Guidelines For The Clinical Management Of Prevention Of Mother To Child Transmission Of HIV

In Myanmar

THIRD EDITION

National AIDS Programme
Department Of Health, Ministry Of Health, Myanmar
2011

World Health Organization
Country Office for Myanmar

GUIDELINES FOR THE CLINICAL MANAGEMENT OF PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV IN MYANMAR

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Contents

List of abbreviations

3TC	lamivudine
ABC	abacavir
AFASS	affordable, feasible, acceptable, safe, sustainable (breastfeeding)
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
AZT	Azidothymidine or zidovudine (ZDV)
BD	twice daily
bPI	boosted protease inhibitor
CD4 count	CD4+ T-lymphocyte count
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
d4T	stavudine
ddI	didanosine
EFV	efavirenz
FTC	emtricitabine
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IDV	indinavir
INH	isoniazid
IPT	isoniazid prophylaxis theraphy
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	ritonavir boosted lopinavir
MTCT	mother-to-child transmission (of HIV)
MDR-TB	Multidrug-resistant tuberculosis
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTP	National Tuberculosic Programme
NVP	nevirapine
OD	once a day
PCP	Pneumocystis pneumonia
PEP	Post exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission (of HIV)
PPE	pruritic papular eruption
/r	low-dose ritonavir to boost another PI
RLC	resource limited country
RLS	resource limited situation
RTV	ritonavir
SQV	saquinavir
TST	tuberculin skin test
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
VL	viral load

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Foreward

Guidelines for the management of HIV/AIDS need to be updated regularly. This is because HIV/AIDS is a relatively new disease and with the passage of years, more experience is gained, new drugs are discovered and new treatment protocols introduced. More and more results of trials involving various aspects of the management of HIV become available and new insights and better understanding of the disease are being obtained. Long term use of ART has also resulted in realization not only of the pros and cons of some drug combinations and treatment regimens but also serious side effects of some of the antiretroviral drugs.

In resource rich countries the latest technology and the newest ART drugs can be employed but in many resource limited situations a balance has to be struck between what resources are available and what is the best possible solution for a PLHIV.

Recommendations would also need to be evidence based. The present guidelines are an update of the Myanmar Guidelines for the Clinical Management of HIV infection in Adults and Adolescents published in 2007 and are also adapted from Antiretroviral Therapy for HIV Infection in Adults and Adolescents – Recommendations for a Public Health Approach, 2010 revision, published by World Health Organization, which is a carefully reviewed evidence-based document for resource limited situations.

These guidelines have been written to serve all medical personnel treating patients with HIV in Myanmar. It is meant not only for the National AIDS-STD programme but also for local and international NGOs, hospital doctors and general practitioners in the public and private sectors. With this objective a workshop was held at Nay Pyi Taw on 10th March 2011. The participants included representatives from the National AIDS-STD programme, Department of Health, National Health Laboratory, professors from Universities of Medicine, physicians from Specialist Hospitals Mingaladon and Thaketa, Nay Pyi Taw General Hospital, representatives from WHO, UNAIDS, UNICEF, UNFPA and also representatives from MSF- Holland, MSF-CH, UNION and also included PLHIV. A consensus was reached on what was to be recommended for the new guidelines and a draft was produced. The draft guidelines were further reviewed by a review team and the final draft was written to encompass all the recommendations .

These guidelines are not written for the specialist physician or for the exceptional patient. The physician has to treat according to what is best for the patient and the individual patient has a right to choose. These guidelines are meant to serve as a rational basis to treat HIV for the average medical doctor working anywhere

in Myanmar so that people living with HIV can have access to treatment and care wherever they are. As facilities and resources will vary from place to place, region to region, options are given and health care providers or implementers of ART programmes can choose what is most suitable and appropriate in a given situation.

Summary of key recommendations for ART in the new guidelines

1. When to start ART
i. HIV positive asymptomatic ARV naïve individuals – CD4 ≤ 350 cells/mm3
ii. HIV positive symptomatic ARV naïve individuals- WHO clinical stage 2 if CD4 ≤ 350 cells/mm3 OR WHO clinical stage 3 or 4 irrespective of CD4 cell count
iii. HIV positive pregnant women – CD4 ≤ 350 cells/mm3 irrespective of clinical symptoms OR WHO clinical stage 3 or 4 irrespective of CD4 cell count
iv. HIV/TB coinfection ARV naïve individuals – presence of active TB disease if CD4 ≤ 500 cells /mm3 (if MDR-TB, ART indicated regardless of CD4 count)
v. HIV/HBV coinfection – individuals who require treatment for their HBV infection irrespective of CD4 cell count

2. What antiretroviral therapy to start
i. HIV positive ARV naïve adults and adolescents – AZT or TDF + 3TC (or FTC) + EFV or NVP (d4T not preferred because of side effects, but if it is used initially, should not be for an extended period and should replace d4T with AZT or TDF)
ii. HIV positive pregnant women – same as above. AZT preferred but TDF acceptable. EFV preferred over NVP if CD4 count ≥ 250 cells/mm^3 because of risk of NVP toxicity; do not initiate EFV in first trimester. HIV positive women with prior exposure to MTCT - for details see text.
iii. HIV/TB coinfection – AZT or TDF + 3TC (or FTC) + EFV ; ART to be started 2 to 8 weeks after start of TB treatment ; NVP not recommended
iv. HIV/HBV coinfection – NNRTI regimens that contain both TDF + 3TC (or FTC)

3. Recommended second-line antiretroviral therapy
i. HIV positive adults and adolescents: a. If d4T or AZT used in first line therapy – TDF + 3TC (or FTC) + ATV/r or LPV/r b. If TDF used in first line therapy – AZT + 3TC (or FTC) + ATV/r or LPV/r
ii. HIV positive pregnant women – same as for adults and adolescents
iii. HIV/TB coinfection – substitute rifabutin (150 mg 3 times/week) for rifampicin if available; if not available same NRTI backbone plus LPV/r or SQV/r with adjusted dose of RTV (LPV/r 400mg/400 mg BD or LPV/r 800 mg/200 mg BD or SQV/r 400 mg/400 mg BD
iv. HIV/HBV coinfection – AZT + TDF + 3 TC (or FTC) + ATV/r or LPV/r

* ABC and ddI can be kept as backup options if AZT or TDF cannot be used

4. PMTCT

i. ART for HIV infected pregnant women who need treatment for own health
ART eligibility criteria
a). All women with CD4 ≤ 350 cells/mm3 irrespective of clinical symptoms
b). Clinical stage 3 or 4 regardless of CD4 count
When to start ART - As soon as feasible
Recommended first line regimens-

- AZT (TDF) + 3TC (FTC)+ NVP or EFV (EFV preferred if CD4 ≥ 250 cells/mm3 but not in first trimester)

Prophylaxis for infants born to pregnant women on ART-

- All infants regardless of feeding mode – daily NVP or AZT (BD) for 4-6 weeks

ii. ARV prophylaxis for pregnant women who do not need treatment for their own health
When to start ARV prophylaxis

- As early as 14 weeks of pregnancy

Prophylaxis regimens for the mother-
Option A :

- AZT during pregnancy plus
- sd-NVP at onset of labour plus
- initiation of AZT + 3TC for 7 days postpartum (omit sd-NVP + 3TC if >4 wk AZT)

Option B: (continued until delivery or if breastfeeding continued until 1 week after breastfeeding has stopped)

- AZT + 3TC+ LPV/r (or ABC or EFV)
- TDF + 3TC (or FTC) + EFV

Prophylaxis regimens for exposed infants
Option A:

- Breastfeeding infants –NVP from birth until 1 week after all exposure to breastfeeding has ended
- Non-breastfeeding infants – NVP or sd-NVP + AZT for 4 – 6 weeks

Option B:

- All infants regardless of infant feeding mode – NVP or AZT for 4 – 6 weeks

iii. Infant feeding recommendation for known HIV- infected women – to decide

- Avoid all breastfeeding only if safe formula feeding is possible (will most likely give infant greatest chance of HIV free survival) or if breastfeeding judged to be best option – exclusive breast feeding for first 6 months, introduce complementary food thereafter, continue breastfeeding for 12 months, wean gradually within 1 month.

Conditions needed to safely formula feed-
Avoiding breastfeeding will most likely give the infant the greatest chance of HIV free survival but only if all the following conditions are met. If these conditions cannot be fulfilled breastfeeding would be the best option for the HIV infected mother.

a. safe water and sanitation are assured at the household level and in the community; and
b. the mother, or other caregiver can reliably provide sufficient formula milk to support normal growth and develoment of the infant; *and*
c. the mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition; *and*
d. the mother or caregiver can, in the first six months, exclusively give infant formula milk; *and*
e. the family is supportive of this practice; *and*
f. the mother or caregiver can access health care that offers comprehensive child health services.

1. Introduction

Mother to child transmission of HIV can occur during pregnancy, during the intrapartum period and during lactation, the majority of infections occurring in the late antenatal period, during labour and during the early lactating months (1, 2). The rate of MTCT of HIV is 15 – 30% if there is no breastfeeding increasing to 20-45% if there is breastfeeding (3,4) . Breastfeeding is an important route of HIV transmission in infants, being responsible for one third of all MTCT in children (5-7). MTCT of HIV is increased if there is premature labour, premature rupture of membranes (8,9), if the mother has STI (10) or has advanced HIV disease, high maternal HIV viral load, or breast feeds, and during lactation if the mother has mastitis or cracked nipples (11). In resource rich countries MTCT of HIV has been reduced to less then 1-2% (12). In such countries three drug combination ART is given early in pregnancy after the first trimester (choosing the most suitable ARV after resistance testing), doing elective caesarean section , giving intrapartum AZT by intravenous infusion, avoiding breastfeeding and giving the infant AZT prophylaxis for 6 weeks (13). Viral loads are monitored monthly to see the response to antiretroviral treatment which is adjusted as necessary . The aim is to lower the viral load of the mother to undetectable levels (< 40 – 50 copies/ml). If the viral load is undetectable transmission to the infant could be <1% (14). If the viral load is < 1000 copies/ml vaginal delivery can be allowed as the transmission rate of HIV to the infant becomes very low . Viral load has a direct relationship to HIV transmission (15-16) which is greatest during primary HIV infection when VL is very high (18) and transmission is very rare at undetectable levels of VL, even though HIV transmission can still occur very rarely (15). Whether viral loads are detectable or not , whatever the CD4 count, ART with 3 drugs is administered. Pregnant mothers who are on ART already have their treatment continued after checking the VL which should be undetectable and if necessary the ART is changed. Infants born to HIV positive mothers are given AZT prophylaxis for 6 weeks.

All this will not be possible in resource limited situations. However, effective prevention of mother to child transmission can still be carried out with a view towards eliminating MTCT and it is possible to reduce the risk of MTCT to less than 5% in breastfeeding populations (from 35%) and to less than 2% in non-breastfeeding populations (from 25%) with current treatment utilizing evidence for recent PMTCT trials (19).

In resource limited situation, low or middle income countries, public health guidelines are used to lower the MTCT of HIV. Public health guidelines usually apply up-to-date evidence from clinical trials to provide the best possible solution with available resources to the largest number of people. The individual patient can choose what she decides is the best for her if it is affordable and feasible for her.

However for the vast majority in resource limited countries, PMTCT is carried out in programmes according to guidelines which are designed to be practical, affordable and feasible with available resources for pregnant women who otherwise will not be able to prevent HIV transmission to their infants.

Guidelines have to be standardized and simplified as much as possible, while maintaining some flexibility, so that they may be used by the largest number of healthcare personnel who do not need to be specialists to carry out PMTCT for the maximum benefit of a large number of pregnant women. The public health approach is a balance between the best proven strategy and what is feasible on a large scale in resource limited settings.

Guidelines are always evolving, since HIV is a relatively new disease and new ARVs as well as new protocols and results of clinical trials become available. They will continue to evolve.

In the most recent WHO recommendations for a public health approach (20), ART is started early at 14 weeks of pregnancy (previous recommendations being at 28 weeks), since the longer the duration of ART and viral suppression, the better the results (21). ART is also started early in terms of immunosuppression, i.e. at CD4 count of $\leq$ 350/mm3. Pregnant women who are at WHO stage 3 or 4 are started on ART at whatever the CD4 count. Triple drug ART may be offered not only to pregnant mothers who need ART for their health but also to pregnant mothers solely for the purpose of PMTCT. Intrapartum ART is given orally. Since in the vast majority of instances it is neither feasible nor safe to avoid breastfeeding in resource limited situations, prevention of HIV infection from breast milk is carried out by giving ARV prophylaxis to the infant or a potent ART combination is given to the lactating mother to reduce HIV concentration in the breast milk. Infant ART prophylaxis is also extended beyond 6 weeks so long as the mother is breastfeeding and is not on ART. The new PMTCT recommendations emphasize on the health of the mother and infant and aim to reduce MTCT of HIV as much as possible. Transmission of HIV to the infant can be disastrous; half of such infants will not survive beyond 2 years of age without treatment (22) and in RLS management of infants with HIV can be difficult.

In the new recommendations CD4 counts are essential for determining eligibility for ART, and should be rapidly available and even though PMTCT can be started without CD4 counts, the aim is to start early at CD4 count of 350/mm^3 since this gives better results than after starting late. The cost of PMTCT will be higher with the new recommendations but looking from a wider context, the lives of more mothers and infants will be saved and the benefit from this cannot be calculated. It is necessary to save the infant as well as the mother and the emphasis is on both.

From available evidence, there are options for PMTCT. Single drug prophylaxis versus three drug ART prophylaxis for the mother, extended infant ARV prophylaxis or three drug ART for the breastfeeding mother to prevent transmission of HIV from breast milk . The mother also has the option to avoid breastfeeding (which is actually the

best way to prevent infection from breast milk) if it is safe to do so. However certain conditions will have to be met to provide formula feeding to the infant *(see below).*

The choice of a particular regimen or method will depend on the circumstances. Programme managers and policy makers will have to decide according to the availability of resources, funds and practical considerations.

No matter what particular regimen or method is used, it is more important to get more pregnant women tested for HIV and to have them started on ART prophylaxis or treatment for PMTCT to get the maximal effect to prevent infection of infants with HIV.

Ideally all pregnant women should be tested for HIV and to do this all women should come for AN care. They should then have "provider initiated HIV testing and counselling (PITC)". This is not mandatory testing but pregnant women are offered HIV testing as part of the medical check-up (after giving necessary information) and they are allowed to "opt-out" if they do not agree to have the test (30). In practical terms this allows most pregnant women to be tested for HIV.

In the care of people with HIV, public education and non-discrimination are always important. PMTCT programmes should also integrate with ART programmes as well as care and counselling services for HIV.

Concerning infant feeding it has to be judged whether to counsel mothers to breastfeed and receive ARV interventions to prevent HIV transmission from breast milk or avoid all breastfeeding as the strategy that will most likely give infants the greatest chance of HIV-free survival if replacement feeding is deemed to be safe i.e. if the following conditions are all met, previously referred to as - AFASS (affordable, feasible, acceptable, safe and sustainable).

a. safe water and sanitation are assured at the household level and in the community; **and**
b. the mother, or caregiver can reliably provide sufficient formula milk to support normal growth and develoment of the infant; **and**
c. the mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition; **and**
d. the mother or caregiver can, in the first six months, exclusively give infant formula milk; **and**
e. the family is supportive of this practice; **and**
f. the mother or caregiver can access health care that offers comprehensive child health services.

2. Antiretroviral drugs for treating pregnant women for their own health and to prevent HIV infection in their infants

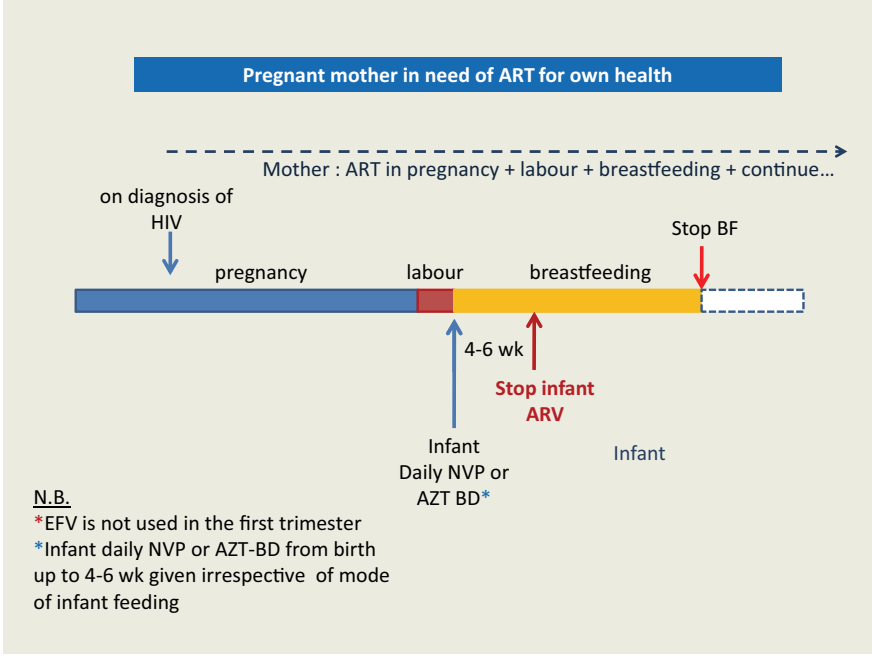
Recommendations

- ART should be started in pregnant women with confirmed HIV infection with CD4 counts of ≤ 350/mm3 irrespective of WHO clinical stage, and in all pregnant women in WHO clinical stage 3 or 4 regardless of CD4 count.
- HIV infected pregnant women in need of ART for their own health should start ART as soon as possible regardless of gestational age and continue throughout pregnancy, childbirth, breastfeeding and thereafter.
- In pregnant women in need of ART the preferred first line ART regimen should include AZT + 3TC plus NVP or EFV . EFV is preferred over NVP in pregnant women with CD4 > 250/mm3. EFV must be avoided in the first trimester. TDF can be used instead of AZT as an alternative when there is anaemia.
- All infants, whether breastfeeding or receiving only replacement feeding, are given daily NVP or twice daily AZT from birth as soon as feasible until 4 to 6 weeks of age.

Table 2.1 Criteria for ARV prophylaxis or antiretroviral treatment for pregnant women with HIV

	CD 4 count not available	CD 4 cell count available	
		CD4 ≤ 350/mm3	CD4 ≥ 350/mm3
WHO clinical stage 1	ARV prophylaxis	ART	ARV prophylaxis
WHO clinical stage 2	ARV prophylaxis	ART	ARV prophylaxis
WHO clinical stage 3	ART	ART	
WHO clinical stage 4	ART	ART	

Figure 2.1 Pregnant mother in need of ART for her own health



ART criteria for pregnant women in need of treatment for their own health

The criteria of CD4 count ≤ 350/mm3 (whatever the WHO clinical stage) for pregnant women in need of ART for their own health is the same as for adults with HIV. Pregnant women with CD4 count ≥ 200/mm3 may be asymptomatic. A CD4 count of 350 is used because it has been shown in adults that the long term prognosis is better when ART is started at this stage. Major opportunistic infections start to occur when the CD4 count is < 200/mm3. CD4 count is therefore essential as soon as a pregnant woman tests positive for HIV. If CD4 count is not available ART can be started at WHO clinical stage 3 or 4, but at this stage a lot of pregnant women may have opportunistic infections which will need to be diagnosed and treated first. ART is started as soon as possible after the treatment of OI is initiated in such cases . Women with CD4 count of ≤ 350 should be started on cotrimoxazole prophylaxis and assessed for presence of OIs and treated as necessary (see adult guideline).

ART regimens for pregnant women in need of ART for their own health

Recommended first line regimens –

- AZT + 3TC NRTI backbone should be included as much as possible. AZT has the longest track record of safety and efficacy for PMTCT .

- 3 drug combinations are always used. So this would be –
  AZT + 3TC + EFV
  AZT + 3TC + NVP
  TDF may substituted for AZT
  FTC may be substituted for 3TC

EFV is not used in the first trimester of pregnancy because of the risk of teratogenecity (<1% risk of neural tube defects) but it may be used in the second or third trimester. It is also avoided in women who may become pregnant. NVP may be substituted in such a situation.

There is a possible risk of NVP toxicity (31-32) especially in women with CD4 > 250/ mm3. EFV is preferred in such cases. NVP toxicity can cause skin rashes which can be severe leading to Stevens-Johnson syndrome and hepatoxicity can be life-threatening. When there is no alternative NVP is used with caution. Close follow up is necessary during the first 12 weeks. NVP is started at half the full dose (OD dose) for 2 weeks after which the full BD dose is given. The frequency of severe NVP toxicity is debated but it is recognized that it does happen and even if it is infrequent it can have serious consequences.[NVP is avoided if the pregnant woman has liver disease (hepatitis B or C associated). Patients on NVP are warned to come back immediately if rash or jaundice develops. NVP is stopped immediately if severe toxicity develops and is not given again; it is substituted with EFV or another regimen].

NVP is not used if rifampicin is used for TB treatment at the same time since rifampicin reduces NVP drug levels. EFV is substituted.

EFV can cause severe giddiness ,insomnia or nightmares but this usually disappears after one or 2 weeks. It can also cause a rash but it is usually mild. EFV is avoided in those with a psychiatric illness or a history of depression.

The major side effect of AZT is anaemia. It is best avoided if Hb $\leq$ 10 g/dl. TDF can be substituted when there is anaemia. When AZT is used, it is important especially in the first 3 or 4 months to look out for anaemia which can be sometimes severe in persons taking AZT and it may be necessary to warn patients to come back immediately if severe pallor or breathlessness develops. Haemoglobin should be checked before giving AZT and also at 4, 8 and 12 weeks.

TDF may cause renal toxicity with proteinuria and rise in creatinine levels but it is infrequent and reversible. Ideally creatinine (to calculate creatinine clearance) should be checked every 6 months. Proteinuria can also be checked.

Fixed dose combination ARVs are available either as BD (e.g. AZT + 3TC + NVP) or as OD (e.g.TDF + 3TC + EFV) forms and should be used since this simplifies drug taking as well as prescription and also improves adherence. Stavudine (d4T) and ddI are not recommended as first line ART. ABC is sometimes employed in special situations(see adult guidelines).

ART regimens are chosen according to cost, availability, potential toxicity and experience.

Table 2.2 ARVs, dose and major side effects

Drug	Class	Dose	Major side effects
AZT	NRTI	300 mg BD	anaemia
3TC	NRTI	150 mg BD	Quite safe
FTC	NRTI	200mg OD	Quite safe
TDF	NtRTI	300 mg OD	Renal toxicity
NVP	NNRTI	200 mg OD x 2 wk then continue 200 mg BD	Severe skin rashes, Stevens- Johnson syndrome, hepatoxicity. Caution in women with CD4 count >250/ mm3
EFV	NNRTI	600 mg OD	Giddiness, nightmares, insomnia, neural tube defects in first trimester of pregnancy (< 1%)
LPV/r	PI/r	400 mg/100 mg BD	Diarrhoea, nausea, hyperlipidaemia, insulin resistance, reduced ethinyl oestradiol level

ART regimen for pregnant women who require treatment for their own health and who had prior exposure to ARVs for PMCT

NVP has a long half-life and it has a low genetic barrier to resistance. Therefore if NVP has been used as a single drug or used as a single drug and stopped, HIV develops resistance to the drug very easily. If NVP is used as part of a 2 or 3 drug combination and if all the drugs are stopped at the same time NVP drug levels persist for about 2 weeks inviting HIV drug resistance. Therefore when stopping NVP another 2 NRTIs have to be given for a minimum of 7 days (a "tail") to cover the persistent NVP drug levels and to avoid or minimize emergence of resistant HIV strains. Similarly EFV has a long half life and may persist for up to 3 weeks in the body. (EFV should also be covered with a "tail" when it is stopped).

In most women who have had exposure to NVP, resistant virus when it develops, can no longer be detected 12 months after exposure (23). However it may remain in latently infected cells for longer periods (24). The choice of ART regimen in a pregnant woman who has had prior exposure to PMTCT in previous pregnancies will depend on whether single dose NVP (sd-NVP) had been used, whether it had been used with other ARVs, whether it was used with or without a "tail" regimen or whether it had been used more than 12 months previously.

- If sd-NVP had been used alone or in combination with other ARVs without a NRTI tail, less than 12 months previously for PMTCT, then NNRTIs are no longer recommended and a boosted PI should be substituted for the NNRTI (e.g. LPV/r). NVP causes cross resistance with another NNRTI – EFV.
- PIs are more costly and may not be readily available. In such a case NNRTIs may be still started but viral load testing should be performed after 6 months of ART and if the VL is > 5000 copies/ml a boosted PI will then be needed for best results. (Viral load again may not be always available and this is a dilemma).
- Women who have received sd-NVP alone or in combination with other drugs with a NRTI tail within the last 12 months can use NNRTI based ART regimen. However VL testing at 6 months should be carried out and if this is > 5000 copies/ml, then the NNRTI should be switched to a boosted PI (e.g. LPV/r).
- For women who had received sd-NVP alone or in combination with other drugs with or without a tail more than 12 months before starting treatment, a standard NNRTI based ART regimen is recommended. However VL testing is recommended after 6 months and if > 5000 copies /ml a boosted PI (e.g. LPV/r) is recommended.

[Protease inhibitors should be used only as boosted PIs. Ritonivir (RTV) increases the drug levels and decreases dosing of other PIs – it is a booster. Lopinavir (LPV) is usually prescribed as LPV 400 mg + RTV 100 BD.

Women receiving ART who become pregnant

If a women receiving ART is found to be pregnant before 28 days of gestation and if she is receiving EFV , this should be stopped and substituted with NVP or a PI. If pregnancy is diagnosed after 28 days EFV is continued.

When women who are receiving ART become pregnant it is necessary to make an assessment to see that the ART regimen is working, i.e. it is causing maximal viral suppression to prevent MTCT of HIV. Clinical as well as immunological assessment (CD4 count) is necessary. If ART failure is suspected it may be necessary to do viral loads and adjust the ART regimen as necessary.

ART regimens for women of childbearing age receiving treatment for their own health

Women of childbearing age should receive ART according to the adult ART guidelines. Contraceptive counselling is an important part of care for women of reproductive age as unintended pregnancies should be avoided. It should be noted that drug interactions with ARVs may lower hormonal contraceptive efficacy. (Ritonavir , nevirapine and efavirenz decrease levels of ethinyl estradiol (25).

If a woman on ART is planning to become pregnant she should receive counselling on the pros and cons of pregnancy. She should be on a fully suppressive ART before conception and this should be maintained throughout pregnancy, labour, delivery and breastfeeding. EFV should be substituted with NVP if a woman is planning pregnancy. If a woman is taking EFV it can be substituted with NVP at the full dose of 200 mg BD without the initial period of reduced dose.

Antiretroviral prophylaxis for infants born to women receiving ART

A short period of ARV prophylaxis for 4 to 6 weeks is indicated for infants born to HIV positive women receiving ART to further reduce peripartum and postpartum transmission. The choice of infant prophylaxis is made according to availability, feasibility, potential toxicity and experience.

Either AZT or NVP is given to the infant within 6 – 12 hours after birth or as soon as feasible until 4 to 6 weeks of age. (Six weeks is often the time of the first immunization visit and target date for early diagnosis testing for HIV exposed infant).

Table 2.3 Infant ARV dose

AZT	15 mg per dose BD if birth weight > 2500 g 10 mg per dose BD if birth weight < 2500 g Potential risk of anaemia but is reversible
NVP	15 mg oral suspension OD if birth weight > 2500 g 10 mg oral suspension OD if birth weight < 2500 g Risk of drug resistance if infant becomes infected in spite of prophylaxis Potential risk of NVP toxicity if mother also taking NVP ART Not effective for HIV-2 (rare outside west Africa)

N.B.- *Measurement of the CD4 count routinely may be done but is not essential for monitoring pregnant mothers on ART but can be used to confirm clinical treatment failure. Absolute CD4 count may decrease in pregnancy because of haemodilution and this should be taken into consideration when interpreting results. Viral load testing may be needed to confirm ART failure.*

3. Maternal and infant ARV prophylaxis to prevent MTCT for HIV-infected pregnant women who do not need treatment for their own health.

Table 3.1 Criteria for ARV prophylaxis or antiretroviral treatment for pregnant women with HIV

	CD 4 count not available	CD 4 cell count available	
		CD4 ≤ 350/mm3	CD4 ≥ 350/mm3
WHO clinical stage 1	ARV prophylaxis	ART	ARV prophylaxis
WHO clinical stage 2	ARV prophylaxis	ART	ARV prophylaxis
WHO clinical stage 3	ART	ART	
WHO clinical stage 4	ART	ART	

Pregnant women with CD4 count > 350/mm3 or who are in WHO clinical stage 1 or 2 (if CD4 count not available) usually do not require antiretroviral treatment for their own health. However they require ARV prophylaxis to prevent transmission of HIV to their infants.

Recommendations

- ARV prophylaxis is started as early as 14 weeks of gestation (second trimester) or as soon as feasible if pregnancy is diagnosed later than this and given during pregnancy, labour and delivery or continued according to the option chosen.
- Two ART options can be given-

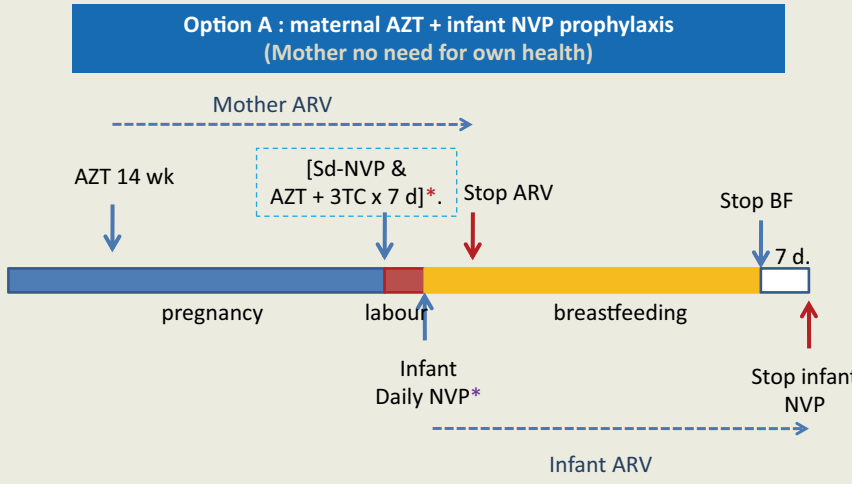
- **Option A :** maternal AZT + infant prophylaxis
  - Antepartum twice daily AZT *plus*
  - Single dose NVP at the onset of labour *plus*
  - Twice daily AZT + 3TC during labour and delivery and this is continued for 7 days postpartum "tail" (ARVs are then stopped for the mother).
    (sd-NVP and AZT + 3TC intrapartum and postpartum can be omitted if the mother received > 4 weeks AZT during pregnancy)
  - Breastfeeding infants – daily NVP from birth until 1 week after all exposure to breast milk has ended (infant prophylaxis)
  - NVP for 4 to 6 weeks if breastfeeding stops before 6 weeks (but 1 week after the early cessation of breastfeeding)
  - If no breast feeding-
    - Daily NVP from birth for 4 to 6 weeks or
    - Single dose NVP at birth plus twice daily AZT from birth until 4 to 6 weeks.

- **Option B** : maternal triple ARV prophylaxis (which will also cover the breastfeeding period as prophylaxis for the breastfeeding infant)
  - Triple ARV prophylaxis is given in pregnancy as PMTCT until delivery and stopped if the mother does not breastfeed and if breastfeeding this is continued throughout the breastfeeding period until 1 week after all exposure to breast milk has ended.
  - For the infant whether or not there is breastfeeding-
    - Daily NVP for 4-6 weeks or
    - Twice daily AZT for 4- 6 weeks
- Recommended 3 drug prophylactic regimens –
  - AZT + 3TC + LPV/r
  - AZT + 3TC + ABC
  - AZT + 3TC + EFV
  - TDF + 3TC (or FTC) + EFV

NB – NVP is not recommended

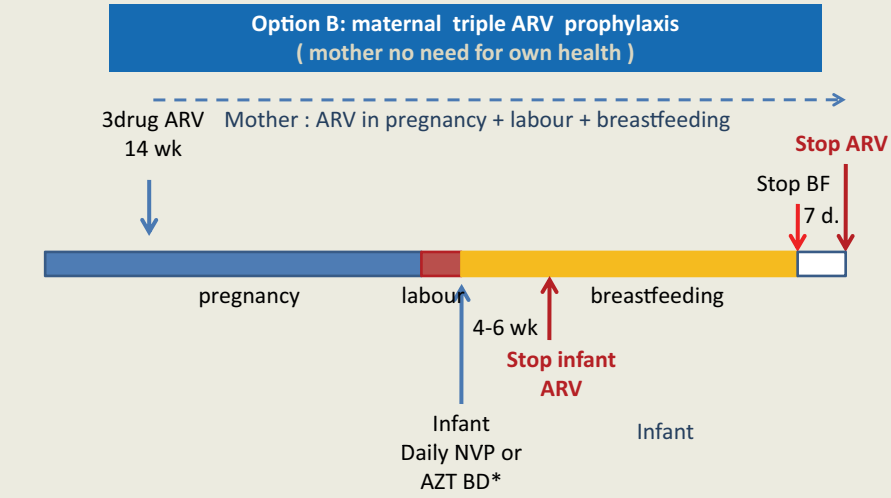
(In option B infant prophylaxis is carried out by ARV for 4 to 6 weeks only, and if there is continued breastfeeding the infant is protected by giving the mother continued 3 drug ARV prophylaxis which is intended to reduce HIV concentration in breast milk) For women presenting late, prophylaxis can be started in the second trimester, labour, delivery or even postpartum but as much as possible of the full prophylaxis regimen should be given.

Fig. 3.1 Option A : maternal AZT + infant NVP prophylaxis



N.B.
*If maternal AZT provided > 4 wk can omit sd-NVP + 3 TC, continue AZT during labour and stop at delivery.
* Infants receiving replacement feeding – daily NVP or sd-NVP + AZT BD from birth until 4-6 wk.

Fig 3.2 Option B: maternal triple ARV prophylaxis



N.B.
*Infant daily NVP or AZT-BD from birth up to 4-6 wk given irrespective of mode of infant feeding

Currently available evidence suggests that option A is almost as effective as option B as PMTCT and both options could be used. [In the Kesho Bora study (26), significant difference was not demonstrated between triple maternal ARV prophylaxis or single AZT prophylaxis plus sd-NVP with AZT + 3TC tail for 1 week at birth (infection rates at birth were 1.8% for maternal triple ART prophylaxis and 2.2% with AZT plus sd-NVP); however the trial started prophylaxis only at 28 – 36 weeks gestation and if started from 14 weeks of pregnancy option B would be a better regimen in terms of completely suppressing viral loads.

Which option to choose will depend on the prevailing local situation taking into account feasibility, acceptability and costs. Programme managers and implementers of PMTCT programmes will have to decide. In a public health programme access to PMTCT services have to be given priority and a balance will have to be struck between the best proven standard of care and what is feasible on a large scale when there are limitations in resources.

From a public health point of view it is more important to have more pregnant women tested for HIV on a wider basis and give PMCT prophylaxis if they are positive, than employing either option .

Option A : Maternal AZT plus infant ARV prophylaxis

This is the same strategy as previously recommended PMTCT guidelines with the exception that AZT is recommended to be started as early as 14 weeks of pregnancy to maximize the period of ARV exposure. This will also lessen delays between HIV testing (at the first AN visit) and starting ARV prophylaxis and minimize the dropout rate .The sd-NVP is to further prevent HIV transmission at the time of delivery and the NRTI tail will minimize emergence of NVP resistance.

In option A the breastfeeding infant is given daily NVP during the whole period of breastfeeding until one week after all exposure to breast milk has ended.

[The BAN trial in Malawi (27) showed no significant difference in MTCT among infants uninfected at 2 weeks, between 6 months of infant NVP prophylaxis and 6 months of maternal triple ARV prophylaxis (1.7% and 2.9%) . Therefore maternal single drug AZT prophylaxis can be combined with infant NVP prophylaxis for maximal effect on MTCT].

N.B. *Option A may not be advisable if the pregnant mother has anaemia with Hb ≤ 10 g/dl. In such a case option B is preferable.*

Table 3.2 Extended infant NVP dosing

Infant age	NVP dose
Birth to 6 weeks • Birth weight 2000-2499 g • Birth weight >2500 g • Low birth weight	 10 mg once daily 15 mg once daily 2 mg/ kg once daily
>6weeks to 6 months	20 mg once daily
>6months to 9 months	30 mg once daily
>9months to end of breast feeding	40 mg once daily

Table 3.3 Simplified infant AZT dosing

Infant age	AZT dosing
Birth to 6 weeks • Birth weight 2000-2499 g • Birth weight >2500 g	 10 mg twice daily 15 mg twice daily

N.B.

- *6 weeks of daily infant AZT together with maternal antepartum AZT for > 4 weeks significantly prevents risk of HIV transmission.*
- *There is no data to compare a 4 week and 6 week duration of AZT prophylaxis in infants. 6 weeks is the time for the first immunization visit and the target date for early diagnose testing of HIV exposed infants.*

- *There is also lack of data comparing NVP and AZT prophylaxis in infants receiving replacement feeding. Both are effective and one or the other may be chosen.*
- *NVP may cause rash and AZT may cause anaemia in the infant but the risk of toxicity is low and it is reversible and benefit outweighs the risk.*
- *NVP has a long-half life and allows the infant to potentially miss some of the daily doses.*
- *The risk of HIV resistance to AZT given as a single ARV to the mother in the short term is believed to be negligible (28).*

Option B: Maternal triple ARV prophylaxis to prevent MTCT

The recommended maternal triple ARV regimens are-

- AZT + 3TC + LPV/r
- AZT + 3TC + ABC
- AZT + 3TC + EFV
- TDF +3TC (or FTC) + EFV
- N.B. NVP is not used because of the risk of hepatotoxicity for women with high CD4 counts (> 350 cells/mm3). AZT is not advised if the maternal Hb is ≤ 10 g/dl. In such a situation use TDF + 3TC (or FTC) + EFV usually as a convenient single combined pill.

For breastfeeding infants (as well as non-breastfeeding infants) maternal triple ARV prophylaxis is combined with daily NVP or twice daily AZT for 4-6 weeks and stopped. If the mother continues to breastfeed maternal triple ARV is continued until all exposure to breast milk has stopped for one week. Continued prophylaxis for the infant is provided by the mother who continues to take triple ARV to minimize the presence of HIV in breast milk. Three drug ARV is definitely more expensive especially if a boosted protease inhibitor (LPV/r) is used. However it would be expected to produce maximal viral suppression and it is known that viral load is a major determinant of mother to child transmission of HIV. This is important especially if the pregnant woman presents late in pregnancy. Option B can be started if the woman presents in labour, and can also be given after labour if there will be continued breastfeeding. Three drug regimen is continued during labour and delivery and but in women who do not breastfeed it is stopped after delivery.

The maternal CD4 count should be checked at the end of breastfeeding to determine if she now qualifies for treatment for her own health (if CD4 has fallen to <350/mm3).

There is the potential problem of multiple drug resistance if the pregnant mother does not take the ARVs regularly in option B, and there is a likelihood of drug resistance in infants who are infected despite prophylaxis.

Three drug ARV is the standard used in resource rich countries where breastfeeding is also avoided to get the best results in PMCT.

Using a 3 drug regimen has also the advantage of using the same ARV drugs for both categories of pregnant mothers who either need ART for their health and those who do not need ART for their own health and this simplifies operational matters. In women who have multiple pregnancies the long term effects of taking a 3 drug ARV off and on is not known.

Option B would provide maximal viral suppression. However current evidence suggests that option A works almost as well as option B (Kesho Bora study) in terms of PMTCT at delivery. Further studies are being carried out to address AZT monotherapy vs triple maternal prophylaxis as well as the effects of stopping triple maternal prophylaxis (PROMISE study) (29).

Infant feeding for known HIV-infected women

Regarding infant feeding it has to be decided whether to counsel mothers to either breastfeed and receive ARV interventions to prevent HIV transmission from breast milk or avoid all breastfeeding (if AFASS) as the strategy that will most likely give infants the greatest chance of HIV free survival. When breastfeeding is decided to be the best option exclusively breastfeed for the first 6 months, introduce appropriate complementary food thereafter and continue breastfeeding for 12 months. Then wean gradually within 1 month.

Whether to breastfeed and receive ARV interventions or avoid breastfeeding should be based on current recommendations and consideration of the :

- Socioeconomic and cultural contexts of the populations served by maternal, newborn and child health services,
- Availability and quality of health services,
- Local epidemiology including HIV prevalence among pregnant women,
- Main causes of maternal and child undernutrition,
- Main causes of infant and child mortality.
- Conditions needed to safely formula feed (previously referred to as AFASS ; all conditions to be met):
    - Safe water and sanitation are assured at the household level and in the community; **and**
    - The mother, or caregiver can reliably provide sufficient formula milk to support normal growth and development of the infant; **and**
    - The mother or caregiver can prepare it cleanly and frequently enough so that it is safe and carries a low risk of diarrhoea and malnutrition; **and**
    - The mother or caregiver can, in the first six months, exclusively give infant formula milk; **and**
    - The family is supportive of this practice; **and**
    - The mother or caregiver can access health care that offers comprehensive child health services.

Pregnant women and mothers known to be HIV-infected should be informed of the infant feeding practice recommended by the national or sub-national authority to improve HIV-free survival of HIV exposed infants and the health of HIV infected mothers and informed that there are alternatives that mothers might wish to adopt. This principle is included to affirm that individual rights should not be forgotten in the course of public health approaches.

In resource limited settings, it should be noted however that even in communities where HIV is not prevalent, infant feeding practices are frequently not optimal and high rates of partial breastfeeding, poor complementary feeding and malnutrition are common. Poor feeding practices and malnutrition greatly increase the risk of infant deaths.

Pregnant mothers will need to be educated and counselled about optimal infant feeding practices whether they breastfeed or not.

4. Special Situations

Women diagnosed during labour or immediately postpartum

The intrapartum-postpartum components of option A or option B prophylaxis or the post partum component of option A or B prophylaxis alone can reduce MTCT and should be started in women who present in labour or immediately postpartum. Prophylaxis should be started immediately and the regimen modified postpartum if the mother is found to require ART for her own health.

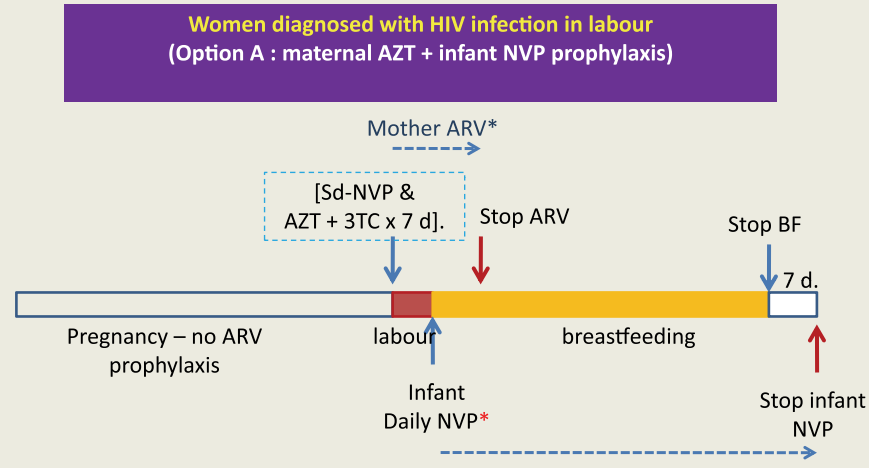
Option B (maternal triple ARV prophylaxis) requires severe weeks or longer to significantly lower the maternal viral load making it critically important for rapid infant protection. Therefore for women identified with HIV infected in labour or immediately postpartum, extended daily infant NVP as in option A may be better than postnatal prevention which relies on maternal triple drug prophylaxis option B.

If the mother is found to require ART for her own health, she is started on triple drug ART. Because it takes some time to reduce the viral load, the infant is continued on daily NVP until the mother has received at least 6 weeks of ART before infant prophylaxis is discontinued.

Table 4.1 Women diagnosed with HIV infection in labour

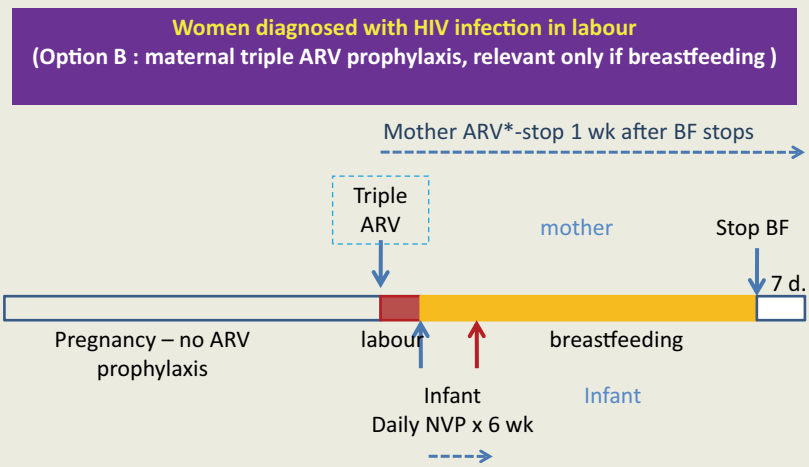
Option A (maternal AZT plus infant ARV prophylaxis) :
Mother : sd-NVP asap during labour and AZT + 3TC twice daily for one week
Infant (if breastfeeding): daily NVP from birth until 1 week after breastfeeding stops
Infant (not breastfeeding) : sd-NVP plus twice daily AZT or daily NVP from birth until 4 to 6 weeks of age
Option B (maternal triple ARV prophylaxis, relevant only if breastfeeding):
Mother : triple ARV prophylaxis during labour until 1 week after all exposure to breast milk has stopped.
Infant: daily NVP (preferred) until 6 weeks of age

Figure 4.1 Women diagnosed with HIV in labour Option A



N.B.
*Infants receiving replacement feeding – daily NVP or sd-NVP + AZT BD from birth until 4-6 wk.
*Mother- assess clinical, CD4 count – start ART if needed for own health; if breastfeeding, infant to continue daily NVP until mother has received 6 wk of ART before stopping infant prophylaxis

Figure 4.2 Women diagnosed with HIV in labour Option B



N.B.
*Mother- assess clinical, CD4 count postpartum – continue life-long ART if needed for own health

Table 4.2 Women diagnosed with HIV infection immediately postpartum

Option A (infant prophylaxis) :
Infant (if breastfeeding) : daily NVP from birth until 1 week after all exposure to breast milk has stopped or for 4-6 weeks if breastfeeding stops before 6 weeks
Infant (not breastfeeding) : sd-NVP plus twice daily AZT or daily NVP from birth until 4-6 weeks of age
Option B (maternal triple ARV prophylaxis, relevant only if breastfeeding) :
Mother: triple ARV prophylaxis until 1 week after all exposure to breast milk has stopped.
Infant: daily NVP from birth until 6 weeks of age (NVP preferred)

N.B. *Clinical assessment and CD4 count are carried out for the mother postpartum. If there is indication for ART for her own health appropriate life-long ART regimen should be given.*

CD4 counts *should be done every 6 months for women taking prophylaxis (including option A and B) to find out the possible need for full treatment for the mother.*

Regular assessment of drug adherence is very important for all women and infants taking ARV drugs.

Figure 4.3 Women diagnosed with HIV immediately postpartum Option A

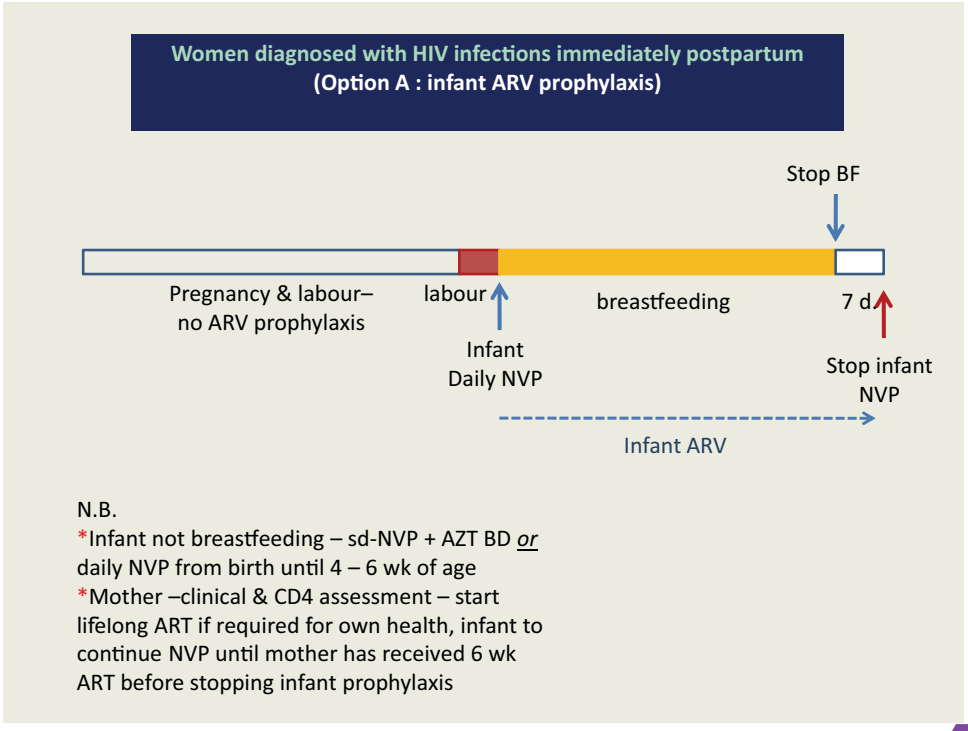
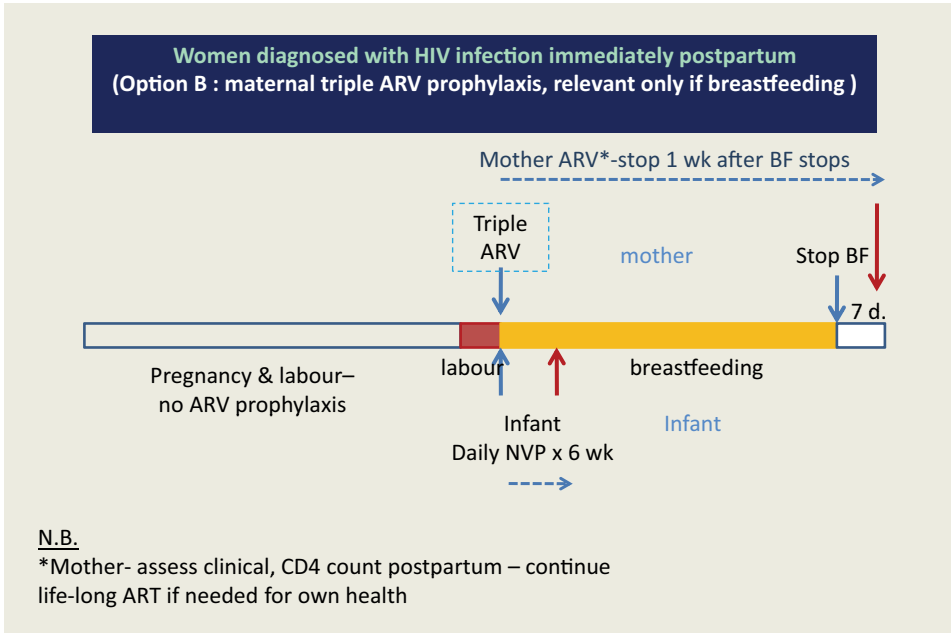


Figure 4.4 Women diagnoned with HIV immediately postpartum Option B



N.B.
*Mother- assess clinical, CD4 count postpartum – continue life-long ART if needed for own health

Women who acquire primary infection during pregnancy or breastfeeding

Women who become infected with HIV during pregnancy or while breastfeeding have a very high risk of transmitting the virus to their infants (about 30% transmission rate to infants among women who acquire HIV during breastfeeding). Women who tested negative early in pregnancy should be offered repeat HIV testing in the third trimester of pregnancy if it is thought that they are at risk (partners of HIV positive persons, partners of bisexual men or IDUs, pregnant women who are IDUs , CSWs, those with STIs and in high prevalence areas); they should have received education and counselling on HIV prevention when they were tested for HIV initially). Standard ARV prophylaxis can be started if she is found to be positive.

Caesarean section in pregnant women with HIV

Caesarean section should be carried out if there are obstetric indications only. It is not recommended routinely for PMTCT especially when the pregnant woman is taking ART . If a caesarean section is indicated for obstetric reasons –

- For elective caesarean section, ARV prophylaxis (sd-NVP + AZT/3TC is given 4 hours before the operation)
- Pregnant women taking lifelong ART treatment should continue their ART regimen
- In an emergency LSCS the pregnant should be given sd-NVP + AZT/3TC prior to the procedure.
- Standard prophylactic antibiotic may be given before the surgical procedure to prevent post-operative infections in women with HIV.

Safer delivery procedures

PMTCT risk is increased by prolonged rupture of membranes (> 4 hours), instrumental delivery, invasive fetal monitoring procedures, episiotomy, vaginal tears and prematurity. Therefore the following may be observed.

- Standard universal precautions
- Avoid artificial rupture of membranes as much as possible
- Do not do repeated vaginal examinations as much as possible
- Avoid instrumental delivery as much as possible
- Disposal of placenta and infectious waste material should be safely carried out.

Women with anaemia

Anaemia is a common problem in pregnancy and may be due to iron deficiency, folate deficiency, thalassaemia, malaria, worms, or opportunistic infections in those with late HIV disease. Anaemia should be looked for and haemoglobin measured and corrected. If haemoglobin is Hb $\leq$ 10 g/dl AZT is not advised since this by itself can cause anemia. TDF (or sometimes d4T) can be substituted for AZT. If a pregnant women develops AZT induced severe anaemia, blood transfusion may be required. Erythropoietin s.c. injections can be also used but may not be available.

Infant haematological (and hepatic) toxicities are not usually associated with antenatal and postnatal exposure to maternal ARV. The use of daily NVP prophylaxis for infants is also not associated with significant toxicities.

Women with active tuberculosis

HIV positive pregnant women with active TB should start ART irrespective of the CD4 count. TB treatment is started first followed by ART within 8 weeks. EFV is the preferred NNRTI for HIV/TB co-infected women with pregnancy since rifampicin reduces NPV drug levels (EFV is given after the first trimester).

Women with hepatitis B or C coinfection

ART is started in all pregnant women coinfected with HIV and HBV when treatment is indicated for HBV infection irrespective of CD4 count or WHO clinical stage. TDF and 3TC (or FTC) are used which have antiviral activity against HBV.
When HBV coinfected pregnant women who do not require HBV treatment or ART for their own health, are given option B prophylaxis (3 drug regimen which may contain TDF or 3TC) and when the prophylaxis is stopped, there may be hepatitis flares with worsening of liver function. In such cases option A (maternal AZT and extended infant NVP prophylaxis) which does not contain ARVs with anti-HBV activity is preferred.
For coinfection with HCV, no specific changes in treatment are recommended and PMTCT is carried out according to the general recommendations. Clinical and laboratory monitoring of liver function is required for such pregnant women.

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