84 Human immunodeficiency virus (HIV)

Richard Basilan and William Salzer

EPIDEMIOLOGY

The number of people living with human immunodeficiency virus (HIV) worldwide reached an estimated 33.4 million in 2008, with 2.7 million new infections and 2 million acquired immune deficiency syndrome (AIDS)-related deaths that same year. The total number of people living with the virus in 2008 was more than 20% higher than the number in 2000, and the prevalence was roughly threefold higher than that in 1990 (1).

Meanwhile, an estimated 1.1 million adults and adolescents were living with diagnosed or undiagnosed HIV in the United States at the end of 2006, according to Centers for Disease Control and Prevention (CDC) estimates (2). During the same year, an estimated 54,230 new infections occurred in the United States (3). Although women make up only 25% of the HIV-infected population in the United States, certain subgroups, particularly African-Americans and Latinas, are disproportionately affected. African-American women, for example, have a prevalence rate nearly 18 times that of the rate of white women (2). In 2005, HIV disease was the third leading cause of death for African-American women aged 25 to 44 years and the fourth leading cause of death for African-American women aged 45 to 54 years (4).

Differences in the rates of HIV maternal to child transmission (MTCT) serve to highlight the disparities between resource-rich and resource-limited areas. While there were 390,000 children newly infected with HIV in sub-Saharan Africa in 2008, there were less than 500 new cases in North America, Western Europe, and central Europe combined (1). Analysis of national surveillance data shows that the number of pediatric AIDS cases that were reported to the CDC decreased from 858 in 1992 to only 41 in 2004, a decrease of about 95% (5). There has also been a marked decline in perinatal HIV transmission from an estimated 1650 in 1991 to between 144 and 236 in 2006 (6). The reduction in perinatal HIV transmission, now estimated to be less than 2% in the United States (7), is the result of a combination of universal maternal prenatal HIV counseling and testing, antiretroviral (ARV) prophylaxis, scheduled cesarean delivery when appropriate, and avoidance of breast-feeding. By contrast, perinatal transmission rates in resource-poor areas can be as high as 25% to 30 % in the absence of any intervention (8).

ETIOLOGY

AIDS was first recognized in June 1981 when five previously healthy men who have sex with men (MSM) presented with *Pneumocystis carinii* pneumonia in Los Angeles (9). This was followed by a report of 26 MSM with Kaposi's sarcoma, with or without *P. carinii* pneumonia in New York and Los Angeles (10). The discovery of the HIV, initially named human T cell leukemia virus III, followed in 1983, and its causal relationship to AIDS was firmly established by the

following year (11,12). A reliable screening test (HIV ELISA) was developed in 1985, and since that time our understanding of HIV and its pathogenesis continues to increase and has led to successful treatment regimens not just for HIV but for other viral illnesses as well.

HIV belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. HIV-1 is the predominant cause of HIV disease in the world. HIV-2, which can also cause AIDS, is closely related to simian immunodeficiency virus and is largely confined to West Africa, although occasional cases occur worldwide. The HIV virion is an icosahedral structure containing numerous external spikes formed by the two major envelope proteins, the external gp120, and the transmembrane gp41. The virion attaches via gp120 to cells expressing the CD4 molecule, which acts as the cell receptor for the virus. The CD4 molecule is expressed mainly in a subset of T lymphocytes responsible for helper function in the immune system, but can also be found on the surface of monocytes/macrophages and dendritic/Langerhans cells (13). A conformational change then occurs in the gp120 molecule, allowing it to bind to one of two cellular coreceptors (CCR5 or CXCR4). Binding is followed by insertion of viral gp41 into the CD4 cell, resulting in membrane fusion followed by release of the viral core into the cell cytoplasm.

HIV, like other retroviruses, is an RNA virus. The virus transcribes its RNA using RNA-dependent DNA polymerase (*reverse transcriptase*) into DNA, which is then incorporated into the host DNA by a viral integrase. Following transcription, HIV mRNA is translated into proteins that are processed further by viral proteases, allowing for assembly of new virions that are then released to infect other cells. These steps in the viral replication cycle have been the target of highly active ARV therapy, which has revolutionized the management of HIV infection.

PATHOPHYSIOLOGY

The most common mode of HIV infection is sexual transmission through the genital mucosa (14), with initial infection of a small number of T lymphocytes, macrophages, and dendritic cells located in the lamina propria. Initial replication occurs in the regional lymph nodes, followed by migration of infected T lymphocytes or virions into the bloodstream, where secondary amplification in the gastrointestinal tract, spleen, and bone marrow results in massive infection of susceptible cells (15). The period of peak viremia, which occurs in the first 6 weeks, results in a symptomatic illness in 40% to 90% of patients, termed *acute HIV infection*. The most common symptoms include fever, fatigue, pharyngitis, lymphadenopathy, and myalgias. A maculopapular rash involving the trunk also occurs in 40% to 80% of patients (16). Oral or genital ulcers can also occur. Given the

nonspecific mononucleosis like symptoms of acute HIV infection, the diagnosis is often missed. A high index of suspicion is required to make the diagnosis, because commonly used screening tests for HIV antibody are negative for the first 4 weeks following infection. Detection of the p24 antigen or HIV RNA by PCR in the absence of HIV antibodies would confirm the diagnosis. This has important public health implications as the patient is unaware of being infected with HIV and yet is highly infectious because of the very high viral load.

Despite the initial immune response during primary HIV infection, the virus continues to replicate at a high rate in untreated patients, with production of 10^{10} virions daily. Viral replication is error prone, producing multiple quasi-species. This helps the virus evade the immune system and facilitates development of resistance to ARV agents. The virus subsequently establishes a reservoir in resting memory CD4+ cells, as well as in immune-sequestered sites such as the central nervous system (CNS). The patient remains asymptomatic during this chronic phase, which on average lasts about 10 years. During this time, there is persistent viral replication and immune activation resulting in a gradual decrease in the number of circulating CD4+ cells. As the CD4+ count falls, patients become more susceptible to opportunistic infections, the hallmark of AIDS.

Transmission of HIV from mother to child can occur in utero, perinatally, or postpartum through breast-feeding (6). Multiple factors have been associated with an increased risk of MTCT, but the greatest risk is with higher maternal plasma HIV RNA levels. Although the risk of MTCT decreases with lower maternal plasma HIV RNA levels (8), particularly when it is <1000 copies/mL, it should be emphasized that MTCT can occur even at low or undetectable HIV RNA levels (17). Other factors that have been found to increase MTCT rates include vaginal delivery with plasma HIV RNA levels >1000 copies/mL, delivery at earlier gestation, prolonged interval between membrane rupture and delivery, chorioamnionitis, coinfection with other sexually transmitted diseases (STDs), illicit drug use, and cigarette smoking.

DIAGNOSIS AND MANAGEMENT

A critical component of caring for HIV-infected patients is knowledge of evidence-based treatment guidelines. Guidelines for management of HIV infection in pregnancy are published by the Department of Health and Human Services (DHHS) in the United States, the European AIDS Clinical Society (EACS) and the World Health Organization (WHO). Differences in CD4-based criteria for initiation of ARV therapy, preferred agents and regimens, and management of infant prophylaxis exist between these guidelines. The practitioner caring for HIV-infected patients should be familiar with the recommendations for their region of the world, as well as the availability of local resources, such as laboratory testing, ARV agents, prevalence of HIV drug resistance and coexisting infections (i.e., TB, malaria, Hepatitis B), demographic and sociocultural issues, and organizational support for the patients.

LABORATORY TESTING

Laboratory testing for HIV infection involves screening with a highly sensitive test, usually an enzyme-linked immunosorbent assay (ELISA), also known as enzyme immunoassay, for

HIV antibodies. The high sensitivity of the test makes it an effective screening tool, but requires a highly specific assay for confirmatory testing, such as western blot for antibodies to specific viral proteins. Virologic assays (PCR for HIV RNA) can be used for confirmatory testing when the western blot is indeterminate. Testing for HIV RNA by PCR is also used in neonates or when acute HIV infection is suspected. In recent years, multiple rapid tests using blood or saliva have been introduced for point-of-care testing, but it should be noted that all rapid tests require further confirmatory testing because of their high false-positive rate.

After a diagnosis of HIV infection is confirmed, further testing includes obtaining the patient's HIV RNA viral level (or viral load), CD4 count, as well as baseline complete blood count (CBC), comprehensive metabolic panel, and for African-Americans, urinalysis. Screening for coinfection with other STDs (gonorrhea, chlamydia, syphilis, hepatitis B and C), tuberculosis, and toxoplasma should also be performed.

The CDC recommends HIV screening for all patients aged 13 to 64 in health-care settings (18). Repeat HIV testing should be offered at least annually to women who use injection drugs, have had an STD in the past year, have had more than one sexual partner since their most recent HIV test, engage in sexual intercourse in exchange for drugs or money, or are partners of injection drug users or HIV-infected persons. Opt-out screening, in which the patient is notified that HIV testing be performed as a routine part of gynecologic and obstetric care unless she declines, should be performed (19). HIV-uninfected women with a known HIV (+) partner should be counseled regarding the risk for acquiring the infection and should have a second HIV test during the third trimester, before 36 weeks if possible. If such a patient presents in labor without a second HIV test, a rapid test should be done. Suspicion for acute seroconversion should prompt both rapid HIV testing and checking for plasma HIV RNA levels (20).

Laboratory testing for neonates must take into account that maternal antibodies cross the placenta and persist in the child's circulation, making tests for HIV antibodies unreliable. Exclusion of HIV infection therefore relies on virologic tests (i.e., p24 antigen testing or plasma HIV RNA levels) done on two separate samples drawn after 1 month of age, with at least one sample being drawn after 4 months of age. HIV antibody tests can be utilized after 6 months of age, but also require verification by repeat testing using a second, separately drawn sample. In addition to negative laboratory test, the child should also have no current or previous AIDS-defining condition before being declared as HIV uninfected (21).

Testing for ARV drug resistance should be done prior to starting ARV therapy (whether for therapy or prophylaxis), as well as when considering modification of a patient's drug regimen. Assays for HIV drug resistance require that the patient has a detectable viral load, which is usually the case in untreated individuals and patients failing therapy.

ARV THERAPY

The use of highly active ARV therapy has revolutionized the management of HIV infection, leading to better quality of life, decreased morbidity, prolonged survival, and decreased transmission, including MTCT. There are now five different

classes of ARV drugs, with 24 individual ARV agents and 6 additional combination pills available for managing HIV infection in the United States. HIV therapy requires the use of drug combinations to decrease the development of drug resistance and requires a minimum of two, and ideally three, fully active agents at a time. As with most chronic infections requiring multidrug therapy, addition of a single agent to a failing regimen should be avoided as this fosters the development of resistance to the added agent.

Nucleoside reverse transcriptase inhibitors (NRTIs) were the first drugs active against HIV to be developed with the introduction of zidovudine or azidothymidine in 1987. The NRTIs are nucleoside analogs and require intracellular phosphorylation in order to become active. They are incorporated into the DNA chain and terminate DNA chain elongation by acting as nonactive substrates for the viral reverse transcriptase. Nonnucleoside reverse transcriptase inhibitors (NNRTIs), on the other hand, bind to the reverse transcriptase enzyme and induce conformational changes at the active site, thereby rendering the enzyme nonfunctional. Protease inhibitors (PIs) target the viral protease, an enzyme required for cleavage of precursor proteins (gag and gag-pol), thereby preventing the final assembly of the inner core of viral particles (22). Entry inhibitors block the penetration of HIV virions into their target cells by either preventing fusion (enfuvirtide) or by blocking the CCR5 coreceptor required for entry (Maraviroc). A newer class of ARVs act by inhibiting the enzyme required for integration of the transcribed viral genome into the host DNA (integrase), aptly named integrase inhibitors. Available ARV agents are summarized in Table 1.

The decision to initiate ARV therapy in adults is based on multiple factors, including the presence or absence of AIDS-related conditions, other comorbidities (such as hepatitis B coinfection or HIV-associated nephropathy), CD4 count, as well as the patient's readiness to start lifelong therapy. There is a general consensus that ARV therapy should be started on all patients with symptomatic HIV infection as well as asymptomatic patients with a CD4 count less than 500 cells/ μ L. Timing of initiation of ARV therapy in asymptomatic patients with CD4 counts >500 cells/ μ L is a subject of continuing debate and is not recommended by the WHO or EACS in asymptomatic patients without significant coinfection or comorbidities (23,24). However, in recent years, data on benefits of earlier initiation of ARV therapy have led to recommendations in the United States to start ARV therapy for all patients with CD4 counts <500 cells/ μ L and to consider starting ARV therapy at CD4 counts >500 cells/ μ L (25). These newer recommendations are based on observational cohort studies showing a potential decrease in mortality as well as in the incidence of such conditions as HIV-associated nephropathy, liver disease progression from hepatitis B or hepatitis C, cardiovascular disease, malignancies (both AIDS defining and non-AIDS defining), neurocognitive decline, and blunted immunologic response in patients started on highly active ARV treatment therapy at CD4 counts >500 (20).

It is recommended that all HIV-infected pregnant women receive ARV therapy regardless of CD4 or viral load. Use of ARV agents in pregnant women should consider two separate, but related issues: treatment of maternal HIV infection and prevention of MTCT. As in all HIV-infected patients,

evaluation of the patient's HIV viral load and CD4 count should be done, as well as initial testing for drug resistance if this has not been done previously. Patients with a CD4 count less than 200 cells/ μ L should be started on prophylaxis for *Pneumocystis jiroveci* (previously named *Pneumocystis carinii*) using trimethoprim sulfamethoxazole at a dose of 80mg/400mg daily. Alternatives include dapsone, atovaquone, or aerosolized pentamidine. A patient with CD4 count less than 50 cells/ μ L is at high risk for other opportunistic infections, including *Mycobacterium avium* complex, and prophylaxis using azithromycin 1200mg weekly is recommended. Like any medication taken during pregnancy, the potential benefits of therapy should be weighed against potential risk to both the mother and the fetus.

For ARV-naïve, nonpregnant patients who meet criteria for initiation of ARV therapy, present guidelines recommend the use of an NNRTI-based, a PI-based, or an integrase inhibitor-based regimen. All regimens would also include two NRTIs. Purely NRTI-based regimens, such as Trizivir (a combination of zidovudine, lamivudine, and abacavir), are no longer recommended as they have been found to have higher rates of virologic failure. For an NNRTI-based regimen, the preferred agents include efavirenz with emtricitabine and tenofovir (available as combination pill AtriplaTM). Use of efavirenz should be avoided during the first trimester of pregnancy, as well as in women who are of reproductive age and are not taking sufficient steps to avoid pregnancy, given its known teratogenicity in animal and human studies. An alternative NNRTI-based regimen would include nevirapine with zidovudine and lamivudine (CombivirTM). It should be noted that nevirapine should be avoided in patients with moderate-to-severe hepatic impairment (Child Pugh B or C), as well as females with a CD4 count >250 cells/ μ L as both groups have an increased risk for potentially fatal hepatitis.

Protease-based regimens may also include emtricitabine and tenofovir, combined with either atazanavir or darunavir boosted with ritonavir. In the pregnant patient, lopinavir boosted with ritonavir (lopinavir/r or KaletraTM) is the preferred PI. The addition of ritonavir at a low dose (boosting) inhibits CYP450 3A4 resulting in an increase in the serum levels of most PIs. An integrase inhibitor-based regimen would use raltegravir in addition to two NRTIs.

A list of preferred initial ARV regimens is presented in Table 2.

The following management strategies have been adapted mainly from present DHHS guidelines (20) unless otherwise stated. Updated versions are available online at www.aidsinfo.nih.org.

ANTEPARTUM CARE

In reproductive age, nonpregnant HIV-infected women, preconception counseling should be done to minimize the risk of unintended pregnancies. ARV agents with known teratogenic potential, such as efavirenz, should be avoided if there is insufficient effort to avoid conception. Ideally, two methods of contraception should be used in such circumstances, noting that certain ARV agents decrease the efficacy of oral contraceptive pills.

If the patient desires to conceive, the risks of MTCT should be discussed with the patient. In couples with discordant HIV

Table 1 Antiretroviral Agents and Common Adverse Effects

Drug	FDA pregnancy category	Common side effects	Notes
NRTIs			
Abacavir (ABC)	C	Lactic acidosis, hepatic steatosis, lipodystrophy Hypersensitivity reaction (can be fatal), rash, possible risk of MI	Test for <i>HLA-B*5701</i> . Do not use if patient is <i>HLA-B*5701</i> positive (high risk for hypersensitivity reaction)
Didanosine (ddI)	B	GI intolerance, peripheral neuropathy, pancreatitis, lactic acidosis, noncirrhotic portal hypertension	Do not use with stavudine (additive toxicities such as lactic acidosis)
Emtricitabine (FTC)	B		Preferred component of therapy during pregnancy
Lamivudine (3TC)	C		
Stavudine (d4T)	C	Highest incidence of lactic acidosis, hepatic steatosis, and lipodystrophy Peripheral neuropathy, Pancreatitis	Do not use with didanosine or zidovudine
Tenofovir (TDF)	B	Renal impairment, decreased bone mineral density, headache, GI intolerance	
Zidovudine (AZT, ZDV)	C	Headache, lactic acidosis, GI intolerance, bone marrow suppression	Preferred component of therapy during pregnancy. Do not use with stavudine (antagonistic effects on HIV activity)
NNRTIs			
Efavirenz (EFV)	D	Rash, including Stevens–Johnson syndrome, Drug–drug interactions Neuropsychiatric, <i>teratogenic</i> in nonhuman primates with reports of <i>neural tube defects</i> in human infants following first-trimester exposure	A component of Atripla, a combination pill used commonly given preferred status. Should be used in pregnancy only if other agents not tolerated and benefits outweigh risk
Etravirine (ETR)	B		Do not use with unboosted PIs, or ritonavir-boosted atazanavir, fosamprenavir, or tipranavir
Nevirapine (NVP)	B	Higher rate of rash, hepatotoxicity (may be severe and life threatening, especially in women w/CD4 count >250)	Risk of hepatotoxicity higher in first 18 months of therapy, hepatitis B or C coinfection, women w/CD4 count >250, men w/CD4 count >400 cells/μL
Protease inhibitors			
Atazanavir (ATV)	B	Hyperlipidemia, insulin resistance and diabetes, lipodystrophy, increased LFTs, drug interactions, osteonecrosis Hyperbilirubinemia, PR prolongation, nephrolithiasis	Do not use with indinavir (additive hyperbilirubinemia)
Darunavir (DRV)	C	Rash, liver toxicity	
Fosamprenavir (f-APV)	C	GI intolerance, rash, possible increased risk of MI	
Indinavir (IDV)	C	Nephrolithiasis, GI intolerance	Do not use with atazanavir
Lopinavir + ritonavir (LPV/r)	C	Possible increased risk of MI, PR, and QT prolongation, GI intolerance	Preferred component of therapy during pregnancy
Nelfinavir (NFV)	B	Diarrhea	
Ritonavir (RTV)	B	GI intolerance, hepatitis	
Saquinavir (SQV)	B	GI intolerance	
Tipranavir (TPV)	C	GI intolerance, rash, hyperlipidemia, liver toxicity, cases of intracranial hemorrhage	
Entry inhibitors			
Enfuvirtide (T-20)	B	Infection site reactions, hypersensitivity reactions, increased risk of bacterial pneumonia	
Maraviroc (MVC)	B	Drug interactions, abdominal pain, hepatotoxicity, rash, URIs	
Integrase inhibitors			
Raltegravir (RAL)	C	Nausea, headache, diarrhea, CPK elevation	

Abbreviations: LFTs, liver function tests; GI, gastrointestinal; MI, myocardial infarction; URIs, upper respiratory infections; CPK; creatine phosphokinase; PIs, protease inhibitors. Source: From Ref. 20.

Table 2 Preferred Initial Antiretroviral Regimen

NNRTI based	Tenofovir/emtricitabine/efavirenz daily
PI based	Atazanavir boosted with ritonavir + tenofovir/emtricitabine daily
	Or Darunavir boosted with ritonavir + tenofovir/emtricitabine
Integrase inhibitor based	Raltegravir + tenofovir/emtricitabine
Pregnancy	Lopinavir boosted with ritonavir + zidovudine/lamivudine
Source: From Ref. 20.	

status, alternative methods for conception, such as in vitro fertilization, should be explored to decrease the risk to the HIV-uninfected partner. Ideally, the patient's HIV viral load should be suppressed to undetectable levels prior to conception. Modifiable factors that decrease MTCT, including avoiding alcohol and illicit drug use, smoking cessation, and STD prevention, should be addressed.

The present consensus for the management of HIV infection in pregnancy is that of recommending ARV therapy or prophylaxis to all pregnant HIV-infected women, regardless of plasma HIV RNA levels. The benefits and risks of therapy should be individualized and discussed with the patient, with particular emphasis on the importance of adherence to drug therapy. Every attempt should be made to coordinate comprehensive services for such patients before, during, and after delivery.

In pregnant HIV patients who have indications for initiation of ARV therapy, the goals of ARV therapy include control of HIV viremia to undetectable levels, immune reconstitution to avoid opportunistic infections, and decreased MTCT. As with other HIV patients, multiple factors should be considered when designing a drug regimen, including comorbidities, patient adherence potential, convenience, potential adverse effects, drug interactions, and results of genotypic resistance testing. In addition, pharmacokinetic (PK) changes in pregnancy (particularly with PIs) and potential teratogenic effects on the fetus and other adverse effects on the fetus or newborn would also need to be considered. ARV agents with teratogenic potential, such as efavirenz, should be avoided particularly during the first trimester unless the risk is outweighed by the anticipated benefits.

Patients who are already on effective therapy (i.e., with undetectable HIV viral load) for their HIV infection should continue the same regimen, with the exception of efavirenz in the first trimester. Patients with detectable viral load should have genotype testing for drug resistance in an effort to design an optimized drug regimen. Patients may require modifications of their ARV regimen, with particular attention to the factors previously noted. For patients who meet criteria for initiation of ARV therapy, the preferred initial regimen consists of zidovudine and lamivudine (available as a combination pill Combivir) and lopinavir boosted with ritonavir (available as a combination pill Kaletra) taken twice a day. All regimens should include zidovudine if possible, as this drug has the best evidence-based data to support efficacy in reducing MTCT and also has good safety data for use during pregnancy (8). Alternative regimens include zidovudine/

lamivudine with either (i) another PI, such as atazanavir/ritonavir, indinavir/ritonavir, nelfinavir, or saquinavir/ritonavir or (ii) an NNRTI such as nevirapine. Efavirenz use after the first trimester can be considered if other alternatives are not tolerated. Nevirapine should not be started in pregnant women with CD4 counts >250 cells/ μ L unless the anticipated benefits outweigh the potential risk of severe, sometime fatal hepatotoxicity. ARV therapy can be started during the first trimester if indicated for maternal health.

Patients who do not meet criteria for initiating ARV therapy (asymptomatic, CD4 counts >> 500 cells/ μ L, low-level viremia) should still be advised to take ARV therapy to decrease maternal viremia and provide prophylaxis for the fetus in an attempt to decrease MTCT. As most drug teratogenic effects occur early in the first trimester while majority (but not all) of maternal-to-child infections occur during late pregnancy and delivery, it would be worthwhile to wait until 10 to 12 weeks of gestation before starting antiviral therapy. However, this approach leaves the fetus exposed to persistent viremia for several weeks, and the risks and benefits of starting ARV therapy early versus waiting until the second trimester should be discussed with the patient.

Combination three-drug therapy with zidovudine/lamivudine and lopinavir/ritonavir would still be recommended in the United States as this regimen appears to be safe and effective in decreasing MTCT. Alternative regimens (first-line regimens per WHO guidelines) include either zidovudine/lamivudine or tenofovir/lamivudine plus either nevirapine or efavirenz, noting that efavirenz should be avoided during the first trimester of pregnancy). Concerns over fetal exposure to multiple drugs during pregnancy may prompt the use of monotherapy with zidovudine as an alternative if the patient's viral load is less than 1000 copies/mL. This approach, derived from the original Pediatric AIDS Clinical Trial Group (PACTG) study to reduce MTCT published in 1994, has been a mainstay in the WHO guidelines particularly because of its availability in resource-limited areas. In the United States, the use of zidovudine monotherapy as maternal prophylaxis for reduction of MTCT is now controversial and is generally not recommended particularly for patients with higher HIV viral RNA levels. ARV therapy given only to decrease MTCT can be discontinued following delivery if there is no indication for therapy for the mother and/or if there are no plans for breast-feeding.

There are conflicting data as to whether ARV drugs are associated with adverse outcomes such as preterm delivery, with some studies showing up to a twofold increase in risk while others fail to demonstrate any increased risk for preterm delivery. Patients on PIs were found in a recent meta-analysis to be at slightly higher risk for premature delivery (odds ratio 1.35) compared with those on regimens without a PI (26). There is also concern regarding mitochondrial dysfunction in neonates exposed to NRTIs, but this occurs rarely. These risks should be discussed with the patient, but are generally thought to be outweighed by the significant benefit of improved maternal health and decreased MTCT of HIV infection. Pregnant patients on ARV therapy should be enrolled in the ARV pregnancy registry available online at www.APREgistry.com.

As there remain limited data on the effects of ARV therapy on the fetus, a second ultrasound during the second trimester

is generally recommended to assess fetal anatomy in addition to the staging ultrasound done in the first trimester. Although no perinatal transmission of HIV infection has been documented following amniocentesis in patients taking ARV therapy, a small risk of MTCT cannot be ruled out. Therefore, amniocentesis should be performed only after initiation of ARV therapy or prophylaxis and ideally with undetectable HIV viral RNA levels. Plasma RNA levels should be rechecked at 34 to 36 weeks to guide the decision regarding the preferred mode of delivery.

INTRAPARTUM MANAGEMENT

Patients already on ARV therapy should be continued on their regimen, with the oral route being preferred whenever possible. Intravenous zidovudine is recommended for all HIV-positive women during labor, even if drug resistance to this drug has been documented. If the patient was taking zidovudine as part of a combination regimen, the other components of her ARV therapy should also be continued. Zidovudine should be given at a dose of 2mg/kg IV over 1 hour, followed by an infusion of 1mg/kg/hour until the time of delivery, and should ideally be started 3 hours prior to surgery in the event of planned caesarian section. This dose is based on the original protocol used in the PACTG 076 (8) published in 1994, which demonstrated a marked reduction in MTCT from 25.5% in the placebo group to 8.3% infants in the zidovudine group. Stavudine (d4T) should be discontinued when administering zidovudine because of antagonism between these two drugs.

Patients presenting in labor with unknown HIV status should have a rapid antibody test performed. A positive result should prompt administration of intravenous zidovudine to the mother and the infant, with continuation of infant prophylaxis for 6 weeks. Please see Table 3 for specific dosing. A confirmatory maternal HIV test should be done postpartum, with discontinuation of infant prophylaxis if the test is negative.

Patients should be counseled regarding risks and benefits of caesarian versus vaginal delivery. In general, HIV-infected

patients undergoing caesarian delivery are at higher risk for surgical complications compared with HIV-infected women undergoing vaginal delivery, as well as compared with HIV-uninfected women undergoing caesarian delivery. However, these risks do not outweigh the benefit of decreased transmission to those at high risk. Therefore, women whose HIV RNA levels are unknown or >1000 copies/mL near the time of delivery should be scheduled for elective caesarian delivery around 38 weeks of gestation regardless of whether or not they are on ARV therapy. The benefits of caesarian delivery after rupture of membranes remain unclear, and the decision as to mode of delivery in such cases should be made after considering other clinical factors. Likewise, caesarian delivery for patients with HIV RNA levels <1000 copies/mL may not decrease the rate of perinatal transmission any further.

Procedures that risk fetal exposure to maternal blood have been suggested to increase MTCT by some authors. Older data have suggested up to a twofold increase in MTCT in these situations, but more recent observation studies have shown much less risk, particularly with the use of ARV therapy. Although limited data exist, invasive fetal monitoring (e.g., fetal scalp electrodes) should be avoided unless obstetrically indicated and the duration is expected to be short. Operative vaginal delivery using forceps or vacuum extractor as well as episiotomy would theoretically have an increased risk of transmission but should not be delayed if clear obstetric indications exist (27,28).

The use of methergine, a drug metabolized through the hepatic CYP3A4 pathway, for postpartum hemorrhage should be avoided in women receiving PIs (potent CYP3A4 enzyme inhibitors) because of the risk of exaggerated vasoconstrictive response. If other alternatives (oxytocin, misoprostol, PGF2 alpha) are not available, a lower dose should be used and the duration of use should be minimized. Conversely, if methergine must be used in a patient taking a potent CYP3A4 inducer (such as efavirenz), additional uterotonic agents may be needed given the possibility of lower methergine levels.

Table 3 Intrapartum Maternal and Neonatal Zidovudine (ZDV) Dosing for Prevention of Mother-to-Child Transmission of HIV		
	Dosing	Duration
Maternal intrapartum	2mg/kg IV over 1 hour, followed by continuous infusion of 1 mg/kg/hr	Onset of labor until delivery of infant
Neonatal		
>35 weeks of gestation	2mg/kg/dose oral Or 1.5mg/kg/dose IV started within 6–12 hours of delivery, then every 6 hours	Birth to 6 weeks
<35 to >30 weeks of gestation	2mg/kg/dose oral Or 1.5mg/kg/dose IV started within 6–12 hours of delivery, then every 12 hours, advanced to every 8 hours at 2 weeks of age	
<30 weeks of gestation	2mg/kg/dose oral Or 1.5mg/kg/dose IV started within 6–12 hours of delivery, then every 12 hours, advanced to every 8 hours at 4 weeks of age	
Source: From Ref. 20.		

POSTPARTUM MANAGEMENT

HIV-infected patients are commonly faced with multiple medical and social challenges, making the coordination of maternal postpartum follow-up between obstetric, pediatric, and HIV specialists even more important. The need for continued counseling and comprehensive medical care cannot be overemphasized in this period. Supportive services should ideally be assured prior to discharge, including obstetric/gynecologic, pediatric, HIV specialty care and mental health services, substance abuse counseling, family planning services, and social work/case worker services.

The decision regarding continuation of maternal ARV therapy during this period would depend on the CD4 count nadir (lowest documented level), clinical symptoms, disease stage, presence of other indications for ARV therapy (e.g., chronic hepatitis B infection), and patient and provider preference. Patients who have had symptomatic HIV infection or are known to have had a CD4 count below the established criteria for starting treatment for asymptomatic patients should be encouraged to continue their ARV regimen. They should also be advised regarding potential challenges with regard to compliance in light of the physiologic and lifestyle changes associated with the postpartum period.

If the only indication for initiation of ARV therapy was to reduce MTCT, then consideration can be given to stopping ARV therapy after delivery. Because NNRTIs have much longer half-lives than drugs from other classes, patients on NNRTIs should be advised to take their NRTIs for at least 7 to 30 days after stopping their NNRTI (NRTI tail) to avoid development of NNRTI resistance. An alternative approach is to substitute a PI for the NNRTI, continuing the regimen for 7 to 30 days, and then stopping all ARV drugs at the same time. This becomes important when the patient presents with a need for ARV therapy, whether for maternal indications or for prophylaxis during subsequent pregnancies. Even single-dose nevirapine, if given without an NRTI tail within the prior 12 months, would necessitate the empiric use of a non-NNRTI-based regimen (i.e., protease- or integrase-based regimen) (24).

Women with positive rapid HIV test result in labor should have their confirmatory tests done prior to discharge, as this would have important implications on infant prophylaxis and breast-feeding options. Further management of newly confirmed HIV infection at this stage would be similar to that of any other newly diagnosed HIV patient.

Ideally, the risk of HIV transmission through breast-feeding would have been discussed with the patient prior to delivery and would be reiterated at this phase. In resource-rich areas where safe alternatives are available and culturally acceptable, such as *in the United States, breast-feeding is not recommended*. MTCT through breast-feeding is a well-documented phenomenon even in patients on ARV therapy, and for patients on ARV therapy, limited data on pharmacokinetics of ARV drugs in breast milk can pose issues related to drug toxicity or drug resistance if drug levels in breast milk are too high or too low. It should be noted that in resource-limited areas where there is limited access to nutritional alternatives or clean water, the benefits of breast-feeding outweigh the risk of MTCT and should be encouraged. Withholding breast-feeding in such scenarios results in increased mortality not only from diarrheal

illnesses, but also from other locally prevalent infectious diseases such as tuberculosis and malaria, as poor nutritional status increases susceptibility to these diseases.

Contraceptive counseling is critical to prevention of MTCT. Condom use is important for prevention of HIV and STD transmission, although the unintended pregnancy rate is high with condom use alone. It should be noted that drug interactions between oral contraceptives and many PIs and NNRTIs could potentially decrease the efficacy of oral contraceptive pills, so more than one method of contraception should be in place at any given time. For women who are certain they do not wish future childbearing, thorough counseling and discussion about permanent contraceptive methods should be done (20).

NEONATAL POSTNATAL CARE

Infants born to mothers with unknown HIV infection status should have rapid HIV antibody testing of the mother or infant performed. If the rapid test is found to be positive, ARV prophylaxis should be started immediately while waiting for the confirmatory tests. If the confirmatory test is negative, then ARV prophylaxis should be discontinued. A positive confirmatory test for HIV antibodies should be followed by a virologic test (HIV RNA by PCR) done on the neonate. A positive virologic test on the neonate should prompt immediate referral to a pediatric HIV specialist for confirmation and initiation of combination ARV therapy as well as pneumocystis pneumonia (PCP) prophylaxis.

All newborns with known ARV exposure in utero should have a CBC with differential performed as a baseline before starting zidovudine, with follow-up depending on the results as well as other clinical factors (gestational age, medications, maternal antepartum therapy, etc.). Liver function tests should also be checked in infants exposed to ARV therapy in utero. If the infant develops severe clinical symptoms of unknown etiology, particularly of the CNS, serum lactate levels should be checked, and ARV prophylaxis discontinued if levels are found to be elevated. Consultation with a pediatric HIV specialist is recommended if significant abnormalities are found with the above tests.

Diagnosis of HIV infection in infants <18 months of age involves the use of virologic tests (HIV RNA levels), which should be done at age 14 to 21 days, 1 to 2 months, and 4 to 6 months. Some experts would also test at birth. Oral PCP prophylaxis using trimethoprim sulfamethoxazole should be initiated at 4 to 6 weeks unless HIV infection has been ruled out. PCP prophylaxis is indicated in HIV-infected infants regardless of CD4 count and should be continued until they are 1 year of age. At 1 year of age, PCP prophylaxis should be continued if the child's CD4 count is <500 cells/ μ L or <15% (29). Physical examination of the newborn, as well as maternal risk factors and laboratory studies, should guide specific testing for coinfection with other agents (cytomegalovirus, herpes simplex virus, hepatitis B and C, syphilis, toxoplasmosis, or tuberculosis) as appropriate.

A 6-week course of zidovudine chemoprophylaxis is recommended for all HIV-exposed neonates in the United States, ideally initiated within 6 to 12 hours of delivery. It may be appropriate to shorten the course to 4 weeks in situations where concerns exist regarding adherence or toxicity, as the

optimal duration for neonatal chemoprophylaxis is not known. In other countries, such as the United Kingdom and Ireland, a 4-week course is the recommended regimen, while WHO guidelines indicate a 4- to 6-week course of zidovudine to be appropriate. Please see Table 3 for specific dosing for zidovudine.

Consultation with a pediatric HIV specialist should be done when dealing with premature babies or when use of additional ARV agents is being considered because of increased transmission risk, such as those with higher maternal HIV RNA levels near delivery or had vaginal delivery.

Children with significant organ system abnormalities of unknown etiology (particularly of the CNS or heart) should be evaluated for mitochondrial dysfunction. As other possible early and late effects of in utero ARV drug exposure are not fully known, follow-up should include a yearly physical examination into adulthood, particularly given the theoretical risk of carcinogenicity of nucleoside analogs.

HIV MANAGEMENT IN RESOURCE-LIMITED SETTINGS

HIV management in resource-limited settings, where the vast majority of perinatal transmission occurs, presents multiple challenges during all stages of pregnancy, and significant differences exist between U.S. (DHHS and UNAIDS) and WHO guidelines. These differences result from limited availability of maternal prenatal HIV testing and limited access to ARV drug therapy. The benefits of earlier initiation of ARV therapy in asymptomatic patients in much of the world is thwarted by limited availability and access to ARV drugs, systems for delivering medical care, monitoring therapy, management of drug toxicity, and assessing drug resistance and having alternative drug regimens for patients with known or suspected drug resistance.

An NNRTI-based regimen (nevirapine or efavirenz with either lamivudine/zidovudine or tenofovir/emtricitabine) is recommended in the WHO guidelines as first-line therapy for maternal prophylaxis to prevent MTCT (as opposed to the United States, where this regimen is considered as an alternative to a lopinavir/ritonavir-based regimen). In addition, monotherapy with zidovudine starting at 14 weeks remains an option, followed by single-dose intrapartum nevirapine and a 1-week NRTI tail consisting of lamivudine and zidovudine.

Despite the well-documented risk of MTCT of HIV infection through breast-feeding, the much greater risk of mortality from malnutrition and infections makes breast-feeding necessary in many areas. Multiple options have been studied in such a scenario where breast-feeding is deemed necessary. Breast-feeding mothers on triple ARV agents for their own health are advised to continue doing so, while the infant should continue to receive the standard twice-daily zidovudine for 4 to 6 weeks. Breast-feeding mothers who are on triple ARV agents for *prophylaxis* should continue doing so until 1 week after cessation of breast-feeding, while the infant continues 4 to 6 weeks of zidovudine. Breast-feeding mothers who were only on zidovudine for *prophylaxis* should receive a single dose of nevirapine at the start of labor, as well as lamivudine and zidovudine at the start of labor up to a week following delivery. In such cases, the infant should receive nevirapine from birth up 4 to 6 weeks, or up to a week after

stopping breast-feeding, if cessation of breast-feeding is done earlier.

These recommendations were based on recent trials, including one done in Malawi comparing maternal with child HIV transmission during a 4-week breast-feeding period. This study showed a higher risk of transmission in the placebo group receiving only single-dose nevirapine and 7 days of zidovudine/lamivudine (5.7%) compared with infants who received nevirapine for 28 days (1.7%, $p < 0.001$) and breast-feeding mothers on ARV therapy for 28 days (2.9%, $p = 0.009$) (30). It has also been shown that three-drug maternal ARV therapy, whether NRTI, NNRTI, or PI based, showed similar rates of virologic suppression and decreased MTCT to 1.1% (31).

A simplified dosing regimen has been developed for use in resource-limited settings for infant prophylaxis. This regimen includes the use of zidovudine 10mg twice a day for infants weighing less than 2.5kg at birth, and 15mg twice a day for infants weighing more than 2.5kg at birth. Another alternative approach has been to give a daily dose of nevirapine for 4 to 6 weeks. Use of combination therapy has been used, but has not been proven to be additional benefit.

The field of HIV management continues to change rapidly. Updated guidelines are available online at www.aidsinfo.nih.gov as well as at the American College of Obstetricians and Gynecologists and WHO Web sites. In the United States, the National Perinatal HIV hotline (1-888-448-8765) also provides free clinical consultation on all aspects of perinatal HIV care.

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