The Use of BCG Vaccine in HIV Infected Patients

(Adopted from SCAS, CHP, DH November 2009)

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Background

1. In many places of the world, the epidemics of human immunodeficiency virus (HIV) and tuberculosis (TB) converge and reinforce each other. Although there is no evidence that HIV is driving the incidence of TB in Hong Kong, TB has become one of the most common primary AIDS-defining illnesses. According to classification by World Health Organisation (WHO), Hong Kong is a place with intermediate TB burden.

2. Whereas there is no viable vaccine against HIV, the BCG (Bacilli Calmette-Guĕrin) strain of *Mycobacterium bovis* has been used to immunise humans since 1921 against TB. In the current infant immunisation schedule, BCG is given to newborn babies in Hong Kong, including those who are HIV exposed or infected as long as they are not significantly immunocompromised.

3. Recently, WHO made the recommendation that BCG should not be given to known HIV infected infants, regardless of symptoms or degree of immunocompromise. The Scientific Committee on AIDS and STI (SCAS) of the Centre for Health Protection has since deliberated on its rationales, practicability and, above all, relevance to the local setting. This statement reflects the position of SCAS on this issue.

The BCG Vaccine against TB

Efficacy against TB disease

4. In spite of some controversy regarding its efficacy, the following about BCG are generally agreed for those who are not HIV infected

- After neonatal vaccination, there is 65%-80% protection against TB-related death, TB meningitis and disseminated TB[1],
- there is no protection against primary infection or reactivation of latent TB, and
- protective efficacy declines to non-significant levels after 10-20 years.

Risks of vaccination

5. Focal complications of BCG vaccination may occur in the form of ipsilateral axillary lymphadenitis, or vaccine site ulceration, abscess, and fistula. Distant and disseminated diseases including osteomyelitis, bacteremia, or meningitis, are much rarer but much more serious (Appendix 1).

6. Particularly for children with compromised cellular immunity, the use of a live virus such as BCG is cause for concern. In fact, serious BCG complications have repeatedly been cited in association with HIV since 1984.[2] Mortality associated with disseminated BCG in HIV disease is generally high at over

70%.[3] Early uncontrolled studies suggested but could not quantify a 'small' increased risk in HIV infected or exposed children.[4]

7. After the advent of highly active antiretroviral therapy (HAART), a new complication emerged, that of immune reconstitution causing focal BCG disease5. Although the risk of mortality is low, it may cause diagnostic confusion and result in inappropriate treatment in the early stage.

Balancing risks and benefits of BCG in HIV-exposed and infected children

8. Until recently, use of BCG vaccine in HIV-exposed or -infected children had been recommended by WHO in TB-endemic countries, as long as the child was asymptomatic.[6] This was an opinion-based position that emphasised the general effectiveness of BCG against serious forms of TB in children. Although this was also the practice in Hong Kong, concern had been raised with regard to the risk of disseminated BCG infection.[7]

9. In 2007, WHO re-examined available evidence and came to recommend against BCG vaccination in children known to be HIV infected, even in TB endemic countries.[8,9] The reversal of position resulted from the possibility of diminished efficacy of BCG in HIV infected children,[10] and especially new knowledge of risks in HIV infected children. In a study carried out in South Africa, the incidence of disseminated BCG was estimated to be as high as 400-1300 per 100,000 HIV-infected vaccinees, almost 1000 times higher than those who was HIV-uninfected.[11]

10. However, early clarification of the HIV status in infancy can only be achieved by sophisticated and costly methods, not generally available in developing countries. Besides, the majority of children born to HIV infected mothers are not infected. Therefore, if local factors do not permit early diagnosis of HIV or if they might create confusion that causes HIV-uninfected children to miss out on vaccination, the same WHO guidelines provide for continuing the current practice of vaccinating asymptomatic HIV-exposed children.

Hong Kong should follow WHO recommendation

11. Nevertheless, Hong Kong is in an eminent position to implement the new position of WHO, by virtue of the following -

- A universal antenatal HIV testing programme, now supplemented by rapid test, has been in place since 2001. It allows diagnosis of maternal infection before birth, timely involvement of HIV physicians and paediatricians, and advice against breast feeding which poses a post-delivery risk of mother-to-child transmission (MTCT).
- Early paediatric diagnosis of HIV is standard of care where HIV infection is mostly ruled out within 6 months by nucleic acid amplification tests. Close followup of HIV-exposed infants by paediatricians is also the rule.
- A good and readily accessible infrastructure exists in Hong Kong for TB case detection, directly observed therapy, and contact tracing.

12. Thus, SCAS recommends against BCG vaccination in all HIV-infected patients. For HIV exposed infants, SCAS recommends a delayed approach, in which vaccination is delayed in those known to have been exposed to HIV *in utero* or during birth, until HIV infection is ruled out. (Appendix 2)

13. In practice, most HIV infected mothers should be known to health care providers in the antenatal period. On a case basis, the obstetrician or HIV physician on consultation should remark in the patient's record that BCG is to be withheld until HIV is ruled out in the infant. This message should also be communicated to the paediatrician who will take care of the baby.

14. Before administration of BCG vaccine in a neonate, it is also recommended for health care providers to consider the possibility of HIV exposure. If it is likely, vaccination should also be withheld. In the meantime, the child should be closely followed for ascertainment of HIV status and BCG vaccination given after HIV infection is excluded.

15. In the event that close follow up of the infant is anticipated to be difficult, as in the case of families with difficult social circumstances, consideration may be given for immediate BCG vaccination but only if the infant is asymptomatic and the likelihood of MTCT estimated to be low, e.g. as with an undetectable maternal viral load and when breastfeeding is not practised. For those families who are leaving Hong Kong, the decision of immediate versus delayed vaccination is more complex and should be based on the endemicity of TB and access to medical care in the destination country, as well as the infant's likelihood of infection.

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Appendix 1

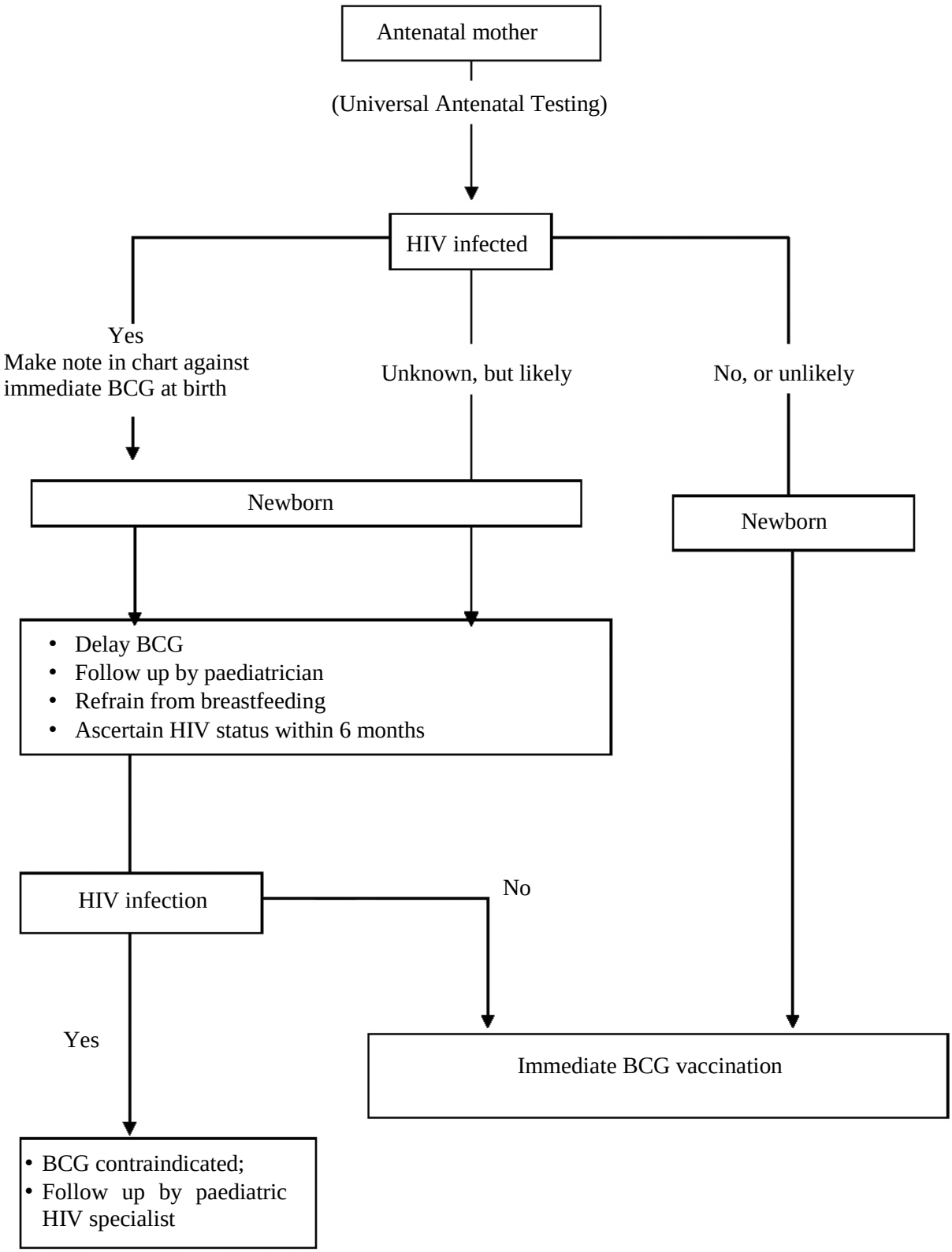
Classification of BCG disease12

Category	Description
Local BCG disease	A local process at the site of vaccination. This includes any of the following • BCG infection site abscess conforming to EPI definitions: ≧ 10 mm X 10 mm • Severe BCG scar ulceration
Regional disease	• Involvement of any regional lymph nodes or other regional lesions beyond the vaccination site: ipsilateral axillary, supraclavicular, cervical and upper arm glands. Lymph node involvement must conform to EPI definition and may include enlargement, suppuration and fistula formation.
Distant disease	• Involvement of any site beyond a local or regional ipsilateral process. This includes any of the following: BCG confirmed from at least 1 distant site beyond the vaccination site, e.g. pulmonary secretions (gastric aspirate, tracheal aspirate), cerebrospinal fluid, urine, osteitis, and distant skin lesion.
Disseminated disease	• BCG confirmed from > 1 remote site, as described under distant disease, and/or from at least 1 blood or bone marrow culture.
BCG IRIS	• Defined as BCG disease that presents in an HIV-infected child within 3 months after the initiation of highly active antiretroviral therapy with/without immunological or viral proof of immune reconstitution

IRIS, Immune Reconstitution Inflammatory Syndrome
EPI, Expanded Programme on Immunization
EPI criteria for local or regional BCG disease:

1. Ipsilateral LN ≧ 15 X 15 mm,
2. Suppurative ipsilateral axillary lymphadenitis,
3. Injection site abscess of ≧ 10 mm
4. Nonresolving BCG papule

Appendix 2



Management of BCG vaccination in HIV-exposed infants

Test paper - The Use of BCG Vaccine in HIV Infected Patients

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1. What is not true about HIV and TB coinfection?

   (a) The importance of TB and HIV coinfection has been rising in many parts of the world
   (b) TB has become one commonest AIDS-defining illness in Hong Kong
   (c) Hong Kong is of intermediate TB endemicity
   (d) None of the above
   (e) (b) and (c)

2. What is not true about BCG (Bacilli Calmette-Guerin) vaccine?

   (a) It was used in human as early as 1901
   (b) It does not protect against primary TB infection or reactivation of latent infection
   (c) Neonatal vaccination protects against TB-related death, meningitis and disseminated TB
   (d) Protective effect is largely lost after 10-20 years of vaccination in neonates
   (e) None of the above

3. Which of the following is incorrect regarding potential risk of BCG vaccination?

   (a) Local BCG disease at the site of vaccination with severe scar ulceration
   (b) Distant disease with BCG confirmed from lung secretions, urine and so on
   (c) Disseminated disease is defined as having >1 distant site of involvement, with or without positive blood or blood culture
   (d) BCG immune reconstitution syndrome in HIV is a new entity after the advent of highly active antiretroviral therapy
   (e) Ipsilateral axillary lymphadenitis is the only regional disease

4. Which of the following is not true regarding BCG vaccination in HIV infected or exposed infants and children?

   (a) Before 2007, World Health Organisation (WHO) recommended BCG vaccination in HIV infected infants if asymptomatic
   (b) There could be an increased risk of BCG complications
   (c) BCG being a live virus makes it a concern for administration in HIV immunocompromised children
   (d) Mortality associated with disseminated disease in HIV is low at <5%
   (e) None of the above

5. Which of the following is not true regarding WHO's new recommendation on BCG vaccination in HIV setting?

   (a) Known HIV infected children should not receive BCG vaccination, irrespective of TB endemicity of the locality
   (b) The new position is related to new knowledge of greatly elevated risk of serious BCG diseases in HIV infected
   (c) The possible diminished efficacy of BCG in HIV infected children is a rationale
   (d) Should local system endanger missing out vaccination of HIV uninfected children, asymptomatic HIV exposed children should be vaccinated

(e) None of the above

6. Which of the following is factor that will influence adoption of new the WHO recommendation?

(a) Laboratory capacity to early clarify HIV status in exposed child
(b) Clinical follow up of exposed children
(c) Communication between obstetricians and paediatricians in managing HIV positive pregnancy and the delivered child
(d) All of the above
(e) (a) and (c)

7. Which of the following is incorrect about Hong Kong's favourable situation to implement the new WHO recommendation?

(a) The universal antenatal HIV testing programme has made non-diagnosis of infected mothers uncommon
(b) The antenatal testing programme makes timely involvement and collaboration of obstetricians, HIV physicians and paediatricians possible
(c) Nuclei acid amplification test is the norm to diagnose infected infant early
(d) A good and readily accessible infrastructure exists for TB case detection, directly observed therapy and contact tracing
(e) None of the above

8. Which of the following is incorrect of the Hong Kong Scientific Committee on AIDS and STI 2009 recommendation on the use of BCG in HIV infected patients?

(a) BCG vaccination is recommended against in all HIV-infected
(b) BCG vaccination is delayed till HIV status is clarified in HIV exposed infant
(c) HIV infection can normally be diagnosed within 6 months of birth
(d) Immediate vaccination may be given for exposed infants who cannot be closely followed up, even if the risk of mother-to-child transmission may not be low
(e) None of the above