We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter
Management Strategies in Perinatal HIV

Kayla Aleshire and Rima Bazzi

Abstract

Current management of perinatal HIV infections and exposures involves the administration of antiretroviral therapy to both the pregnant mother and to her child after delivery. Striving to achieve safe and effective medication management is key in preventing new pediatric HIV infections. Maternal HIV testing and subsequent monitoring can help to identify fetal HIV exposures during pregnancy, maternal nonadherence, insufficient treatment regimens, and otherwise undiscovered exposures during the delivery process. There are several well-constructed guidelines that offer expert references for healthcare providers. This chapter will summarize current recommendations from the United States, with a brief insight into select international guidelines. Although available guidelines provide a structured framework for the healthcare team, there has recently been a significant drive to advance current perinatal management and outcomes.

Keywords: pregnancy, perinatal, HIV, antiretrovirals, transmission

1. Introduction

Nearly 30 years ago, the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 Study Group identified a reduction in the relative risk of perinatal transmission by almost 70 percent with the use of zidovudine monotherapy [1]. Zidovudine was administered to women starting in their second trimester and continued through the duration of the pregnancy [1]. Additionally, the medication was given to the mother during the intrapartum period, and postnatally to the infants [1]. A few decades later, triple antiretroviral therapy (ART) administered during pregnancy in the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial proved more effective at reducing mother-to-child HIV transmission than with zidovudine monotherapy [2]. The PROMISE trial also demonstrated that there is a concern for transmission through breastfeeding, although this risk may be minimal with the use of ART [3]. Recent statistical evidence estimates that vertical transmission of HIV from mother to child is less than 1% in the United States [4], although it can exceed 10% in some countries [5]. Success in reducing perinatal transmission can presumably be attributed to the advancements in HIV care. Over the last three decades, prevention of mother-to-child transmission (MTCT) strategies have been continuously improving. There are several accepted guidelines that provide step-by-step recommendations for maternal HIV testing, management of acute HIV infection in the pregnant individual, use of
Future Opportunities and Tools for Emerging Challenges for HIV/AIDS Control

antiretroviral (ARV) medications during pregnancy, the intrapartum period, and post-exposure prophylaxis to the newborn after delivery. The guideline recommendations provide slightly different options for treatment and prevention of perinatal HIV that are vital to controlling viremia in the pregnant mother and the developing child. Despite current information, therapeutic recommendations are more apt to utilize previously accepted regimens in the pregnant and neonatal populations. More recently, there is momentum directed toward conducting research trials with early pregnancies and neonates. Additional information regarding ARV safety and efficacy has the potential to further increase the therapeutic options in these respective populations.

2. Epidemiology

Nearly 5000 young women across the globe become infected with HIV each week, representing a profound population that warrants attention [6]. Centers for Disease Control and Prevention (CDC) data from the US population indicates that over 70% of new diagnoses in 2019 among females were those of childbearing age [4]. Of women who become pregnant, global estimates suggest that 80% have access to ART [6]. With many pregnant women having access to ARVs, it is important to consider implications in treatment management. Medications should be safe and effective in controlling maternal viremia to prevent newborn acquisition. In addition, HIV testing can help to identify new infections, thus enhancing earlier access to therapy. Over the last decade, new HIV diagnoses in children worldwide have dropped by half [6]. According to CDC statistics in the US population from 2015 to 2019, most children with perinatal HIV exposures in whom seroconversion did not occur were born to mothers who received HIV testing prior to the pregnancy [4]. Within the same period, the rates of acquired perinatal HIV were less than 1% in the United States [4]. Although testing prior to pregnancy is important, women can seroconvert later in the gestational period. Repeat testing should not be neglected as it has been demonstrated that a higher percentage of perinatal transmissions occur after 36 weeks’ gestation [7]. In a US Epicenter for HIV, only about 80% of mothers were restested in their third trimester [8]. Furthermore, a study of pregnant women living with HIV in South Africa showed that only 11% of women were receiving all recommended tests throughout the perinatal period [9]. These examples highlight missed opportunities and the underutilization of HIV testing in some areas.

3. Future goals and challenges

In 2015, the United Nations endorsed a set of global goals to achieve a more promising future for all. One goal presented was to End AIDS by 2030 [10]. Subsequently, the United States advocated for Ending the Epidemic in the US—a plan for a 90% reduction in new HIV infections by 2030 [11]. More specifically, the CDC goal for HIV elimination is to reduce perinatal transmission to an incidence of <1 infection per 100,000 live births and a rate of <1% among infants exposed to HIV [12]. An essential component to achieving these goals is to understand the current approaches to the management of pregnant and pediatric populations and to identify barriers to treatment success. The optimization of medication therapy and performance of pertinent HIV tests are key strategies for preventing perinatal transmission [12–14]. Furthermore, the unique physiologies of neonates and pregnant women present challenges to enhancing medication therapy [15]. The paucity of data in these populations
limits the recommended medication choices available for treatment and prophylaxis of HIV [12–14]. Currently, recommendations for medication dosing in pregnant women and neonates are often modeled after data obtained from non-pregnant adults or older pediatrics respectively. If efficacy and safety data were more comprehensive for the pregnant and neonatal populations, this would likely have a profound effect on achieving the elimination of MTCT. Additionally, opportunities exist for utilizing HIV testing during pregnancy and surrounding the time of delivery [8, 9]. Adhering to the current recommendations for HIV screening would shorten the time to treatment and potentially reduce viral exposure to the newborn [8].

4. Pharmacokinetic considerations for antiretroviral medications

The study of pharmacokinetics (PK) seeks to identify if an administered medication possesses the ability to reach therapeutic concentrations in the body, reach the proper site of action to exert its intended effect, and how long the intended effect will remain. Pharmacokinetic drug parameters include the absorption of drugs into the body, metabolism, and the excretion or removal of the drug and waste components from the body. Metabolism can create an active drug from a non-active one or change an active drug into non-active waste products. The products of a medication that result from a metabolic process in the body are termed metabolites. Drug metabolites can be eliminated by the liver or excreted by the kidneys. Another drug parameter to consider is drug distribution. Some medications readily exit the vascular system and distribute into neighboring tissues. Other medications predominantly remain within the vascular compartment. Many medications have a theoretical value, known as the volume of distribution (Vd), that describes this distribution property [16]. Pregnant women and neonates exhibit unique physiological properties that greatly alter medication PK [16, 17].

4.1 Pregnancy

Maternal physiology changes throughout the gestational period, thus PK parameters of a drug may be increasingly altered as the pregnancy progresses through each trimester. Most ARVs are administered orally and must be absorbed from the gastrointestinal tract. Consider a patient who is suffering from nausea and vomiting during pregnancy. If emesis occurs, then transit time in the stomach for an orally administered medication will be reduced and the medication may not be fully absorbed. If the patient requires antacids to alleviate symptoms, this, in turn, may increase the pH of the stomach. If the administered medication requires a low pH or acidic environment for absorption, an altered pH could affect therapeutic outcomes. Also, during pregnancy, there is a propensity for increased stomach pH, delayed gastric emptying, and slower intestinal motility altering the bioavailability of oral drugs. Enzymes, predominantly in the liver, are responsible for drug metabolism and are altered in the pregnant state. Some have increased activity (e.g., CYP3A4, CYP2D6, CYP2C9, UGT1A4, and UGT1A1/9), while others have decreased activity (e.g., CYP2C19, CYP1A2). This can have significant implications on how much active drug is available, and how fast or slow the administered medication is metabolized in the body. It changes the rate of conversion from active to inactive components or vice versa, depending on the properties of the drug. There is increased renal blood flow and glomerular filtration rate (GFR), resulting in increased elimination of renally-cleared medications, which may
result in shorter half-lives and potential underdosing of those medications. During pregnancy, a woman’s body fat, plasma volume, and water volume also significantly increase. In theory, this may create a larger Vd for both lipophilic and hydrophilic medications, requiring higher doses to maintain therapeutic drug concentrations. Albumin concentrations are markedly reduced when pregnancy progresses, and this affects the binding and transport of medications throughout the body. Medications that typically bind well to albumin may be found to have higher free or unbound concentrations, leading to greater efficacy, or an increase of unintended adverse effects. The placenta acts as a membrane where small, lipophilic medications are free to cross, thus medications with these properties may have more influence on the fetus [16].

Medications in the integrase strand transfer inhibitor (INSTI) and protease inhibitor (PI) classes have displayed altered PK in pregnancy. A small sample size of pregnant women living with HIV taking the combination of INSTI, elvitegravir, boosted with cobicistat at the approved doses, showed low concentrations of each drug in the third trimester. In most of these women, elvitegravir did not achieve the minimum effective concentration. Additionally, the boosting agent cobicistat was shown to have reduced AUC by about 50% [18]. Similar PK profiles were also observed in an earlier trial by Momper et al. [19]. Of the PI class, both darunavir and atazanavir, boosted with cobicistat have exhibited approximately 50% reductions in plasma concentrations in the third trimester [20]. Treatment regimens utilizing cobicistat as a boosting agent are not recommended in pregnancy by the United States Department of Health and Human Services (DHHS), the European AIDS Clinical Society (EACS), and the British HIV Association (BHIVA) guidelines [12–14]. The PK of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are not expected to be altered during pregnancy [12].

4.2 Neonatal

Neonatal physiologic considerations are important when selecting safe and effective medications. Once clamping of the umbilical cord occurs, a newborn’s body must compensate for life outside the womb. Neonatal development occurs rapidly within the first weeks of life. Throughout this period, the PK of medications can be varied as they are dependent on the maturity of the infant. Gestational age at birth and age after birth both influence pharmacokinetics and the sum of the two ages can be expressed as the postmenstrual age (PMA). Current neonatal dosing recommendations are commonly extrapolated from older pediatric populations and even sometimes from the adult population. Medications are often dosed by PMA and weight; however, this weight-based dosing strategy does not always account for the underexpression of liver enzymes required for drug metabolism and clearance. Full enzyme expression ranges from several days to years (e.g., CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A1). A few enzymes are expressed in the womb but are eventually suppressed after birth (e.g., CYP3A7, FMO1). Medications that require adult enzyme expression for elimination may be overdosed in a newborn still expressing fetal enzymes. Hepatic blood flow rates increase as the newborn develops, so in the early stages of life, medications that are predominantly removed by the liver, exist in the body for a much longer period regardless of enzymatic expression. Weight-based dosing is not a perfect indicator of renal drug clearance either. Although larger infant body weight can be reflective of greater renal function, there is often slower renal development for premature neonates born at less than 34 weeks’ gestation. Neonates have lower albumin concentrations which can lead to higher free drug concentrations.
that usually have a high binding affinity to albumin. Neonates have larger water volume, but they have low fat and muscle content. This can be further exaggerated in premature neonates. Lipophilic drugs with a propensity to enter adipose tissue could remain in the vasculature much longer, while hydrophilic drugs may exit the vasculature to a higher degree. Premature infants may also have slightly impaired gastrointestinal absorption [17].

Nevirapine is a medication often used in neonatal prevention of HIV and is largely dependent on CYP liver enzymes for elimination [12–14, 21]. DHHS guideline recommendations for gestational age of greater than 34 weeks up to 1 month are investigational and based on results from the IMPAACT P1115 trial [12, 22, 23]. The PACTG 1043 trial included a two-drug regimen for prophylaxis in infants with a high risk of perinatal exposure. This regimen was composed of standard zidovudine doses and additional fixed-dose nevirapine administered at 0, 2, and 6 days of life, for infants of at least 32 weeks gestational age [24]. The DHHS guidelines categorize this regimen as an option for high-risk exposure in infants born at 32 weeks’ gestation or older [23]. A more recent study of premature infants used weight-based nevirapine dosing for post-exposure prophylaxis at a dose of 2 mg/kg/dose on days 0, 2, and 6 of life. This strategy resulted in no clinically significant adverse events. Infants with a gestational age of 28 weeks at birth who received this regimen achieved effective concentrations for prophylaxis and concentrations continued to remain above target concentrations at 2 weeks old. However, for infants greater than 28 weeks’ gestational age at birth, plasma concentrations were shown to decline at day 12 [21]. Dosing under the age of 1 month has not been yet approved by the FDA due to insufficient data [23]. Though there is limited evidence for drug approval in the US, these trials illustrate the variability of pharmacokinetics in the neonate and highlight the necessity for additional studies for neonatal ARV dosing recommendations.

4.3 Drug-drug interactions

People living with HIV should be exposed to adequate concentrations of ARVs to achieve and maintain virological suppression. After considering the PK and pharmacodynamics (PD) of pregnancy, attention must be directed to important potential drug-drug interactions (DDIs) involved with HIV management in pregnancy. DDIs can occur at any step of the pharmacokinetic process where drug parameters are affected. As mentioned earlier, this may include absorption, distribution, metabolism, and elimination. DDIs can result in an increased concentration of ARV or concomitant drug, leading to potentially adverse effects. Alternatively, DDIs can lead to decreased ARV concentrations resulting in subtherapeutic concentrations and potential development of resistance.

Drug absorption can be affected by transit time in the stomach, chelation, or changes in pH. As discussed earlier, transit time can be reduced due to nausea and vomiting during pregnancy, slower intestinal motility, and delayed gastric emptying. Chelation occurs when components of an INSTI’s chemical structure bind to polyvalent cations present in other medications such as calcium supplements, multivitamins, iron products, or antacids. The resultant chelated compounds are less likely to be absorbed and thus exhibit potential for reduced efficacy of the INSTI. As medications containing polyvalent cations are commonly used during pregnancy, mindful separation of these products from an INSTI-containing regimen is critical. As administration directions for each INSTI and polyvalent cations vary, in general,
the recommendation is to give the INSTI about 2 h prior to any of the aforementioned medications to allow absorption to occur. If the supplement is administered first, then the INSTI is advised to be administered 4–6 h afterward. Some ARVs require an acidic environment for complete absorption. Acid-reducing agents such as proton pump inhibitors (PPIs), H2 receptor antagonists (H2RAs), or antacids will influence the absorption of these drugs. Ritonavir-boosted atazanavir is a PI recommended to be given during pregnancy. If a PPI or H2RA medication is utilized, it should be given about 12 h apart from ART. Rilpivirine, an NNRTI, should be given with food and separated from the H2RA. However, PPIs are specifically contraindicated with rilpivirine [12].

Hepatic metabolism can be influenced, not only by the pregnant state but also by select ARVs that are administered. PIs and their boosters inhibit many metabolizing enzymes, resulting in reduced elimination and increased plasma levels of other medications. Ondansetron is used to alleviate nausea and is a substrate of hepatic enzymes. Administration with PIs and their boosters can increase the side effects of ondansetron, notably cardiac prolongation of the QT interval. Clinical monitoring including electrocardiogram (ECG) assessments is recommended for prolonged concomitant drug therapy. Fentanyl plasma concentrations can be significantly increased by ritonavir, however, intrapartum epidural administration of fentanyl over a short period of 24 h has been suggested to be safe [12].

Although boosted atazanavir is expected to increase the concentrations of the NRTI tenofovir disoproxil fumarate (TDF), it is also apparent that TDF causes lower plasma concentrations of atazanavir (ATV) in the third trimester if the agents are combined in a regimen [12–14]. The BHIVA guidelines recommend that if this combination is used then therapeutic drug monitoring may be considered. They inform that it is not necessary to adjust the dose of ATV, when used in combination with TDF, but that dosage adjustments may be made on a case-by-case basis [14]. Furthermore, the combination of ATV and TDF is not recommended with additional use of an H2RA. If these three agents are still utilized concomitantly, then it is further recommended adjust the ATV dose from 300 to 400 mg daily [14]. The DHHS guidelines also do not recommend ATV in combination with TDF and an H2RA in a treatment experienced pregnant patient. They also do not instruct providers to adjust the dose if it is utilized. Instead, they inform that the increased dose reaches adequate plasma concentrations, and they provide recommendations from the FDA package insert for atazanavir. The Federal Drug Administration (FDA) label recommendation is that increased atazanavir dosing may be utilized if used in combination with both TDF and an H2RA [12]. All guidelines recommend that ATV is to be boosted with ritonavir during pregnancy [12–14].

Health care providers should consider that concentrations of methylergonovine, a medication used for post-partum hemorrhage, can be altered by ART. PIs and their boosters can increase the effect of methylergonovine resulting in increased uterine smooth muscle tone, posing risk for uterine tetany. Patients on ART containing PIs or boosting agents should not be prescribed methylergonovine unless oxytocin or misoprostol are not available. In contrast, methylergonovine can be reduced by medications in the NNRTI class, such as rilpivirine or efavirenz as they induce liver enzymes and increase the elimination of methylergonovine [12]. Due to the complexities of DDIs and ARVs, and the dire consequences of subtherapeutic ARV concentrations leading to potential resistance, health care prescribers are encouraged to refer to the product insert, treatment guidelines, online DDI websites or to consult with an HIV pharmacist for further assistance.
5. Antiretroviral selection and initiation in the treatment naïve pregnant person living with HIV

One of the major goals of therapy in HIV treatment during pregnancy is to reduce the risk of transmission to the fetus. Since the initial use of zidovudine as monotherapy throughout pregnancy and intrapartum, it has been well established that the risk of perinatal transmission can be decreased when viral suppression is achieved [1]. When choosing a new regimen for a treatment naïve pregnant patient living with HIV, it is important to consider DDIs, PK, and side effects that may influence treatment efficacy or incur harm to the fetus.

Recommendations for the treatment of HIV during pregnancy vary slightly between the European AIDS Clinical Society (EACS), British HIV Association (BHIVA), and United States Department of Health and Human Services (DHHS) guidelines and preferred agents are summarized below (e.g., Table 1). ART is recommended for all pregnant women with HIV. The timeframe in which to initiate treatment in a pregnant woman living with HIV who is not currently on therapy is debated. If a pregnant woman is newly diagnosed with HIV, treatment should not be delayed according to DHHS and EACS, regardless of the patient’s viral load, CD4 count, or pending resistance genotype results. In contrast, BHIVA recommends that treatment be started preferably during the second trimester, although it is permitted to start earlier if the patient’s viral load exceeds 100,000 copies/ml or CD4 is less than 200 cells/mm³. BHIVA also recommends that treatment not be initiated before HIV resistance genotype results are reviewed, except for women who present to care in the third trimester.

Collectively, the guidelines recommend a dual NRTI backbone in combination with a third agent as the choice treatment. The selected agents preferred in each of the dual NRTI backbones, and the third agent differ slightly among the guidelines. The guidelines share recommendations for an NRTI dual backbone of abacavir/lamivudine (ABC/3TC) and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) with the exclusion of any NRTI combination that includes zidovudine (ZDV). Zidovudine-based therapy is no longer preferred in the adult population due to concerns about toxicity, so aside from its short-term use in intrapartum care and infant prophylaxis, it has become an alternative agent. HLA-B*5701 testing

<table>
<thead>
<tr>
<th>Backbone</th>
<th>Third Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual NRTI</td>
<td>INSTI</td>
</tr>
<tr>
<td>DHHS</td>
<td>ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>TAF/FTC</td>
</tr>
<tr>
<td>EACS</td>
<td>ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>TAF/FTC</td>
</tr>
</tbody>
</table>

*RAL 400 mg and DVR/r 600 mg/100 mg are recommended to be dosed twice daily.

*ATV should only be initiated after 14 weeks’ gestation according to EACS guidance.

Table 1.
Preferred ARV agents in the pregnant person living with HIV.
should be done prior to initiation of any regimen containing abacavir (ABC) to rule out hypersensitivity to the drug.

Regarding the tenofovir formulation, DHHS recommends that either tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF) may be used as a preferred agent. EACS includes TAF among their preferred NRTI backbone options as well, but TAF is an alternative agent according to the BHIVA guidelines. BHIVA and EACS indicate that if TAF is to be included in a regimen, it should be used after 14 weeks of gestational age, due to its unevaluated safety and efficacy within the first trimester of pregnancy. Contrastingly, the DHHS panel does not place gestational age limits on the drug as the guidelines suggest the two agents have similar efficacy and safety profiles when used in pregnancy [12–14].

INSTIs have the ability to suppress viral load quickly and efficiently. As for the third agent comprising a complete regimen, INSTIs are preferred as indicated in both EACS and DHHS guidelines [12, 13]. In contrast, BHIVA suggests that INSTI regimens are to be reserved for pregnant patients presenting with high baseline viral loads of greater than 100,000 copies/ml or those with current ART that have failed to achieve adequate viral suppression [14]. Dolutegravir (DTG) is the INSTI of choice across the guidelines, though DHHS and EACS additionally include raltegravir (RAL) [12, 14]. It is important to note, however, that if raltegravir is used, it must be dosed twice daily in pregnancy, as there is insufficient information regarding the use of daily dosing of raltegravir during pregnancy [12]. In contrast to the US guidelines, both European guidelines state for dolutegravir to be included in a regimen, it should be started preferably after 6 weeks of gestation [13, 14]. This restriction is due to the previously proposed association of infant neural tube defects with dolutegravir use in pregnancy [25]. The guidelines further express that those pregnant women living with HIV should be fully informed prior to making the decision to initiate or switch therapy to dolutegravir [13, 14].

Although INSTIs are preferred agents to be included in a three-drug regimen within the EACS and DHHS guidelines, all three guidelines additionally recommend the use of a PI as the third ARV in a regimen [14]. Within the DHHS and BHIVA guidelines, ritonavir-boosted atazanavir (ATV/r) is recommended as a first-line agent from the PI class [12, 14]. Along with boosted atazanavir, DHHS also includes ritonavir-boosted darunavir (DTV/r) with twice-daily dosing as an appropriate third agent in a first-line treatment regimen [12]. In contrast, EACS lists DRV/r as a preferred agent only when used with a tenofovir-based NRTI backbone, not with ABC/3TC. Boosted atazanavir is not included in the EACS preferred regimens for pregnant patients initiating therapy [13]. The preferred boosting agent is ritonavir as regimens boosted with cobicistat have resulted in treatment failure during pregnancy, as mentioned previously [12–14].

Notably, the BHIVA guidelines also recommend efavirenz, an NNRTI, as an additional preferred agent to be used in combination with a dual NRTI backbone. This is due to its historically extensive use during pregnancy, thereby possessing the most data for its efficacy and safety [14]. In opposition to this BHIVA recommendation, DHHS and EACS both indicate that efavirenz is an alternative option for use in an ARV drug regimen during pregnancy [12, 13]. It should be carefully considered that NNRTI agents are not active against HIV-2 and so should be avoided in this population [12–14].

6. Testing and monitoring HIV clinical status in pregnancy

The DHHS guidelines recommend that all women be tested for HIV with each pregnancy at their earliest visit with their Obstetrician (OB). They further
recommend repeat testing during the third trimester, even if the initial test was nega-
tive for mothers who may have a heightened risk of acquiring HIV. These women are
identified as those who receive care in facilities or jurisdictions that have an increased
incidence of HIV, women with behaviors that impose a high risk of HIV acquisition,
or who present at any time during the pregnancy with another sexually transmitted
infection (STI). Additionally, there are select states within the US that require a third
trimester HIV test to be performed. If a mother presents in labor and her HIV status
is unknown, HIV testing should be expedited with results available within the hour,
to help determine if additional measures should be taken to prevent transmission to
the child. If there was no HIV test conducted at any time during the pregnancy or
during labor, it is advised that a mother is tested immediately postpartum to further
determine any risk to the child. The HIV test that is recommended is a combina-
tion antibody/antigen test. Since it takes time for complete antibody development
in response to an infection, this test could produce a false negative during the first
14 days of an acute HIV infection. Therefore, if an acute HIV infection is suspected,
an HIV-1 RNA PCR test (viral load) is recommended as it can detect maternal viremia
as early as 10 days post-exposure [12].

Several studies have demonstrated that maternal HIV testing may be underutilized
[8, 9]. In a study conducted in a US epicenter for HIV, about 20% of women did not
receive a second HIV test during their 3rd trimester. This is very unfortunate, as it
could lead to delays in detection of previously unknown maternal HIV, thus resulting
in delays to ARV access to the mother and to her child after birth.

One focus for improvement could be increasing provider awareness. Providers
should be aware of the local prevalence of HIV infections and recommendations for
HIV screening during all trimesters. Furthermore, conducting nonbiased social and
sexual health histories during pregnancy would be useful to identify high-risk women
who may benefit from a repeat HIV screening test in the third trimester [8].

If a pregnant mother has been living with HIV or is newly diagnosed during
the pregnancy, there are additional testing recommendations for monitoring the
clinical status of HIV, as well as the risk of transmission to the child. An HIV-1 RNA
test should be conducted at the initial OB visit for any woman living with HIV. This
helps to assess baseline viremia and establish immediate goals of care. The viral load
is recommended to be repeated after 2–4 weeks if therapy is initiated or adjusted.
Furthermore, once stabilized on an antiretroviral regimen, the viral load should be
performed every month until viral suppression is achieved, then performed every
3 months thereafter. There should be an additional viral load conducted between 34
and 36 weeks’ gestation in anticipation of delivery. This viral load will help to deter-
mine treatment measures that need to take place during the intrapartum and post-
partum periods to prevent transmission. The CD4 count is not as critical to monitor
throughout pregnancy if a mother has been previously stable on a regimen for at least
2 years. In this scenario, an initial CD4 collected at the first visit will suffice. However,
if a mother was not virally suppressed on her ARV regimen, or has newly switched
or initiated a ARVs during pregnancy, then CD4 testing should be conducted every
3 months until delivery. Antiretroviral resistance testing recommendations are similar
to those in non-pregnant adult patients. As such, it is recommended that resistance
testing be performed prior to initiation of ART, upon modification of a regimen, or if
there is inadequate control of the viral load [12]. Resistance testing should not cause
delays in care; thus, a clinician does not need to wait for the results of the genotype
in order to start therapy. The therapy can be adjusted when the genotype results are
available.
Based on monitoring during pregnancy, the child’s risk for HIV acquisition can be categorized. The maternal viral load is the most important criterion for defining risk. Perinatal transmission can occur in utero at any time during the gestational period. It is especially important to assess the viral load late in the pregnancy, nearest to the time of delivery, as it is presumed that this time period is where most transmissions occur [7]. If a viral load is undetectable just prior to delivery, it is suggested that the infant is at low risk for the acquisition of HIV [12]. However, if the viral load is high during the late gestational period, the infant’s risk is heightened [7, 12]. Other factors to consider in determining MTCT risk are the timing of the mother’s antiretroviral treatment initiation, adherence to ARV medication throughout the pregnancy, and acute HIV infection during the pregnancy or during the breastfeeding period [12].

7. Antiretroviral selection for the intrapartum period

The PACTG 076 trial led to the recommendation of IV zidovudine during labor [1]. This initial recommendation preceded the current recommendations for women living with HIV to be on triple ART throughout pregnancy and as close to their normal schedule as possible even during the labor and delivery period [2, 12–14]. Thus, if the viral load is less than 50 copies/ml, the DHHS, BHIVA, and EACS guidelines agree that a pregnant mother on effective ART may proceed with a spontaneous vaginal delivery and the addition of IV zidovudine is not warranted [12–14]. However, if the viral load is not suppressed, the guidelines all support the use of IV zidovudine at the time of delivery. Zidovudine is administered as an initial loading dose of 2 mg/kg/h over the first hour of treatment, followed by a continuous infusion of 1 mg/kg/h until clamping of the umbilical cord has been performed [1, 12–14]. In the EACS guidelines, the threshold for when IV zidovudine is required is a viral load above 50 copies/ml or an unknown HIV status [13]. Contrastingly, BHIVA and DHHS provide that viral loads within the range of 50–1000 copies/ml do not necessitate IV zidovudine, although other factors, such as adherence, are to be considered when making the decision whether to initiate zidovudine [12–14]. Any time that a pregnant patient’s HIV status is unknown or newly diagnosed during delivery, the guidelines agree that IV zidovudine should be initiated [12–14]. BHIVA furthermore recommends that the mother receive a single oral dose of nevirapine followed by oral zidovudine, lamivudine, raltegravir dosed twice daily, and IV zidovudine administered during delivery. BHIVA also indicates that if the infant is unlikely to take oral medications due to prematurity or other reasons, consider the addition of an oral double dose of TDF to the maternal oral regimen received prior to delivery [14]. The maternal viral load also influences the mode of delivery. Scheduled cesarean section (c-section) is strongly recommended by DHHS guidelines if the mother’s viral load near delivery is >1000 copies/ml or unknown [12]. The urge for scheduled c-section is expressed by BHIVA guidelines with >400 copies/ml [14]. This threshold is further reduced in the EACS recommendations, at a viral load of 50 copies/ml or greater [13]. All c-sections are recommended to be scheduled at 38 weeks’ gestation in hopes that the mother will not yet go into active labor [12–14].

8. Antiretroviral selection in the infant exposed to HIV

In order to determine the appropriate ARVs to initiate in the newborn who is born to a mother living with HIV, a clinical assessment of transmission risk needs to be
Management Strategies in Perinatal HIV
DOI: http://dx.doi.org/10.5772/intechopen.105451

performed. Risk stratification dictates whether a newborn will receive post-exposure prophylaxis (PEP) or an empiric initial ART. This stratification of risk is based on several factors. As discussed previously, it is important to appreciate the mother’s viral load at or near the time of delivery. As a reflection of the viral load, it should be determined if the mother received the appropriate intrapartum antiretroviral medication(s). The mode of delivery should be noted. If the mother delivers via a spontaneous vaginal delivery, an assessment of the timing of placental rupture of membranes (PROM) is also an important consideration [12]. A duration of membrane rupture of greater than 4 h prior to delivery increases the chance of perinatal HIV transmission [26].

The recommendations for PEP of infants born to mothers with HIV are similar among both BHIVA and DHHS guidelines and are summarized below (e.g., Table 2) [12, 14]. BHIVA guidelines divide perinatal exposures into very low risk, low risk, and high risk [14]. The DHHS guidelines divide exposures into three groups as well, defined as low-risk, high-risk, and presumed newborn HIV infection [12]. In contrast, EACS defers PEP recommendations to local guidelines and only offers treatment recommendations for infants diagnosed with HIV [13].

According to the BHIVA panel, ARVs should be started within 4 h of delivery [14]. The DHHS broadens this window slightly to within 6 h of delivery [12]. The first risk category in the BHIVA guidelines is very low-risk and an infant is assigned this category when all the following criteria are met: the mother has been on appropriate antiretroviral therapy for greater than 10 weeks, had two documented HIV-1 RNA <50 copies/ml during pregnancy which were at least 4 weeks apart, and HIV-1 RNA <50 copies/ml at or after 36 weeks. Only 2 weeks of zidovudine monotherapy is indicated for such an infant [14]. The lowest risk category listed in the DHHS guidelines is the low-risk category, where the infant’s mother received appropriate ART during pregnancy, and achieved viral suppression within 4 weeks, with no adherence concerns. In this scenario, a low-risk infant should receive 4 weeks of zidovudine monotherapy [12]. The BHIVA panel also recommends 4 weeks of zidovudine monotherapy for an infant in their low-risk category. An infant is considered low risk if the previous criteria are not met for very low risk, but maternal viral suppression is achieved at or after 36 weeks for a term baby, or near the delivery of a premature

<table>
<thead>
<tr>
<th>DHHS</th>
<th>BHIVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk category</strong></td>
<td><strong>ART</strong></td>
</tr>
<tr>
<td>Low risk</td>
<td>ZDV for 4 weeks</td>
</tr>
<tr>
<td>High risk</td>
<td>ZDV for 6 weeks* 3TC/NVP* or 3TC/RAL for 2–6 weeks</td>
</tr>
<tr>
<td>Presumed HIV Infection</td>
<td>ZDV for 6 weeks* 3TC/NVP* or 3TC/RAL for 2–6 weeks</td>
</tr>
</tbody>
</table>

*RAL should be considered for infants at high risk of perinatal HIV-2 transmission because HIV-2 is not susceptible to NVP [12]. In infants exposed to HIV-2, ZDV/3TC/RAL should be initiated until expert advice is available [14].

+Duration of therapy depends on patient-specific risks and expert advice is recommended [12].

Note: EACS defers PEP recommendations to local guidelines [13].

**Table 2.**
Antiretroviral post-exposure prophylaxis in the infant exposed to HIV.
Future Opportunities and Tools for Emerging Challenges for HIV/AIDS Control

baby [14]. According to the DHHS guidelines, if a mother did not receive antepartum therapy, only received intrapartum ARVs, viral suppression was not achieved within 4 weeks of delivery on a regimen, or an acute or primary HIV infection was discovered during pregnancy, the infant would fall within the high-risk category [12]. For those in this DHHS high-risk category, presumptive HIV therapy should be initiated with at least 6 weeks of zidovudine and 2–6 weeks of lamivudine and nevirapine. One may also alternatively administer zidovudine, lamivudine, and raltegravir [12].

The BHIVA panel recommends that if maternal viral suppression was not achieved by the day of birth, viral load is unknown, or there is adherence uncertainty, this is considered high-risk and a 4-week course of combination PEP is indicated consisting of zidovudine, lamivudine, and nevirapine [14]. The DHHS panel recommends presumptive therapy for those newborns who are clinically suspected to have acquired HIV infection. This is when mothers with unconfirmed HIV status have at least one positive HIV test at delivery or postpartum or there is a positive HIV antibody test for the newborn [12]. The three-drug ART recommendations are similar in the DHHS high-risk category and the presumptive treatment category. The doses prescribed may change slightly with confirmed HIV infection [12]. For confirmed newborn HIV infection, EACS recommends that the infant be started on a three-drug combination regimen consisting of the dual NRTI-backbone zidovudine and lamivudine with the third agent options of lopinavir/ritonavir, nevirapine, or raltegravir [13].

9. Testing in the infant exposed to HIV

Once a child is known to have perinatal exposure, seroconversion must be ruled out or identified with HIV testing. In the neonate, antibody/antigen tests cannot be recommended. The general concept of passive immunity ensures that a mother protects her newborn infant from infections, by passing along her own antibodies through the placenta until the baby’s own immune system can develop. The 4th generation antibody/antigen combination test is often performed for the adult population; however, this test could provide false results in an infant born to a mother living with HIV due to the presence of maternal antibodies in the infant’s blood. Due to the underdeveloped immune system of the infant, the antigen test would not be as sensitive as virologic testing, thus it is important to test for HIV using virologic HIV RNA or HIV DNA Nucleic Acid Amplification Testing (NAAT). If a non-breastfeeding infant was exposed intrauterine or during the labor process, then either NAAT is recommended at birth and should be repeated 2–6 weeks after the cessation of PEP medications [12, 23]. According to DHHS protocol, infants born at high-risk for perinatal transmission should be tested as soon as possible and before initiation of ART so as not to skew test results. Despite this recommendation, however, ART should never be delayed [12]. A positive test within the first 2 days likely reflects an early intrauterine exposure. In non-breastfeeding infants who test negative during their first week of life, but test positive upon repeat testing, it can generally be assumed that they were exposed intrapartum, or later during the pregnancy [7].

10. Breastfeeding considerations

Perinatal transmission of HIV can occur in utero, labor, and delivery, or during the breastfeeding period. There are concerns about transmission risk to the infant
Management Strategies in Perinatal HIV
DOI: http://dx.doi.org/10.5772/intechopen.105451

...through breastmilk versus the benefits that breastmilk can provide. These concerns differ between high-income (HIC) and low-middle income countries (LMIC). It can be estimated that postnatal vertical transmission rates during breastfeeding range from 5 to 20% without intervention [27]. HIV viral load is collected from plasma samples for monitoring, however, there is less information on viral load in breastmilk.

The Undetectable = Untransmittable (U = U) concept derived from the PARTNER study provides that people living with HIV who are on ART and are undetectable cannot sexually transmit the virus to their partners [28]. There is interest in expanding the U = U concept to breastfeeding mothers on ART. Part of the PROMISE study compared postpartum ARV prophylaxis in mother-baby pairs where breastfeeding occurred. The pairs were randomized to one of two ARV prophylaxis arms where either maternal ART versus daily infant NVP was administered [3]. In the primary analysis, the same number of infants were infected with HIV-1 from each arm. Thus, there was no difference between arms with vertical transmission and infant HIV-free survival at 24 months of age was high in both arms [3]. Importantly, the trial was not able to demonstrate a difference between arms due to the low degree of acquired infections. This demonstrates that both regimens were very effective in preventing transmission [3]. However, a secondary analysis of the trial did result in two infants in the maternal ART arm acquiring HIV despite maternal viral loads of less than 40 copies/ml [12]. Although U = U in the setting of breastfeeding is still undetermined, data from women in LMIC and emerging data from HIC show the transmission risk is low in the setting of strict adherence to ART and being virally suppressed [29, 30]. Although transmission risk is low, it is still possible. A summary of the breastfeeding recommendations by each guideline is provided in Table 3 [12–14].

11. Modern considerations for ethics and research

In 2018, clinical alarm spread across the globe after results from the Tsepamo surveillance study in Botswana suggested a relationship between dolutegravir exposure at conception and infant neural tube defects [25]. At the time, Botswana...
had switched from efavirenz-based to dolutegravir-based first-line therapy for the adult treatment of HIV [25]. Dolutegravir is a vivid example of how newly approved medications become available to the majority of women of child-bearing age, despite having never been tested in the pregnant population. Fortunately, by 2020, additional data collection on the prevalence of neural tube defects in infants exposed to dolutegravir at the time of conception stabilized the previously alarming numbers to less than 0.2%. This was comparable to the 0.11% prevalence rate of neural tube defects in infants of mothers who were not on dolutegravir at conception [31]. As discussed earlier, dolutegravir is now recommended as a preferred agent by the DHHS guidelines for women of childbearing potential [12]. However, it is not recommended until after the first trimester by other panels [13, 14]. The dolutegravir-scare sparked an international momentum for modifying the ethical considerations surrounding drug research and pregnancy [32]. The Tsepamo study highlights the importance of conducting earlier and more frequent trials including large study populations of pregnant women.

The intricate nature of balancing maternal benefit versus fetal harm has been a long-standing phenomenon in the field of drug research. This balancing act teeters between providing effective therapy for a pregnant mother while preventing harm to her developing child. For a long time, the scales tilted in favor of omitting useful medications, thus avoiding potential harm to the fetus. This one-sided sway reflects the perception that the fetus is so vulnerable to harm that providing appropriate maternal treatment for an array of maternal medical conditions does not provide sufficient benefit [15, 32]. This view also assumes that what may be safe for the fetus is also most appropriate for the mother [33]. First, this idea is an underrepresentation of how effective maternal medication management, directly improving maternal health, can indirectly result in improved pregnancy outcomes for the child-in-utero [33]. Second, this concept neglects a pregnant mother’s ability to make decisions for herself and for her own child [33, 34]. Instead, it leaves both providers and their pregnant patients to make less informed decisions from the limited academic information available to them [33–35]. Third, it results in more off-label use in the post-marketing pregnant population rather than use in carefully conducted and monitored trials [33, 34]. Fortunately, HIV is one chronic medical condition for which there have been considerable efforts through the years to obtain pregnancy data [32, 33]. This can be largely attributed to organizations such as the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network [36, 37]. The IMPAACT network was originally established 16 years ago as the Pediatric AIDS Clinical Trials Group (PACTG) and the Perinatal Scientific Working Group of the HIV Prevention Trials Network (HPTN) joined forces to end the HIV epidemic with a special focus on pediatric and pregnant populations. The IMPAACT Network is a global collaborative effort based in the United States to conduct quality research [37]. The PANNA study is a European Network that collects pharmacokinetic data in pregnant women and aims to obtain information on new antiretroviral medications with little to no information on this population [36]. Although there is some clinical research information available for antiretrovirals in pregnancy, it is a research area with a great opportunity [15, 32–34]. Generally, pregnancy data for ARVs are obtained when women living with HIV become pregnant on a stable ART, and the decision is made to continue the regimen throughout the pregnancy. Aside from the limited pregnancy data available, guideline recommendations are often based on extrapolations from the non-pregnant adult population. Most research today does not present separate PK data for men and
women, therefore extrapolation can be difficult to draw from women of childbearing potential to women who become pregnant when it often includes male data [16]. The agencies that influence drug approval in the United States are the Federal Drug Association (FDA) and DHHS. There are drug research regulations that were originally designed to protect human rights in drug trials, including the protection of women of child-bearing potential, pregnant women, and their children [38, 39]. Additionally, there are provisions for these populations in DHHS protocols [38]. Although adherence to these DHHS protocols is not mandated in FDA-conducted drug trials, the FDA still has recommended the DHHS guidance to be followed [38]. Historically, regulations have emphasized much effort in protecting the fetus, and pregnant women are often excluded from drug research trials [39]. If there was a shift in focus from protecting women and their unborn children by omitting them from drug trials to including them, there could be great potential. This could provide more available treatment options and identify early in the gestational period if medications are not effective. There would be information on how to adjust medication doses during pregnancy [33, 34]. This shift in focus can also be applied to the neonatal population. If there were additional information on the PK and PD of ARVs in the neonatal population, there could be more successful outcomes. Luckily, there has recently been a turning point in history. In 2017, the Third Conference on Antiretroviral Drug Optimization (CADO 3) was held to discuss the implications of newer antiretroviral agents to current standards of care, and the re-sequencing of first-, second-and third-line therapies for the future [40]. Shortly following this, the statistical results of neural tube defects discovered by the Tsepamo study raised a global alert [25] and the FDA issued draft guidance for reconsidering the ethics and science behind drug research regulations for the pregnant population [38]. The World Health Organization (WHO) also held a pediatric antiretroviral drug optimization (PADO) meeting in which the regulatory framework for research in pregnancy was determined to be outdated [32]. The CADO and PADO experts, among many others, proposed adjusting the drug approval timeline to shorten the delay of access to new antiretroviral medications for pregnant women [32, 40]. A WHO-IMPAACT-led workshop was held to address evidence gaps and identify opportunities for change. The workshop included experts from the fields of research and pharmacokinetic studies, regulatory agencies, public organizations, and stakeholders. Their consensus statement was published in 2019 which proposes earlier conducted research trials and the barriers that need to be addressed to conduct these trials [15]. In July 2020, The PHASES Working Group - Pregnancy and HIV/AIDS: Seeking Equitable Study issued a 12-step recommendation pathway for the industry [33, 34]. It stressed evidence gaps in dosing, fetal safety, and maternal outcomes and identified that in order to close these gaps changes needed to be made to the concept of ethics in pregnant women. Their call-to-action plan sought to address the inequities presented to pregnant women in access to first-line therapies, respecting pregnant women by allowing them to choose a therapy that would enhance their own health outcomes, and protection from drug-related risks when using medications “off-label” because there is no pregnancy data [33, 34]. At the end of 2021, the World Health Organization (WHO), the IMPAACT Network, and the International AIDS Society launched another “Call-to-Action” campaign [35]. This was a call for the inclusion of the female voices of women living with HIV and to change from viewing pregnant women as a vulnerable population to a population with many intricacies that should be addressed. This call to action speaks to stop protecting patients by excluding them and to instead protect them by including them [35].
12. Conclusion

The ethical considerations for pregnancy and neonatal populations are beginning to change. The focus is shifting in the direction of protecting these populations by conducting medication research trials that are inclusive. There are many advancements in HIV management, however, the field continues to evolve with more research and practical world experience. As more data unfolds, this may lead to more drug therapy options for the management of perinatal HIV. In turn, it may result in the use of safer and more effective ARVs in the pregnant and neonatal populations. With the availability of more reliable ARV options, utilization of these medications, and adherence to recommended HIV screening guidelines, there is more potential to reduce the transmission of HIV from mother to child, moving the HIV field toward achieving ending the HIV epidemic globally.

Acknowledgements

We would like to acknowledge our dear friend and colleague in the field of HIV Jean C. Lee, PharmD, AAHIVP for her invaluable support and feedback for our chapter.

Conflict of interest

The authors declare no conflict of interest.

Author details

Kayla Aleshire and Rima Bazzi*
PharmD AAHIVP, Beaumont Health, Dearborn, USA

*Address all correspondence to: rima.bazzi@beaumont.org

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References


