Recommended Clinical Guidelines on the Prevention of Perinatal HIV Transmission

Scientific Committee of the
Advisory Council on AIDS, Hong Kong
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Preamble

In 1994, interim findings from the landmark study Pediatric AIDS Clinical Trials Group (PACTG) 076 indicated that the use of zidovudine (ZDV) significantly reduced the mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV). This was followed by other studies that either elucidated the risk factors associated with transmission or evaluated alternative interventions to prevent MTCT. It is imperative that these scientific findings be translated into standard clinical practice if their full potential in public health can be realised.

These guidelines are developed under the auspices of the Scientific Committee on AIDS (SCA). They are intended to suggest preferable approaches toward the prevention of HIV by mother-to-child-transmission (MTCT) based on synthesis of scientific evidence. Application of these guidelines, however, should be flexible, in order to accommodate the wide-ranging circumstances whereby the clinical problem may present itself.

The principles

I. Universal testing of HIV antibody should be performed for antenatal women in Hong Kong.

II. The prevention of mother-to-child transmission of HIV involves the administration of antiretroviral prophylaxis.

III. Clinical management should include that for the maternal HIV infection.

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

V. Paediatric management should be offered to reduce the risk of MTCT of HIV.

VI. Coordinated efforts should be made to strengthen our knowledge base regarding MTCT of HIV in Hong Kong.

Recommendations and Rationales

I. Universal testing of HIV antibody should be performed for antenatal women in Hong Kong.

In Hong Kong, about half the mothers of perinatally exposed children were diagnosed of HIV infection only after delivery (surveillance data of the AIDS Unit, Department of Health). The fact that effective treatment is available to help prevent an incurable infection argues strongly for testing all antenatal mothers for HIV. Before its recommendation on universal HIV antibody testing, the SCA has evaluated the seroprevalence of HIV in antenatal clients and the potential impact on health care resources, in accordance with guidelines of UNAIDS[1]. A pilot study of universal testing in a local hospital also demonstrated a high level of acceptance (97.5%) in antenatal mothers[2].

Since HIV testing is a clinical procedure with potentially serious social and medical implications, informed consent and pre- and post-test counselling should be provided. The SCA reckons that the standards of testing should not be compromised by universal testing, and the right of refusal to be tested should be respected.

II. The prevention of mother-to-child transmission of HIV involves the administration of antiretroviral prophylaxis.

Antiretroviral regimen for prophylaxis against MTCT of HIV is effective. It should be administered in the event of a diagnosis of HIV infection in an antenatal mother continuing her pregnancy. PACTG 076[3] [4], a randomised controlled trial of the standard regimen below, has demonstrated a 66% reduction of MTCT in women with CD4 count above 200/ul, from 23% to 8%. The efficacy of this regimen was corroborated by PACTG 185[5] with women of advanced disease and prior ZDV therapy. However, there is evidence that efficacy is reduced if both the antepartum and postpartum components are shortened[6]. Alternative regimens have also been evaluated and found to be useful (see appendix II). Nevertheless, it is unlikely that they are superior to the standard ZDV regimen, pending a direct comparison trial.

II.A The standard regimen comprises the use of zidovudine (ZDV) beginning as early as 14 weeks of pregnancy, continuing through labour by intravenous administration, and followed by treatment of the newborn for 6 weeks.

II.B Alternative antiretroviral prophylaxis should be administered in special circumstances where the standard regimen is considered not practicable.

II.C When maternal HIV infection is not diagnosed until labour, the options of antiretroviral prophylaxis are:

(i) ***standard regimen of ZDV abbreviated to intrapartum and postpartum components only;***

(ii) ***nevirapine (NVP) one dose to mother and one dose to newborn at 48-72h;***

(iii) ***ZDV/3TC intrapartum, and to newborn for 7 days, and;***

(iv) ***abbreviated ZDV + nevirapine***

Details of these options are in appendix I and II. It is noted that the ZDV/3TC regimen, i.e. option (iii), is modified in non-breast feeding women by the deletion of the maternal postpartum component. The use of abbreviated ZDV combined with nevirapine, i.e. option (iv), is based on theoretical considerations. This regimen may yield better protection in those mothers who have viruses resistant to either ZDV or NVP, but may also result in more toxicity.

The choice depends on the considerations of compliance, potential toxicity, likelihood of resistant viruses, and the availability of drugs. Studies on the relative efficacy of these regimens are not available.

II.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.

The regimen is a 076 regimen abbreviated to the postpartum component only (see appendix I and II). The rationale of this abbreviated regimen is based on the results of an observational study[7]. It is noted that therapy given at 3 days or later after birth is unlikely to be useful. The use of additional drugs in this situation has not been studied. Besides the balance between additional efficacy and toxicity is unknown.

III. Clinical management should include that for the maternal HIV infection

III.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.

Evidence is accumulating that optimal control of maternal HIV disease is beneficial to reducing MTCT as both the magnitude of viral load and CD4 count are related to transmission[8 9 10]. The major standards of care[11] in HIV disease are:

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

(ii) antiretroviral treatment as determined by viral load, CD4 count and clinical history.

Regular CD4 cell enumeration and viral load testing are indicated as in non-pregnant patients. A viral load result near term is preferable to help determine the mode of delivery. Modern day management of HIV infection is complex and consultation with specialists should be sought.

III.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.

It is important to distinguish drugs used for maternal HIV disease from those for prophylaxis against MTCT, as their indications are different. In cases where HAART is not indicated for maternal HIV infection, standard ZDV regimen is recommended for prophylaxis against MTCT, as explained above.

If medical therapy of maternal HIV disease is also indicated, the best regimen for both mother and foetus is one that has the greatest antiretroviral potency, minimal teratogenicity and toxicity, and maximal efficacy against MTCT. ZDV should be incorporated in the HAART regimen unless contraindicated. Apart from the usual parameters in non-pregnant patients, the choice of other components of a HAART regimen should also be based on potential toxicity to mother and foetus, altered pharmacokinetics in pregnancy, and compliance. However, if there is intolerance to ZDV, then the nevirapine regimen may be substituted (see appendix II).

While the use of ZDV in pregnancy is probably safe[12], data on other antiretrovirals are sparse. At any rate, 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.

III.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.

For these clients, reevaluation of the antiretroviral regimen is required to maximise control of HIV disease, minimise teratogenicity and provide prophylaxis against MTCT. As one consideration might compromise another, the mother's wishes are important, and full explanation should be given of the rationales of continuing or altering the regimen.

If the current regimen does not contain ZDV, it should be added or substituted even if the mother has had prior experience with the drug. If there is intolerance to ZDV, the nevirapine regimen may be used for prophylaxis against MTCT (see appendix II).

At any rate, the toxicity including teratogenicity to the foetus would be greatest in the first trimester. Some mothers may choose to interrupt treatment in the first 10 – 12 weeks of gestation. The potential adverse effect on disease progression and MTCT of HIV should be made known to the mother.

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

The finding that elective caesarean section before rupture of membranes confers additional protection against MTCT should be taken into consideration, along with other factors, in the decision on the mode of delivery. The wish of the mother should be respected.

Studies have validated the independent protection from MTCT conferred by elective cesarean section[13] [14]. However, it cannot be overemphasised that the operation carries obstetric risks of its own. The efficacy of elective caesarean section in reducing MTCT should only be one of many factors in the final decision on the mode of delivery. Examples of those factors relating to HIV disease include the use of antiretroviral prophylaxis, the viral load near term, and expected compliance with the postpartum component of ZDV prophylaxis[15].

Prolonged rupture of membranes (especially if more than 4 hours), invasive foetal monitoring, and instrumental vaginal delivery should be avoided to reduce MTCT.

V. Paediatric management should be offered to reduce the risk of MTCT of HIV.

The paediatrician should be involved early and before delivery in each case of HIV exposed pregnancy. Apart from continuing the prophylactic regimen against transmission of HIV, the paediatrician shall look for possible congenital defects or other consequences as a result of exposure to antiretrovirals.

The most common adverse effect of ZDV in the newborn is anaemia. As data on teratogenicity are rare, the paediatrician should also be on the lookout for unexpected congenital abnormalities.

The mother shall be advised against breastfeeding. It has been estimated that the added risk of transmission by breastfeeding was 16.7%[16]. In Hong Kong, the

benefits of breastfeeding are outweighed by the risk of HIV transmission it carries.

For management of paediatric HIV infection, please refer to guidelines on this subject by the SCA[17].

VI. Coordinated efforts should be made to strengthen our knowledge base regarding MTCT of HIV in Hong Kong.

The science of treating and preventing HIV infection is evolving. In Hong Kong, a coordinated effort is needed to track the local epidemiology of HIV infection in women, use of prophylactic measures against perinatal transmission, and outcome of such treatment. This knowledge base will be useful in formulating strategies toward preventing this disease in children.

Implementation strategies

In realising the objective of achieving prevention of MTCT, it is proposed to:

(a) promote the adoption of the principles in the health care settings in both the private and public service in Hong Kong,

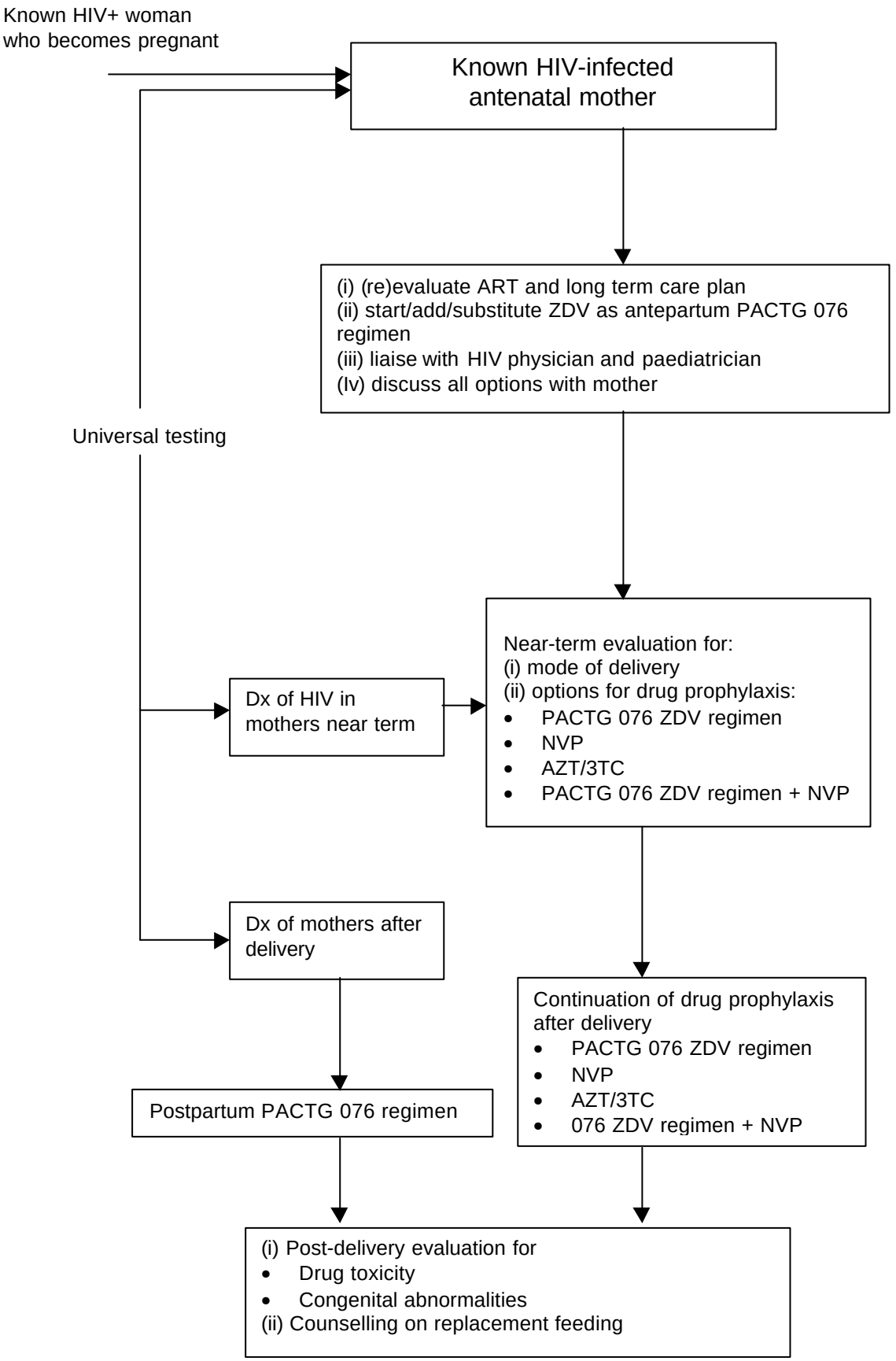
(b) encourage the development of protocols relevant to individual service, based on the recommended principles,

(c) enhance the understanding of the health care profession and the community about the importance of preventing MTCT,

(d) establish a sustainable system and build capacity in the health care services involved in the prevention of MTCT, and

(e) evaluate and monitor the progress of implementation of universal antenatal testing.

Appendix I. Management algorithm to prevent perinatal HIV transmission



Appendix II. 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 tds) 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[18])	Transmission rate was 7.6%; Placebo group was 22.6% (PACTG 076[3 4])	No breastfeeding
AZT/3TC	3-part regimen: (ZDV 300 mg + 3TC 150 mg) bid from 36 wk to labour; (ZDV 300 mg + 3TC 150 mg) q3h during labour; (ZDV 4mg/kg + 3TC 2mg/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 labour; NVP 2 mg/kg to newborn at 48-72h	Transmission rate was 13.1% at 14-16 wk Comparison arm (ZDV intrapartum and to newborn for 7 d) was 25.1% (HIVNET-012[20])	Breastfeeding in 95% Rapid emergence of resistance in mother[21]
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[7])	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 labour; *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 48-72h	Unknown; based on extrapolation from existing data	

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