

# CHAPTER VII: ANTIRETROVIRAL THERAPY IN PREGNANT WOMEN AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (PMTCT) OF HIV

## TABLE OF CONTENTS

<b>INTRODUCTION AND BACKGROUND</b> .....	VII-2
<b>GENERAL RECOMMENDATIONS REGARDING THE ANTENATAL CARE OF PREGNANT WOMEN WITH HIV INFECTION</b> .....	VII-2
<b>PMTCT ANTIRETROVIRAL THERAPY RECOMMENDATIONS: SPECIFIC SCENARIOS</b> .....	VII-2
<b>PMTCT OPTIONS AND RECOMMENDATIONS BY CLINICAL SCENARIO: DISCUSSION</b> .....	VII-5
Scenario A: Non-Pregnant Woman Who Needs ART for Her Own Health .....	VII-6
Scenario B: Woman Who Is Already Receiving ART at the Time She Becomes Pregnant .....	VII-6
Scenario C: Pregnant Woman, Not on HAART, Who Now Requires HAART for Her Own Health .....	VII-7
Scenario D: Pregnant Woman Who Does Not Require HAART for Her Own Health .....	VII-8
Scenario E: HIV-Infected Woman without Prenatal Care Who Presents in Labour .....	VII-9
Scenario F: Woman of Unknown HIV Status Who Presents in Labour.....	VII-9
Scenario G: Infants Born to Women Who Received No Antiretroviral Therapy for PMTCT Either Prepartum or During Labour .....	VII-10
<b>GENERAL RECOMMENDATIONS FOR MANAGEMENT OF THE HIV-INFECTED MOTHER DURING LABOUR AND DELIVERY</b> .....	VII-10
<b>RECOMMENDATIONS REGARDING BREASTFEEDING AND POSTPARTUM MANAGEMENT OF THE MOTHER</b> .....	VII-11
 <b>TABLES</b>	
<i>Table 1: PMTCT Options and Recommendations by Clinical Scenario</i> .....	VII-3
<i>Table 2: Selected clinical Trials of Prophylactic ARV Regimens for PMTCT</i> .....	VII-13
 <b>APPENDICES</b>	
<b>APPENDIX A: DOSING OF ARVs IN PMTCT REGIMENS</b> .....	VII-12
<b>APPENDIX B: EFFICACY OF PMTCT INTERVENTIONS: SUMMARY OF THE EVIDENCE</b> .....	VII-13
<b>APPENDIX C: MANAGING THE RISKS OF RESISTANCE ASSOCIATED WITH PMTCT REGIMENS</b> .....	VII-17
<i>Resistance to AZT</i> .....	VII-17
<i>Resistance to 3TC</i> .....	VII-17
<i>Resistance to NVP</i> .....	VII-17
<i>Potential Strategies to Reduce the Risk of NVP Resistance Associated with PMTCT Regimens</i> ..	VII-19
<i>Implications for Women Initiating HAART who received SD NVP or 3TC in the Past</i> .....	VII-20
<i>Implications for Women who have received SD NVP in the past and are now Pregnant again</i> ...	VII-20
<b>APPENDIX D: RISKS OF ANTIRETROVIRAL THERAPY IN PREGNANCY</b> .....	VII-21
<b>APPENDIX E: ANTIRETROVIRAL DRUG PHARMACOKINETIC AND TOXICITY DATA IN HUMAN PREGNANCY AND RECOMMENDATIONS FOR USE FOR TREATMENT OF PREGNANT WOMEN WITH HIV INFECTION</b> .....	VII-24

## VII. ANTIRETROVIRAL THERAPY IN PREGNANT WOMEN AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (PMTCT) OF HIV

### INTRODUCTION AND BACKGROUND

Mother-to-child transmission (MTCT) of HIV can occur during pregnancy, during delivery, or postpartum via breastfeeding. Without treatment, MTCT occurs in 15% to 30% of pregnancies in non-breastfeeding HIV-infected women. In breastfeeding populations, the rate is as high as 30% to 45%.

Several clinical trials have clearly established that interventions exist for the HIV-infected pregnant woman that can dramatically reduce the rate of HIV transmission to her infant. Combination antiretroviral therapy (ART) and avoidance of breastfeeding can reduce this rate to 2% or less. Even where alternatives to breastfeeding are unavailable or unacceptable, appropriate ART can significantly reduce the risk of MTCT. *Elective* caesarean section has also been demonstrated to reduce the risk of vertical transmission *in women receiving limited (e.g., AZT alone) or no ART* during pregnancy. It is controversial as to whether caesarean delivery would offer additional benefit in women who receive combination ART during pregnancy, in whom the risk of transmission is low and therefore any additional benefit of caesarean delivery in preventing transmission may not outweigh the potential risk of complications in the mother. Furthermore, in most resource-limited settings, caesarean section is not commonly available and is often unsafe, reducing the relevance of this intervention in PMTCT efforts.

These guidelines present specific recommendations for PMTCT in various clinical scenarios, followed by a discussion of the evidence from clinical trials that form the basis of these recommendations.

### GENERAL RECOMMENDATIONS REGARDING THE ANTENATAL CARE OF PREGNANT WOMEN WITH HIV INFECTION

Identification of HIV-infected women prior to or during pregnancy is essential in order to properly administer PMTCT and optimal therapy for the infected mother. Voluntary HIV counselling and testing (VCT) is therefore recommended for **all** pregnant women. Strict confidentiality must be maintained at all levels.

All HIV-infected pregnant women should be enrolled into appropriate antenatal clinical care that includes consideration of PMTCT options. The importance of adherence and of maintaining all medical appointments should be emphasised. Where possible, any potential barriers to adherence should be addressed prior to initiation of ART (see [Chapter IV](#) for more details). Standard antenatal investigations should be performed on all HIV-infected pregnant women, including haemoglobin, blood typing, haemoglobin electrophoresis (or sickle test if this is unavailable), syphilis serology, and hepatitis B screening. Counselling on nutrition and the benefits and risks of breastfeeding should be provided, and investigation into the possibility of formula-feeding should begin in the antenatal period.

Mothers who receive ART for PMTCT should be taught how to self-medicate during labour to ensure prompt compliance at the onset of labour, and the ARV(s) that will be taken during labour should be dispensed by thirty-six weeks gestation.

### PMTCT ANTIRETROVIRAL THERAPY RECOMMENDATIONS: SPECIFIC SCENARIOS

*Table 1* summarizes the ART options for various clinical scenarios, which are reviewed in further detail in the text that follows the table. Please refer to [Appendix A](#) for details regarding the exact dosing options for the ARVs described. [Appendix B](#) summarizes the evidence from clinical trials that form the basis of these recommendations. [Appendix C](#) reviews the risks of resistance associated with PMTCT regimens, and details strategies that can be used to manage these risks.

**Table 1: PMTCT Options and Recommendations by Clinical Scenario (page 1 of 3)**

Scenario	Mother	Infant	Comments
<b>A: Non-pregnant woman who needs HAART for her own health and may become pregnant</b>	First line regimen per <a href="#">Chapter IV</a> : (AZT or d4T) + 3TC + NVP	N/A	<ul style="list-style-type: none"> <li>- Efavirenz should be avoided in women who may become pregnant due to potential teratogenicity</li> <li>- issues of potential resistance, adherence, and prior treatment regimens should be considered in the design of the woman's HAART regimen, as detailed in <a href="#">Chapter IV</a>.</li> <li>- Demonstrated efficacy of AZT in reducing risk of MTCT favours its inclusion in HAART regimens of women who may become pregnant; however, if poorly tolerated or unavailable, another NRTI (e.g. d4T) can be used instead</li> <li>- a significantly higher risk of liver toxicity is seen in women with CD4 counts over 250 who initiate NVP-based HAART, hence NVP should be avoided or used with caution in these women; see <a href="#">Chapter IV</a> for more details</li> </ul>
<b>B: Woman who is already receiving HAART at the time she becomes pregnant</b>	<ul style="list-style-type: none"> <li>- <b>Do not discontinue HAART</b>; continue during pregnancy, labour and post-partum</li> <li>- If she is on EFV and within the 1<sup>st</sup> trimester, substitute a PI or NVP;</li> <li>- avoid combination of ddI + d4T in pregnancy</li> </ul>	Three options: AZT for one week;* <i>or</i> AZT for one week* plus SD NVP; <i>or</i> SD NVP	<ul style="list-style-type: none"> <li>- <b>If receiving efavirenz-based therapy and is in first trimester of pregnancy, efavirenz should be discontinued and replaced by another drug; See text</b></li> <li>- so long as mother continues to receive HAART during pregnancy, AZT alone can be administered to the infant; this strategy is associated with an MTCT rate of &lt;2% in US and European studies</li> <li>- if mother is on a regimen containing ddI <i>and</i> d4T, would substitute a different NRTI for one of these agents due to excess toxicity associated with this combination in pregnancy</li> </ul>
<b>C: Pregnant woman not on HAART who now requires HAART per local guidelines</b>	<ul style="list-style-type: none"> <li>- Initiate HAART: First line regimen per <a href="#">Chapter IV</a>, ideally AZT + 3TC + NVP</li> <li>- continue HAART during labour and post-partum</li> </ul>	Three options: AZT for one week;* <i>or</i> AZT for one week* plus SD NVP; <i>or</i> SD NVP	<ul style="list-style-type: none"> <li>- issues of potential resistance, adherence, and prior treatment regimens should be considered in the design of the woman's HAART regimen, as detailed in <a href="#">Chapter IV</a></li> <li>- treatment should not be delayed if mother requires it for her own health and the drugs can be initiated during the first trimester</li> <li>- A PI is preferred over NVP in women with CD4 counts over 250 because a significantly higher risk of liver toxicity is seen in women with CD4 counts over 250 who initiate NVP</li> <li>- Demonstrated efficacy of AZT in reducing risk of MTCT favours its inclusion in HAART regimens of pregnant women; however, if poorly tolerated or unavailable, another NRTI (e.g. d4T) can be used instead</li> </ul>

\* Extend infant's course of AZT to four weeks if the mother received less than four weeks of ART prior to delivery.

Scenario	Mother	Infant	Comments
<b>D: Pregnant woman who does not require HAART for her own health</b> <i>Two preferred options</i>	<b>Option 1.</b> AZT starting at 28 weeks or as soon as feasible thereafter; continued during labour, with or without SD NVP at onset of labour ( <i>see Comments</i> )	AZT for one week plus SD NVP*	- in order to reduce risk of NVP resistance, maternal dose of SD NVP may be omitted if mother receives at least four weeks of AZT immediately prior to delivery and the infant is given single-dose NVP immediately at birth. Alternatively, a seven day ‘tail’ of AZT/3TC can be given to the mother following delivery if she received SD NVP ( <i>see Appendix C for details</i> )
	<b>Option 2.</b> HAART; preferred regimen: AZT + 3TC + (PI or NVP); continue during labour; discontinue following delivery	<u>Three options:</u> AZT for one week;* <i>or</i> AZT for one week* plus SD NVP; <i>or</i> SD NVP	- a significantly higher risk of liver toxicity is seen in women with CD4 counts over 250 who initiate NVP-based HAART, hence NVP should be avoided or used with caution in these women; <i>see Chapter IV</i> for more details - Demonstrated efficacy of AZT in reducing risk of MTCT favours its inclusion in HAART regimens of pregnant women; however, if poorly tolerated or unavailable, another NRTI (e.g. d4T) can be used instead - Consider giving seven day ‘tail’ of AZT/3TC to mother following delivery to reduce risk of NVP resistance ( <i>see Appendix C for details</i> ).
<b>Scenario D continued: four alternative options</b>	<b>Option 3.</b> AZT starting at 28 weeks or as soon as feasible thereafter; continued during labour	AZT for 1-6 weeks	- Associated with a significant reduction in the risk of PMTCT, but not as effective as options 1 or 2 above; See text
	<b>Option 4.</b> SD NVP at onset of labour	SD NVP	- Associated with a significant reduction in the risk of PMTCT, but not as effective as options 1 or 2 above; See text - Consider giving seven day ‘tail’ of AZT/3TC to mother following delivery to reduce risk of NVP resistance ( <i>see Appendix C for details</i> ).
	<b>Option 5.</b> AZT + 3TC starting at 32 weeks or as soon as possible thereafter, and continued during labour	AZT + 3TC for 1 week	- Associated with a significant reduction in the risk of PMTCT, similar efficacy as AZT + SD NVP but more complex; See text
	<b>Option 6.</b> AZT + 3TC starting at 32 weeks or as soon as feasible thereafter, continued during labour, with SD NVP	SD NVP plus AZT/3TC for one week	- Associated with a significant reduction in the risk of PMTCT, similar efficacy as AZT + SD NVP but more complex; See text - Consider giving seven day ‘tail’ of AZT/3TC to mother following delivery to reduce risk of NVP resistance ( <i>see Appendix C for details</i> ).

\* Extend infant’s course of AZT to four weeks if the mother received less than four weeks of ART prior to delivery.

Scenario	Mother	Infant	Comments
<b>E: HIV-infected woman without any prenatal ART who presents in labour</b>	<b>Option 1:</b> SD NVP + AZT immediately	SD NVP plus AZT for four weeks	- Mother must be assessed postpartum for need for ART and enrolled into appropriate HIV care - Consider giving seven day ‘tail’ of AZT/3TC to mother following delivery to reduce risk of NVP resistance ( <i>see Appendix C for details</i> ).
	<b>Option 2:</b> AZT/3TC immediately	AZT/3TC for 7 days	- Continue AZT/3TC for the mother for an additional week if she is breastfeeding - Mother must be assessed postpartum for need for ART and enrolled into appropriate HIV care
	<b>Option 3:</b> SD NVP immediately	SD NVP	- If mother delivers within 2 hours of receipt of NVP, give the infant NVP as soon as possible, plus one week of AZT if available - Mother must be assessed postpartum for need for ART and enrolled into appropriate HIV care - Consider giving seven day ‘tail’ of AZT/3TC to mother following delivery to reduce risk of NVP resistance ( <i>see Appendix C for details</i> ).
<b>F: Woman of unknown HIV status who presents in labour</b>	Test for HIV (ideally using rapid test); if positive, manage as scenario E	If mother tests HIV-positive, but did not receive intrapartum ART, see scenario G below	- If mother tests positive for HIV infection, she must be assessed postpartum for need for ART and enrolled into appropriate HIV care
<b>G: HIV-infected woman who has received no ART for PMTCT, either prepartum or during labour</b>	N/A	SD NVP as soon as possible, plus 4 weeks of AZT	- SD NVP unlikely to be useful for infants if not given within 3 days of birth. - Mother must be assessed postpartum for need for ART and enrolled into appropriate HIV care

## PMTCT OPTIONS AND RECOMMENDATIONS BY CLINICAL SCENARIO: DISCUSSION

### **SCENARIO A: NON-PREGNANT WOMAN WHO NEEDS ANTIRETROVIRAL THERAPY FOR HER OWN HEALTH**

Treatment recommendations generally follow those described in *Chapter IV: Recommendations for Antiretroviral Therapy for Adults and Adolescents with HIV Infection*. However, the design of the HAART regimen for women with the potential to become pregnant must involve a consideration of the possibility that the ARVs may be received early in the first trimester, before the recognition of pregnancy and during the primary period of foetal organ development. Efavirenz (EFV) should therefore be avoided in these women due to its potential for teratogenicity. Women who are receiving HAART and do not wish to become pregnant should have effective and appropriate

contraceptive methods available to them in order to reduce the likelihood of unintended pregnancy. In those women for whom effective contraception can be assured, EFV could be considered for inclusion in the HAART regimen, with careful counselling of the woman regarding the potential for congenital abnormalities should she become pregnant while receiving EFV. In women who plan to become pregnant, use of AZT in their HAART regimen should be considered given the proven efficacy of AZT in reducing the risk of MTCT.

### ***SCENARIO B: WOMAN WHO IS ALREADY RECEIVING ANTIRETROVIRAL THERAPY AT THE TIME SHE BECOMES PREGNANT***

#### ***Mother***

Generally, she should continue her HAART regimen. **If she is receiving EFV-containing HAART and becomes pregnant, and this is recognized during the first trimester, EFV should be discontinued and replaced by another drug.** In this scenario NVP could be substituted for EFV even if she has a CD4 count greater than 250 cells/mm<sup>3</sup> because symptomatic NVP-associated hepatotoxicity has been primarily observed in *antiretroviral-naïve* patients *initiating* NVP-based HAART. If NVP is substituted for EFV, close monitoring for hepatotoxicity is recommended. Alternatively, a protease inhibitor could be substituted for EFV. If the woman is already in the second or third trimester when pregnancy is recognized, EFV could be continued, given that the high risk exposure has already occurred; the exposure and risk should be discussed with the patient, and adequate contraception should be ensured for the postpartum period. Suspension of HAART during the first trimester to avoid potential teratogenicity is not recommended; some patients who discontinue HAART experience a dramatic rise in HIV viraemia, and in a pregnant woman, this may elevate the risk of *in utero* HIV transmission. The HAART regimen should be continued intrapartum and postpartum.

#### ***Infant***

Options include:

- SD NVP; or
- AZT for one week;\* or
- SD NVP plus AZT for one week.\*

***SCENARIO C: PREGNANT WOMAN NOT ON HAART WHO NOW REQUIRES HAART FOR HER OWN HEALTH*** (e.g. a woman who was diagnosed with HIV infection and AIDS at the same time as her pregnancy was diagnosed; or a woman who deteriorated clinically after she became pregnant and is now at a stage where HAART is indicated for her own health)

#### ***Mother***

- Treatment should generally be initiated as soon as possible. Delaying the initiation of therapy until after the first trimester minimises the risk of teratogenicity, but treatment should **not** be delayed if the mother is seriously ill. Unless specifically contra-indicated, the HAART regimen should consist of AZT plus 3TC plus NVP.
- AZT is favoured because of its proven efficacy in preventing MTCT, but if the mother cannot take this agent (e.g. severe anaemia or other toxicities), d4T or another NRTI can be substituted.
- NVP should be reasonably safe in this scenario. If the mother requires HAART for her own health, her CD4+ T cell count is very likely less than 250 cells/mm<sup>3</sup>, and her risk of severe hepatotoxicity is relatively low. If NVP is used for a woman with a known CD4 count greater than 250 cells/mm<sup>3</sup>, close monitoring for hepatotoxicity is recommended. If NVP is contra-indicated (e.g. history of past NVP toxicity or resistance to NVP strongly suspected), substitution of a PI or ritonavir-boosted PI (PI/r) is reasonable. EFV can be used

\* Extend infant's course of AZT to four weeks if the mother received less than four weeks of ART prior to delivery.

instead of NVP in the second or third trimester, but only if effective postpartum contraception can be guaranteed.

- The HAART regimen should be continued intrapartum and postpartum.

### ***Infant***

Options include:

- SD NVP; or
- AZT for one week;\* or
- SD NVP plus AZT for one week.\*

## ***SCENARIO D: PREGNANT WOMAN WHO DOES NOT REQUIRE HAART FOR HER OWN HEALTH***

Though she does not require ART for her own health, ART in some form is indicated to reduce the risk of MTCT. Several options exist, but two are generally favoured:

### ***Option 1: AZT Boosted by SD NVP***

This regimen is now favoured by the World Health Organisation (WHO) based on results of the PHPT-2 trial, because it was associated with an MTCT rate of just 2% in a non-breastfeeding population – a rate similar to transmission rates seen in mothers who receive HAART during pregnancy. Mothers who take this regimen are at risk for developing NVP resistance, which may or may not compromise their response to future NNRTI-based HAART regimens (*see Appendix C for details*). However, the WHO endorses this as a preferred PMTCT regimen for resource-constrained settings because it offers a potent, simple, and relatively inexpensive intervention, and the true clinical impact of prior SD NVP-exposure on the response to future NNRTI-based regimens remains controversial. If available, administration of AZT/3TC for 7 days postpartum after receipt of single dose NVP may reduce the risk of development of NVP resistance in the mother. Furthermore, the risk of NVP resistance is greatest among women with higher viral loads and lower CD4+ T cell counts who would likely require HAART for their own health; the risk of NVP resistance is lower in women who do not require antiretroviral therapy for their own health.

### ***Mother***

- AZT starting at twenty-eight weeks gestational age (or as soon as possible thereafter) plus AZT during labour plus SD NVP during labour.
- Consider giving seven day ‘tail’ of AZT/3TC following delivery to reduce risk of NVP resistance (*see Appendix C for details*).

### ***Infant***

- SD NVP (within seventy-two hours of birth) plus AZT for one week.\*

### ***Option 2: HAART***

Treating the mother with HAART is attractive because it offers effective reduction of the risk of MTCT (with HAART the risk is estimated to be 1% to 2% in women who do not breastfeed), while minimising the risk that she may develop resistance to any ARVs, thereby preserving her future options for HAART. Drawbacks chiefly include the expense and the risks of adverse effects both for the mother and for the infant. Additionally, the design of the HAART regimen for a relatively healthy pregnant woman is complicated by four factors: 1) the risk of severe NVP toxicity in pregnant women with CD4+ T cell counts of  $>250$  cells/mm<sup>3</sup> is high; 2) EFV should not be used in the first trimester; 3) PI-based HAART may not be easily obtainable; and 4) data on the pharmacokinetics of PIs in pregnancy are limited [the greatest experience is with nelfinavir (NFV) (1,250mg twice daily) or saquinavir (SQV) with low-dose ritonavir (RTV)-boosting [e.g. 800mg SQV/100mg RTV twice daily]].

\* Extend infant’s course of AZT to four weeks if the mother received less than four weeks of ART prior to delivery.

## ***Mother***

- Unless specifically contra-indicated, the HAART regimen should consist of AZT plus 3TC plus (PI or NVP).
- AZT is favoured due to its proven efficacy in preventing MTCT, but if the mother cannot take this agent (e.g. severe anaemia or other toxicities), d4T or another NRTI can be substituted.
- The risk of severe NVP toxicity in pregnant women with CD4+ T cell counts of >250 cells/mm<sup>3</sup> is high; hence a PI-based regimen is preferred for these women.
- If NVP is used, the woman should have close monitoring for liver toxicity during the first 12 weeks of therapy.
- The HAART regimen should be continued intrapartum.
- The HAART regimen should be discontinued after delivery if the mother does not require continued therapy for her own health. If the HAART regimen contained NVP and is discontinued after delivery, consider giving seven day 'tail' of AZT/3TC following delivery to reduce risk of NVP resistance (*see Appendix C for details*).

## ***Infant***

### Options include:

- SD NVP; or
- AZT for one week;\* or
- SD NVP plus AZT for one week.\*

***Other Options*** (*these represent valid options that have also been demonstrated to significantly reduce the risk of HIV transmission to the infant*)

***1. AZT Monotherapy:*** The PACTG 076 protocol of oral AZT started in the second trimester, intravenous (IV) AZT during labour, and six weeks of AZT for the infant following delivery was associated with a 66% reduction in the rate of HIV transmission in a non-breastfeeding population. Simpler AZT regimens (e.g. oral AZT prepartum, oral AZT in labour, and one to six weeks of AZT for the infant following delivery) have been associated with a roughly 50% reduction in the rate of HIV transmission.

***2. SD NVP.*** SD NVP administered to the mother during labour and another dose administered to the infant following delivery has been associated with an approximately 42% reduction in the rate of HIV transmission, even in breastfeeding women. The risk of NVP resistance is greatest among women with higher viral loads and lower CD4+ T cell counts; that is, women who would likely require HAART for their own health. Thus, the risk of development of NVP resistance would be less among women who do not require HAART for their own health. Nevertheless, one may consider giving a seven day 'tail' of AZT/3TC following delivery to reduce risk of NVP resistance (*see Appendix C for details*).

***3. AZT plus 3TC Dual Therapy.*** The PETRA trial, conducted among a population of breastfeeding women in South Africa, found that AZT/3TC administered antepartum, orally intrapartum, and postpartum to the infant reduced the rate of transmission to approximately 6% at six weeks postpartum. The potential for developing resistance to 3TC remains a concern with this regimen. Additionally, the efficacy of this regimen was significantly diminished at age eighteen months with breastfeeding.

***4. AZT plus 3TC Boosted by SD NVP.*** This regimen, combined with SD NVP and one week of AZT for the infant following delivery, was associated with an HIV transmission rate of approximately 5% in a mixed breast- and bottle-feeding population in Côte d'Ivoire. This regimen may be inadvisable given that it does not appear to offer more efficacy than the AZT monotherapy boosted by SD NVP regimen described above, yet could in theory promote the development of resistance to 3TC in the mother's strain of HIV.

\*Extend infant's course of AZT to four weeks if the mother received less than four weeks of ART prior to delivery.

### ***SCENARIO E: HIV-INFECTED WOMAN WITHOUT PRENATAL CARE WHO PRESENTS IN LABOUR***

Because much of the transmission of HIV is thought to occur around the time of delivery, intervention at this stage with ART can still substantially reduce the risk of the infant becoming infected. Three options exist.

#### ***Option 1: SD NVP + AZT immediately***

##### ***Mother***

- AZT and SD NVP, administered immediately

##### ***Infant***

- SD NVP plus AZT for four weeks.

Two doses of NVP are recommended for the infant (one at birth and the second at seventy-two hours) if the mother delivered before or within two hours of receiving the intrapartum NVP dose.

For women who received a single dose of NVP in false labour, a repeat NVP dose during established labour should *not* be given as the risk of NVP resistance is higher following two NVP doses. In such instances, the infant should receive NVP as soon as possible after birth (plus four weeks of AZT).

If available, consider giving a seven day ‘tail’ of AZT/3TC to the mother following delivery to reduce risk of NVP resistance (*see Appendix C for details*).

#### ***Option 2: PETRA Regimen: AZT/3TC dual therapy***

In the PETRA trial, conducted among a population of breastfeeding women in sub-Saharan Africa, this regimen was associated with an HIV transmission rate of 8.9% at six to eight weeks postpartum, significantly less than the transmission rate of 15.3% seen in the placebo arm. However, the efficacy of this regimen was diminished in breastfeeding women, and was no longer statistically significant at age eighteen months.

##### ***Mother***

- AZT/3TC dual therapy in labour (plus AZT/3TC for one week postpartum if breastfeeding).

##### ***Infant***

- AZT/3TC dual therapy for one week.

#### ***Option 3: HIVNET 012 Regimen: SD NVP***

##### ***Mother***

- SD NVP in labour.

##### ***Infant***

- SD NVP at forty-eight to seventy-two hours postpartum.

Two doses of NVP are recommended for the infant (one at birth and the second at seventy-two hours) if the mother delivered before or within two hours of receiving the intrapartum NVP dose.

For women who received a single dose of NVP in false labour, a repeat NVP dose during established labour should *not* be given as the risk of NVP resistance is higher following two NVP doses. In such instances, the infant should receive NVP as soon as possible after birth plus one week of AZT, as per recommendation for Scenario G.

If available, consider giving a seven day ‘tail’ of AZT/3TC to the mother following delivery to reduce risk of NVP resistance (*see Appendix C for details*).

### ***SCENARIO F: WOMAN OF UNKNOWN HIV STATUS WHO PRESENTS IN LABOUR***

If available, a rapid HIV serologic (antibody) test should be administered as soon as feasible. If the rapid test result is positive for HIV infection and she is still in labour, she should be managed as in scenario E. If the test result becomes available only after she has delivered – either because she delivered before the test was administered, or rapid testing was unavailable and therefore standard serologic testing was used – then she should be managed as in scenario G, below.

***SCENARIO G: INFANTS BORN TO WOMEN WHO RECEIVED NO ANTIRETROVIRAL THERAPY FOR PMTCT EITHER PREPARTUM OR DURING LABOUR***

AZT plus SD NVP administered to the infant is more effective than NVP alone in this setting. Because in this situation, no maternal antenatal and intrapartum therapy is received, and clinical studies suggest that longer infant prophylaxis may be important if maternal prophylaxis is very short, 4 weeks of infant AZT are recommended rather than 1 week.

If the infant does not present for medical care until more than two days following the delivery (as might happen if the birth occurred outside of a medical facility), the efficacy of this intervention is doubtful.

***Infant***

- SD NVP at birth (or as soon as possible following birth) plus four weeks of AZT.

**GENERAL RECOMMENDATIONS FOR MANAGEMENT OF THE HIV-INFECTED MOTHER DURING LABOUR AND DELIVERY**

During labour, universal precautions should be followed. Gowns, gloves, boots, and protective eyewear should be worn during the delivery of all patients. Additional strategies to reduce the risk of MTCT as well as the risk of HIV exposure to personnel assisting with the delivery include:

- Avoid unnecessary invasive procedures
- Avoid episiotomy unless otherwise indicated
- Avoid artificial rupturing of the membranes
- Avoid prolonged rupture of membranes, as rupture of membranes for more than four hours is associated with an increased risk of HIV transmission to the infant
- Avoid the use of straight suture needles if possible, to reduce the risk of needle stick injury
- Clamp and cut the umbilical cord immediately after delivery, and, if possible, avoid the use of a scalpel to cut the umbilical cord
- Exercise special care in handling the placenta
- Handle the infant with gloves until bathing, and bathe the infant as soon as possible with soap and water
- Clean the infant's eyes with sterile swabs
- Perform routine post-delivery care, including the weighing and measuring of the infant
- Ensure that the infant receives antiretroviral prophylaxis as outlined above
- Ensure the examination of the infant by a paediatrician as soon as possible.

## **RECOMMENDATIONS REGARDING BREASTFEEDING AND POSTPARTUM MANAGEMENT OF THE MOTHER**

Breastfeeding women with indications for HAART for their own health should receive and continue HAART during and after lactation. Thus, if the mother was already on HAART at the time she became pregnant, or if she initiated HAART during pregnancy for her own health needs, then HAART should be continued.

If she initiated HAART during pregnancy solely for the purposes of PMTCT, her need for continued HAART following delivery should be carefully assessed and discontinuation of HAART should be considered if she does not require therapy for her own health. If an antiretroviral PMTCT regimen was administered during her pregnancy consisting of just one or two ARVs, these agents should be discontinued after delivery, as the risk of development of resistance is higher with use of non-suppressive mono- or dual-therapy regimens. If single-dose NVP has been given alone or in combination with AZT, administering a one week 'tail' of AZT+3TC to the mother after delivery to reduce this risk can be considered (*see Appendix C for details*).

The safety and efficacy of HAART administered during the postpartum period solely to reduce breastmilk HIV transmission is not known. Passage of antiretroviral drugs into breast milk in humans has been evaluated for only a few antiretroviral drugs (i.e., AZT, 3TC, nevirapine); the drugs can be found in milk but at varying levels (AZT and 3TC appear in higher levels in milk than in plasma, while nevirapine is present at lower levels than in plasma). If a drug is found in low levels in the breast compartment, it could promote the development of drug resistance in virus in that compartment. The toxicity of chronic antiretroviral exposure of the infant via breast milk is unknown. Finally, while HAART has been found to decrease HIV RNA levels in milk, it does not appear to decrease cell-associated virus. For women who require HAART for treatment of HIV infection, the benefit to their own health of continuing HAART during lactation outweighs these potential risks. However, in women who do not require HAART for their own health, use of HAART solely to prevent breastmilk transmission needs to include considerations of potential harm and lack of proven efficacy. Several studies are ongoing to address the efficacy and safety of this approach in prevention of postnatal MTCT.

Where feasible and acceptable alternatives exist, efforts should be made to discourage HIV-infected mothers from breastfeeding in order to interrupt this potential route of HIV transmission to the infant. However, for many women in resource-limited countries, breastmilk alternatives are not acceptable, feasible, affordable, sustainable, or safe. If an infant is breastfed, exclusive breastfeeding is recommended, with weaning as soon as it is safe and feasible for the infant to do so (e.g. at age six months). With early weaning, it is critical to provide the mother with instructions as to how to meet the nutritional needs of the infant (including food supplementation, if needed and available) and to avoid provision of unsafe fluids (e.g., contaminated water). Exclusive breastfeeding means giving the infant *only* breastmilk and no water, other liquids, or solid foods except prescribed medicines. While the use of expressed and heat-treated breastmilk has been suggested, data are limited on the efficacy of heat treatment in reducing HIV in breastmilk as well as on the effect of such heat treatment on constituents of breastmilk (including immune components) that are important for the infant's health. Therefore, the use of heat-treated breastmilk cannot be generally recommended at this time, although further research on this approach is warranted.

## **CONTINUITY OF CARE FOR THE HIV-INFECTED MOTHER AND HER FAMILY**

Many women are first diagnosed with HIV infection through routine prenatal screening. Appropriate referral and follow-up care for the mother, her infant, and other members of the family who may be HIV-infected must be ensured. Avenues of communication may need to be strengthened between adult, paediatric, and obstetrical programs in order to facilitate continued care and treatment of the HIV-infected mother and her family.

## APPENDIX A: DOSING OF ARVs IN PMTCT REGIMENS

Recommendations regarding the dosing of ARVs in PMTCT regimens are complicated by 1) the fact that a variety of dosing schedules have been used in clinical trials; and 2) head-to-head comparative data are lacking to establish which dosing schedule is most effective. Hence, where different dosing options exist, it is reasonable to use clinical judgment to decide which option would be the most effective for a given patient and to consider factors such as cost, convenience, and regional availability of the relevant formulations.

### RECOMMENDED ARV DOSING OPTIONS (*see text for a discussion of clinical scenarios*)

#### ***Maternal Prepartum ARV Dosing***

ARVs are dosed in the same manner in pregnancy as they are for non-pregnant women, with the following caveats:

- Though the PACTG 076 trial involved maternal AZT dosing of 100mg five times daily, the generally accepted dosing of AZT in pregnancy (before onset of labour) is 300mg twice daily (as it is for non-pregnant women).
- SQV should be administered with low-dose RTV-boosting (either SQV-SGC, 800mg + RTV, 100mg [each agent twice daily] or SQV-SGC, 1,000mg + RTV, 100mg [each agent twice daily]).
- NFV dosed at 1,250mg b.i.d. results in adequate drug levels in pregnant women and is generally well tolerated at this dose. NFV dosing at 750mg t.i.d results in variable and generally low levels in pregnant women. RTV-boosting is not recommended with NFV.
- Limited data exist on the use of other PIs in pregnancy. IDV by itself results in low plasma levels in pregnant women, hence RTV-boosting is indicated, but clinical trial data in pregnancy are lacking to define the optimal dose.

#### ***Maternal ARV Dosing in Labour***

- a. AZT: either administer 300mg orally every three hours, or administer a 600mg oral loading dose at the onset of labour, followed by 300mg orally every three hours.
- b. NVP: 200mg orally given once at the onset of labour.
- c. 3TC: 150mg orally twice daily.
- d. HAART: continue prepartum regimen through labour.

#### ***ARV Dosing for the Infant Following Delivery***

- a. AZT: 2mg/kg orally four times daily OR 4mg/kg orally twice daily.\*
- b. NVP: 2mg/kg orally given once. Generally, this dose is administered at forty-eight to seventy-two hours, with two caveats:
  - if the infant will be leaving the hospital prior to forty-eight to seventy-two hours, the dose of NVP can be administered as early as twenty-four hours;
  - if the mother did NOT receive her intrapartum dose of NVP, or received it less than two hours prior to delivery, the dose of NVP should be administered to the infant as soon as possible after birth. Some clinicians would recommend repeating the infant dose (2mg/kg) at forty-eight to seventy-two hours as well in this scenario.
- c. 3TC: 2mg/kg orally twice daily.

\* There have been no comparative studies of these alternative regimens. The 2mg/kg four times a day regimen was used in PACTG 076 and in the Thailand PHPT-1 and PHPT-2 studies, whereas the 4mg/kg twice-daily regimen has been used in most PMTCT studies in Africa. The twice-daily regimen offers the potential benefit of increased adherence since it is given less frequently, although the four times a day regimen is used in more developed country settings.

## APPENDIX B: EFFICACY OF PMTCT INTERVENTIONS - SUMMARY OF THE EVIDENCE

Table 2 summarises in tabular form the clinical trials that have established the efficacy of ART in reducing the risk of MTCT. Data from these studies suggest that several options exist for the pregnant HIV-infected mother.

Clinical trials have been performed in both breastfeeding and non-breastfeeding populations. The risk of breast milk transmission is higher in women with symptomatic HIV disease or those who become newly infected with HIV while breastfeeding, and may vary by pattern (exclusive versus mixed) and duration of breastfeeding. Some data suggest the risk of breast milk transmission may be highest during the first month of life, but the risk of transmission continues for the duration of breastfeeding.

It is recognised that avoidance of all breastfeeding is the most reliable way to prevent postnatal transmission of HIV. Therefore, when replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-infected women is recommended. In all other settings, exclusive breastfeeding is recommended during the first months of life, because observational data from several studies in South Africa, Zimbabwe, and Cote d'Ivoire suggest that exclusive breastfeeding is associated with a lower risk of HIV transmission than mixed feeding. Additionally, the full protective effect of breastmilk against other pathogens (such as diarrhoeal or respiratory pathogens) as well as infant mortality is greatest with exclusive breastfeeding, and less with mixed feeding.

The efficacy and safety of maternal or infant ART in preventing postnatal breast milk HIV transmission is not yet known. Several international clinical trials are evaluating a variety of approaches to preventing breast milk transmission, including administration of one or more ARVs to the infant and/or HAART to the mother during the breastfeeding period. Approaches have included the administration of ARVs (NVP, 3TC, or AZT) to the infant for six weeks to six months while breastfeeding, or administration of HAART to the mother during lactation; however, the efficacy and safety of such approaches have not yet been defined and therefore they cannot yet be recommended.

**TABLE 2: SUMMARY OF SELECTED CLINICAL TRIALS OF PROPHYLACTIC ARV REGIMENS FOR PMTCT\***

Study (location)	Drugs	Antenatal/ Intrapartum	Postpartum	Median Maternal CD4+ T Cell Count by Arm at Enrollment	Mode of Infant Feeding	Vertical Transmission Rate (VTR) and Efficacy
PACTG 076/ANRS 024 Trial USA; France	ZDV vs. placebo	Long (from 14 weeks), IV intrapartum	Long (6 weeks) (infant only)	538, 560	Formula	VTR 7.6% in intervention arm vs. 22.6% in placebo arm at 18 months (68% efficacy)
Bangkok CDC Short-Course ZDV Trial Thailand	ZDV vs. placebo	Short (from 36 weeks), oral intrapartum	None	411, 427	Formula	VTR 9.4% in intervention arm vs. 18.9% in placebo at 6 months (50.1% efficacy)
Thai Perinatal HIV Prevention Trial Thailand	ZDV different regimens, no placebo	Long (from 28 weeks), short (from 36 weeks)	Long (for 6 weeks), short (for 3 days) (infant only)	350, 380	Formula	Short-short arm was stopped (VTR 11%). VTR 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in the short-long arm at 6 months

\* Adapted from: World Health Organization. Antiretroviral drugs for treating pregnant women and prevention HIV infection in infants: guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva, 2004.

Study (location)	Drugs	Antenatal/ Intrapartum	Postpartum	Median Maternal CD4+ T Cell Count by Arm at Enrollment	Mode of Infant Feeding	Vertical Transmission Rate (VTR) and Efficacy
						(statistical equivalence) <i>In utero</i> transmission significantly higher with short compared to long maternal therapy regimens (5.1% vs. 1.6%)
Côte d'Ivoire CDC Short-Course ZDV Trial Côte d'Ivoire	ZDV vs. placebo	Short (from 36 weeks)	None	528, 548	Breast	VTR 15.7% in intervention arm vs. 24.9% in placebo at 3 months (37% efficacy)
DITRAME/ANRS 049a Trial Côte d'Ivoire; Burkina Faso	ZDV vs. placebo	Short (from 36 weeks)	Short (1 week) (mother only)	535, 568	Breast	VTR 18.0% in ZDV arm, 27.5% in placebo at 6 months (38% efficacy); 21.5% vs. 30.6% (30% efficacy) at 15 months; 22.5% vs. 30.2% (26% efficacy) in pooled analysis with other Côte d'Ivoire trial at 24 months
PETRA Trial South Africa; Tanzania; and Uganda	ZDV + 3TC in 3 regimens vs. placebo	Short (from 36 weeks)	Short (7 days) (mother and infant)	435, 475	Breast	VTR 5.7% at 6-8 weeks for antenatal/intrapartum/neonatal ZDV + 3TC, 8.9% for intrapartum/neonatal ZDV + 3TC, 14.2% for intrapartum ZDV + 3TC only, and 15.3% for placebo (efficacy compared to placebo, 63%, 42%, and 0%, respectively)  VTR 14.9% at 18 months for antenatal/intrapartum/neonatal ZDV + 3TC, 18.1% for intrapartum/neonatal ZDV + 3TC, 20.0% for intrapartum ZDV + 3TC only and 22.2% for placebo (efficacy compared to placebo, 34%, 18%, and 0%, respectively)
French ZDV + 3TC/ANRS 075 Trial France	Open label, non-randomised ZDV + 3TC	ZDV (from 14 weeks) with 3TC added at 32 weeks	3TC and ZDV for 6 weeks (infant only)	426	Formula	VTR 1.6%; 5x lower than in historical controls receiving ZDV only
Thai ZDV + 3TC Trial Thailand	Open label, non-randomised ZDV + 3TC	Short (from 34 weeks)	Long (ZDV, 4 weeks) (infant only)	274	Formula	VTR 2.8% at 18 months
PACTG 316 Trial (USA; Europe;	NVP vs. placebo in women	Non-study ART antenatal.	SD 2mg/kg within 72 hours of	423, 441	Formula	77% women received combination ARV during pregnancy

Study (location)	Drugs	Antenatal/ Intrapartum	Postpartum	Median Maternal CD4+ T Cell Count by Arm at Enrollment	Mode of Infant Feeding	Vertical Transmission Rate (VTR) and Efficacy
Brazil; Bahamas)	already receiving ZDV or ZDV plus other ART	Intrapartum: SD NVP 200mg plus ZDV continuous infusion IV	birth plus non-study ART including 6 weeks ZDV (infant only)			Trial stopped early due to very low VTR in both arms VTR 1.4% in intervention arm vs. 1.6% in placebo arm
HIVNET 012 Trial Uganda	NVP vs. ZDV	No antenatal ART  Intrapartum: SD NVP 200mg vs. oral ZDV	SD NVP 2mg/kg within 72 hours of birth vs. short ZDV (7 days) (infant only)	426, 461	Breast	Placebo arm was stopped VTR 13.1% in NVP arm vs. 25.1% in ZDV arm (47% efficacy) at 14-16 weeks VTR 15.7% in NVP arm vs. 25.8% in ZDV arm (41% efficacy) at 18 months
SAINT Trial South Africa	NVP vs. ZDV + 3TC	No antenatal ART  Intrapartum: SD NVP 200mg vs. ZDV + 3TC	SD NVP within 48 hours of birth (infant only) vs. short ZDV + 3TC (7 days) (mother and infant)	384, 404	Breast (42%) and formula	VTR 12.3% in NVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (not significantly different)
DITRAME Plus/ANRS 1201.0 Trial Abidjan, Côte d'Ivoire	Open label, ZDV boosted by SD NVP	ZDV from 36 weeks, NVP one dose at onset of labour	SD NVP, plus one week ZDV (infant only)	370	Breast (50%) and formula	VTR 6.4% at 6 weeks
DITRAME Plus/ANRS 1201.1 Trial Abidjan, Côte d'Ivoire	Open label, ZDV + 3TC boosted by SD NVP	ZDV + 3TC from 32 weeks (stopped at day 3 postpartum), SD NVP at onset of labour	SD NVP, plus one week ZDV (infant only)	439	Breast and formula	VTR 4.6% at 6 weeks
Thai Perinatal HIV Prevention Trial-2 Thailand	ZDV alone vs. ZDV plus mother/infant NVP vs. ZDV plus mother NVP	ZDV from 28 weeks and intrapartum  Intrapartum: ZDV alone or plus SD	One week ZDV with or without SD NVP (infant only)		Formula	ZDV alone arm was stopped due to higher transmission rate than maternal/infant NVP arm (VTR 6.3% vs. 1.1%)  Final result comparing two NVP arms: VTR not significantly

Study (location)	Drugs	Antenatal/ Intrapartum	Postpartum	Median Maternal CD4+ T Cell Count by Arm at Enrollment	Mode of Infant Feeding	Vertical Transmission Rate (VTR) and Efficacy
		NVP at onset of labour				different when infant received vs. did not receive SD NVP (2.0% vs. 2.8%).
SIMBA Trial Rwanda; Uganda	NVP vs. 3TC postnatally in neonates exposed antenatally and 1 week postpartum to ZDV + ddi	ZDV + ddi from 36 weeks and given intrapartum	ZDV + ddi for 1 week (mother only), SD NVP then b.i.d vs. 3TC b.i.d while breastfeeding (infant only)	423, 432	Breast (median duration 3.4 months, inter-quartile range: 2.9–5.1 months)	VTR 7.8% at 6 months (no difference between the two arms). Transmission rate between 4 days and 6 months of age: 2.4% (1.0% between 1 and 6 months)
NVAZ Trial ( <b>late presenters–no maternal SD NVP</b> ) Malawi	Neonatal NVP vs. NVP + ZDV	None (latecomers)	SD NVP right after birth; ZDV b.i.d for 1 week (infant only)	Not reported	Breast	Overall VTR at 6-8 weeks 15.3% in NVP + ZDV arm and 20.9% with NVP only. VTR at 6-8 weeks in infants who were negative at birth 7.7% and 12.1%, respectively (36% efficacy)
NVAZ Trial (early presenters–mothers got SD NVP) Malawi (JAMA)	Neonatal NVP vs. NVP + ZDV	SD NVP intrapartum	SD NVP right after birth; ZDV b.i.d for 1 week (infant only)	Not reported	Breast	Overall VTR at 6-8 weeks 16.3% in NVP + ZDV arm and 14.1% with NVP only. VTR at 6-8 weeks in infants who were negative at birth 6.9% and 6.5% respectively (no efficacy)

## **APPENDIX C: MANAGING THE RISKS OF RESISTANCE ASSOCIATED WITH PMTCT REGIMENS**

Several studies have confirmed the efficacy of short-term ART involving only one or two ARVs in significantly reducing the risk of vertical HIV transmission. The relative simplicity and low cost of these PMTCT strategies make them attractive options in resource-limited settings. However, administration of ART that does not fully suppress HIV replication promotes the development of drug resistance. Therefore, the use of just one or two ARVs in pregnancy can induce ARV resistance that could compromise the efficacy of future HAART regimens for the mother (as well as for the infant, should the infant become infected despite the PMTCT intervention). Drugs that lose efficacy following the development of a single resistance mutation, such as 3TC or NVP, are especially vulnerable to this complication. It is not clear at this time just how serious a problem this poses, making it difficult to establish firm recommendations. However, a brief review of the relevant data is warranted.

### **Resistance to AZT**

Resistance to AZT typically develops only after several months of partially-suppressive ART. Clinical data document a low prevalence of AZT resistance following short-course AZT regimens, hence it is not likely that short-term administration of this agent for PMTCT will compromise the efficacy of this agent in future HAART regimens for the mother.

### **RESISTANCE TO 3TC**

Resistance to 3TC can develop rapidly even when combined with AZT, because a single mutation in the HIV genome can result in high-level resistance to this agent. The ANRS 075 study, a cohort study in France involving the use of AZT with 3TC added after thirty-two weeks gestation, reported an overall resistance rate of 39% to 3TC six weeks following delivery, although the risk of developing resistance depended heavily on the length of exposure to the regimen. No 3TC resistance was reported with the use of this regimen for less than one month, whereas one to two months of prophylaxis was associated with a 20% risk of 3TC resistance, and over two months of prophylaxis was associated with a 50% risk of 3TC resistance. However, in the PETRA trial, 12% of women who received a regimen of oral AZT plus 3TC (starting at thirty-six weeks antepartum and continued intrapartum and postpartum for one week) developed resistance to 3TC.

### **RESISTANCE TO NVP**

Low levels of HIV (approximately 1 in 1,000 viral particles) with mutations associated with NVP resistance are present in treatment-naïve individuals. Following administration of Single-Dose Nevirapine (SD NVP), there is a rapid selection of resistant virus due to the long half-life of the drug: detectable NVP levels can persist for three weeks or longer following a single dose. For example, the HIVNET 012 trial involved SD NVP administered to the mother during labour and another dose to the infant after delivery. 25% of NVP-exposed women had evidence of NVP resistance at six weeks postpartum, as did 46% of the infants who became infected with HIV. Unfortunately, cross-resistance with other agents in the NNRTI class, such as EFV, is very common.

The frequency with which resistance is detected appears to depend upon several variables, including the subtype (clade) of HIV-1 involved; the mother's clinical, immune and virologic status at the time she receives SD NVP; the time at which resistance testing is performed after delivery; and the sensitivity of the resistance assay used. Studies involving clade B virus, the predominant clade of HIV-1 in the Caribbean, have documented detectable NVP resistance following delivery in 15 to 40% of women who received SD NVP (with or without other ARVs) during labour.

The degree to which viral resistance induced by SD NVP is associated with diminished clinical response to subsequent NNRTI-based highly active antiretroviral therapy (HAART) in women has not been clearly established. A preliminary assessment of response to NNRTI-based therapy in women who required initiation of HAART at some time after delivery was performed as a follow-up study of the PHPT-2 trial. The PHPT-2 trial included both AZT and NVP in its PMTCT regimen. AZT was administered to the mother starting at twenty-eight weeks gestation

and orally during labour, and one week of AZT was given to the infant following delivery (four to six weeks if the mother received less than four weeks of AZT). SD NVP was also administered to the mother during labour and to the infant following delivery. NVP resistance was detected ten to fourteen days after SD NVP exposure in 20% of ninety randomly selected trial participants, and was more likely to develop in women with higher HIV viral loads and lower CD4+ T cell counts.

Women who required HAART after completion of the study received a NVP-based HAART regimen (primarily d4T/3TC/NVP). A preliminary analysis compared the virologic outcome after three and six months of NVP-based HAART among women who had received SD NVP as part of their PMTCT regimen versus a small group of women who did not receive SD NVP. No significant differences in clinical response (as demonstrated by weight gain following initiation of therapy), immunologic response at three and six months following initiation of therapy (both groups with an increase of about 100 cells at six months), or in virologic response to <400 copies/mL were seen between women who received or did not receive SD NVP. However, women who received SD NVP and who had genotypic resistance to NVP detected at two weeks postpartum were less likely to achieve an HIV viral load <50 copies/mL after six months of therapy than women who had not received SD NVP (38% versus 68%, respectively). The rate of virologic suppression to <50 copies/mL in women who had received SD NVP but did not have virus with detectable genotypic NVP resistance was intermediate between the two groups (52%).

#### ***Response to NVP-based HAART after SD NVP: impact of timing of HAART initiation***

Follow-up analysis of women who had developed NVP resistance in the HIVNET 012 trial found that resistance was no longer detectable by conventional resistance assays one year following delivery (conventional assays require 15% to 20% or more of viral quasispecies to contain the mutation to be detectable). However, there has been concern that resistant strains of HIV may remain 'archived' in body compartments (e.g., resting T-cells) at levels undetectable by conventional resistance assays, even after the ARV that induced the resistance is withdrawn. The resistant strain may subsequently re-emerge under selective drug pressure when a HAART regimen containing that ARV is initiated at a later date, potentially resulting in treatment failure.

A recent study from South Africa using highly sensitive resistance assays found that although NVP resistance mutations were present in a high proportion of women who received SD NVP at 6 weeks postpartum, the mutations rapidly faded to low levels over time and resistant variants were detected less frequently in cellular DNA, with persistence in this compartment by 12 months post-SD NVP in only a small minority of women. These data are consistent with recent clinical trials results suggesting that response to NVP-based HAART might not be compromised in women who initiate HAART more than six months after their exposure to SD NVP. In a preliminary report on a study from Botswana in which women received short course AZT with or without SD NVP, virologic response (defined as the likelihood of viral load suppression to less than 400 or less than 40 copies/mL) to subsequent NVP-based HAART varied by the time of initiation of HAART after SD NVP exposure. Women who initiated HAART less than 6 months following SD NVP exposure had a poorer virologic response than women without prior SD NVP exposure; however, women who initiated HAART more than 6 months following SD NVP exposure experienced a virologic response that was similar to the response seen in women without prior SD NVP exposure. Similarly, preliminary data from South Africa indicate that response to NVP-based HAART is similar in women who received SD NVP 18 months or more prior to starting HAART to those without SD NVP exposure (Coovadia, CROI 2006, Abs. 641).

Hence, it is difficult to draw definitive conclusions regarding the relevance of resistance incurred by antiretroviral PMTCT regimens that do not fully suppress HIV replication. It is clear that such regimens can and often do lead to the selection of HIV resistance mutations, but the clinical impact of this resistance on future therapeutic options for the mother awaits further clarification.

## POTENTIAL STRATEGIES TO REDUCE THE RISK OF NVP RESISTANCE ASSOCIATED WITH PMTCT REGIMENS

Firm data are lacking to strongly endorse or refute any of the following strategies; however, until further clinical data become available to clarify their relative advantages and disadvantages, the following options are presented for consideration. These strategies should be discussed by national and regional policymakers and, where appropriate, options reviewed with the patients themselves.

1. **Administer a “tail” of two NRTIs for a period of time following the administration of SD NVP.** If the mother begins taking two NRTIs (e.g., AZT and 3TC) immediately after the administration of SD NVP and continues taking the NRTIs for a defined period of time, during that time period the HIV in her serum will be exposed to three ARVs rather than just NVP, which should discourage the emergence of NVP resistance. Indeed, several small clinical trials of this strategy have documented some (but not complete) success in preventing the development of NVP resistance following SD NVP. However, the ideal length of administration of the 2 NRTI tail has not been determined, and may vary between different women because the half-life of NVP varies across individual patients. Administration of a tail that is too short risks promotion of NVP resistance, while administration of too long a tail may promote resistance to one or both of the NRTIs used in the tail. The studies that have shown decreased NVP resistance have used a 3 to 7 days tail of AZT/3TC. In the TOPS study, for example, the rate of NVP resistance was 60% without the tail versus 12% with a 4 day tail of AZT/3TC versus 10% with a 7 day tail of AZT/3TC. The optimal duration of the tail and the optimal components are not known; studies are ongoing to define this. Because there are no data on the safety and efficacy of a prolonged tail (more than 1 week) after SD NVP, if a tail is used a duration of 7 days might be chosen based on the available studies.
2. **Administer short-course AZT boosted by SD NVP (with infant SD NVP given at birth), but omit the maternal dose of SD NVP.** Omitting the maternal dose of SD NVP avoids any risk of inducing maternal NVP resistance. The obvious drawback of this approach is that it might compromise the effectiveness of this intervention in reducing the risk of HIV transmission to the infant. However, results from the Mashi trial, conducted in a mixed breastfeeding and non-breastfeeding population in Botswana, found that omission of the maternal dose of SD NVP did not result in an increased risk of HIV transmission to the infant, so long as the rest of the regimen (AZT to mother and infant, plus SD NVP to infant at birth) was administered appropriately. Validation from other clinical trials is needed before this approach can be universally endorsed, but clinicians may nevertheless want to consider this option. If this option is chosen, AZT should be initiated at 34 weeks gestation, as in the Mashi trial, and administered to the infant for 4 weeks postpartum. *Omission of the maternal SD NVP can be considered only if the maternal and infant AZT regimens are properly administered.*
3. **Administer HAART to all HIV-infected pregnant women for PMTCT, regardless of clinical status.** It is important to note that this strategy does not necessarily solve the problem. First, the choice of drug regimen is complicated because the risk of symptomatic NVP-related hepatic toxicity, which can be life-threatening, is markedly increased in women with CD4 counts greater than 250 cells/mm<sup>3</sup> at the time of therapy initiation. Thus, NVP-based HAART would not be an optimal choice for use in such women, and if prescribed the woman would need close monitoring for liver toxicity. Additionally, if NVP-based HAART is prescribed for a pregnant woman who does not herself have clinical indications for starting antiretroviral therapy, then HAART should be discontinued following delivery. When the HAART regimen is stopped, however, serum levels of the NRTIs (e.g., AZT and 3TC) in her HAART regimen will drop much more rapidly than that of NVP, resulting in the same problem of prolonged HIV exposure to just NVP. Indeed, NVP resistance has been documented in a cohort of pregnant women in Mozambique in whom this strategy was employed. If, however, a PI-based HAART regimen is prescribed instead, the risks of NVP toxicity and inducing NVP resistance are avoided altogether. If NVP-based HAART is used, administration of a 7 day “tail” of AZT/3TC following discontinuation of NVP at delivery to reduce the risk of NVP resistance can be considered.

4. **Use PMTCT regimens that do not contain NVP**, such as AZT monotherapy, AZT/3TC combination therapy, or PI-based HAART. Resistance to AZT requires prolonged duration of exposure, and multiple mutations must develop before resistance is observed; thus resistance to AZT following AZT single drug prophylaxis is much less frequent than that observed with NVP or 3TC, for which a single mutation induces resistance. However, AZT monotherapy for PMTCT is not as effective as AZT boosted by SD NVP. Prepartum/intrapartum/postpartum AZT/3TC combination therapy has similar efficacy to AZT plus SD NVP but is more complex, and risks the promotion of 3TC resistance (which was documented in six of 50 women [12%] who received AZT/3TC prepartum, intrapartum, and postpartum in the PETRA trial). The intrapartum/postpartum AZT/3TC regimen is less effective than AZT plus SD NVP, and antenatal treatment is recommended when possible to prevent in utero transmission as well as peripartum transmission. PI-based HAART, if administered appropriately, constitutes a very potent PMTCT regimen with very little risk of generating resistance, but is generally more expensive and less convenient than other PMTCT regimens. Additionally, appropriate dosing of many PI drugs in pregnancy needs to be defined: SQV boosted with low dose RTV will achieve adequate levels in pregnant women; NFV given twice daily may achieve adequate levels but there is significant variability of levels between women; and LPV/RTV may require an increased dosage in the third trimester due to low levels observed in the third trimester in one study.
5. **Reserve the use of SD NVP PMTCT regimens for women with relatively high CD4 counts and low HIV viral loads.** Studies of SD NVP for PMTCT suggest that the presence of a high HIV viral load and/or low CD4 count in the mother at the time of SD NVP administration elevates her risk of developing resistance to NVP. This underscores the importance of evaluating CD4 cell count in all HIV-infected pregnant women. Limiting the administration of SD NVP to women with relatively low HIV viral loads and high CD4 counts would likely reduce the overall risk of promoting NVP resistance and would also reduce the likelihood that women receiving SD NVP would be initiating HAART within six months of delivery (recent clinical trials suggest that the impact of SD NVP on a woman's subsequent response to HAART may be confined to women who initiate HAART within six months of their exposure to SD NVP). Certainly, all efforts should be made to start HIV-infected women who require therapy for their own health (as indicated by clinical symptoms, low CD4 count, and/or high HIV viral load) on HAART. These women are at highest risk of both disease progression and transmission of HIV to their infants, and HAART will significantly reduce the risk of each of these events. Additionally, such women are at greatest risk for development of NVP resistance following administration of SD NVP; if HAART is started instead and continued postpartum, this risk is avoided. Also, if available, administration of a 7 day "tail" of AZT/3TC following single-dose NVP can be considered to further reduce the risk of NVP resistance.

#### **IMPLICATIONS FOR WOMEN INITIATING HAART WHO RECEIVED SD NVP OR 3TC IN THE PAST:**

Based on current information, prior administration of SD NVP-containing prophylaxis for PMTCT should not preclude the use of these agents as part of a HAART regimen initiated for treatment of HIV disease in women. It may be prudent to consider prescribing protease inhibitor (PI)-based HAART for women with recent (within six months) exposure to SD NVP. However, if a PI-based HAART regimen is inconvenient or not readily available, an NNRTI-based regimen should be initiated. Similarly, women who received 3TC in the past as part of a non-HAART PMTCT regimen (e.g. AZT/3TC) are at some risk for having developed 3TC resistance, but this should not necessarily preclude the use of 3TC in subsequent HAART regimens.

#### **IMPLICATIONS FOR WOMEN WHO HAVE RECEIVED SD NVP IN THE PAST AND ARE NOW PREGNANT AGAIN:**

The potential for SD NVP to induce NVP resistance in the mother raises the possibility that SD NVP may not be as effective for a woman who has received SD NVP in the past. However, recent retrospective and prospective studies of repeat pregnancies in women who have received SD NVP in the past suggest that the efficacy of SD NVP for PMTCT is not reduced as a consequence of prior exposure to SD NVP. (Eure C et al, CROI 2006, Abs. 125; Martinson NC et al, CROI 2006, Abs. 722).

## **APPENDIX D: RISKS OF ANTIRETROVIRAL THERAPY IN PREGNANCY**

Fortunately, the risks associated with ART in pregnancy are generally far outweighed by the potential benefit in interrupting transmission of HIV to the infant and in potentially preserving the mother's health. However, certain risks should be considered, and the pregnancy should be carefully managed to minimise these risks.

### ***RISKS TO THE MOTHER'S HEALTH***

Certain toxicities related to ARVs may occur more frequently in pregnant women and deserve special consideration.

#### ***NVP Toxicity***

Toxicities commonly associated with NVP include liver and skin toxicity, which typically develop within the first eighteen weeks of therapy.

Signs and symptoms of liver toxicity include nausea, jaundice, abdominal pain, hepatic tenderness, hepatomegaly, fatigue, and malaise; elevated transaminases are typically seen on laboratory testing. Hepatic toxicity occurs more frequently in women than in men, and the degree of risk for hepatic toxicity varies with CD4+ T cell count; women with CD4+ T cell counts of greater than 250 cells/mm<sup>3</sup> have a significantly increased risk of symptomatic hepatic toxicity.

Skin toxicity is most commonly a mild, self-limited rash that does not warrant discontinuation of NVP. However, though rare, severe skin toxicity can occur, including potentially fatal Stevens-Johnson syndrome. The rash may also be more frequent in women with higher CD4+ T cell counts.

Although deaths due to hepatic failure and Stevens-Johnson syndrome have been reported in HIV-infected pregnant women receiving NVP as part of a combination ARV regimen, it is unknown if pregnancy increases the risk of hepatotoxicity or rash in women receiving NVP or other ARVs. Some preliminary data suggest that the risk of hepatic toxicity with NVP may be higher in pregnant than non-pregnant women. Patients with symptomatic hepatitis or who have asymptomatic but severe transaminase elevations and those with severe rashes should discontinue NVP and not receive NVP therapy in the future. Pregnant women who take NVP-containing combination ART warrant monitoring for signs and symptoms of liver or skin toxicity, especially in the first eighteen weeks of therapy. If resources permit, this monitoring should optimally include serum transaminases levels at baseline, every two weeks for the first month, monthly through four months, and every one to three months thereafter.

NVP toxicity has **not** been described in pregnant women who use only a single dose of the agent in labour to reduce the risk of vertical transmission to their infants.

#### ***NRTI-Induced Mitochondrial Toxicity***

NRTI-containing HAART regimens may induce mitochondrial toxicity via an interaction with DNA polymerase gamma, a key mitochondrial enzyme whose function is critical to normal cellular oxidative phosphorylation. This toxicity is thought to be responsible for several toxicities associated with HAART, including lactic acidosis, pancreatitis, steatohepatitis, cardiomyopathy, and possibly peripheral neuropathy. The risk of severe mitochondrial toxicity appears to be highest with the dideoxynucleosides d4T, didanosine (ddI), and zalcitabine (ddC). Several cases of fatal lactic acidosis have been documented in pregnant women on HAART whose regimens included both d4T and ddI; for this reason, the use of these two agents together in pregnant women is strongly discouraged.

The clinical presentation of NRTI-induced mitochondrial toxicity may mimic other potentially severe complications of pregnancy, such as acute steatohepatitis or the HELLP\* syndrome. It is not known if pregnant women on NRTI-containing HAART regimens are at an elevated risk for developing this potentially fatal complication as compared with non-pregnant women on similar HAART regimens. While screening lactate levels are not recommended, clinicians should consider the diagnosis of mitochondrial toxicity in pregnant women receiving NRTI drugs who develop compatible signs and symptoms such as fatigue, abdominal pain, nausea, malaise, respiratory distress, or evidence of hepatic dysfunction. In such cases, appropriate evaluations, such as serum lactate, serum bicarbonate

\*Haemolysis, elevated liver enzymes, low platelets

and anion gap, and serum transaminases should be performed, and ART should be suspended if clinical and laboratory manifestations of lactic acidosis syndrome occur. More information on lactic acidosis/hyperlactataemia can be found at the end of *Chapter IV: Recommendations for Antiretroviral Therapy for Adults and Adolescents with HIV Infection*.

### ***Other Potential Maternal Complications of ART***

While some studies have suggested that combination ART during pregnancy may increase the risk of preterm delivery or low birth weight infants, other studies have failed to detect such an association. PIs have been associated with insulin resistance in non-pregnant individuals, and pregnancy is itself a risk factor for hyperglycaemia; it is unknown if the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycaemia. Some data suggest that pregnant women receiving a protease inhibitor have a slightly higher risk of developing gestational hyperglycaemia or diabetes than HIV uninfected women or HIV-infected women receiving either no therapy or NRTI drugs only, although a recent study did not find an association of PI use with glucose intolerance in pregnant women (although HIV-infected pregnant women appear to have a higher risk than the general population). There is no clear evidence that pregnancy accelerates the course of HIV infection or increases the risk of virologic failure.

## ***RISKS TO THE INFANT'S HEALTH***

### ***Teratogenicity of ARVs***

Limited evidence exists regarding the potential teratogenicity and carcinogenicity of ARVs; the data available are summarised in *Appendix B*. Most agents are classified by the U.S. Food and Drug Administration (FDA) as Class B or C. EFV is now classified as Class D and is specifically contra-indicated in pregnancy, due to the occurrence of severe central nervous system (CNS) congenital abnormalities in three of twenty infants born to monkeys who received EFV during pregnancy, and four cases of neural tube defects in human newborns whose mothers were exposed to EFV during the first trimester of pregnancy, as identified in retrospective case reports in the Antiretroviral Pregnancy Registry.

The Antiretroviral Pregnancy Registry is an international registry that is designed to evaluate any major teratogenic effect of *in utero* ARV exposure. Information is obtained from the healthcare provider or from pregnant women receiving ARVs in an entirely voluntary and confidential manner, with follow-up for pregnancy outcomes.\* The Registry has accumulated a significant amount of follow-up data on infants exposed to ARVs *in utero*; fortunately, data collected to date fail to demonstrate an association between ART in general and an increased risk of birth defects. Furthermore, no increased risk of birth defects could be demonstrated in association with exposure to AZT, 3TC, d4T, NVP, or NFV--agents that have been most frequently included in maternal ARV regimens. However, the database is not extensive enough and the follow-up not long enough to rule out the possibility of an association between ARV exposure *in utero* and rare birth defects. Given that most MTCT occurs at or around the time of delivery, it is reasonable to defer maternal ART used solely for prevention of MTCT until after the first trimester of pregnancy, which is the maximal period of organogenesis. However, for pregnant women who are severely ill and require HAART for their own health, the benefit of early therapy clearly outweighs any potential foetal risks, and therapy should be initiated as soon as possible in these cases.

### ***Mitochondrial Toxicity***

Since some ARVs are associated with mitochondrial dysfunction in HIV-infected persons receiving chronic therapy, there have been concerns that *in utero* exposure to such drugs might result in mitochondrial dysfunction in exposed infants. The data on this are mixed. In a French cohort of approximately 2,600 uninfected infants with *in utero* exposure to ARVs, the incidence of mitochondrial dysfunction, predominantly consisting of neurologic symptoms and, in some cases, lactic acidosis, was 0.25%; there were two deaths, for a mortality rate of 0.07%. However, a review of data from more than 16,000 HIV-uninfected children with and without *in utero* ARV exposure from several U.S. databases identified no deaths similar to those reported from France, nor any cases with clinical findings

\*The international telephone number of the Antiretroviral Pregnancy Registry is (910) 256-0238; its website is <http://www.APRegistry.com>.

suggestive of mitochondrial dysfunction. Additionally, review of data from over 2,400 uninfected infants followed in the European Collaborative Study found no association of perinatal ARV exposure with any clinical findings suggestive of mitochondrial dysfunction. Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal ARV exposure. If such disorders occur, they appear to be rare and should be compared against the clear benefit of ARV prophylaxis in reducing transmission of a fatal infection by 50% or more. However, long-term follow-up is recommended for any child with *in utero* exposure to ARVs, and mitochondrial dysfunction should be considered in uninfected children with perinatal ARV exposure who present with severe, persistent clinical findings of unknown aetiology, particularly neurologic findings.

***Risk of Preterm Birth***

As reviewed above, evidence is mixed regarding a possible association between ART and preterm delivery. If an association does exist, the risk appears to be very small and outweighed by the potential benefits of ART.

**APPENDIX E: ANTIRETROVIRAL DRUG PHARMACOKINETIC AND TOXICITY DATA IN HUMAN PREGNANCY AND RECOMMENDATIONS FOR USE FOR TREATMENT OF PREGNANT WOMEN WITH HIV INFECTION #**

ARV DRUG	FDA PREGNANCY CLASS <sup>v</sup>	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
<i>NRTI/NRTIs</i>			See text for discussion of potential maternal and infant mitochondrial toxicity.	
<b>RECOMMENDED AGENTS</b>				
Zidovudine (AZT, ZDV)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination ARV regimens in pregnancy based on efficacy studies and extensive experience; should be included in treatment regimen unless significant toxicity or d4T use.
Lamivudine (3TC)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with 3TC in pregnancy in combination with AZT, 3TC plus AZT is the recommended dual NRTI backbone for treatment of pregnant women.
<b>ALTERNATE AGENTS</b>				
Didanosine (ddI)	B	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together.	Alternate NRTI for dual nucleoside backbone of combination regimens. ddI should be used with d4T only if no other alternatives are available.
Emtricitabine (FTC)	B	No studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine (d4T)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together.	Alternate NRTI for dual nucleoside backbone of combination regimens. d4T should be used with ddI only if no other alternatives are available.

ARV DRUG	FDA PREGNANCY CLASS <sup>v</sup>	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
				Do not use with AZT due to potential for antagonism.
Abacavir (ABC)	C	Phase I/II study in progress.	Hypersensitivity reactions occur in ~5-8% of non-pregnant persons, a much smaller percentage is fatal and usually associated with re-challenge; rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.
<b>INSUFFICIENT DATA TO RECOMMEND USE</b>				
Tenofovir (TDF)	B	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased foetal growth and reduction in foetal bone porosity within 2 months of starting maternal therapy. Clinical studies in humans (particularly children) show bone demineralisation with chronic use; clinical significance unknown.	Due to lack of data on use in human pregnancy and concern regarding potential foetal bone effects, TDF should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
<b>NOT RECOMMENDED</b>				
Zalcitabine (ddC)	C	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available.
<b>NNRTIs</b>				
<b>RECOMMENDED AGENTS</b>				
Nevirapine (NVP)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence human teratogenicity. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with	NVP should be initiated in pregnant women with CD4+ T cell counts of >250/mm <sup>3</sup> who do not require therapy for own health only if the benefit

ARV DRUG	FDA PREGNANCY CLASS <sup>v</sup>	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
			CD4+ T cell counts of >250/mm <sup>3</sup> when first initiating therapy; unclear if pregnancy increases risk.	clearly outweighs the risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts; if used, monitor closely for liver toxicity in first 18 weeks of therapy. Women who enter pregnancy on NVP regimens and are tolerating well may continue therapy, regardless of CD4+ T cell count.
<b>NOT RECOMMENDED</b>				
Efavirenz (EFV)	D	No studies in human pregnancy.	Significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving EFV during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; 4 case reports of neural tube defects in humans after first trimester exposure; relative risk unclear.	Use of EFV should be avoided in the first trimester, and women of childbearing potential must be counselled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of childbearing potential. Use after the second trimester of pregnancy can be considered if other alternatives not available and if adequate contraception can be assured postpartum.
Delavirdine (DLV)	C	No studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available.
<b>PIs</b>			Hyperglycaemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs; see	

ARV DRUG	FDA PREGNANCY CLASS <sup>v</sup>	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
			text.	
<b>RECOMMENDED AGENTS</b>				
Nelfinavir (NFV)	B	Adequate drug levels are achieved in pregnant women with NFV 1,250mg b.i.d.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant. NFV dosing at 750mg t.i.d produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, NFV-based regimens had a lower rate of viral response compared to LPV/r- or EFV-based regimens, but similar viral response compared to ATV- or NVP-based regimens.
Saquinavir (SQV)-soft gel capsule [SGC] (Fortovase®)/ritonavir	B	Adequate drug levels are achieved in pregnant women with SQV-SGC 800mg boosted with RTV 100mg b.i.d. Recommended adult dosing of SQV-SGC 1,000mg <i>plus</i> RTV 100mg may be used. No pharmacokinetic data on SQV-hard gel capsule [HGC]/ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.	Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women when SQV-SGC given alone at 1,200 mg t.i.d.	Given pharmacokinetic data and moderate experience with use in pregnancy, RTV-boosted SQV-SGC can be considered a preferred PI for combination regimens in pregnancy.
<b>ALTERNATE AGENTS</b>				
Indinavir (IDV)	C	Two studies involving 18 women receiving IDV t.i.d showed markedly lower serum drug levels during pregnancy compared to those postpartum, although HIV viral suppression was seen.	Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinaemia in the neonate, but minimal placental passage. Use of IDV during pregnancy without RTV-boosting not recommended.	Alternate PI to consider if unable to use NFV or SQV-SGC/r, but would need to give IDV as RTV-boosted regimen to achieve adequate levels during pregnancy. Optimal dosing for RTV-boosted IDV in pregnancy is not known.

ARV DRUG	FDA PREGNANCY CLASS <sup>v</sup>	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
Lopinavir/Ritonavir (LPV/r)	C	Phase I/II safety and pharmacokinetic study in progress using LPV 400mg and RTV 100mg b.i.d.	Limited experience in human pregnancy.	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result not observed, consider increasing dose in consultation with a specialist with expertise in HIV in pregnancy.
Ritonavir (RTV)	B	Phase I/II study in pregnancy showed lower serum drug levels during pregnancy compared to postpartum.	Minimal experience in human pregnancy.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose RTV “boost” to increase levels of second PI.
<b>INSUFFICIENT DATA TO RECOMMEND USE</b>				
Amprenavir (APV)	C	No studies in human pregnancy.	Oral solution contra-indicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolised during pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use of capsules during pregnancy. Oral solution contra-indicated.
Fosamprenavir (f-APV)	C	No studies in human pregnancy.	No experience in human pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.
Atazanavir (ATV)	B	No studies in human pregnancy.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinaemia in the neonate, although transplacental passage of other PI’s has been low.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.
Tipranavir	C	No studies in human pregnancy	No experience in human pregnancy	Data are insufficient regarding the safety and pharmacokinetics in pregnant to recommend

ARV DRUG	FDA PREGNANCY CLASS <sup>√</sup>	PHARMACOKINETICS IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE FOR TREATMENT OF HIV-INFECTED WOMEN DURING PREGNANCY
				use during pregnancy.
<b><i>Fusion Inhibitors</i></b>				
<b>INSUFFICIENT DATA TO RECOMMEND USE</b>				
Enfuvirtide	B	No studies in human pregnancy.	No experience in human pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.

# This table represents information abstracted from *Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy - February 24th, 2005*, a supplement to the *United States Public Health Service Task Force 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 - February 24th, 2005* (both documents available at <http://www.aidsinfo.nih.gov/guidelines>). The reader is encouraged to consult these documents for a more detailed discussion of the safety and toxicity of individual ARVs in pregnancy.

<sup>√</sup>FDA Pregnancy Categories:

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the foetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).

B: Animal reproduction studies fail to demonstrate a risk to the foetus and adequate and well-controlled studies of pregnant women have not been conducted.

C: Safety in human pregnancy has not been determined, animal studies are either positive for foetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the foetus.

D: Positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X: Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

\*Triple NRTI regimens including ABC have been less potent virologically compared to PI-based HAART regimens. These regimens should be used only when an NNRTI or PI-based HAART regimen cannot be used (e.g. due to significant drug interactions). A study evaluating use of AZT/3TC/ABC among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.