governmental order, an emergency syringe-exchange program, the first in Indiana, was started; within 6 months, 277 persons who injected drugs had enrolled, and more than 97,000 sterile syringes were distributed and returned. Currently, persons who inject drugs can access sterile needles and syringes through syringe services programs[16] and through pharmacies without a prescription. Although less common, access to sterile needles and syringes may also be possible through a prescription written by a physician and through other health care services. Syringe services programs are an effective component of a comprehensive integrated approach to HIV prevention among intravenous drug users, are becoming more prevalent across the United States, and may serve as an additional tool to combat HIV incidence among women.

Finally, HIV transmission through intravaginal insemination of donor semen has been reported.[17] Use of assisted reproductive technologies, which include sperm washing and intracytoplasmic sperm injection, reduces horizontal transmission from an HIV-infected man to an HIV-negative woman to almost zero.[18–21] Although these techniques are promising, they require specialized laboratories, are expensive, and are typically not covered by insurance and therefore are not accessible to most couples (see "Strategies to Prevent Heterosexual Transmission" and "Fertility Issues"). With the advancement in powerful biomedical prevention strategies such as "treatment as prevention" and preexposure prophylaxis (PrEP), assisted reproduction with sperm washing may no longer be necessary within serostatus-discordant couples, as the risk of transmission from a partner living with HIV with virologic suppression is extremely low.[22]

Racial and Ethnic Disparities in HIV Incidence

HIV disproportionately affects women of color: among all women with an HIV diagnosis in the United States in 2015, 61% (4524) were African American, 19% (1431) were white, and 15% (1131) were Hispanic/Latina.[5] To this day, the HIV diagnosis rate for black women remains 16 times as high as that of white women and almost 5 times that of Hispanic women.[3] Although the number of HIV diagnoses among African-American women decreased 42% from 2005 to 2014, the rate is still disproportionally higher than rates in women of other races and ethnicities.[23] A number of factors seem to increase risk among African-American women for acquisition of HIV, including higher rates among African-American men, higher prevalence of STIs in the African-American population, stigma, poverty, structural racism, less access to health care, and higher rates of incarceration, all of which can disrupt social networks and decrease the number of available partners for women.[3] Of note, the highest rates of new HIV diagnoses among women were among black women living in the northeastern (52.4/100,000) and southern (36.1/100,000) states.[24]

Age Patterns in Women Living With HIV in the United States

HIV incidence is more common in women of childbearing age; in 2015, 66% of new HIV infections among women were diagnosed in girls and women between 15 and 44 years of age. However, an increasing percentage of new infections among women (currently 34%) occur in women 45 years old or older. Estimates indicate that by 2030, more than 70% of people living with HIV in the United States will be 50 years old or older.[25,26] Older women may not recognize themselves as being at risk for HIV infection,[27] may experience more stigma within their communities than younger women,[28–30] and are more likely to present to HIV care later in the course of infection. Older women living with HIV have particular psychosocial and medical needs,[31] including frailty,[32] worsening neurocognitive function,[33] issues with sexuality,[34,35] bone loss,[36] and menopause.[37] Therefore, designated care paradigms for women aging with HIV, tailored to address both the medical and the psychosocial gaps in this unique population, are indicated.

HIV Care Continuum Among Women

Within the United States, more than 1.1 million people are living with HIV infection, and 12% of women are still unaware of their infection, a rate that has been decreasing over time.[23] Overall in the United States, the typical HIV care continuum outcomes are still inadequate: Among women living with HIV, 88% have had HIV diagnosed; 64% are linked to care; 50% are retained in care; and 48% have achieved the goal of ART, specifically virologic suppression.[38] The gravity of the HIV epidemic among women in the United States is often not appreciated by individuals at risk and by the broader community.[39] A cohort study of high-risk women in the northeastern and southeastern states found an annual HIV incidence of 0.32%; older age, substance use, and knowing that a partner had HIV were associated with higher HIV prevalence.[40] With the increasing use of routine rapid HIV testing of adults in the United States and in the era of universal ART (starting ART as soon as HIV is diagnosed, regardless of CD4 T-cell count), more people, including women, should be identified earlier and started promptly on ART. The goals of the National HIV/AIDS Strategy, a comprehensive plan to address the HIV epidemic established by the United States in 2010 and now updated to 2020, are to reduce new infections, increase access to care and improve health outcomes, reduce HIV-related health disparities, and achieve a more coordinated national response[41]; these goals are especially important to address among women.

Worldwide Epidemiology

Disproportionate Impact on Young Women

Updated estimates from the Joint United Nations Programme on HIV/AIDS (UNAIDS) (2017 update)[2] continue to report more HIV infections worldwide than at any point in history, with 36.7 million currently infected. Since the start of the epidemic, there have been 76.1 million infections overall and 35 million people have died of AIDS-associated illnesses.[1] Of the 36.7 million people living with HIV as of the end of December 2016, 34.5 million are adults, and more than 50% (17.8 million) of those are women. HIV infection has been reported from all over the world, but more than 95% of all infections are in resource-limited settings, and two-thirds of people living with HIV reside in sub-Saharan Africa.[2] Global efforts have been mounted to address the epidemic, and there has been significant progress, with new HIV infections declining by an estimated 11% among adults from 2010 to 2016 and by 47% among children.[2] Despite this progress, approximately 1.8 million people were newly infected with HIV in 2016, which equates to approximately 5000 new infections per day. Of those 5000 new infections a day, 64% were in sub-Saharan Africa, and 4500 were in adults; of those, 22% were in young women (ages 15–24).

Despite this progress, the rate of decline for new HIV infections has varied significantly by region, by age group, and, importantly, by sex. Young women continue to be a highly affected group when it comes to new infections in high-prevalence settings compared with men in the same age group. For instance, in 2016, new infections in young women 15 to 24 years of age were 44% higher than in men in the same age group.[2] Young women in this age group represented 26% of all new infections in eastern and southern Africa in 2016, although this demographic represents only 10% of the population.[2] These discrepant rates reflect the biologic and social vulnerability of young women to HIV infection,[42] young women partnering with older men,[43] and inaccurate perceptions of young women of their own risk,[44] all of which require targeted interventions and an intense focus.

As of World AIDS Day, December 1, 2017, UNAIDS provided an update in a landmark document called "Right to Health"[45] that 20.9 million people (57%) of the 36.7 million people infected worldwide were on ART. These rates were generally not discrepant by sex; indeed, in many countries, women had higher rates of ART access than men, likely due to accessing ART through antenatal settings.[2] Annual AIDS-related deaths have declined by 48% from 2005 to 2016 (from 1.9 million to 1.0 million) largely due to global scale-up of ART.[2]

Update on Perinatal Transmission Rates

Rates of perinatal transmission from mother to child during pregnancy or breastfeeding have decreased as access to prevention of maternal-to-child transmission (PMTCT) services has increased. New infections in children declined by 47% from 2010 to 2016, with 300,000 new infections in 2010 compared with 160,000 new infections reported as of December 2016.[2] This decrease corresponds to an increase in antiretroviral (ARV) coverage for pregnant women from 47% in 2010 to 76% by 2016 (Fig. 126.1).[2]

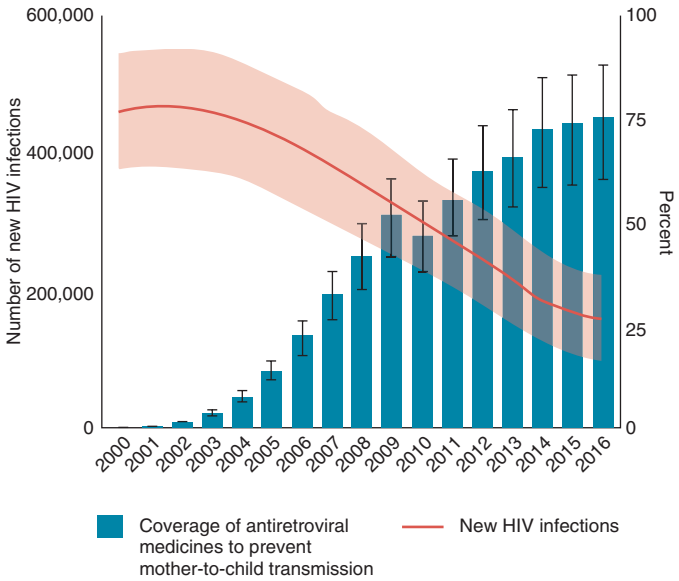

FIG. 126.1 New human immunodeficiency virus (HIV) infections among children (age 0–14 years) and coverage of antiretroviral regimens to prevent mother-to-child transmission globally 2000–2016. *(From UNAIDS Data 2017.* http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf. *Accessed December 15, 2017.)*

Risk Factors for HIV Transmission to Women Worldwide

Worldwide, HIV infection is spread primarily through heterosexual contact, although injection drug use and its subsequent contribution to HIV transmission varies geographically. Because female drug users have sexual partners who are at high risk for HIV infection and because injection drug use can lead to exchange of sex for drugs or money, there may be underrecognition and underreporting of cases spread through dual mechanisms. Several more recent studies suggest that unprotected anal sex between men may be a more important factor in the epidemics in sub-Saharan Africa than is commonly believed. These men may then transmit HIV infection to women if they have sex with both men and women.[46] Gay men and other MSM accounted for 12% of new infections globally in 2015, whereas sex workers and people who inject drugs accounted for 5% overall.[2]

Regional Variation in HIV Incidence and the Impact on Women

As summarized earlier, sub-Saharan Africa remains the hardest hit in terms of the HIV epidemic. Nearly two-thirds of people living with HIV reside in sub-Saharan Africa, and 64% of new infections in 2016 occurred in this region.[2] Despite this continued prevalence and incidence, the largest reductions in HIV incidence worldwide were observed in eastern and southern Africa with approximately 40,000 fewer new adult HIV infections reported in the region in 2015 than in 2010. More gradual declines in incidence have been observed in the Asia and Pacific region and in western and central Africa.[2] Moreover, rates of new adult HIV infections were relatively static in Latin America and the Caribbean, western and central Europe, North America, the Middle East, and North Africa, whereas the annual numbers of new HIV infections in eastern Europe and central Asia have increased significantly over the past several year (57% increase from 2015 to 2016).[2] Because the implications for subpopulations such as women are unclear in regions where data are not accurately recorded, efforts are underway to collect and analyze national data with greater accuracy and precision.

AIDS-Related Mortality and Its Impact on Women and Families

The high mortality rate for HIV/AIDS continues to have a major impact on families. As of 2016, approximately 17 million children and adolescents worldwide had been orphaned by loss of one or both parents to AIDS.[2] More than 90% of these children live in sub-Saharan Africa. Saving the lives of parents through access to ART in countries with limited health care resources and helping to alleviate poverty and improve education are central to the global response to the orphan crisis.[47] The United States Agency for International Development (USAID) and the U.S. President's Emergency Plan for AIDS Relief Orphans and Vulnerable Children Program[23] have provided funding and technical support to protect, care for, and support children affected by HIV. These agencies invest in programs that enable children to stay in school; help extended family members serve as primary caregivers; and provide legal and child protection to improve access to essential services and prevent and respond to child abuse, exploitation, and family separation. A variety of interventions have also focused on keeping orphaned adolescents safe from HIV acquisition during the vulnerable period of young adulthood.[48]

In 2014, UNAIDS launched a campaign to end the AIDS epidemic with the 90-90-90 targets: By 2020, 90% of people living with HIV should know their status, 90% of people living with HIV who know their status should be on treatment, and 90% of people on treatment should achieve virologic suppression.[49] In 2015, the United Nations General Assembly adopted their new Sustainable Development Goals (SDGs), which included a target to end the AIDS epidemic by 2030.[50] With the science showing that starting ART as early as possible both keeps people living with HIV in better health[51,52] and prevents HIV transmission,[53] many countries have adopted the recent World Health Organization (WHO) recommendations of treating everyone living with HIV with ART regardless of $CD4^+$ counts or viral load.[54] According to the *Ending AIDS: Progress Towards the 90-90-90 Targets* report, by 2016, 70% of all people living with HIV globally knew their HIV status, 77% of whom were accessing ART (20.9 million people or more than half of all people living with HIV), and more than 82% of people on treatment were virally suppressed.[49] These target achievements did not vary significantly between men and women worldwide.

TRANSMISSION AND ACQUISITION IN WOMEN AND PREVENTIVE STRATEGIES

Heterosexual Transmission

Efficiency of Transmission

Globally, heterosexual transmission accounts for the spread of HIV infection in approximately 90% of people living with AIDS, and the fastest growing subset of the epidemic is in women due to heterosexual transmission.[2] However, mechanisms of heterosexual transmission remain poorly understood.[55] HIV has been isolated from semen of HIV-infected men and from cervicovaginal secretions of HIV-infected women. However, HIV is not transmitted consistently by sexual contact. Although some individuals become infected after a single exposure to HIV-infected semen, others remain uninfected despite hundreds of exposures.[56,57] This lack of transmission may be due to the amount of virus in the semen or cervicovaginal fluid, the host immune response, the relative virulence of HIV isolates, or some combination thereof.

HIV-infected women can transmit HIV to their uninfected male sexual partners, but heterosexual transmission seems to be more efficient from men to women than from women to men.[58,59] The HIV risk by exposure type in the absence of ART was estimated in a systematic review, which found that the risk of HIV infection for receptive penile-vaginal intercourse was 1 in 1250 compared with 1 in 2500 for insertive penile-vaginal intercourse.[60] In comparison, the risk of receptive anal intercourse is much higher with a risk of 1 HIV infection per 72 exposure acts.[60] As noted earlier, female-to-female HIV transmission has been reported but is exceedingly rare.[9,61] The explanation for this difference in ease of HIV spread from men to their female partners relates to the larger volume of semen compared with cervicovaginal secretions transferred in the coital act and to the higher concentration of HIV on average in seminal fluid. Other factors include increased surface area and thinner epithelium in the female genital tract, rendering it more susceptible to infection. Finally, changes in the protective immune response driven by hormonal fluctuation over the menstrual cycle in women may increase the risk of HIV acquisition.

Factors Associated With Transmission

Factors that have been associated with a greater likelihood of transmitting HIV between heterosexual partners include high HIV viral loads or more advanced immunodeficiency in the infecting partner, the presence of any STI including ulcerative and nonulcerative disease in either partner, sexual activity during menses, receptive anal sex, unprotected vaginal sex, traumatic sex, and increased number of sexual contacts (Table 126.1).[62–64] Baeten and associates[65] demonstrated that genital HIV-1 RNA levels independently predicted HIV-1 transmission risk even after adjusting for plasma HIV-1 RNA concentrations, suggesting that genital HIV viral load could be used as an independent marker of HIV-1 sexual transmission risk.

Male circumcision was shown in randomized trials in Africa to decrease female-to-male HIV transmission by 60%, making male circumcision a highly effective strategy for HIV prevention.[66,67] Because male circumcision provides only partial protection, however, higher risk behaviors could nullify the effect of circumcision. Additionally, circumcision among HIV-infected men may not directly decrease acquisition of HIV among women in serostatus-discordant couples.[66] Roll-out of voluntary circumcision is an active HIV prevention strategy recommended by WHO.[68] Implementation of male circumcision is challenging and has experienced variable success rates around the world because it requires surgical training, aseptic techniques, acceptability, availability, and cultural and religious considerations.[69,70]

The dynamic nature of the female genital tract, cyclical reproductive hormones, and hormonally mediated immune defenses create a "window of vulnerability" to HIV and other infectious agents when the humoral, cell-mediated, and innate immune defenses are suppressed during the ovulatory phase of the menstrual cycle.[71] Cervical mucus and cervicovaginal mucus have been shown to impede the diffusion of HIV, helping to elucidate why conditions such as bacterial vaginosis that can disrupt this protective mucus have been associated with increased HIV acquisition risk in women.[72]

Impact of Hormonal Contraception on HIV Transmission and Acquisition

Hormonal contraceptives, specifically the progestin-only injectable depot medroxyprogesterone acetate (DMPA), have been associated with increased risk for HIV-1 transmission and acquisition in some studies, mostly retrospective studies or studies designed to assess different outcomes.[73] Heffron and coworkers[74] conducted secondary data analyses from the Partners in Prevention HSV/HIV Transmission Study among 3790 heterosexual HIV-discordant couples enrolled in two longitudinal studies in seven African countries. Incidence of HIV infection among female hormonal contraception nonusers was 3.8/100 person-years compared with 6.9/100 person-years among users of injectable forms of contraception ($P = .04$) and 5.9/100 person-years in oral contraceptive users ($P = .33$).[74] Among male partners, the incidence of HIV infection was 1.5/100 person-years when the female partners were HIV-positive and using hormonal contraception compared with 2.6/100 person-years in male partners of female partners using injectable drugs ($P < .05$) and 2.5/100 person-years in male partners of female partners using oral contraceptives ($P = .31$).[74]

Several biologically plausible mechanisms have been postulated to explain how various hormonal contraceptive methods could increase risk of HIV acquisition in women, including thinning or disruption of epithelial barriers, alterations in HIV target cells, or changes in secreted immune defense molecules.[75–78] Polis and colleagues[73] performed a systematic review of studies that assessed the impact of hormonal contraceptives on the risk of HIV acquisition and 31 relevant studies for their analysis: 24 specific to oral contraceptives, 24 specific to progestin-only injectables, and 3 including progestin-containing implantable contraceptives. There was no evidence to suggest that oral contraceptive pills or contraceptive implants increased the risk of HIV acquisition; however, this systematic review indicated that DMPA increased the risk of HIV acquisition by a hazard ratio of 1.4.[73] Due to the observational nature of these studies, there were several confounding factors that could not be controlled for, including misreporting of condom use or difference in sexual behavior. Clinicians and patients need to weigh the potential risk for hormonal contraception on HIV transmission or acquisition risk with known risks for unwanted pregnancy, with its known morbidity and mortality,[79] and the efficacy of implantable or injectable forms of contraception.

Given the substantial public health implications of limiting contraception options for women at risk of acquiring HIV and the previously mentioned limitations with the observational nature of the data, WHO convened a meeting of stakeholders in December 2016 and in 2017 published their most recent guidance statement on hormonal contraceptive methods for women at high risk of HIV and living with HIV.[80] They recommended that the medical eligibility criteria (MEC) for combination hormonal contraceptives, progestogen-only pills, and levonorgestrel and etonogestrel implants remain at 1 (no concern) among women at high risk of HIV infection. However, the MEC recommendation for injectables (DMPA and norethisterone enanthate) was changed to 2, indicating some concern that their use may lead to an increased risk of HIV acquisition.[80] The CDC generally adopted the same guidance as WHO for inclusion in the US MEC guidance for the use of contraceptives, also changing the MEC category for DMPA from 1 (no concern) to 2 (some concern), based on the theoretical risks that DMPA may increase the risk of HIV acquisition in women already at risk.[81]

TABLE 126.1 Risk Factors Associated With Sexual Transmission of HIV

Sexually transmitted infections
Ulcerative/nonulcerative diseases
Genital tract inflammation
HIV disease
Higher viral loads
Lower $CD4^+$ levels
Acute HIV infection
Lack of effective antiretroviral therapy
Lack of heterozygosity or homozygosity for inactivating 32-base pair deletion in chemokine receptor gene (*CCR5*)
Anatomic factors
Lack of circumcision
Cervical ectopy
Leukocytospermia
?Hormonal contraception
Sexual practices
Receptive anal intercourse
Sexual activity during menses
Bleeding during intercourse (disruption of vaginal mucosa through trauma)
Lack of barrier protection
HIV viral features
Syncytium formation
Certain viral clades

HIV, Human immunodeficiency virus.

Sexually Transmitted Infections

STIs, particularly infections associated with genital ulcers, increase the efficiency of HIV transmission and the susceptibility to HIV infection.[82] Genital ulcerative diseases, which include syphilis, chancroid, and genital herpes, are thought to enhance the access of HIV to mucosal tissues, lymphatic drainage, and systemic lymphocytes.[82,83] Epidemiologic studies suggest that nonulcerative STIs also increase susceptibility to HIV infection; female sex workers in Zaire had an increased risk for HIV seroconversion even with nonulcerative STIs,[84] and seroconversion was more likely in HIV serostatus–discordant sex partners if the previously HIV-negative sex partner had ulcerative and nonulcerative STIs.[85] Nonulcerative STIs, such as gonorrhea, chlamydial infection, and trichomoniasis, seem to increase the number of lymphocytes, monocytes, and Langerhans cells in the endocervix in susceptible seronegative women, providing more potential targets for HIV infection.[86–88] Similarly, nonulcerative STIs may increase the number of cells harboring HIV in the genital tracts of HIV-positive transmitters.[86,87]

Bacterial vaginosis has been associated with higher concentrations of HIV RNA in the genital tract of HIV-infected women,[89] increased risk for HIV transmission to male partners,[90] and a 60% increased risk for HIV acquisition in women.[91] Cohen and coworkers[90] studied 2236 HIV-seropositive women and their HIV-uninfected male partners from

the African Partners in Prevention HSV/HIV Transmission Study to see if bacterial vaginosis was associated with increased HIV transmission. Incidence of HIV in men whose HIV-infected female partners had bacterial vaginosis was 2.91 versus 0.76 per 100 person-years in men whose female partners had normal flora (hazard ratio [HR], 3.62; 95% confidence interval [CI], 1.74–7.52). After controlling for sociodemographic factors, sexual behavior, male circumcision, STIs, pregnancy, and plasma HIV-1 RNA levels in female partners, bacterial vaginosis was associated with a greater than threefold increased risk for female-to-male HIV-1 transmission (adjusted HR, 3.17; 95% CI, 1.37–7.33).[90] However, there were several limitations affecting the generalizability of these results, including that all the participants were involved in a clinical trial and underwent couples HIV counseling and testing, and index participants had baseline $CD4^+$ counts greater than or equal to 250 cells/mm^3 and were seropositive for herpes simplex virus type 2 (HSV-2). Mitchell and associates[89] studied 53 HIV-infected women in the United States and Kenya prospectively and found that HIV shedding was greater in women coinfected with certain bacterial vaginosis–associated species only if on ART. Among these women, vaginal *Lactobacillus* spp. were associated with a lower risk of genital HIV shedding, whereas certain bacterial vaginosis–associated species increased that risk.[89] Bacterial vaginosis commonly recurs despite appropriate antibiotic therapy, and strategies such as partner treatment, disruption of the biofilm with boric acid, and improvement of *Lactobacillus* colonization have been largely unsuccessful in recurrent cases.[92]

HIV Infection Within the Genital Tract

Much research has been dedicated to isolation, identification, and quantification of the amount of HIV present within cervicovaginal secretions. The presence of HIV in the female genital tract is necessary for heterosexual transmission of HIV and for perinatal transmission of HIV during labor and delivery.[93] HIV-1 has been isolated from cervical and cervicovaginal secretions obtained using cervicovaginal lavage, vaginal aspirates, and vaginal or cervical swabs or wicks.[94] Although viral loads in genital secretions tend to be lower after initiation of effective ARV medications, detectable HIV in genital secretions has been reported in men and women with undetectable plasma HIV levels.[95–97] Patients with a low plasma virus burden still may potentially transmit HIV to a sexual partner or perinatally to an infant through pregnancy or breastfeeding, although the risk is low.[98,99]

HIV has been detected in menstrual blood, and having intercourse during menses increases the risk for infecting the male partner.[100] Menstruation introduces approximately 80 mL of blood into the genital tract over a 3- to 5-day period. This menstrual blood is likely to contain HIV-infected cells and free virus, reflecting the HIV viral load of peripheral blood. Menstrual blood also changes the microbiota in the vagina and increases the pH in the vagina to the neutral range, which improves the viability of HIV shed in menses and HIV in semen deposited in the vagina during intercourse.[101] Higher levels of HIV in the genital tract may be seen with conditions that increase the vaginal pH such as blood in the vagina, bacterial vaginosis, lack of *Lactobacillus,* menopause, intercourse, and possibly the use of some forms of birth control.[74,102,103] The hormonal changes of the menstrual cycle also play a role, specifically in that genital viral loads are lower in the periovulatory phase and highest during menses, suggesting that local factors may affect the genital viral load compartment independent of plasma viral load.[104]

Strategies to Prevent Heterosexual Transmission

Barrier Methods

Barrier contraceptives constitute an effective means of preventing HIV transmission when used consistently. One study found no heterosexual transmission events among 124 HIV serostatus-discordant couples who used condoms consistently and a seroconversion rate of 4.8 per 100 person-years among 121 serostatus-discordant couples who used condoms inconsistently.[85] Diaphragms are not an effective barrier form of protection against HIV acquisition.[105] Given inconsistent use of condoms as a barrier form of protection against both HIV and pregnancy, most experts recommend dual forms of contraception in the context of HIV risk.[106]

Treatment of Sexually Transmitted Infections

Treatment of STIs alone is unlikely to significantly decrease transmission of HIV and susceptibility to HIV infection. In a Tanzanian clinical trial conducted in subjects in rural communities, universal STI screening and treatment of symptomatic cases of STI resulted in a 40% decrease in HIV incidence compared with a village in which no STI screening or treatment was available.[107] However, a randomized, placebo-controlled trial in HIV-negative, HSV-2–seropositive women in Africa and MSM in Peru and the United States demonstrated that acyclovir 400 mg twice daily suppressed HSV-2 genital ulcers but was not effective in reducing HIV-1 acquisition in HSV-2–seropositive women and MSM.[108] Other studies of strategies to treat STIs in individuals at risk of HIV infection or individuals with HIV have been similarly ineffective, leading to a focus on more effective strategies of combating HIV infection as outlined further on.

Microbicides

A woman-controlled method of reducing the risk of HIV acquisition would help combat the biologic and social vulnerability to HIV in women. One such approach involves a gel, cream, or ring applied locally in the vagina, cervix, or anus to deliver product that can reduce the risk of HIV. However, until more recently, the history of microbicide research has been discouraging.[109,110] Although nonoxynol-9, a commonly used spermicidal agent, has anti-HIV activity in vitro, there have been safety concerns after reports of vaginal ulceration and inflammation during clinical studies.[111,112] A placebo-controlled trial of nonoxynol-9 in sex workers in four countries did not show a protective effect of nonoxynol-9 on HIV-1 transmission and actually showed an association with an increased risk of HIV acquisition when the product was used more frequently.[112] Nonoxynol-9 may cause toxic effects enhancing HIV-1 infection and should not be used as a potential HIV prevention method.

Assessment of other non–ARV-based microbicides, such as carrageenan (Carraguard) vaginal gel, over many studies and years have been largely unsuccessful.[113] Therefore, current microbicides in trials are focused on directly acting antiviral agents.[110] Vaginal tenofovir gel (used either pericoitally or daily) showed promise in early studies[114] but was not shown to be protective in larger studies, likely owing to poor adherence.[115,116] Barriers to adherence included messiness associated with a vaginal gel, lack of discreteness, and bulky packaging. Two trials tested the efficacy of a vaginal ring containing a nonnucleoside reverse transcriptase inhibitor (NNRTI), dapivirine, in reducing HIV acquisition in young African women. The dapivirine vaginal ring provided modest protection against HIV infection in both trials.[117,118] Issues with adherence to the ring were also seen in these studies, however, with no efficacy seen among younger women (ages 18–21 years) likely due to low adherence. When participants used the ring most of the time, HIV protection approached 70%.[117] Future studies of the microbicide ring should focus on extended use of the vaginal ring and safety in adolescents and pregnant women. Finally, the Microbicide Trials Network has started phase I trials of a vaginal ring that will provide contraception as well as HIV protection. This ring combines dapivirine with levonorgestrel, a contraceptive hormone, both of which are slowly released over the course of 3 months. It is hoped that this ring is the first among many combination rings that will be tested to protect against unwanted pregnancy and HIV risk.[119]

Treatment as Prevention

The introduction of potent combination ART in 1996 and the public health approach to HIV treatment in health care resource–limited settings in 2002 have changed the course of the HIV/AIDS epidemic.[120] ART to reduce the infectiousness of individuals with HIV[98,121,122] and oral PrEP for uninfected individuals to prevent HIV acquisition[123] are the most promising approaches for decreasing the spread of the virus. ART given to HIV-infected partners with the purpose of achieving and maintaining full virologic suppression has been shown to prevent linked HIV transmission in a randomized controlled study from the HIV Prevention Trials Network (HPTN 052) among serostatus-discordant couples.[122] In this study, early treatment of the HIV-infected members

of the couples resulted in a 96% reduction in transmission to non–HIV-infected partners.[122]

These results were confirmed in two observational studies of serostatus-discordant couples (PARTNERS study and Opposites Attract) in which the partner living with HIV had already achieved viral suppression on ART, and there was no use of PrEP by the HIV-negative partner or condoms by the couple. After approximately 75,000 combined sex acts, there were no HIV transmissions within partnerships in both cohorts.[121,124] A meta-analysis concluded that there is minimal risk for sexual transmission to women in heterosexual serostatus-discordant partnerships when the HIV-positive male partner has full viral suppression, with caveats regarding lack of information on sexual intercourse type, STIs, and condom use.[125] Indeed, a growing movement, Undetectable = Untransmissible, implies that there is essentially no risk of sexual transmission from a person with HIV who is consistently virologically suppressed on ART.[54] Therefore ART should be a key component for all combination prevention strategies, especially in the context of ongoing efforts to improve worldwide access to ART.

Preexposure Prophylaxis in Women

Another strategy to decrease the sexual transmission of HIV involves the use of ART for primary prevention (i.e., PrEP) among individuals at risk for HIV (Table 126.2).[126] Although randomized clinical trials of PrEP have demonstrated the efficacy of daily oral tenofovir disoproxil fumarate (TDF)–containing regimens for reduction of HIV acquisition, this efficacy has been highly variable across trials. There was a relative reduction in HIV acquisition of 44% in MSM and transgender women (Preexposure Prophylaxis Initiative [iPrEx] trial),[127] 67% to 75% in heterosexual HIV serostatus-discordant couples in which the HIV-negative partner knew the HIV-positive status of his or her partner (Partners PrEP),[128] 62% in heterosexual men and women (Botswana TDF2),[129] and 49% in individuals who inject drugs (Bangkok Tenofovir Study [BTS]).[130] However, two placebo-controlled studies of daily oral TDF-based PrEP conducted specifically among young sexually active African women at risk for HIV infection (FEM-PrEP and VOICE) failed to demonstrate efficacy of daily PrEP in reducing HIV acquisition.[115,131]

FEM-PrEP and VOICE together enrolled greater than 5000 women, but the results in these trials were not consistent with subgroup analyses among women in trials that enrolled heterosexual couples (Partners PrEP, TDF2, BTS) where efficacy was convincingly demonstrated. In Partners PrEP, which included 1785 Kenyan and Ugandan women with an HIV-infected partner (52% of the overall study population), efficacy among women was 66% with TDF/emtricitabine (FTC) and 71% with TDF, and efficacy remained between 64% and 84% even among subgroups of women at the highest risk.[128,132] In the TDF2 study conducted among heterosexual men and women in Botswana, efficacy of daily oral TDF/FTC among the 557 women in the trial (45.7% of the overall study population) was 49%, although statistical power was reduced by the limited number of end points in each subgroup.[129] In BTS, which included 489 women who used injection drugs in Thailand (20% of the overall study population), efficacy of daily oral TDF in women was 79% in reducing HIV acquisition.[130]

Overall, high adherence was noted in trials that reported high PrEP efficacy, and low adherence was noted in trials without efficacy. Of critical importance to the interpretation of PrEP trials was the incorporation of pharmacologic measures of adherence, where drug levels were measured in a biomatrix such as plasma.[133] HIV acquisition across studies, including studies that enrolled women, was associated with lower PrEP adherence as adjudicated by pharmacologic or objective measures. For instance, in both FEM-PrEP and VOICE, self-reported

TABLE 126.2 Clinical Trials of Oral Preexposure Prophylaxis in Which Women Were Enrolled

STUDY	STUDY POPULATION	LOCATION	INTERVENTION	OUTCOME	COMMENTS
TDF2[129]	1219 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% age 21–29 years	Botswana	Daily oral TDF/FTC vs. placebo	63% protection (95% CI, 22%–83%; $P = .01$)	>30% did not complete study; greater TDF blood concentrations in subjects who remained HIV uninfected compared with subjects who acquired HIV; cannot draw definitive conclusions for women and men separately
Partners PrEP Study[403]	4758 heterosexual serostatus-discordant couples; 38% negative female partner, 68% negative male partner; median age 33 years	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF, TDF/FTC, or placebo	67% protection with TDF alone; 75% protection with TDF/FTC; TDF vs. FTC/TDF not statistically significant in primary analysis	TFV detected in blood samples from 82% of subset of HIV-uninfected subjects vs. 31% of subjects who acquired HIV; detection of TFV in blood associated with 86%–90% protection
FEM-PrEP[131]	2120 heterosexual women at high risk for infection age 18–35 years	Kenya, South Africa, Tanzania	Daily oral TDF/FTC vs. placebo	Trial discontinued in April 2011 due to lack of efficacy for HIV prevention	TFV consistently detected in blood samples from <30% of subset of HIV-uninfected subjects
VOICE (MTN-003)[115]	5029 heterosexual women age 18–45 years in high-prevalence areas	South Africa, Zimbabwe, Uganda	Daily oral TDF, FTC/TDF, or placebo or daily vaginal TDF gel or placebo gel	TDF and TDF gel discontinued early due to lack of efficacy for HIV protection. No study drug significantly reduced risk for HIV acquisition: HIV incidence was 5.7 per 100 person-years (range, 0.8–9.9 per 100 person-years). Effectiveness was –48.8% for TDF; –4.2% for TDF/FTC; and 14.7% for TDF gel	Adherence to study drugs was low[404]: TFV was detected in 30% of oral TDF arm, 29% in oral TDF/FTC arm, and 25% in TDF gel arm
HPTN 052[98]	1763 heterosexual serostatus-discordant couples; 50% negative female partner, 50% negative male partner; 94% married; 61% age 26–40 years	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand	Immediate or delayed oral antiretroviral therapy in partner with HIV	96% protection. No linked infections seen when HIV infection stably suppressed by ART over 5-year follow-up	Suppression of viremia on therapy ensured by routine monitoring

ART, Antiretroviral therapy; *CI,* confidence interval; *FTC,* emtricitabine; *HIV,* human immunodeficiency virus; *TDF,* tenofovir disoproxil fumarate; *TFV,* tenofovir.
Modified from Kashuba ADM, Patterson KB, Dumond JB, et al. Pre-exposure prophylaxis for HIV prevention: how to predict success. Lancet. *2012;379:2409–2410.*

adherence was greater than 90%, but adherence rates to the active drug were less than 40% among women in FEM-PrEP and approximately 30% among women in VOICE when based on plasma tenofovir levels.[115,131] Furthermore, more than half of the women in VOICE had no tenofovir detected in plasma during any study visit, suggesting that most women in this trial were not taking the provided PrEP drug at all.[115] In Partners PrEP, by contrast, 82% of participants who did not acquire HIV had detectable plasma tenofovir levels; detectable tenofovir levels were associated with 86% to 90% risk reduction in HIV acquisition.[128] Similarly, in TDF2, 80% of participants who did not acquire HIV had detectable plasma TDF levels, and participants who did not acquire HIV were more likely than participants who did to have detectable study drug.[129] In BTS, 66% of participants overall had detectable plasma tenofovir levels; detectable levels were associated with a 70% risk reduction in HIV acquisition.[130]

Although adherence is critical, there may be biologic differences among men and women that explain some of the discrepant findings in the pivotal PrEP clinical trials. For instance, PrEP efficacy in FEM-PrEP and VOICE differed from that in iPrEx (conducted among men and transgender women), despite similar proportions of participants with detectable study drug. Poor adherence may have greater consequences for women than men in the context of PrEP due to sex differences in tissue levels of drug. Specifically, concentrations of TDF are up to 100-fold higher in rectal tissue than vaginal tissue after TDF administration,[134–136] suggesting that higher levels of adherence (six or seven doses per week) to daily TDF/FTC–based PrEP may be necessary for protection from vaginal exposure.[137] Concentration thresholds for tenofovir or its metabolites in various biomatrices that correlate with protection from HIV infection have been estimated for MSM based on pharmacokinetics modeling in conjunction with incidence data from PrEP studies. For instance, a regimen of four doses a week of TDF/FTC seems to provide 96% protection against HIV for MSM.[138,139] Similar data to allow for analogous modeling studies in women are urgently needed. Finally, although bacterial vaginosis may impact concentrations of 1% tenofovir gel in the vaginal tract, pathogenic species of bacterial vaginosis do not affect tenofovir concentrations in the cervicovaginal tract from oral TDF/FTC–based PrEP,[140] allaying concerns that disruptions in vaginal flora may impact the efficacy of PrEP in women.[141]

REPRODUCTIVE CARE OF WOMEN LIVING WITH HIV

Women living with HIV have long been stigmatized against childbearing,[142] and such stigma is still lingers today.[143] On the one hand, health care providers of women living with HIV should discuss reproductive desires at every patient visit to ensure that they are supporting those desires. On the other hand, because more than half of all pregnancies among women with HIV in the United States are unintended and contraception is underused,[22] it is important that comprehensive family planning and preconception care be integrated into routine health visits. Providers should initiate and document a nonjudgmental conversation with all women of reproductive age concerning their reproductive desires because women may be reluctant to initiate this discussion.[144,145] All women should be offered effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy, including hormonal contraception and intrauterine devices, and offered emergency contraception as appropriate.[146] Providers should be aware of potential interactions between ARV medications and hormonal contraceptives that could lower contraceptive efficacy (Table 126.3). For women who desire pregnancy, providers should discuss options for safer conception, as discussed next.

Conception for Women Living With or at Risk of HIV

Reproductive Desires

With the improved clinical outlook of individuals with HIV, women living with HIV are increasingly interested in having children. In a national survey of people with HIV under care in the United States in 1998, 28% to 29% desired children in the future; among respondents desiring children, 69% of women and 59% of men expected to have one child or more in the future.[147] In a survey of women living with HIV under care in an American university HIV clinic in 2004, most of the 118 women (91%) had borne children, and one-third wanted to have children in the future, suggesting that women with HIV have reproductive patterns similar to HIV-negative women.[148] In a cross-sectional survey conducted by telephone in 2006 to 2007, 61% of the 700 women with HIV on ART believed they could safely have children, although 59% of them thought that society strongly urged them not to have children.[143] More recent studies have suggested that among women receiving HIV care, fertility intent may be higher than these prior estimates.[149–151]

Fertility Issues

Factors associated with fertility desires and intentions in women living with HIV are listed in Table 126.4. Reduced fertility among women with HIV has been observed in both developed and developing countries. Lower fertility rates may be due to reproductive choices, previous infection with other STIs, an effect of HIV infection or induced immunosuppression (i.e., anovulation, effect on sperm, higher rates of spontaneous abortion), and decreased sexual activity. The decrease in the conception rate in three African cities due to the HIV epidemic was estimated to be 16% to 26%.[152] In one study of infertile women with HIV and their partners, the women often presented with unexplained tubal occlusions and the men had abnormal semen parameters.[153] Anovulation is another relatively frequent cause of infertility and is associated with low $CD4^+$ counts, high HIV RNA levels, and a history of substance use.[154] Among concordant couples, the male infertility factor may also be important. Men with advanced HIV infection are more likely to have low testosterone levels and abnormal semen analyses compared with HIV-negative control subjects.[154] A significant positive correlation between sperm count and $CD4^+$ count has been observed.[155] However, as ART becomes increasingly available, these differences in fertility among HIV-positive and HIV-negative women and men are narrowing, indicating ART might improve fertility among women living with HIV.[156,157]

If fertility treatment is required, a limited amount of data have shown that in vitro fertilization (IVF) outcomes in couples with HIV, including clinical pregnancy and live birth rates, are comparable to couples without HIV and with no cases of horizontal or vertical transmission.[158,159] HIV infection does not appear to affect ovarian response among women with HIV who are otherwise healthy,[160] and there is no evidence that HIV infection influences ovarian aging.[161] Most fertility centers are open to assisting HIV-infected couples or individuals with conception.[162] The guidelines from the American Society for Reproductive Medicine published in 2015[163] state that "there is no ethical reason to withhold fertility services at clinics with the necessary resources to provide care to HIV-infected individuals and couples who are willing to use recommended risk-reducing therapies. Clinics without sufficient resources to offer care should assist in referral to providers equipped to manage such patients."[164]

Safe Conception

Serostatus-discordant couples attempting conception have several options for strategies to prevent sexual transmission of HIV. Couples should be counseled on HIV transmission risks and prevention strategies and come to an agreement using shared decision making. Most importantly, the infected partner should receive ART and achieve optimal virologic suppression before attempting conception. If the man is living with HIV and the woman is not, donor sperm insemination can also be offered. Other options for preventing HIV transmission but attempting conception include (1) timed intercourse around the time of ovulation to minimize HIV exposure (sexual intercourse without a condom limited to the 2–3 days before and the day of ovulation [peak fertility])[146]; (2) the use of PrEP with TDF/FTC for the uninfected member of the couple; (3) intrauterine or intravaginal insemination if the woman is living with HIV and the man is not; and (4) sperm washing if the man is living with HIV, ideally once he has achieved nondetectable plasma HIV RNA levels.[165] Sperm washing is based on the premise that HIV-infective material exists primarily in the seminal fluid and not within sperm cells. The sperm have no receptors for HIV, in contrast to the plasma and nonsperm cells, which may contain virus. The technique

TABLE 126.3 Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives

ARV DRUG	EFFECT ON CONTRACEPTIVE DRUG LEVELS AND CONTRACEPTIVE EFFECTS ON ART AND HIV	CLINICAL STUDIES	DOSING RECOMMENDATION/CLINICAL COMMENT FOR CONTRACEPTION OPTIONS
EFV	COC • No effect on EE concentrations • ↓ active metabolites of norgestimate LN AUC ↓ 83%; norelgestromin AUC ↓ 64% • Etonogestrel (in COC) C24 ↓ 61% DMPA • No effect on DMPA levels Etonogestrel implant • Etonogestrel AUC ↓ 63%–82% LN Implant • LN AUC ↓ 47% • LN (emergency contraception) AUC ↓ 58% Changes in ARV levels and/or effects on HIV COC • No effect on EFV concentrations • EFV C12 ↓ 22%; was under therapeutic threshold in 3/16 subjects DMPA • No effect on HIV disease progression • No effect on EFV concentrations LN implant • No effect on HIV disease progression	COC • Pregnancy rates no difference • Pregnancy rate higher (13%) in women using COCs and EFV vs. COCs alone • Progesterone >3 (surrogate for ovulation) in 3/16 • No ovulations DMPA • No increase in pregnancy • Low progesterone Etonogestrel implant • Pregnancy rate higher with EFV vs. no ART but still lower than other hormonal methods • Presumptive ovulation in 5% LN implant • 12% pregnancy rate • 15% pregnancy rate • Pregnancy rate higher with EFV vs. no ART but still lower than other hormonal methods	Consider alternative method (or a reliable method of barrier contraception) in addition to COC/POP/implants No additional contraception needed with DMPA[a]
ETR	EE: AUC ↑ 22% NE: No significant effect	COC • No ovulations	No additional contraceptive protection is needed
NVP	EE: AUC ↓ 29% and no change in 2 different studies NE: AUC ↓ 18% Etonogestrel (in COC) C24 decreased 22% DMPA: No significant change LN implant • LN AUC ↑ 35% Changes in ARV levels and/or effects on HIV COC • NVP no significant effect DMPA • No effect on HIV disease progression LN implant • No effect on HIV disease progression	COC • No increase in pregnancy rate • No ovulation DMPA • No increase in pregnancy rate • No ovulations Etonogestrel implant • No increase in pregnancy rate LN implant • No increase in pregnancy rate	No additional contraceptive protection is needed
RPV	EE: AUC ↑ 14% NE: No significant change Changes in ARV levels and/or effects on HIV COC • No change in RPV levels vs. historical controls	COC • No change in progesterone	No additional contraceptive protection is needed
ATV/r	EE: AUC ↓ 19% Norgestimate: AUC ↑ 85% POP • NE AUC ↑ 50%	N/A	No additional contraceptive protection is needed
DRV/r	EE: AUC ↓ 44% NE: AUC ↓ 14%	N/A	Consider an alternative method (or a reliable method of barrier contraception) in addition to COC/POP/implants No additional contraception needed with DMPA[a]
LPV/r	EE AUC ↓ 55% NE AUC ↓ 17% Patch • EE AUC ↓ 45% • Norelgestromin AUC ↑ 83% DMPA • AUC ↑ 46% Etonogestrel implant • Etonogestrel AUC ↑ 52% Changes in ARV levels and/or effects on HIV Patch • LPV/r level ↓ 19% DMPA • No effect on HIV disease progression • LPV/r no change	COC • Increased pregnancy rate, but CIs overlap Patch • No ovulations DMPA • No pregnancies, no ovulations • Increased pregnancy rate, but CIs overlap Etonogestrel implant • No increase in pregnancy rate LN implant • No increase in pregnancy rate	No additional contraceptive protection is needed
SQV/r	↓ EE Changes in ARV levels and/or effects on HIV COC • SQV/r no change	N/A	Consider alternative method (or reliable method of barrier contraception) in addition to COC/POP/implants No additional contraception needed with DMPA[a]
ATV	COC • EE AUC ↑ 48% • NE AUC ↑ 110%	N/A	Prescribe oral contraceptive that contains no more than 30 μg of EE, or recommend alternative contraceptive method No additional contraception needed with DMPA/POP/implants

TABLE 126.3 Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives—cont'd

ARV DRUG	EFFECT ON CONTRACEPTIVE DRUG LEVELS AND CONTRACEPTIVE EFFECTS ON ART AND HIV	CLINICAL STUDIES	DOSING RECOMMENDATION/CLINICAL COMMENT FOR CONTRACEPTION OPTIONS
ATV/c	Drospirenone AUC ↑ 2.3-fold EE AUC ↓ 22%	N/A	**Contraindicated** with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia Consider alternative or additional contraceptive method
DRV/c	Drospirenone AUC ↑ 1.6-fold EE AUC ↓ 30%	N/A	In combination with drospirenone-containing COCs, clinical monitoring is recommended due to potential for hyperkalemia Consider alternative or additional contraceptive method
IDV	COC • EE AUC ↑ 22% • NE AUC ↑ 26%	COCs • No pregnancies among women taking IDV and COCs	No additional contraceptive protection is needed
NFV	COC • EE AUC ↓ 47% • NE AUC ↓ 18% DMPA • No change NFV • AUC ↓ 18%	COCs • 1 small study suggested that women using COCs and NFV may have had higher pregnancy rates than women using COCs alone DMPA • No pregnancies, no ovulations • $CD4^+$ count/HIV RNA: no change	Can consider alternative method (or reliable method of barrier contraception) in addition to this method No additional contraception needed with DMPA[a]
MVC	COC • No significant effect on EE or LN	N/A	No additional contraceptive protection is needed
RAL	COC • EE no change • Norgestimate AUC ↑ 14%	N/A	No additional contraceptive protection is needed
DTG	COC • No significant effect on norgestimate or EE • DTG AUC no change	N/A	No additional contraceptive protection is needed
EVG/c	EVG/COBI/FTC/TDF COC • Norgestimate AUC ↑ 126% • EE AUC ↓ 25%	N/A	No additional contraceptive protection is needed

[a]Because the hormonal levels achieved with DMPA are substantially higher than are required for contraception, any small reduction in hormonal level due to ARVs is unlikely to reduce contraceptive effectiveness.

ART, Antiretroviral therapy; *ARV,* antiretroviral; *ATV,* atazanavir; *ATV/c,* atazanavir/cobicistat; *ATV/r,* atazanavir/ritonavir; *AUC,* area under the curve; *CHC,* combination hormonal contraceptives; *CI,* confidence interval; *COBI,* cobicistat; *COC/P/R,* combined oral contraceptives/patch/ring; *DMPA,* depot medroxyprogesterone acetate; *DRV/c,* darunavir/cobicistat; *DRV/r,* darunavir/ritonavir; *DTG,* dolutegravir; *EE,* ethinyl estradiol; *EFV,* efavirenz; *ETR,* etravirine; *EVG,* elvitegravir; *EVG/c,* elvitegravir/cobicistat; *HIV,* human immunodeficiency virus; *IDV,* indinavir; *LN,* levonorgestrel; *LPV/r,* lopinavir/ritonavir; *MVC,* maraviroc; *N/A,* no data available; *NE,* norethindrone; *NFV,* nelfinavir; *NVP,* nevirapine; *PI,* protease inhibitor; *PI/r,* ritonavir boosted-protease inhibitor; *POP,* progesterone-only oral contraceptive pills; *RAL,* raltegravir; *RPV,* rilpivirine; *RTV,* ritonavir; *SQV/r,* saquinavir/ritonavir; *TDF,* tenofovir disoproxil fumarate.

Data from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf; and Department of Health and Human Services. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated November 2017. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

TABLE 126.4 Factors Associated With Fertility Desires and Intentions in Women Living With HIV Infection

POSITIVE INFLUENCES	NEGATIVE INFLUENCES
Younger age	Personal health concerns
No children	Having had one or more children
Antiretroviral therapy	Concerns about infecting partner
Interventions to prevent mother-to-child transmission	Concerns about infecting child
Partner's/family members' wish for children	Negative or judgmental attitudes of health care workers, family, and community
HIV-related stigma	HIV-related stigma
New male partner	Fear of disclosure

Modified from Hoyt MJ, Storm DS, Aaron E, et al. Preconception and contraceptive care for women living with HIV. Infect Dis Obstet Gynecol. *2012;2012:604183.*

uses density-gradient fractionation to separate sperm from seminal plasma and nonsperm cells.[166] However, with the increasing availability of potent ART regimens and higher rates of HIV viral suppression on effective ART, the use of sperm washing, given its expense and the need for specialized expertise, is rapidly waning. Finally, the risk of HIV superinfection or infection with a resistant virus is negligible when both partners are on ART and have fully suppressed plasma viral loads.[146,167]

PrEP with oral TDF/FTC for uninfected partners is an additional strategy to decrease the risk for HIV sexual transmission among couples trying to conceive. In a prospective study of 53 serostatus-discordant couples (man with HIV) opting to use only timed intercourse with or without PrEP, the pregnancy rate after natural conception was 26% for the first attempt and increased to 75% after 12 attempts.[168] No cases of HIV transmission occurred. To participate in this study, the male partner had to have undetectable HIV RNA in the plasma (<50 copies/mL), no reports of STIs, and no unprotected sex with other partners. Luteinizing hormone in the urine was tested to determine the optimal time of conception, and oral PrEP with TDF alone was given at the luteinizing hormone level peak and 24 hours later. Fertility evaluations were suggested after six unsuccessful attempts, and advanced age in the female partner was found to be a predictor for infertility.[168]

Contraception for Women With or at Risk of HIV

Protection against STIs is a critical aspect to consider when determining the optimal contraceptive plan for women living with or at risk of HIV. The most effective methods to prevent forward transmission of both STIs and HIV in women living with HIV are barrier methods. Although individuals with HIV have relied on barrier methods for the prevention of STIs, including HIV, WHO categorizes male and female condoms as only somewhat effective contraceptives.[169] Male condoms also require partner cooperation, so dual methods are recommended for optimal birth control among women with or at risk of HIV.

Impact of Hormonal Contraceptives on HIV Progression

At the present time, available highly effective reversible birth control options include hormonal methods such as the pill, vaginal ring, transdermal patch, implant, and levonorgesteral intrauterine device (IUD) and the nonhormonal copper IUD. Technologies for a dual purpose microbicide (dapivirine) and contraceptive (levonorgesteral) vaginal ring are in development as summarized in "Strategies to Prevent Heterosexual Transmission." In terms of the question of HIV disease progression in women with HIV using contraceptives, a systematic review identified 13 high-quality studies that evaluated the risk of HIV disease progression and hormonal contraception use.[170] Only 1 of the 13 studies demonstrated an increased risk of disease progression with concomitant use of hormonal contraceptives. A secondary analysis from a randomized trial of 595 women showed an increased risk of declining $CD4^+$ count among 302 women randomly assigned to hormonal contraceptives (DMPA or combined oral contraceptive [COC] pills) compared with 293 women randomly assigned to the copper IUD (HR, 1.56; 95% CI, 1.08–2.26 for DMPA; HR, 1.69; 95% CI, 1.09–2.64 for COC).[171] However, loss to follow-up and changing contraceptive method were common; therefore the intent-to-treat analysis failed to show an association between hormonal contraception and HIV disease progression.[171] Conversely, a more recent and larger study in a prospective cohort of 2269 women with HIV in sub-Saharan Africa found that the use of injectable contraceptives (DMPA and norethisterone enanthate), but not COCs, was associated with a lower likelihood of disease progression, defined as a composite measure of ART initiation, $CD4^+$ count decreasing to less than 200 cells/mm^3, or atraumatic death (adjusted HR, 0.74; $P = .04$ for injectable contraceptive users; adjusted HR, 0.83; $P = .5$ for COC users).[172] Taken together, these data do not indicate a serious concern for the hastening of HIV disease progression with hormonal contraceptive use.

Drug-Drug Interactions Between ART and Hormonal Contraceptives

Another potential concern raised with hormonal contraceptives and HIV is the potential for drug-drug interaction between the hormonal contraceptive and ARVs, resulting in a decrease in systemic ART exposure or exogenous hormone concentrations. A few pharmacokinetics studies have found that exogenous hormone exposure influenced ART exposure. One study found statistically lower efavirenz (EFV) concentrations when given with an oral contraceptive pill containing ethinyl estradiol/desogestrel.[173] Another study of the contraceptive transdermal patch (ethinyl estradiol/norelgestromin) plus lopinavir/ritonavir–based ART identified significantly lower ritonavir exposures.[174] Also, one study observed slightly higher nevirapine (NVP) and lower nelfinavir exposure when these ARVs were combined with DMPA.[175] Despite these statistically significant changes, the changes in exposures were not lower than 80% of previously observed concentrations, and therefore the changes are unlikely to be clinically significant. In addition, most studies of drug interactions between more modern ARVs currently in use and hormonal contraceptives do not show a significant lowering in exposure to the former with the latter.[176] Based on these data, the impact of hormonal contraceptives on ART exposure, if any, is small and unlikely to be clinically significant. Overall, the available data indicate that hormonal contraceptives do not impact the rate of disease progression for women living with HIV, either by primary impact on HIV disease or by secondary impact on ART pharmacokinetics.

However, clinicians need to be aware of the potential for pharmacologic interactions between most protease inhibitors and NNRTIs with both the ethinyl estradiol and the progestin components of hormonal contraceptives, as shown in Table 126.3.[22,176] Both ethinyl estradiol and progestins are metabolized by the cytochrome P-450 (CYP) enzyme system. Generally, protease inhibitors are CYP inhibitors, and NNRTIs are CYP inducers, possibly leading to increasing hormone exposure and reduced hormone exposure, respectively. A reduced progestin exposure could impact contraceptive efficacy, as the contraceptive effect is primarily due to the progestin. An increase in progestin exposure is generally well tolerated. Reduced ethinyl estradiol exposure could lead to an increased amount of breakthrough bleeding and thus might lead to reduced adherence to the contraceptive but would not primarily impact contraceptive efficacy. Increased ethinyl estradiol exposure could lead to increased side effects such as breast tenderness, headache, and nausea, which could similarly negatively impact contraceptive adherence. More concerning, increased estrogen exposure is related to estrogen-induced hepatic production of clotting factors and subsequent thrombosis-related complications such as venous thromboembolism, myocardial infarction, and cerebrovascular accident. Moreover, increases in the circulating levels of angiotensinogen with increased estrogen exposure could lead to increases in blood pressure. These effects are largely theoretical, and widespread tolerability concerns due to the effects of ART on increasing hormonal contraceptive levels have not been observed.

In terms of ART and the effectiveness of contraceptives, to date only EFV-based ART has been reported to lead to clinically significant drug-drug interactions that decrease the effectiveness of hormonal contraceptives (Table 126.3).[22,176] This concern is most relevant to levonorgestrel-based and etonogestrel-based implants, but not DMPA. Two studies have shown that DMPA in conjunction with selected protease inhibitor–based and NNRTI-based regimens remains efficacious in suppressing ovulation with clinically insignificant changes in medroxyprogesterone acetate levels and with no significant changes in ARV levels.[175,177,178] However, two pharmacokinetics studies evaluated levonorgestrel and etonogestrel subdermal implants in Ugandan women living with HIV on EFV-based ART, on NVP-based ART, and on no ART.[179,180] In both studies, the researchers found a significant drop in the geometric mean for both levonorgestrel and etonogestrel concentration levels over the first 6 months of having the implant placed when women were on EFV-based ART. In the first study, three pregnancies occurred within the first year of having the levonorgestrel implant placed (3/20 = 15%) in women on EFV-based ART, with no pregnancies or significant drops in levonorgestrel levels in the NVP-based or no-ART arms.[179] Another study followed a large cohort of 24,560 women contributing 37,635 years of follow-up with 3337 incident pregnancies in East Africa.[181] In women using implants, adjusted pregnancy incidence was three times higher for women on EFV-based ART than for women on NVP-based ART (1.1 per 100 person-years [95% CI, 0.72–1.5] for NVP-based ART users; 3.3 per 100 person-years [95% CI, 1.8–4.8] for EFV-based ART users [adjusted incidence rate ratio, 3.0; 95% CI, 1.3–4.6]). In women on DMPA, the adjusted pregnancy incidence was not significantly different for women on either EFV-based ART or NVP-based ART. However, overall, women on implants had lower contraceptive failure rates than women receiving all other contraceptive methods except for IUDs; the overall conclusion was that effective contraceptive options including implants should be made available for women worldwide.[181]

In terms of the interaction between EFV and emergency contraception, oral levonorgestrel is the hormone in Plan B, the most prevalent over-the-counter emergency contraception option for women. Levonorgestrel levels appeared to drop after administration of EFV and Plan B.[182] Although the minimal effective concentration of levonorgestrel for emergency contraception is unknown, the pharmacokinetics information suggests that higher doses (greater than the standard 1.5 mg) might be needed in women taking EFV to prevent pregnancy. A study in the AIDS Clinical Trials Group (ACTG) is underway to study this question.

Other non–EFV-based ARVs do not have significant drug-drug interactions with hormonal contraceptives. Maraviroc is a substrate of

CYP3A enzymes, but it is neither an inducer nor an inhibitor of the CYP3A system, and no significant interactions with hormonal agents have been demonstrated.[176] Likewise, no clinically significant interactions between hormonal contraceptives and unboosted integrase inhibitors including raltegravir or dolutegravir have been noted. However, hormonal therapies with at least 30 µg ethinyl estradiol are recommended when taking elvitegravir and the booster cobicistat (COBI), a CYP3A4 inhibitor, because of the COBI effect of the combination on ethinyl estradiol levels.[176] One study investigated interactions between the transdermal contraceptive patch (ethinyl estradiol/norelgestromin) and lopinavir/ritonavir.[174] The 45% decrease in the area under the curve of ethinyl estradiol from this study with the patch was comparable to results from interaction studies with oral hormonal contraceptive therapies.[174] To date, pharmacokinetics studies between the contraceptive intravaginal ring and ARV agents have not been published.

The IUD, both copper and levonorgestrel, is widely used internationally and increasingly being used in the United States. Both of these methods are safe and effective in women with HIV and are not associated with HIV transmission.[183–185] The levonorgestrel-releasing intrauterine system has been shown to be safe, effective, and well tolerated and to reduce menstrual bleeding in HIV-infected women.[186,187] There are no known pharmacokinetics interactions between the levonorgestrel-releasing IUD and ART.[176] IUDs do not influence genital tract HIV RNA shedding, and their use among HIV-infected women is not associated with increased risk for transmission of the virus to sexual partners.[185,187,188] WHO MEC for contraceptive use has a level 3 recommendation (use of IUD is not usually recommended unless other more appropriate methods are not available or not acceptable) for women with WHO stage 3 or 4 clinical disease, but for all other women infected with HIV, including women with mild HIV disease (WHO stage 1 or 3), IUD use falls into WHO level 2 recommendation (the method can generally be used because the benefits of the method outweigh the risks).[169]

HIV AND PREGNANCY

Guidelines on Use of Antiretroviral Agents in Pregnant HIV-Infected Women

Since mid-1997, the US Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents has issued recommendations for the use of ARV agents in adults living with HIV. These recommendations are updated on a regular basis, with the most recent information available on the AIDS*info* website, a web-based service of DHHS (http://AIDSinfo.nih.gov).[189]

The DHHS Perinatal Guidelines panel revises its recommendations for the use of ARV drugs in pregnant women living with HIV on an ongoing basis, and the recommendations are also fully accessible online.[22] Although there are no controlled clinical trials demonstrating the safety or efficacy of most ARV agents during pregnancy, both panels recommend that ART in pregnant women be the same as for nonpregnant women, unless clear fetal or maternal contraindications exist. Combination ARV regimens both to benefit the health of the mother and to prevent perinatal HIV transmission should be provided to all pregnant women living with HIV, regardless of $CD4^+$ count and HIV RNA copy number. The greatest risk factor for perinatal transmission is maternal HIV viral load, which is why reducing HIV viral loads to undetectable via effective ART benefit both the pregnant mother and the unborn fetus.[146]

The DHHS Perinatal Guidelines state that pregnancy is not a reason to defer standard suppressive ART, but the guidelines outline unique considerations for ART use including potential need to alter dosing as a result of physiologic changes associated with pregnancy, potential for adverse short-term or long-term effects on the fetus and neonate, and efficacy in reducing the risk for perinatal transmission.[146] The current pharmacokinetics and toxicity data in human pregnancy and recommendations for use in pregnancy for approved ARV agents are presented in Table 126.5.[22]

Perinatal Transmission: Timing, Risk Factors, and Strategies to Eliminate

Before the use of ARV medications, estimates of the frequency of perinatal transmission ranged from 13% in Europe to more than 60% in Africa, with frequencies of 14% to 33% reported in the United States.[190] As the number of women who became infected with HIV during their childbearing years increased, so would the number of children infected perinatally unless access to ART could be ensured to prevent maternal-to-child transmission. Effective ARV medications for PMTCT can reduce perinatal HIV transmission to less than 1% in the absence of breastfeeding and to less than 5% by 6 months of age in breastfeeding infants.[191,192] WHO has called for the "virtual elimination" of pediatric HIV infection, and access to ARV agents for PMTCT continues to increase; in 2011, only 57% of pregnant women living with HIV in low-income and middle-income countries were receiving ARVs, but by 2016, 76% of the estimated 1.4 million pregnant women living with HIV globally received ART.[193] A growing number of countries including Armenia, Belarus, Cuba, and Thailand have been formally validated for having eliminated mother-to-child transmission of HIV.[193] Fig. 126.1 in "Update on Perinatal Transmission Rates" under "Worldwide Epidemiology" summarizes the increase of ART access among pregnant women worldwide as tabulated by UNAIDS.[2]

There has been much progress along the road to ART for all people living with HIV, including all pregnant women living with HIV. In 2013, WHO revised guidelines for PMTCT to recommend lifelong three-drug ART for all women regardless of $CD4^+$ count or clinical stage of disease (Option B+).[192] These guidelines override any former recommendations of using ART only if the $CD4^+$ count was a certain value, using ART for women with high $CD4^+$ counts during pregnancy only, or stopping ART after breastfeeding had ceased. Once-daily EFV with two nucleosides such as TDF plus lamivudine (3TC) (or FTC) remains the recommended first-line regimen for pregnant women globally. In the past, EFV had been avoided during pregnancy due to concerns primarily originating from teratogenicity studies in animals. However, data from the Antiretroviral Pregnancy Registry (APR) showed that the rate of birth defects reported in association with EFV is similar to that of other ARVs.[194,195] In the latest iteration of the guidelines, dolutegravir has been listed as an alternative first-line regimen for people living with HIV worldwide, and studies to examine the safety of dolutegravir in pregnancy and for prevention of perinatal transmission are underway.

Outdated recommendations for PMTCT have been studied in cost-effectiveness analyses and examined in relationship to mortality benefit.[191] Although the recommendations by WHO to provide Option B+ (lifelong ART for all pregnant women regardless of $CD4^+$ count) were provided in 2013,[192] the overall treatment guidelines issued by WHO for all adults living with HIV infection changed in 2015.[54] These guidelines stipulate that all people living with HIV—regardless of $CD4^+$ count, sex, pregnancy status, hepatitis B status, etc.—should be on ART. The overwhelming individual-level and public health benefits of putting all people living with HIV on ART led to this change in guidelines, and the concept of varying strategies to prevent perinatal transmission is now fading into the past with this new dictum.

Barriers to ART provision for pregnant women in settings with limited health care resources still exist. These barriers include distance between antenatal care sites where HIV diagnosis is made and ART sites where treatment is started; transportation costs; and human resource constraints that lead to long waiting times, frequent ART stock shortages, and scheduling difficulties. The CDC reported on the implementation of Option B+ in the third quarter of 2011 in Malawi, when the Malawi Ministry of Health began a program in which all pregnant and breastfeeding women with HIV were eligible for lifelong ART regardless of $CD4^+$ status.[196] In Malawi, the number of pregnant and breastfeeding women started on ART per quarter increased by 748%, from 1257 in the second quarter of 2011 before program implementation to 10,663 in the third quarter of 2012, which was 1 year after implementation of Option B+ policy.[196] More than 77% of women in Malawi started on ART while pregnant or breastfeeding continued on ART 1 year later, a finding similar to that of the national ART program. The removal of the barrier of requiring $CD4^+$ counts, decentralization of ART into all antenatal care sites, and training of nearly all nurses and clinical officers on the new integrated PMTCT/ART guidelines greatly facilitated the increase in the number of pregnant and breastfeeding women started on ART in Malawi. Option B+ as well as the parent policy of having all people living with HIV worldwide on ART has been an important innovation

TABLE 126.5 Antiretroviral Drug Use in Pregnant Women Living With HIV: Pharmacokinetics and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

ARV DRUG	PK IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE IN PREGNANCY
NRTIs/NtRTIs		Potential maternal and infant mitochondrial toxicity	Used as part of combination regimens; use of single or dual NRTIs alone is not recommended for treatment of HIV infections
Abacavir (ABC)	PK not significantly altered; no change in dose indicated High placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects); hypersensitivity reactions occur in approximately 5%–8% or more of nonpregnant persons; rate in pregnancy is unknown; previous screening for HLA-B5701 should be done and documented as negative before starting ABC	One of several preferred NRTIs for dual nucleoside backbone of combination regimens in pregnancy ABC *should not be used* in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction Abacavir/3TC is preferred NRTI combination for use in pregnancy Patients should be educated regarding symptoms of hypersensitivity reaction
Emtricitabine (FTC)	PK study shows slightly lower levels in third trimester compared with postpartum; no clear need to increase dose High placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) If HBV coinfection, possible HBV flare if drug is stopped	One of several preferred NRTIs for dual nucleoside backbone of combination regimens in pregnancy Tenofovir/FTC is preferred NRTI combination for use in pregnancy
Lamivudine (3TC)	PK not significantly altered; no change in dose indicated High placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects); well-tolerated, short-term safety demonstrated for mother and infant If HBV coinfection, possible HBV flare if drug is stopped	One of several preferred NRTIs for dual nucleoside backbone of combination regimens in pregnancy ABC/3TC and tenofovir/FTC (or with 3TC) are preferred NRTI combinations for use in pregnancy
Tenofovir alafenamide (TAF)	No data are available on placental transfer of TAF	Insufficient data to assess for teratogenicity in humans; no evidence of teratogenicity in rats Renal function should be monitored because of potential for renal toxicity	
Tenofovir disoproxil fumarate (TDF)	Limited studies in human pregnancy; data indicate AUC lower in third trimester than postpartum, but trough levels adequate High placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects); clinical studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy Human studies demonstrate no consistent link to low birth weight, but data are conflicting about potential effects on growth outcomes later in infancy If HBV coinfection, possible HBV flare if drug is stopped	One of several preferred NRTIs for dual nucleoside backbone of combination regimens in pregnancy TDF is preferred NRTI in combination with 3TC or FTC in women with chronic HBV infection Because of potential for renal toxicity, renal function should be monitored Tenofovir/FTC (or with 3TC) is preferred NRTI combination for use in pregnancy
Zidovudine (ZDV)	PK not significantly altered; no change in dose indicated High placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects); well-tolerated, short-term safety demonstrated for mother and infant	Alternative NRTI for dual nucleoside backbone of combination regimens (ZDV/3TC) in pregnancy; should not be included in regimen if significant toxicity or d4T use
NNRTIs		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear whether increased in pregnancy	NNRTIs are recommended for use in combinations with two NRTI drugs
Efavirenz (EFV)	AUC decreased during third trimester compared with postpartum, but nearly all exceeded target exposure levels, and no change in dose is indicated Moderate placental transfer to fetus	Significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 cynomolgus monkeys receiving EFV during first trimester at dose comparable to human therapeutic exposure FDA advises women to avoid becoming pregnant while taking EFV and to avoid using EFV in first trimester, as fetal harm may occur EFV should be continued in pregnant women receiving virologically suppressive EFV-based regimen, as ARV drug changes during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission	EFV plus a preferred two-NRTI backbone is alternative initial regimen in pregnancy Concern because of birth defects seen in primate study, but data not borne in human studies and extensive experience in pregnancy Preferred regimen in women who require coadministration of drugs with significant interactions with PIs or prefer convenience of coformulated, single-tablet, once-daily regimen Screening for antenatal and postpartum depression is recommended
Etravirine (ETR)	Limited PK studies in human pregnancy; in four pregnant women, drug levels and AUC similar to nonpregnant women, suggesting no dose modification needed Variable placenta transfer, usually in moderate to high categories, 0.19–4.25 (data from 19 mother-infant pairs).	Limited experience in human pregnancy; no evidence of teratogenicity in rats and rabbits	Safety and PK in pregnancy data are insufficient to recommend use during pregnancy Not recommended in ART-naïve populations

TABLE 126.5 Antiretroviral Drug Use in Pregnant Women Living With HIV: Pharmacokinetics and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a]—cont'd

ARV DRUG	PK IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE IN PREGNANCY
Nevirapine (NVP)	PK not significantly altered; no change in dose indicated High placental transfer to fetus	No evidence of human teratogenicity Increased risk for a symptomatic hypersensitivity reaction, often with rash, and potentially fatal liver toxicity among women with $CD4^+$ counts >250 cells/mm^3 when first initiating therapy; unclear whether pregnancy increases risk	NVP is not recommended because of greater potential for adverse events, complex lead-in dosing, and low barrier to resistance NVP should be used with caution when initiating ART in women with $CD4^+$ counts >250 cells/mm^3 Use NVP and ABC together with caution; both can cause hypersensitivity reactions within first few weeks after initiation
Rilpivirine (RPV)	Moderate to high placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)	RPV plus a preferred two-NRTI backbone (RPV/TDF/FTC) is an alternative initial regimen but is not recommended with pretreatment HIV RNA >100,000 copies/mL or $CD4^+$ count <200 cells/mm^3 Do not use with proton-pump inhibitors
PIs		Hyperglycemia, new-onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear whether pregnancy increases risk Data conflicting regarding risk for preterm delivery in women receiving PIs	PIs are recommended for use in combination with two NRTI drugs
Atazanavir (ATV)/ritonavir (RTV) ATV/cobicistat (COBI)	Two of three intensive PK studies of ATV with RTV boosting during pregnancy suggest that standard dosing results in decreased plasma concentrations compared with nonpregnant adults; ATV concentrations further reduced by approximately 25% with concomitant TDF use Low placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) Must be given with low-dose RTV-booster regimen during pregnancy Theoretical concern regarding increased indirect bilirubin levels causing significant exacerbation in physiologic hyperbilirubinemia in neonates has not been observed in clinical trials to date	One of preferred PIs for use in combination regimens in pregnancy; must be given with low-dose RTV once daily Package insert recommends increased ATV dosing for ARV-experienced pregnant women in second and third trimester also receiving either TDF or H2 receptor antagonist or ARV-naïve pregnant women receiving EFV ATV should not be used in patients receiving both TDF and H2 receptor antagonist or in ARV-experienced patients also taking EFV
Darunavir (DRV)/RTV	PK study demonstrated plasma concentrations were decreased by 17%–35% with once-daily and twice-daily dosing in third trimester Low placental transfer to fetus	No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity	One of preferred PIs for use in combination regimens in pregnancy when used with low-dose RTV twice daily in pregnancy Better tolerated than LPV/RTV
Lopinavir (LPV)/RTV	AUC decreased in second and third trimesters with standard dosing; PK studies suggest increasing to LPV 600 mg/150 mg bid or LPV 500 mg plus RTV 125 mg bid in second and third trimesters Low placental transfer to fetus More nausea than preferred agents	No evidence of human teratogenicity; abundant experience and established PK in pregnancy	One of alternative PI-boosted regimens for use in combination regimens in pregnancy PK studies suggest need for increased dosing in second and third trimesters If standard dosing is used, monitor virologic response and LPV drug levels, if available Once-daily LPV/RTV is not recommended in pregnancy
RTV (as a single PI)	Phase I/II study in pregnancy demonstrates lower levels during pregnancy compared with postpartum Minimal placental transfer to fetus	No evidence of human teratogenicity (can rule out twofold increase in overall birth defects) Limited experience at full dose in human pregnancy; should be used as low-dose RTV boosting with other PIs	RTV as single PI is not recommended because of inferior efficacy and increased toxicity
INSTIs			
Dolutegravir	High placental transfer to fetus	No evidence of teratogenicity in mice, rats, or rabbits Preliminary data suggest no increased risk of teratogenicity in humans Safety and PK in pregnancy data are limited but increasing experience in pregnancy	One of alternative INSTI-based regimens for use in combination regimens in pregnancy Available as fixed-dose combination with ABC, requiring HLA-B5701 testing, administered once daily In nonpregnant adults, associated with lower rates of INSTI resistance than RAL and therefore suggested for women with acute infection in pregnancy
Elvitegravir (EVG/c (available in fixed-drug combination TDF/FTC/EVG/COBI (brand name: Stribild[b]) and EVG/COBI/TAF/FTC brand name Genvoya[c])	Evidence of high placental transfer of EVG and low transfer of COBI	No evidence of teratogenicity in rats and rabbits with all four components of medications If HBV coinfection present, possible HBV flare if drug stopped postpartum	EVG/c **is not recommended** for initial use in pregnancy For women who become pregnant while taking EVG/c, consider switching to more effective, recommended regimen If EVG/c regimen is continued, viral load should be monitored frequently, and TDM (if available) may be useful

Continued

TABLE 126.5 Antiretroviral Drug Use in Pregnant Women Living With HIV: Pharmacokinetics and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy[a]—cont'd

ARV DRUG	PK IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE IN PREGNANCY
Raltegravir (RAL)	High placental transfer to fetus	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)	One of preferred INSTI-based regimens for use in combination regimens in pregnancy Case report of markedly elevated liver transaminases with use in late pregnancy Severe, potentially life-threatening, and fatal skin and hypersensitivity reactions have been reported in nonpregnant adults Has been associated with rapid viral load reduction Useful when drug interactions with PI regimens are a concern Twice-daily dosing required

[a]Approved ARV medications that are toxic in pregnancy or less potent than other available ARV medications and therefore not recommended for use in pregnancy have not been included in this table, including stavudine, didanosine, enfuvirtide, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir, and maravoric.
[b]Stribild package insert: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203100s030lbl.pdf.
[c]Genvoya package insert: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207561s002lbl.pdf.
3TC, lamivudine; *ABC,* abacavir; *ART,* antiretroviral therapy; *ARV,* antiretroviral; *ATV,* atazanavir; *AUC,* area under the curve; *COBI,* cobicistat; *d4T,* stavudine; *DRV,* darunavir; *EFV,* efavirenz; *ETR,* etravirine; *EVG/c,* elvitegravir/cobicistat; *FDA,* US Food and Drug Administration; *FTC,* emtricitabine; *HBV,* hepatitis B virus; *HIV,* human immunodeficiency virus; *INSTI,* integrase strand transfer inhibitor; *LPV,* lopinavir; *NNRTI,* nonnucleoside reverse-transcriptase inhibitor; *NRTI,* nucleoside reverse-transcriptase inhibitor; *NtRTI,* nucleotide reverse-transcriptase inhibitor; *NVP,* nevirapine; *PI,* protease inhibitor; *PK,* pharmacokinetics; *RAL,* raltegravir; *RPV,* rilpivirine; *RTV,* ritonavir; *TAF,* tenofovir alafenamide; *TDF,* tenofovir disoproxil fumarate; *TDM,* therapeutic drug monitoring; *ZDV,* zidovudine.
Modified from US Public Health Service Task Force. Department of Health and Human Services. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated November 14, 2017. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

that has the potential to accelerate the goal of eliminating mother-to-child transmission of HIV worldwide.

Timing of Perinatal Transmission

HIV can be transmitted from a woman living with HIV to her child during intrauterine gestation, at delivery, or in the postpartum period through breastfeeding. HIV-1 has been isolated from fetal blood samples taken before elective terminations[197] and from fetal tissues at 8 weeks of gestation. In half of the infants who eventually are proven to be HIV-infected, HIV-1 can be identified by culture, polymerase chain reaction, or p24 antigen detection at or shortly after birth, which suggests that they were infected in utero before delivery.[198] HIV-infected infants who test negative for HIV by polymerase chain reaction or culture at birth may have been infected late in pregnancy or during birth. The differences in onset and progression of HIV infection in infants may reflect timing of infection, where infants infected earlier in pregnancy typically have more rapid progression to AIDS than infants infected at birth, who present with asymptomatic HIV infection and have prolonged survival.[199] Perinatal transmission is thought to occur near or during delivery in most cases.[192,200] Twin studies in the pre-ART era were used to further understanding of the timing of perinatal HIV transmission. Goedert and coworkers[201] studied 22 pairs of HIV seropositivity–discordant twins, and in 18 of the 22 pairs, the presenting twin was the infected sibling. Data from the International Registry of HIV-Exposed Twins suggest that the risk for infection in the twin who is born first is twice that in the second-born twin (26% and 13%, respectively).[201] The greater infection rates of first-born twins may be linked to increased contact with maternal secretions during birth.

Risk Factors for Perinatal Transmission

Perinatal transmission is a multifactorial process, influenced by viral, immune, and clinical factors in the mother and the infant (Table 126.6). Maternal plasma viral load is the strongest predictor of the risk for transmitting HIV perinatally.[202] In the pre-ART era, women with more advanced HIV disease and lower $CD4^+$ and higher $CD8^+$ T-cell counts were at increased risk to transmit HIV perinatally.[203,204] In a nested case-control study within a prospectively followed cohort of HIV-infected women, Thea and colleagues[205] found that high maternal viral load increased the likelihood of perinatal transmission in women without AIDS. Primary HIV infection in pregnancy or during breastfeeding associated with acute high-titer HIV viremia also is associated with increased rates of transmission. No threshold has been observed below which transmission does not occur; women with undetectable plasma HIV RNA have transmitted HIV perinatally. In a collaboration of studies, Ioannidis and coworkers[206] identified 44 cases of perinatal HIV-1 transmission among 1202 women with HIV-1 RNA viral loads less than 1000 copies/mL at delivery or at the measurement closest to delivery. The transmission rate was approximately 1% for women on ART, which was significantly lower than the 9.8% rate for untreated mothers. Multiple RNA measurements were obtained during pregnancy or at the time of delivery in 12 cases, of which 10 had a mean viral load greater than 500 copies/mL.[206] However, these are rare events, and perinatal HIV-1 transmission may be almost eliminated with combination ARV prophylaxis accompanied by complete and persistent suppression of maternal viremia.[192,206]

Use of ARV regimens for perinatal prophylaxis that are not completely suppressive (e.g., zidovudine [ZDV] or NVP monotherapy) may result in the development of resistance mutations and possibly increase the risk for perinatal transmission or progression in infected infants. Perinatal transmission of HIV with mutations associated with ZDV resistance has been described.[207] The current Recommendations for Use of Antiretroviral Drugs in Pregnant Women With HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States advise that all pregnant HIV-infected women should receive a combination ARV drug regimen to prevent perinatal transmission regardless of plasma HIV RNA copy number or $CD4^+$ cell count, and women with detectable HIV RNA should have ARV drug resistance studies performed before starting or modifying ART.[22]

Many reports have correlated perinatal transmission with numerous factors, including virologic, immunologic, sociodemographic, and lifestyle factors, which are listed in Table 126.6. Other factors are less well proven such as the role of HIV genotype. HIV-1 can be classified into at least nine different genotypes (clades) based on differences in the envelope region of the viral genome.[190] The distribution of subtypes differs around the world: Subtype B predominates in the United States and Europe; subtypes A, C, and D predominate in Africa; and subtypes B and E predominate in Thailand.[190] The role of subtypes in perinatal transmission is as yet undefined, but some epidemiologic studies have suggested that subtype E may be transmitted sexually more efficiently than subtype B, perhaps accounting for at least some of the differences in transmission rates seen between countries.[208]

In women with HIV who are not virally suppressed, various obstetric factors are believed to be associated with increased perinatal HIV transmission including chorioamnionitis; placenta previa; preterm delivery; and invasive interventions such as scalp monitoring, chorionic villus sampling, amniocentesis, cord blood sampling, and placental biopsy.[209,210]

TABLE 126.6 Potential Factors Influencing Perinatal Transmission of HIV Especially in the Setting of HIV Viremia

Maternal Factors
Lack of effective antiretroviral therapy
Advanced HIV disease as measured by
Clinical staging
Low $CD4^+$ lymphocyte count
Higher viral loads
p24 antigenemia
Primary HIV infection
Viral phenotype: syncytium inducing
Viral genotype: virulent mutant strain of HIV
Coinfection with other sexually transmitted diseases
First-born twins
Obstetric events
Vaginal delivery
Invasive procedures or fetal monitoring during labor
Prolonged premature rupture of membranes (>4 hours)
Older maternal age
Cigarette smoking and illicit drug use during pregnancy
Breastfeeding
Unprotected sexual intercourse with multiple partners
Fetal or Placental Factors
Chorioamnionitis
Prematurity
Low birth weight
Labor or Birth Canal Factors
Cervicovaginal viral load
Local HIV-specific immune response
Maternal-fetal transfusion of blood
Immune Factors
Humoral
Neutralizing antibody
Antibody-dependent cellular cytotoxicity
gp120 V3 loop antibody
MHC concordance and homozygosity
Maternal HLA-A*2301
Other
Cell Mediated
Cytotoxic T lymphocytes
$CD8^+$ suppression
Mucosal immunity
Other

HIV, Human immunodeficiency virus; *MHC,* major histocompatibility complex.
Modified from Sprecher S, Soumenkoff G, Puissant F, et al. Vertical transmission in a 15-week fetus. Lancet. *1986;2:228, © by The Lancet Ltd., 1986; and Bryson YJ. Perinatal HIV-1 transmission: recent advances and therapeutic interventions.* AIDS. *1996;3:533–542.*

In women on suppressive ART, data suggest that invasive procedures such as artificial rupture of membranes, amniocentesis, and episiotomy should be considered, if clinically indicated, as they would be for women without HIV. Promotion of safer sexual practices including condom use and limiting sexual partners and abstaining from drug, tobacco, and alcohol use also may reduce the risk for perinatal transmission.[192]

Use of Antiretroviral Drugs to Decrease Perinatal Transmission

The goals of ART in pregnancy are to optimize maternal health, to provide maximal suppression of the viral load, to prevent perinatal HIV transmission, to prevent horizontal HIV transmission to sexual partners, and to avoid potential maternal or fetal toxicity. This section reviews data on the use of ARV medications in pregnancy and the current guidelines for ART to decrease perinatal HIV transmission. In the subsequent section, the use of ARV medications in pregnancy and the optimal management of pregnant HIV-infected women are addressed.

Combination drug regimens are considered the standard of care for both the treatment of HIV infection and the prevention of perinatal HIV transmission.[146] One of the major achievements in HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group Protocol 076 Study (PACTG 076) in February 1994 that administration of ZDV to the pregnant woman and her infant could reduce the risk for perinatal transmission by 67.5%.[211,212] In PACTG 076, women with $CD4^+$ counts greater than 200 cells/mm^3 were randomly assigned to a ZDV treatment group or to a control group in which placebo was given. The women in the treatment group received 100 mg of ZDV five times daily starting between 14 and 34 weeks of gestation and continued throughout pregnancy, followed by intrapartum ZDV (given as an intravenous loading dose of 2 mg/kg over 1 hour during labor, then a continuous intravenous infusion of 1 mg/kg/h until delivery), with oral administration of ZDV to the infant (syrup 2 mg/kg every 6 hours) for 6 weeks. The rate of perinatal transmission was decreased to 8.3% in the 205 women who received ZDV from a rate of 25.5% in the 204 women who received no ART ($P = .00006$).[211] In August 1994, the US Public Health Service Task Force issued recommendations for the use of ZDV for reduction of perinatal HIV-1 transmission,[213] followed in July 1995 by recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with informed consent for all pregnant women in the United States.[214] Subsequent epidemiologic studies in the United States, France, and other countries with higher level health care resources showed successful use of the PACTG 076 ZDV regimen in the real world coupled with increased antenatal HIV counseling, and testing rapidly demonstrated dramatic reductions in perinatal transmission rates.[146,215,216]

Subsequent clinical trials and observational studies demonstrated that combination ARV prophylaxis (initially dual and then triple combination therapy) given to the mother antenatally was associated with further declines in transmission to less than 2%.[217–219] It is currently estimated that less than 100 infected infants are currently born each year in the United States.[5] However, although new perinatal HIV infections are becoming rare in countries with good access to health care resources, infections continue to occur, and the birth of an infected infant is a sentinel event representing missed opportunities and barriers to prevention of this infection.[146] Important obstacles to eradication of perinatal transmission of HIV in the United States include the continued incidence of HIV infection among women of childbearing age; delayed or lack of prenatal care, particularly in women with substance use or mental health issues; acute (primary) infection in pregnant women and in women who are breastfeeding; poor adherence to prescribed ARV regimens; and lack of full implementation of routine, universal prenatal HIV counseling and testing.[146]

Potential Mechanisms of Antiretroviral Drugs to Reduce Perinatal Transmission

There are several mechanisms through which ARV drugs can reduce perinatal transmission. One important mechanism is by decreasing maternal viral load in the blood and genital secretions via antenatal drug administration, particularly in women with high viral loads. However, ARV drugs have been shown to reduce the risk for transmission even among women with HIV RNA levels of less than 1000 copies/mL.[220] Additionally, the level of HIV RNA at delivery and receipt of antenatal ART are each independently associated with the risk for transmission, suggesting that ARV prophylaxis does not work solely through reduction in viral load.[212,218]

An additional mechanism of protection is preexposure infant prophylaxis provided by administration of ARV drugs that cross the placenta from the mother during labor, resulting in adequate systemic drug levels in the infant at a time of intensive exposure to maternal genital tract virus during passage through the birth canal.[146] Infant PrEP is provided through administration of drug to the infant after birth; this would protect against cell-free or cell-associated virus that might have obtained access to the fetal/infant systemic circulation through maternal-fetal transfusion during uterine contractions occurring in labor or through systemic dissemination of virus swallowed by the infant during passage through the birth canal.[146]

It is likely that efficacy of ARVs in reducing perinatal transmission is multifactorial, and each of these mechanisms is contributory. The efficacy of ARV regimens administered during labor or to the neonate or both in reducing perinatal transmission demonstrates the importance

of the preexposure and postexposure components of prophylaxis in decreasing perinatal transmission.[146,221–223]

Combination ARV regimens are far superior to single-drug regimens in decreasing HIV viral load and perinatal transmission. A longer three-part regimen (e.g., starting at or before 28 weeks of gestation) given antenatally, intrapartum, and postpartum was superior to a shorter two-part antepartum/intrapartum (e.g., starting at 36 weeks of gestation) or intrapartum/postpartum regimen in preventing perinatal transmission; hence current guidelines recommend that all pregnant women with HIV should be treated with combination suppressive ART as soon as possible, and that ART be continued for life.[146] Longer duration of ART in pregnancy has been associated with reduced transmission rates compared with shorter treatment duration.[146,224]

Research on the optimal management of infants born to women with HIV has informed the current Pediatric HIV Guidelines.[225] Data from PACTG 1043 showed that 1746 infants born to women living with HIV who received no ARV prophylaxis during pregnancy were randomly assigned to three infant prophylaxis regimens: the standard 6-week ZDV regimen; 6 weeks of ZDV plus three doses of NVP given during the first week of life (at birth, 48 hours later, and 96 hours after the second dose); and 6 weeks of ZDV plus 2 weeks of 3TC/nelfinavir.[146,217,226] The risk for intrapartum transmission was significantly lower with the two-drug and three-drug arms (2.2% and 2.5%, respectively) compared with ZDV alone (4.9%) ($P = .046$ for each arm compared with ZDV alone).[146] Although transmission rates with the two combination regimens were similar, neutropenia and anemia have been associated with the three-drug regimens, including 3TC in infants.[146,226] In the United States, data from PACTG 316 demonstrated that the addition of a two-dose oral NVP regimen (200 mg intrapartum/2 mg/kg dose to neonates) to the standard antepartum combination ARV regimens used for prophylaxis or treatment in pregnant women is not recommended because it does not appear to provide additional efficacy in reducing transmission and may be associated with the development of NVP resistance.[146,217]

Impact of Pregnancy on HIV Infection

Although both pregnancy and HIV infection are immunosuppressive conditions, large studies in the United States and Europe failed to show that pregnancy accelerates HIV replication or disease progression, even in the pre-ART era.[227–229] Pregnancy does not seem to result in acceleration of HIV disease in most HIV-infected women; however, women with more advanced disease who are not virally suppressed tend to experience disease progression over a shorter period than that typical of women with less advanced disease, suggesting that the pregnancy may enhance progression of HIV disease in such cases.[230]

Impact of HIV Infection on Pregnancy Outcomes

Women taking ART may be at increased risk for adverse pregnancy outcomes including preterm birth or delivery (delivery before 37 weeks of gestation), low-birth-weight infants (<2500 g), and small-for-gestational-age infants (birth weight <10th percentile expected for gestational age).[194] Most studies that showed an association between HIV and adverse pregnancy outcomes involved women not on ARV or starting ART. A large meta-analysis of 11,224 women in 14 European and American studies did not demonstrate, for example, an increased rate of preterm delivery among women using ART during pregnancy.[231] The PROMISE trial compared ZDV alone with lopinavir/ritonavir–based ART combined with a dual nucleoside reverse-transcriptase inhibitor (NRTI) backbone of either ZDV/3TC or TDF/FTC.[232] Compared with women receiving ZDV alone, higher rates of extremely preterm delivery were reported in women receiving ZDV/3TC/lopinavir/ritonavir ($P < .001$), but not in women receiving TDF/FTC/lopinavir/ritonavir ($P = .77$). In contrast, extremely preterm delivery rates were higher among women receiving TDF/FTC/lopinavir/ritonavir than women receiving ZDV/3TC/lopinavir/ritonavir ($P = .04$).[233] These rates of very preterm delivery were not significantly different compared with women receiving ZDV alone ($P = .10$). The potential mechanism of action by which protease inhibitors may increase a woman's risk of preterm delivery is unknown.

Of the 15 studies that have addressed effects of ART on birth weight, 5 demonstrated an association between any ART use and low birth weight.[22] When comparing the initiation of monotherapy in pregnancy versus ART initiated before pregnancy and continued during pregnancy, ART was associated with small gestational weight for age (HR, 1.34; 95% CI, 1.05–1.7).[233] Zash and colleagues[234] reported on an observational birth outcomes surveillance study in Botswana that compared all live births and stillbirths (>24 weeks) with exposure to three-drug ART from conception. Among 11,932 HIV-exposed infants, 5780 (48.4%) were exposed to ART from conception. Adverse birth outcomes were more common among HIV-exposed infants than infants not exposed to HIV (39.6% vs. 28.9%; adjusted relative risk [RR], 1.40; 95% CI, 1.36–1.44). The risk for any adverse birth outcome was lower among infants exposed from conception to TDF, FTC, and EFV compared with other ART regimens including NVP-based and lopinavir/ritonavir–based ART.[234] As ART becomes more widely available for pregnant women in settings with limited health care resources, it will be critical to monitor carefully pregnancy outcomes, including congenital anomalies, preterm birth, stillbirth, and infant mortality, to assess risks and benefits of the different regimens used to treat women living with HIV and maximize HIV-free survival in infants.[22]

Antepartum Care of Women Living With HIV

Medical care of the pregnant woman living with HIV requires coordination and communication among prenatal care providers, primary and HIV specialty care providers, obstetric providers, and other needed service providers including mental health and drug abuse treatment services and public assistance programs.[146] An initial evaluation of a pregnant woman living with HIV should include an assessment of HIV disease status and recommendations regarding initiating, continuing, or modifying ART (see Chapter 128). In addition to the usual antenatal assessments, this assessment should include evaluating past and current $CD4^+$ count, current plasma HIV RNA copy number, past and current ART, and previous ARV drug use in pregnancy; assessing the need for prophylaxis against opportunistic infections such as *Pneumocystis jirovecii* pneumonia or *Mycobacterium avium* complex; and reviewing results of previous and current HIV ARV drug resistance studies, prior HLA B5701 assays, and assessing supportive care needs.[22] The history should identify any factors known to be associated with enhanced perinatal transmission such as a history of STIs, drug and alcohol use, tobacco use, and high-risk sexual activity including lack of condom use, as altering these practices may decrease perinatal transmission risk. A complete physical examination including a pelvic examination can reveal concurrent conditions that may warrant therapy. Plasma HIV RNA levels of pregnant women with HIV should be monitored at the initial visit, 2 to 4 weeks after initiating or changing ARV medications, monthly until RNA levels are undetectable, and then at least every 3 months during pregnancy.[146] HIV RNA levels also should be assessed at approximately 34 to 36 weeks of gestation to inform decisions about mode of delivery and about optimal treatment of the newborn (see Chapter 127). $CD4^+$ count should be monitored at the initial antenatal visit and every 3 to 6 months during pregnancy. HIV drug resistance studies should be performed before starting ARV regimens in all ARV-naïve women whose HIV RNA levels are above the threshold for resistance testing (i.e.>500 to 1000 copies/mL) or who have suboptimal virologic response to ART started during pregnancy; however, therapy should not be delayed while waiting for resistance testing results. ART may need to be modified based on resistance assay result. Ongoing routine obstetric care and decisions about initiating, continuing, or adjusting ART should be the same as for nonpregnant women living with HIV.

DHHS guidelines recommend advising women living with HIV in the United States and other regions with good health care resources where safe alternative infant feedings exist to refrain from breastfeeding to avoid postnatal transmission of HIV to their infants through breast milk.[235] Women living with HIV should also avoid premastication of food for their infants, a potential risk factor for transmission.[236,237]

Decisions regarding the use and choice of an ARV regimen should be individualized based on the woman's health, previous treatment, and known or suspected drug resistance. The known benefits and known

and unknown risks of such therapy during pregnancy should be considered and discussed (see Table 126.5). Risks of these drugs during pregnancy should be placed in perspective by also discussing benefits of ART for the health of the infected woman and for reducing the risk for HIV transmission to her infant. The importance of adherence to ART should be emphasized. Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment may be essential to ensure adherence of the infected woman to ART regimens and ultimate success of ART for her own health and for preventing perinatal transmission.[22]

Although the risk for teratogenicity is greatest during the first 10 weeks of gestation, data to date do not support major teratogenic effects of any of the ARV drugs.[146] In most cases, women who present for obstetric care on fully suppressive ARV regimens should continue their current regimens. All pregnant women should initiate ART as soon as possible, including in the first trimester. The clinical, immunologic, and virologic status of the mother must be weighed against the potential effect on the fetus. Discontinuing ARV medications may result in a rebound of viral load, however, which may have an impact on HIV transmission, disease progression, and subsequent ability to obtain rapid virologic control. Although the rates of HIV infection are low in women with undetectable or low HIV RNA levels, there is no threshold below which the lack of transmission can be ensured.[146] Dual combination therapy (i.e., ZDV/3TC) without the addition of a third drug (i.e., protease inhibitor, NNRTI, or integrase strand inhibitor) is not recommended because of the potential for inadequate viral suppression and rapid development of resistance, most commonly the M184V mutation.[146,238]

HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs

All pregnant women living with HIV should receive potent combination ART, regardless of CD4$^+$ count or plasma HIV RNA copy number, that generally consists of two NRTIs plus an integrase strand inhibitor, NNRTI, or boosted protease inhibitor, with consideration regarding continuing the ARV regimen after delivery being the same as for nonpregnant individuals (Table 126.7).[189] Studies of ZDV in prevention of perinatal transmission suggest that an important mechanism of infant PrEP is transplacental drug passage. Thus when selecting an ARV regimen for pregnant women, the two preferred dual NRTI agent backbones with high placental transfer include abacavir (ABC), 3TC, FTC, and TDF.[146] Although ZDV/3TC was a preferred NRTI combination for ARV-naïve pregnant women in the past, based on efficacy studies in preventing perinatal transmission and extensive experience with safe use in pregnancy, this combination is now an alternative regimen due to known side effects, and ABC/3TC (fixed-dose combination), TDF/FTC (fixed-dose combination), and TDF/3TC are now considered preferred NRTIs (see Table 126.7). TDF/FTC and ABC/3TC are the preferred two NRTI components for pregnant adults with HIV based on increased experience with use in pregnancy, availability as a single combination tablet with once-daily dosing, enhanced activity against hepatitis B, and less frequent toxicity compared with ZDV/3TC. As TDF has potential renal toxicity, TDF-based dual NRTI combinations should be used with caution in patients with renal toxicity. Although tenofovir alafenamide (TAF), a prodrug of tenofovir, has shown improvements in renal function and bone density, there are inadequate studies

TABLE 126.7 Initial Combination Regimens for Antiretroviral-Naïve Pregnant Women

	DRUGS	COMMENTS
Preferred Regimens		
Two-NRTI backbones	ABC/3TC	Available as fixed-dose combination; can be administered once daily; should not be used if HLA-B*5701–positive because of risk of hypersensitivity reaction or with ATV/r or with EFV if pretreatment HIV RNA >100,000 copies/mL
	TDF/FTC or TDF/3TC	Fixed-dose combination available and can be given once daily; TDF has potential renal toxicity and should be used with caution in patients with renal insufficiency
PI regimens	ATV/r + preferred two-NRTI backbone	Once-daily administration; extensive experience in pregnancy; maternal hyperbilirubinemia; no clinically significant neonatal hyperbilirubinemia or kernicterus reported, but neonatal bilirubin monitoring recommended; cannot be administered with proton-pump inhibitors; specific timing recommended for dosing with H2 blockers
	DRV/r + preferred two-NRTI backbone	Better tolerated than LPV/r; increasing use in pregnancy; given twice daily in pregnancy
INSTI regimen	RAL + preferred two-NRTI backbone	Increasing experience in pregnancy; rapid viral load reduction; twice-daily administration; avoids drug interactions with PIs
Alternative Regimens		
Alternative NRTI backbone	ZDV/3TC	Fixed-dose combination available; must be given twice daily; potential for hematologic toxicity
Alternative PI regimen	LPV/r + preferred two-NRTI backbone	Abundant experience in pregnancy; more nausea than preferred agents; twice-daily administration; dose increase recommended in third trimester
Alternative NNRTI regimen	EFV + preferred two-NRTI backbone	Concern because of birth defects in primate study; risk in humans is unclear; convenient single tablet; once-daily regimen; avoids drug interactions with PIs; screening for antenatal and postpartum depression is recommended
Alternative NNRTI regimen	RPV/TDF/FTC (or RPV + preferred two-NRTI backbone)	RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4$^+$ count <200 cells/mm^3; do not use with proton-pump inhibitor; available in co-formulated single pill; once-daily regimen
Insufficient Data in Pregnancy to Recommend Routine Use in ART-Naïve Women		
	BIC, COBI, EVG/COBI/TDF/FTC fixed-drug combination, EVG/COBI/TAF/FTC fixed-drug combination, FPV, MVC	
Not Recommended for Use in ART-Naïve Pregnant Women		
	d4T, ddI, FPV/r, IDV/r, NFV, RTV, SQV/r, ETR, NVP, T20, TPV/r, ABC/3TC/ZDV regimen by itself	

[a]Drugs are listed alphabetically. See Table 126.5 for additional information regarding individual drugs.
3TC, Lamivudine; *ABC,* abacavir; *ART,* antiretroviral therapy; *ARV,* antiretroviral; *ATV/r,* atazanavir/ritonavir; *BIC,* bictegravir, *COBI,* cobicistat; *d4T,* stavudine; *ddI,* didanosine; *DRV/r,* darunavir/ritonavir; *DTG,* dolutegravir; *EFV,* efavirenz; *ETR,* etravirine; *EVG,* elvitegravir; *FPV/r,* fosamprenavir/ritonavir; *FTC,* emtricitabine; *HIV,* human immunodeficiency virus; *IDV/r,* indinavir/ritonavir; *INSTI,* integrase strand transfer inhibitor; *LPV/r,* lopinavir/ritonavir; *MVC,* maraviroc; *NFV,* nelfinavir; *NRTI,* nucleoside reverse-transcriptase inhibitor; *NNRTI,* nonnucleoside reverse transcriptase inhibitor; *NVP,* nevirapine; *PI,* protease inhibitor; *RAL,* raltegravir; *RPV,* rilpivirine; *RTV,* ritonavir; *SQV/r,* saquinavir/ritonavir; *T20,* enfuvirtide; *TAF,* tenofovir alafenamide; *TDF,* tenofovir disoproxil fumarate; *TPV,* tipranavir; *T20,* enfuvirtide; *ZDV,* zidovudine.
Modified from US Public Health Service Task Force. Department of Health and Human Services. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated November 14, 2017. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

of its use in pregnancy, and thus it cannot be recommended for use in pregnancy at this time.[146]

The important study HPTN 052, a multinational, randomized trial evaluating treatment of HIV-infected individuals within serostatus-discordant couples, demonstrated that immediate initiation of ART among HIV-infected participants with $CD4^+$ counts between 350 cell/mm^3 and 500 cell/mm^3 reduced both HIV-related events or death and sexual transmission of HIV to their HIV-negative partners by more than 96%.[122] Of the 28 transmissions that were virologically linked to the infected partner, only 1 occurred in the immediate-therapy arm compared with participants who started ART only after their $CD4^+$ counts decreased to less than 250 cells/mm^3 (deferred study arm) (HR, 0.04; 95% CI, 0.01–0.27; $P < .001$).[98] All pregnant women should be initiated or maintained on a combination ART regimen during pregnancy to prevent perinatal transmission and to continue on suppressive ART lifelong, given current data on the benefits and risks to the woman and its prevention of sexual transmission to her sexual partners.[146]

HIV-Infected Pregnant Women Who Are Currently Receiving Antiretroviral Therapy

Women who have been receiving ART for HIV infection should generally continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load, a subsequent decline in immune status, disease progression, and adverse consequences for both the fetus and the woman including increased risk for transmission. EFV, an alternative NNRTI for nonpregnant adults, is now also an alternative NNRTI for pregnant women with HIV who have started it before pregnancy. There have been concerns regarding use of EFV in the first trimester and potential for neural tube defects based on nonhuman primate data and retrospective case reports. However, an updated meta-analysis including data on 2026 women with first-trimester EFV exposure from 21 prospective studies did not find an increased relative risk of overall birth defects in infants born to women receiving EFV-based versus non–EFV-based regimens (RR, 0.78; 95% CI, 0.56–1.08).[195] Because unnecessary ARV drug changes during pregnancy may be associated with loss of viral control and increased risk for perinatal transmission, EFV-based regimens may be continued in pregnant women, provided that the ARV regimen is well tolerated and results in virologic suppression. In women who present on drugs not recommended for initial use because of concerns about viral breakthrough (i.e., fixed-dose combinations of EVG/COBI/TDF/FTC or EVG/COBI/TAF/FTC), providers should consider switching to more effective recommended regimens. If an EVG/COBI regimen is continued, viral load should be monitored frequently, and therapeutic drug monitoring (if available) may be useful.[146]

Stopping Antiretroviral Therapy During Pregnancy

Discontinuation of ART during pregnancy may be indicated in some situations including serious treatment-related toxicity, pregnancy-induced hyperemesis, acute illnesses or planned surgeries that preclude oral intake, lack of available medication, and patient request.[146] Women who are having an elective cesarean section can take oral medications before the scheduled surgery and restart drugs after surgery; given that most ARV medications are now given once or twice daily, the women either would not miss any doses or at most receive the postpartum dose a few hours late.[146]

If discontinuation of ART is indicated, all ARV drugs should be stopped simultaneously and reintroduced simultaneously as soon as possible. However, drugs with long half-lives such as NVP and EFV may be detected for 21 days or longer after discontinuation.[239–241] As other drugs with shorter half-lives are cleared, only the NNRTI may persist, resulting in functional monotherapy that can increase the risk for selection of NNRTI-resistant mutations. To prevent this functional monotherapy, some experts recommend either stopping the NNRTI first and continuing the other ARV drugs for a period of time[240] (at least 7 days is recommended) or switching from an NNRTI-based regimen to a protease inhibitor–based regimen or integrase inhibitor–based regimen.[146] The current recommendation is for lifelong ART, so most experts would recommend switching to another better-tolerated regimen with the goal of obtaining and then maintaining viral suppression.

HIV-Infected Pregnant Women Who Have Previously Received Antiretroviral Therapy but Are Not Currently Receiving Medication

There is concern that some women with previous time-limited use of ARV drugs during previous pregnancies may have developed genotypic resistance to one or more components of the initial ARV regimen, potentially limiting the efficacy of standard regimens (i.e., regimens containing the dual NRTI backbone of ZDV/3TC or ABC/3TC). Given the lack of substantive data, it is reasonable to make preliminary decisions about ARV regimens based on results of previous resistance testing. In general, ART should be initiated before receiving results of current ARV resistance studies because longer ART has been associated with reduced transmission rates compared with shorter treatment periods.[224,242] Careful monitoring of virologic response to the chosen ARV regimen is important, and adjustments to therapy should be guided by repeat resistance testing in consultation with a clinician experienced in HIV treatment.

Monitoring of the Woman and Fetus During Pregnancy

Plasma HIV RNA levels of pregnant women with HIV should be monitored at the initial visit, 2 to 4 weeks after initiating or changing ARV drug regimens, monthly until RNA levels are undetectable, and at least every 3 months during pregnancy. HIV RNA levels (viral load) should also be assessed at 34 to 36 weeks of gestation to inform decisions about mode of delivery and about optimal treatment of the newborn (see "Risk Factors for Perinatal Transmission").[146] The recommended monitoring of viral load in pregnancy is more frequent than in nonpregnant women because of the need to lower viral load as rapidly as possible to decrease transmission risk.

$CD4^+$ counts should be monitored at the initial antenatal visit and every 3 to 6 months in pregnant patients on ART. Monitoring of $CD4^+$ count can be performed every 6 months in patients on combination ART with consistently suppressed viral load who have $CD4^+$ counts well above the threshold for opportunistic infection risk.[146]

ARV drug resistance testing should be performed on women who have persistently detectable plasma HIV RNA levels despite receiving ARV drugs. Because NRTI drugs may be associated with development of lactic acidosis, pregnant women receiving NRTI drugs should have hepatic enzymes and electrolytes monitored more frequently, and any new symptoms of potential hepatotoxicity should be evaluated thoroughly.

Because of physiologic changes such as hemodilution during pregnancy, the CD4 T-cell percentage may be more stable than the absolute $CD4^+$ count during pregnancy.[243] Monitoring for complications of ARV drugs during pregnancy should be based on what is known about side effects of the drugs that the woman is receiving (see Table 126.5). An ultrasound scan in the first trimester is recommended for confirmation of gestational age and to guide potential timing of scheduled cesarean delivery, if needed, as scheduled cesarean deliveries for prevention of HIV transmission should be performed at 38 weeks of gestation in the setting of maternal HIV viremia.[146] Most experts would recommend assessment of fetal anatomy in women who have received combination ART, given the limited data on the effect of combination therapy on the fetus. If the patient is not seen until later in gestation, second-trimester ultrasound can be performed to both scan anatomy and determine gestational age.[146]

Although data are still limited, the risk for transmission does not appear to be increased with amniocentesis or other invasive diagnostic procedures in women receiving effective ART resulting in viral suppression.[244,245] This is in contrast to the pre-ART era, when amniocentesis and chorionic villus sampling were associated with a 2- to 4-fold increased risk for perinatal transmission (see "Risk Factors for Perinatal Transmission," earlier). Some experts consider chorionic villus sampling and cordocentesis too risky to offer to women living with HIV and recommend limiting invasive procedures to amniocentesis, but existing data on transmission risk associated with these procedures are limited.[246]

Women with HIV receiving ART during pregnancy should receive glucose screening with a standard 1-hour, 50-g glucose loading test at 24 to 28 weeks of gestation.[146] Some experts recommend performing earlier glucose screening in women with ongoing protease inhibitor–based therapy initiated before pregnancy, similar to recommendations for women with a high-risk factor for glucose intolerance such as maternal obesity, advanced maternal age, and family history of diabetes mellitus.[146]

Teratogenicity

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself but also on the dose ingested; the gestational age of the fetus at exposure; the duration of exposure; the interaction with other agents to which the fetus is exposed; and, to an unknown extent, the genetic makeup of the mother and the fetus.[146] Based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester compared with later ARV drug exposures, women can be counseled that ART during pregnancy generally does not increase the risk of birth defects.

EFV use in pregnancy has received increased scrutiny because of studies on small nonhuman primates. Significant malformations were observed in 3 of 20 infant cynomolgus monkeys receiving EFV from gestational days 20 to 150 at a dose resulting in plasma concentrations comparable to systemic human exposure at therapeutic dosage.[247] The malformations included anencephaly and unilateral anophthalmia in one monkey, microphthalmia in one monkey, and cleft palate in the third monkey. In humans, sufficient numbers of first-trimester exposures to EFV have been monitored in the APR to detect at least a twofold increase in the risk of overall birth defects, without any such increase detected. The current Perinatal Guidelines do not include the restriction of use before 8 weeks of gestation, consistent with both the British HIV Association and WHO guidelines for use of ARV drugs in pregnancy (which note that EFV can be used throughout pregnancy).[146]

The major toxicity of NRTIs is related to effects on mitochondrial DNA synthesis; these drugs have varying affinity for mitochondrial DNA polymerase gamma, resulting in depletion and dysfunction of mitochondrial DNA.[146] Clinical disorders linked to mitochondrial toxicity may be subtle (mild peripheral neuropathy or myopathy) or fulminant (hepatic steatosis, lactic acidosis, and liver failure). The relative potency of NRTIs in inhibiting mitochondrial DNA polymerase gamma in vitro is highest for zalcitabine, followed by didanosine, stavudine, ZDV, 3TC, ABC, and TDF (TAF).[147] Toxicity related to mitochondrial dysfunction has been reported to occur in infected patients receiving long-term treatment with NRTIs and generally has resolved with discontinuation of the drugs; a possible genetic susceptibility to these toxicities has been suggested.[248]

A comprehensive review of use of TDF in pregnant women for treatment of HIV or hepatitis B (or for PrEP) found no evidence of an increased risk of pregnancy loss, stillbirth, preterm birth, small gestational weight for age, or infant mortality compared with similar women receiving placebo or alternate ARV drug regimens.[249] In the APR, sufficient numbers of first-trimester exposures have been monitored to detect at least a 2-fold increase in risk of overall birth defects for darunavir, didanosine, EFV, indinavir, raltegravir, rilpivirine, and stavudine; no such increases have been detected to date. For ABC, atazanavir, FTC, 3TC, lopinavir, nelfinavir, NVP, ritonavir, TDF, and ZDV, sufficient numbers of first-trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems; no such increases have been detected to date.[146] Human data on teratogenicity of all ARV agents approved by the US Food and Drug Administration (FDA) can be found in Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy of the Perinatal Guidelines[146] and are briefly summarized in Table 126.5.

Intrapartum Antiretroviral Therapy

Women should continue taking antepartum combination ART on schedule as much as possible during labor and before scheduled cesarean delivery.[146] Intravenous ZDV administration is recommended for pregnant women with HIV RNA greater than 1000 copies/mL or unknown HIV RNA levels near delivery, regardless of antepartum regimen or mode of delivery. Many experts choose to continue to give intravenous ZDV to all HIV-positive women during labor and to neonates regardless of the antepartum ARV regimen, even though intrapartum prophylaxis has not been associated with a lower risk for transmission in women with HIV RNA less than 400 copies/mL at delivery.[146] There are inadequate data to determine whether administration of intravenous ZDV to women with HIV RNA between 50 and 999 copies/mL provides any additional protection against perinatal transmission, but some experts recommend administering intravenous ZDV to these women because the transmission risk is slightly higher when HIV RNA is in the range of 50 to 999 copies/mL compared to <50 copies/mL.[146]

For women who have received antepartum ARV drugs but have suboptimal viral suppression near delivery (i.e., HIV RNA >1000 copies/mL), scheduled cesarean delivery at 38 weeks of gestation is recommended to minimize perinatal transmission of HIV, and intravenous ZDV administration should begin 3 hours before the scheduled operative delivery.[146] If ZDV was not used in the antenatal ART regimen because of known or suspected ZDV resistance, intrapartum ZDV is still recommended in women with HIV RNA >1000 copies/mL near delivery except in women with documented histories of hypersensitivity. The addition of intrapartum/neonatal single-dose NVP is not recommended.[146]

Women with unknown HIV status who present in labor should have rapid HIV antibody testing performed and intravenous ZDV initiated if the test is positive (without waiting for results of the confirmatory test) and infant ZDV therapy initiated.[146] Factors that may increase risk of infection include diagnosis of a sexually transmitted disease, illicit drug use, exchange of sex for money or drugs, multiple sexual partners during pregnancy, a sexual partner at risk of or with known HIV infection, signs and symptoms of acute HIV infection, or living in a region with an elevated incidence of HIV in women of childbearing age.[146] If the expedited antigen/antibody results are positive, an HIV-1/HIV-2 antibody differentiation test and an HIV-1 RNA assay should be done as soon as possible; maternal (intravenous ZDV) and infant (combination ARV prophylaxis) ARV drugs should be initiated pending results of the differentiation test. If the follow-up HIV antibody testing is negative, results of the HIV RNA test should be reviewed to rule out acute infection as a cause of the initial positive test before ART is stopped. The choice of intrapartum/postpartum ART regimen for women without antepartum ART should include intravenous ZDV immediately to prevent perinatal transmission of HIV. Although intrapartum/neonatal ARV medications will not prevent perinatal transmission that occurred before labor, most transmission occurs near to or during labor and delivery.[146]

PrEP for the fetus can be provided by giving mothers a drug that rapidly crosses the placenta, producing fetal systemic ARV drug levels during intensive exposure to HIV in maternal genital secretions and in blood during birth. Most experts recommend ARV agents that cross the placenta well; ZDV and other NRTIs, NNRTIs, and the integrase strand inhibitor raltegravir cross the placenta well, whereas protease inhibitors do not (see Table 126.5). If HIV antibody is positive, adding ARV agents to the neonatal portion of the intrapartum/neonatal ZDV regimen can further reduce perinatal transmission of HIV for mothers who have received no antepartum ARV drugs (see "Care of Newborn").[146]

If HIV antibody is negative, infant ARVs can be stopped.[146] In the past, HIV was considered a relative contraindication to operative vaginal delivery with forceps or vacuum. More recent data from greater than 3000 deliveries between 2008 and 2016 suggest that operative delivery, if indicated based on best obstetric practices, is a safe option in women who are virally suppressed.[146,245]

Artificial rupture of membranes performed in the setting of ART and virologic suppression is not associated with increased risk of perinatal transmission and can be performed for standard obstetric indications.[146] Women experiencing postpartum hemorrhage due to uterine atony are often managed with oral or parenteral methylergonovine (Methergine) or other ergot alkaloid as a first-line agent. However, methylergonovine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors such as protease inhibitors and COBI. The concomitant use of ergotamines and these CYP3A4-inhibiting drugs has been associated with exaggerated vasoconstrictive responses. If alternative treatments for postpartum hemorrhages are not available, methylergonovine should be used in as low a dose and for as short a time as possible.[146]

Practitioners who provide health care for HIV-infected pregnant women and their neonates should report prospectively all cases of prenatal exposure to any ARV medication (either alone or in combination) to the APR (Research Park, 1011 Ashes Drive, Wilmington, NC 28405; telephone: 1-800-258-4263; fax: 1-800-800-1052; www.APRegistry.com).[194] Treatment and prophylaxis of opportunistic infections during pregnancy should follow guidelines similar to those for nonpregnant women.[250] Pregnant women who develop active opportunistic infections including tuberculosis should receive a drug regimen developed by obstetric and infectious diseases specialists. As with ARV medications, the potential benefits of prophylactic agents must be weighed against their potential risks. Pneumococcal, hepatitis B, and inactivated influenza vaccines may be given if indicated during pregnancy. Live vaccines such as for rubella, measles, mumps, and varicella are contraindicated in patients with severe immunosuppression ($CD4^+$ count <200 cells/mm^3) and during pregnancy, labor, and the early postpartum period.

Care of Newborn

Currently all newborns perinatally exposed to HIV should receive postpartum ARV drugs to reduce the risk of perinatal transmission of HIV.[146] The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission. The uses of ARV regimens in newborns include the following:

- **ARV prophylaxis:** The administration of one or more ARV drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition.
- **Empirical HIV therapy:** The administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empirical HIV therapy is intended to be preliminary treatment for a newborn who is later confirmed to have HIV but also serves as prophylaxis against HIV acquisition for newborns who are exposed to HIV in utero, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV therapy:** The administration of a three-drug combination ARV regimen at treatment dosages (ART) to newborns with confirmed HIV infection (see Tables 127.2 and 127.3).[146]

For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week ZDV prophylaxis regimen can be used. Newborns at higher risk of HIV acquisition should receive a combination ARV regimen, ARV prophylaxis, or empiric HIV therapy based on the clinician's assessment of risk.[146] Newborns of women with unknown HIV status who test positive on expedited HIV testing performed during labor or shortly after birth should be initiated on an ARV regimen based on the clinician's assessment of risk. If supplemental testing is negative, the ARV regimen can be discontinued. For newborns with confirmed HIV, ART should be initiated as soon as possible. In the United States, the use of ARV drugs other than ZDV, 3TC, and NVP cannot be recommended for any indication in premature newborns (<37 weeks of gestational age) because of lack of dosing and safety data.[146] Providers with questions about ARV management of perinatal HIV exposure should consult the Clinician Consultation Center at the University of California, San Francisco for perinatal HIV consultation at 1-888-448-8765, which provides free clinical consultation on all aspects of perinatal HIV including newborn care.

Postpartum Follow-Up of HIV-Infected Women

ART should be continued in all HIV-infected women after delivery to reduce the risk of disease progression and to prevent HIV sexual transmission. Plans for modifying ART after delivery should be made in consultation with the woman and her HIV care provider, ideally before delivery, taking into consideration the preferred regimens for nonpregnant adults.[146] The immediate postpartum period poses unique challenges for ART adherence,[251–254] and new or continued supportive services including mental health and substance abuse treatment should be ensured before hospital discharge. A number of studies have suggested that postpartum depression is common among women with HIV.[255] The US Preventive Services Task Force recommends screening all women for postpartum depression using a validated tool; this is especially important for women living with HIV who appear to be at increased risk for postpartum depression and for poorer ART adherence during the postpartum period. Women should be counseled that postpartum physical and psychological changes and the stresses and demands of caring for an infant may make adherence more difficult, and additional support may be needed during this period.[146]

Women with a positive rapid HIV antigen/antibody test result during labor require comprehensive follow-up. This comprises confirmation of HIV infection, full health assessment including evaluation for associated medical conditions, counseling related to newly diagnosed HIV infection, and assessment of the need for opportunistic infection prophylaxis.[146]

Breastfeeding is not recommended for women living with HIV in the United States, where safe, affordable, and feasible alternatives are available and culturally acceptable. However, clinicians should be aware that women may face social, familial, and personal pressures from cultures where breastfeeding is important, as women may fear that formula feeding would reveal their HIV status.[146] Therefore it is important to address these possible barriers to formula feeding during the antenatal period.

Contraceptive counseling is a critical aspect of postpartum care. Although condoms are universally recommended for prevention of STI and HIV transmission, the unintended pregnancy rate with condom use alone is high. The postpartum period provides an opportunity to review and optimize women's health care including cervical cancer screening; routine immunizations; future reproduction options and need for contraception; mental health and substance abuse treatment as indicated; and assessment for signs of postpartum depression and alcohol and drug use, which may interfere with adherence.[146,235,251] For a detailed discussion of postnatal care of neonates born to women living with HIV, see Chapter 127.

Guidelines for prevention of perinatal HIV and information on the management of HIV during pregnancy are changing rapidly. The reader is encouraged to obtain the most current information about HIV and women from up-to-date sources on the Internet. One of the best sources on HIV/AIDS is AIDS*info* (see "Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States"), which offers current information on research, clinical trials, and treatment to patients and health care providers.[22] There are links to the most current guidelines for management of women during pregnancy and for information on the safety and toxicity of ARV agents in pregnancy.[146] The US government also has published *A Guide to the Clinical Care of Women with HIV/AIDS, 2013 Edition* (https://hab.hrsa.gov/sites/default/files/hab/clinical-quality-management/womenwithaids.pdf). Because optimal HIV care must be individualized and incorporate rapidly changing knowledge, consultation with an HIV/AIDS expert is strongly recommended.

CLINICAL MANIFESTATIONS OF HIV INFECTION IN WOMEN

In the beginning of the HIV epidemic, initial data on clinical manifestations of HIV infection were derived from predominantly male cohorts. Subsequent data on the clinical manifestations of HIV infection in women suggested few sex differences in nongynecologic opportunistic processes and HIV disease progression. Women can present with gynecologic disease, however, that is influenced by their HIV-induced immunosuppression, as summarized in this section.

Opportunistic Processes and Nongynecologic Malignancies

Although Kaposi sarcoma is infrequent among women, HIV infection dramatically increases the risk for this malignancy. In the multicenter Women's HIV Interagency Study (WIHS), the largest cohort study of HIV infection in HIV-infected and at-risk women in the United States, the standardized incidence ratio for this malignancy was 275.8.[256] Kaposi sarcoma has a different presentation in women than in men. Women with this malignancy may have a highly aggressive disease course and an increased incidence of noncutaneous disease, lymphedema, lymph

node disease, and visceral Kaposi sarcoma.[257] Radiographic findings can include nodular opacities, peribronchovascular opacities, thickened interlobular septa, pleural effusions, and lymphadenopathy.[258] Women also may have gynecologic involvement. There is at least one case report of Kaposi sarcoma manifesting as a vulvar mass[259] and two cases diagnosed by cervical biopsy.[260]

The incidence of non–AIDS-defining cancers in patients living with HIV has increased more recently. In a cohort of Italian patients from 1985 to 2011, the incidence rates before and after the introduction of ART were examined, and standardized incidence ratios (SIRs) were used to compare the cancer risk of subjects with HIV with the age-matched and sex-matched general population.[261] In women, the risks were higher than expected for cancer of the vulva (SIR, 69.2), Hodgkin lymphoma (SIR, 7.5), anal cancer (SIR, 41.2), and lung cancer (SIR, 4.8). However, in a more recent review in the United States, the incident lung cancer rates among WIHS participants found these rates did not differ by HIV status or by time period (before ART vs. after ART).[262] Women with HIV and lung cancer are typically young smokers (mean age, 40 years) with stage IV adenocarcinoma who have a poor prognosis. All WIHS women with lung cancer were noted to be smokers, and the risk increased with cumulative tobacco exposure.[262]

Multiple reviews of breast cancer have not found an excess incidence among women with HIV compared with women without HIV. Patients with HIV infection and breast cancer tend to present with more advanced stage and aggressive disease.[263] A summary of case reports of women in the pre-ART era found histopathology results uniformly describing poorly differentiated or undifferentiated tumors. These reviews substantiate the observation that women with HIV and breast cancer generally, but not always, present at a younger age and have increased bilateral disease, unusual histology, and a poorer outcome compared with women without HIV.[263] Chemotherapy-induced myelosuppression can be problematic, and patients often require hematopoietic growth factor and dose reduction during treatment of their breast cancer.[264]

Population studies of women with HIV have shown lower than expected cases of breast cancer in selected African and Western countries.[265] One explanation is competing mortality. Pantanowitz and Dezube[265] offer additional hypotheses including the possibility that the immunodeficiency state may be protective and women with HIV could have fewer risk factors compared with the general female population. HIV infection may actually be protective for breast cancer at the molecular level. Neoplastic breast cells express *CXCR4,* but not *CCR5*. In vitro, binding of HIV to the *CXCR4* receptor induces apoptosis of neoplastic breast cells.[266] In a nested case-control study among WIHS and HIV Epidemiology Research Study (HERS) participants living with HIV, a significantly higher proportion of the controls had *CXCR4*-tropic HIV compared with cases with breast cancer (28% vs. 9%).[266] Breast cancer risk was decreased with *CXCR4* tropism and menopause, after adjustment for $CD4^+$ count, HIV RNA level, and ARV drug exposure.[266] Women living with HIV should follow guidelines established for the general female population for mammographic screening.

Gynecologic Infections and Disease

Human Papillomavirus Infections

Cervical Infection

Human papillomavirus (HPV) infection, particularly with HPV-16 and HPV-18, is the major risk factor for development of cervical cancer,[267] most anal cancers,[268] and some vulvar and vaginal cancers.[269] Additionally, HPV-6 and HPV-11 can cause condylomata acuminata, or genital warts.[270] Women living with HIV are two to three times more likely than women without HIV to have detectable levels of HPV DNA in cervicovaginal specimens due to increasing rates of acquisition and decreased clearance.[271,272] Women with higher HIV viral load and lower $CD4^+$ counts are at elevated risk of HPV acquisition; lower $CD4^+$ counts were also associated with decreased HPV clearance.[271] Therefore women with HIV are more likely to have HPV-related disease including vulvar, cervical, and anal dysplasia and cancer and condylomata acuminata.[273–277] In the United States, women living with HIV have significantly higher rates of cervical cancer than women in the general population,[278] and there is a direct relationship between $CD4^+$ counts and cervical cancer risk.[279] Bacterial vaginosis and *Trichomonas vaginalis* infections, which are less likely to be cleared in women with HIV, increase the risk for acquisition or reactivation of HPV infection, which suggests that the local cervicovaginal milieu may play a role in the susceptibility to HPV infection.[280]

Women with HIV are more likely to progress from HPV infection to HPV-related disease such as low-grade[281–283] or high-grade[284–287] squamous intracellular lesions, likely related to HIV-associated immunosuppression.[273] Two studies found that persistence of HPV and presence of low-grade squamous intraepithelial lesions (SILs) were stronger predictors of developing high-grade SILs than HIV status.[285,288] Crack cocaine has been associated with oncogenic HPV infection, SILs, and a decrease in the clearance of SILs over time.[289] Vitamin A may play a protective role. In one study, women living with HIV with low serum retinol levels (<1.05 mol/L) were more likely to have cervical SILs (multivariate odd ratio, 1.75; $P = .02$) even after adjustment for HPV status, nutritional status, and HIV disease stage.[290] In the era of ART,[271] data regarding the impact of ART on the incidence of HPV infection are conflicting, with some data indicating lowering of HPV incidence[291,292] (all and high-risk HPV types) by ART, and other data failing to show an impact of ART on HPV incidence.[293,294]

Women living with HIV should be screened for cervical cancer and precancers similarly to women without HIV with a few notable exceptions.[295] Given the higher prevalence of HPV-related cervical disease in women with HIV, screening for cervical cancer with a Pap test should begin 1 year after the onset of sexual activity, but no later than 21 years of age.[250] Pap tests should continue annually until there are three consecutive negative results, and then tests can occur at 3-year intervals until 30 years of age, when co-testing with an HPV test should begin at 3-year intervals (provided that three normal Pap tests were obtained previously).[250] Screening for cervical cancer should continue indefinitely for women living with HIV. Young women 21 to 24 years of age who have an atypical squamous cells of undetermined significance result should have a reflex HPV test; if positive, they should be triaged to colposcopy rather than repeat Pap test. Young women with HIV have a high rate of progression of abnormal cytology,[288] and 30% of adolescents who were perinatally infected had abnormal Pap tests at the time of their first test.[296] Generally, women living with HIV with cervical intraepithelial neoplasia should be managed similarly to women without HIV according to the American Society for Colposcopy and Cervical Pathology Guidelines.[297] Low-grade or high-grade cervical lesions are less likely to regress in the setting of HIV infection; therefore it may be preferable to proceed with management for young women if adherence to care is a concern.[250]

Extracervical Infection

Approximately 95% of all vulvar intraepithelial neoplasia (VIN), the precursor to vulvar cancer, is associated with HPV infection.[298] Similar to cervical HPV infection, vulvar HPV infection and associated VIN are more prevalent in women with HIV infection.[277,299,300] Women with HIV develop VIN at a younger age, and the lesions are more often multifocal.[275] Additionally, women with HIV are at increased risk of recurrent VIN and progression to invasive vulvar carcinoma.[275] The impact of ART on the natural history of VIN is not known due to the small number of studies all with small sample size.[300,301] There is no screening procedure for vulvar cancer; however, close examination of the vulva and vagina is particularly important for women with HIV. Biopsy should be performed promptly for any lesions identified as suspicious for VIN or vulvar cancer.[250]

Genital warts are most commonly caused by HPV-6 or HPV-11. Women with HIV may have larger or more numerous genital warts, which may be more difficult to treat.[300,302] Many genital warts regress without treatment, but refractory lesions require biopsy to rule out intraepithelial neoplasia. When treatment is requested due to patient discomfort or request or extensive lesions, topical treatments such as patient-applied imiquimod or provider-applied trichloroacetic acid are usually attempted first. Surgical treatments are used for dense lesions that are less likely to respond to topical therapy.[250]

Anal cancer has been associated with HPV-16 infection; however, for individuals living with HIV, the fraction of anal cancer attributable to HPV-16 is smaller.[303] The prevalence of high-grade anal intraepithelial

neoplasia and anal cancer is higher in women with HIV compared with women without HIV.[304,305] Some studies have evaluated the cost-effectiveness of screening for anal intraepithelial neoplasia and anal cancer in women with HIV using anal cytology.[306–308] At the present time, there are no national recommendations for routine screening of anal cancer for women with HIV. However, anal cancer screening with cytologic screening or high-resolution anoscopy is recommended by some experts in the care of women with HIV.[250,307] Anal cytology should be collected only if there is availability of high-resolution anoscopy,[250] as any abnormal cytology should be evaluated with high-resolution anoscopy.

Prevention of Human Papillomavirus Infection

All three HPV vaccines have been shown to prevent HPV infection and thus HPV-related cancers. Studies of two of these vaccines (bivalent and quadrivalent vaccines) have shown the HPV vaccination is safe and effective in girls and women living with HIV ranging from 13 to 26 years of age; however, the immune response is lower among women with HIV compared with women without HIV, especially if $CD4^+$ counts were <200 cells/mm^3.[309,310] HPV vaccination is recommended for girls and women with HIV 9 through 26 years old, ideally before the onset of sexual activity.[250] Consistent male condom use has also been shown to decrease risk of HPV infection by 70% in women.[311] Additionally, male circumcision has been shown to decrease the rate of HPV infection of the penis in randomized controlled trials,[312,313] and observational studies have shown an association between male circumcision and decreased cervical cancer risk.[314,315] However, evidence is currently insufficient to recommend adult circumcision for decreasing penile HPV risk and prevention of cervical cancer.[250]

Vaginal Infections

Bacterial Vaginosis

Bacterial vaginosis has been the most frequent vaginal infection in some US cohorts of women living with HIV, occurring in 35% to 47% of women.[316,317] Factors associated with bacterial vaginosis among US women with HIV include alcohol use, smoking, douching, and multiple sex partners.[316,318] HIV infection and induced immunosuppression may modify the course of bacterial vaginosis. Bacterial vaginosis is more persistent in women with HIV compared with women without HIV, particularly women with lower $CD4^+$ counts.[319] Although women with HIV may have more severe or persistent bacterial vaginosis infections,[319] there are no unique treatment recommendations. Bacterial vaginosis has been associated with various adverse outcomes such as preterm birth, transmission and acquisition of STIs including HIV,[90,320] and increased genital HIV shedding[89] possibly due to the increased local inflammatory response.[321] Bacterial vaginosis–associated organisms that have been significantly associated with genital HIV shedding include BVAB3, *Leptotrichia,* and *Sneathia*.[89] Treatment can normalize vaginal flora back to the protective lactic acid–producing bacteria and should be considered as a prevention strategy for STI and HIV acquisition and prevention.[89]

Vulvovaginal Candidiasis

The prevalence and cumulative incidence of candida vaginal colonization[322] as well as vulvovaginal candidiasis (VVC)[323] are greater in women living with HIV than in women without HIV. Lower $CD4^+$ count and higher viral load have been associated with VVC in women with HIV.[323] The symptoms of VVC are similar to symptoms experienced by women without HIV.[323] Therapy for VVC in women with HIV should not differ from therapy in women without HIV, but prolonged (i.e., 7–14 days) courses of conventional antimycotic treatments may be necessary for women with severe VVC, very low $CD4^+$ counts, or additional immunocompromising conditions such as diabetes or receipt of corticosteroid treatment.

Trichomonal Vaginitis

Trichomonal vaginitis is one of the most common STIs in women with and without HIV, affecting an estimated 3.7 million persons in the United States.[324] Proportions of women with HIV with a diagnosis of vaginal infection caused by *Trichomonas* have ranged from 6% to 27% in various US cohorts.[325] Reinfection is common, occurring in 36% of women with HIV, and is associated with a history of another STI (RR, 1.52; 95% CI, 1.08–2.14).[325] Becoming pregnant may be protective (RR, 0.59; 95% CI, 0.39–0.87).[325] A large clinical trial of women living with HIV determined a 7-day course of metronidazole is more effective than a single dose for treatment of *Trichomonas*.[326] A concurrent bacterial vaginosis infection was associated with failure of single-dose metronidazole treatment.[327]

Pelvic Inflammatory Disease

Several studies performed in the United States and Africa compared the presentation and course of pelvic inflammatory disease (PID) in women with and without HIV. Four studies[328–331] found that women with HIV had a lower admission white blood cell count, and five studies[328–330,332,333] noted that women with HIV were more likely to have tubo-ovarian abscesses or require surgical intervention. One study from the pre-ART era found that women with HIV were more likely to have persistent fevers refractory to antibiotic therapy,[328] and another study found higher temperatures and mean clinical severity scores.[332] Barbosa and colleagues[331] noted that women with HIV were more likely to remain febrile 48 hours after initiation of antimicrobial therapy. By day 5 or 6 of therapy, however, there was no statistically significant difference in the presence of fever.

The microbiology of PID in these studies is similar to that described in women without HIV but with PID, although the frequency of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* may be lower among women with HIV.[310,334] One study showed *Mycoplasma* spp. and *Streptococcus* spp. were more likely to be isolated in endometrial biopsy specimens of women with HIV ($P < .05$).[330] Another study of Kenyan women with PID found that the prevalence of bacterial vaginosis was significantly higher in women with HIV with low $CD4^+$ counts,[334] and in a South African study it was noted that *T. vaginalis* infection of the lower genital tract was significantly associated with a clinical PID diagnosis in women with HIV ($P = .002$).[335] Taken together, these studies suggest HIV infection might increase the risk of more severe PID; however, there is no indication that the response to therapy is different for women with HIV compared with women without HIV. Women with HIV should receive the conventional recommended antibiotic regimens.[336]

Genital Ulcer Disease

The most common causes of genital ulcer disease among women with HIV are HSV and syphilis. Women with lower $CD4^+$ counts are more likely to have active and severe genital ulcer disease due to HSV.[336] Because HIV seems to modify the course of HSV, the CDC has specific recommendations regarding the treatment of episodic infections or suppression for people living with HIV. In general, doses of acyclovir, famciclovir, and valacyclovir are higher, and duration of treatment is longer.[336] Persistent large ulcerations resistant to HSV treatments may herald either acyclovir resistance or the presence of idiopathic aphthous ulcerations, described subsequently. ART reduces the severity and frequency of symptomatic genital herpes, but subclinical genital HSV shedding still occurs.[337,338]

In women with advanced HIV disease, idiopathic vulvar or vaginal ulcers are rare manifestations[339–341]; the ulcers can be intractable, progress to fistula formation, and cause severe bleeding. In a national retrospective review of 29 women with idiopathic genital ulcers (defined by either negative HSV and syphilis test results or a nondiagnostic ulcer biopsy specimen), the median $CD4^+$ count was only 50 cells/mm^3, and 68% had a previous AIDS-defining event.[341] In 37% of patients, oral ulcers coexisted; in 19%, genital ulcers progressed to fistula formation. Although the numbers were small, there was often a good response to either corticosteroid treatment (topical, intralesional, or systemic) or initiation of ART in ARV-naïve women.[341] Thalidomide also was used successfully in the pre-ART era.[342]

CMV rarely can cause disease in the lower female genital tract. Women present with labial, vulvar, and cervical ulcerations, and typically they are severely immunocompromised. They often have coexistent cytomegaloviral retinal or gastrointestinal tract disease. In addition to painful genital ulcers, some women have had fevers and significant cervical bleeding. Women with this manifestation generally responded to intravenous ganciclovir (see Chapter 137).[343–345]

SEX DIFFERENCES IN HIV INFECTION AND TREATMENT RESPONSES

In the beginning of the HIV epidemic, initial data on the natural history of HIV infection were derived from predominantly male cohorts. As data from women became available, however, a few differences in the natural history of HIV infection by sex began to emerge. Beyond natural history, we also examine sex differences in virology, immunology, HIV reservoir, pharmacokinetics, treatment adherence, and treatment outcomes and toxicities in this section.

Sex Differences in Clinical Progression

Studies from early in the history of the HIV epidemic reported faster rates of progression to clinical outcomes and AIDS in women than men.[346,347] However, these differences, on further adjustment, seemed to be due to lower access to effective ARVs or late entry into care in women. Furthermore, higher rates of psychosocial factors among women in the United States, such as substance use, mental illness, stigma, and poverty, seemed to contribute to disparate care outcomes, rather than inherent biologic differences by sex.[348–350] Studies conducted after more wide-scale dissemination of ART worldwide showed similar clinical presentations and rates of progression to AIDS and death for women and men.[351,352] In the most recent era, a meta-analysis examining 31 studies with a total sample size of 86,233 men and 117,719 women in low-income and middle-income countries revealed that men living with HIV have a significantly greater hazard rate of all-cause mortality compared with women.[353] This effect seemed secondary to later diagnoses in men (with women being diagnosed earlier and entering care, for example, through the antenatal care setting). Other factors included reduced engagement and retention in care, later initiation of ART, and lower adherence rates to ART in men compared with women.[353]

Virologic and Immunologic Differences Between Men and Women Off ART

There are distinct biologic differences between women and men in the natural history of and immunity to HIV-1 infection.[354] HIV-1 RNA levels are approximately 0.5 $\log_{10}$ lower (range, 2-fold to 6-fold) in women than men early on in HIV infection[355] for approximately 5 to 7 years following seroconversion.[356] As $CD4^+$ counts decline and HIV-1 progresses off ART, this sex difference in HIV viral loads abates and then disappears. Despite having lower viral loads earlier in HIV disease than men, women do not have a slower rate of progression to AIDS. Indeed, for a given viral load early on in infection, women may actually progress more quickly to AIDS than men, possibly secondary to immunologic differences by sex.

Women have higher absolute $CD4^+$ counts than men (approximately100 cells/mm^3) early on in infection.[357,358] However, women actually have a more rapid depletion of $CD4^+$ counts during the natural history of HIV disease. A possible mechanism is that interleukin-7 levels tend to be higher (by 40%) in HIV-1–infected women compared with men, and there is an inverse correlation between circulating interleukin-7 levels and $CD4^+$ counts.[358] Other mechanisms underlying sex-based differences in the immune response are incompletely understood but have precedence in disparate rates of autoimmune diseases by sex,[354] differential responses to vaccination, and sex-specific responses to other infections. For instance, there are sex-specific differences in varicella-zoster virus reactivation rates,[359,360] fulminant hepatitis E infection,[361,362] and rates of spontaneous hepatitis C clearance.[363] Differential responses to vaccines by sex may further be mediated by hormonally mediated differences in the induction of Toll-like receptor response genes.[364]

Female-predominant sex hormones (i.e., progesterone, estrogen) have direct effects on immune responses. Estrogen downregulates tumor necrosis factor-α expression,[365,366] and progesterone-induced blocking factor influences the cytolytic function of lymphocytes including natural killer cells.[367] Women in the third trimester of pregnancy, when estrogen and progestin levels are very high, demonstrate transiently reduced peripheral blood CD4 T-cell counts. Finally, human lymphocytes express a glucocorticoid receptor with a distinct progesterone-binding domain, with progesterone exerting a dose-dependent inhibitory effect on *CCR5* expression in activated T cells[368] leading to lower *CCR5* density in women.[369] *CCR5* coreceptor expression on CD4 T cells has been linked to lower viral setpoints,[370] which could contribute to the virologic differences between men and women seen early on in infection.

Sex Differences in the HIV Reservoir and Possible Impact on Cure Strategies

Other sex-specific factors might influence the biology of the HIV reservoir. HIV persistence results from HIV seeding reservoir sites such as lymph nodes, thymus, central nervous system, and genital tract. Research efforts have focused on decreasing or even eradicating the reservoir in an attempt to elicit HIV remission or cure.[371] Although none of the current strategies being pursued have had success to date, the research on cure is ongoing and active and is employing a variety of strategies to explore the reduction of the HIV reservoir. Sex differences in HIV persistence or the reservoir may lead to the need for tailoring strategies attempting HIV cure by sex.

There are limited studies examining sex differences in HIV persistence when men and women are on ART. However, one analysis compared levels of the HIV-1 reservoir in a well-matched cohort of men and premenopausal women on ART with documented and long-standing virologic suppression.[372] Levels of HIV-1 DNA were not significantly different between the groups, but cell-associated HIV-1 RNA and low-level viremia by a highly sensitive assay were lower in women than in men. Consistent with this finding, markers of T-cell activation were also significantly reduced in women compared with men.[372] Other studies have suggested a higher incidence of posttreatment control in women[373] and prolonged time to viral rebound after ART is discontinued.[374]

One major strategy being pursued on the pathway to cure is to reverse HIV latency in the reservoirs. However, current methods known to aid in latency reversal are insufficient and have not led to eradication. In a genome-wide short hairpin RNA screen, one group identified the estrogen receptor ESR-1 as a cellular factor critical to reversing HIV-1 latency in a cell model.[375] If estrogen is directly repressive of HIV-1 transcription in latency models, estrogen blockade may help potentiate provirus latency reversal with known agents (e.g., histone deacetylase inhibitors) in women. This observation is the basis of an ongoing study in the Adult ACTG of a combination of tamoxifen and vorinostat (a histone deacetylase inhibitor) and their effects on viral reactivation among postmenopausal HIV-infected women on ART. Further work is needed to study the impact of female-specific hormones and their cycling in the context of reproductive-aged women on the reservoir, the impact of decreased concentrations of female hormones on the reservoir in postmenopausal women, and how to harness these findings into strategies directed toward cure.

Sex Differences in Responses to Antiretroviral Therapy and Pharmacokinetics

Treatment Outcomes

In general, women have equal rates of achieving virologic suppression on effective ART compared with men. In fact, women are more likely to be virologically suppressed than men in many regions of the world[49,376] where women are linked into care earlier (due to accessing care through antenatal settings) than men. In general, the choice of ARV regimen does not change according to the sex of the individual. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living With HIV provides the latest recommendations for the treatment of HIV and is updated frequently.[189]

In contrast, a number of studies have shown that women may have more adverse effects on ART than men, an observation that was more common with the older ARV agents. For example, women are more likely to experience rash and hepatic toxicity on NVP (an NNRTI) than men.[377] These toxicities on NVP occur more frequently when patients are started on the agent at higher $CD4^+$ counts: >250 cells/mm^3 for women and >400 cells/mm^3 for men.[189] The older thymidine analogue NRTIs stavudine and didanosine were associated with higher rates of lactic acidosis among women than men.[377] Finally, there are higher rates of gastrointestinal side effects, perturbations in lipids, and likely lipodystrophy (body changes that involve central fat accumulation and

peripheral atrophy) in women than men on protease inhibitor–based therapies.[377] The higher rate of adverse effects in women compared with men on ART can have consequences including a higher rate of discontinuation due to tolerability issues.[378]

Pharmacokinetics

Differences in adverse effects among women and men are most likely due to sex differences in the pharmacokinetics of ARVs.[379,380] In 1999, the National Institutes of Health published a six-volume report entitled the *Agenda for Research on Women's Health for the 21st Century,*[381] which, among other dicta, claimed that because "gaps in knowledge remain regarding the behavior of drugs in women … [and] over-reliance on traditional male-oriented medical practices may ill serve women … gender-related pharmacokinetic and pharmacodynamic differences" must necessarily be assessed. The FDA mandated in 1998 that applications for new drugs must include data that are sex-stratified, providing information on the safety, tolerability, and effectiveness of the drug by sex. However, a 2001 investigation by the US General Accounting Office revealed that more than one-third of the FDA-approved drugs since the 1998 mandate were approved without provision of any sex-specific information.[382] In HIV medicine, even if women are enrolled in clinical trials investigating new drugs, the data on pharmacokinetics, side-effect profiles, and efficacy are not always provided, or the numbers of women in the trial are often too low to stratify analyses by sex.

Despite this, a few pharmacokinetics comparisons of various ARVs between men and women have shown that women in general tend to have higher exposure to various ARVs at the same dose than men.[380,383] There are a number of postulated mechanisms for differential ARV concentrations by sex, as each of the components of the pharmacokinetics cascade (drug absorption, distribution, metabolism, and distribution) can be influenced by either female-predominant hormones or differences in organ/body size by sex. For example, in terms of absorption, women have slower emptying times in the stomach than men, which may lead to increased rates of drug absorption. Moreover, the emptying time may vary throughout the menstrual cycle depending on progesterone levels, which vary by phase of the cycle. In terms of distribution, ARVs are distributed by plasma binding proteins (e.g., albumin and α_1-acid glycoprotein). Estrogen decreases α_1-acid glycoprotein concentrations, which may lead to greater concentrations of free drug in the plasma. In terms of metabolism, female hormones have differential effects on CYP enzymes, the main metabolizing enzymes at the level of the liver for a variety of ARVs. In terms of elimination, women have smaller organs and may clear drugs less quickly as a result. Overall, the sex differences in pharmacokinetics parameters for ARVs tend to lead to higher drug concentrations in women compared with men, which may explain the higher rates of toxicities on ARVs among women.[380]

Sex Differences in Comorbidities

Given the increasing uptake of ART across the world and the subsequent reductions in HIV-related morbidity and mortality, there is a burgeoning focus on noncommunicable or comorbid complications of chronic HIV infection. Men and women are at increased risk for comorbid diseases at relatively earlier ages compared with the general population. Such comorbidities include cardiovascular disease, cerebrovascular disease, osteopenia and osteoporosis, various cancers, and geriatric syndromes such as falls and frailty,[384–392] all of which may have sex differences in incidence and prevalence in the general population. Beyond sex differences in hormones playing a differential role in the incidence of comorbidities among women, higher rates of immune activation and inflammation[354,393] and higher rates of smoking[394] have been postulated to play a role in comorbidity prevalence and severity among women living with HIV in particular.

Men are still at more risk of cardiovascular and cerebrovascular disease than women, even with concomitant HIV infection. Recent evidence has shown higher rates of ischemic stroke in women with HIV compared with women without HIV.[395] Women with HIV are also more at risk for osteopenia and osteoporosis[396] than men living with HIV, as in the general population. In terms of cancers, breast cancer does not seem to have a higher incidence in women with HIV than women in the general population, and indeed it is postulated that *CXCR4* positivity on breast cancer cells (and their subsequent destruction by HIV) may lead to lower rates of breast cancer in women living with HIV than in women without HIV.[266] However, all people living with HIV are at a higher risk than their non–HIV-infected counterparts for Epstein-Barr virus–associated lymphomas, human herpesvirus 8–associated cancers such as Kaposi sarcoma and Castleman syndrome, HPV-associated cancers including cervical cancer and anal cancer, and some non–AIDS-related cancers such as colon cancer and lung cancer.[388]

Finally, it is important to note that, although not related to immunosuppression from HIV, some concomitant mental health conditions are more prevalent in women in the United States living with HIV than men.[397] Poverty, stigma, and structural racism contribute to these differences,[350] especially as women with HIV in the United States are more likely to be racial or ethnic minorities than men (see "Epidemiology in United States"). Finally, the high rates of intimate partner violence among women with HIV in the United States puts this group more at risk for nonadherence to ART, nonsuppressed viral loads, and death.[398]

Sex Differences in Aging

Women with HIV may enter menopause earlier than their non–HIV-infected counterparts and have a higher rate of vasomotor symptoms.[399] In women with HIV, lower $CD4^+$ count, injection drug use, and low physical activity all have been associated with an earlier onset of menopause than in women without HIV.[400] Women with HIV may also have a greater severity of vasomotor symptoms with menopause than their non–HIV-infected counterparts, necessitating close attention to symptoms and hormone replacement therapy when needed.[400]

INCLUSION OF WOMEN IN CLINICAL RESEARCH

Women and minority populations have not been represented in clinical trials of HIV medications and interventions to the extent that reflects their burden of disease.[401] Many treatment strategies for women are extrapolated from studies performed almost exclusively in men. Despite the importance of the HIV cure research agenda, women account for only 8.3% of subjects in studies related to cure, which does not correspond to the prevalence of infection in women either domestically or globally.[402] Given the sex-based differences in immune responses and virologic parameters detailed in this chapter, it is imperative to enroll adequate numbers of women in cure trials and to continue to unravel basic mechanisms related to the effects of sex hormones on HIV persistence and the reservoir to guide eradication strategies that may be tailored to women.

Pharmaceutical companies have increasingly focused on women-specific studies only after an ARV agent is approved, leading to use of a medication in women without knowledge of sex-specific differences in tolerability or efficacy. Strategies to include greater numbers of women in HIV-specific studies could include revisiting the strict enrollment criteria around pregnancy, reviewing overly stringent contraceptive requirements, having after-hours study visits, and providing transportation and child care.[399] Given the importance of sex differences in HIV medicine and the burden of the epidemic among women, an increasing focus on enrolling adequate numbers of women in clinical trials and performing sex-stratified analyses to help differentiate tailored strategies for women is essential.

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127 Pediatric Human Immunodeficiency Virus Infection

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SHORT VIEW SUMMARY

EPIDEMIOLOGY

- A remarkable decline in US pediatric human immunodeficiency virus (HIV) infection has occurred because most currently infected children are surviving into young adulthood, and there has been tremendous success in preventing mother-to-child transmission (MTCT). Such success may be achieved globally wherever effective HIV screening and therapy for pregnant women are accomplished.
- Influx of HIV-infected immigrants, refugees, and adoptees, in addition to residual domestic MTCT, will continue to contribute to a small but definite presence of pediatric HIV infection in the United States.
- An alarming increase in adolescent acquisition of HIV infection is occurring among young men who have sex with men, especially African-American and Hispanic men.

ELIMINATION OF NEW PEDIATRIC HIV INFECTION IN THE UNITED STATES

- Prevention of pediatric HIV infection critically depends on prevention of HIV MTCT, which in turn depends on primary prevention of HIV infection in women, universal HIV testing of pregnant women to identify those who are HIV infected, and appropriate antiretroviral therapy in HIV-infected women and their infants.
- Each episode of perinatal HIV infection in the United States should be viewed as a sentinel public health event, indicating a woman whose HIV infection was undiagnosed before or during pregnancy or a woman with a known diagnosis who did not receive appropriate interventions during prenatal care to prevent MTCT.
- Prevention of adolescent HIV infection involves similar strategies to those used for adults (safer sex, avoidance of intravenous or injection drug use) but with special attention to the adolescent's unique developmental and biopsychosocial challenges. Additional challenges may be posed by interrupted health insurance, homelessness, and stigma among young men who have sex with men.

THERAPY FOR AGING HIV-INFECTED YOUTH

- Disclosure of the diagnosis of perinatal HIV infection to the aging child requires discussion and planning and is a process that may take place over months to years based on several factors, including the developmental level of the child, and the parent's or caretaker's readiness to disclose. Disclosure is best accomplished by early adolescence to more fully engage youth in their own care, preferably before the age of sexual debut.
- Adherence with medical care may suffer during adolescence because of issues revolving around psychosocial developmental, confidentiality, peer pressure, and socioeconomic factors. This contributes to the substantial presence of antiretroviral resistance of HIV strains in adolescents with perinatal HIV infection.
- Transition from the pediatric care model to the adult care model is a multifaceted process that requires time and planning to keep the aging adolescent successfully engaged in care.
- Complications of long-standing perinatal HIV infection and its therapy among maturing youth include impaired growth and bone mineral accrual, possibly increased cardiovascular risk factors, increased incidence of behavioral and psychiatric disorders, and increased risk for cervical dysplasia and preterm delivery among young women.

Although the pathogenesis of human immunodeficiency virus (HIV) infection and the general virologic and immunologic principles underlying the use of combination antiretroviral therapy (cART) are similar for HIV-infected children and adults, unique considerations apply to infants, children, and adolescents.[1] These include (1) the acquisition of infection through perinatal exposure for the vast majority of children (i.e., a primary infection acquired in the context of an immature immune system); (2) in utero exposure to antiretroviral medications, HIV infection, and altered inflammatory milieu; (3) differences in immunologic markers, viral load, and diagnostic strategies in young infants; (4) changes in pharmacokinetic parameters with age; (5) considerations related to the formulation and palatability of medications, and fewer medication options adequately tested and available for use by children[2,3]; (6) issues of adherence in infants and young children dependent on others for medication administration and in adolescents facing adherence challenges from developmental issues, including peer pressure; and (7) challenges in the disclosure of HIV diagnosis to children and adolescents. The salient pediatric-specific issues in the diagnosis, clinical manifestations, and treatment of pediatric HIV infection are addressed in a previous edition of this textbook and elsewhere.[3,4–13,14–16,17,18] Table 127.1 lists frequently updated Internet-based sources of information.

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

The focus of this chapter is on current successes and the remaining challenges in domestic pediatric and adolescent HIV infection.

CURRENT EPIDEMIOLOGY OF DOMESTIC PEDIATRIC AND ADOLESCENT HIV INFECTION

The epidemic of acquired immunodeficiency syndrome (AIDS) was first recognized in adults in the United States in 1981, although sporadic cases in the United States and Europe had occurred since at least the mid-1970s.[19–23] In retrospect, it is known that pediatric cases occurred almost as early as adult cases.[24–26] During the peak of the US pediatric HIV epidemic, approximately 10% of people living with HIV infection in the United States were children (<13 years of age) and adolescents (13–19 years of age); currently in the United States, children and adolescents together account for less than 1% of people living with HIV infection.[27] This remarkable 90% decline in the prevalence of pediatric HIV infection is the result of striking advances in both the prevention of mother-to-child transmission (MTCT) of HIV, reducing the incidence of new infection, and the increased survival of infected children aging into young adulthood.[27,28]

Since reporting began in 1981, approximately 9600 cases of AIDS in children younger than 13 years have been reported by the Centers for Disease Control and Prevention, with most occurring in children of color (59% black, 21% Hispanic, 16% white).[27,29,30] The greatest

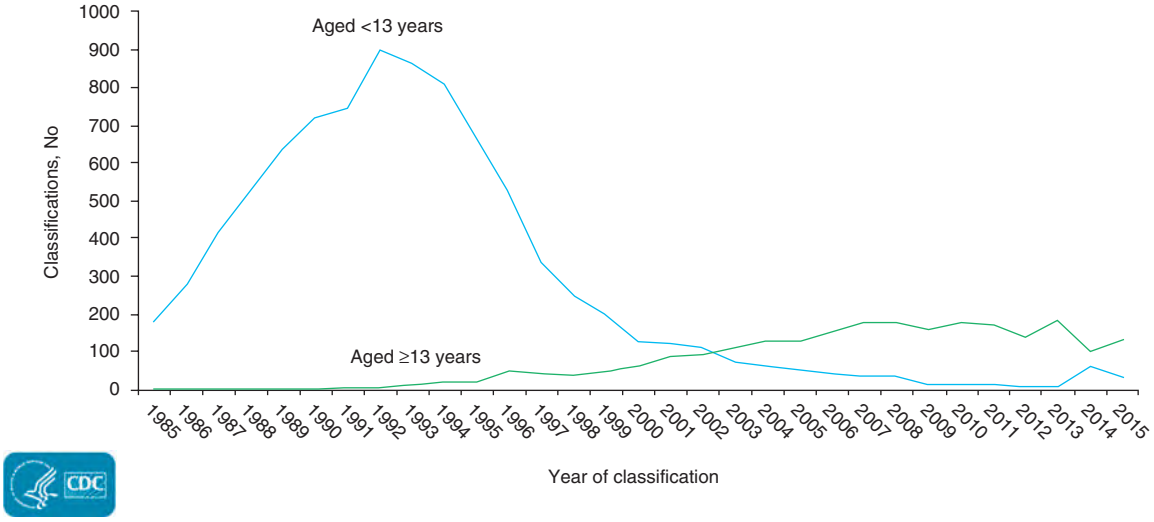

FIG. 127.1 Acquired immunodeficiency syndrome (AIDS) cases in the United States and six dependent areas acquired perinatally, by year of, and age at, diagnosis, 1985–2015. *(From Centers for Disease Control and Prevention. Pediatric HIV surveillance slide set.* https://www.cdc.gov/hiv/library/slideSets/index.html. *Accessed June 1, 2018.)*

TABLE 127.1 Useful Websites for Information on Pediatric HIV/AIDS

WEBSITE	SPONSOR	COMMENTS
https://aidsinfo.nih.gov	US National Institutes of Health	Continuously updated clinical practice guidelines for management of HIV infection and HIV–related opportunistic infections; information on clinical trials and other research efforts
https://www.hivguidelines.org/	New York State Department of Health AIDS Institute	Updated practice guidelines and chapters on management issues
https://www.cdc.gov/hiv	Centers for Disease Control and Prevention (CDC)	Compendium of information, websites, telephone and fax numbers; Spanish language links
https://www.niaid.nih.gov/ and https://www.oar.nih.gov/	National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) NIH Office of AIDS Research (OAR)	Summary of NIAID and NIH-wide activities and information on HIV/AIDS topics
www.nccc.ucsf.edu	Clinician Consultation Center, University of California, San Francisco	Telephone consultation and Internet-based information on perinatal HIV issues including antepartum and intrapartum management of women with HIV infection, and postpartum management of HIV-exposed infants (perinatal HIV hotline: 888-448-8765); also, management of children and youth with HIV infection (telephone consultation: 800-933-3413)
http://www.who.int/hiv/en	World Health Organization (WHO)	Information, practice guidelines, and other HIV resources for international providers
http://www.unaids.org/	Consortium of United Nations Agencies including WHO and United Nations Children's Fund (UNICEF)	Information and statistics relevant to international providers
https://aidsetc.org/	Health Research Services Administration (HRSA)	Educational and consultation resources
https://www.accessdata.fda.gov/scripts/cder/daf/gov/scripts/cder/daf/	US Food and Drug Administration (FDA)	Access latest information about FDA-approved drugs

All sites accessed December 14, 2018.
AIDS, Acquired immunodeficiency virus; *FDA,* US Food and Drug Administration; *HIV,* human immunodeficiency virus.

number of pediatric AIDS cases (cumulative through 2016, recognizing that case numbers of HIV infection, not just AIDS, are likely much greater) have been reported in New York (2430), Florida (1569), New Jersey (810), California (710), Texas (411), Pennsylvania (374), and Puerto Rico (404). The mode of infection for more than 95% of the cumulatively reported cases of pediatric AIDS is MTCT. Less than 1% of cases have been reported to have no identifiable risk factor; early in the epidemic, some cases were the result of transfusion of tainted blood components. Rarely, cases have been attributed to sexual abuse or assault and only very rarely to household, school, child care, and hospital or clinic exposure. Breastfeeding is an important mode of HIV transmission in lower resource settings, but in the United States, where nutritionally complete infant formula and clean water are readily available, HIV-infected women are counseled to avoid breastfeeding.[5,17,31,32] Premastication or prewarming of infant food by an HIV-infected caregiver is a possible source of pediatric HIV infection and also is contraindicated.[33,34]

In the 5 years after antenatal, intrapartum, and neonatal zidovudine MTCT prophylaxis was implemented as the standard of care in the United States for pregnant women with HIV infection, the number of pediatric AIDS cases reported in the United States decreased by 86% among infants younger than 1 year and by 78% in children 1 to 5 years of age.[28,35–40] These changes reflected a clear success in decreasing perinatal transmission and in better antiretroviral therapy (ART) and prophylactic medications to prevent progression of pediatric HIV infection to AIDS. In 1991 the annual number of perinatally infected infants in the United States peaked at 1650; by 2013, only 69 perinatally infected children were born, an affirmation that the combination of clinical investigation, public health policy implementation, and continued antiretroviral drug development has sharply curtailed the rate of perinatally acquired pediatric HIV/AIDS in the United States (Fig. 127.1).[28–29,30] The total number of HIV-exposed births (i.e., pregnancies among HIV-infected women) is likely decreasing but is still substantial, such that continued efforts to prevent MTCT will be required.[1,29,30]

Similar remarkable decreases in MTCT of HIV have been reported from the United Kingdom, Ireland, France, and wherever prenatal testing and identification of HIV-infected pregnant women and provision of cART to pregnant women and their infants is achieved.[41–43]

Pediatric HIV infection in the United States is now considered as a condition that could be eliminated—a nearly unimaginable concept just 2 decades ago. Globally, however, the 2.1 million children younger than 15 years living with HIV accounted for approximately 6% of all 36.7 million people living with HIV; 160,000 new pediatric infections represented 9% of all incident infections, and 120,000 child deaths accounted for 12% of all AIDS-related deaths.[44] New infections in children across the world have declined by 47% since 2010, as the proportion of HIV-infected pregnant women with access to cART has increased from 47% to 76%. The influx of HIV-infected immigrants, refugees, and international adoptees, and uncommon instances of MTCT, will continue to contribute to a small but definite presence of HIV-infected children in the United States for a number of years to come.

In addition, some areas of the United States continue to experience MTCT of HIV from missed opportunities in case identification of, or care provision for, infected pregnant women.[45] Public health efforts must be strengthened to truly eliminate domestic pediatric HIV infection.

In contrast to the tremendous success in decreasing new perinatal HIV infections through aggressive MTCT prevention programs, the incidence of HIV infection in US youth remains stable. The lack of substantial progress in reducing HIV infection in youth represents a confluence of the majority of perinatally infected children now surviving into adolescence and the continued acquisition of HIV infection during adolescence through sexual contact (especially among young men who have sex with men) and, to a lesser extent, intravenous drug use.[46] In 2016, 21% of the newly reported infections with HIV were in adolescents and young adults ages 13 to 24 years.[46] Among these youth with new HIV diagnoses, most (55%) were black or Latino (23%), and more than 80% were young men who have sex with men.

REMAINING CHALLENGES IN DOMESTIC PEDIATRIC HIV INFECTION

Elimination of New Pediatric HIV Infection

The reader is referred to Chapter 126 for a more detailed discussion of ART of pregnant women living with HIV; essential points are reiterated here, along with newer information on management of the HIV-exposed infant.

Maternal Determinants of Mother-to-Child Transmission

The MTCT rate is estimated to range from 13% to 39% in infants born to HIV-infected women who did not receive ART during pregnancy or intrapartum.[5,17,35] In the United States, the transmission rate decreased from 25% to 8% in 1995, after incorporation of an antenatal, intrapartum, and neonatal regimen of zidovudine (Pediatric AIDS Clinical Trials Group [PACTG] 076 study) into standard-of-care guidelines, and currently the rate of MTCT in the United States is less than 2%.[5,27,29,30] Correlates of MTCT include late initiation of, or absence of, cART during pregnancy, maternal HIV viral load greater than 1000 copies/mL, low $CD4^+$ T-cell count, prolonged rupture of membranes, preterm delivery, concomitant genital ulcerative disease, and seroconversion during pregnancy.[6,47–51] Cesarean section is recommended for the prevention of transmission if viral load suppression (<1000 copies/mL) has not been achieved by delivery.[5,6,52] It is clear that vertical transmission is most significantly decreased by the use of ART in pregnant women and their neonates.[1,5] Furthermore, MTCT is significantly lower in women who start ART before conception, compared with those starting ART during pregnancy.[5,53] When analyzed independently of plasma viral load, the MTCT rate of pregnant women followed in the French Perinatal Cohort who initiated ART before conception was 0.2% (6/3505), compared with 1.1% (50/4570) who initiated therapy during the pregnancy.[53] Remarkably, none of the subset of 2651 pregnant women who received ART from before conception and maintained less than 50 copies/mL plasma viral load at delivery transmitted HIV infection to their infants (0/2651; MTCT rate, 0%; 95% confidence interval, 0%–0.1%).[53]

In the absence of ART, the majority of MTCT occurs during labor and delivery (50%), with an additional 25% occurring antenatally and 25% postnatally through breastfeeding among women not receiving ART.[1,5] Acute HIV infection late in pregnancy or during breastfeeding greatly increases the rate of HIV MTCT.[5] Preventive therapies and other measures have differential effects depending on the stage of pregnancy in which they are applied and whether infants are breastfed. Appropriately designed antenatal ART optimizes maternal health and prevents antenatal and intrapartum transmission.[1,5,31] Interventions initiated at delivery have no effect on those infants already infected in utero but can decrease the rate of intrapartum transmission.[5,54,55] Even neonates born to HIV-infected women who did not receive antenatal and intrapartum therapy may benefit from ART if it is begun in the first 12 hours after birth.[37,39,56] When HIV infection is newly diagnosed in a pregnant woman or child, it is essential to recommend HIV testing to the mother's other children regardless of age.[5,17]

Postpartum Mother-to-Child Transmission

The rate of infection among infants of HIV-infected women who breastfeed is notably greater than that among infants of women who do not breastfeed, even if antiretroviral agents were administered during pregnancy and intrapartum.[5,17,31,32] HIV has been detected in both the cellular and the cell-free fractions of human breast milk, and high maternal plasma viral load is likely a risk factor for transmission through breastfeeding.[57–59] In high-resource settings such as the United States, all HIV-infected women should completely avoid breastfeeding to prevent HIV transmission to their infants.[5,17] Although there remains a medical contraindication to breastfeeding in order to maximize prevention of HIV transmission, there is an increasing recognition that some women in the United States and similar industrialized nations face social, cultural, and other reasons that may lead them to breastfeed despite such counseling, making it important for providers to enable honest conversations about infant feeding intentions and to provide women who insist on breastfeeding additional information to minimize risk.[60–62] When women living with HIV infection continue cART after delivery, postpartum MTCT rates decline even with breastfeeding.[5,6,31] Thus in lower-resource settings such as sub-Saharan Africa, the further decrease in HIV transmission through avoidance of breastfeeding needs to be balanced against the substantially increased risk for respiratory and diarrheal disease morbidity and mortality in infants who are not breastfed.[5,6,31] The World Health Organization has suggested that each country should decide if it should adopt the strategy of counseling mothers to breastfeed while receiving antiretroviral interventions, or of counseling to avoid all breastfeeding, when considering how to provide infants the greatest chance of HIV-free survival.[31]

Elimination of Mother-to-Child Transmission

Prevention of pediatric HIV infection critically depends on primary prevention of HIV infection in women (including those who are pregnant), universal HIV testing of pregnant women to identify those who are HIV infected, and, finally, appropriate ART in HIV-infected women and their infants.[1,5] Currently, each episode of perinatal HIV infection in the United States should be viewed as a sentinel public health event, indicating a woman whose HIV infection was either undiagnosed before or during pregnancy, or a woman with a known diagnosis who did not receive adequate prenatal care including appropriate interventions to prevent MTCT.[1,30,45] One or more missed opportunities for prevention (defined as lack of prenatal care; lack of early maternal HIV testing; lack of prenatal, intrapartum, or infant antiretroviral prescriptions; failure to perform scheduled cesarean delivery for eligible women; and breastfeeding by HIV-infected women) were present in 74% of perinatally HIV-infected infants (and 52% of uninfected but perinatally HIV-exposed infants) among 8000 births in 15 US jurisdictions during 2005 to 2008. Although substantial challenges remain in ensuring universal prevention, identification, and appropriate therapy of HIV infection among girls and women of childbearing age, near elimination of US MTCT

is achievable with current initiatives such as universal HIV opt-out testing of adolescents, adults, and pregnant women; early treatment of HIV-infected men and women to reduce transmission to heterosexual partners; and solidification of standard ART for infected pregnant women during antenatal and intrapartum periods, along with infant prophylaxis.[1,5,6,17] Residual MTCT from acute HIV infection acquired late in pregnancy or during breastfeeding of previously uninfected women or from transmission of antiretroviral-resistant HIV will likely make achieving zero cases of perinatal HIV transmission impossible, but reductions of another order of magnitude from the current 100 to 200 infected births per year is feasible.

MANAGEMENT OF THE HIV-EXPOSED INFANT

General Measures

Decisions surrounding mode of delivery—avoidance of the routine use of fetal scalp electrodes for fetal monitoring and, if possible, avoiding the use of forceps or vacuum extraction—are made at delivery.[5,6] In the United States and other resource-rich areas where safe and affordable infant formula is available, breastfeeding is contraindicated except in extraordinary circumstances (see earlier).[5,31,60–62] Standard (universal) precautions are indicated in the delivery room and nursery; once the infant's condition has been stabilized, bathing, administration of vitamin K, and ophthalmia neonatorum prophylaxis are performed, as is routine with non–HIV-exposed infants.

Antiretroviral Agents

All newborns exposed to HIV should receive antiretroviral drugs in the neonatal period to reduce perinatal transmission of HIV; selection of the appropriate type of antiretroviral regimen is guided by the level of transmission risk as judged by consideration of factors such as maternal use of cART and maternal viral load at delivery, maternal health, mode of delivery of the infant, and gestational age at delivery. Current thinking is that HIV MTCT risk falls along a spectrum, and that consequently different antiretrovirals are indicated for different scenarios of infant perinatal HIV exposure.[5,6] The risk of MTCT is greater for infants born to:

- Mothers who received neither antepartum nor intrapartum antiretroviral drugs
- Mothers who received only intrapartum antiretroviral drugs, or who initiated antiretroviral drugs in only the late second or the third trimester of pregnancy
- Mothers who received antepartum and intrapartum antiretroviral drugs, but who have detectable viral load near delivery (usually defined as confirmed HIV RNA level above the lower limits of detection of an ultrasensitive assay, although some experts would use a threshold of >400–1000 copies/mL)
- Mothers with acute or primary HIV infection during pregnancy or breastfeeding
- Mothers with unknown HIV status who test positive at delivery (or whose newborns have a positive HIV antibody test result)

An infant born to a mother living with HIV infection who received cART throughout pregnancy, had sustained viral load suppression (below detectable RNA level) near delivery, and who had no concerns related to ART adherence is considered to be at low risk of perinatal HIV acquisition.

Historically, the use of antiretroviral drugs in the newborn period was referred to as *antiretroviral prophylaxis*; recently, the different scenarios of risk noted earlier have generated the terminology of neonatal prophylaxis, empirical treatment, and treatment of infants for HIV infection.[5,6] In this context, *neonatal antiretroviral prophylaxis* refers to the administration of antiretroviral drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition. Antiretroviral prophylaxis may include the routine administration of a *single agent*, usually zidovudine, or *combinations* of two (zidovudine and nevirapine) antiretroviral drugs (or even three antiretrovirals, such as zidovudine, lamivudine, and either nevirapine or raltegravir). *Empirical HIV therapy* refers to the administration of a three-drug combination antiretroviral regimen to newborns at highest risk of HIV acquisition, intended primarily to serve as early treatment for a newborn who is likely later confirmed to have acquired HIV; it also serves as antiretroviral prophylaxis against HIV acquisition for those newborns who are exposed to HIV in utero, during the birthing process, or during breastfeeding and who do not acquire HIV. Finally, the term *HIV therapy* is used to denote administration of a three-drug combination antiretroviral regimen to newborns with HIV infection confirmed through early birth detection (see later section on infant diagnosis). It is noteworthy that, with the important exception of nevirapine, the neonatal antiretroviral dosing for prophylaxis, empirical therapy, and therapy is the same as that for treatment with all antiretroviral drugs currently recommended for newborns. For those infants with documented HIV infection, therapy will be given lifelong per current practice guidelines.[5,6,18] As newer agents or newer data become available for use in newborns, it is possible that other additional differences in dosing will emerge.

The precise interval during which newborn antiretroviral prophylaxis or empirical HIV therapy can be initiated and still be of benefit is undefined; however, most studies support providing prophylaxis as early as possible after delivery, preferably within the first 6 to 12 hours of life.[5,6]

Table 127.2 provides an overview of neonatal antiretroviral management according to risk of perinatal HIV in the newborn. Data supporting these recommendations are discussed in the US Department of Health and Human Services (DHHS) Pediatric Antiretroviral Guidelines.[5] Single- and multiple-agent antiretroviral prophylaxis recommendations have been derived from both randomized controlled clinical trials (e.g., the PACTG 076 and National Institute of Child Health and Human Development–HIV Prevention Trials Network [NICHD-HPTN] 040/PACTG 1043 trials) and observational studies.[5] Recommendations for empirical therapy have been formulated mainly by consensus, after the realization that infected infants given cART very early in infancy can suppress HIV replication and even lessen their viral reservoir, although the infection is not cured.[5] Empirical therapy recommendations are consistent with use of postexposure prophylaxis and are being studied in current clinical trials.[5]

Table 127.3 summarizes the dosing recommendations for antiretroviral agents in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks' gestational age), can be found in the guidelines[5] and by contacting the National Perinatal HIV Hotline (888-448-8765), a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns.

Diagnosis of HIV Infection in the HIV-Exposed Infant

Proper use of diagnostic tests for pediatric HIV infection is heavily dependent on the age of the child (also see Chapter 120).[4,5,17,63] Beyond the age of 18 months, standard serologic testing evaluations with a fourth-generation antibody-antigen immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen, followed by (if reactive) a supplemental antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies, may be performed, as for an adult.[5,17,63]

In contrast, infants born to HIV-seropositive women pose a special diagnostic challenge because they are seropositive at birth, whether or not they are infected, owing to transplacental passage of maternal antibody to HIV. Because maternal antibody is detectable in the infant for as long as 18 months after birth, tests that rely on detection of HIV antibody are not useful for diagnosis in children younger than 18 months.[4,5,17] Rather, tests that detect the presence of the virus itself must be performed. Nucleic acid tests (NATs), including DNA polymerase chain reaction (PCR) and RNA assays such as reverse-transcriptase PCR or transcriptase-mediated amplification assays are the most widely available of these tests and are equally preferred for the diagnosis of HIV infection in infants.[5,17,63] Recommended testing of infants born to HIV-infected women includes two or three HIV NATs, performed at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months (Fig. 127.2).[5,17] Some experts perform an additional NAT in the first 48 hours of life to identify infected infants early, especially in infants at higher risk for in utero infection (e.g., no antenatal antiretroviral treatment or high level of maternal viremia in late pregnancy). Many such high-risk infants will also be those receiving enhanced antiretroviral prophylaxis regimens (i.e., multiagent antiretroviral prophylaxis or empirical HIV treatment),

TABLE 127.2 Newborn Antiretroviral Management According to the Risk of HIV Acquisition

CATEGORY OF RISK GROUP	DESCRIPTION OF RISK GROUP	NEONATAL ARV MANAGEMENT *(CURRENT TERMINOLOGY)*[b]
Low risk of perinatal HIV transmission	Mothers received standard cART during pregnancy with sustained viral suppression near delivery and no concerns related to ARV drug adherence	*(Neonatal single agent ARV prophylaxis)* 4 weeks of ZDV
Higher risk of perinatal HIV transmission	Mothers who received neither antepartum nor intrapartum ARV drugs Mothers who received only intrapartum ARV drugs, or who initiated ARV drugs in only the late second or third trimester of pregnancy Mothers who received antepartum and intrapartum ARV drugs, but who have detectable viral load near delivery Mothers with acute or primary HIV infection during pregnancy or breastfeeding	*(Neonatal combination agent ARV prophylaxis)* 6 weeks of ZDV PLUS three doses of NVP, given within 48 h of birth, 48 h after first dose, and 96 h after second dose (NVP given at prophylaxis dose) OR *(Empirical HIV therapy)* 6 weeks of three-drug combination—either ZDV + 3TC + NVP (NVP given at prophylactic dose) or ZDV + 3TC + RAL
Presumed newborn HIV exposure	Mothers with unknown HIV status who test positive at delivery or postpartum, or whose newborns have a positive HIV antibody test	*(Empirical HIV therapy)* (some experts would choose to use *Neonatal combination agent ARV prophylaxis* in this scenario)
Newborn with confirmed HIV infection	Newborn with confirmed positive HIV NAT result	*(HIV therapy)* cART with ZDV + 3TC + NVP (treatment doses) or ZDV + 3TC + RAL

[a]Modified from Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. US Department of Health and Human Services guidelines for the use of antiretroviral agents in pediatric HIV infection, December 14, 2018. https://aidsinfo.nih.gov/. Accessed December 14, 2018.
[b]For explanation of current terminology, see text. All ARVs are to be given to infant as soon as possible after delivery, preferably within the first 6 to 12 hours of life. Dosing information given in Table 127.3.
ARV, Antiretroviral; *cART,* combination antiretroviral therapy; *HIV,* human immunodeficiency virus; *NAT,* nucleic acid test; *NVP,* nevirapine; *RAL,* raltegravir; *3TC,* lamivudine; *ZDV,* zidovudine.

TABLE 127.3 Newborn Antiretroviral Dosing Recommendations

DRUG	ORAL DOSING
ZDV (zidovudine): Prophylaxis and treatment dosage *Note:* ZDV is the only agent available as an intravenous formulation for newborns unable to tolerate oral agents. The intravenous dose is 75% of the oral dose, administered at the same intervals.	*≥35 weeks' gestation at birth* Birth to age 4–6 weeks: • 4 mg/kg/dose twice daily *≥30 to <35 weeks' gestation at birth* Birth to age 2 weeks: • 2 mg/kg/dose twice daily *Age 2 weeks to 4–6 weeks:* • 3 mg/kg/dose twice daily *<30 weeks' gestation at birth* Birth to age 4 weeks: • 2 mg/kg/dose twice daily Age 4–6 weeks: • 3 mg/kg/dose twice daily
3TC (lamivudine): Prophylaxis and treatment dosage	*≥32 weeks' gestation at birth* Birth to age 4 weeks: • 2 mg/kg/dose twice daily Age 2 weeks to 4–6 weeks: • 4 mg/kg/dose twice daily
NVP (nevirapine): Prophylaxis dosage	*Birth weight 1.5–2 kg* • 8 mg/dose once daily (actual dose, NOT mg/kg) *Birth weight >2 kg* • 12 mg/dose once daily (actual dose, NOT mg/kg)
NVP: Treatment dosage	*≥37 weeks' gestation at birth* Birth to age 6 weeks: • 6 mg/kg/dose twice daily *34–37 weeks' gestation at birth* Birth to age 1 week: • 4 mg/kg/dose twice daily Age 1–6 weeks: • 6 mg/kg/dose twice daily
RAL (raltegravir): Prophylaxis and treatment dosage	*≥37 weeks' gestation and ≥2 kg at birth* Birth to age 1 week: • 1.5 mg/kg/dose once daily Age 1–4 weeks: • 3 mg/kg/dose twice daily Age 4–6 weeks: • 6 mg/kg/dose twice daily

Modified from Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. US Department of Health and Human Services guidelines for the use of antiretroviral agents in pediatric HIV infection, December 14, 2018. https://aidsinfo.nih.gov/. Accessed December 14, 2018.

leading some experts to recommend that an additional NAT be performed 2 to 4 weeks after cessation of antiretroviral administration (i.e., at 8–10 weeks of age), because of the theoretical possibility that early multiagent antiretroviral use may decrease the diagnostic sensitivity of NAT assays (see Fig. 127.2).[5] Any positive NAT result constitutes presumptive evidence of HIV infection; a second diagnostic test should be performed immediately, using either the same assay on a different blood sample or one of the other assays (i.e., RNA assay if DNA PCR assay was used, or DNA PCR assay if RNA assay was used) on the original sample to confirm the diagnosis. Two or more negative NAT results (and the absence of any other positive NAT result), both performed at 2 or more weeks of age and at least one performed at 1 or more month of age, are sufficient to *reasonably* exclude HIV infection in the nonbreastfed infant. Two or more negative NAT results (and the absence of any other positive NAT result), one performed at 4 or more weeks of age and one performed at 4 or more months of age, are sufficient to *definitively* exclude HIV infection in the nonbreastfed infant.[5,17] Some experts continue to perform a serologic test (enzyme immunoassay) at 15 to 18 months to confirm the absence of HIV infection (seroreversion), even in those children with all negative NAT results in infancy.

ADOLESCENT HIV INFECTION

Prevention of Infection

The routes of transmission of HIV in adolescents are similar to those in adults (mostly sexual contact and, to a smaller extent, intravenous drug use), such that prevention goals are similar to those used in adult medicine—serologic testing, counseling on safer sex practices, pregnancy planning, evaluation for use of preexposure prophylaxis (PrEP)[5,17] (see Chapter 119), and avoidance of intravenous drug use. However, the adolescent's ongoing psychosocial development, independence in seeking and following health care recommendations, and frequent difficulty in modifying current behavior for future benefits may complicate prevention efforts and necessitate a different focus from that used for adults.[5,13,14–16,17–18] In addition, special focus on the increasing demographic of young men who have sex with men, especially those of ethnic and racial minorities, may be required to successfully decrease new adolescent HIV infections.[46]

Issues in the Care of Aging HIV-Infected Youth

Disclosure of the HIV Diagnosis

Disclosing to a child that he or she has had HIV infection since birth is simultaneously one of the most difficult and important aspects of

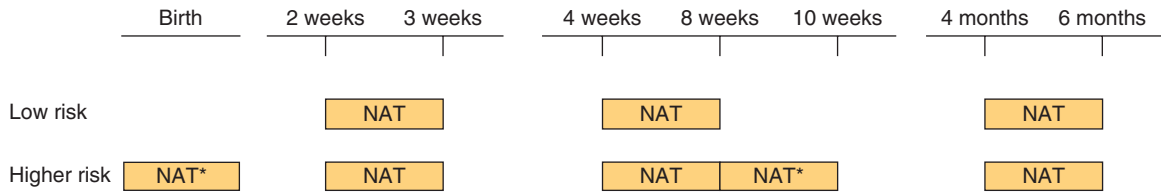

FIG. 127.2 Recommended virologic testing schedule for infants exposed to HIV by perinatal transmission risk. Low Risk: Infants born to mothers who received standard antiretroviral therapy *(ART)* during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence. Higher Risk: Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum antiretrovirals *(ARV),* received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (late second or third trimester), were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression. *For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of life). *NAT,* nucleic acid test. *(Modified from Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. US Department of Health and Human Services guidelines for the use of antiretroviral agents in pediatric HIV infection, December 14, 2018.* http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. *Accessed December 14, 2018.)*

caring for such children. The process for disclosure should be discussed and planned with the parents (or caretakers) and generally represents a process that takes place over many visits and several years, based on multiple factors, including the child's developmental level and questions about reasons for medications and medical visits, the child's health status, the approaching age of potential sexual debut, and the parent's or caretaker's readiness for disclosure to the child.[5,17,64–68] Parents' concern about revealing their own HIV status when disclosing information about HIV to their infected children can contribute to reluctance and delays in disclosure to children.[65] Observational studies show that most children learn of their diagnosis at 8 to 10 years of age.[64,67,68] However, delayed disclosure is unfortunately common, even occurring after sexual debut in some cases.[66] It is important and developmentally appropriate to disclose perinatal HIV infection no later than early adolescence to more fully engage youth in their own care goals, enable them to discuss their HIV status with sexual partners, and allow them to draw on social support to improve their health outcomes.[66,67] Research gaps and remaining challenges in this important area of research and care have been reviewed.[68]

Care Refusal and Low Adherence Among HIV-Infected Youth

The advent of effective cART has transformed perinatal HIV infection from a progressive, fatal infection into a chronic disease.[5,14–16,17,18] In addition to the concern for the development of cardiovascular and other long-term complications, survivors of perinatal HIV infection must also confront the usual challenges of adolescence and adulthood faced by peers without HIV infection.

Despite frequent contact with the pediatric medical care system, HIV-infected adolescents are often inexperienced with adult health care provision systems, may fear or deny their HIV infection, and may distrust any information given to them by the medical establishment.[5] Adolescents may also have complex biopsychosocial issues such as low self-esteem, chaotic and unstructured lifestyles, peer pressures not to be singled out with illness, and a lack of family support, all of which may reduce adherence with prescribed therapy.[5,17] The concrete thought processes of adolescents might make it difficult for them to understand why medications are necessary during periods of asymptomatic infection, especially if they have experienced any adverse effects of medication. Adolescents with perinatal HIV infection have often developed substantial antiretroviral resistance after serial, nonsuppressive regimens through childhood and continue to struggle with medication adherence.[69] Finally, in adolescents with behaviorally acquired HIV infection, ART is less likely to be initiated even in the era of universal treatment recommendations, and adolescents in adult care sites are more likely to discontinue ART than those receiving care at pediatric and adolescent clinics.[70,71]

Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with a realistic assessment of existing and potential support systems for the adolescent to adhere to such a regimen.[5,18] Rather than focusing simply on choosing "the right antiretroviral regimen" and avoidance of opportunistic illnesses, care plans for HIV-infected youth may require a strong focus on school success and career choices, reproductive health and plans for marriage and families, and transition to adult medical care.

Transition of HIV-Infected Youth From the Pediatric Care Model to the Adult Care Model

Transition to the adult medical care model takes time and advance planning because the pediatric and adult chronic-care models are different.[5,17,72–75,76] Transition is "a multifaceted, active process that attends to the medical, psychosocial, and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system."[73] Care models for children and adolescents with perinatally acquired HIV tend to be family centered, consisting of a multidisciplinary team of physicians, nurses, social workers, and mental health professionals. Many adolescents have had long-standing relationships with pediatric clinic staff and are often reluctant or anxious about adjusting to a new provider. In the pediatric setting, they have depended on substantial psychosocial support and are accustomed to a family-oriented setting that is not as easily externally identified as a clinic for treating people with HIV infection as are many adult care settings. Most adolescents are unfamiliar with the typical adult care model, which tends to be more individual centered, manages higher patient volumes, and has stricter consequences for lateness and missed appointments. In addition, the transition to adult care is often complicated by loss of insurance coverage that was relatively stable before adulthood.[74,75] Opportunities for the pediatric care provider and adult medical care provider to communicate early about timing of and expectations for transition of adolescents can lead to a smoother process. Pediatric care providers should have a formal plan to transition adolescents to adult care that considers factors such as adherence and HIV clinical status, presence of cognitive impairment or mental illness, level of family or other social support, financial and housing stability, and history of incarceration. Several groups have proposed specific models and approaches for transition programs.[74,76]

ADULT COMPLICATIONS OF PERINATAL HIV INFECTION

In many respects, the long-term complications of perinatal HIV infection and its treatment will be similar to those for HIV infection acquired in adulthood. However, there may be additional effects of exposures to HIV itself or to ART during critical periods of growth and development that lead to unique or more severe adverse outcomes as perinatally infected youth age through adulthood.

Many perinatally infected adolescents have had impaired growth during long periods of poorly controlled HIV infection in earlier childhood before the advent of combination antiretroviral regimens. As a result, their final adult stature is likely to be permanently shorter than their genetic potential, despite recovery of body mass.[77–80]

Similarly, perinatal HIV infection is associated with higher risk for poor bone mineral accrual during the first 20 years of life, when bone

mass normally is accrued to produce the early adulthood peak; the resulting compromise of peak bone mass may put these young adults at higher risk for fractures and osteoporosis at an early age.[81]

It is established that cardiovascular risk factors in childhood predict cardiovascular disease in adulthood and that atherosclerosis has a clinically silent onset early in life.[82–84] It has also been reported that HIV infection in adults appears to be an independent risk factor for cardiovascular disease, even with effective ART.[85] Taking these observations together, there is substantial concern that the prolonged exposure to dyslipidemia, chronic inflammation, and other cardiovascular risk factors related to HIV and its treatment throughout childhood may create particularly early onset and high risk for cardiovascular disease as perinatally HIV-infected youth reach adulthood.

Although active cART has drastically lowered the rate of pediatric HIV encephalopathy, the rates of cognitive deficits, attention deficits, and psychiatric disorders appear to remain higher than expected among perinatally HIV-infected youth.[15] Determining an appropriate comparison group confounds these analyses, but there are data supporting significantly higher rates of behavioral, educational, and pharmacologic interventions among perinatally infected youth.[86] In addition, perinatally infected youth 6 to 17 years of age have notable cognitive, academic, and social functioning deficits despite being in relatively good HIV virologic and immunologic control.[87]

Female adolescents with HIV infection have a high rate of cervical dysplasia (approaching 60%) and should undergo cervical Papanicolaou testing at HIV diagnosis, in 6 months, and then (if results are normal) yearly, rather than waiting until 21 years of age.[16] Contraceptive counseling regarding estrogen-containing oral contraceptives is complicated by the use of some concurrent antiretroviral agents. More than 100 pregnancies among US adolescent and young adult women with perinatally acquired HIV infection now have been reported.[66,88] Common but not consistent features among these reported pregnancies include greater rates of preterm birth, cervical dysplasia, and sexually transmitted infections, although not increased MTCT of HIV.[66,88]

The actual risks for adverse long-term growth, bone, cardiovascular and other health outcomes are not completely known, because the first wave of perinatally infected youth has just reached early adulthood. Thus, it will be important for adult medical care providers to be able to identify which of their adult patients acquired HIV infection perinatally, to monitor them appropriately, and to continue to research long-term complications of perinatally acquired HIV infection.

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128 Antiretroviral Therapy for Human Immunodeficiency Virus Infection

Athe M.N. Tsibris and Martin S. Hirsch

SHORT VIEW SUMMARY

DEFINITION
- Treatment of human immunodeficiency virus (HIV) infection uses a combination of at least three drugs to arrest virus replication and disease progression.

THERAPY CHOICES
- Antiretroviral therapy targets and inhibits HIV-specific enzymes.
  - Nucleoside and nucleotide reverse-transcriptase inhibitors (see Table 128.1)
  - Nonnucleoside reverse-transcriptase inhibitors (see Table 128.2)
  - Protease inhibitors (see Table 128.3)
  - Integrase inhibitors (see Table 128.4)
- Maraviroc and ibalizumab are the only drugs to target a host protein.
  - Entry inhibitors (see Table 128.4)

THERAPY STRATEGIES
- Preferred regimens will generally use two nucleoside reverse-transcriptase inhibitors (one of which is lamivudine or emtricitabine) in combination with an integrase strand transfer inhibitor.

THERAPY GOALS
- The goal of antiretroviral therapy, in all patients, is durable suppression of viral load to levels undetectable in commercial assays.

In June of 1981, the description of five cases of acquired immunodeficiency in the United States began our modern understanding of the human immunodeficiency virus (HIV) epidemic.[1] While HIV was first recognized clinically in the 1980s, recent work has shown that the virus may have been introduced into the United States through New York City around 1970.[2] Although HIV prevention and vaccine development efforts have continued since that time, the rapid advances made in the development and implementation of combination antiretroviral therapy (ART) have transformed care of the patient with HIV. In the developed world, substantial reductions in HIV-associated morbidity and mortality have changed an HIV diagnosis from a potential death sentence into a manageable chronic illness.[3] The life expectancy of adults with well-controlled HIV infection is beginning to approximate the life expectancy of uninfected persons.[4] These successes in developed nations should not obscure the magnitude of the ongoing worldwide HIV epidemic, because dedicated efforts to export these therapeutic advances to developing and impoverished nations have often met financial, organizational, and, in some cases, political, obstacles. Since the US Food and Drug Administration approval of zidovudine in 1987, antiretroviral agents have been developed that target many of the critical steps in the HIV replication cycle: entry, reverse transcription, integration, and proteolytic processing (Fig. 128.1). The preponderance of clinical evidence now demonstrates the superiority of integrase inhibitor–containing regimens as first-line therapy for HIV infection. While there are still roles for protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) in certain clinical situations, they are now less likely to be used as part of an initial treatment regimen. The clinical use of combination HIV ART requires attentive consideration of the pharmacology of, the clinical experience with, and the emergence of resistance to antiretroviral agents.

ANTIRETROVIRAL AGENTS

Nucleoside and Nucleotide Reverse-Transcriptase Inhibitors

Nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs) block the RNA-dependent DNA polymerase—reverse transcriptase (RT)—from synthesizing viral complementary DNA (cDNA) from HIV RNA. Drugs from this class were the first antiretrovirals to enter clinical use but, because of drug-associated toxicities, these early agents have largely been replaced in clinical practice by newer drugs with improved therapeutic, toxicity, and dosing profiles. All drugs in this class are analogues of native nucleotides, and almost all of them share the common motif of lack of a 3′-hydroxyl (OH) group on their ribose ring, which prevents the addition of nucleotides to the elongating proviral DNA strand; this effectively terminates proviral DNA synthesis (Fig. 128.2 and Table 128.1). The structural exception is tenofovir, which causes chain termination because of the lack of an intact ribose moiety.

Drugs in this class must be phosphorylated by intracellular kinases into their active triphosphate form before they can effectively inhibit RT, and all of these agents can, to a much lesser extent, inhibit the activity of normal cellular DNA polymerases—most notably the mitochondrial DNA (mtDNA) polymerase-γ (pol-γ). This NRTI-associated inhibition of mitochondrial function and replication accounts for certain drug-specific adverse effects, for instance, hyperlactatemia, lactic acidosis, hepatic steatosis, peripheral neuropathy, myopathy, and lipoatrophy. The dideoxynucleoside RT inhibitors exhibit the tightest binding to and the most inefficient exonucleolytic removal ("proofreading") from DNA pol-γ; this leads to the greatest degree of mtDNA synthesis inhibition via chain termination.[5–7] The rank order of NRTIs associated with mitochondrial dysfunction is dideoxyinosine > stavudine > zidovudine ≫ lamivudine-emtricitabine = abacavir = tenofovir. Lamivudine, emtricitabine, abacavir, and tenofovir are the NRTIs least likely to be associated with adverse drug effects resulting from mitochondrial dysfunction.

Lamivudine-Emtricitabine

Lamivudine [(−)2′,3′-dideoxy-3′-thiacytidine; 3TC] is a cytosine analogue with activity against HIV and hepatitis B virus (HBV). Emtricitabine (2′,3′-dideoxy-5-fluoro-3′-thiacytidine; FTC) is chemically related to lamivudine. Given their similar activities and toxicities, these drugs are discussed together. Of importance, however, these drugs should not be used together clinically. Lamivudine and emtricitabine can be taken with or without food and require dose reductions in patients with renal insufficiency. These drugs have minimal DNA pol-γ inhibitory effects.

Lamivudine or emtricitabine forms part of the backbone of nearly all currently recommended antiretroviral regimens. Emtricitabine is available in several fixed-dose combinations with other antiretroviral drugs, including tenofovir, efavirenz, rilpivirine, and elvitegravir. Lamivudine is available coformulated with abacavir, with zidovudine, or with both abacavir and zidovudine. Comparisons of lamivudine and emtricitabine

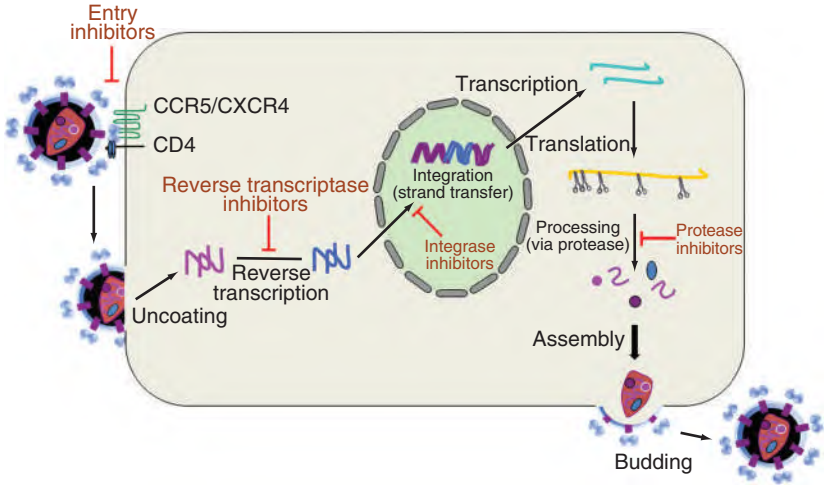

FIG. 128.1 The human immunodeficiency virus replication cycle. Combination antiretroviral therapy disrupts multiple viral processes to suppress replication. Fusion inhibitors can block the virus-coreceptor interaction and late stages of virus–cellular membrane fusion. Reverse transcription in the cytoplasm is inhibited by structural analogues of native nucleotides/nucleosides. Newly formed viral complementary DNA is incorporated into preintegration complexes and actively transported into the nucleus. Viral integrase catalyzes both the cytoplasmic processing of viral DNA and chromosomal integration (known as strand transfer); integrase inhibitors block strand transfer. Once viral DNA is transcribed and translated, homodimeric viral proteases cleave and process polypeptides into mature virions; protease inhibitors render these virions noninfectious. Virions bud from the infected cellular surface and are released, continuing the cycle. *CCR5,* C-C motif of chemokine receptor 5; *CXCR4,* C-X-C chemokine receptor 4.

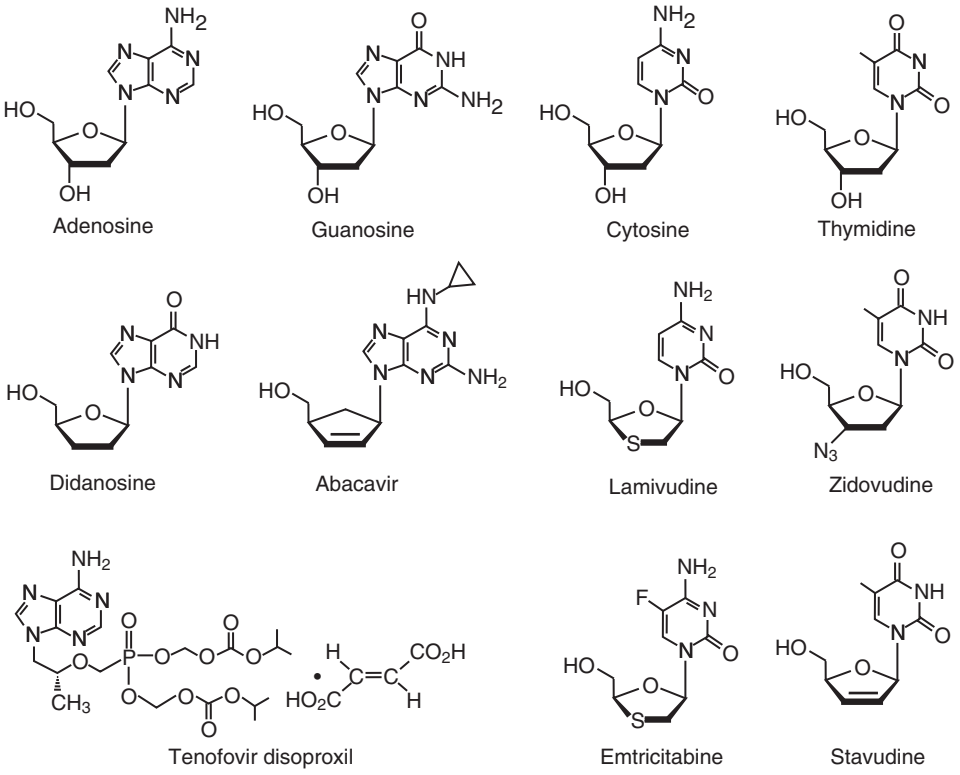

FIG. 128.2 Nucleoside and nucleotide analogue reverse-transcriptase inhibitors. Shown on top are the naturally occurring nucleosides (adenosine, guanosine, cytosine, and thymidine); below each of them are analogues used in antiretroviral therapy.

suggest the two drugs are clinically equivalent.[8] In general, regimens with an emtricitabine–tenofovir disoproxil fumarate (TDF) NRTI backbone have outperformed regimens with a zidovudine-lamivudine backbone.[9]

Lamivudine and emtricitabine are each well tolerated. Headache, nausea, fatigue, and neutropenia have been reported. Care should be taken when discontinuing lamivudine or emtricitabine in patients coinfected with HBV because HBV rebound and worsening hepatitis can occur.

High-level resistance to lamivudine and emtricitabine, up to 1000-fold, is conferred by a point mutation at position 184 in the *RT* gene (M184V). This mutation comes with a fitness cost to HIV that results in a 0.3 to 0.6 $\log_{10}$ reduction in plasma HIV RNA levels.[10,11] This fitness cost to HIV is often exploited clinically by continuing lamivudine or emtricitabine therapy in patients harboring virus with the M184V mutation. M184V can also hypersensitize HIV to inhibition by zidovudine, restore sensitivity to zidovudine in the presence of thymidine analogue mutations (TAMs),[12] and delay or prevent the emergence of TAMs.[10]

TABLE 128.1 Approved Nucleoside and Nucleotide Reverse-Transcriptase Inhibitors

AGENT	TRADE NAME	ORAL BIOAVAILABILITY (%)	SERUM HALF-LIFE (hr)	INTRACELLULAR HALF-LIFE OF TRIPHOSPHATE (hr)	ELIMINATION	ADULT DOSE[a]	DOSAGE FORMS
Zidovudine	Retrovir	64	1.1	3–4	Hepatic glucuronidation Renal excretion	300 mg twice daily During labor and delivery: 2-mg/kg IV loading dose, followed by 1 mg/kg/h until umbilical cord is clamped	300-mg tablet 100-mg capsule 50-mg/5-mL syrup 10-mg/mL solution for IV infusion
Didanosine	Videx Videx EC	40 fasted	1.5	25–40	Cellular metabolism	≥60 kg: 400 mg once daily 25 kg < weight < 60 kg: 250 mg once daily	125-, 200-, 250-, and 400-mg capsules 2- and 4-g powder packets (make 20-mg/mL solution)
Stavudine	Zerit	86	1.1	3	Renal excretion	≥60 kg: 40 mg twice daily <60 kg: 30 mg twice daily	15-, 20-, 30-, and 40-mg capsules 1-mg/mL oral solution
Lamivudine	Epivir	86	2.5	12–18	Renal excretion	300 mg once daily or 150 mg twice daily	100-, 150- and 300-mg tablets 5- and 10-mg/mL solutions
Abacavir	Ziagen	83	1.5	3.3	Hepatic glucuronidation and carboxylation	600 mg once daily or 300 mg twice daily	300-mg tablet 20-mg/mL solution
Tenofovir disoproxil fumarate (TDF)	Viread	39 with meal	12–14	>11[b]	Renal excretion	300 mg once daily	150-, 200-, 250-, and 300-mg tablets 40-mg/g oral powder
Emtricitabine	Emtriva	93	8–10	>24	Renal excretion	200 mg once daily Solution: 240 mg once daily	200-mg capsule 10-mg/mL solution
Zidovudine + lamivudine	Combivir[c]					One tablet twice daily	Zidovudine 300-mg/lamivudine 150-mg tablet
Abacavir + lamivudine	Epzicom[c] Kivexa[d]					One tablet once daily	Abacavir 600-mg/lamivudine 300-mg tablet
TDF + emtricitabine	Truvada[c]					One tablet once daily	TDF 300-mg/emtricitabine 200-mg, TDF 250-mg/emtricitabine 167-mg, TDF 200-mg/emtricitabine 133-mg, TDF 150-mg/emtricitabine 100-mg tablets
Zidovudine + lamivudine + abacavir	Trizivir[c]					One tablet twice daily	Zidovudine 300-mg/lamivudine 150-mg/abacavir 300-mg tablet
TDF + emtricitabine + efavirenz	Atripla[c]					One tablet once daily on an empty stomach	TDF 300-mg/emtricitabine 200-mg/efavirenz 600-mg tablet
TDF + emtricitabine + rilpivirine	Complera Eviplera[c,d]					One tablet once daily with a meal	TDF 300-mg/emtricitabine 200-mg/rilpivirine 25-mg tablet
TDF + emtricitabine + elvitegravir + cobicistat	Stribild[c]					One tablet once daily with food	TDF 300-mg/emtricitabine 200-mg/elvitegravir 150-mg/cobicistat 150-mg tablet
Tenofovir alafenamide (TAF) + emtricitabine + elvitegravir + cobicistat	Genvoya					One tablet once daily with food	TAF 10-mg/emtricitabine 200-mg/elvitegravir 150-mg/cobicistat 150-mg tablet
TAF + emtricitabine + rilpivirine	Odefsey					One tablet once daily with a meal	TAF 25-mg/emtricitabine 200-mg/rilpivirine 25-mg tablet
TAF + emtricitabine	Descovy					One tablet once daily	TAF 25-mg/emtricitabine 200-mg tablet
Abacavir + lamivudine + dolutegravir	Triumeq[c]					One tablet once daily	Abacavir 600-mg/lamivudine 300-mg/dolutegravir 50-mg tablet
Bictegravir + emtricitabine + TAF	Biktarvy					One tablet once daily	Bictegravir 50-mg/emtricitabine 200-mg/TAF 25-mg tablet

[a]For pediatric dose, see Chapter 127.
[b]Diphosphate form in activated cells.
[c]Pharmacokinetic properties are similar to those of the component drugs used separately.
[d]Trade name as marketed in Europe.

Abacavir

Abacavir—(1*S*, *cis*)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl)]-2-cyclopentene-1- methanol (ABC)—is a synthetic guanosine analogue administered orally as either 300 mg twice daily or 600 mg once daily. Mild hepatic dysfunction necessitates a decrease in dose to 200 mg twice daily; the use of abacavir in patients with moderate-to-severe hepatic dysfunction is contraindicated. The use of abacavir with ribavirin or ganciclovir can increase the likelihood of mitochondrial, hepatic, and pancreatic toxicities. Abacavir is not a substrate for or inhibitor of the cytochrome P-450 (CYP) enzyme complex, can be taken with or without food, and is metabolized primarily by glucuronidation. Abacavir is available as fixed-dose combinations with lamivudine, and with lamivudine and zidovudine.

Until recently, abacavir-lamivudine was typically classified as an alternative nucleoside backbone combination for antiretroviral-naïve patients. However, recent guidelines now include certain abacavir-lamivudine–containing combinations as recommended initial regimens.[13–15] Results from the AIDS Clinical Trials Group (ACTG) 5202 trial that compared TDF-emtricitabine to abacavir-lamivudine, in combination with either efavirenz or ritonavir-boosted atazanavir (atazanavir/r), demonstrated reduced virologic responses in participants with initial viral loads greater than 100,000 copies/mL who were randomized to receive abacavir-lamivudine.[16] In participants with baseline viral loads less than 100,000 copies/mL, similar times to virologic failure for the NRTI backbones of abacavir-lamivudine or TDF-emtricitabine were observed when used in combination with efavirenz or atazanavir/r.[17] Abacavir use was associated with a shorter time-to-regimen modification when combined with boosted atazanavir or efavirenz and a shorter time-to-safety event when combined with efavirenz. A similarly designed smaller study also comparing abacavir-lamivudine with TDF-emtricitabine, combined with ritonavir-boosted lopinavir (lopinavir/r), showed no differences in responses among individuals with high initial viral loads.[18] A 48-week study that included prescreening for the human leukocyte antigen (HLA)-B*5701 allele demonstrated superior virologic efficacy of TDF-emtricitabine over abacavir-lamivudine when either was combined with efavirenz.[19] In another trial in treatment-naïve subjects, the addition of abacavir to a three-drug regimen of zidovudine, lamivudine, and efavirenz did not improve treatment results.[20]

Several studies have evaluated switching a patient's NRTI backbone regimen to include abacavir. Substitution of either abacavir or TDF for stavudine or zidovudine in patients with lipoatrophy led to significant increases in limb fat.[21] Two studies that investigated the effects of a switch to TDF-emtricitabine or abacavir-lamivudine from the subject's existing NRTI backbone demonstrated no statistically significant differences in treatment failure rates, increased lipids or cardiovascular events with abacavir, or decreased bone mineral density (without increased fracture rate) associated with tenofovir-containing therapy.[22,23]

Abacavir is a weak inhibitor of DNA pol-γ and exhibits few mitochondrial-associated toxicities. The most significant acute adverse effect of abacavir use is a potentially fatal hypersensitivity syndrome. The presence of fever, abdominal pain, and rash, usually within 2 weeks of starting abacavir, generally requires discontinuation of the drug. This syndrome has been linked to the presence of the HLA-B*5701 allele, found in 5% to 8% of white populations with HIV. Screening for the HLA-B*5701 allele led to reductions in both clinically diagnosed and immunologically confirmed hypersensitivity reactions, and screening is now recommended before considering abacavir therapy.[24] Patients who are HLA-B*5701 positive should not receive abacavir. Data from a large cohort study raised concerns about increased rates of myocardial infarction in patients taking abacavir.[25] An association between abacavir and cardiovascular event risk has subsequently been corroborated, weakly corroborated, or refuted in a series of studies.[26–35] No consensus on abacavir-associated cardiovascular risk has yet been reached. Caution should therefore be exercised when considering abacavir therapy in patients at high risk for cardiovascular disease.

Reduced phenotypic susceptibility and resistance to abacavir can be conferred by the *RT* gene mutations K65R, L74V, Y115F, and M184V.[36] L74V reduced abacavir susceptibility twofold, K65R by roughly threefold, and Y115F by threefold, whereas the M184V mutation in isolation did not reduce abacavir activity unless paired with more than two TAMs.[37–40] The combination of M184V with either L74V or K65R resulted in a fivefold to eightfold decrease in abacavir susceptibility. As is the case for other NRTIs, high-level abacavir resistance accompanies the Q151M complex and T69 insertion mutations.

Tenofovir

Tenofovir is a nucleotide adenosine 5′-monophosphate derivative that, because of poor oral bioavailability, is commercially available in two prodrug forms: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). Tenofovir has activity against both HIV and HBV. TDF is administered orally at a dose of 300 mg once daily without regard to food and is also available as fixed-dose combinations with emtricitabine, as well as with emtricitabine and either efavirenz, rilpivirine, or elvitegravir-cobicistat. TAF is available in fixed-dose combinations with emtricitabine as well as emtricitabine with either rilpivirine, elvitegravir-cobicistat, or bictegravir. Dosing for TDF should be decreased in patients with renal insufficiency; TAF is not recommended for patients with creatinine clearance less than 30 mL/min. No dose adjustment is needed for hepatic impairment, although TAF has not been studied in patients with severe liver disease. After ingestion, TDF or TAF is hydrolyzed to tenofovir and then phosphorylated and incorporated into HIV DNA, causing chain termination. TAF administration results in higher intracellular concentrations and lower plasma concentrations of tenofovir, when compared to TDF.[40a] Tenofovir has low affinity for cellular DNA polymerases, including the mtDNA pol-γ. The majority of tenofovir is excreted unchanged in the urine via glomerular filtration, although the drug is also actively secreted across the renal tubule. Tenofovir is not a substrate for or inducer of the CYP enzymes but can reduce atazanavir concentrations; ritonavir and atazanavir increase tenofovir exposure. Tenofovir and didanosine should not be coadministered.

Tenofovir prodrugs are now included in many preferred first-line antiretroviral regimens, and can also be used in treatment-experienced patients whose virus lacks the K65R mutation. TDF or TAF, in combination with either lamivudine or emtricitabine, is often used in patients coinfected with HIV and HBV. In general, regimens that include a nucleoside backbone of TDF or TAF and either emtricitabine or lamivudine, along with either a boosted PI, an NNRTI, or an integrase inhibitor, are likely to achieve durable HIV responses.[9,41–44] There are exceptions to this rule. Some patients receiving tenofovir prodrugs in combination with emtricitabine (or lamivudine) and nevirapine have experienced early virologic failure,[45,46] and certain triple nucleoside combinations that include TDF (e.g., TDF-lamivudine-abacavir and TDF-lamivudine-didanosine) have fared less well than some comparator regimens.[47] The triple-NRTI combination of TDF-zidovudine-lamivudine has antiviral activity but has never been compared directly with more standard regimens.[48]

There has been some concern about the cumulative nephrotoxic potential of TDF, given its structural similarity to the nephrotoxic nucleosides adefovir and cidofovir. In an observational cohort, the use of TDF was associated with a greater decline in renal function than was seen with other NRTIs.[49] Decreased glomerular filtration rates (GFRs) in patients receiving TDF were modest within 6 months of starting therapy (–14 mL/min/1.73 m^3) and appeared to stabilize after 18 months (GFR decline of –19 mL/min/1.73 m^3); these findings were not associated with an increased rate of TDF discontinuation.[50] TDF, in combination with boosted PIs, was associated with greater declines in renal function compared with TDF in combination with NNRTIs, although it is not always clear that observed decreases in GFR in patients on TDF are clinically significant.[51] More recent large studies have confirmed an association between TDF and renal dysfunction; 50% of patients after 10 years of TDF therapy had estimated GFRs below 90 mL/min/1.73 m^3.[52,53] Monitoring of renal function in patients receiving TDF (serum creatinine, urinalysis, and urine electrolytes) is warranted. TDF is also associated with decreases in bone mineral density,[54–57] although the precise clinical implications of these findings remain to be fully elucidated. Bone loss associated with a TDF-containing regimen can be mitigated by vitamin D and calcium supplementation.[58] TAF has noninferior virologic efficacy and appears to have less renal and bone toxicity compared to TDF, defined as lower serum creatinine increases,

changes in proteinuria, and percent change in bone mineral density at the hip and spine.[59] Switching from TDF to TAF was associated with maintenance of virologic suppression and improved bone mineral density.[60] However, fasting lipid levels may increase with TAF when compared to TDF. In patients switching from coformulated TDF and emtricitabine to coformulated TAF and emtricitabine, median total, low-density lipoprotein, and triglyceride levels increased by approximately 10 mg/dL; total cholesterol–to–high-density lipoprotein ratios did not change.[60a]. Over 96 weeks, increases over baseline levels in total (29 mg/dL), high-density lipoprotein (6 mg/dL), and low-density lipoprotein (17 mg/dL) cholesterols, along with triglycerides (19 mg/dL), were significantly greater in participants who received the fixed-dose combination of TAF, emtricitabine, elvitegravir, and cobicistat when compared to participants who received the fixed-dose combination of TDF, emtricitabine, elvitegravir, and cobicistat.[60b]

Resistance to tenofovir prodrugs is selected by the K65R mutation and confers a twofold reduction in tenofovir activity. The TAM1 pathway (41L, 210W, 215Y/F) reduces tenofovir susceptibility fourfold, whereas the TAM2 pathway has less of an effect on tenofovir activity.[61–63] Insertion mutations at position 69 confer high-level resistance to the NRTIs, including TDF, whereas tenofovir retains significant activity in the presence of the Q151M complex.[64–66]

Integrase Strand Transfer Inhibitors

After viral entry into a target cell and subsequent uncoating, HIV RNA is reverse transcribed in the cytoplasm. The viral cDNA is then processed and transported to the nucleus, where integration into the cellular genome occurs as a result of strand transfer. HIV integrase catalyzes both the cDNA processing and strand transfer, and integrase strand transfer inhibitors (INSTIs; see Fig. 128.3 and Table 128.2) block the strand transfer reaction, thereby inhibiting HIV types 1 and 2 (HIV-1 and HIV-2) replication.[67] The safety profiles and superior efficacy of INSTI-containing regimens is reflected in their recommended first-line use worldwide.

Raltegravir

Raltegravir was the first approved antiretroviral drug that inhibits the catalytic activity of HIV integrase. Raltegravir is administered orally, 400 mg twice daily with or without food, or as two 600-mg tablets orally once daily. No dose adjustment is recommended for patients with mild-to-moderate hepatic dysfunction or renal insufficiency. Raltegravir is not known to induce or inhibit the CYP enzyme complex, and is primarily metabolized by glucuronidation. Caution is suggested when raltegravir and inducers of glucuronidation enzymes (rifampin, rifabutin, phenytoin, or phenobarbital) are used concurrently. When coadministered with rifampin, the raltegravir dose should be doubled to 800 mg twice daily. Antacids that contain aluminum or magnesium reduce raltegravir absorption; coadministration is not recommended. Calcium carbonate–containing antacids may be coadministered with raltegravir dosed 400 mg twice daily but not with 1200 mg once daily.

Raltegravir may be used in treatment-experienced patients with HIV and is considered a recommended treatment option by several guideline panels, when coadministered with a tenofovir prodrug (TDF or TAF) and emtricitabine.[13–15] The combined results of two similar phase III trials demonstrated a greater suppression to plasma viral loads less than 50 copies/mL through 48 weeks of treatment in chronically infected, treatment-experienced subjects receiving raltegravir compared with placebo, in both groups combined with optimized background therapy.[68,69] In a 48-week study in treatment-naïve subjects, a raltegravir-based regimen resulted in noninferior virologic outcomes to efavirenz-based combination therapy, with fewer central nervous system (CNS) side effects; these benefits persisted over 5 years of raltegravir-based therapy.[70,71]

A raltegravir once-daily regimen, administered as two 600-mg tablets, may be used in treatment-naïve patients with HIV or in virologically suppressed people with HIV who had been receiving a twice-daily raltegravir-containing regimen. In a phase III study of raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, both in combination with coformulated emtricitabine and TDF, in 797 treatment-naïve people with HIV, noninferior rates of virologic suppression at 48 weeks were observed in participants who received raltegravir 1200 mg once daily.[71a] Mean changes from baseline $CD4^+$ T-cell counts and the proportion of drug-related adverse events were similar between the two groups. The proportion of participants with HIV-1 RNA levels less than 40 copies/mL at 48 weeks was 89% and 88% in participants who received raltegravir 1200 mg once daily or 400 mg twice daily, respectively. Among participants with baseline HIV-1 RNA levels greater than 100,000 copies/mL, rates of suppression with once- or twice-daily raltegravir were similar (87% vs. 84%, respectively). Raltegravir resistance occurred in four participants (1%) randomized

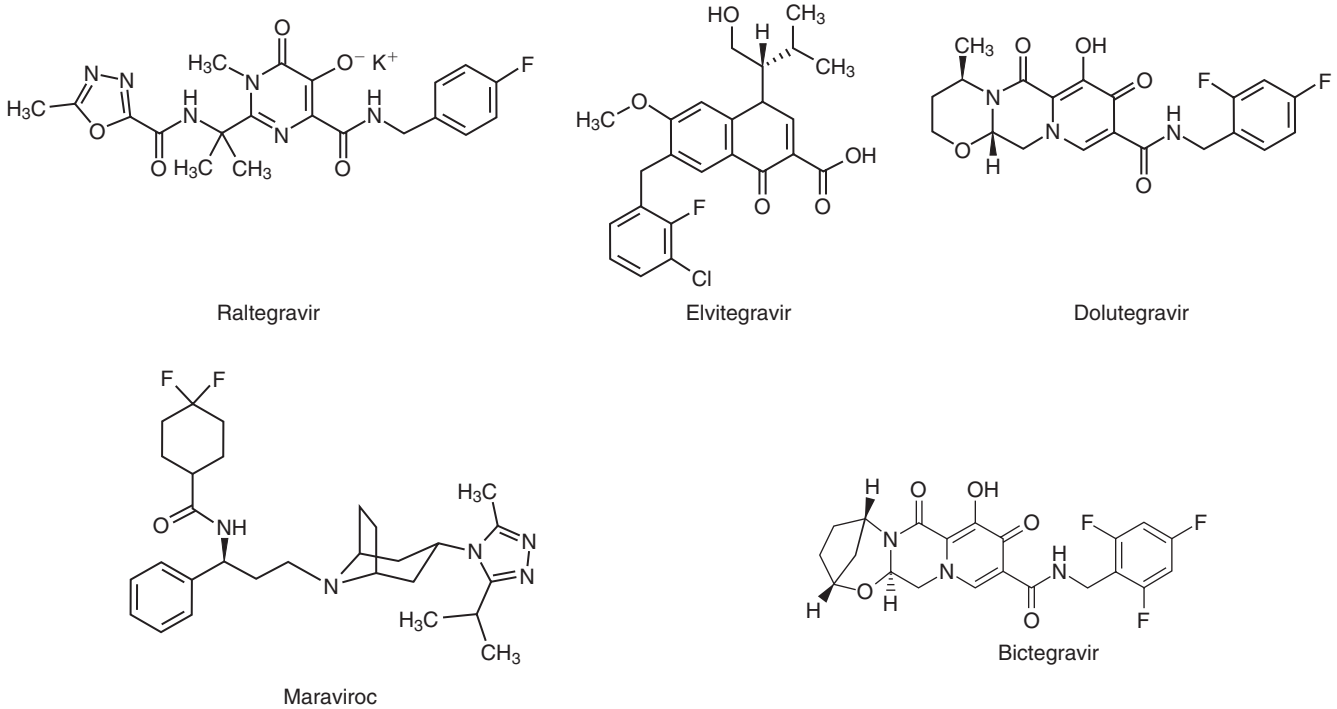

FIG. 128.3 **Entry inhibitor and integrase strand transfer inhibitors.**

TABLE 128.2 Approved Entry Inhibitors and Integrase Inhibitors

AGENT	TRADE NAME	BIOAVAILABILITY (%)	SERUM HALF-LIFE (hr)	ELIMINATION	ADULT DOSE[a]	AVAILABILITY
Enfuvirtide	Fuzeon	84	3.8	Catabolism to constituent amino acids	90 mg subcutaneously twice daily	90-mg single-use vials
Maraviroc	Selzentry Celsentri[b]	33	14–18	Hepatic metabolism via CYP3A	300 mg twice daily	25-, 75-, 150- and 300-mg tablets 20-mg/mL solution
Ibalizumab	Trogarzo	100	64	Intracellular catabolism	2000 mg IV loading dose, then 800 mg IV every 2 wk	150-mg/mL solution
Raltegravir	Isentress	Not established	9	UGT1A1-mediated glucuronidation	Treatment-naïve: 400 mg twice daily or 1200 mg once daily Treatment-experienced: 400 mg twice daily	400- and 600-mg tablets Chewable 25- and 100-mg tablets 100-mg packet
Dolutegravir	Tivicay	Not established	14	UGT1A1-mediated glucuronidation Hepatic metabolism via CYP3A	Treatment- or INSTI-naïve: 50 mg once daily INSTI-experienced or when coadministered with UGT1A/CYP3A inducers: 50 mg twice daily	10-, 25-, and 50-mg tablets

[a]For pediatric dose, see Chapter 127. Elvitegravir is not available as a single drug.
[b]Trade name as marketed in Europe.
CYP3A, Cytochrome P-450 isoenzyme 3A; *INSTI,* integrase strand transfer inhibitor; *UGT1A1,* UDP glucuronosyltransferase 1A1.

to once-daily raltegravir and no participants who received twice-daily raltegravir; concomitant emtricitabine resistance was seen in all four participants with raltegravir resistance mutations. Similar virologic suppression rates were maintained after 96 weeks of follow-up (81% vs. 80%, respectively). The results of this study differ from a prior study of raltegravir dosed at 800 mg once daily that demonstrated inferior virologic efficacy when compared to twice-daily dosing.[71b]

Two raltegravir switching strategies have been explored with disparate results. In a study of treated, virologically suppressed patients on a lopinavir/r regimen, participants were randomized either to continued PI therapy or to a raltegravir regimen.[72] A switch to raltegravir was associated with improved lipid profiles but at a cost of greater virologic failure rates. Raltegravir switching was virologically inferior to maintaining a lopinavir/r regimen. In a second study that enrolled fewer patients with prior virologic failure, a raltegravir switch met noninferiority criteria compared with continuing a boosted PI-based regimen.[73]

Adverse effects that occur more often in raltegravir-treated than placebo subjects have included fatigue, nasopharyngitis, rash, herpes zoster infection, elevations of alanine aminotransferase and aspartate aminotransferase, and increased triglycerides. Increases in creatine kinase, myalgia, and proximal myopathy have been associated with raltegravir use.[74,75] Neuropsychiatric side effects have been reported with raltegravir (e.g., depression and insomnia) but the precise relationship between drug and effect requires further study. HIV resistance to raltegravir is conferred by amino acid substitutions that occur in proximity to the integrase catalytic residues.[67,68] Raltegravir is considered to have a low genetic barrier to resistance; single mutations (E92Q, Q148H, N155H) confer 5-fold to 10-fold decreases in drug sensitivity and contribute to virologic failure.[76]

Elvitegravir

Elvitegravir is an INSTI that is available as the fixed-dose combination of 150 mg elvitegravir, 300 mg TDF, 200 mg emtricitabine, and 150 mg cobicistat or as elvitegravir, cobicistat, emtricitabine, and 10 mg TAF. Elvitegravir absorption is increased with food; fixed-dose combinations should be taken once daily with a meal. Cobicistat is a CYP3A inhibitor with no antiviral activity that is used to enhance exposure to elvitegravir, a CYP3A4 substrate, and is analogous to ritonavir boosting of PIs. Pharmacokinetic boosting extends the half-life of elvitegravir to 9 hours. The fixed-dose combination of elvitegravir that contains TDF should not be used in patients with a creatinine clearance less than 70 mL/min and must be discontinued when the creatinine clearance falls below 50 mL/min. The fixed-dose combination of elvitegravir with TAF should not be used in patients with creatinine clearances below 30 mL/min. Cobicistat inhibits tubular secretion of creatinine and results in a 0.1- to 0.2-mg/dL increase in serum creatinine; GFRs are not affected. No dose adjustments are required in patients with mild-to-moderate hepatic insufficiency. Elvitegravir coformulated with TAF is not recommended in patients with severe hepatic impairment. The fixed-dose combinations of elvitegravir can alter the concentrations of drugs that are metabolized by the CYP2D6 and CYP3A isoenzymes.

The fixed-dose elvitegravir-containing products are currently recommended by the US Department of Health and Human Services (HHS) Antiretroviral Guidelines Panel for initial therapy in certain clinical situations for people with HIV.[14] Two phase III studies demonstrated the noninferiority of coformulated elvitegravir, cobicistat, emtricitabine, and TDF when compared with either coformulated efavirenz, emtricitabine, and TDF or the combination of atazanavir/r and coformulated emtricitabine and TDF after 48 weeks of therapy.[77,78] Elvitegravir coformulated with TDF remained noninferior to the atazanavir/r-containing regimen after 96 weeks.[79] Overall rates of antiretroviral drug resistance were similar between the coformulated elvitegravir-containing and coformulated efavirenz-containing regimens; drug resistance was not observed in the atazanavir/r-containing regimen. Of 13 participants whose virus developed resistance on coformulated elvitegravir, 3 demonstrated triple-class resistance and 9 had mutations to both elvitegravir and emtricitabine (M184I/V). Elvitegravir selects for resistance at positions E92, G140, Q148, and N155 of integrase and should not be used in subjects with prior resistance to raltegravir.

The fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and TAF has been evaluated as initial therapy in two studies in people with HIV and creatinine clearances greater than 50 mL/min.[59] Patients randomized to either TAF or TDF coformulated with elvitegravir, cobicistat, and emtricitabine demonstrated noninferior rates of virologic suppression. At 48 weeks, 92% of participants who received coformulated elvitegravir and TAF and 90% of participants who received coformulated elvitegravir and TDF had plasma HIV-1 RNA levels less than 50 copies/mL. Virologic failure with resistance developed in similar proportions (0.8%–0.6%) in the two arms. Eight of 12 patients with resistance developed primary INSTI mutations, all developed M184V, and 1 selected for K65R. The most common side effects were nausea, diarrhea, and headache. Noninferiority was again seen at week 96, but by week 144, elvitegravir coformulated with TAF demonstrated superior virologic efficacy to elvitegravir coformulated with TDF (84% vs. 80%, with plasma HIV-1 RNA levels <50 copies/mL).[60b,79a]

The most common adverse events associated with coformulated elvitegravir are nausea and diarrhea. Neuropsychiatric adverse events have been reported in people receiving INSTIs, including elvitegravir.[79b]

Clinically relevant drug-drug interactions are possible with the elvitegravir-containing fixed-dose combinations and are mainly due to the CYP3A and CYP2D6 modulation by cobicistat. Antacids reduce cobicistat levels, whereas histamine type 2 (H2) receptor antagonists and proton pump inhibitors do not; the administration of elvitegravir-containing regimens and antacids should be separated by 2 hours. Coformulated elvitegravir is contraindicated in patients taking lovastatin, simvastatin, and rifampin.

Dolutegravir

Dolutegravir is an INSTI that has a higher genetic barrier to resistance than raltegravir or elvitegravir, does not require pharmacologic boosting, and can be taken with or without food.[80] In antiretroviral-naïve patients, dolutegravir has been administered orally as 50 mg once daily; a 50 mg twice-daily dose has been studied in treatment-experienced patients with genotypic resistance to raltegravir.[81,82] Dolutegravir has a half-life of 14 hours, is primarily metabolized by glucuronidation, and does not inhibit or induce CYP isoenzymes.[83] Dolutegravir can inhibit tubular secretion of creatinine, resulting in increased serum creatinine concentrations without changes in glomerular filtration.[84] Polyvalent cations can reduce dolutegravir absorption; dolutegravir-containing regimens should be taken 2 hours before or at least 6 hours after antacids or cation-containing laxatives. Dolutegravir is available in 10-mg, 25-mg, and 50-mg tablets and in a fixed-dose once-daily combination of dolutegravir, abacavir, and lamivudine, and has been coformulated with rilpivirine. Dolutegravir in combination with abacavir-lamivudine or a tenofovir prodrug (TDF or TAF) with emtricitabine is recommended as an initial regimen for antiretroviral-naïve patients.[14,15]

A dose-ranging phase IIb study of dolutegravir 50 mg with the fixed-dose combination of abacavir 600 mg and lamivudine 300 mg demonstrated superiority to a fixed-dose combination of efavirenz, emtricitabine, and TDF.[85] This difference in virologic response was driven primarily by discontinuation of the efavirenz-containing regimen at a higher rate than is typically seen in clinical practice. A phase III study in antiretroviral-naïve participants demonstrated virologic noninferiority of a once-daily dolutegravir regimen compared with twice-daily raltegravir in combination with a two-NRTI backbone.[81] Dolutegravir was superior to ritonavir-boosted darunavir (darunavir/r) when combined with either abacavir and lamivudine or TDF and emtricitabine,[86] and, when combined with abacavir and lamivudine, demonstrated superiority to an efavirenz-containing regimen.[87] Once-daily dolutegravir was associated with statistically significant increases, albeit small, in serum creatinine (0.1 mg/dL) over 48 weeks. Nausea, headache, nasopharyngitis, and diarrhea were observed in similar proportions of participants receiving dolutegravir or raltegravir. A phase III study of treatment-naïve participants with HIV demonstrated the superior efficacy, safety profile, and time to viral suppression of a dolutegravir plus abacavir-lamivudine regimen through 48 weeks when compared with the fixed-dose combination of efavirenz, TDF, and lamivudine[87]; the dolutegravir-containing regimen remained superior at week 144.[87a] In treatment-naïve women with HIV, the fixed-dose combination of dolutegravir, abacavir, and lamivudine demonstrated superior virologic efficacy when compared to a regimen of TDF, emtricitabine, and atazanavir/r.[87b]

The most common adverse reactions to dolutegravir are headache and insomnia. Dolutegravir has been associated in case report series with neuropsychiatric side effects, although the precise mechanism of these effects and their relationship to dolutegravir require further investigation.[79b,87c–87g]

Dolutegravir use in the first trimester of pregnancy may be associated with a risk of neural tube defects.[87h–87j] While a definitive association has not been established and additional clarifying data are anticipated, three HHS Antiretroviral Guidelines Panels have jointly issued interim recommendations on the use of dolutegravir in persons with HIV who are pregnant or of child-bearing potential.[87j] A negative pregnancy test is recommended prior to initiating dolutegravir. Those persons currently receiving dolutegravir should be counseled on the potential risks of neural tube defects within the first 12 weeks after conception. For those on dolutegravir who may be in this window of risk, switching to a non–dolutegravir-containing ART regimen is recommended. Persons who are pregnant and are 8 weeks or more from their last menstrual period may initiate or continue dolutegravir-based regimens. This warning is based on neural tube defects detected in 4 infants born to 426 women in Botswana; data from additional births in 500 women who used dolutegravir since conception are expected in the near future.[87j]

Most major integrase inhibitor resistance mutations decrease dolutegravir susceptibility, including E92Q, G140S/A, and Q148H/R/K. The exception is Q155H; Q155H-containing virus retains in vitro dolutegravir sensitivity.[88] In a study of 24 patients with raltegravir-resistant virus, 75% of participants who received 24 weeks of dolutegravir 50 mg twice daily, with an optimized background regimen, achieved plasma HIV-1 RNA levels less than 50 copies/mL.[82] The presence of more than two INSTI resistance mutations at baseline was associated with virologic failure. Given the limited patient enrollment and duration of follow-up in this study, the use of dolutegravir in patients with INSTI resistance mutations should be restricted to research studies or to those patients without additional antiretroviral treatment options, until additional outcomes data are reported.

Bictegravir

Bictegravir is an INSTI that is available as the fixed-dose combination of 50 mg bictegravir, 200 mg emtricitabine, and 25 mg TAF. The fixed-dose combination does not require boosting and can be taken without regard to food. Bictegravir has a half-life of 18 hours, is highly protein bound, and is metabolized by glucuronidation and the CYP3A4 isoenzyme. CYP3A4 is, however, neither induced nor inhibited. Bictegravir inhibits the tubular secretion of creatinine and results in an approximately 0.1-mg/dL increase in serum creatinine after 48 weeks of use; GFRs are not affected. The fixed-dose combination that contains bictegravir should not be used in patients with a creatinine clearance less than 30 mL/min or in patients with severe hepatic impairment. Bictegravir should not be used in combination with rifampin, rifamycins, or dofetilide. Bictegravir in combination with emtricitabine and TAF is recommended as an initial regimen by the HHS Antiretroviral Guidelines Panel.[14]

Two phase III studies demonstrated the noninferiority of the fixed-dose combination of bictegravir, emtricitabine, and TAF when compared to two dolutegravir-containing regimens. In a study that compared coformulated bictegravir, emtricitabine, and TAF to the fixed-dose combination of dolutegravir, abacavir, and emtricitabine for initial therapy in 629 adults with HIV, noninferior rates of virologic suppression to less than 50 HIV-1 RNA copies/mL were observed at 48 weeks.[88a] Fewer than 10% of enrolled participants were women. The proportions of participants with HIV-1 RNA levels less than 50 copies/mL after 48 weeks of therapy were 92.4% versus 93% in an intention-to-treat analysis and 99.3% versus 98.6% in the per-protocol (missing-as-excluded) analysis. HIV-1 resistance to either fixed-dose combination was not observed. Greater rates of nausea and drug-related nausea were observed with the fixed-dose combination of dolutegravir, abacavir, and emtricitabine, a finding attributed to previously observed greater rates of nausea with abacavir, relative to TDF or TAF. Serum creatinine increases of 0.1 mg/mL at week 48 were seen with both antiretroviral regimens.

In a study that compared the fixed-dose combination of bictegravir, emtricitabine, and TAF to dolutegravir and coformulated emtricitabine and TAF for initial therapy in 645 adults with HIV, noninferior rates of virologic suppression to less than 50 HIV-1 RNA copies/mL were observed after 48 weeks of therapy.[88b] The study population was 12% female. The proportion of participants with HIV-1 RNA levels less than 50 copies/mL at 48 weeks were 89% versus 93% in an intention-to-treat analysis and 99% versus 99.7% in the bictegravir and dolutegravir arms, respectively, in a per-protocol analysis. While the incidence and severity of adverse events were similar in the two treatment arms, study drug-related adverse events were significantly less common with the bictegravir fixed-dose combination. No participant developed treatment-emergent HIV-1 resistance with either antiretroviral regimen. Serum creatinine increases of 0.1 mg/mL at week 48 were seen with both antiretroviral regimens.

The bictegravir-containing fixed-dose combination may also be considered for use in virologically suppressed people with HIV who switch regimens. Two unpublished studies evaluated the safety and efficacy of switching to a bictegravir-containing fixed-dose combination

from regimens composed of either dolutegravir, abacavir, and lamivudine or coformulated abacavir and lamivudine or coformulated emtricitabine and tenofovir in combination with atazanavir or darunavir. A total of 1140 participants were studied. At 48 weeks, similar rates of continued virologic suppression were observed between participants who switched to the fixed-dose combination of bictegravir, emtricitabine, and TAF and those who maintained their prescribed antiretroviral regimen.[88c,88d]

Nonnucleoside Reverse-Transcriptase Inhibitors

NNRTIs bind RT but, in contrast to NRTIs, do so in a pocket far from the active site (Fig. 128.4 and Table 128.3). NNRTIs are noncompetitive inhibitors that induce conformational changes in RT, thereby reducing its activity. Available NNRTIs have long half-lives (25–55 h), do not require phosphorylation, and are HIV-1 specific; they have no activity against HIV-2. The NNRTI binding pocket on RT is nonessential to enzymatic function and can tolerate mutations without significant loss of RT activity. NNRTIs are hepatically metabolized and are substrates for the CYP enzymes. The potential for clinically relevant drug-drug interactions is, therefore, higher in NNRTIs than NRTIs.

The barrier to HIV-1 resistance is low for NNRTIs. Single-point mutations in RT can inactivate all members of this class, with the exception of etravirine. Given this low resistance barrier, NNRTIs are often used early in therapy when the probability of HIV resistance to these agents is lowest and the combined protective effect of three fully active drugs is maximized. NNRTI resistance mutations do not affect in vitro viral fitness, but it is not clear whether this observation has clinical relevance.[89] However, drug discontinuation in patients harboring NNRTI resistance mutations often leads to the loss of circulating viruses with mutations over time, suggesting at least some in vivo fitness disadvantage to those viruses.

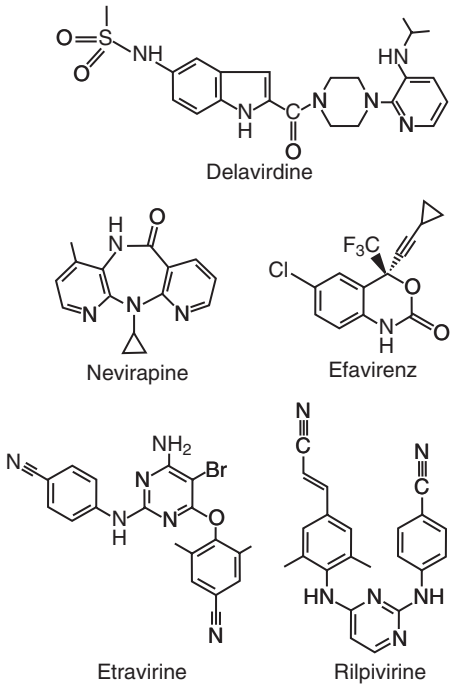

FIG. 128.4 **Non-nucleoside reverse-transcriptase inhibitors.**

Efavirenz

Efavirenz is an NNRTI that is administered orally as a 600-mg tablet once daily, usually in the evening. Efavirenz is also available as a coformulation with TDF and emtricitabine. Efavirenz should be taken on an empty stomach; a high-fat meal increases bioavailability and toxicity. No dose adjustment is needed in renal failure. Efavirenz is a major substrate of CYP2B6 and 3A4; a moderate inhibitor of CYP2C9, 2C19, and 3A4; and an inducer of CYP2B6 and 3A4. Concomitant use with other drugs acting at CYP3A4 carries a high likelihood of drug-drug interactions. All PIs are substrates of CYP3A4, and drug-specific dose adjustments are necessary.[14] There is no significant interaction between efavirenz and fluconazole, but an efavirenz dose adjustment is needed when coadministered with voriconazole.

Efavirenz is now an alternative agent for use in initial antiretroviral regimens according to some guidelines panels.[20,54] Superior virologic outcomes have been seen when efavirenz-based therapy was compared with some PI-based (nelfinavir, indinavir, and lopinavir-ritonavir) or triple NRTI-based regimens.[47,90–93] Comparable virologic outcomes were noted in a comparison to an atazanavir-, an elvitegravir-, or a raltegravir-containing regimen.[70,77–79,94] However, an efavirenz-containing regimen was inferior to a dolutegravir-containing regimen in one comparative trial.[87] Concerns exist regarding certain CNS-related toxicities of efavirenz and a possible association with suicidality.[95]

As with other NNRTIs, efavirenz can cause rash and hepatotoxicity, although less commonly than nevirapine. The two major toxicities of efavirenz are CNS adverse effects and teratogenicity. Efavirenz may cause QTc prolongation, and alternative antiretrovirals should be considered in patients at higher risk for torsades de pointes. Efavirenz use has been associated with neural tube defects in human embryos following first-trimester exposure, and CNS birth defects in nonhuman primates have been observed.[96] Alternative regimens should be considered in sexually active persons not using effective contraception. Efavirenz can be initiated in persons who present for antenatal care after the first trimester, or continued in persons who present for care during the first

TABLE 128.3 Approved Non-Nucleoside Reverse-Transcriptase Inhibitors

AGENT	TRADE NAME	ORAL BIOAVAILABILITY (%)	SERUM HALF-LIFE (hr)	ELIMINATION	ADULT DOSE[a]	DOSAGE FORMS
Nevirapine	Viramune	>90	45 after first dose 25–30 after 2 wk	Hepatic metabolism via CYP3A4 and 2B6	200 mg once daily for 14 d, then, if no rash develops, 200 mg twice daily or 400 mg XR once daily	100-, 200-, 400-mg tablets 50-mg/5-mL solution
Delavirdine	Rescriptor	85	5.8	Hepatic metabolism via CYP3A4	400 mg three times daily	100- and 200-mg tablets
Efavirenz	Sustiva Stocrin[b]	40–45	40–55	Hepatic metabolism via CYP2B6 and 3A4	600 mg once daily on an empty stomach	50- and 200-mg capsules 600-mg tablet
Etravirine	Intelence	Unknown	41 ± 20	Hepatic metabolism via CYP3A4, 2C9, and 2C19	200 mg twice daily after meals	25-, 100-, and 200-mg tablets
Rilpivirine	Edurant	Unknown	50	Hepatic metabolism via CYP3A	25 mg once daily with a meal	25-mg tablet

[a]For pediatric dose, see Chapter 127.
[b]Trade name as marketed in Europe.
CYP, Cytochrome P-450; *XR,* extended-release.

trimester. A definitive association between efavirenz use and birth defects has not been observed in one meta-analysis.[96a]

Up to 50% of patients starting efavirenz can experience some CNS adverse effects, although these usually decrease over the first several weeks of therapy and can be partially ameliorated by evening dosing. Adverse CNS effects include vivid dreams, insomnia, dizziness, and difficulty concentrating. Hallucinations, depression, suicidal ideation, and psychosis have been reported less commonly. Efavirenz is often avoided in persons with preexisting psychiatric conditions. A higher rate of suicidality was observed among efavirenz-treated patients in ACTG studies, an association not subsequently seen in analyses of three large observational cohorts or a retrospective cohort study.[95,96b–96d]

Efavirenz resistance is most commonly conferred by the K103N substitution in RT, but all NNRTI mutations at positions 100, 106, 181, 188, 190, and 225 abrogate efavirenz activity.[97] Y181C is uncommonly selected during efavirenz therapy. The standard commercial genotypic assays cannot reliably detect resistance mutations present at less than 20% of the viral population.[98] Consequently, some importance should also be placed on ascertaining past NNRTI treatment history as a surrogate guide to the possible presence of key resistance mutations.

Significant interactions can occur with antituberculosis therapies, particularly rifampin, although a large study demonstrated comparable virologic outcomes in patients receiving concomitant efavirenz-based therapy and antituberculosis treatment.[99] Like nevirapine, efavirenz decreases plasma methadone levels and can precipitate acute withdrawal.[100]

Rilpivirine

Rilpivirine is an NNRTI that is administered orally as a 25-mg tablet once daily with food. It is also available as a fixed-dose combination with dolutegravir or with emtricitabine and TDF or TAF. Fixed-dose combinations that contain rilpivirine have received increased interest recently primarily due to their smaller pill size, an advantage for some patients. No dosage adjustment is recommended for patients with renal dysfunction, including patients who require hemodialysis or peritoneal dialysis, or patients with mild-to-moderate hepatic insufficiency. The use of rilpivirine in patients with severe hepatic impairment has been insufficiently studied. Rilpivirine has a half-life of 50 hours and is metabolized by CYP3A4-mediated hepatic oxidation; no inhibition or induction of CYP isoenzymes has been reported. Rilpivirine absorption is sensitive to gastric pH; proton pump inhibitors should not be coadministered, and H2 receptor antagonists and antacids require spacing of doses. Rifamycins and efavirenz decrease rilpivirine concentrations, whereas PIs and azole antifungals increase plasma rilpivirine levels. Supratherapeutic rilpivirine plasma levels may prolong the cardiac QTc interval.

Two similar randomized phase III trials demonstrated noninferior efficacy of rilpivirine compared with efavirenz over 48 to 96 weeks of therapy when combined with TDF and emtricitabine.[101,102] However, a pooled analysis demonstrated lower response rates and higher rates of virologic failure in patients who received rilpivirine and had either baseline plasma viral loads greater than 100,000 copies/mL or adherence less than or equal to 95%, relative to patients taking efavirenz.[103] The incidence of serious adverse events was similar for rilpivirine and efavirenz, although rilpivirine had lower rates of discontinuation because of adverse events and fewer grade 2 to 4 laboratory abnormalities. Rates of virologic failure-associated drug resistance after 96 weeks were higher with rilpivirine and were more likely to be accompanied by NRTI resistance-associated mutations, most commonly at position 184 of RT (M184I or V). The 2018 HHS Antiretroviral Guidelines Panel lists the fixed-dose combination of rilpivirine, tenofovir (TDF or TAF), and emtricitabine as one of the recommended initial regimens in certain clinical situations for use in ART-naïve patients with $CD4^+$ T-cell counts greater than 200 cells/mm^3 and plasma viral loads less than 100,000 copies/mL.[14]

The most common rilpivirine-associated NNRTI resistance mutation is E138K, a mutation that confers resistance to all NNRTIs, including etravirine. The K101E, Y181C, and V189I NNRTI resistance mutations can also be selected by rilpivirine therapy; K103N has not been reported. Adverse effects associated with rilpivirine use include depressive disorders, headache, insomnia, and rash. Rash is significantly less likely to occur with rilpivirine than efavirenz.[103]

Protease Inhibitors

HIV relies on its aspartyl protease to cleave Gag and Gag-Pol polyproteins into their essential structural and enzymatic (RT, integrase) components. Many human monomeric aspartyl proteases (e.g., renin, pepsin) exist, but it is the homodimeric structure of HIV-1 and HIV-2 protease that selectively binds to, and is inhibited by, PIs (Fig. 128.5 and Table 128.4). Although viral particles can still be formed in the presence of PIs, they are rendered noninfectious. As a class, PIs are hepatically metabolized via the CYP isoenzyme CYP3A4. Ritonavir is a potent inhibitor of CYP3A4 metabolism; this property has been exploited to beneficially increase, or "boost," plasma drug levels of other PIs by coadministering subtherapeutic doses of ritonavir. CYP3A4 inhibition can lead, however, to drug-drug interactions with other medication classes that include immunosuppressants, antiarrhythmics, antimycobacterials, other antiretroviral drugs, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), methadone, and oral contraceptives. Atorvastatin, lovastatin, rosuvastatin, and simvastatin either are contraindicated with PI-based antiretroviral therapies or have maximum dosing limits.

PIs can be effective components of initial, second-line, and salvage antiretroviral regimens, although dyslipidemias can be a problem with some agents, and may develop within weeks to months of starting PI-based therapy.[104–107] PIs have also been implicated in the development of insulin resistance.[108–111] Although certain PIs may increase the risk of insulin resistance and diabetes, this is unlikely to be a class-wide effect and, in certain cases, may have more to do with a regimen's NRTI backbone.[112–118] Recent large observational cohort studies have found an association between PI use and an increased risk of cardiovascular events.[26,31] Atazanavir was a PI exception, and male patients with HIV who take atazanavir may have lower rates of cardiovascular events when compared to men receiving other antiretroviral regimens.[118a,119] Some data suggest a possibly increased risk of preterm delivery in pregnant persons receiving PI-based ART.[120]

PIs often have a higher genetic barrier to resistance than either NNRTIs or integrase inhibitors and typically require multiple mutations to substantially lose antiviral activity, although exceptions exist (e.g., saquinavir, nelfinavir). With most PIs, a major (or primary) mutation limits antiviral effectiveness and is followed by one or more minor (or secondary) mutations that by themselves do not dramatically affect phenotype but can improve viral fitness.[97] Ritonavir-boosted PIs select resistance mutations based on the main PI and not the low-dose ritonavir. The genotypic mutation patterns associated with PIs can be particularly complex and challenging to interpret; phenotypic resistance testing can often help resolve these clinical ambiguities.[121] Limited data exist on PI resistance mutations selected during boosted PI therapy in treatment-naïve patients, primarily because these patients usually fail with resistance to the NRTI backbone and not to the boosted PI.[97]

Boosted PI monotherapy has been studied as a strategy to limit drug toxicities and regimen cost. Unfortunately, boosted PI monotherapy leads to inferior rates of viral suppression and the emergence of drug resistance in treatment-naïve patients.[122] Boosted PI monotherapy has also been studied as maintenance, or consolidation, therapy to maintain viral suppression; results have been less effective than combination therapy.[123,124] Simultaneous double ritonavir-boosted PI therapy has also not demonstrated benefit over the more traditional single-boosted PI approach.[125,126]

Boosted Atazanavir

Atazanavir can be administered either as a 400-mg capsule once daily in treatment-naïve patients, or preferably as a 300-mg capsule combined with either 100-mg ritonavir or 150-mg cobicistat, both once daily, for treatment-naïve and treatment-experienced patients. Both boosted and unboosted atazanavir should be taken with food. No dose adjustment is needed for renal dysfunction in treatment-naïve patients, but a recommendation exists not to use atazanavir in treatment-experienced dialysis patients. Moderate hepatic impairment necessitates a dose reduction of atazanavir to 300 mg once daily, and the drug should not be used in severe (Child-Pugh class C) hepatic insufficiency. Atazanavir is metabolized by CYP3A4 and can also affect CYP2C8 and UDP glucuronosyltransferase 1A1 substrates. Methadone steady-state levels appear unaffected by atazanavir.[127] The absorption of atazanavir requires a low

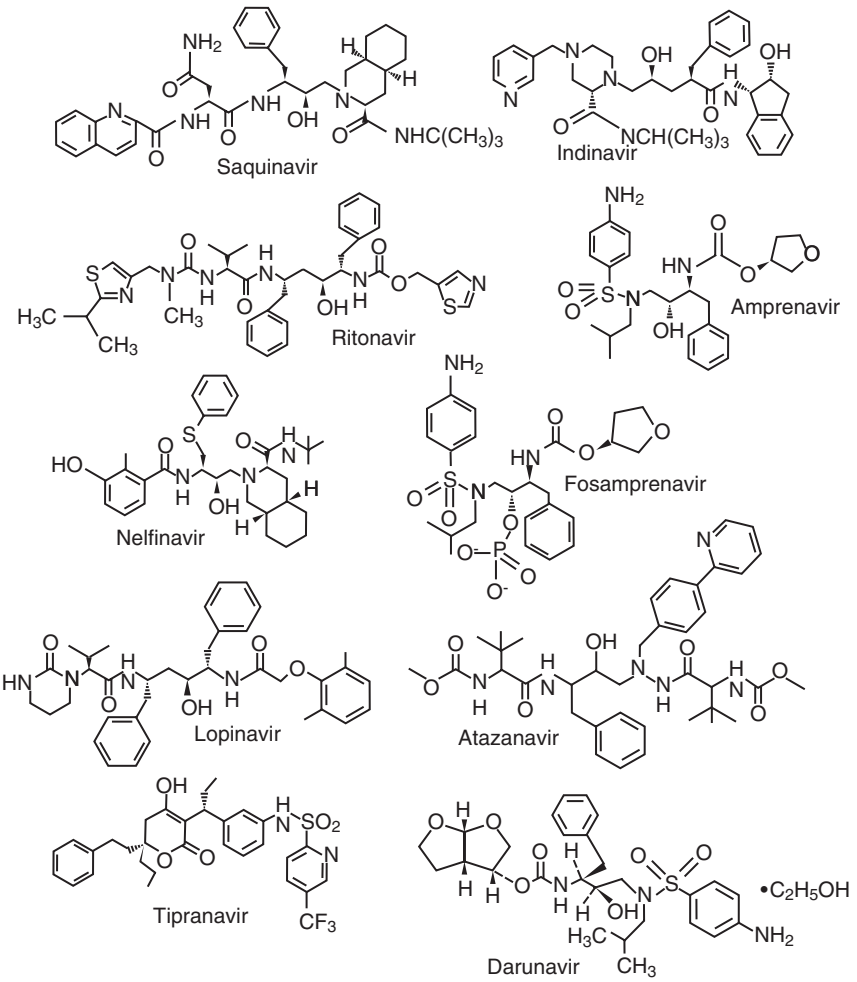

FIG. 128.5 **Protease inhibitors.**

gastric pH; interactions with antacids and H2 antagonists are possible. Atazanavir and proton pump inhibitors should not be coadministered in treatment-experienced patients.[14] Nevirapine should not be coadministered with either boosted or unboosted atazanavir.

The recommendation for ritonavir boosting of atazanavir in treatment-naïve patients is derived from two studies, one that directly compared boosted and unboosted atazanavir over 96 weeks and a second that compared atazanavir/r with lopinavir/r over 48 weeks.[41,128] Similar virologic response rates were seen with unboosted and boosted atazanavir, although there were more treatment failures and atazanavir resistance in participants receiving an unboosted atazanavir-containing regimen. Atazanavir/r demonstrated noninferiority to lopinavir/r over 48 weeks of therapy. There were fewer cases of dyslipidemia and diarrhea in participants receiving atazanavir/r, although this trial used an older lopinavir/r formulation that is no longer available. Atazanavir/r had similar antiviral efficacy compared with efavirenz when used with the NRTI backbones of either abacavir and lamivudine or TDF and emtricitabine.[129] Using a combined end point of antiviral efficacy and tolerability, atazanavir/r was inferior to either darunavir/r or raltegravir when used in combination with TDF and emtricitabine.[130] Atazanavir/r demonstrated similar virologic efficacy when compared to the fixed-dose combination of elvitegravir, cobicistat, TDF, and emtricitabine over 144 weeks.[130a] The CYP3A inhibitor cobicistat was found to have similar efficacy and tolerability compared to ritonavir when administered with atazanavir-TDF-emtricitabine.[131] Atazanavir/r has recently been evaluated more specifically in women. In a study of 575 women that compared atazanavir/r to cobicistat-boosted elvitegravir, both with TDF-emtricitabine, virologic suppression rates to viral loads less than 50 copies/mL were superior with the elvitegravir-containing fixed-dose combination after 48 weeks (87% vs. 81%, respectively).[131a] A 495-women study of a fixed-dose combination of dolutegravir, abacavir, and lamivudine versus atazanavir/r plus TDF and emtricitabine demonstrated significantly greater virologic suppression to HIV-1 RNA levels less than 50 copies/mL at 48 weeks for the dolutegravir-containing regimen when compared to the atazanavir-containing regimen (82% vs. 71%, respectively).[87b] The study was designed as a noninferiority study with a margin of −12%; the mean difference of superior virologic suppression with the dolutegravir-containing fixed-dose combination was 10.5%.

Adverse effects associated with atazanavir include nausea, hyperbilirubinemia with jaundice and scleral icterus, rash, cholelithiasis, and nephrolithiasis.[132–135] Atazanavir has less effect on serum cholesterol and triglycerides than do other PIs and was not associated with an increased risk of cardiovascular disease events.[119] Ritonavir boosting of atazanavir comes at a cost of more hyperbilirubinemia and a greater adverse effect on serum lipid profiles. The primary atazanavir resistance mutation is the I50L substitution; I84V also significantly limits drug activity. Minor mutations occur at positions 10, 16, 20, 24, 32, 33, 34, 36, 46, 48, 53, 54, 60, 62, 64, 71, 73, 82, 85, 90, and 93. In general, the presence of three or more of these mutations predicts a loss of virologic response to atazanavir.[136] For the practicing clinician, the simplest approach may be to order a resistance phenotype that will integrate all of the aforementioned genotypic information in a more concise and straightforward manner.

Boosted Darunavir

Darunavir is a PI with activity against some PI-resistant viruses. Its efficacy was first validated when boosted with ritonavir in treatment-experienced patients. On the basis of additional trials, darunavir/r is considered as a first-line PI in patients initiating ART. No dose adjustments are needed for patients with mild or moderate renal insufficiency