Pun Institute of Pathology	2857 4113	2858 2684	8/F, SYP Jockey Club Polyclinic, 134 Queen's Road West, Hong Kong	
T-lymphocyte test				
Department of Health Social Hygiene Service				
Head Office	2150 7370	West Kowloon Health Centre, 3/F Cheung Sha Wan Government Offices, 303 Cheung Sha Wan Road, Kowloon		
Social Hygiene Clinics (Hong Kong)				
(A) Western Social Hygiene Clinic	2859 8302	3/F Sai Ying Pun Jockey Club Polyclinic 134 Queen's Road West, Sai Ying Pun		
<i>Male & female</i>				

(B) Tang Shiu Kin Social Hygiene Clinic <i>Male</i> 2831 6853 <i>Female</i> 2831 6853	1/F Tang Shiu Kin Hospital, 282 Queen's Road East, Wanchai
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(C) Chaiwan Social Hygiene Clinic <i>Male & female</i> 2595 7500	LG5 Polyclinic Block Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chaiwan
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Social Hygiene Clinics (Kowloon)

(A) Yau Ma Tei Social Hygiene Clinic <i>Male</i> 2359 4377 <i>Female</i> 2388 6634	3-4/F Yau Ma Tei Jockey Club Polyclinic 145 Battery Street Yau Ma Tei
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(B) Yung Fung Shee Social Hygiene Clinic <i>Male & female</i> 2727 8315	Yung Fung Shee Memorial Centre 79 Cha Kwo Ling Road Kwun Tong
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Social Hygiene Clinics (New Territories)

(A) South Kwai Chung Social Hygiene Clinic <i>Male & female</i> 2421 4010 2425 6921	3/F South Kwai Chung Polyclinic 310 Kwai Shing Circuit Kwai Chung
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(B) Tuen Mun Social Hygiene Clinic <i>Male & female</i> 2459 2958	9/F Tuen Mun Hospital Ambulatory Care Centre Tsing Chung Koon Road, Tuen Mun
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(C) Lek Yuen Social Hygiene Clinic <i>Male & female</i> 2692 8120	3/F Lek Yuen Health Centre, 9 Lek Yuen Street, Shatin
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<div style="background-color: black; color: white; padding: 2px 5px;">Council for the AIDS Trust Fund</div> Funding support to community-based HIV prevention and care initiatives	2973 8136 2840 0467 www.info.gov.hk/atf 19-20/F., Health & Welfare Bureau, Murray Building, Garden Road, Central, Hong Kong
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AIDS Non-government Organizations and community-based information sources

(A) The Hong Kong Coalition of AIDS Service Organizations (HKCASO)	http://hkaims.med.cuhk.edu.hk/hkcaso/ hkcaso@cuhk.edu.hk PO Box 9886, General Post Office, Hong Kong
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(B) AIDS Concern	2898 4411	25051682	http://hkaims.med.cuhk.edu.hk/aimscon	17B, Block F, 3 Lok Man Road, Chai Wan, Hong Kong
(C) Action for Reach Out	2700 1065	2770 1201		PO Box 98108, T.S.T., Post Office, Kowloon
(D) Hong Kong AIDS Foundation	2560 8528	2560 4154	www.aids.org.hk	5/F., Shaukeiwan Jockey Club Clinic, 8 Chai Wan Road, Hong Kong
(E) St John's Cathedral HIV Education Centre	2523 0351	2523 1581		St. John Cathedral, 4-8 Garden Road, Central, Hong Kong
(F) Teen AIDS	2870 1222	2870 3623	www.teenaidshk.org	Flat E, 2/F., Cheong Hong Mansion, 25- 33 Johnston Road, Wan Chai, Hong Kong
(H) The Society for AIDS Care SAC Centre	2559 2006	2521 7668	www.aidscares.com.hk	Dock F, Kai Tak Government Building, 5 Arrivals Road, Kowloon, Hong Kong
(G) The Hong Kong Council of Social Service – AIDS Project	2864 2930	2862 2530		Room 1105, 11/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong
(I) Community Planning Forum on AIDS			http://come.to/cppforum/	
(J) Hong Kong AIDS Information Network			http://hkaims.med.cuhk.edu.hk	
(K) iAIDS			http://go.to/iAIDS	

Information Sources on Internet

Site / agency	Information	Address
<ul style="list-style-type: none"> • AIDS Education Global Information System (AEGIS) 	Daily news on HIV/AIDS	www.aegis.com
<ul style="list-style-type: none"> • AIDS Education Training Centers National Resource Center (AETC) of HRSA HIV/AIDS Bureau 	HIV/AIDS Treatment guidelines	www.aids-ed.org
<ul style="list-style-type: none"> • HIV/AIDS Treatment Information Service (ATIS) of US Department of Health and Human Services 	HIV treatment guidelines	www.hivatis.org
<ul style="list-style-type: none"> • Centers for Disease Control and Prevention (CDC) 	HIV/AIDS Prevention and surveillance guidelines	www.cdc.gov http://www.cdc.gov/nchstp (National Center for HIV, STD and TB Prevention) http://www.cdc.gov/ncidod (National Center for Infectious Diseases)
<ul style="list-style-type: none"> • HIV Insite of UCSF 	<i>HIV Insite Knowledge Base</i> – online textbook on HIV medicine from UCSF and San Francisco General Hospital edited by Laurence Peiperl and Paul Volberding; other general information on HIV/AIDS	http://hivinsite.ucsf.edu
<ul style="list-style-type: none"> • International AIDS Society – USA (IAS-USA) 	Treatment guidelines	www.iasusa.org
<ul style="list-style-type: none"> • JAMA HIV/AIDS Resource Center 	Journal articles and practice guidelines on HIV/AIDS	www.ama-assn.org/aids
<ul style="list-style-type: none"> • Johns Hopkins AIDS Service 	Full text of <i>Medical Management of HIV</i> by Dr John Bartlett and his team (updated yearly); management guidelines, conference.	www.hopkins-aids.edu
<ul style="list-style-type: none"> • Medscape 	CME activities on HIV, infectious diseases, immunology	www.medscape.com

<ul style="list-style-type: none">• Joint United Nations Programme on HIV/AIDS (UNAIDS)	All aspects of HIV/AIDS including policy development, prevention, care, surveillance and best practice sharing.	www.unaids.org (UNAIDS Headquarters in Geneva) www.unchina.org/unaids (UNAIDS China)
<ul style="list-style-type: none">• Virtual AIDS Office of Hong Kong (VAO)	Collection of guidelines, surveillance information and other documents on HIV/AIDS in Hong Kong	www.aids.gov.hk
<ul style="list-style-type: none">• World Health Organization (WHO)	Documents and information on the public health prevention and control of HIV/AIDS	www.who.int (WHO Headquarters in Geneva) www.wpro.who.int (WHO Western Pacific Region)



APPENDIX VI

ABBREVIATIONS

APPENDIX VI. ABBREVIATIONS

3TC	Lamivudine, an NRTI
ABC	Abacavir, an NRTI
ADI	AIDS-defining illness
AFB	acid fast bacilli
AGCUS	atypical glandular cells of undetermined significance
AIDS	acquired immune deficiency syndrome
APV	Amprenavir, a PI
Ara-C	cytosine arabinoside
ART	antiretroviral therapy
ARV	AIDS related virus (an outdated term for HIV); not to be confused with Antiretrovirals in some cases
ASCUS	atypical squamous cells of undetermined significance
ATRA	all trans retinoic acid
AZT	Zidovudine or zdv
BAL	bronchoalveolar lavage
BCG	Bacille Calmette-Guerin
BCM	body cell mass
bDNA	branched DNA
BIA	bioimpedance analysis
BMI	body mass index
BW	body weight (= fat + LBM)
Bx	biopsy
CBP	complete blood picture
CCNU	N-(2-chloroethyl)-N' cyclohexyl-N-nitrosourea (lomustine)
CCR5	The CC chemokine receptor 5
CD4	Cluster of differentiation (CD)4 molecule
CIN	cervical intraepithelial neoplasia
CLR	Clarithromycin
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CRAg	cryptococcal antigen
CS	cesarean section
CSF	cerebrospinal fluid
CT	computerised tomography
CTL	cytotoxic T lymphocyte
CXR	chest X ray
d4T	Stavudine, an NRTI
ddC	Zalcitabine, an NRTI
ddI	Didanosine, an NRTI
DEXA	dual energy X-ray absorptiometry
DFA	direct fluorescent antibody test
DGE	dark ground examination
DHPC	dihydropteroate synthesis
DLCO	diffusing capacity of lung for carbon monoxide
DLV	delavirdine, an NNRTI
dMAC	disseminated MAC
DNA	deoxyribonucleic acid
DOT	directly observed treatment
DS	double strength
EC	enteric coated
EFV	Efavirenz, an NNRTI

EIA	enzyme immunoassay
ELISA	enzyme linked immunosorbent assay
ELS	early latent syphilis
EM	extracellular mass
EMB	Ethambutol
EPOCH	Etoposide, Vincristine, Doxorubicin, Cyclophosphamide, Prednisone
FNAB	fine needle aspiration biopsy
FTA-Abs	fluorescent treponemal antibody absorption
G6PD	glucose 6 phosphate dehydrogenase
gp	glycoprotein
HAART	highly active antiretroviral therapy
hCG	human chorionic gonadotropin
HCW	health care worker
HHV	human herpes virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSIL	high grade SIL
HSV	herpes simplex virus
HTLV	human T lymphotropic virus
HUS	hemolytic uremic syndrome
IDV	indinavir, a PI
IFN	interferon
IgA	immunoglobulin class A
IgG	immunoglobulin class G
IgE	immunoglobulin class E
INH	Isoniazid
IPT	Isoniazid preventive therapy
IPV	inactivated poliovirus vaccine
IVIG	intravenous immunoglobulin
KS	Kaposi's sarcoma
LAV	lymphadenopathy associated virus (an outdated term for HIV)
LBM	lean body mass (=EM + BCM)
LDH	lactate dehydrogenase
LDS	lipodystrophy syndrome
LFT	liver function test
LGV	lymphogranuloma venereum
LLS	late latent syphilis
LP	lumbar puncture
LSIL	low grade SIL
MAC	<i>Mycobacterium avium</i> intracellular complex
MAI	<i>Mycobacterium avium</i> intracellular
mBACOD	Methotrexate, Bleomycin, Doxorubicin, cyclophosphamide, vincristine, dexamethasone
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mTB	<i>Mycobacterium tuberculosis</i>
MTCT	mother to child transmission
MTX	Methotrexate
NASBA	nucleic acid sequence based amplification
NAT	nucleic acid test
NFV	Nelfinavir, a PI
NHL	non Hodgkin's lymphoma
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor

NS	neurosyphilis
NVP	nevirapine, an NNRTI
OAI	occupationally acquired infection
OPV	oral poliovirus vaccine
p	protein
PCP	<i>Pneumocystis carinii</i> pneumonia
PCR	polymerase chain reaction
PGL	persistent generalised lymphadenopathy
PI	protease inhibitor
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivatives
PRE	progressive resistance exercise
PS	primary syphilis
PZA	pyrazinamide
RFB	rifabutin
RFT	renal function test
rhGH	recombinant human growth hormone
RIF	Rifampicin
RNA	ribonucleic acid
RTV	Ritonavir, a PI
RVVC	recurrent vulvovaginal candidiasis
SIL	squamous intraepithelial lesion
SIV	simian immunodeficiency virus
SM	Streptomycin
SMZ	Sulphamethosazole
SPECT	Single Photon Emission Tomography
SQV	Saquinavir, a PI
SQV-HGC	SQV hard gel capsule
SQV-SGC	SQV soft gel capsule
SS	single strength
STD	sexually transmitted disease
STI	structured treatment interruption
TB	tuberculosis
TBB	transbronchial biopsy
TEE	total energy expenditure
TIS	tumour - immunity - systemic illness
TK	thymidine kinase
TMP-SMZ	Trimethoprim-Sulphamethosazole
TNF	tumor necrosis factor
TOP	termination of pregnancy
TPHA	<i>Treponema pallidum</i> hemagglutination assay
TST	tuberculin skin test
TTP	thrombocytopenic purpura
VCT	voluntary counselling and testing
VDRL	Venereal Disease Research Laboratory (test)
VL	viral load
VP16	Etosiposide
VZIG	varicella zoster immunoglobulin
VZV	varicella zoster virus
WR	Walter Reed (staging)
ZDV	Zidovudine (AZT), an NRTI



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