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## **10 Prevention of HIV transmission from HIV-infected mothers to their infants**

Optimizing clinical management and effective interventions  
towards eliminating new paediatric HIV infections

Clinical Protocol for the WHO European Region  
(2012 revision)

## KEYWORDS

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## Abbreviations and acronyms

|       |   |
|-------|---|
| 3TC   | lamivudine  |
| ACTG  | AIDS Clinical Trial Group                               |
| Ag    | antigen   |
| ABC   | abacavir  |
| ANC   | antenatal clinic  |
| AOR   | adjusted odds ratio                                     |
| APR   | antiretroviral pregnancy register                       |
| ART   | antiretroviral therapy                                  |
| ARV   | antiretroviral  |
| ATV   | atazanavir  |
| AUC   | area under the curve                                    |
| CD4   | cell differentiation marker 4                           |
| CNS   | central nervous system                                  |
| DNA   | deoxyribonucleic acid                                   |
| DOT   | directly observed therapy                               |
| EFV   | efavirenz   |
| FTC   | emtricitabine   |
| ELISA | enzyme linked immunosorbent assay                       |
| HBV   | hepatitis B virus                                       |
| HCV   | hepatitis C virus                                       |
| HLA   | human leucocyte antigen                                 |
| IRIS  | immune reconstitution inflammatory syndrome             |
| IV    | intravenous   |
| LPV   | lopinavir   |
| MDR   | multidrug resistance                                    |
| MTCT  | mother-to-child transmission                            |
| NAS   | neonatal abstinence syndrome                            |
| NVP   | nevirapine  |
| NNRTI | non-nucleoside analogue reverse transcriptase inhibitor |
| NRTI  | nucleoside analogue reverse transcriptase inhibitor     |
| OI    | opportunistic infection                                 |
| OR    | odds ratio  |
| OST   | opiate substitution therapy                             |
| PCP   | pneumocystis pneumonia                                  |
| PCR   | polymerase chain reaction                               |
| PI    | protease inhibitor                                      |
| PLCS  | pre-labour, pre-rupture of membranes caesarean section  |
| PMTCT | prevention of mother-to-child transmission              |
| PTD   | preterm delivery  |
| PP    | post-partum   |
| RCT   | randomized controlled trial                             |
| RNA   | ribonucleic acid  |
| SROM  | spontaneous rupture of membranes                        |
| STI   | sexually transmitted infection                          |
| SQV   | saquinavir  |
| T1    | first trimester   |
| T2    | second trimester  |
| T3    | third trimester   |
| TB    | tuberculosis  |
| TDF   | tenofovir   |
| TDM   | therapeutic drug monitoring                             |
| VL    | viral load  |
| XDR   | extreme drug resistance                                 |
| ZDV   | zidovudine  |

## Acknowledgements

This document is an update of the version of this clinical protocol released in 2007. It is one of 13 clinical protocols released by the WHO Regional Office for Europe as a part of the HIV/AIDS Treatment and Care Clinical Protocols of the WHO European Region.

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## Background

Since publication of the last version of this protocol for the European Region, in 2007, considerable progress has been made in prevention of HIV mother-to-child transmission. Where the recommended interventions have been available and utilized, transmission of HIV infection to infants has become a rare event. However, regional challenges remain, especially in prevention of HIV mother-to-child transmission in women who inject drugs or represent other marginalized populations. The particular aims of this document are to build on the 2007 version and consider the global WHO 2010 recommendations for a public health approach *Antiretroviral drugs for treating pregnant women and preventing HIV infections in infants (1)*, and to help assure that the European Region is providing the most effective interventions available for clinical management and progress towards the elimination of new paediatric infections.

The list of clinical scenarios in this version is greatly extended and addresses uncomplicated and complicated pregnancy; coinfections with HBV, HCV, TB; drug dependency; management of pre-term born infants; infant feeding options, etc. It responds to the requests of health care providers in the field for more specific guidance in the management of HIV-positive pregnant women presenting in a broad range of clinical conditions.

The process of the protocol revision included consultation with Regional clinical experts through a 2010 meeting in Kyiv, Ukraine (2) and electronic communication with them, ensuring that the updated version corresponds to the countries' needs and reflects diverse implementation capacities.

Wherever possible the recommendations are based on data from randomized controlled studies (RCTs) and are supported by the grade of evidence. However, in some cases the field has moved on from such data, e.g. the role of pre-labour caesarean section and the use of zidovudine (ZDV) monotherapy and single-dose nevirapine (NVP) as the main stays of PMTCT without resort to further RCTs. Therefore, these guidelines need to be considered in the light of new evidence as it emerges. Furthermore, for many of the scenarios presented there have been no such studies and it is clear from the grading of recommendations that much of the guidance is "expert opinion". Finally, every case is different and may have elements of more than one scenario, or components not considered here that will lead the health care provider to choose an alternative management strategy.

To the researcher, these guidelines should be seen as a challenge to examine each scenario and seek out the evidence base that is missing for most. While prospective RCTs remain the gold standard, retrospective analysis of existing databases, singly and together, is of proven value and can justifiably inform and improve clinical practice and provide timely data.

# Grading of recommendations

|   |
|---|
| <p><b>1A</b></p> <ul style="list-style-type: none"> <li>• strong recommendation</li> <li>• high quality evidence</li> <li>• benefits clearly outweigh risk and burdens, or vice versa</li> <li>• consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form; further research unlikely to change confidence in the risk–benefit estimate</li> <li>• can apply to most patients in most circumstances without reservation</li> </ul> <p>Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.</p>   |
| <p><b>1B</b></p> <ul style="list-style-type: none"> <li>• strong recommendation</li> <li>• moderate quality evidence</li> <li>• benefits clearly outweigh risk and burdens, or vice versa</li> <li>• evidence from randomized, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design; further research may impact confidence in the risk–benefit estimate</li> <li>• applies to most patients</li> </ul> <p>Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</p> |
| <p><b>1C</b></p> <ul style="list-style-type: none"> <li>• strong recommendation</li> <li>• low quality evidence</li> <li>• benefits appear to outweigh risk and burdens, or vice versa</li> <li>• evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws; any estimate of effect uncertain</li> <li>• applies to most patients, but some of the supporting evidence is low quality</li> </ul>  |
| <p><b>1D</b></p> <ul style="list-style-type: none"> <li>• strong recommendation</li> <li>• very low quality evidence</li> <li>• benefits appear to outweigh risk and burdens, or vice versa</li> <li>• evidence limited to case studies</li> <li>• based mainly on case studies and expert judgment</li> </ul>  |
| <p><b>2A</b></p> <ul style="list-style-type: none"> <li>• weak recommendation</li> <li>• high quality evidence</li> <li>• benefits closely balanced with risks and burdens</li> <li>• consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form; further research unlikely to change confidence in the risk–benefit estimate</li> <li>• weak recommendation, best action depends on circumstances or patient’s or societal values</li> </ul>  |
| <p><b>2B</b></p> <ul style="list-style-type: none"> <li>• weak recommendation</li> <li>• moderate quality evidence</li> <li>• benefits closely balanced with risks and burdens with some uncertainty in the estimates</li> <li>• evidence from randomized, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise); further research may change the risk–benefit estimate</li> <li>• alternative approaches likely to be better for some patients under some circumstances</li> </ul>   |
| <p><b>2C</b></p> <ul style="list-style-type: none"> <li>• weak recommendation</li> <li>• low quality evidence</li> <li>• uncertainty in the estimates of benefits, risks and burdens, which may be closely balanced</li> <li>• evidence from observational studies, unsystematic clinical experience or randomized, controlled trials with serious flaws; any estimate of effect uncertain</li> <li>• alternatives may be reasonable</li> </ul>   |
| <p><b>2D</b></p> <ul style="list-style-type: none"> <li>• very weak recommendation</li> <li>• very low quality evidence</li> <li>• uncertainty in the estimates of benefits, risks, and burdens, which may be closely balanced</li> <li>• evidence limited to case studies and expert judgment</li> <li>• alternatives may be equally reasonable</li> </ul>   |

# I. Provider-initiated HIV testing in the antenatal care setting

## 1. First contact

The identification, through the universal offer and recommendation of HIV testing in the antenatal setting, of previously undiagnosed or undisclosed HIV infection is an essential first step in the intervention pathway that now can reduce the rate of HIV mother-to-child transmission (MTCT) to less than 1%. In addition, it is an important entry point for the treatment and care of HIV-positive women and their children.

The intent of the HIV antenatal screening programme is to identify every HIV infected pregnant woman as early as possible in order to provide a package of interventions to prevent mother-to-child transmission (PMTCT) and minimize risk of HIV transmission to the baby during pregnancy, labour and postpartum.

While it is essential that HIV testing should be voluntary, it is increasingly recognized, in many areas of HIV management, that normalization of HIV testing as a basic part of pregnancy and general medical care is important to improving treatment access. In this regard, specific counselling (beyond that provided for other routine antenatal screening tests), referral outside the antenatal clinic (ANC) setting and requesting written consent, all formerly commonplace, are now considered barriers to testing (3,4). All obstetrician-gynaecologists and midwives should be able to discuss and recommend HIV testing non-judgementally, with documentation in the case notes. Where this strategy has been adopted, HIV antenatal screening has become both normal and acceptable with uptake rates approaching 100%, and higher than background HIV prevalence has been reported among the pregnant women who decline the offer (5). The reasons for this may include fear of disclosure; these women should be given the opportunity to further discuss HIV testing with a dedicated, experienced and sympathetic health care worker. The post-test discussion of an HIV-negative result should include education on risk reduction (6).

The time and resources previously given to pre-test counselling are reserved for post-test care. Where possible, women diagnosed with HIV infection should be seen by a health care worker experienced in HIV infection during pregnancy in particular, to ensure that the natural concerns of the mother can be confidently and immediately addressed. The initial assessment of HIV status should include:

- an offer and recommendation of an HIV antibody test;
- serological testing for HIV antibodies (typically ELISA and/or rapid tests), followed by a suitable confirmatory test if positive (western blot) and HIV-1/2 typing (if epidemiologically relevant); and
- post-test discussion, including information on reducing risky behaviour, irrespective of the results.

If a woman is HIV infected, her sexual partner(s) should be offered HIV testing. Further evaluation of HIV-infected women is needed in collaboration with an HIV specialist to determine the clinical stage. CD4 cell count and viral load (VL) (where available) are essential components of basic evaluation for all HIV-infected pregnant women and guide development of a PMTCT management strategy.

Among the key aspects of the booking visit is identifying any drug use (including injecting/recreational drug use) to ensure that appropriate care is provided regardless of HIV status. Drug use and dependence in particular can have a large impact on pregnancy and foetal development, requiring special medical assistance during pregnancy, labour and the postpartum period for both mother and foetus/infant. If a woman injects illicit drugs and shares needles/syringes or other paraphernalia with other injectors, HIV testing should be offered to all her injecting partners. For more about the assessment of drug dependence and withdrawal symptoms in pregnant women, see section III.

## **2. Post-test evaluation**

After the initial HIV evaluation, a package of additional screening should be offered where relevant to HIV-infected pregnant women, combined with counselling on the following:

- condom use for prevention of STIs;
- the risk of HIV transmission to the foetus/neonate and how to prevent it;
- the risks and benefits of ARV prophylaxis or ART for her own health and as part of PMTCT strategy;
- the risks and prevention of perinatal transmission of hepatitis B (HVB) and hepatitis C (HVC) viruses;
- the risks of perinatal STIs and the need for testing and treatment of syphilis, gonorrhoea and chlamydia to reduce the risk of HIV transmission;
- the impact of drug use on foetal development, including drug withdrawal syndrome and drug interactions;
- harm-reduction and drug-dependence treatment programmes, including substitution therapy where appropriate;
- the implications of different modes of delivery in reducing the risk of HIV transmission, including the benefits and adverse effects of pre-labour, pre-rupture of membranes caesarean section (PLCS);
- the risk of post-partum transmission through breastfeeding and advice on formula feeding (feeding with infant formula milk is acceptable, feasible, affordable, sustainable and safe throughout most of the region); and
- family planning options and modern contraception to avoid unintended pregnancy in the future.

With complete and accurate information about possible risks and management options, an HIV-positive woman can make an informed decision on whether to deliver or to terminate her pregnancy. HIV infection in the mother per se is not considered an indication for a medical termination of pregnancy and under no circumstance should she be coerced to terminate a pregnancy.

## II. Scenarios: pregnancy, delivery and post-partum

More than one scenario can apply to a patient. They describe the management of HIV infection during pregnancies that are uncomplicated (section 1) and complicated (section 2). Scenarios are also presented in tables 1 and 2. The list of scenarios, while greatly extended compared to the 2007 protocol, is not exhaustive.

### 1. Uncomplicated pregnancy (basic scenarios)

#### 1.1. Scenario 1: Mother does not yet require treatment for HIV infection

According to adult treatment guidelines treatment is not routinely indicated. Currently (2012) this would apply to patients with asymptomatic HIV infection and a CD4+ T-lymphocyte count above 350 cells/mm<sup>3</sup>.

*Goals:* Safe, short-term reduction of the HIV VL to undetectable levels (currently <50 copies/ml), prevention of HIV transmission during pregnancy and delivery, minimize risk of drug resistance development.

*Issues:* If the CD4 count is too high to use NVP (see Annex 1), efavirenz (EFV) (also applies to NVP) is more difficult to use because with its long half-life the “tail” requires additional cover after discontinuing therapy, to minimize the risk of non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) resistance. Treatment with a boosted protease inhibitor (choose from saquinavir (SQV), lopinavir (LPV) and atazanavir (ATV)) and a dual nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone provides flexibility but there are concerns of an increased risk of preterm delivery (PTD) with protease inhibitor (PI)-based therapy. The combination of zidovudine (ZDV), lamivudine (3TC) and abacavir (ABC) has been associated with lower rates of PTD and may be considered an alternative provided maternal HIV VL is <100 000 copies/ml (see Annex 1).

Though there is most experience with a nucleoside backbone of ZDV and 3TC, in many guidelines for non-pregnant adults tenofovir (TDF) plus emtricitabine (FTC) is now the first line choice. Safety concerns with ZDV plus 3TC, particularly in regard to mitochondrial toxicity, have not been completely resolved (see Annex 1). The potential bone and kidney toxicity of TDF remains. The safety and efficacy of non-ZDV-based therapy has been reported to be comparable to ZDV-based therapy in a retrospective cohort analysis (7).

Optimal timing for short-term ART for PMTCT purposes has not been determined (see section V.1). MTCT prophylaxis should be deferred until completion of the first trimester. The time required to reach an undetectable VL is determined by the baseline VL and varies with combinations. If the maternal VL is >32 000 copies/ml, commencing treatment before week 21 of gestation increases the likelihood of an undetectable VL at week 36 (8). There is no evidence to support the use of ZDV intravenous (IV) during labour in women with an undetectable VL.

The optimal duration of infant prophylaxis following delivery when maternal VL is undetectable and the mother receives ART has not been determined (see section V.1). In the absence of breastfeeding, four weeks is the standard recommendation although there is some evidence from an RCT that three days may be sufficient (9), and there is no evidence to suggest that ARV prophylaxis beyond four weeks is required. With the exception of data from NVP-based PMTCT studies, only the safety and efficacy of neonatal ZDV has been studied in any detail.

**Preferred option:** PI-based (or ABC-based) short-term ART initiated between weeks 14 and 24 and discontinued after clamping the cord at delivery. A fixed-dose nucleoside backbone combination of ZDV plus 3TC. Infant antiretroviral prophylaxis with ZDV for a maximum of four weeks. IV ZDV during labour not recommended, but the oral ARV prophylaxis should be continued during labour. See Scenario 5 for peripartum management if maternal VL >50 copies/ml at 36 weeks.

*Special circumstances:* Previous antiretroviral exposure for PMTCT. Archived mutations conferring resistance to NVP and EFV should be presumed in mothers previously treated with single-dose (sd) NVP. Mutations reducing sensitivity to ZDV are uncommon following the use of ZDV monotherapy to reduce the risk of MTCT (see Annex 1). Drug resistance has also been reported following NVP-based ARV prophylaxis (10). When treatment history indicates the probable presence of resistance mutations and in the absence of drug sensitivity testing at the appropriate time, boosted PI-based therapy is preferred.

Since ART is universally available throughout the Region alternatives to short-term ART (ZDVm, sd NVP) are not discussed.

## **1.2. Scenario 2: Mother should start ART for her own health**

*Goals:* Safe reduction of HIV VL to undetectable levels to enable restoration of maternal immune function and to maximize the mother's health, as well as to prevent HIV transmission to the infant during pregnancy and delivery. This is a commitment to lifelong treatment.

*Issues:* Specific issues are the timing of therapy initiation, prophylaxis and treatment for opportunistic infections (OIs) and choice of ART.

Treatment according to local adult treatment guidelines should be initiated (For further reference please see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents, (2012 revision)*). Although EFV is generally preferred to NVP in non-pregnant adults, there is considerably more experience with NVP in pregnancy and this may be preferred if the CD4 is <250 cells/mm<sup>3</sup>. Despite reports of toxicity with NVP initiated during pregnancy (11,12), many cohorts have reported both safety and tolerability (13–16). When the immediate OI risk is relatively low, deferring treatment until the start of the T2 is recommended; see the notes on preferred nucleoside backbone in Scenario 1. When pneumocystis pneumonia (PCP) prophylaxis is required some experts will defer ART for up to two weeks to reduce the risk of introducing concurrent therapies with overlapping toxicity, particularly rash. Any opportunistic infection should be treated immediately, with ART introduced once tolerance has been established. The ART regimen may be changed following pregnancy. ART for patients with advanced HIV infection and at further OI risk should not be unnecessarily delayed by pregnancy, and if appropriate treatment may be initiated during the T1 (Note: women who conceive while on ART are advised not to discontinue therapy).

**Preferred option:** CD4 <250 cells/mm<sup>3</sup> – fixed dose combination ZDV plus 3TC plus NVP. If CD4 >250 cells/mm<sup>3</sup> substitute EFV or boosted PI for NVP. Infant ARV prophylaxis with ZDV for a maximum of four weeks. Aim for normal vaginal delivery. IV ZDV during labour not recommended if VL <50 copies/ml. See Scenario 6 for peripartum management if maternal VL >50 copies/ml at week 36.

*Alternative:* Fixed dose combination TDF plus FTC or ABC plus 3TC with NVP (<250 cells/mm<sup>3</sup>) or EFV or boosted PI.

### 1.3. Scenario 3: Mother conceives on ART, viral load is <50 copies/ml

*Goals:* Safe (for mother and foetus), effective treatment of HIV infection, maintaining an undetectable level of HIV to protect the maternal immune function and prevent HIV transmission during pregnancy and delivery.

*Issues:* The specific issues are ART safety during T1 for the embryo and foetus, the tolerability and adherence of maternal therapy and the choice of therapy for infant prophylaxis.

There are as yet insufficient data to exclude a small increased risk of neural tube defects with EFV, but as described in Annex 1, prospective data on its safety during T1 are encouraging, with no teratogenic signal identified in two large prospective studies. EFV-based ART should not be interrupted. Automatic substitution of another agent for EFV during T1 is not recommended and consideration must be given to the gestational age at presentation, EFV's long half-life, the individual's treatment history, the extent of the new agent's safety, the observed risk from prospective studies and the patient's preference. Switching therapy after the neural tube has closed (day 26 or approximately 40 days from the last menstrual period) has no biological substance and even with earlier presentations continued exposure occurs due to EFV's long half-life.

Intolerance of ART and other medication during pregnancy due to early morning sickness can usually be managed by a combination of rescheduling dose timing (e.g. once daily to evening) and antiemetic therapy. Occasionally in *hyperemesis gravidarum* interruption of ART to avoid treatment failure is indicated. This should be for as short a period as possible but balanced with the risk of reintroducing ART too early.

Unless there is a history of treatment failure on ZDV or of archived mutations associated with resistance to it, it should be used for infant prophylaxis regardless of the maternal regimen. Otherwise, the choice of infant prophylaxis should be determined by treatment history and viral genotype but single agent prophylaxis remains the first option.

**Preferred option:** Continue successful ART regimen. Aim for normal vaginal delivery. IV ZDV during labour is not recommended. Infant antiretroviral prophylaxis with ZDV (unless there is a ZDV resistant virus) for a maximum of four weeks.

### 1.4. Scenario 4: Mother conceives on ART, viral load is >50 copies/ml

*Goals:* Safe (for mother and fetus) effective treatment of HIV infection, control of viral replication to protect the maternal immune function and prevent HIV transmission during pregnancy and delivery.

*Issues:* to determine whether this is treatment failure with resistance, treatment failure due to inadequate drug concentrations (see section VI.3) or inadequate adherence. Diagnosing treatment failure early in the pregnancy allows assessment of drug adherence, and the viral sequence and measurement of drug concentrations. The principles of HIV management in non-pregnant adults apply, with the selection of a new effective regimen the first priority. However, selecting a new regimen without addressing the underlying cause(s) of treatment failure is a recipe for further failure.

Scenario 6 addresses treatment failure later in pregnancy. The choice of infant prophylaxis will be determined by the treatment history.

**Preferred option:** Selection of an effective regimen to fully suppress HIV replication is not unduly influenced by the pregnancy. Carefully monitor the response. Consider directly observed therapy (DOT) in some circumstances.

### **1.5. Scenario 5: Mother on short-term ART, viral load >50 copies/ml at 36 weeks**

**Goals:** Safe delivery of an uninfected infant.

**Issues:** when to elect PLCS and when treatment should be intensified.

This is a common scenario if baseline VL is high regardless of when treatment is initiated, but particularly if short-term ART was delayed as discussed in the first scenario. There are two common causes: poor adherence (see section II.3.6) and the slower decay in VL after the first phase even with fully effective therapy.

If maternal VL is >1000 copies/ml at 36 weeks, and it is highly likely that delivery will occur prior to complete suppression of viral replication, delivery by PLCS at 39 weeks (see section IV) is recommended (unless there are significant risks to future maternal health). Infant prophylaxis with standard ZDV monotherapy remains appropriate (as per data from ZDVm plus PLCS strategy (see Annex 1), but some experts would offer triple ART to infants in this scenario. If maternal VL at 36 weeks is 50 <1000 copies/ml and VL is falling, a number of options are available: PLCS as above; spontaneous vaginal delivery with sd NVP at onset of labour (for mothers not on NNRTI-based regimen); spontaneous vaginal delivery and continue the current regimen. Whilst European Collaborative Study (ECS) data indicate reduced transmission rates with PLCS even when VL is <1000 on therapy; these data include patients on established treatment (Scenario 4). There are no data to support intensification of early non-failing ART prior to labour. The use of sd NVP is supported by RCT but not specifically in this setting.

**Preferred option:** Continue ARV prophylaxis and deliver by PLCS. Provide sd NVP to mother in case of spontaneous labour. IV ZDV may be given peripartum. Infant prophylaxis with ZDV or triple ART for four weeks for the infant if VL >1000 copies/ml.

### **1.6. Scenario 6: Mother on ART, viral load >50 copies/ml at 36 weeks**

**Goal:** Re-suppression of viral replication, preservation of therapeutic options and safe delivery of uninfected infant.

**Issues:** VL has been fully suppressed and is now detectable, reflecting treatment failure. There is limited time to fully evaluate, select and introduce a new combination that will achieve these goals. It is important to determine whether this is treatment failure with resistance, treatment failure due to inadequate drug concentrations (see section VI.3) or inadequate adherence, but the immediate goal is prevention of MTCT of HIV. PLCS is effective in reducing risk regardless of degree of VL and drug sensitivity. PLCS should be planned for 38 weeks to reduce the likelihood of spontaneous labour. Since the infant will potentially be exposed to drug resistant virus, infant post-exposure prophylaxis should be triple ART for four weeks, preferably selected according to maternal virus genotype or treatment history. Consider DOT if treatment failure is due to poor adherence. Depending on local services this can be undertaken in the community with either peer or professional supervision. When this fails or is not possible, hospitalization should be offered. Consider switching to a once daily regimen to facilitate DOT if possible.

**Preferred option:** PLCS at 38 weeks; optimize new combination of therapy; triple therapy infant prophylaxis for four weeks. IV ZDV is only indicated if ZDV is part of current regimen.

### **1.7. Scenario 7: Late presentation >32 weeks, before onset of labour, CD4 >350 cells/mm<sup>3</sup>**

*Goals:* Rapid suppression of HIV VL with short-term ART to reduce risk of MTCT of HIV.

*Issues:* Unless pre-treatment VL is relatively low, treatment is unlikely to achieve full suppression of viral replication prior to delivery. CD4 count precludes use of NVP. Treatment is likely to be short-term. PLCS is effective to reduce risk regardless of the degree of VL and drug sensitivity. PLCS should be planned for 38 weeks to reduce the likelihood of spontaneous labour. ART taken for more than 14 days has been associated with low MTCT rates (17). There are as yet insufficient data to recommend integrase-inhibitor-based ART.

*Preferred option:* Assumes the VL would remain detectable at week 38 (from the previous trend of VL measurements, specifically VL at baseline, which is later than 32 weeks), initiate PI-based short-term ART and plan PLCS at 38 weeks. IV ZDV 2–4 hours prior to and during PLCS can be given if assumed VL would be >1000 copies/ml (18). Triple ART infant prophylaxis for four weeks – Preferred infant regimen ZDV, 3TC and NVP (see section V.1 for doses).

### **1.8. Scenario 8: Late presentation >32 weeks, before onset of labour, CD4 <350 cells/mm<sup>3</sup>**

*Goals:* Rapid suppression of HIV viral replication to reduce risk of MTCT of HIV and long-term treatment for maternal health.

*Issues:* Unless the pre-treatment VL is relatively low, treatment is unlikely to achieve fully suppression of viral replication prior to delivery. CD4 count >250 but <350 precludes use of NVP. Treatment should be long-term allowing first-line NNRTI-based therapy. However, careful consideration of the circumstances by which new HIV diagnosis is made late in pregnancy is required to avoid initiating long-term treatment in unfavourable circumstances (e.g. before the mother has had sufficient time to assimilate the implications of the diagnosis and prepare for life-long therapy or access to therapy and follow-up is not assured). EFV is an option if NVP is precluded on the basis of CD4 count, but if long-term therapy is unlikely for the reasons given, boosted PI-based ART should be considered. It may also be considered if there is a risk of infection with a drug-resistant virus. Where drug resistance testing is not routinely available, assessment of risk is based on local, regional or national surveillance data or epidemiological risk assessment. In either situation, treatment needs to be initiated straight away without waiting for drug sensitivity analysis. NNRTI reduces the VL more rapidly and crosses the placenta more efficiently than boosted PIs. As yet there are insufficient data to recommend first-line treatment with an integrase inhibitor in this scenario, but the more rapid VL suppression observed with this class may prove attractive. PLCS is effective in reducing risk regardless of the VL or drug sensitivity. PLCS should be planned for 38 weeks to reduce the likelihood of spontaneous labour.

*Preferred option:* NNRTI-based therapy; PLCS at 38 weeks; IV ZDV prior to and during PLCS can be given; triple ART infant prophylaxis for four weeks.

Basic clinical scenarios of uncomplicated pregnancy are summarized in table 1.

| <b>TABLE 1.</b> |   | <b>UNCOMPLICATED PREGNANCY (BASIC SCENARIOS)</b>   |  |   |   |
|-----------------|---|--|--|---|---|
|                 | <b>Scenario</b>   | <b>Maternal Management</b>   | <b>Intra-partum/Obstetric Management</b>   | <b>Infant Management</b>  | <b>Strength of Recommendation</b>             |
| <b>1</b>        | Patient does not yet require treatment for HIV  | Short course highly active antiretroviral therapy with dual NRTI + ritonavir boosted PI or triple nucleoside (ZDV, 3TC, ABC if VL <100,000).   | VL at week 36 < 50 copies/ml: Recommend vaginal delivery unless obstetric indications for PLCS.<br>Maternal VL at week 36 >50: See Scenario 5. | 4 weeks ZDV<br><br>Maternal VL at week 36 >50:<br>See Scenario 5. | 1C  |
| <b>2</b>        | Patient requires HIV treatment for own health   | Initiate ART – defer to after T1 unless high risk of OI. Preferred option: fixed dose combination of ZDV plus 3TC with NVP (CD4 <250) or boosted PI (CD4 >250 cells/mm <sup>3</sup> ). | VL at week 36 < 50 copies/ml: Recommend vaginal delivery unless obstetric indications for PLCS.<br>Maternal VL at week 36 >50: See Scenario 6. | 4 weeks ZDV<br><br>Maternal VL at week 36 >50:<br>See Scenario 6. | Antepartum 1A;<br><br>IP 1C;<br><br>Infant 1C |
| <b>3</b>        | Patient conceives on ART, VL < 50   | Continue ART.  | Vaginal Delivery   | 4 weeks ZDV   | 1C  |
| <b>4</b>        | Patient conceives on ART, VL > 50   | Change to new ART regimen.   | Vaginal Delivery provided maternal VL <50 at week 36   | 4 weeks ZDV   | 1C  |
| <b>5</b>        | VL >50 at 36 weeks on short-term ART (Resistance risk low)  | Re-assess adherence and risk for treatment failure; if unlikely, continue short-term ART; if likely → Scenario 6   | PLCS at 39 weeks<br>Provide sdNVP for spontaneous labour   | 4 weeks ZDV<br>Consider triple ART if maternal VL >1000           | Antepartum 1C<br>IP 1B<br>Infant 1C           |
| <b>6</b>        | VL >50 at 36 weeks on ART (Resistance risk high)  | Re-assess adherence. Change to new ART regimen based on viral sequence or treatment history. Consider DOT.   | PLCS at 38 weeks   | Triple ART prophylaxis based on maternal treatment history        | Antepartum 1C;<br>IP 1B<br>Infant 1C          |
| <b>7</b>        | Late presentation >32 weeks; pre-labour, pre rupture of membranes; Treatment naïve; CD4>350 cells/mm <sup>3</sup> | Initiate boosted PI-based ART  | PLCS at 38 weeks   | Triple ART prophylaxis  | Antepartum 1D<br>IP 1B<br>Infant 1C           |
| <b>8</b>        | Late presentation >32 weeks; pre-labour, pre rupture of membranes; Treatment naïve; CD4<350 cells/mm <sup>3</sup> | CD4 < 250 cells/mm <sup>3</sup> : Initiate NVP based ART.<br>CD4>250 cells/mm <sup>3</sup> : Consider EFV-based ART unless transmitted resistance suspected.                           | PLCS at 38 weeks   | Triple ART prophylaxis  | Antepartum 1D<br>IP 1B<br>Infant 1C           |

## 2. Complicated pregnancy (less common scenarios)

### 2.1. Scenario 9: Threatened preterm delivery/rupture of membranes, viral load undetectable (<50 copies/ml)

*Goals:* Safe delivery of infant with mature lungs, prevention of ascending infection, PMTCT.

*Issues:* Balancing the risk of HIV transmission with the risk of preterm morbidity. More severe prematurity increases the risk of morbidity and mortality. Specialist neonatal care resources differ among centres. The HIV transmission risk depends on the VL. For patients on long-term or short-term ART with undetectable VL, obstetric decisions take priority and early delivery to reduce the risk of HIV transmission is not indicated. Systemic steroids should be given to mature foetal lungs. Some experts advise the use of antibiotic therapy early after the rupture of membranes to prevent ascending infection; this differs from the routine practice of giving antibiotics after 24 hours of ruptured membranes. Premature infants may be unable to absorb oral ART. ZDV is the only drug available intravenously.

*Preferred option:* Continue suppressive maternal ART. Give 24 hours steroids for foetal maturation. Consider early use of antibiotics for spontaneous rupture of membranes (SROM). Neonatal ZDV monotherapy for four weeks.

### 2.2. Scenario 10: Threatened preterm delivery/rupture of membranes, viral load detectable (>50 copies/ml)

*Goals:* Safe delivery of infant with mature lungs, prevention of ascending infection, PMCTC.

*Issues:* Balancing the risk of HIV transmission with the risk of preterm morbidity. More severe prematurity increases the risk of morbidity and mortality. Specialist neonatal care resources differ among centres. The HIV transmission risk depends on the VL. If the VL is detectable, balance the risk of infection with the mortality and morbidity risk of severe prematurity based on local data. Systemic steroids should be given to mature foetal lungs. Some experts advise use of antibiotic therapy early after the rupture of membranes to prevent ascending infection; this differs from the routine practice of giving antibiotics after 24 hours of ruptured membranes. Premature infants may be unable to absorb enteral ART. ZDV is the only drug available intravenously.

Single dose maternal NVP > 2 hours before delivery results in up to seven days of NVP cover in the infant, so loading the premature foetus with ART via the placenta before birth is very important. However, transplacental induction of foetal liver enzymes has been reported in mothers on regular NVP, and those neonates have significantly increased rates of NVP clearance (19), so regular NVP would be indicated as part of a triple therapy regimen if tolerated. Parenteral enfuvirtide may be available in some centres and be useful in the context of treatment failure with multidrug resistance.

*Preferred option:* Continue suppressive maternal ART. Give 24 hours steroids for foetal maturation. Consider early use of antibiotics for SROM. Consider sd maternal NVP (regardless of maternal CD4 count) if the VL is detectable and the neonate is unlikely to be tolerate oral therapy. Triple ART prophylaxis for infant for four weeks. Avoid LPV/r if possible (see Annex 1)

### **2.3. Scenario 11: Term pre-labour rupture of membranes, HIV undetectable (<50 copies/ml)**

*Goals:* Safe delivery, prevention of ascending infection, PMTCT.

*Issues:* The maternal VL determines the risk. If the VL is <50 copies/ml plasma on therapy, standard management of pre-labour SROM at term is recommended with pharmacological induction of labour.

The timing of antibiotic cover may differ; current practice for women infected with HIV is to initiate antibiotics immediately rather than waiting for 18 hours of rupture of membranes as per standard guidelines. The rationale is to prevent ascending infection and local inflammation but there is no evidence to support this in women on ART with fully suppressed VL. Indications for caesarian section will be obstetric and HIV infection can be ignored.

*Preferred options:* Manage labour as if HIV uninfected, but consider early use of antibiotic prophylaxis. Infant prophylaxis is ZDVm 4 weeks.

### **2.4. Scenario 12: Term pre-labour rupture of membranes, HIV detectable (>50 copies/ml)**

*Goals:* Safe delivery, prevention of ascending infection, PMTCT.

*Issues:* The maternal VL determines the risk. There is an additional 2% risk of transmission associated with each additional hour of duration of rupture of membranes (data from the pre-ART era) (20). In cohort studies of patients on ART, the duration of the rupture of membranes was no longer associated with the risk of transmission. Many experts continue to recommend early caesarean section due to the risk of transmission of a resistant virus with prolonged rupture of membranes.

*Preferred options:* If the mother is not on NVP, add single dose NVP immediately and proceed to caesarean section at least two hours later. If the mother is already on NVP (or another NNRTI), proceed to caesarean section immediately. Sd NVP is safe at all CD4 cell counts. Give the infant triple ART for four weeks. If the mother is not on long-term ART, manage as Scenario 13.

### **2.5. Scenario 13: Mother presents in labour (known or unknown HIV status)**

*Goals:* Rapid identification of HIV status; safe delivery, PMTCT, preservation of maternal treatment options.

*Issues:* When HIV status is unknown, risk assessment is notoriously unreliable; where HIV testing is routine, the absence of a prior ANC HIV test is a risk factor for HIV infection. Availability of the HIV Rapid Test, also known as a Point of Care Test is also an issue.

*Preferred option:* If available, an HIV Rapid Test should be offered and recommended to the mother and performed without delay. If it is reactive, treatment should be initiated **immediately** based on this result only. Do not repeat and do not wait for confirmation by standard serological assays, although later formal confirmation of HIV status is essential. The risk of false positives should be explained to the mother. If the HIV Rapid Test is non-reactive, manage as for HIV uninfected unless there is a considerable risk of primary HIV infection (efficacy of fourth generation HIV Rapid Test in detecting Ag positive Ab negative may not be equal to standard fourth generation laboratory assays).

For a known HIV-positive mother or HIV Rapid Test reactive: give NVP 200mg to mother immediately (oral NVP is simple and quick to administer) and commence cover with combination therapy to minimize risk of NNRTI resistance. Initial cover can be with fixed dose combinations of ZDV plus 3TC or TDF plus FTC (ABC plus 3TC not preferred as risk of hypersensitivity unless HLA B57\*01 status is known). The role of IV infusion with ZDV in this setting is uncertain. When used, ZDV is infused at 2mg/kg over 1 hour followed by 1mg/kg/hr until the cord has been clamped. (ZDV infusions take time to set up and require IV access). If delivery is imminent allow vaginal delivery, as caesarean section at this stage has little impact on transmission rates. If in early labour caesarean section is indicated, two hours post administer NVP. Infant prophylaxis is triple ART four weeks (see section V).

Confirm maternal HIV status, CD4 count and HIV VL. If appropriate continue ART for maternal health with NNRTI + dual nucleoside backbone. If treatment for maternal health not indicated or infeasible, treat with fixed dose nucleoside backbone plus boosted PI for two weeks to cover NVP tail. If available confirm drug sensitivity of maternal virus on baseline sample.

#### **2.6. Scenario 14: HIV infection in mother diagnosed after delivery but <48 hours**

*Goal:* Reduced risk of HIV MTCT from labour and delivery.

*Issues:* In the absence of any intervention during labour and delivery, the efficacy of post-exposure prophylaxis has been demonstrated for combination ART and ZDVm up to 48 hours post partum (21).

*Preferred option:* Initiate infant triple ART post-exposure prophylaxis up to 48 hours post partum. Baseline HIV DNA polymerase chain reaction (PCR) or HIV RNA quantification. Follow guidelines for treatment and assessment of non-pregnant adults (please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents (2011 revision)*).

#### **2.7. Scenario 15: HIV infection in mother diagnosed after delivery >48 hours**

*Goal:* Early detection and treatment of HIV infection in the neonate.

*Issues:* There is no evidence of the efficacy of post-exposure prophylaxis at this late stage. The risk of transmission through breastfeeding during the previous 48 hours is probably too low to recommend initiation of post-exposure prophylaxis if the mother has been breastfeeding.

*Preferred option:* Baseline HIV DNA PCR or HIV RNA quantification and repeat after 4 weeks and 3 months.

Clinical scenarios of complicated pregnancy are summarized in table 2.

| <b>TABLE 2.</b> |   | <b>COMPLICATED PREGNANCY (LESS COMMON SCENARIOS)</b>   |  |  |                                   |
|-----------------|---|--|--|--|-----------------------------------|
|                 | <b>Scenario</b>   | <b>Maternal Management</b>   | <b>Intra-partum/Obstetric Management</b>   | <b>Infant Management</b>                                   | <b>Strength of recommendation</b> |
| 9               | Threatened pre-term delivery/rupture of membranes VL undetectable | Continue suppressive ART. Give 24 hrs. maternal steroids to mature foetal lungs. Manage as HIV uninfected.   | As directed by obstetric considerations  | ZDV per oral or IV 4 weeks                                 | 1D                                |
| 10              | Threatened pre-term delivery/rupture of membranes VL detectable   | Continue ART. Add sd NVP regardless of CD4 count. Give 24 hrs maternal steroids to mature foetal lungs.  | Expedite delivery if considered beneficial to neonate compared with risks of prematurity.        | Triple ART for 4 weeks (if able to tolerate enteral feeds) | 1D                                |
| 11              | Term pre-labour rupture of membranes on ART VL undetectable       | Continue suppressive ART. Manage as HIV uninfected.  | As directed by obstetric considerations  | ZDV 4 weeks  | 1D                                |
| 12              | Term pre-labour rupture of membranes on ART VL detectable         | Continue ART. Add sd NVP regardless of CD4 count unless on NNRTI-based ART.  | Emergency caesarean, at least 2 hours after maternal sd NVP                                      | Triple ART for 4 weeks                                     | 1D                                |
| 13              | Patient presents in labour  | Rapid HIV diagnostics Treat if reactive. Do NOT await confirmation. Start sd NVP 200mg. Initiate IV ZDV. Initiate PI-based ART pending maternal workup and to protect NNRTI options. | If unlikely to deliver imminently, recommend emergency caesarean, at least 2 hours after sd NVP. | Triple ART for 4 weeks                                     | 1D                                |
| 14              | Maternal HIV diagnosed after delivery but <48 hrs                 |  |  | Triple ART for 4 weeks                                     | 1D                                |

### 3. Special Circumstances

#### 3.1. Scenario 16: Hepatitis B coinfection

*Goals:* Safe use of ART for the mother, prevention of transmission of HIV and of HBV, preservation of maternal HBV and HIV treatment options.

*Issues:* Use of therapies that treat both viruses and avoidance of resistance with suboptimal therapy. Avoid use of NVP especially if abnormal LFTs/detectable HBV DNA.

*Preferred options:* HBV DNA quantification at baseline if available. Use of fixed-dose TDF plus FTC as part of ART will suppress HBV and reduce risk of resistance. Avoid using 3TC or FTC in the absence of TDF when starting or switching therapy. Use boosted PI or EFV in initial ART. Mode of delivery same as for HIV mono-infection. Infants get standard HIV prophylaxis plus hepatitis B vaccination. Anti HBV Ig if there is high maternal HBV DNA.

Grade of Recommendation: 1C

#### 3.2. Scenario 17: Hepatitis C coinfection

*Goals:* Safe use of ART for mother; prevention of transmission of HIV and of HCV.

*Issues:* Avoid use of NVP, especially if abnormal LFTs/detectable HCV RNA. If HCV treatment with interferon/ribavirin is available, defer it until post-partum. There is increased risk of HIV/HCV transmission with coinfection.

*Preferred options:* HCV RNA quantification at baseline if available; boosted PI or EFV for initial ART. Mode of delivery: consider PLCS unless HCV RNA is undetectable. Infants receive standard HIV prophylaxis.

Grade of Recommendation: 1C

#### 3.3. Scenario 18: Coinfection with *Mycobacterium tuberculosis*

*Goals:* Safe management of maternal coinfection, prevention of HIV transmission, prevention of TB transmission.

*Issues:* Drug interactions, immune reconstitution inflammatory syndrome (IRIS). Early treatment to reduce HIV VL to prevent transmission may be required even in patients with good CD4 counts.

*Preferred options:* Initiate standard first-line quadruple anti-tuberculosis therapy as per non-pregnant adult: Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. For treatment of MDR and XDR TB please refer to Protocol 4, *Management of tuberculosis and HIV coinfection (in press)* and seek expert opinion. Consider drug safety and teratogenicity in pregnancy as per non-HIV infected mother; notably streptomycin, ethionamide and prothionamide should be avoided.

Initiate ART. Timing will depend on gestational age and maternal VL. If TB is diagnosed early in pregnancy (T1/ early T2) it may be possible to complete two months induction treatment before initiating ART. If TB is diagnosed in late T2 or T3 early treatment with ART to prevent transmission is essential especially if HIV VL is > 32 000 copies/ml. In this setting the preferred

option is to allow a minimum of 1–2 weeks between initiating TB and HIV treatment to minimize overlapping toxicities, especially rash and drug-induced hepatitis. In exceptional cases, e.g. after 32 weeks, both therapies may be started simultaneously. The preferred ART combination is EFV (increase dose if body weight >60kg to 800mg once daily) plus dual nucleoside backbone (standard dose of Rifampicin). The alternative is NVP (if baseline CD4 <250 cells/mm<sup>3</sup> or if VL on treatment is <50 copies/ml) at standard dose.

If NNRTI use is not possible due to resistance or toxicity, use boosted PI with reduced dose of rifabutin (150mg three times weekly). There is however a paucity of data on use of rifabutin in pregnancy and it is not widely available.

If the patient has a low VL (<32 000 copies/ml) and good CD4 count (>350 cells/mm<sup>3</sup>) and will be initiated on a short-term ART to reduce risk of MTCT, the combination of three NRTIs – ABC, 3TC, ZDV – may be a suitable option until delivery and will allow optimal anti-TB treatment with a rifampicin-containing regimen.

PCP prophylaxis with co-trimoxazole is recommended regardless of the baseline CD4 count.

Infants born to HIV-positive mothers with smear-positive pulmonary TB who are being breast-feed have a high risk of TB. Six months isoniazid preventive therapy (IPT), followed by BCG vaccination is recommended.<sup>1</sup>

TB and HIV coinfection therapy is summarized in table 3.

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<sup>1</sup> See also *Implementing the WHO Stop TB Strategy*. Geneva, World Health Organization, 2008 ([http://whqlibdoc.who.int/publications/2008/9789241546676\\_eng.pdf](http://whqlibdoc.who.int/publications/2008/9789241546676_eng.pdf), accessed

| <b>TABLE 3.</b>   |   | <b>SUMMARY OF THERAPY FOR TB AND HIV COINFECTION</b>  |  |   |
|---|---|---|--|---|
| <b>Pregnancy term, time of initiation TB and ART treatment, no evidence of TB drug resistance</b> |   |   |  |   |
| Gestational Age   | CD4 cells/mm <sup>3</sup><br>VL copies/ml | Interval between TB treatment and ART   | Recommended ART for use with Rifampicin-based TB therapy | Rationale, evidence   |
| Under 14 weeks  | CD4 >350                                  | 8 weeks   | 1. EFV-based<br>2. ABC-based                             | No difference in survival if CD4 >50 RCT 1B (for time to start).  |
| Under 14 weeks  | CD4 >250<br><350                          | 2 weeks   |  | CD4 > 50 can be delayed 2 weeks to reduce risk of IRIS  |
| Under 14 weeks  | CD4 <250                                  | ART can be delayed up to 2 weeks or initiated with TB therapy if CD4 <50.                       | NVP based ART is a further option.<br>2C                 | Starting treatment immediately improves survival if CD4 <50.  |
| 14–32 weeks   | CD4 >350,<br>VL <32 000                   | ART can be delayed up to week 24 or 2 weeks after initiating TB treatment, whichever is longer. | EFV-based<br>ABC-based                                   | Timing of ART in relation to TB treatment as above but time constraints on starting ART in pregnancy especially if VL >32 000<br>1D |
| 14–32 weeks   | CD4 <350<br>or<br>VL >32 000              | Start ART 1–2 weeks after initiating TB treatment or at week 32, whichever is sooner.           | EFV-based<br>ABC-based                                   | As above  |
| Over 32 weeks   | CD4 >250                                  | Start ART and TB treatment simultaneously.  | EFV-based<br>ABC-based                                   | 1D  |
| Over 32 weeks   | CD4 <250                                  |   | NVP based ART is an option                               | 1D  |

### 3.4. Scenario 19: HIV-2 infection

**Goals:** Safe treatment of maternal infection and prevention of HIV-2 MTCT.

**Issues:** Assessment of risk and sensitivity of HIV-2 to ART: NNRTI's have no activity; ZDV resistance occurs with fewer mutations than for HIV-1 and should not be used as a monotherapy; HIV-2 has innate resistance to fusion inhibitors (enfuvirtide); PIs have mixed outcomes (e.g. ATV has no anti-HIV-2 activity in vitro and amprenavir and fos-amprenavir should be avoided unless combined with low dose ritonavir); nelfinavir has a low level of resistance. LPV, SQV, darunavir and tripanavir have good activity. There are limited data on integrase inhibitors, but raltegravir appears active and may be used in a second-line regimen.

**Preferred options:** Consider the possibility of HIV-2 (and HIV-1/HIV-2 coinfection in patients from West Africa). Measure HIV-2 VL. If the VL is undetectable and CD4 >500 cells/mm<sup>3</sup>, no antiretroviral therapy is required. Avoid breastfeeding. Allow normal delivery. If the VL is detectable, treat with ART using ARVs with good activity against HIV-2. LPV/r with TDF and FTC is the preferred first-line therapy.

### 3.5. Scenario 20: Illicit drug use during pregnancy

*Goals:* Safe management of pregnancy and HIV infection in mother, risk reduction from illicit drug use in foetus/neonate and prevent of HIV transmission.

*Issues:* Increased risk of adverse pregnancy outcomes, risk of coinfections (manage as per scenarios 16 and 17). Drug interactions: notably increased metabolism of methadone with LPV/r (section III.7); non-adherence (Scenario 21); drug toxicity to foetus and drug withdrawal in neonate. Risks to foetus/neonate include sedation (benzodiazepines), withdrawal (opiates), and cerebral haemorrhage (cocaine).

*Preferred options:* Once daily regimen with agents of relatively short half-life may be preferred, e.g. TDF 245mg, FTC 200mg, ATV 300mg plus ritonavir 100mg (see Annex 1 for advice on dose adjustments in the third trimester [T3]). This regimen also has no significant interactions with methadone. See section III.5 for interactions between antiretroviral therapy and opioid substitution therapy.

Managed substance use with dose reductions during pregnancy and increased foetal monitoring is recommended. Treatment of HIV infection may be linked with the methadone or buprenorphine supply (DOT) in some settings.

### 3.6. Scenario 21: Management of non-adherence

*Goals:* Safe management of pregnancy and preservation of maternal treatment options. PMTCT of HIV, including avoidance of transmitted drug resistance.

*Issues:* T1/2 adherence difficulties may be due to *emesis gravidarum*, psychosocial factors or adverse events. ART is generally well tolerated in pregnancy.

*Preferred options:* The simplest option for *emesis gravidarum* is to switch the dosing schedule to avoid times of nausea; this may include a switch to a once daily regimen. A number of antiemetics may be safely used in pregnancy: cyclizine or promethazine may be preferred with prochlorperazine and metoclopramide as second line.

If medications are not tolerated complete interruption of ART may be considered. For regimens that contain only agents with a short half-life this is simple. For combinations that contain agents with a long half-life (e.g. NVP and EFV), the preferred option is to discontinue these first while covering the long half-life with a short half-life agent such as a boosted PI. If this is not possible, discontinuation of the regimen at a time of fully suppressed viral replication is less likely to result in the development of resistance than persevering with a poorly taken, poorly absorbed therapy. Aim to reintroduce ART as soon as emesis has settled.

Where non-adherence is due to psychosocial factors, they need to be addressed in detail; they include, but are not limited to, fear of disclosure, fear of toxicity, denial and inability to swallow medication. In some cases directly observed therapy, various prompts to take medication and peer-support may help. Treatment simplification should always be considered. If adherence remains a problem and viraemia is detected in T3 see Scenario 6.

### **3.7. Scenario 22: Use of invasive diagnostic techniques**

*Goal:* Minimizing risk of HIV transmission through amniocentesis/choriovillous sampling.

*Issue:* Timing of amniocentesis/choriovillous sampling in relation to HIV diagnostics and ART.

*Preferred Option:* In addition to other risks, amniocentesis/choriovillous sampling is associated with risk of HIV transmission to the foetus. This can be minimized by prior ART (22). Therefore amniocentesis/choriovillous sampling should not be performed prior to determining HIV serostatus. If HIV diagnosis is confirmed, amniocentesis/choriovillous sampling should be deferred until ART has been initiated and HIV replication suppressed. If presentation for antenatal care is late and amniocentesis/choriovillous sampling cannot be delayed, initiation of ART with the addition of sd NVP (if not part of the ART regimen) at the time of the procedure is recommended.

### **III. Management of HIV-infected active drug users during pregnancy**

Pregnant women using drugs have a greater than normal risk of medical complications. They should be managed according to the possible impact of their dependency on the pregnancy, the foetus and their own health. The key issue for the management of drug-using pregnant women is therefore stabilization of illicit drug use or its reduction to the lowest possible level. Management is aimed at harm reduction and requires identification of the specific risks to the mother and the foetus/newborn. Risks to the mother include overdose, coinfection, risks associated with route of administration (thromboembolism, sepsis), disturbed adherence and drug interactions including unanticipated withdrawal. Risks to the foetus and newborn include increased transmission of HIV and coinfections, preterm delivery, drug toxicity and withdrawal.

#### **1. Organization of services**

To manage pregnant HIV-positive IDUs effectively, they need to be persuaded to utilize health care services as early in pregnancy as possible, and the relevant services need to be accessible during the entire pregnancy. A key strategy is a team approach centred around antenatal, intrapartum and postpartum services that are linked to:

- harm-reduction services that refer pregnant IDUs to ANCs
- drug-dependency treatment experts (throughout the pregnancy)
- HIV/AIDS services
- psychological and social services
- specialist obstetric/midwifery services
- paediatrics/neonatology.

#### **2. Assessing drug dependence and withdrawal symptoms in pregnant women**

Underreporting of illicit drug use is common. Women who admit substance use, as well as those who do not but have injection marks or other signs suggesting such use, should be examined further.

Drug-using women are often dependent on more than one psychoactive substance (nicotine, alcohol, cannabis, opiates, cocaine, ecstasy, amphetamines, benzodiazepines) (23), and clinical signs and symptoms of use and withdrawal can be difficult to identify. It is also important to differentiate clinical signs of pregnancy and symptoms of complications from signs and symptoms of drug intake or withdrawal.

Women who use drugs may or may not be drug dependent. As drug dependency has implications for patient management strategy, it is crucial to assess it. A simple and rapid initial assessment can be done by ANC staff, based on 10 questions adapted from the *ICD-10 Symptom checklist for mental disorders* (24) (see also Protocol 5, *HIV/AIDS treatment and care for injecting drug users* (2007, Annex 2)). Several other validated and standardized drug-dependence screening and assessment instruments are available, including the Addiction Severity Index (ASI) (see Protocol 5, *HIV/AIDS treatment and care for injecting drug users* (2007), Annex 1) However, further evaluation of drug-dependence severity and appropriate treatment strategy should be done by or in close collaboration with a drug dependency treatment expert.

### 3. Impact of psychoactive substances during pregnancy and withdrawal

The effects of psychoactive substances during pregnancy are divided into withdrawal symptoms (Table 4) and the effects of drug use on the foetus and neonate (Table 5).

| <b>TABLE 4. SIGNS AND SYMPTOMS OF WITHDRAWAL FROM SPECIFIC SUBSTANCES DURING PREGNANCY</b>   |   |
|--|---|
| <b>Substance</b>   | <b>Signs/symptoms</b>   |
| Alcohol  | Agitation, tremors, sleep disturbance, tachycardia, hypertension, nausea, dilated pupils, seizures  |
| Delta-9-tetrahydrocannabinol (in cannabis, marijuana, hashish)   | Restlessness, irritability, mild agitation, insomnia, nausea, cramping  |
| Tobacco  | Irritability, restlessness, difficulty concentrating, impaired task performance, anxiety, hunger, weight gain, sleep disturbance, cravings, drowsiness                  |
| Central nervous system (CNS) sedative hypnotics: alprazolam, barbiturates, chlordiazepoxide, diazepam, flurazepam, glutethimide, meprobamate, methaqualone, etc. | Tremulousness, insomnia, chronic blink reflex, agitation, toxic psychosis, seizure, anxiety, agitation, muscle cramps, sleep disturbance, hypertension, fever, anorexia |
| CNS stimulants: methamphetamines, cocaine, methylphenidate, phenmetrazine, dimethyltryptamine, phencyclidine (PCP)   | Muscle aches, abdominal pain, hunger, prolonged sleep, suicidal ideas, bradycardia, craving, depression   |
| Opiates: codeine/oxycodone, heroin, hydromorphone, triplennamine   | Flu-like syndrome, agitation, dilated pupils, abdominal cramps, insomnia, anxiety, craving, tachycardia, hypertension   |

Source: Rayburn, Bogenschutz (25).

| <b>TABLE 5. THE EFFECTS OF PSYCHOACTIVE SUBSTANCES ON THE FOETUS, NEONATE AND PREGNANCY OUTCOME</b> |  |
|---|--|
| <b>Substance</b>  | <b>Effects</b>   |
| Alcohol   | Spontaneous abortion, microcephaly, growth deficiency, CNS dysfunction including mental retardation and behavioural abnormalities, craniofacial abnormalities (short palpebral fissures, hypoplastic philtrum, flattened maxilla), behavioural abnormalities                                     |
| Tobacco   | No congenital anomalies, intrauterine growth restriction (200 g lighter), preterm birth, placenta previa, placental abruption  |
| Marijuana (Delta-9- tetrahydrocannabinol)   | No congenital anomalies, reduction of 0.8 weeks in the length of gestation, corresponding decrease in birth weight, subtle behavioural alterations   |
| CNS stimulants: antiobesity drugs, methamphetamines, cocaine, methylphenidate, phenmetrazine        | Spontaneous abortion, hyperactivity in utero, congenital anomalies (heart, biliary atresia), depression of interactive behaviour, urinary tract defects, symmetric growth restriction, placental abruption, cerebral infarction, brain lesions, foetal death, neonatal necrotizing enterocolitis |
| Narcotics: codeine, heroine, hydromorphone, meperidine, morphine, opium, pentazocine, triplennamine | Foetal growth restriction, no anomalies, intrauterine withdrawal with increased foetal activity, depressed breathing movements, preterm rupture of membranes, preterm delivery, meconium-stained amniotic fluid, perinatal death   |

Source: Rayburn, Bogenschutz (25)

#### **4. Counselling on drug dependency and its treatment**

Counselling is an essential component in managing treatment of drug-dependent HIV-infected pregnant women. It should cover:

- the risks to the fetus and neonate from drugs;
- the benefits of opioid substitution therapy (OST) for the health of both mother and fetus;
- the risk of foetal stress due to uncontrolled withdrawal attempts without medical and psychological support;
- the effects of pregnancy on OST dose maintenance and the possible need to increase it;
- interactions between opioid substitutes and ARVs as part of PMTCT; and
- adherence to OST and ART.

#### **5. OST during pregnancy**

If opioid-using pregnant women meet the criteria for dependency (see Protocol 5, *HIV/AIDS Treatment and Care (2007)*, Annex 3) they should be counselled about the risks and benefits of OST, and an agreement should be reached for adherence to a treatment programme (26–28). Medications for the treatment of drug dependency (both opioid and non-opioid) in pregnant women are shown in Annex 2 below.

##### **5.1. Methadone substitution therapy**

Methadone substitution treatment is the currently recommended standard of OST for dependent pregnant women. OST prevents resumption of illicit drug use, withdrawal symptoms and craving, and it also reduces pregnancy-related complications (27,28). It has advantages and disadvantages, described in Table 6. It should be combined with prenatal care and psychosocial counselling, such as support groups, community reinforcement, contingency treatment, cognitive behavioural skills training, motivational therapy and marital behavioural therapy.

Data show that medical withdrawal of opioid-using pregnant women (including those on methadone) during pregnancy carries an increased risk to the foetus of intrauterine death, even under optimal conditions (27). There is evidence that methadone maintenance treatment, combined with prenatal services, promotes foetal growth, while continued use of heroin during pregnancy may result in infant morbidity (27).

| <b>TABLE 6. ADVANTAGES AND DISADVANTAGES OF METHADONE TREATMENT FOR PREGNANT WOMEN</b>  |   |
|---|---|
| <b>Advantages</b>   | <b>Disadvantages</b>  |
| Avoids contaminants that may harm the unborn child  | Increases the severity and duration of neonatal withdrawal compared to that of infants of untreated opioid-dependent mothers<br><br>Involves longer hospitalization and treatment of newborn infants<br><br>Leads to greater neonatal weight loss<br><br>Reduces demand of infant to feed |
| No known foetal abnormalities are associated with pure heroin or methadone  |   |
| Involves a known, regular dose  |   |
| Avoids periods of drug withdrawal that may be associated with miscarriage early in the pregnancy, or foetal growth retardation and stillbirth late in pregnancy |   |
| Reduces the incidence of premature birth  |   |
| Reduces the risk of intrauterine growth retardation   |   |
| Increases use of ANC services.  |   |

Source: Brown et al. (27)

Methadone is a long-acting substance which, if adequately prescribed, provides a relatively non-stressful environment in which the foetus can develop throughout pregnancy. Methadone provision should begin as early in pregnancy as possible; the T1 is optimal for both foetus and mother, and is associated with higher birth weights.

#### **5.1.1. Dosage**

The methadone dose should always be individually determined by the absence of subjective and objective abstinence symptoms and reduction of drug craving. The lowest effective dose should be used. Doses below 60 mg/day are not effective, and low-dose policies for pregnant patients often result in increased illicit drug use as well as reduced programme retention (27). A small number of methadone patients are aberrant metabolisers, and some medications may speed liver metabolism. Such cases may require doses in excess of 120 mg/day.

#### **5.1.2. Dosage reduction (detoxification)**

Once a patient is stabilized on methadone, it should be decided in consultation with her whether a slow reduction, finishing sometime before the birth, is realistic, or whether methadone maintenance must continue. Dose reduction is only possible to consider if the pregnancy is stable and has reached the T2. Dose reductions of 2.5–5.0 mg per week are considered safe (27). Withdrawal symptoms should be avoided as much as possible, as they cause the foetus considerable distress.

#### **5.1.3. Dosage increase**

During the later stages of pregnancy, methadone dosage may have to be increased or split (half each in the morning and evening) to produce a beneficial effect since greater plasma volume, an increase in plasma proteins that bind methadone and renal blood flow during pregnancy can contribute to a reduced plasma blood level of methadone. It may therefore be necessary to increase the methadone dosage by 5–10 mg to avoid withdrawal symptoms and prevent concurrent drug use. Note that the administration of NVP or EFV as part of a PMTCT regimen requires an increase of methadone.

#### 5.1.4. Interactions between methadone and ARVs

Interactions between methadone and ARVs are the same in pregnant women as in other patients. If a pregnant woman receives an NNRTI (NVP or EFV) as part of a PMTCT regimen, the dose of methadone has to be increased, as NNRTIs significantly decrease the concentration of methadone and generate withdrawal symptoms. In a case series of chronic methadone recipients initiating NVP, 50–100% increases in the daily methadone doses were required to treat opiate withdrawal. Withdrawal symptoms generally occurred between four and eight days after starting NVP (27).

SQV/r slightly reduces levels of methadone; no dosage adjustment is necessary, but continual monitoring is required. No significant effect with ATV (boosted or unboosted). LPV/r decreases methadone concentrations by 26–28% with the potential for withdrawal symptoms.

Methadone significantly increases ZDV concentration (up to 43%), which may increase the risk for adverse effects; close monitoring rather than routine dose adjustment is required.

Other NRTIs, maraviroc and raltegravir do not interact significantly with methadone.

#### 5.2. Buprenorphine substitution therapy

Although buprenorphine has not been recommended during pregnancy, North American and European studies (29,30) have shown that maternal treatment with buprenorphine reduces both the duration of treatment for neonatal abstinence syndrome (NAS) and the neonate's length of hospital stay, compared to methadone. In the RCT no differences from methadone were observed in maternal or neonatal adverse outcomes (29). A small number of HIV-positive women were included in the Swedish study, which compared a prospective cohort treated with buprenorphine to a retrospectively analysed historical control group taking methadone (26).

As with methadone therapy, attention must be given to potential interactions between buprenorphine and ART, particularly NNRTIs, with a 50% reduction in buprenorphine concentrations (a trough and area under the curve [AUC] reported in non-pregnant women with EFV, and a similar effect is anticipated with NVP). ATV may increase buprenorphine concentrations by about 60%, whereas LPV has little or no effect and therefore may be preferred. No interactions with NRTIs, maraviroc or raltegravir are reported.<sup>2</sup>

### 6. Management of HIV-infected drug-dependent women presenting in labour

Many drug-using women do not attend an ANC and only arrive at the maternity ward around the time of labour. In such cases, maternity wards should be prepared to:

- assess drug dependence (see Protocol 5, *HIV/AIDS Treatment and Care for Injecting Drug Users (2007), Annex 1*) and inform the neonatologist;
- offer rapid HIV testing if status is unknown or was negative during pregnancy;
- provide relevant treatment for withdrawal symptoms;
- initiate OST as necessary; and
- counsel about the effects of drugs on the pregnancy outcome, the newborn infant and treatment approaches.

<sup>2</sup> See for example the Liverpool HIV Pharmacology Group's drug interactions website at <http://www.hiv-druginteractions.org/>, accessed 10 August 2011).

See Table 4 above for a PMTCT regimen for HIV-infected women who have not received ARV prophylaxis during pregnancy, irrespective of their drug-dependence status. For opioid-dependent women presenting in the maternity ward who receive ARVs at the onset of labour, methadone should be sufficient to prevent withdrawal symptoms.

Pain relief requires special attention during labour and the postpartum period, especially after a caesarean section. Pain management for opioid dependent pregnant women should be addressed in the same way as for other pregnant woman. A higher dose of analgesia may be needed to relieve pain. Epidural anaesthesia should be used as early in the delivery as possible, and can be continued in the early postpartum period, especially after a caesarean section.

## **7. Choice of ART regimen for drug users during pregnancy**

Confirmation of drug usage by urine toxicology will inform management. Many mothers will wish to reduce usage during pregnancy. The choice of ART will include consideration of adherence and coinfection factors. Despite low CD4 counts NVP may not be preferred because of coinfection with hepatitis viruses and abnormal liver function and the risk of treatment failure with poor adherence. Although once daily treatment, especially if observed administration is indicated, is likely to be preferred, EFV may not be suitable due to psycho-neurological side effects and the risk of drug resistance development (as with NVP) if adherence is an issue. Thus, a ritonavir-boosted PI that can be dosed once daily (e.g. ATV), may be preferred with a once-daily nucleoside backbone, especially if the mother is on methadone OST. The use of unboosted ATV in pregnancy is not recommended (see Annex 1). Data on ATV concentrations during T3, even when boosted with ritonavir, if administered with TDF, suggest that an alternative backbone to fixed-dose TDF-FTC may be preferred. Fixed-dose ABC-3TC once daily may be considered as an alternative. The methadone dose may need to be increased at initiation of LPV/r, which results in a 30% reduction in methadone concentrations. Conversely, LPV/r may be preferred if buprenorphine OST is recommended.

## IV. Management of labour and delivery

The management of labour and delivery is to a large extent determined by whether the patient is on ART with an undetectable HIV VL (<50 copies/ml), usually assessed at 36 weeks of gestation, on ART with a detectable VL or not on ART.

### 1. Patients on ART with an undetectable HIV viral load

#### 1.1. Term delivery

Continue oral ART throughout labour. If the patient has elected for a normal vaginal delivery labour and delivery should be managed as per an HIV uninfected pregnancy with the exception of invasive monitoring. Failure of labour to progress or obstetric complications should be managed as per routine practice and there is no indication to expedite delivery by caesarean section as the risk of HIV MTCT in this setting approaches zero. This also applies to spontaneous rupture of membranes in the absence of labour at term.

#### 1.2. Preterm delivery, <34 weeks

Spontaneous rupture of membranes: antibiotics to prevent ascending infection and steroids to mature lungs. Deliver as per HIV-uninfected pregnancy. Spontaneous/threatened labour: tocolysis and steroids to mature lungs. Deliver as per HIV uninfected pregnancy.

### 2. Patients on ART with detectable HIV viral load

#### 2.1. Term delivery

If ART was initiated during pregnancy and the VL is still in decline, consider the addition of sdNVP and deliver by caesarean section if in early labour; give standard triple prophylaxis to infant. If ART was initiated before or during pregnancy and the VL is not in decline, consider ARV resistance. SdNVP without intensification/change of a failing regimen does not improve transmission rates but does give rise to NVP resistance (31). Deliver by caesarean section if in early labour. Consider alternative triple prophylaxis to infant (PI-based).

Spontaneous rupture of membranes pre-labour: deliver by caesarean section at earliest opportunity.

#### 2.2. Preterm delivery, <34 weeks

Spontaneous rupture of membranes: antibiotics to prevent ascending infection and steroids to mature lungs. Delivery by caesarean section is advised but morbidity and mortality of severe preterm delivery in the local setting must be balanced with a low risk of HIV transmission. Maternal sdNVP will provide prophylaxis for up to one week in a neonate that may not be able to tolerate oral therapy or is at risk of necrotizing enterocolitis. Spontaneous/threatened labour: tocolysis and steroids to mature lungs. Deliver as per SROM above.

### 3. Detectable virus not on ART

#### 3.1. Term delivery

Spontaneous labour or rupture of membranes: sdNVP reduces transmission by 50% (32), therefore give it without delay. Efficacy of intrapartum ZDV is less certain and IV ZDV may not significantly reduce transmission (10%), provided neonatal prophylaxis is commenced within

48 hours of delivery (9.3%) (33). Deliver by caesarean section. If this is sooner than two hours after the maternal NVP dose, the first neonatal NVP is to be given immediately (34).

### **3.2. Preterm delivery, <34 weeks**

Initiate maternal ART, including sdNVP and manage as per detectable HIV on ART, but the risk of resistance (unless the maternal virus has transmitted resistance) is less.

PLCS reduces HIV MTCT by 80% in a population not selected by HIV VL (35). PLCS rates vary considerably across Europe, with differences in local practice lower in northern Europe than in southern (36). This ECS analysis also demonstrates the protection of PLCS even when maternal viraemia is <400 copies/ml (AOR 0.2 95% CI 0.05 – 0.65).

The efficacy of caesarean section once labour has started or following SROM is less clear. The lack of efficacy of emergency caesarean in some studies likely reflects the late nature of this intervention after many hours of labour/ROM as well as the independent HIV transmission risk associated with some of the indications for emergency caesarean section. Future analysis of its efficacy should categorize the indication into obstetric only and PMTCT.

## V. Management of an HIV-exposed Infant

There are no data to indicate that special cleansing methods are beneficial; routine care of the neonate is appropriate. ARV for the infant should be initiated as soon as possible after birth and in all cases before four hours.

### 1. Antiretroviral therapy

Neonatal ZDV was part of the sentinel Aids Clinical Trial Group (ACTG) 076 study which first demonstrated the efficacy of ZDV in PMTCT (37), but the study was not designed to demonstrate the contribution of the respective antepartum, peripartum and neonatal components. The efficacy of neonatal ZDV monotherapy is implied from cohort studies such as that of the New York State HIV PCR service, in which neonatal ZDV monotherapy reduced transmission compared to no therapy, provided it was administered within 48 hours (33). In most trials and cohort studies the infant component has been ZDV monotherapy and, as in the United Kingdom and Ireland cohort (17), very low rates of transmission are observed, in combination either with maternal ZDVm plus PLCS or maternal ART.

In the absence of data most clinicians and some guidelines<sup>3</sup> have recommended combination therapy if the neonate has been exposed to HIV late in pregnancy, either due to late maternal presentation, maternal treatment failure or non-compliance. In the National Institute of Child Health & Human Development/HIV Prevention Trials Network 040 study, triple ART regimens initiated within 48 hours of birth to reduce HIV MTCT in infants whose mothers had no ART during pregnancy were compared. The in utero transmission rate was 5.7% with no significant differences among the therapies. However, both the addition of three doses of NVP in the first week (2.2%) and of 3TC with nelfinavir for two weeks (2.5%) to the standard ZDV for six weeks treatment reduced peripartum transmission from 4.5% with ZDVm (21). Interpatient variability was large and nelfinavir concentrations frequently low in these infants (38). Although nelfinavir is no longer prescribed, these data lend support to the use of triple ARV post-exposure prophylaxis in this setting. The choice of combination should be informed by maternal HIV sequence data or, if this is not available, the maternal treatment history. Where wild type virus is known (or suspected) to be present, ZDV 4mg/kg every 12 hours with 3TC 2mg/kg every 12 hours for four weeks plus NVP (2mg/kg daily for the first week increasing to 4mg/kg daily for the second week, after which NVP can be discontinued), is recommended, and is most readily available in syrups, with supportive pharmacokinetic data.

When treatment with ZDV, 3TC and NVP is inappropriate (likely to fail due to pre-existent resistance) alternative PI-based treatment is indicated. Available agents (as syrups) are LPV/r (300mg/m<sup>2</sup> twice daily, but doses for neonates less than 14 days are not confirmed.<sup>4</sup> Local epidemiological data on the prevalence of transmitted resistance should inform treatment choices. Attention has been drawn to the high concentration of propylene glycol and ethanol content in some liquid formulations and case reports of cardiotoxicity and other life-threatening conditions (39). Clinical and biochemical evidence of adrenal suppression has also been reported in term neonates treated with LPV/r (see Annex 1). Any infant treated with LPV/r must be very closely monitored for evidence of adrenal suppression.

<sup>3</sup> For example, those of the Children's HIV Association (CHIVA) at <http://www.chiva.org.uk/professionals/health/guidelines/mtct/perinatalcare.html>

<sup>4</sup> See the Children's HIV Association website's "Paediatric HIV drug dosing chart" at <http://www.chiva.org.uk/health/dosing>, accessed 10 August 2011.

## 2. Treatment of the preterm infants

Severely preterm infants may not absorb oral medication and may be placed at increased risk of necrotizing enterocolitis. Where maternal treatment has been adequate, parenteral ZDV monotherapy remains the treatment of choice. For late presenting mothers, maternal NVP during labour will reduce the risk of transmission with persistence of transplacentally acquired NVP in the neonate for up to 10 days.<sup>5</sup> (The addition of an intrapartum maternal dose of TDF with FTC has been shown to reduce the frequency of detection of NVP-related mutations (41) but a double dose of maternal TDF is required to achieve adequate concentrations (42). The only other compound available for parenteral administration is enfuvirtide for which there are limited dosing data in infants (43). LPV/r should be avoided in preterm neonates because of the increased risk of adrenal suppression (see Annex 1) and the toxicities described above.

## 3. Duration of preventive ART in the infant

Therapy in the neonatal component of ACTG 076 was continued for six weeks. In the United Kingdom and Ireland cohort low transmission rates in the absence of breastfeeding (<1%) have been achieved despite reducing it to four weeks. The best data on the efficacy of different durations of neonatal ZDV are from a Thai study in which short and long maternal and infant regimens were compared (6). In this ZDV monotherapy study, short maternal therapy (3 days) was initiated at 36 weeks, and long maternal therapy (6 weeks) started at 28 weeks. The “short-short” regimen had the highest transmission rate, but extending infant therapy from three days to six weeks did not improve outcomes provided that the mother had initiated therapy at 28 weeks. Despite these data being published for more than 10 years, guidelines have continued to recommend four weeks ZDV regardless of maternal therapy. When mothers are on ART, have an undetectable VL and intend to formula-feed, a strong case can be made for reducing neonatal ZDV exposure to one week. The case for this includes reduced drug exposure, reduced risk of inadvertent disclosure, potentially improved adherence and normalization of the early maternal experience.

When an infant is prescribed combination therapy for a perceived increased risk of exposure, it should be given, as per adult guidelines, for 4 weeks. (There are no data to suggest longer treatment is beneficial).

## 4. Infant Feeding

Avoidance of breastfeeding completely eliminates the risk of post-partum HIV MTCT (43-45). This is recommended provided the AFASS criteria (acceptable, feasible, affordable, safe and sustainable) are met (see Annex 3). Exceptions are determined by resources and local circumstance and not by geography. Despite the desire by many mothers to breastfeed and many social and cultural pressures, exclusive infant-formula feeding has been accepted by the majority of HIV positive mothers in AFASS settings in the European Region and others. Indeed, choosing to expose a baby to HIV through breastfeeding has been considered a child protection issue in some countries.

A post-hoc analysis of a vitamin A supplementation study revealed higher rates of transmission with mixed feeding than with exclusive breastfeeding (46). Exclusive breastfeeding for six months followed by rapid weaning was recommended, but many studies in resource-poor settings reported high morbidity and mortality following early weaning (47,48). In RCT in Kenya, HIV-free survival was significantly lower ( $p < 0.02$ ) in the breastfeeding arm (58%) compared with the formula-feeding arm (70%) (49).

<sup>5</sup> Clearance is faster in term babies exposed continually, i.e., for several weeks, to NVP in utero (19).

Data from cohorts (50, 51–53) and subsequently from RCTs in Africa (54,55) demonstrated that post-partum maternal ART significantly reduced HIV MTCT, leading to a new WHO global recommendation for exclusive breastfeeding for five months followed by gradual weaning with maternal ART until cessation of all breastfeeding when the use of infant formula does not meet AFASS criteria, unless the mother was not treated with ART during pregnancy, in which case continued infant daily NVP is recommended (56). A joint position statement by the British HIV Association and the Children’s HIV Association has considered the implications of these new data for the United Kingdom, where exclusive formula feeding is AFASS compliant. They note that although the post-partum transmission risk is significantly reduced, transmissions do occur (up to 3%), and conclude that exclusive formula feeding should continue to be recommended (57). They also specifically recommend that prolonged infant NVP not be used in this setting until further safety data are available.

The Region in general supports infant formula feeding of HIV exposed infants. Still considering breastfeeding as a possible option in some settings of eastern Europe, the Regional Office for Europe set a target to virtually eliminate MTCT in the Region, considering MTCT rate < 2% in non-breastfeeding and <5% in breastfeeding populations in its European HIV/AIDS Plan 2011–2015, endorsed at the WHO Regional Committee in September 2011 (58).

HIV-infected mothers should be helped to make the best choice according to their circumstances and to carry out their decision. They should thus receive counselling that includes information about the risks and benefits of various infant feeding options, based on local conditions, and guidance in selecting the most suitable option for their situation. Whichever infant feeding option is chosen, mothers should be supported in carrying it out safely and appropriately. While commercial infant formula will be acceptable, feasible, affordable, sustainable and safe for many HIV-positive women in the European Region, some women will choose other options according to their personal circumstances.

#### **4.1. Scenario 23: Infant formula milk feeding is AFASS**

*Goal:* Prevention of post-partum HIV MTCT.

*Issue:* Exclusive breastfeeding and mixed feeding without the use of ART carry significant risks of post-partum transmission. Data from RCTs in settings where use of infant formula milk does not satisfy the AFASS criteria show low but not zero rates of HIV transmission during up to six months of exclusive breastfeeding with gradual weaning, in the presence of maternal or infant ARVs.

*Preferred option:* Where resources allow safe use of infant formula milk is the preferred option and carries no risk of HIV transmission.

#### **4.2. Scenario 24: Infant formula milk feeding is not AFASS**

*Goal:* Prevention of post-partum HIV mother to child transmission.

*Issue:* In settings where the use of infant formula milk is not AFASS, data from RCTs of ART show low but not zero rates of HIV transmission during up to six months of exclusive breastfeeding with gradual weaning, if mother or infant receive ARVs. Mothers established on ART during pregnancy continued this throughout the breastfeeding period. Mothers who took ZDV during the T2 plus sdNVP in labour with a dual nucleoside backbone to cover the NVP tail stopped therapy and NVP monotherapy was given to the infant throughout the breastfeeding period. There are no data on gradually weaning with continued maternal ART as advocated in

the current WHO guidelines on infant feeding (56), but it is thought to be safer than rapid weaning with cessation of ART at six months.

*Preferred option:* Continuation of maternal ART significantly reduces the risk of post-partum MTCT and should be continued until completion of weaning by 12 months infant age.

## 5. Management of dependence and withdrawal syndrome in neonates

### 5.1. Clinical examination

Neonatal withdrawal or abstinence syndrome (NAS) occurs in 50–80% of infants exposed to opioids in utero, usually within the first 24–72 hours after birth. However, only 5–20% of these infants have severe symptoms and need pharmacotherapy (59). NAS from buprenorphine peaks within three or four days and lasts for five to seven days; NAS from methadone generally lasts up to four days (60). Clinical symptoms of NAS vary in severity and duration and include tremors, increased muscle tone, restlessness and sleeping problems; protracted crying, hyperactive reflexes; regurgitation, vomiting and diarrhoea; tachypnoea and minor symptoms such as fever, sneezing, sweating, nasal stuffiness and yawning.

Infants of mothers known or suspected to be drug users who show signs of withdrawal should be scored every four hours. The scoring should be applied in a consistent manner. Please see the scoring system for the signs and symptoms of NAS in Annex 4, which provides a basis for deciding treatment dosages (see also Table 8 below).

### 5.2. Treatment of NAS

The aim of NAS treatment is to give the infant a chance to rest, get enough sleep and eat enough food; it will not eliminate all symptoms. The treatment should be carried out as follows (61).

- *First stage, supportive therapy:* Provide a low-stress environment (quiet room, reduced illumination, swaddling, holding, hammock, pacifier), frequent small feedings (on demand) and no abrupt changes. If symptoms worsen, proceed to the second stage.
- *Second stage, pharmacological therapy:* According to the *Cochrane Review*, first-line treatment for NAS due to opiate exposure in utero is with an opiate (62). When additional therapy with a sedative is required, phenobarbitone is preferred to diazepam. Therapeutic doses of morphine for NAS treatment vary (Table 7) depending on the NAS score (Annex 3). Occasionally, vomiting may be very serious, in which case the pharmacological agent should be temporarily replaced with chlorpromazine (2–3 mg/kg/day in 3 or 4 doses intramuscularly). Sublingual buprenorphine 15.9mcg/kg/day in 3 divided doses has been used in the treatment of NAS, resulting in reduced duration of treatment compared to morphine. However, the treatment involved preparation of buprenorphine for injection with 30% ethanol (60) and sucrose (63,64).

| Abstinence score | Solution                  |                         |
|------------------|---------------------------|-------------------------|
|                  | Morphine 1 mg/ml          | Phenobarbital 10 mg/ml  |
| 8–10             | 0.32 mg/kg/day in 4 doses | 6 mg/kg/day in 3 doses  |
| 11–13            | 0.48 mg/kg/day in 4 doses | 8 mg/kg/day in 3 doses  |
| 14–16            | 0.64 mg/kg/day in 4 doses | 10 mg/kg/day in 3 doses |
| 17+              | 0.80 mg/kg/day in 4 doses | 12 mg/kg/day in 3 doses |

Interactions among ARV drugs for neonates as part of PMTCT and the dosage of the NAS treatment have not yet been studied. However, although LPV/r does not affect buprenorphine metabolism, concerns over potential toxicity due to the ethanol and propylene glycol content of the liquid formulation remain. Though liver enzyme induction in neonates exposed to NVP in utero occurs, no interaction with morphine is reported (in adults). Ritonavir (in the doses used as a pharmacological enhancer) may reduce morphine concentrations through induction of glucuronidation.

## 6. Immunization

Immunization of HIV-infected children with bacille Calmette-Guérin (BCG) is no longer recommended, even in high incidence regions, due to the risk of disseminated BCG disease and the relative lack of efficacy in HIV-infected infants.<sup>6</sup>

For infants born to HIV-infected mothers in regions where the incidence of TB is greater than 20 cases per 100 000 population and where early HIV diagnostic testing can be performed, BCG can be deferred until diagnostic test results excluding HIV infection are available. In settings where BCG is routinely given, and HIV early diagnosis is not available, BCG still should be given to all. Other vaccinations should be considered, taking into account the national vaccination programmes.

## 7. Diagnosis of infant HIV status

Goal: early HIV infant diagnosis for proper clinical management of infant, including prompt initiation of ART if the infant is infected

If resources allow, the first DNA PCR test for HIV should be performed within 48 hours of birth. Testing of the umbilical cord blood should not be done due to possible risk of contamination with maternal blood. A positive test will provisionally mean that the newborn infant is infected and further HIV DNA/RNA testing should be undertaken straight away to confirm the diagnosis and enable an early switch from ZDVm to ART. If negative, further HIV DNA tests at six and twelve weeks from birth should be performed. The third test may be more important if the risk of transmission is considered to be high and ART prophylaxis is prescribed for four weeks. Further investigation of any positive result should be undertaken without delay to allow appropriate early therapy if HIV infection is confirmed. Where HIV DNA testing is not available, HIV RNA assays can be used but the pitfalls of both low copy number RNA false positives and negative results during or shortly after infant ART for PMTCT need to be recognized and such results interpreted with caution. Even for HIV-exposed children testing negative, follow up and documentation of seroreversion by an HIV antibody test is recommended at 15–18 months. The sensitivity of fourth generation assays means low titres of maternal antibody can be detected even at 15 months in uninfected children and should be interpreted with caution or the test delayed until 18 months.

HIV diagnostic testing for infants should be accompanied by counselling for caregivers, explaining the results and the need for additional testing to definitively determine the child's infection status. Only infants considered at high risk of HIV infection should be treated with co-trimoxazole prophylaxis from four weeks of age, against *Pneumocystis jirovecii* (PJP), until all their HIV diagnostic results are available. Please see Protocol 11, *Paediatric HIV/AIDS Treatment and Care (2012 revision)*, section II.1.

<sup>6</sup> See the Global Advisory Committee on Vaccine Safety bulletin at [http://www.who.int/vaccine\\_safety/topics/bcg/hiv\\_infected/Jan\\_2010/en/index.html](http://www.who.int/vaccine_safety/topics/bcg/hiv_infected/Jan_2010/en/index.html), (accessed 7 September 2011)

## VI. Starting, stopping and monitoring antiretroviral therapy

### 1. Timing of initiation of antiretroviral therapy in pregnancy

Most authorities would agree that unless imperative for the immediate well-being of the mother, ART should be deferred until completion of T1. This removes any concern regarding teratogenicity and avoids the introduction of therapies associated with nausea and vomiting at a time when these symptoms might be compounded by the hormonal changes of pregnancy. Given the high, normal early miscarriage rate, regardless of HIV status, this strategy also avoids unnecessary, short-course treatment in women who have an early spontaneous abortion, who would only be prescribed ART to prevent HIV MTCT. If deferred until completion of organogenesis, treatment given primarily for maternal health reasons should be started immediately after completion of T1 (65).

The optimal timing of treatment primarily for PMTCT is less certain. Studies have demonstrated the efficacy of ART initiated from early T2 (37) as well as in T3 (9). Consistent with these data Townsend et al. demonstrated good efficacy in women who had been on treatment for at least 14 days (17). However, most studies indicated preterm delivery rates of 13–20%. In the absence of robust early predictors of PTD, earlier treatment is recommended to mitigate this risk. Twenty-eight weeks has been regarded as the latest time to initiate ARVs, and there is a case for maternal therapy from foetal viability (~24 weeks). In a retrospective study, Reid et al. have demonstrated the importance of baseline VL to the probability of achieving viral replication suppression (as measured by an undetectable VL) by the time of delivery (8). They found that in women with baseline HIV VL >100 000 copies/ml, only 10% of those starting treatment after 21 weeks had achieved an undetectable VL (<50 copies/ml) by delivery. By quartiles, only the upper quartile (VL >32 000 copies/ml) had significantly higher rates of detectable viraemia at delivery. This relatively small study did not observe an increased risk of transmission in this group. However, some guidelines, recommend PLCS if VL remains detectable at delivery and the authors argue therefore that early ART will reduce the incidence of PLCS.

### 2. Monitoring therapeutic response

The baseline CD4 cell count, ideally repeated once before initiating ART, is sufficient to determine the recommended duration of therapy, and further measurement of the CD4 during pregnancy is of limited value. The exception is where the baseline CD4 count is less than 200 cells/mm<sup>3</sup>, in which case further measurements are required to determine when to discontinue OI prophylaxis.

Measuring HIV VL two weeks after initiating long-term or short-term ART allows an early assessment of therapeutic response. This is particularly important in pregnancy, when the time to undetectable is even more important than in non-pregnant patients. A further VL eight weeks into therapy is helpful to further assess the response to therapy and detect any problems. A VL at 36 weeks gestational age is essential to ensure the absence of detectable HIV RNA in plasma as the pregnancy reaches term. Failure to achieve the expected response at any time will necessitate further assessment as per Scenario 5.

Where resources available sequencing of HIV at baseline allows appropriate treatment with drugs that are fully effective.

### 3. Therapeutic Drug Monitoring (TDM)

Measurement of pre-dose concentrations of ART is useful when ARVs are being used in pregnancy under the following conditions:

- unknown pharmacokinetics of the ARV in pregnancy
- non-standardized dosage
- important drug-drug interaction known or anticipated
- suspected dose-related toxicity.

TDM can be used to adjust therapy to the individual, especially when wide inter-patient variability of drug concentrations has been reported. This can help avoid unnecessarily increasing doses during the later stages of pregnancy. TDM can also be used in cases of treatment failure where poor adherence or non-adherence is suspected, but it is not a substitute for routine adherence monitoring. TDM is not at present widely available in the Region and thus is not recommended as a routine practice.

### 4. Stopping ART used for PMTCT

Common practice is to discontinue ART started in pregnancy under these circumstances. Since pregnancy was not included in the studies of early HIV therapy with treatment interruptions, it is not known whether the concerns regarding the incidence of HIV-related disease, both infectious and inflammatory, apply to short courses of ART for PMTCT. In a retrospective cohort study, good maternal health was observed during a median of 33 months follow-up post-partum regardless of the treatment type and duration during pregnancy, but numbers were small and data collection likely to be incomplete (66). In a study comparing women who continued ART post-partum with those who discontinued it, the latter tended to have better immune function and the outcomes did not differ significantly, although AIDS-defining events and all cause deaths were lower in the former (67). The characteristics of the cohorts differed considerably, with a history of illicit drug use rare in the United Kingdom study (3%) and common (38%) in the American study. The CD4 count at presentation when HIV infection is diagnosed through antenatal screening is much higher than when HIV is diagnosed through other testing strategies and a significant number of women have CD4 counts  $>500$  cells/mm<sup>3</sup> and persistently low HIV VLs. Studies to determine whether ART once initiated, even for PMTCT, should be continued indefinitely are required to inform practice. Until such time, the health care team should balance the risks of continuing or discontinuing ART based on current data and the wishes and circumstances of the patient, on a patient-by-patient basis. A multicentre programme in Africa and Thailand found that the cumulative probability of pregnant women with baseline CD4 counts  $>400$  cells/mm<sup>3</sup> and treated with short term or single-dose ARV for PMTCT becoming eligible for long-term ART at 24 months post-delivery was 28% (68).

## VII. Suggested minimum data to be collected at the clinical level

The suggested minimum data collections are important in the development of key indicators of access to PMTCT services and their success. Such indicators assist managers in decision-making to strengthen and expand these services to all women who need them. The following data should be collected at the clinical level on a regular basis (e.g. monthly, quarterly or semi-annually).

ANCs should collect the numbers of:

- pregnant women
- pregnant women offered and recommended an HIV test
- pregnant women tested for HIV
- pregnant women tested positive for HIV
- HIV-infected pregnant women terminating pregnancy
- HIV-infected pregnant women receiving ART for their own health
- HIV-infected pregnant women receiving ART for PMTCT purposes only
- HIV-infected pregnant women who are opioid-dependent injecting drug users
- HIV-infected pregnant women receiving OST
- HIV-infected pregnant women receiving OST and ARV prophylaxis.

Maternity inpatient services should collect the numbers of:

- women presenting without prior HIV testing during pregnancy and
  - receiving a rapid HIV test and
  - testing HIV positive (rapid test reactive)
  - testing HIV positive (confirmed)
- known HIV-infected women presenting without receiving ARV prophylaxis during pregnancy
- HIV-infected women receiving ARV prophylaxis during labour
- HIV-infected opioid-dependent injecting drug users and those receiving OST during labour
- HIV-infected women having vaginal delivery
- HIV-infected women having caesarean section and those
  - having a PLCS
  - having CS for which the only indication was PMTCT
- neonates born to HIV-infected women and those
  - receiving ARV prophylaxis
  - receiving infant formula milk feeding
  - exclusively breastfed and those
    - on long-term ARV prophylaxis
    - whose mothers were on long-term ART
- HIV-infected neonates born to HIV-infected women, diagnosed by PCR
- neonates born to opioid dependent women
- neonates receiving NAS treatment.

## Annex 1. ARVs during pregnancy

### 1. Nucleoside/tide analogue reverse transcriptase inhibitors

No changes in the dosage of nucleoside/tide analogues are required during pregnancy.

**Zidovudine (ZDV)** has been widely used in the prevention of HIV MTCT since the ACTG 076 study in 1994, first as monotherapy and later as part of ART. In the study, ZDV monotherapy (ZDVm) reduced MTCT by 67% with a regimen of maternal ZDV from the end of T1, IV ZDV infusion during labour and delivery and infant ZDVm four times daily for six weeks (37). The relative contribution of each component has not been defined. In a study from Thailand a mean of 25 days ZDVm with oral dosing during labour and no infant therapy reduced transmission by 50% (69), and six weeks infant ZDV was no better than three days, provided the mother had been treated with ZDV from gestational age 28 weeks (9,70).

Prospective reporting to the Antiretroviral Pregnancy Registry (APR) has not revealed any increased risk of congenital malformations with T1 exposure, and sufficient cases have been reported to exclude a greater than 1.5-fold risk increase. Severe mitochondrial toxicity attributed to ZDV in HIV-exposed uninfected children exposed to ZDV ± 3TC in utero and ZDV in the first weeks of life was reported from the French cohort, with additional anecdotes (69). This effect seems rare and it has been suggested that it is less common with ART that fully suppresses HIV replication. Self-limiting, albeit prolonged, anaemia and neutropenia are reported in infants exposed to ZDV, but treatment is rarely required.

ZDV is generally well tolerated in pregnancy. The most common initial side effects are headache, nausea and vomiting, which are usually transient. ZDV causes skin and nail pigmentation. It can be continued despite nearly universal macrocytosis, but it may need to be avoided in patients presenting with anaemia. ZDV treatment during pregnancy does not usually cause lipodystrophy but this is eventually common.

In many countries ZDV is no longer routinely prescribed as first-line therapy in adults and consequently many HIV-positive women conceive on non-ZDV containing regimens. Despite ZDV's proven efficacy in PMTCT, there are no data to suggest that switching to it is required in a patient successfully treated with ART. ECS and National Study of HIV in Pregnancy and Childhood data have shown no difference in the safety or efficacy of non-ZDV containing ART and ZDV-based ART (7). Thus, though ZDV remains a common component of ART in pregnancy, it is no longer considered an essential component of ART for PMTCT. The indications for IV ZDV during labour/caesarean section are ZDVm with PLCS and spontaneous labour with detectable HIV VL. Infant treatment with ZDV is given twice daily and generally shortened to four weeks only. ZDV crosses the placenta efficiently and much of its efficacy in PMTCT is attributed to its prophylactic effect.

The efficacy of ZDVm in PMTCT has been demonstrated in a number of RCTs, but they predated the availability of ART and transmission rates remained at ≥ 6%. Three PMTCT strategies have been associated with transmission rates of ~1- 2%: ART; ZDVm plus single dose NVP and ZDVm plus pre-labour; and PLCS. Until recently data on ART in PMTCT were available only from cohort studies. In the Women Infants Transmission Study (WITS), transmission was 1.1% among women on ART during pregnancy (71), while the National Study of HIV in Pregnancy and Childhood – which included more than 90% of all HIV-positive pregnant women in the United Kingdom and Ireland – the overall transmission rate was 1.2%, regardless of treatment,

reflecting both the high uptake of interventions and the 0.1% transmission rate among 2117 infants born to women on ART with an undetectable HIV VL at delivery (17). Similar findings have been reported from the ANRS French Perinatal Cohort with a 0.4% transmission rate if the HIV VL was undetectable at delivery (72). Neither study demonstrated lower transmission rates with ART compared to ZDVm, although in the French cohort all women had been treated with ART since 2004.

In the United Kingdom, ZDVm has remained an option provided four criteria are met: the mother did not require ART for her own health, willingness to delivery by PLCS, an HIV VL < 10 000 copies/ml and no genotypic evidence of reduced susceptibility to ZDV. There were no transmissions among the 464 women who elected for this approach (17). In a study from Thailand of non-breastfeeding women, the addition of one maternal and one infant sdNVP to standard ZDVm resulted in a 1.9% transmission rate compared with 6.3% with ZDVm alone (73). In a study from Botswana women with counts  $\leq 200$  cells/mm<sup>3</sup> were commenced on NVP plus ZDV and 3TC while women with CD4 counts  $> 200$  cells/mm<sup>3</sup> were randomized to a triple NRTI regimen (ABC, 3TC, ZDV) or a PI-based regimen (LPV/r plus 3TC and ZDV). The overall transmission rate was 1.1%, inclusive of 6 months exclusive breastfeeding while continuing therapy, with no significant differences between the arms of the study (55). Given the efficacy of ART without the need for PLCS, ART has become the option of choice for the majority of HIV-positive pregnant women and ZDVm is now rarely used.

**3TC** is well tolerated in pregnancy. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 exposure and sufficient cases have been reported to exclude a greater than 1.5-fold risk increase. The addition of 3TC to ZDV reduces HIV transmission, but resistance develops rapidly with this dual therapy and this should be avoided (74,75). 3TC crosses the placenta efficiently.

**Didanosine** is well tolerated in pregnancy. However, there is a signal from the APR that there may be an increased risk of congenital malformations with T1 exposure, despite no pattern of abnormality. Didanosine is now less commonly prescribed in adults than previously. The combination of didanosine with stavudine must not be prescribed in pregnancy due to an increased risk of lactic acidosis with reported fatalities. The maternal:cord blood ratio is 1:0.3.

**Stavudine** is well tolerated in pregnancy. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 exposure and sufficient cases have been reported to exclude a greater than two-fold risk increase. Stavudine was commonly prescribed instead of ZDV to avoid anaemia, but mitochondrial toxicity is more common, particularly disabling peripheral neuropathy. The combination of stavudine with didanosine must not be prescribed in pregnancy due to an increased risk of lactic acidosis with reported fatalities. Stavudine is no longer recommended in the management of adults with HIV infection.

**Abacavir** is well tolerated in pregnancy. HLA genotyping to detect HLA-B57\*01 and avoid ABC hypersensitivity syndrome is recommended. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 exposure and sufficient cases have been reported to exclude a greater than two-fold risk increase. ABC crosses the placenta well with cord blood equivalent to maternal blood concentrations. The maternal:cord blood ratio is 1.03 (76).

**Emtricitabine**'s safety, tolerability and efficacy in pregnancy are not well documented, despite its wide prescription in combination with TDF. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 exposure and sufficient cases have been reported to exclude a greater than two-fold risk increase. Pharmacokinetic studies are

being conducted by the European PANNA Network and in the United States by the IMPAACT study team.

**Tenofovir** is well tolerated in pregnancy. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 exposure and sufficient cases have been reported to exclude a greater than two-fold increase risk. Pharmacokinetic studies are being conducted by the European PANNA Network. In animal studies, impaired bone development was observed with in utero exposure, but this has not been replicated in human data. Proteinuria in pregnant women on TDF requires careful evaluation and interpretation.

## 2. Non-nucleoside reverse transcriptase inhibitors

**Nevirapine** has been widely used in pregnancy and no dose adjustment is required. Pharmacokinetic data on EFV and etravirine are limited. There are insufficient data to comment on the safety, teratogenicity, tolerability and efficacy of etravirine during pregnancy. The merits of prescribing etravirine during pregnancy for maternal and child health must be compared with the unknown risks.

NVP's safety, tolerability and efficacy of NVP in pregnancy have been extensively documented. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 exposure and sufficient cases have been reported to exclude a greater than two-fold risk increase.

NVP is well tolerated in pregnancy. Data from non-pregnant adults demonstrate an increased risk of severe undesirable effects, particularly hepatitis and Stevens-Johnson syndrome in females with a CD4 lymphocyte count in the range 250–400 cells/mm<sup>3</sup> or higher. Adverse events have also been reported in pregnant women (12,77), but a number of studies have reported good safety with NVP during pregnancy even when prescribed at CD4 cell counts greater than 250cells/mm<sup>3</sup> (14,15,78). Other risk factors for hepatitis with NVP are coinfection with hepatitis viruses and abnormal liver function tests (79). Together these caveats now restrict the use of NVP in the treatment naïve setting to a carefully characterized group of women. Switching treatment in women (pregnant or not) with fully suppressed HIV replication is now considered to be safe, however (80).

The efficacy of NVP in reducing MTCT has been demonstrated in several RCTs. In HIVNET 012, sdNVP given in labour and supplemented with an infant dose at 48–72 hours reduced HIV MTCT at age 3 months by 47% compared to intrapartum oral ZDV (33). As described above, the addition of sdNVP to ZDVm reduced transmission from 6.3% to 1.9%<sup>68</sup>. The rapid development of resistance to NVP (and EFV) with the sdNVP approach is also well documented (81), along with the impact on HIV suppression rates with a subsequent NVP-based regimen (82,83). Strategies to reduce this include the addition of other ART to cover the NVP tail: ZDV-3TC (84), TDF-FTC (85) and provision of sdNVP to the neonate only. When sdNVP is used in the Europe, for example, as part of the management of late presentation or preterm delivery, delaying delivery until two hours after the maternal NVP dose will allow adequate drug concentrations to be achieved in the neonate (35,86). For NVP and preterm delivery, see the section on PTD and protease inhibitors below.

**Efavirenz'** use in pregnancy has been significantly restricted following the reporting of congenital malformations in 3/20 cynomolgus macaques exposed to it in utero. The abnormalities were anencephaly, anophthalmous and cleft palate. Subsequently, retrospective reports of

myelomeningocele and Dandy-Walker Syndrome were followed by a reclassification of EFV from C to D in the United States Food and Drug Administration classification of congenital malformation risks. Category D is reserved for compounds with a proven increased risk of congenital malformation. However, prospective reporting to the APR has not revealed any increased risk in congenital malformations with T1 EFV exposure, and sufficient cases have been reported to exclude a greater than two-fold risk increase (87).

Although reassuring, these data are insufficient to exclude a small increased risk of neural tube defects with T1 EFV exposure. Data from general populations for neural tube defects vary with a risk of 4.6 cases of myelomeningocele per 10 000 live births reported for the United States and 10 neural tube defects (inclusive of myelomeningocele, anencephaly and encephalocele per 10 000 live births for Europe, with some variation within Europe over time (88). Only two cases of myelomeningocele have been reported prospectively to the APR out of 12 652 reports. One of these infants was exposed to EFV during T1 (1/604 T1 exposure reports). The two cases of Dandy-Walker syndrome and the second case of myelomeningocele were not associated with NNRTI exposure. In the Ford et al. meta-analysis of EFV exposure one case of myelomeningocele was identified among 1132 pregnancies with T1 exposure. The authors conclude that there is no increased risk of neural tube defect compared to the background rate of the general population (89). These data are particularly important given the high rates of pregnancy termination now reported among some cohorts of women on EFV-based ART in Africa. Furthermore, they enable a measured approach to the management of HIV infection in women who have conceived while on EFV. These data support the continuation of effective, replication-suppressing ART with no need to switch ARVs during T1. Additional factors to consider for optimal management of these women include maternal choice, timing of presentation of pregnancy (neural tube closure complete at foetal age 24 days i.e. 5–6 weeks from the last menstrual period) and the long half-life of EFV.

There appears to be no contra-indication to initiation of EFV in pregnancy although data on tolerability of starting treatment and on pharmacokinetics are limited. Pharmacokinetic studies are being conducted in the United Kingdom by the PANNA Network.

**Etravirine** data is limited mostly to anecdotal reports with respect to use during pregnancy. Pharmacokinetics studied in four women showed similar values to those of non-pregnant adults (90).

### 3. Protease inhibitors

**Indinavir**, **full dose ritonavir** and **nelfinavir** are no longer used in the management of HIV infection in adults, so will not be discussed.

The best available data in pregnancy are for SQV, LPV and ATV, all boosted by ritonavir. These are considered the first-line protease inhibitors for use during pregnancy and are discussed in detail below. Where previous treatment failure or intolerance precludes the use of these agents, the merits of alternative PIs (darunavir, amprenavir, fos-amprenavir and tipranavir) for maternal and child health must be weighed against the unknown risks. Data on the safety, teratogenicity, tolerability and efficacy of these PIs are limited: pharmacokinetic studies of them are included in the framework of the PANNA Network.

The pharmacokinetics of protease inhibitors, where they have been adequately studied, vary within the class. Two pregnancy issues and one neonatal class-related issue have been reported, concerning gestational diabetes, preterm delivery (PTD) and neonatal adrenal insufficiency.

### *Neonatal adrenal insufficiency*

Evidence of biochemical and clinical adrenal insufficiency in neonates, especially preterm, treated with LPV/r, regardless of in utero exposure (but with evidence of greater abnormalities with in utero exposure), was reported in July 2011(91). Biochemical evidence of adrenal insufficiency was reported in 14% of neonates treated with LPV/r, with clinical manifestations in three preterm neonates. The abnormalities resolved spontaneously after cessation of therapy. It is not clear from these new data whether LPV, ritonavir or the combination is implicated. The authors recommend avoidance of LPV/r in preterm neonates and careful electrolyte monitoring if used in term neonates. Until proven otherwise, the latter advice should be applied to any PI, particularly when co-prescribed with ritonavir.

### *Gestational diabetes*

An increased frequency of gestational diabetes has been reported in some cohort studies (92,93), while others particularly addressing glucose tolerance in pregnancy with PIs, have found no effect (94–96).

### *Preterm delivery*

Untreated HIV infection per se is a risk factor for PTD, which is a risk factor for MTCT. Attention to a possible increased risk of PTD with ART was first reported from the Swiss cohort (33% PTD rate with dual or triple ARV therapy compared to 14% with no ARVs and 17% with ZDVm) (97). These findings in a small cohort were supported by data from the ECS, in which after multivariate analysis, PI-based therapy was associated with a 2.6 odds ratio (OR) for PTD compared with no treatment, whereas treatment without a PI had a 1.8 OR for PTD (98). Further analysis from the ECS demonstrated an increased risk of PTD over time, coincident with increasing use of ART, with an overall PTD rate of 24.9% during 2000–2004 and a 7.4% mortality among severely preterm babies (<34 weeks) (99). Compared to ZDVm, PI-based therapy has also been associated with PTD in studies from Austria and Germany (OR 3.4) (100) and the United Kingdom (101). In the latter, the PTD rate in mothers treated with ZDVm was 5.8% compared to 20% among mothers initiating ART during pregnancy. Different indications for therapy may confound such data, but an updated analysis from this cohort has found initiation of ART for PMTCT during pregnancy for women who would have been eligible for ZDVm remains associated with PTD (28.1% vs 6.2% ZDVm), with PTD strongly associated with PI-based ART (39% vs 0% for non-PI-based ART) (102).

Two large North American cohorts have not identified ART with PTD. In the Paediatric Spectrum of Diseases study, PTD occurred in 22–35% of the study population (103), while in the WITS cohort the PTD rate with ZDVm was 16% and did not differ from the rate seen in combination therapy (15%) (92). However, reports of increased PTD with ART are not restricted to Europe. In a cohort study from Brazil, despite relatively high PTD rates overall, conception on ART was associated with an average OR of 5.0 for PTD compared to dual therapy commenced during pregnancy (104). Cotter et al. in Miami found an increased risk of PTD with PI-based ART compared to any non-PI based combination, with an OR of 1.8 (105). In an RCT initiating ART during pregnancy for PMTCT (all women had CD4 count >200 cells/mm<sup>3</sup>, PTD in the triple NRTI arm was 15% compared to 23% with PI-based ART. Data from the ECS have also pointed to a lower rate of PTD with an NRTI-only regimen. In a United Kingdom study, PTD was significantly more common with PI-based ART (22.3%) than with NNRTI-based ART (11.2%,  $p = 0.02$ ) (102).

In summary, the precise relationship between ART, PI vs non-PI-based therapy, time of initiation of therapy and PTD remains unclear. Most studies from North America do not find a link

between ART and PTD, while European studies do. The question is not whether ART should be used in pregnancy for maternal health and PMTCT, but whether particular compounds or classes should be preferred. More detailed studies addressing the many confounders are essential to resolve this question.

**Saquinavir** (ritonavir boosted) is well tolerated in pregnancy; although a high rate of abnormal liver function tests have been reported, they are generally mild (grade 1/2) (106). Pharmacokinetic studies indicate that no change to the SQV 1000mg /ritonavir 100mg twice daily regimen is required in T3 (107,108).

Prospective reporting to the APR has not revealed any increased risk in congenital malformations with T1 SQV exposure and sufficient cases have not yet been reported to exclude a greater than two-fold risk increase (87). An increase in QT and PR intervals has been observed in non-pregnant adult volunteer subjects, leading to the following recommendations: baseline ECG prior to prescription of SQV; avoid if QT >4500 milliseconds (ms); repeat ECG after 3–4 days therapy and discontinue if QT interval has increased by >20 ms; one week induction of SQV 500mg/ritonavir 100mg twice daily in HIV treatment naïve patients. No adverse events relating to a prolonged QT interval have been reported during 14 years of post-license surveillance (109).

**Lopinavir** (ritonavir-boosted) (Kaletra™) is well tolerated in pregnancy. Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 LPV exposure and sufficient cases have been reported to exclude a greater than two-fold risk increase (87). Pharmacokinetic studies have revealed lower drug concentrations (AUC 12 and trough) during T3 compared to the same patients during T2 or post-partum (PP). In patients treated with Kaletra 133mg/33mg, 3 capsules twice daily, a 32% reduction in AUC was observed during T3 compared to PP (110). Neither treatment failure nor lack of PMTCT efficacy have been reported, and trough levels usually remain above the target minimum concentration of non-pregnant adults (110,111). Considerable interpatient variability is noted and trough concentrations may also be lower than PP in T2. T3 LPV concentrations equal to the PP values in the same patients are achieved by a temporary increase in the LPV/r dose to 533mg/133mg (112).

The Kaletra™ tablet formulation has better bioavailability, and an 18% increase in LPV concentrations has been documented during pregnancy with this new formulation compared to capsules (113). This, along with a decrease in protein binding during pregnancy that increases the protein-free fraction by 18% (114) may sufficiently compensate for the physiological decrease in total drug concentrations observed in T3. Some clinicians therefore choose to continue standard dosage while others increase the dose during T3. This can be achieved by addition of one paediatric strength (100mg/25mg) tablet. Where TDM is available this is preferred to optimize individual patient management and should be first performed in T2 (111).

**Atazanavir** (ritonavir-boosted) is generally well tolerated in pregnancy with a low incidence of rash (4%). Nausea and vomiting were the most common undesirable effects, reported in 33% of patients. Liver function test abnormalities were reported in 8% but were generally mild with only one grade 3 abnormality. Treatment was continued throughout pregnancy in 96% of the 155 women, of whom 93 had conceived on ATV (115).

Prospective reporting to the APR has not revealed any increased risk of congenital malformations with T1 ATV exposure and sufficient cases have been reported to exclude a greater than two-fold increase risk (87). Pharmacokinetic studies have drawn differing conclusions.

A study from Italy found little difference between T3 and PP concentrations with geometric mean trough concentrations (486ng/ml) well above the recommended 150ng/ml (116). ATV pharmacokinetics measured during pregnancy and 6–12 weeks post-partum in an American study show a 30–34% reduction in T3 concentrations and a further 25% reduction when ATV is co-administered with TDF (117). It is notably the difference between the two studies of the PP concentrations that accounts for these differing outcomes, with much higher PP concentrations documented in the latter study. HIV VL was undetectable at delivery in 11/16 women on ATV with no TDF and in 17/19 on ATV with TDF and there were no HIV transmissions. The  $C_{\text{trough}}$  target was met by 7/8 women not on TDF and 17/20 on TDF. Some transplacental ATV transfer occurs with cord:maternal blood ratios of 0.13 and 0.18 reported in the aforementioned studies. The authors conclude that a dose increase of ATV/ritonavir 400mg/100mg may be required. Where TDM is available, it is preferred for optimizing individual patient management and should be first performed in T2. As with LPV, there are no data to indicate that the lower total ATV concentrations during T3 are associated with reduced efficacy. In Samuel's study, HIV VL was undetectable (<50 copies/ml) at delivery in 80% and the one transmission (1/127, 0.8%) occurred in a patient with poor adherence (115).

For the occasional patient intolerant of ritonavir TDM is essential, as ATV concentrations are variable and several increases in ATV dose may be required to ensure adequate ATV concentrations throughout pregnancy (Taylor, unpublished data). Unboosted ATV should only be used with caution where TDM is not available.

**Ritonavir** (low dose) used as a pharmacological booster is well tolerated during pregnancy. Prospective reporting to the APR (APR) has not revealed any increased risk of congenital malformations with T1 ritonavir exposure, and sufficient cases have been reported to exclude a greater than two-fold risk increase (87). Ritonavir PK has been studied in the ATV and LPV studies described above. Ritonavir concentrations are reduced in T3 and a proportion of patients have undetectable ritonavir concentrations. This may contribute to the reduced concentrations of boosted PIs reported above.

In the context of pregnancy, the important ritonavir drug interactions are with methadone and anti-mycobacterial therapy. While therapeutic concentrations of ritonavir (400mg or more) increase the metabolism of methadone – resulting in a relative reduction in effect of ~30% – ritonavir 100mg used as a pharmaco-booster for other PIs has no significant effect on methadone. However, LPV/r reduces methadone concentrations by 26–28%, sufficient to cause withdrawal symptoms (118), though it does not always do so (119). If LPV/r is used, a transient increase in methadone dosage may be required. Ritonavir inhibition of CYP450 significantly reduces rifampicin metabolism and these therapies must not be co-administered. If there is no alternative to PI-based therapy, rifabutin 150mg three times per week may be substituted.

#### 4. Integrase inhibitors

**Raltegravir** has not generated sufficient data for its safety, teratogenicity, tolerability and efficacy during pregnancy to be established. The merits of prescribing it during pregnancy for maternal and child health must be weighed against the unknown risks. There is considerable interest in its use either early in pregnancy (for example if an amniocentesis is indicated) or in late presenters. The rapid reduction in HIV VL seen in non-pregnant adults has been anecdotally reported to occur in pregnancy (120). Preliminary pharmacokinetic data indicate excellent raltegravir concentrations during T3 and efficient (cord:maternal blood ratio 1.0) transplacental transfer (121).

## 5. Entry inhibitors

**Enfuvirtide** (T-20) has been licensed since 2004, relatively few patients have been exposed to this parenteral therapy during pregnancy and there are insufficient data to comment on its safety, teratogenicity, tolerability and efficacy during pregnancy. Therefore, the merits of prescribing T-20 during pregnancy for maternal and child health must be weighed against the unknown risks. Anecdotal reports have indicated successful management of patients during pregnancy and prevention of transmission of multiclass resistant HIV when T-20 has been included in salvage therapy.

**Maraviroc** has not generated sufficient data for comment on its safety, teratogenicity, tolerability and efficacy during pregnancy. Therefore, the merits of prescribing it during pregnancy for maternal and child health must be weighed against the unknown risks. Exclusive CCR-5 tropism of the circulating virus should be confirmed prior to use.

## Annex 2. Currently available medications for substance-dependence treatment during pregnancy

| <b>TABLE 8. MEDICATIONS AVAILABLE FOR TREATING SUBSTANCE DEPENDENCE DURING PREGNANCY</b> |   |   |   |
|--|---|---|---|
| <b>Medication</b>  | <b>Dosage</b>   | <b>Side-effects</b>   | <b>Clinical considerations</b>  |
| <b>Opioid dependence</b>   |   |   |   |
| Clonidine  | 0.1–0.2 mg every 4–6 hours, monitoring of withdrawal syndromes  | Hypotension and sedation  | More effective for somatic than psychological symptoms; will require adjunct drugs  |
| Naltrexone   | 50 mg/d, or 100 mg Monday and Wednesday and 150 mg Friday   | Abdominal pain, elevated liver enzymes in patients older than 40  | Maintenance and withdrawal; do not administer if opioids have been used within one week   |
| Buprenorphine  | 2–4 mg for induction a max. of 8 mg on first day; second day dosages up to 16 mg/d, depending on symptoms; may be given every other day at 8 mg dosage; | Mild withdrawal Syndromes, constipation, sedation   | Maintenance and withdrawal; only office-based treatment; do not use within 24 hours of opioid use   |
| Methadone  | Dosage over 60 mg usually more effective  | Sedation, constipation, decreased libido, ankle oedema  | Maintenance of opioid dependence; restricted to licensed narcotics treatment programmes   |
| <b>Smoking cessation</b>   |   |   |   |
| Nicotine patch   | 4 weeks of 21 mg/24 h then 2 weeks of 14 mg/24 h, then 2 weeks of 7 mg/24 h (Nicoderm CQ); or 15 mg/16 h (Nicotrol) 8 weeks                             | Local skin irritation, insomnia   | Lower patch dose in those smoking <10 cigarettes/day; place new patch on different site daily   |
| Nicotine gum   | 2 mg for those who smoke <25 cigarettes/day and 4 mg for those who smoke 25 or more/day   | Jaw and mouth soreness, hiccups, dyspepsia  | Schedule doses 1 piece every 1–2 hours rather than as needed; do not eat or drink 15 minutes before chewing or during chewing;  |
| Bupropion sustained release  | Start with 150 mg each morning for 3 days one week before quitting smoking; then 150 mg BID for 7–12 weeks; may be used up to 6 months                  | Insomnia and dry mouth; contraindicated with a history of seizures, eating disorders, head injury or in those who have used monoamine oxidase inhibitor within 14 days; pregnancy FDA class B | Prescription; alternative for those who do not want nicotine replacement  |
| <b>Alcohol withdrawal</b>  |   |   |   |
| Chlordiazepoxide   | 25–100 mg per dose  | Sedation, dizziness, ataxia, confusion  | Long half-life; may be given as a loading dose to reduce symptoms, then discontinued  |
| Diazepam   | 15–60 mg per dose   | Same as chlordiazepoxide  | Shorter half-life, no active metabolites and not dependent on hepatic metabolism; generally requires dosing every 4–6 hours   |
| Carbamazepine  | 400 mg loading dose, then 200 mg three times daily, tapering over 5 days  | Sedation, dizziness, ataxia, confusion, nausea and vomiting, bone marrow suppression  | Effective for moderate-to-severe withdrawal, not well studied for severe withdrawal   |
| <b>Alcohol dependence</b>  |   |   |   |
| Disulfiram   | 250–500 mg every day or two   | Hepatitis, neuritis, peripheral neuropathy, disulfiram alcohol reaction (if alcohol is consumed)  | Efficacy is enhanced by monitoring compliance; may also have efficacy for cocaine dependence  |
| Naltrexone   | Same as for opioid dependence   | Same as for opioid dependence   | Screen carefully for covert opioid dependence to avoid precipitating withdrawal; contraindicated in those anticipating surgery or needing narcotics for pain management |

Source: Rayburn, Bogenschutz (25)

## Annex 3. Definitions of acceptable, feasible, affordable, sustainable and safe replacement feeding

The following terms can serve as a starting point that should be adapted in the light of local conditions and unfolding research.

**Acceptable.** The mother perceives no barrier to replacement feeding, whether due to cultural or social causes or to fear of stigmatization or discrimination. If replacement feeding is acceptable to the mother, she is either under no social or cultural pressure to breastfeed and is supported by family and community in opting for replacement feeding, or will be able to cope with pressure to breastfeed and deal with any stigma attached to replacement feeding.

**Feasible.** The mother (and family) has the time, knowledge, skills and other resources needed to prepare the replacement food and feed the infant up to 12 times every 24 hours. The mother can understand and follow the instructions for preparing infant formula, and with family support where available she can prepare sufficient replacement food every day and night, despite any disruptions it might cause in preparation of other family food or other work.

**Affordable.** The mother (and family), with community or health-system support if necessary, can pay the cost of purchasing/producing, preparing and using replacement food, including all ingredients, fuel, clean water, soap and equipment, without compromising the health and nutrition of the family. The concept of affordability also extends to access to medical care for diarrhoea if necessary and the cost of such care.

**Sustainable.** A continuous and uninterrupted supply and dependable system of distribution for all ingredients and products needed for safe replacement feeding should be available for as long as the infant needs it, up to one year of age or longer. If replacement feeding is sustainable, there should be little risk that formula will ever be unavailable or inaccessible, and another person will always be available to prepare the food and feed the child in the mother's absence.

**Safe.** Replacement foods should be correctly and hygienically prepared and stored, and fed in nutritionally adequate quantities with clean hands and utensils, preferably using a cup. Safety means that the mother or caregiver is able to:

- access a reliable supply of safe water (from a piped or protected-well source);
- prepare replacement food that is nutritionally sound and free of pathogens;
- wash hands and utensils thoroughly with soap and regularly sterilize the utensils;
- boil water to prepare each of the baby's feedings; and
- store unprepared food in clean, covered containers protected from rodents, insects and other animals.

Source: WHO (122)

## Annex 4. Neonatal abstinence syndrome scores

| <b>TABLE 10. MODIFIED FINNEGAN NEONATAL ABSTINENCE SCORE SHEET</b> |              |
|--|--------------|
| <b>Sign or symptom</b>   | <b>Score</b> |
| <b>Central nervous system disturbances</b>                         |              |
| Excessive high-pitched (or other) cry < 5 minutes                  | 2            |
| Continuous high-pitched (or other) cry > 5 minutes                 | 3            |
| Sleeps <1 hour after feeding                                       | 3            |
| Sleeps <2 hours after feeding                                      | 2            |
| Sleeps <3 hours after feeding                                      | 1            |
| Hyperactive Moro reflex  | 2            |
| Markedly hyperactive Moro reflex                                   | 3            |
| Mild tremors when disturbed  | 1            |
| Moderate–severe tremors when disturbed                             | 2            |
| Mild tremors when undisturbed                                      | 3            |
| Moderate–severe tremors when undisturbed                           | 4            |
| Increased muscle tone  | 2            |
| Excoriation (specify areas)  | 1            |
| Myoclonic jerks  | 3            |
| Generalized convulsions  | 5            |
| <b>Metabolic/vasomotor/respiratory disturbances</b>                |              |
| Sweating   | 1            |
| Fever 37.2–38.3 °C   | 1            |
| Fever > 38.4 °C  | 2            |
| Frequent yawning (>3–4 times per scoring interval)                 | 1            |
| Mottling   | 1            |
| Nasal stuffiness   | 1            |
| Sneezing (>3–4 times per scoring interval)                         | 1            |
| Nasal flaring  | 2            |
| Respiratory rate >60/min   | 1            |
| Respiratory rate >60/min with retractions                          | 2            |
| <b>Gastrointestinal disturbances</b>                               |              |
| Excessive sucking  | 1            |
| Poor feeding (infrequent/uncoordinated suck)                       | 2            |
| Regurgitation ( $\geq$ 2 times during/post feeding)                | 2            |
| Projectile vomiting  | 3            |
| Loose stools (curds/seedy appearance)                              | 2            |
| Watery stools (water ring on nappy around stool)                   | 3            |

Source: Finnegan (123)

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