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Recommended Clinical Guidelines on the Prevention of Perinatal HIV Transmission

Scientific Committee on AIDS and STI (SCAS)

Centre for Health Protection
Department of Health

January 2007

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(c) to keep under review local and international development of HIV/AIDS and STI.

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Introduction

1. Without intervention, the risk of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) ranges from 13% to 42%, depending on the presence of certain risk factors. In 1994, the landmark study, Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076, conclusively showed that use of zidovudine (ZDV) reduced the transmission risk.[1] [2] This finding was quickly followed by a number of studies that evaluated the effects of alternative antiretroviral regimens and mode of obstetric delivery on MTCT.

2. To translate these scientific findings into real public health gains, universal HIV testing of antenatal women in Hong Kong was implemented in 2001.[3] At the same time, clinical recommendations were made by the Scientific Committee of the Advisory Council on AIDS to assist in the management of HIV positive pregnancy.[4]

3. Experience with the programme has been encouraging in that MTCT was largely prevented, especially in women who presented early for antenatal care. However, testing and hence antiretroviral prophylaxis were suboptimal in those who presented late, e.g. when in labour. In addition, the knowledge base of antiretroviral prophylaxis has continued to increase in the last few years, so that certain previous clinical recommendations have been rendered obsolete.

4. It was under these circumstances that the Scientific Committee on AIDS and STI (SCAS) of the Centre for Health Protection, Department of Health, embarked on a revision and update of the clinical guidelines on the prevention of MTCT transmission.

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Goal

5. These clinical guidelines were developed with a view to eradication of MTCT of HIV by the combined approach of early diagnosis and timely evidence-based interventions.

Principles

I. Universal HIV antibody testing should be performed as part of routine antenatal care for women in Hong Kong, supplemented by rapid testing where necessary.

II. Clinical management should include that of maternal HIV infection as well as prevention of mother-to-child transmission of HIV.

III. HIV infected pregnant women who present late would still benefit from use of antiretroviral to reduce mother-to-child transmission.

IV. The mode of delivery and its management should be considered on the grounds of HIV status as well as obstetric indications.

V. Paediatric management should be offered to reduce the risk of mother-to-child transmission.

VI. Multidisciplinary and coordinated efforts should be made to strengthen our knowledge base and practice regarding mother-to-child transmission of HIV in Hong Kong.

Recommendations and Rationales

I. Universal HIV antibody testing should be performed as part of routine antenatal care for women in Hong Kong, supplemented by rapid testing where necessary

6. HIV antibody testing for pregnant women should be performed as an integral part of antenatal care. This should not be interpreted as compulsory testing as women are allowed to 'opt out'. Since 2001 when universal testing was implemented, there have been high coverage rates consistently exceeding 97%, attesting to wide acceptance of testing. Overall, the prevalence of HIV in antenatal mothers was found to be less than 0.05%.[5]

7. Nevertheless, it is noted that in the public sector there has been a decreasing trend of the proportion of deliveries with known maternal HIV status, from 91% in 2003, to 86% in 2004 and 83.4% in 2005 (unpublished data from the Dept of Health). It is likely that this was due to an increasing proportion of women who presented late to obstetric services, e.g. while in labour, thus missing out on antiretroviral prophylaxis and other effective preventive measures offered by an early HIV diagnosis.

8. Conventional HIV antibody testing requires screening with ELISA followed by Western blot for confirmation. Its typical turnaround time is 2 weeks. This is unacceptable when testing is done in late pregnancy, during labour or after delivery, as delay in administration of antiretroviral prophylaxis significantly diminishes its impact. The opportunity of performing an elective caesarean section may also be lost.

9. The new generation of rapid HIV tests may be performed at point of care and are highly sensitive and specific. Results are quickly available in terms of minutes. A negative result effectively rules out infection except in those who are in the process of seroconversion. Although confirmation with Western blot is still required, a positive result is highly suggestive and prophylactic interventions should be implemented against MTCT.[6]

10. Provision of rapid test should not deviate from the standards of

conventional testing. Testing is voluntary and mothers may opt out after explanation is given of testing itself and the effectiveness of available interventions in reducing MTCT. In Hong Kong, rapid testing has been studied in a Voluntary Counselling and Testing service, showing a high degree of client satisfaction.[7] Overseas studies of rapid test in late presenting women in labour also showed that it was feasible and acceptable.[8] It has now been recommended as standard of care.[9]

II. Clinical management should include that of maternal HIV infection as well as prevention of mother-to-child transmission of HIV

II.A As part of routine medical care, HIV infected women of childbearing potential should receive counselling on contraception to avoid unintended pregnancies. For those who would like to conceive, a careful risk assessment is required.

11. With the availability of highly active antiretroviral therapy (HAART), HIV disease as we know it today has become a chronic treatable disease with a vastly improved prognosis. Nevertheless, it is still important that HIV infected women of reproductive age receive counselling on effective contraception to avoid unintended pregnancies. Yet, not uncommonly, couples who previously rejected pregnancy are now contemplating children. They should receive information on their risks of MTCT, effectiveness of interventions, and available options of assisted reproduction to assist in their decision. Risk assessment and prevention of horizontal transmission are particularly important for serodiscordant couples.

II.B A woman who is diagnosed HIV positive in the antenatal period shall receive the same standards of care established for HIV-infected nonpregnant patients. HAART incorporating ZDV is the recommended regimen to prevent MTCT. To best balance benefits and risks for the mother and her infant, management should involve a physician experienced in HIV medicine.

12. Optimal control of maternal HIV disease is beneficial to reducing MTCT, as both viral load and CD4 cell count are related to

transmission. Current major standards of care in HIV disease[10] are:

(i) prophylaxis against opportunistic infections based on history and CD4 count, and

(ii) individualised HAART based on viral load, CD4 count and clinical history, the immediate goal of treatment being virological suppression to undetectable levels.

13. Regular CD4 cell enumeration and viral load testing are indicated and may need to be repeated frequently to ensure satisfactory control of HIV disease near term. Testing for viral resistance should be considered if resistance is suggested by clinical history or the drop of viral load is unsatisfactory.

14. In those with symptomatic disease and low CD4 counts, HAART is indicated, which is also the preferred regimen to prevent MTCT. Although ZDV monotherapy is also effective for the latter, evidence is now accumulating that HAART reduces MTCT to a much greater extent. In PACTG 316, the transmission rate was only 1.5% in a group of women who mostly used combination therapy.[11] In a large European cohort, transmission was only 1.2% in those on HAART.[12] However, since ZDV has the best evidence, excellent transplacental passage, and a good safety record in this setting, ZDV should be incorporated in the HAART regimen. The intrapartum and postpartum components of ZDV continue to be recommended.

15. For those mothers whose HIV disease does not otherwise require treatment, HAART as recommended above is still preferred for MTCT prevention, although lesser therapy such as ZDV monotherapy or double nucleoside with ZDV and lamivudine may theoretically be justifiable in those with very low viral loads who also wish to minimise exposure to antiretrovirals.

16. In either case, a physician experienced in HIV Medicine should be involved to assess for the most appropriate antiretroviral regimen based on the clinical stage, pharmacokinetics, toxicity to the mother and foetus, and antiretroviral efficacy, as guided by the CD4 cell count, viral load, viral resistance, and a detailed clinical assessment including that of any known

source of infection. Since toxicity including teratogenicity to the foetus would be greatest in the first trimester, it is therefore acceptable that treatment be postponed until 10-12 weeks of gestation. The potential adverse effect on disease progression and MTCT of HIV should be made known to the mother to facilitate informed decision.

17. Throughout pregnancy, the HIV physician is responsible for monitoring the response to treatment and applying the usual standards of HIV care, such as various prophylactic treatments. Special considerations, however, should be given to the unique state of pregnancy with its altered pharmacokinetics and propensity to certain adverse effects such as lactic acidosis and hyperglycaemia. The HIV physician should also alert the obstetrician and paediatrician in the event of real or expected antiretroviral toxicity and unfavourable virological response, as these may impact obstetric and paediatric management. A long term HIV care plan should be put in place which may include a strategy to discontinue therapy postnatally in those mothers who do not otherwise require treatment.

II.C Other than zidovudine, lamivudine and a protease inhibitor are recommended as the other components of the HAART regimen in the antenatal period, unless otherwise contraindicated.

18. The best regimen for both mother and foetus is one that has the greatest antiretroviral potency, minimal teratogenicity and toxicity, and maximal efficacy in treating HIV disease and decreasing MTCT. A HAART regimen typically comprises three drugs: 2 nucleoside reverse transcriptase inhibitors (NRTI) in combination with one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI). Other than ZDV, lamivudine (3TC) is the other preferred NRTI based on extensive experience of its use in pregnant women. Among the other commonly used NRTI, stavudine (d4T) and didanosine (ddI) are not generally recommended because of their association with mitochondrial toxicity and lactic acidosis. d4T and ddI must not be used together in pregnancy.

19. Of the available PIs, nelfinavir (NFV) and Kaletra® capsules are recommended based on available experience and pharmacokinetic data regarding their use in pregnancy. Ritonavir-boosted saquinavir and indinavir

are both acceptable alternatives, although the latter is associated with indirect hyperbilirubinemia that may exacerbate neonatal jaundice. Very limited data are available with regard to the other PIs. Hyperglycaemia is a class adverse effect of PI which is of particular importance in pregnancy.

20. Although nevirapine (NVP) has proven efficacy in preventing MTCT, it should be used with caution, as rash and hepatotoxicity are particularly common in women with a CD4 count above 250/µl. The other NNRTI, efavirenz, is teratogenic in monkeys. Neural tube defects have also been reported in humans. In general, this drug is contraindicated in the first trimester. Both NVP and efavirenz have long and often unpredictable half lives. For this reason, development of resistance is a major concern if they are discontinued without cover of other antiretrovirals. In this case, a temporary coverage with 2 NRTIs, e.g. ZDV plus 3TC, of 7 days may be effective. Some experts may add a protease inhibitor and cover for a longer period of time.

21. It cannot be overemphasised that, in order to arrive at an optimal HAART regimen, flexibility should be exercised in interpreting these guidelines. Clinical circumstances such as past medical history, anticipated poor adherence, virological failure or potential interactions with other drugs may require deviation from the recommended regimen. For instance, patients who have chronic hepatitis B should not generally be given antiretrovirals that are also active against hepatitis B, such as lamivudine and tenofovir, unless it also requires treatment. Throughout and after pregnancy, close communication among all members of the medical team is required to ensure the best care for the mother and child, and reduce the risk of MTCT to the minimum (Table 1).

II.D For those women 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.

22. For these patients, re-evaluation of the antiretroviral regimen is required with the same considerations applicable to those newly diagnosed in pregnancy. In particular, if the current regimen does not already contain ZDV,

it should be added even if the mother has had prior experience with the drug, unless contraindicated. Treatment response has to be reviewed and a viral resistance test considered for those with detectable viral loads. Ideally, all pregnancies should be planned so that evaluation could have been made prior to conception regarding the most appropriate regimen.

23. Since foetal toxicity including teratogenicity would be greatest in the first trimester, some mothers may choose to interrupt treatment in the first 10 - 12 weeks of gestation. Such interruption should be supervised by an experienced HIV physician taking into account the different half lives of antiretroviral agents.

III. HIV infected pregnant women who present late would still benefit from use of antiretroviral to reduce mother-to-child transmission

III.A When maternal HIV infection is not diagnosed until labour, or when a known HIV infected woman who has received no prior antiretroviral therapy is in labour, antiretrovirals administered intrapartum and postpartum are still indicated to reduce MTCT.

24. In this scenario, the use of rapid HIV test is critical, without which interventions would not even be contemplated. Although the opportunity of a full course of treatment has been lost, commencement of antiretrovirals in labour is still useful to reduce MTCT. The standard 076 regimen of ZDV abbreviated to its intrapartum and postpartum components has been observed to decrease transmission risk, though to a lesser extent.[13] Other effective regimens include the use of ZDV plus 3TC intrapartum to mother and for one week to the newborn,[14] and single dose nevirapine to mother and at 48-72 h to newborn.[15] There are no data to support the superiority of any one regimen over the others. However, there is some evidence that the combination of NVP and ZDV may confer additive protection, though the risk of resistance development in the mother is substantial.[16 17]

25. Therefore, to maximise protection in a scenario of high MTCT risk, the SCAS recommends the use of ZDV intrapartum and 6 weeks

postpartum to newborn, in combination with 3TC 150 mg bid and single dose NVP 200 mg to mother. Another single dose of NVP 2 mg/kg is given to the newborn at 48-72 h. After delivery, the mother is to be continued on ZDV 300 mg bid and 3TC 150 mg bid for 7 days,[18] in order to limit the development of resistance (Table 2). Single dose NVP as used in labour has not been associated with hepatotoxicity or skin rash.

26. It is important that an HIV physician be involved to assist in the management of any complication related to HIV disease and to determine as soon as possible the subsequent treatment plan.

III.B For infants born to HIV-infected mothers who have not taken antiretroviral therapy during the antenatal and intrapartum periods, the recommended regimen is single dose nevirapine in combination with 6 weeks of ZDV to be started as soon as possible after birth.

27. In a randomised controlled trial, either ZDV or NVP initiated in newborns within 24 h of birth to mothers who had not received antiretroviral therapy resulted in transmission risks lower than historical controls.[19] To maximise the reduction of MTCT, it is therefore recommended that the infant should receive the same regimen of ZDV plus NVP as recommended in the above scenario where treatment was begun in labour. However, because no intrapartum NVP or ZDV has been given, the infant does not benefit from transplacental passage of the drugs. Therefore, both ZDV and NVP should be started as soon as possible (Table 3).

28. It is noted that treatment initiated after 48 h is likely to be futile and will contribute to viral resistance should infection occur. Thus it should be given only in exceptional cases and after consultation with experts in the field.

IV. The mode of delivery should be considered on the grounds of obstetric indications as well as HIV status

29. For the purpose of MTCT prevention, elective caesarean section is the preferred mode of delivery based on data confirming its independent effect on reducing MTCT, especially in those with a viral load

above 1000/ml.[20] [21] However, it should be emphasised that the operation carries risks of its own which may be further increased in HIV infected women. The efficacy of elective caesarean section in reducing MTCT should therefore be only one of many factors in the final decision on the mode of delivery.[22] Obstetric factors should be considered as well as factors relating to HIV disease such as use of antiretroviral prophylaxis, the viral load near term, and anticipated problems with adherence to postpartum antiretrovirals for the infant.

30. For those mothers who proceed to vaginal delivery, prolonged rupture of membranes (especially if more than 4 hours), invasive foetal monitoring and instrumental delivery should be avoided to reduce MTCT.

V. Paediatric management should be offered to reduce the risk of mother-to-child transmission

31. A paediatrician experienced in HIV disease and managing babies born to HIV infected mothers should preferably be involved early and before delivery. He would be responsible for completion of the antiretroviral regimen for the neonate and assess for toxicity and congenital defects resulting from maternal use of antiretrovirals. Toxicities that should be ruled out include anaemia secondary to ZDV, lactic acidosis resulting from NRTI, and hyperglycaemia from PI. The infant should also be followed closely for the possibility of HIV infection. Reference should be made to local guidelines in this respect.[23]

32. The mother is advised against breast-feeding as it has been estimated that the added risk of transmission by breastfeeding was high at 16.7%.[24] In developing countries, breastfeeding may be justified by its other benefits. In Hong Kong, it is not. Every effort should be made to assist the mother in replacement feeding.

33. At present, the long term effects of antiretrovirals on the future development of the child are not clear. Thus it is important that all such children should be followed by the paediatrician for an extended period of time.

VI. Multidisciplinary and coordinated efforts should be made to strengthen the knowledge base and practice regarding mother-to-child transmission of HIV in Hong Kong

34. Were the goal of eradicating MTCT to be ever possible, it is imperative that all stakeholders be enlisted for their contribution. The fact that optimal prevention of MTCT requires early diagnosis highlights the importance of a strong overall public health programme. Universal antenatal testing should continue and be closely monitored so that gaps could be filled quickly. Experience of health care providers should also be shared within and across disciplines to identify the model of best practice. It is a most trying time for the mother who often is also beset with difficult psychosocial circumstances. Overlooking this aspect of care risks non-adherence and failure of otherwise effective interventions. Each and every instance of MTCT is a tragedy and should be reviewed carefully so that improvement can be made.

Centre for Health Protection
January 2007

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Table 1. Recommended antiretroviral prophylaxis against MTCT of HIV

Period and regimen	Dosing	Remarks
Antepartum: HAART (ZDV + 3TC + PI or NVP)	• ZDV 300 mg po bid • 3TC 150 mg po bid • Nelfinavir 1250 mg po bid • Kaletra® 3 capsules po bid, increased to 4 capsules po bid in 3rd trimester • Saquinavir HGC 1000 mg with RTV 100 mg po bid • NVP 200 mg po qd in first 2 weeks, then NVP 200 mg po bid • IDV 800 mg with RTV 100 mg po bid (do not use IDV unboosted))	• Regimen subject to evaluation by HIV physician • Viral resistance test could be useful to optimise regimen • Assess virological response to HAART, esp. near term • Pre-plan for postnatal treatment • Follow for adverse effects of ARV: ♦ Anaemia ♦ Hyperglycaemia ♦ Lactic acidosis • Efavirenz generally contraindicated • Avoid NVP in those with CD4 count >250/μl
Intrapartum: ZDV	• Recommended: IV loading dose of 2 mg/kg in 1 h, then 1mg/kg/h till delivery; begin at onset of labour or 3 h before elective caesarean section • Continue antepartum HAART regimen	
Postpartum: HAART for mother and ZDV for newborn	Mother: • Continue antepartum HAART regimen, or • Discontinue under supervision of HIV physician Newborn at 8-12 h: • ZDV syrup 2 mg/kg po q6h for 6 wk, or • ZDV 1.5 mg/kg IV q6h for 6 wk	• Modify dosage in preterm infants <35 wk gestation: ♦ 1.5 mg/kg IV or 2 mg/kg po q12h, then q8h at ♦ 2 wk if gestation >30 wk, or ♦ 4 wk if gestation <30 wk • No breastfeeding

HAART, highly active antiretroviral therapy; ZDV, zidovudine: 3TC, lamivudine; NVP, nevirapine; HGC, hard gel capsule; RTV, ritonavir; ARV, antiretroviral
Adapted from: US PHS. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. October 12, 2006 (Available at http://AIDSinfo.nih.gov. Accessed Nov 23, 2006)

Table 2. Recommended antiretroviral prophylaxis in women presenting in labour

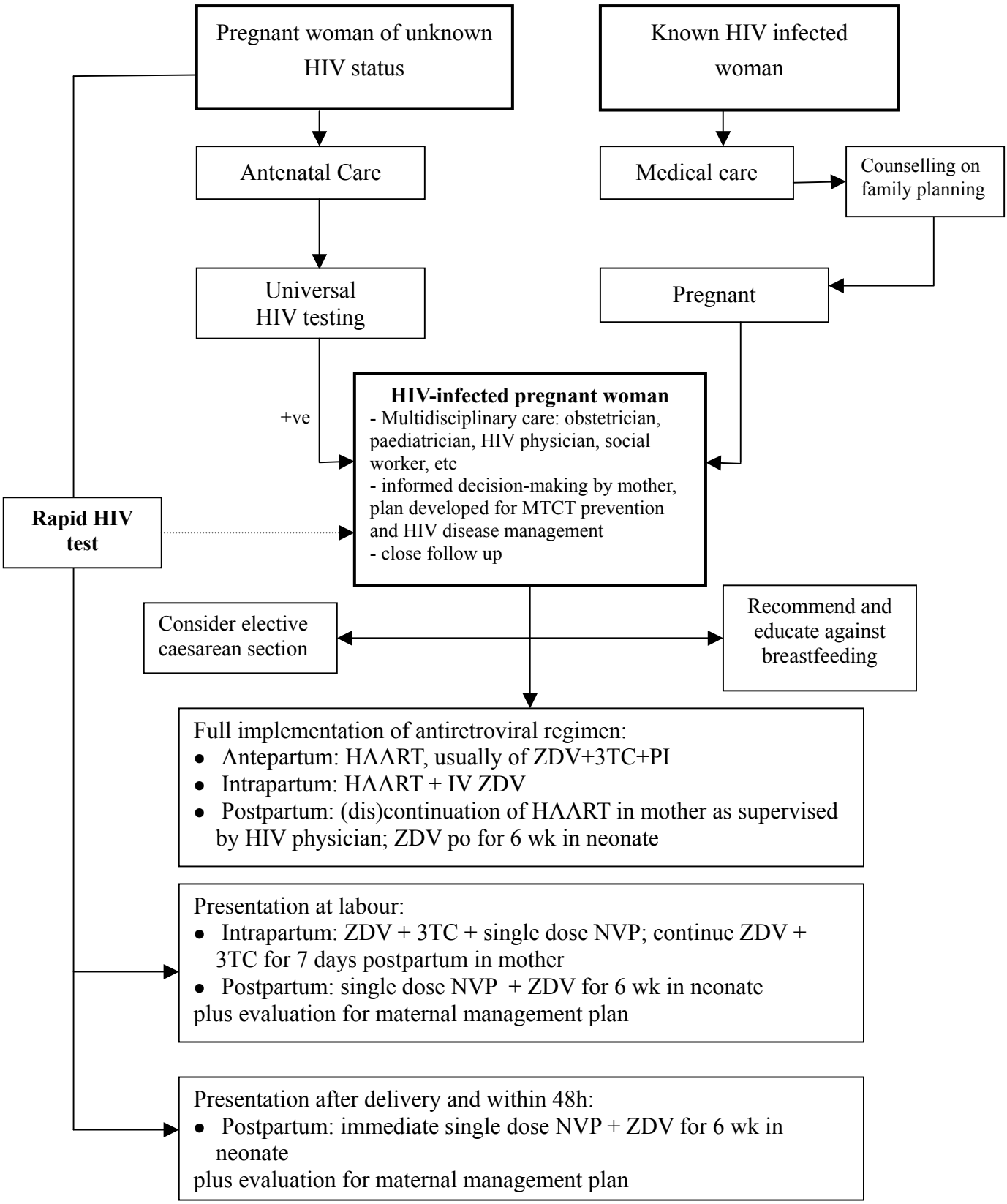
Period and regimen	Dosing	Remarks
Intrapartum: ZDV + 3TC + single dose NVP	ZDV - ● Recommended: IV bolus of 2 mg/kg, then 1mg/kg/h till delivery; begin at onset of labour or 3 h before elective caesarean section ● Alternative: 600 mg po loading dose, then 300 mg po q3h till delivery 3TC - ● 150 mg po at onset of labour, then 150 mg po q12h till delivery NVP - ● Single dose 200 mg at onset of labour	
Postpartum: ZDV + 3TC for mother and ZDV + single dose NVP for newborn	Mother: ● ZDV 300 mg po bid for 7 days ● 3TC 150 mg po bid for 7 days Newborn: ZDV - ● 2 mg/kg po q6h for 6 wk, or ● 1.5 mg/kg IV q6h for 6 wk NVP - ● Single dose of 2 mg/kg at 48-72h	♦ ZDV and 3TC given to mother to reduce likelihood of viral resistance ♦ No breastfeeding ♦ Refer to HIV physician for management of maternal HIV disease

Table 3. Recommended antiretroviral prophylaxis in women presenting after delivery

Regimen	Dosing	Remarks
Postpartum: ZDV + single dose NVP for newborn	Immediate use of ZDV: ● 2 mg/kg po q6h for 6 wk, or ● 1.5 mg/kg IV q6h for 6 wk NVP: ● Single dose of 2 mg/kg	♦ ARV not advised if after 48h of birth ♦ Refer to HIV physician for management of maternal HIV disease ♦ No breastfeeding

ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; ARV, antiretroviral

Algorithm. Overview of management principles in preventing MTCT of HIV



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