10 Prevention of HIV Transmission from HIV-infected Mothers to Their Infants

Clinical Protocol for the WHO European Region
I. Policy issues

- Clinical prevention of mother-to-child transmission of HIV (PMTCT) should be a part of the continuum of care for HIV-infected women and their children. Services providing PMTCT should be linked to other relevant governmental and nongovernmental services, such as HIV treatment and care, reproductive health, paediatric services, drug-dependence treatment, harm-reduction services, psychosocial support, child protection services, etc.
- Pregnant injecting drug users (IDU) should have the same non-discriminatory access to health care services – including antiretroviral treatment (ART), reproductive choices, PMTCT and maternity care – as pregnant women who do not use drugs.
- All medical records, whether or not they involve HIV-related information, should be treated according to appropriate standards of confidentiality. Only health care professionals with a direct role in the management of patients or clients should have access to such records, and only on a “need-to-know” basis.
II. Background

Increasing numbers of women living with HIV are becoming pregnant, and their infants will be at high risk for acquiring HIV infection in utero, during labour or through breastfeeding. In the absence of interventions, the risk of mother-to-child transmission (MTCT) of HIV is 15–30% in non-breastfeeding populations; breastfeeding increases the risk to 20–45% (1).

Effective interventions for the prevention of MTCT (PMTCT) of HIV infection do now exist. Where these interventions are freely available and utilized, MTCT rates of 1% or 2% have been achieved (1–3). They include:

- antiretroviral (ARV) prophylaxis during pregnancy, labour and the first weeks of life;
- obstetrical interventions, including pre-labour caesarean section (PLCS); and
- avoidance of breastfeeding (4–6).

The challenge is to achieve similar rates throughout the WHO European Region, particularly in countries where the HIV epidemic is fuelled by injecting drug use and health systems are adversely affected by economies in transition. Several factors – high-level coverage of antenatal care (ANC), the availability of an extensive health care infrastructure, high literacy levels, a relatively low number of infections and the existence of effective interventions to reduce MTCT – offer an opportunity to eliminate infant HIV infection in the Region and thus provide a model for the rest of the world.

WHO promotes a four-pronged comprehensive strategic approach to the prevention of HIV infection in infants and young children:

1. primary prevention of HIV infection
2. prevention of unintended pregnancies among HIV-infected women
3. prevention of HIV transmission from mothers to their infants
4. treatment, care and support for HIV-infected mothers and their families (7).

This protocol focuses on the third prong of the strategy, prevention of HIV transmission from mothers to their children. It is consistent with the Region’s goal of preventing HIV in infants in Europe (8), specifically to eliminate HIV infection in infants by 2010 as indicated by reducing the infection rate among infants to less than 1 per 100 000 live births and the infection rate among infants born to HIV-infected women to less than 2%.

The European goal is congruent with the global goal set at the 2001 United Nations General Assembly Special Session (UNGASS) on HIV/AIDS of reducing the proportion of infants infected with HIV by 50% by 2010 (9).

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1 Please see Protocol 9, Support for sexual and reproductive health of people living with HIV.
III. Initial evaluation

1. Initial evaluation of pregnant women in antenatal care settings

Antenatal HIV counselling and testing of pregnant women is an effective medical intervention that contributes to lowering rates of MTCT of HIV. In addition, it is an important entry point for the treatment and care of HIV-positive women and their children.

The intend of HIV testing is to capture every HIV infected pregnant woman as early as possible in order to introduce a package of PMTCT interventions and minimize risk of HIV transmission to her baby during pregnancy, labour and postpartum.

HIV testing should be voluntary and not forced. Women should provide written consent to the test and be able to refuse it. Testing should include obligatory counselling.

An initial assessment for determining HIV status should include:
- pretest counselling;
- serological testing for HIV antibodies (typically ELISA and/or rapid tests), followed by a western blot confirmatory test if positive; and
- post-test counselling, including information on reducing risky behaviour, irrespective of the results.

For women infected with HIV, further evaluation is needed in collaboration with an HIV specialist to determine the clinical stage and to develop a PMTCT management strategy.

Among the key aspects of pretest HIV counselling is identifying any drug use (including injecting drug use) and evaluating the risks of the woman’s exposure to HIV from sexual partners. Drug use and especially drug dependence can have a large impact on pregnancy and fetal development, and they require special medical assistance during pregnancy, labour and the postpartum period for both mother and fetus/infant.

For more about the assessment of drug dependence and withdrawal symptoms in pregnant women, see section IV.2.3 below.

2. Patient counselling

After the initial evaluation, HIV-infected pregnant women should be counselled on the following, where relevant to their condition:
- condom use for prevention of sexual transmission of HIV and other STIs;
- the risk of HIV transmission to the fetus/neonate and how to prevent it;
- the risks and benefits of ARV prophylaxis as part of PMTCT strategy;
- the risks of hepatitis B and C virus (HBV and HCV) perinatal transmission and how to reduce them;
- the risks of perinatal syphilis transmission, and the need for treatment of syphilis, gonorrhoea and chlamydia to reduce the risk of HIV transmission;
- the impact of drug use on fetal development, including drug withdrawal syndrome and drug interactions (see section IV.4.2 below);
- referral to harm-reduction and drug-dependence treatment programmes, including substitution therapy where appropriate;

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1 Rapid HIV serological testing should be available in maternities for those women only presenting in health care service during labour
2 For clinical and laboratory evaluation please refer to Protocol 1, Patient evaluation and antiretroviral treatment for adults and adolescents.
• the implications of different modes of delivery in reducing the risk of HIV transmission, including the benefits and adverse effects of caesarean section (CS); and
• instruction on infant feeding (see also section IV.3.1 below).

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. Under no circumstance should she be coerced to terminate a pregnancy.
IV. PMTCT management in antenatal care settings and maternity wards

Randomized controlled trials (RCTs), open-label trials and observational studies have provided evidence of the effectiveness of ARV prophylaxis (4, 10–24) and caesarean section in PMTCT.

- Zidovudine (ZDV) administered early in pregnancy, during labour and delivery and postpartum to mother and infant has been shown to reduce vertical transmission from 25.5% to 8.3% in a non-breastfeeding population (25–27).
- In mother–infant pairs receiving triple combination therapy including a protease inhibitor (PI), the MTCT rate can decrease to 0.9–1.3% (5, 28).
- The protective role of caesarean section was demonstrated in both a meta-analysis (28) and a randomized clinical trial (RCT) (29) prior to the widespread use of combination therapy in pregnancy. However, mounting observational data demonstrating very low levels of transmission in women on therapy with undetectable viral loads who deliver vaginally have led to changes in the advice on their method of delivery (30).
- If the decision is made to perform pre-labour caesarean delivery to prevent HIV transmission, it should be done at 38 weeks’ gestation, as determined by the best clinical estimate, and amniocentesis should be avoided (31).

Administration of ARV regimen for PMTCT should be considered in close collaboration with health providers of ANC services and HIV specialists. The package of prevention interventions for pregnant women should be based on:
- the need for ART
- the gestation stage at presentation
- the level of the clinical setting (primary health care, specialist referrals)
- the history of previous ARV use
- the presence of concomitant diseases or conditions
- the availability of ARVs.

For HIV-infected pregnant women, PMTCT rates are those same for those who use drugs as for those who do not.

The decision on when to start ART for pregnant women should be based on the WHO HIV/AIDS clinical staging system in combination with immunological criteria (see Protocol 1, Patient evaluation and antiretroviral treatment for adults and adolescents, Table 6 and Annex 2).

1. Possible scenarios for PMTCT management in ANC services and maternity wards

The vast majority of HIV-positive pregnant women fit in one of the following categories:
1. those who do not presently need ART for the sake of their personal health (see Table 1)
2. those who do need or might need ART for the sake of their health (see Table 2)
3. those who started ART before pregnancy (see Table 3)
4. those who do not present until around labour (see Table 4).
### 1.1. Pregnant women who do not yet need ART for their own health

<table>
<thead>
<tr>
<th>Gestational age and CD4 count</th>
<th>ARVs during pregnancy</th>
<th>ARVs during labour</th>
<th>Postpartum ARVs</th>
<th>Mode of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>From 24–28 weeks CD4 &gt;350 cells/mm³</td>
<td><strong>If viral load (VL) is available and ≤10,000 copies/ml and patient is ZDV-naive</strong>&lt;br&gt;<strong>ZDV</strong> (300 mg) per os, twice daily (PO, BID) (32)&lt;br&gt;Monitor haemoglobin level.&lt;br&gt;<strong>If PLCS:</strong> Continue ZDV® only.&lt;br&gt;<strong>If spontaneous labour before CS date:</strong> ZDV (300 mg) every 3 hours until delivery + 3TC (150 mg), PO, BID + single-dose NVP (200 mg) at onset of labour&lt;br&gt;<strong>With NVP during labour (preferred):</strong>&lt;br&gt;Mother: ZDV (300 mg) + 3TC (150 mg) PO, BID x 7 days after delivery&lt;br&gt;Infant: ZDV syrup (4 mg/kg body weight) + 3TC (2 mg/kg body weight) PO, BID x 7 days + single-dose NVP (2 mg/kg body weight) after birth&lt;br&gt;<strong>PLCS at 38 weeks of pregnancy or spontaneous delivery</strong>&lt;br&gt;Mother: Stop ZDV.&lt;br&gt;Infant: ZDV syrup (4 mg/kg body weight) PO, BID x 7 days. Start within first 8 hours.</td>
<td><strong>Without NVP during labour</strong>&lt;br&gt;Mother: Stop all three drugs after delivery.&lt;br&gt;Infant: ZDV syrup (4 mg/kg body weight), PO, BID for 7 days. Start within first 8 hours.</td>
<td><strong>If VL is unavailable or &gt;10,000 copies/ml, or if there is a known history of ZDV exposure</strong>&lt;br&gt;<strong>ZDV</strong> (300 mg) + 3TC (150 mg) + SQV/r (800 mg /100 mg) BID, PO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Continue the same regimen until delivered</td>
</tr>
</tbody>
</table>

<sup>a</sup>If mother received ARV prophylaxis for less than four weeks during pregnancy, the infant should receive ZDV for up to four weeks. In preterm infants the dose of ZDV should be 1.5 mg/kg IV or 2.0 mg/kg PO.

<sup>b</sup>The woman should make the final decision of delivery method after knowing risks and benefits. In vaginal delivery, avoid invasive obstetrical procedures, such as fetal scalp monitoring and episiotomy.

<sup>c</sup>If mother has been exposed to ART or is at risk for having a resistant virus, baseline resistance can help guide ART choice.

<sup>d</sup>Lopinavir boosted with low dose ritonavir (LPV/r) (400 mg/100 mg) or nelfinavir (NFV) (1250 mg) BID, PO could be used as an alternative.

<sup>e</sup>Adherence could be problematic due to pregnancy-associated complications.

<sup>f</sup>Avoid invasive obstetrical procedures, such as fetal scalp monitoring and episiotomy. Episiotomy must not be performed routinely, but reserved for cases where there is a clear obstetric indication for the procedure (33).
1.2. Pregnant women who need ART for their own health

Pregnant women who need ART for their own health but have not yet received it should be given a first-line highly active antiretroviral treatment (HAART) regimen. ARV regimens containing ZDV, 3TC and NVP are recommended as first-line treatment options and for preventing MTCT (19, 34, 35). ART should be continued in such women after delivery for the benefit of their own health.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>PREGNANT HIV-POSITIVE WOMEN WHO NEED OR MIGHT NEED ART FOR THEIR OWN HEALTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age and CD4 count</td>
<td>ARVs during pregnancy and labour</td>
</tr>
<tr>
<td>Any gestational age CD4 &lt;200 cells/mm³</td>
<td>ZDV (300 mg) + 3TC (150 mg) + NVP (200 mg)</td>
</tr>
<tr>
<td></td>
<td><em>Comments:</em> Start NVP with 200 mg once daily (OD) for the first 2 weeks, and then continue with 200 mg BID. Monitor liver enzymes at baseline, 2 weeks of treatment, 4 weeks, and every 4 weeks thereafter.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Any gestational age CD4 is 200–350 cells/mm³</td>
<td>ZDV (300 mg) + 3TC (150 mg) + SQV/r (800/100 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>a Close monitoring of haemoglobin is required. ZDV can be replaced by TDF or ABC in anaemic symptomatic women and women who are ZDV-intolerant.</td>
<td></td>
</tr>
<tr>
<td>b The risk of NVP-associated hepatotoxicity substantially increases if CD4 &gt;250 cells/mm³ (36).</td>
<td></td>
</tr>
<tr>
<td>c If the mother received ARV prophylaxis for less than four weeks during pregnancy, the infant should receive ZDV up to four weeks. In preterm infants, the dose of ZDV should be 1.5 mg/kg IV or 2.0 mg/kg PO.</td>
<td></td>
</tr>
<tr>
<td>d Risks and benefits should be discussed with the woman, who should make the final decision. In case of vaginal delivery, avoid invasive obstetrical procedures such as fetal scalp monitoring and episiotomy. Episiotomy must not be performed routinely, but reserved for cases with a clear obstetric indication (33).</td>
<td></td>
</tr>
<tr>
<td>e LPV/r (400/100 mg BID) or NFV (1250 mg BID, PO) can be used instead of SQV/r. If PIs are not available, efavirenz (EFV) can be administered, but not earlier than the second or third trimester, due to risk of teratogenicity associated with its use in the first trimester.</td>
<td></td>
</tr>
</tbody>
</table>
### 1.3. Pregnant women who initiated ART before pregnancy

#### Table 3. Pregnant HIV-positive women who initiated ART before pregnancy

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>ARVs during pregnancy and labour</th>
<th>Postpartum ARVs</th>
<th>Mode of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age</td>
<td>Continue current ARV regimen if it does not contain EFV. If a woman is on a regimen that contains EFV and is in her first trimester, consider substituting SQV/r 800 mg/100 mg or ABC; where CD4 count &lt;250, NVP can be used. The benefits of a second-line regimen outweigh the risks. Keep on current regimen during pregnancy, labour and afterwards.</td>
<td><em>Mother</em> Continue same maternal ARV treatment after delivery. <em>Infant</em> Oral ZDV syrup (4 mg/kg body weight) BID for 7 days. Start within first 8 hours. In preterm infants the ZDV dose is 1.5 mg/kg IV or 2.0 mg/kg PO.</td>
<td>If VL &lt;1000 copies/ml at 36–38 weeks, await spontaneous labour. If VL &gt;1000 copies/ml at 36–38 weeks opt for PLCS at 38 weeks. If VL is unavailable and adherence to HAART &lt;95%, opt for PLCS at 38 weeks. If VL is unavailable and adherence to HAART &gt;95%, opt for spontaneous labour.</td>
</tr>
</tbody>
</table>

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a Anecdotal cases of neural tube defects have been reported with EFV use in the first trimester. While it is important to discontinue EFV in the pre-conception period, the decision to replace EFV with another ARV should be carefully considered. Switching to another drug has the potential of viral rebound, while the fetus’s neural tube formation should be finished by six weeks of gestation. In many western European hospitals, experienced HIV physicians continue an EFV-based regimen if the woman first presents to ANC providers at eight weeks of pregnancy or later. If a decision is made to stop EFV, do not discontinue the EFV-containing regimen without switching to another ARV compound in order to avoid the risk of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.

b LPV/r (400 mg/100 mg) or NFV (1250 mg) BID, PO can be used instead of SQV/r.

c The risk of NVP-associated hepatotoxicity substantially increases if CD4 >250 cells/mm$^3$ (36); for dosage refer to Table 2 above.

d Risks and benefits should be discussed with the woman, who should make the final decision regarding the delivery method. In case of vaginal delivery, avoid invasive obstetrical procedures such as fetal scalp monitoring and episiotomy. Episiotomy must not be performed routinely, but reserved for cases with a clear obstetric indication (33).
**1.4. Pregnant women who first present around labour**

Women presenting in labour without any antenatal assistance are often from vulnerable populations, such as IDUs or sex workers. It is important to assess their HIV status, as they may be at high risk for being infected. Offer a rapid test, and provide ARV prophylaxis for PMTCT if the woman is found to be HIV-positive after confirmation by western blot.

**Table 4.** PREGNANT HIV-POSITIVE WOMEN WHO FIRST PRESENT IN LABOUR (NO ARVS DURING PREGNANCY)

<table>
<thead>
<tr>
<th>Time of admission to hospital</th>
<th>ARVs during labour and delivery</th>
<th>Postpartum ARVs</th>
<th>Mode of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>During labour and delivery</td>
<td>ZDV (300 mg) every 3 hours until delivery + 3TC (150 mg) at onset of labour and then every 12 hours until delivery + NVP (200 mg once) at onset of labour</td>
<td><em>Mother</em> ZDV (300 mg) + 3TC (150 mg) BID x 7 days after delivery&lt;sup&gt;a&lt;/sup&gt; <em>Infant</em>&lt;sup&gt;b&lt;/sup&gt; ZDV&lt;sub&gt;c&lt;/sub&gt; 4 mg/kg body weight BID for 4 weeks + 3TC 2 mg/kg body weight BID for 4 weeks + single-dose NVP 2 mg/kg at 48–72 hours after birth&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Spontaneous vaginal delivery:&lt;sup&gt;g&lt;/sup&gt; Avoid invasive obstetrical procedures such as fetal scalp monitoring and episiotomy.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Further strategy for the ART and case management of a woman identified as HIV-infected during labour should be based on CD4 count, VL and clinical examination as soon as possible after delivery.  
<sup>b</sup> Postpartum AZT and 3TC for infants should be initiated between 8 and 12 hours after birth if the mother received AZT and 3TC prophylaxis during labour and as soon as possible after birth if the mother did not receive ARV prophylaxis during labour.  
<sup>c</sup> In preterm infants, the dose of ZDV should be 1.5 mg/kg IV or 2.0 mg/kg PO.  
<sup>d</sup> If the mother misses a NVP dose, or takes NVP less than two hours before delivery, then the infant should be given an NVP dose immediately after delivery and a second dose at age 72 hours.  
<sup>g</sup> For women not in active labour and with intact fetal membranes, PLCS can be suggested.

**1.5. PMTCT in pregnant HIV-infected women with active tuberculosis**

For HIV-infected pregnant women with active tuberculosis (TB), the first priority should be to treat the TB. For more information about TB treatment, refer to Protocol 4, *Management of tuberculosis and HIV coinfection*.

- Most first-line anti-TB drugs are safe for use during pregnancy except streptomycin, which is ototoxic to the fetus.
- If the length of the TB treatment jeopardizes ARV prophylaxis of MTCT, then ARV prophylaxis has to be prescribed concomitantly with the TB treatment.
- ARV regimens containing NVP or unboosted PIs should not be used concomitantly with rifampicin due to drug interactions (37–41).
- The recommended ARV regimen for PMTCT in HIV-infected pregnant women receiving rifampicin is ZDV + 3TC + SQV/r (for dosage, refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*). Close monitoring of liver enzymes is required. In the absence of SQV/r, ABC may also be considered. However, further research on use of ABC in pregnant women is needed.
- ZDV/3TC/ABC is available as a fixed-dose combination (three drugs in one tablet). Triple-nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) regimens appear to be less potent than NNRTI and boosted PI regimens (42).
- If rifabutin is used instead of rifampicin, ARV regimens for the purpose of PMTCT remain as described above. Rifabutin levels may increase when coadministered with LPV/r; consequently, the rifabutin dosage may have to be reduced (37).
2. Management of HIV-infected active IDUs during pregnancy

Pregnant women using drugs have a greater than normal risk of medical complications. They should be managed according to the possible impact their dependency has on their pregnancy, their fetus and their own health (see Table 6 below) (43). 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.

2.1. 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 ANC
- drug-dependency treatment experts (throughout the pregnancy)
- HIV/AIDS services
- psychological and social services.

2.2. Assessment of 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 (see Table 5), should be examined further.

Drug-using women are often dependent on more than one psychoactive substance (nicotine, alcohol, cannabis, opiates, cocaine, ecstasy, other amphetamines, benzodiazepines) (44), 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 pregnancy complications from signs and symptoms of drug intake or withdrawal.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Signs/symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Agitation, tremors, sleep disturbance, tachycardia, hypertension, nausea, dilated pupils, seizures</td>
</tr>
<tr>
<td>Delta-9-tetrahydrocannabinol (in cannabis, marijuana, hashish)</td>
<td>Restlessness, irritability, mild agitation, insomnia, nausea, cramping</td>
</tr>
<tr>
<td>Tobacco (e.g. cigarettes)</td>
<td>Irritability, restlessness, difficulty concentrating, impaired task performance, anxiety, hunger, weight gain, sleep disturbance, cravings, drowsiness</td>
</tr>
<tr>
<td>Central nervous system (CNS) sedative hypnotics: alprazolam, barbiturates, chlordiazepoxide, diazepam, flurazepam, glutethimide, meprobamate, methaqualone, etc.</td>
<td>Tremulousness, insomnia, chronic blink reflex, agitation, toxic psychosis, seizure, anxiety, agitation, muscle cramps, sleep disturbance, hypertension, fever, anorexia</td>
</tr>
<tr>
<td>CNS stimulants: methamphetamine, cocaine, methylphenidate, phentermine, dimethyltryptamine, phenylcyclidine (PCP)</td>
<td>Muscle aches, abdominal pain, hunger, prolonged sleep, suicidal ideas, bradycardia, craving, depression</td>
</tr>
<tr>
<td>Opiates: codeine/oxycodone, heroin, hydromorphone, tripelennamine</td>
<td>Flu-like syndrome, agitation, dilated pupils, abdominal cramps, insomnia, anxiety, craving, tachycardia, hypertension</td>
</tr>
</tbody>
</table>

Source: adapted from Rayburn & Bogenschutz (45).
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 *ICD-10 symptom checklist for mental disorders* (see Annex 3 in Protocol 5, *HIV/AIDS treatment and care for injecting drug users*). Several other validated and standardized drug-dependence screening and assessment instruments are available, including the Addiction Severity Index (ASI) (see Annex 1 of the same protocol for European version 6 (EuropASI6) (44)). 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.

2.3. Impact of psychoactive substances during pregnancy and withdrawal

The effects of psychoactive substances during pregnancy are divided into the effects of drug use on the fetus and neonate (Table 6) and withdrawal symptoms (Table 5 above).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Spontaneous abortion, microcephaly, growth deficiency, CNS dysfunction including mental retardation and behavioural abnormalities, craniofacial abnormalities (short palpebral fissures, hypoplastic philtrum, flattened maxilla), behavioural abnormalities.</td>
</tr>
<tr>
<td>Tobacco (e.g. cigarettes)</td>
<td>No congenital anomalies, intrauterine growth restriction (200 g lighter), preterm birth, placenta previa, placental abruption.</td>
</tr>
<tr>
<td>Delta-9- tetrhydrocannabinol (in cannabis, hashish)</td>
<td>No congenital anomalies, reduction of 0.8 weeks in the length of gestation, corresponding decrease in birth weight, subtle behavioural alterations.</td>
</tr>
<tr>
<td>CNS stimulants: antiobesity drugs, methamphetamine, cocaine, methylphenidate, phenmetrazine</td>
<td>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, fetal death, neonatal necrotizing enterocolitis.</td>
</tr>
<tr>
<td>Narcotics: codeine, heroine, hydromorphone, meperidine, morphine, opium, pentazocine, triptenamine</td>
<td>Fetal growth restriction, no anomalies, intrauterine withdrawal with increased fetal activity, depressed breathing movements, preterm rupture of membranes, preterm delivery, meconium-stained amniotic fluid, perinatal death.</td>
</tr>
</tbody>
</table>

Source: adapted from Rayburn & Bogenschutz (45).

2.4. 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 all the issues mentioned in section IV.1, with emphasis on the following:

- 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 fetal stress due to uncontrolled withdrawal attempts without medical and psychological support;\(^4\)
- the effects of pregnancy on OST dose maintenance and the possible need to increase it;\(^5\)
- interactions between opioid substitutes and ARVs as part of PMTCT; and
- adherence to OST and ART.

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\(^4\) It is important that mothers understand that the fetus will also experience withdrawal symptoms.

\(^5\) To avoid resistance to a dosage increase, the patient should be reassured that it has no relationship to drug dependency in the newborn child.
2.5. Opioid substitution therapy during pregnancy

If opioid-using pregnant women meet the criteria for dependency (see Annex 4 in Protocol 5, HIV/AIDS treatment and care for injecting drug users) they should be counselled about the risks and benefits of OST, and an agreement should be reached for a treatment programme and adherence to it (44, 46, 47). Medications for the treatment of drug dependency (both opioid and non-opioid) in pregnant women are shown in Annex 1 of the present protocol.

2.5.1. Methadone substitution therapy (46)

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 (44, 46). 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 fetus of intrauterine death, even under the most optimal conditions (46). There is evidence that methadone maintenance treatment, combined with prenatal services, promotes fetal growth, while continued use of heroin during pregnancy may result in infant morbidity (46).

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoids contaminants that may harm the unborn child.</td>
<td>Increases the severity and duration of neonatal withdrawal compared to that of infants of untreated opioid-dependent mothers.</td>
</tr>
<tr>
<td>No known fetal abnormalities are associated with pure heroin or methadone.</td>
<td>Involves longer hospitalization and treatment of newborn infants.</td>
</tr>
<tr>
<td>Involves a known, regular dose.</td>
<td>Leads to greater neonatal weight loss.</td>
</tr>
<tr>
<td>Avoids periods of drug withdrawal that may be associated with miscarriage early in the pregnancy, or fetal growth retardation and stillbirth late in pregnancy.</td>
<td>Reduces demand of infant to feed.</td>
</tr>
<tr>
<td>Reduces the incidence of premature birth.</td>
<td></td>
</tr>
<tr>
<td>Reduces the risk of intra-uterine growth retardation.</td>
<td></td>
</tr>
<tr>
<td>Increases use of ANC services.</td>
<td></td>
</tr>
</tbody>
</table>

Source: Brown et al. (46).

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

2.5.1.1. Dosage

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 (46). A small number of methadone patients are aberrant metabolizers, and some medications may speed liver metabolism. Such cases may require doses in excess of 120 mg/day.

2.5.1.2. 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 second trimester. Dose reductions of 2.5–5.0 mg per week are considered safe (46). Withdrawal symptoms should be avoided as much as possible, as they cause the fetus considerable distress.

2.5.1.3. 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.

2.5.1.4. Interactions between methadone and ARVs
Interactions between methadone and ARVs are the same in pregnant women as in other patients (cf. Protocol 5, HIV/AIDS treatment and care for injecting drug users, section on Drug-drug interactions and IDUs). 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 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 (46).

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

SQV/r slightly reduces levels of methadone; no dosage adjustment is necessary, but continual monitoring is required.

2.5.2. Buprenorphine substitution therapy
As a Category C drug, buprenorphine has implications for pregnancy (49–51). While studies have not shown that buprenorphine is harmful to the fetus, it cannot be recommended for pregnant or lactating women. Its use can be considered if potential benefits justify the risks to the fetus (52), for example, if methadone is not available or the patient cannot tolerate it. Women should be informed about the risks of buprenorphine use, and its use for patients who are or may become pregnant should be made carefully and on a case-by-case basis. Limited case reports from Europe and Australia indicate that doses can range from 0.4 to 24 mg/day, with pregnancies generally progressing normally (50).

2.6. Management of HIV-infected drug-dependent women presenting in labour
The majority of drug-using women do not attend ANC and only arrive at the maternity ward around the time of labour. In such cases, maternity wards should be prepared to:

- assess drug use dependence (see Protocol 5, HIV/AIDS treatment and care for injecting drug users, 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 pregnancy outcome, on the newborn infant and on treatment approaches.

According to the United States Food and Drug Administration, a Class C rating for use during pregnancy means that studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal or other) and that there are no controlled studies in women or studies in animals (48).
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.

2.6.1. Pain relief
Pain relief requires special attention during labour and the postpartum period, especially after CS. 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 (53).

Epidural anaesthesia should be used as early in delivery as possible, and can be continued in the early postpartum period, especially after CS.

3. Postpartum management
PMTCT postpartum pharmacological management is described in Tables 1–4 above. All women with HIV infection should also be counselled on infant feeding options and contraception while in the maternity ward.

3.1. Counselling on infant feeding

Even when peripartum ARV prophylaxis is used, infants remain at substantial risk of acquiring infection during breastfeeding, which has been shown to result in HIV transmission to 14% of at-risk infants (54–56). WHO recommends that HIV-infected mothers do not breastfeed at all when replacement feeding is acceptable, feasible, affordable, sustainable and safe (for definitions of these terms, see Annex 2). Otherwise, exclusive breastfeeding is recommended during the first months of life and should be discontinued as soon as these conditions for replacement feeding are met. Evidence suggests that exclusive breastfeeding in the first three months carries a lower risk of transmission than mixed feeding, which is therefore not recommended (57, 58).

Counselling on infant feeding should stress the risks of transmission through breastfeeding and recommendations for replacement feeding, the importance of not breastfeeding during replacement feeding and how to safely prepare and administer the food. Mothers should have a follow-up visit to the paediatric outpatient clinics within two weeks after birth to check and ensure that there are no feeding problems.

3.2. Counselling postpartum contraception

Condoms remain the preferred option for reducing the risk of unintended pregnancy and HIV transmission. Lactational amenorrhoea (LAM) cannot be recommended as a contraceptive method, since breastfeeding is not recommended. (For more information, refer to Protocol 9, Support for sexual and reproductive health of people living with HIV, section on Lactational amenorrhea method.)

4. Neonate management in the maternity ward

4.1. Laboratory diagnosis of HIV in neonates

The first deoxyribonucleic acid polymerase chain reaction (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. A second HIV DNA test at six to eight weeks from birth should be performed regardless of the outcome of the first test. If PCR is not available, an HIV antibody test is recommended at 15–18 months, with a confirmatory western blot test.

HIV diagnostic testing for infants should be accompanied with counselling for caregivers, explaining the results and the need for additional testing to definitively determine the child’s infection status.

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7 For further information regarding pain management for IDUs, refer to Protocol 5, HIV/AIDS treatment and care for injecting drug users, section on Management of acute and chronic pain.
Please see the algorithm 1 for HIV diagnosis in infants in Protocol 11, Paediatric HIV/AIDS treatment and care, section on laboratory diagnosis of HIV.

4.2. Management of dependence and withdrawal syndrome in neonates

4.2.1. 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, sleeping problems, protracted crying and hyperactive reflexes;
- regurgitation, vomiting and diarrhoea;
- tachypnea; and
- minor symptoms, such as fever, sneezing, sweating, nasal stuffiness and yawning.

Infants of mothers known or suspected to be drug users who are showing 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 3, which provides a basis for deciding treatment dosages (see Table 8 in the next below).

4.2.2. Treatment of NAS (51)

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

- **First stage is: 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 is: pharmacological therapy.** Phenobarbital solution is the agent of choice. If it is not successful or if convulsions occur, switch to morphine solution. Therapeutic doses for NAS treatment vary depending on NAS score; see Table 8 below, and Annex 3 for scoring. Occasionally, vomiting may be very serious, in which case replace the pharmacological agent temporarily with chlorpromazine (2–3 mg/kg/day in 3 or 4 doses intramuscularly (IM)).
### Table 8. Therapeutic doses for NAS

<table>
<thead>
<tr>
<th>Abstinence score</th>
<th>Phenobarbital solution</th>
<th>Morphine solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–10</td>
<td>6 mg/kg/day in 3 doses</td>
<td>0.32 mg/kg/day in 4 doses</td>
</tr>
<tr>
<td>11–13</td>
<td>8 mg/kg/day in 3 doses</td>
<td>0.48 mg/kg/day in 4 doses</td>
</tr>
<tr>
<td>14–16</td>
<td>10 mg/kg/day in 3 doses</td>
<td>0.64 mg/kg/day in 4 doses</td>
</tr>
<tr>
<td>17+</td>
<td>12 mg/kg/day in 3 doses</td>
<td>0.80 mg/kg/day in 4 doses</td>
</tr>
</tbody>
</table>

*Source:* adapted from Finnegan et al. (51)

Interactions between ARV drugs for neonates as part of PMTCT and the severity of the NAS treatment have not yet been studied.

### 4.3. Immunization

In countries with an incidence of more than 20 TB cases per 100 000 population (61), all HIV-exposed asymptomatic children should be immunized with bacille Calmette-Guérin (BCG) in the maternity ward on the same schedule as infants who have not been exposed to HIV.

In countries with low TB incidence, BCG vaccine should not be administered to HIV-infected children, regardless of their clinical stage or immunodeficiency status. Other vaccinations should be considered, taking into account the national vaccination programmes. For further recommendations concerning immunization, please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*

### 5. Referrals

The continuum of care for HIV-infected women, their neonates and their families requires a team approach that should ensure provision of:

- paediatric care for the neonate, including HAART and prevention of opportunistic infections in the first year of life, if indicated;
- postpartum contraception for the mother;
- treatment and care of HIV/AIDS; and
- treatment for drug dependency and harm reduction.

To ensure proper follow-up, detailed reports on the ART received by the mother and neonate in the maternity ward should be sent to the mother’s and child’s physicians. For further information on treatment and care please refer to protocols 1, *Patient evaluation and antiretroviral treatment for adults and adolescents* and 11, *Support for sexual and reproductive health in people living with HIV.*
V. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to PMTCT services and its success. Such indicators assist managers in decision making on ways 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):

*Antenatal care services should collect data on the:*
- number of pregnant women
- number of pregnant women who were tested for HIV
- number of pregnant women who tested positive for HIV
- number of HIV-infected pregnant women who had an abortion
- number of HIV-infected pregnant women who received ARV prophylaxis during pregnancy
- number of HIV-infected pregnant women who are opioid-dependent injecting drug users
- number of HIV-infected pregnant women receiving OST
- number of HIV-infected pregnant women receiving OST and ARV prophylaxis.

*Maternity services should collect data on the:*
- number of HIV-infected pregnant women who presented in the maternity services;
- number of pregnant women who presented in the maternity services without prior HIV testing during pregnancy:
  - among these how many received a rapid HIV test:
    - among these how many tested HIV positive;
- number of HIV-infected pregnant women who presented in the maternity services without receiving ARV prophylaxis during pregnancy;
- number of HIV-infected pregnant women who received ARV prophylaxis during labour;
- number of HIV-infected opioid-dependent injecting drug users in the maternity services:
  - among these how many received OST treatment during labour;
- number of HIV-infected pregnant women who had a vaginal delivery;
- number of HIV-infected pregnant women who had a planned caesarean section;
- number of neonates born to HIV-infected women:
  - among these number who received ARV prophylaxis;
  - among these how many received milk formula feeding;
  - among these how many received exclusive breastfeeding;
- number of HIV-infected neonates, born to HIV-infected mothers, diagnosed by PCR;
- number of neonates born to opioid dependent women;
- number of neonates who received NAS treatment.
### Annex 1. Currently available medications for substance-dependence treatment during pregnancy

<table>
<thead>
<tr>
<th><strong>Table 9. Medications available for treating substance dependence during pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td><strong>Opioid dependence</strong></td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Naltrexone</td>
</tr>
<tr>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td><strong>Smoking cessation</strong></td>
</tr>
<tr>
<td>Nicotine patch</td>
</tr>
<tr>
<td>Nicotine gum</td>
</tr>
<tr>
<td>Bupropion sustained release</td>
</tr>
</tbody>
</table>
### Prevention of HIV transmission from HIV-infected mothers to their infants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Side-effects</th>
<th>Clinical considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohol withdrawal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>25–100 mg per dose</td>
<td>Sedation, dizziness, ataxia, confusion</td>
<td>Long half-life; may be given as a loading dose to reduce symptoms, then discontinued</td>
</tr>
<tr>
<td>Diazepam</td>
<td>15–60 mg per dose</td>
<td>Same as chlordiazepoxide</td>
<td>Shorter half-life, no active metabolites and not dependent on hepatic metabolism; generally requires dosing every 4–6 hours</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400 mg loading dose, then 200 mg three times daily (TID), tapering over 5 days</td>
<td>Sedation, dizziness, ataxia, confusion, nausea and vomiting, bone marrow suppression</td>
<td>Effective for moderate-to-severe withdrawal, not well studied for severe withdrawal</td>
</tr>
</tbody>
</table>

| **Alcohol dependence** |                        |                                                                              |                                                                                          |
| 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 |

*According to the United States Food and Drug Administration (48), Class B use in pregnancy rating means that either animal studies have revealed no evidence of harm to the fetus, with no adequate and well-controlled studies in pregnant women; or that animal studies have shown an adverse effect, while adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Source: adapted from Rayburn & Bogenschutz (45).
Annex 2. 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, either she is under no social or cultural pressure to breastfeed and is supported by family and community in opting for replacement feeding, or she 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 at 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:* adapted from WHO (57).

If the above criteria are not met, exclusive breastfeeding is recommended during the first months of life and should then be discontinued as soon as feasible. HIV-positive 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 in accordance with their personal circumstances.
## Annex 3. Neonatal abstinence syndrome scores

<table>
<thead>
<tr>
<th>TABLE 10.</th>
<th>NEONATAL ABSTINENCE SYNDROME SCORES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sign or symptom</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td><strong>Central nervous system disturbances</strong></td>
<td></td>
</tr>
<tr>
<td>High-pitched cry</td>
<td>2</td>
</tr>
<tr>
<td>Continuous high-pitched cry</td>
<td>3</td>
</tr>
<tr>
<td>Sleeps &lt;1 hour after feeding</td>
<td>3</td>
</tr>
<tr>
<td>Sleeps &lt;2 hours after feeding</td>
<td>2</td>
</tr>
<tr>
<td>Sleeps &lt;3 hours after feeding</td>
<td>1</td>
</tr>
<tr>
<td>Hyperactive Moro reflex</td>
<td>2</td>
</tr>
<tr>
<td>Markedly hyperactive Moro reflex</td>
<td>3</td>
</tr>
<tr>
<td>Mild tremors when disturbed</td>
<td>1</td>
</tr>
<tr>
<td>Moderate–severe tremors when disturbed</td>
<td>2</td>
</tr>
<tr>
<td>Mild tremors when undisturbed</td>
<td>3</td>
</tr>
<tr>
<td>Moderate–severe tremors when undisturbed</td>
<td>4</td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>2</td>
</tr>
<tr>
<td>Excoriation (specify areas)</td>
<td>1</td>
</tr>
<tr>
<td>Myoclonic jerks</td>
<td>3</td>
</tr>
<tr>
<td>Generalized convulsions</td>
<td>5</td>
</tr>
<tr>
<td><strong>Metabolic/vasomotor/respiratory disturbances</strong></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Fever &lt;101 °F (99–100.8 °F, or 37.2–38.2 °C)</td>
<td>1</td>
</tr>
<tr>
<td>Fever &gt;101 °F (38.4 °C and higher)</td>
<td>2</td>
</tr>
<tr>
<td>Frequent yawning (&gt;3–4 times)</td>
<td>1</td>
</tr>
<tr>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>1</td>
</tr>
<tr>
<td>Sneezing (&gt;3–4 times)</td>
<td>1</td>
</tr>
<tr>
<td>Nasal flaming</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory rate &gt;60/min</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate &gt;60/min with retractions</td>
<td>2</td>
</tr>
<tr>
<td><strong>Gastrointestinal disturbances</strong></td>
<td></td>
</tr>
<tr>
<td>Excessive sucking</td>
<td>1</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>2</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>2</td>
</tr>
<tr>
<td>Projectile vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Loose stools</td>
<td>2</td>
</tr>
<tr>
<td>Watery stools</td>
<td>3</td>
</tr>
</tbody>
</table>

*Source: Finnegan et al. (51).*
References

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