REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

Challenges in the Elimination of Pediatric HIV-1 Infection

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Pediatric acquired immunodeficiency syndrome (AIDS) was first described in 1982, 18 months after the first cases were reported in adults.[1] The majority of pediatric infections are acquired through mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1), which can occur during pregnancy, delivery, or breast-feeding (Fig. 1). The maternal viral load is a strong independent predictor of the risk of transmission, regardless of timing; transmission rates are extremely low when viral replication is fully suppressed.[2,3] Before the development of effective preventive interventions, the rate of transmission from mother to child ranged from 15 to 25% among infants who were formula-fed and from 25 to 40% among infants who were breast-fed.[4]

One of the greatest public health success stories has been the development and implementation of interventions to prevent mother-to-child transmission of HIV-1. In 1994, the Pediatric AIDS Clinical Trials Group Protocol 076, known as the 076 trial, showed that the single antiretroviral drug zidovudine, given orally to the mother during pregnancy, intravenously during labor, and orally to the newborn for 6 weeks, reduced in utero and intrapartum HIV-1 transmission in infants who were not breast-fed by nearly 70%.[5] This regimen was rapidly adopted in the United States, with a subsequent precipitous decline in the rates of mother-to-child transmission. Observational studies suggested that two- or three-drug antiretroviral regimens given during pregnancy further reduced transmission, as compared with zidovudine alone.[2] Women with HIV-1 infection in resource-rich countries are advised not to breast-feed, since HIV-1 can be transmitted through breast-feeding and since affordable replacement feeding and clean water are available. With the routine use of combination antiretroviral therapy during pregnancy and avoidance of breast-feeding, current mother-to-child transmission rates in the United States and other resource-rich settings are below 1%.[6]

However, most pediatric HIV-1 infections occur in resource-limited countries, with the majority (>90%) in sub-Saharan Africa. After the results of the 076 trial were released, international trials initially evaluated short-course regimens of single antiretroviral drugs, with a focus on preventing in utero and intrapartum HIV-1 transmission, and then built sequentially on previous results to improve approaches to the prevention of mother-to-child transmission of HIV-1 in resource-limited settings.[7,8] The World Health Organization (WHO) guidelines for prevention evolved as the results from such clinical trials became available.[8]

The development of antiretroviral interventions to reduce HIV-1 transmission through breast milk has been another key to turning the tide of the pediatric HIV-1 epidemic in resource-limited countries. In these settings, breast-feeding is the cornerstone of infant survival. Although shortening the duration of breast-feeding reduces the risk of mother-to-child transmission of HIV-1, it also markedly reduces

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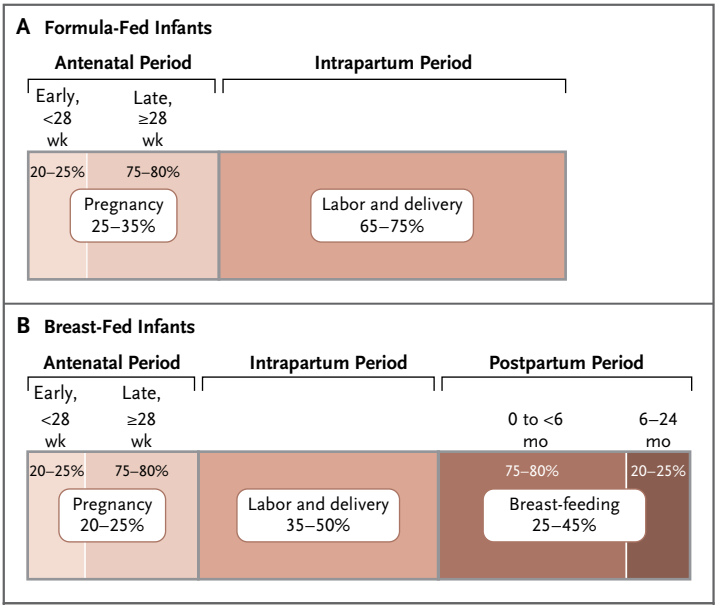

Figure 1. Relative Proportion of HIV-1 Transmission from an Untreated Mother to Her Infant, According to Gestational Period and Mode of Infant Feeding.

The relative proportion of overall mother-to-child transmission occurring during pregnancy, during labor and delivery, or after birth in the absence of antiretroviral therapy is shown according to whether the infants are formula-fed (Panel A) or breast-fed (Panel B). The overall absolute risk of transmission in the absence of antiretroviral therapy is 15 to 25% in formula-fed infants and 25 to 40% in breast-fed infants. The antenatal and postpartum periods have been divided into segments showing the approximate percentage of transmission that is believed to occur during the early and late portions of each period.

infants' survival.[9,10] Recent clinical trials have shown that the provision of antiretroviral therapy to lactating women or extended prophylaxis to breast-feeding infants safely and effectively reduces transmission through breast milk.[11] With the use of these regimens, the rate of postnatal transmission of HIV-1 from mother to child can be reduced to less than 2% — a level that makes it possible to contemplate not only prevention but also the potential elimination of mother-to-child transmission of HIV-1, even in settings where resources are limited.

STEPS TOWARD ELIMINATING MOTHER-TO-CHILD TRANSMISSION

The growing global availability of antiretroviral therapy for HIV-1–infected patients in general and for pregnant women specifically has created an opportunity for the global elimination of new pediatric HIV-1 infections. Recent randomized clinical trials have shown that treatment of all infected persons, regardless of immune status, unequivocally reduces morbidity and mortality and that the use of combination antiretroviral therapy during pregnancy is the most effective intervention for the prevention of mother-to-child transmission, regardless of the mother's CD4+ cell count.[12,13] Given these results, the innovative but initially controversial "Option B+" program initiated in Malawi in 2011, in which all HIV-1–infected pregnant and breast-feeding women begin lifelong antiretroviral therapy regardless of their CD4+ cell counts, has now become the standard of care, with initiation of treatment recommended as soon as HIV-1 is diagnosed.[14,15] Antiretroviral therapy that is started before conception and continued throughout pregnancy results in extremely low rates of mother-to-child transmission. In a study in France, there were no infections among 2651 infants born to HIV-1–infected women who received therapy that was initiated before conception and who had a plasma HIV-1 RNA level of less than 50 copies per milliliter at the time of delivery.[16]

With improved strategies for the prevention of mother-to-child transmission, the number of newly infected infants has decreased by 58% worldwide, from an estimated 520,000 in 2000 to 220,000 in 2014; 41% of this decline occurred between 2010 and 2014 — a greater decline than in the entire previous decade.[17] In July 2015, Cuba was the first country to receive WHO validation of the elimination of mother-to-child transmission of HIV-1, which was defined as fewer than 50 cases per 100,000 live births, a transmission rate below 5% if mothers are breast-feeding and below 2% if they are not breast-feeding for at least 1 year, an awareness of HIV-1 status among more than 95% of pregnant women, and the receipt of antiretroviral drugs by more than 95% of pregnant women with HIV-1 infection.[18] Given this achievement in Cuba, there is great optimism that the global elimination of new pediatric infections acquired through maternal transmission is attainable.

However, the elimination of new infections will require more than the availability of antiretroviral therapy. A comprehensive approach is

needed, including the reduction of new HIV-1 infections among women of reproductive age and actions to address unmet family-planning needs.[19] Unfortunately, the number of new HIV-1 infections among women of reproductive age remains high; it declined by only 16%, from 740,000 new infections in 2009 to 620,000 in 2013.[17] In studies involving African women who were breast-feeding their infants, acute HIV-1 infection in the mother was associated with a significantly elevated risk of transmission to the infant during the postpartum period (odds ratio, 2.9; 95% confidence interval [CI], 2.2 to 3.9) or during pregnancy and the postpartum period combined (odds ratio, 2.3; 95% CI, 1.2 to 4.4) as compared with the risk in mothers with chronic HIV-1 infection.[20] Although the unmet need for family planning has decreased worldwide between 1990 and 2010, 146 million women still have inadequate access to such services; in 2010, 23% of women of reproductive age in Africa had unmet family-planning needs.[21]

The prevention of transmission of HIV-1 from mother to child requires a series of sequential interventions targeted to women and their infants, with profound reductions in the effectiveness of the interventions with even small losses in the number of women and infants who are reached at each step (Fig. 2).[17,22-24] Unless health care systems can reach the majority of pregnant women and unless each step along the pathway to prevention is carried out with more than 95% reliability, the goal of eliminating transmission will not be reached.[23] Data from the WHO for the 22 designated priority countries, in which more than 90% of pregnant women with HIV-1 reside, indicate that only 44% of pregnant women were tested for HIV-1 and received results in 2013. Of those with known HIV-1 infection, 73% received effective antiretroviral treatment to prevent transmission of HIV-1 to their infants in 2014. The percentage of women who were reported to have received antiretroviral therapy during breast-feeding decreased to 61%; only 50% of infants were reported to have received antiretroviral prophylaxis.[17,24] Only 44% of infants exposed to HIV-1 underwent virologic testing within 2 months after birth in 2013; the number of children tested at the cessation of breast-feeding is unknown, but it is likely to be significantly lower.[24] Finally, only 32% of infants found to have HIV-1 infection were receiving antiretroviral therapy.

The postpartum period, in particular, presents many barriers to mothers' adherence to sustained treatment and engagement in care for themselves and their infants.[25,26] In 2013, the WHO-designated priority countries had a collective rate of mother-to-child transmission of HIV-1 of 7% at 6 weeks after delivery; this rate rose to 16% after breast-feeding ended.[17] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in more than half the cases of infants who acquired HIV-1 infection from their mothers in 2013, transmission occurred during breast-feeding, in part because health care programs have been focused on the antepartum components of prevention, with less emphasis on systematic follow-up and retention in care during prolonged breast-feeding.

The initiation of lifelong antiretroviral therapy in all pregnant women with HIV-1 infection has the potential to substantially improve maternal health and survival, as well as to make perinatal HIV-1 infection a rare event, but it will also lead to a rapid increase in fetal exposure to antiretroviral drugs. Although there are overwhelming benefits of such treatment for both mother and infant, there are also risks, including a possible increase in rates of preterm delivery and other adverse outcomes of pregnancy.[27] Further research is needed to determine how to optimize antiretroviral therapy so as to make possible safer, healthier pregnancies for HIV-1–infected women and to improve health outcomes for their uninfected infants. It will also be critical to monitor rates of adverse outcomes among pregnant women with HIV-1 infection who are receiving antiretroviral therapy to determine whether the rates exceed those observed in the general population, whether adverse outcomes differ among antiretroviral regimens, and whether exposure to antiretroviral drugs affects infant mortality and morbidity. Research to identify potential causal mechanisms will be important to determine whether there are interventions that could reduce adverse outcomes.

In sum, although great progress has been made, there is still much more to be done before mother-to-child HIV-1 transmission is eliminated. Even under the most optimistic scenarios for implementation of preventive measures, in which

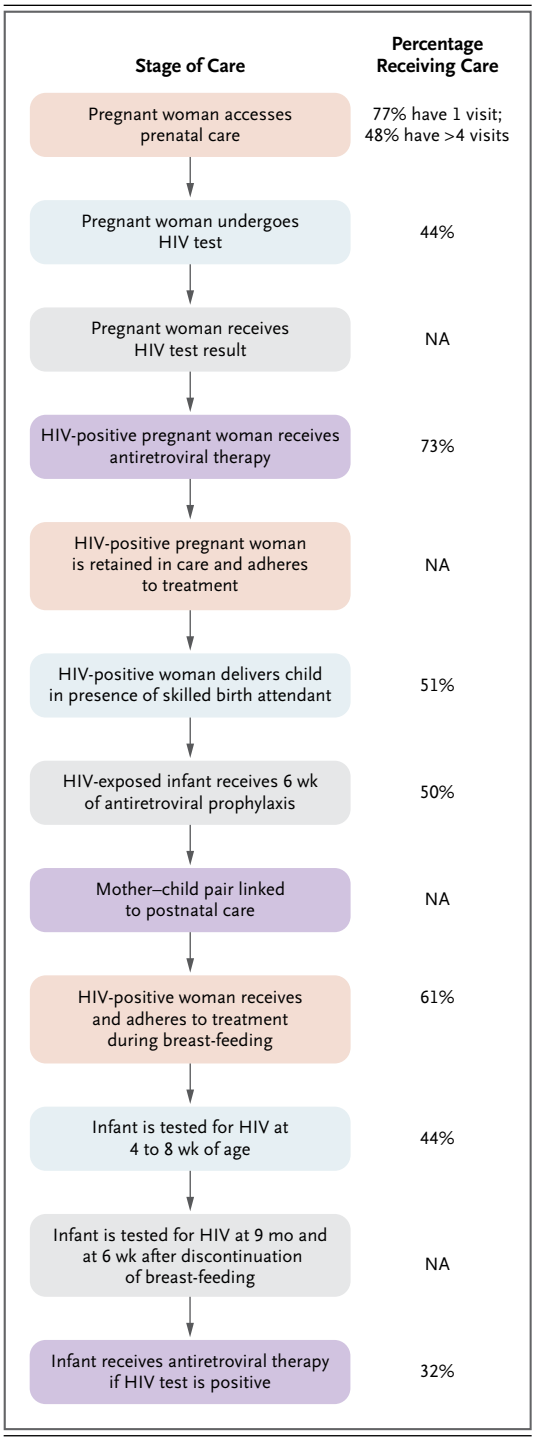

Figure 2. Pathway of Care for the Prevention of Mother-to-Child Transmission of HIV-1.

The percentages of mothers and infants who are receiving preventive care at each stage are shown, with current rates from cross-sectional studies listed when available. Data on prenatal care and the presence of skilled birth attendants are from the World Health Organization (WHO) and apply to the African region. Percentages with respect to HIV-1 testing and treatment are from WHO data on 22 priority countries in which more than 90% of women with HIV-1 infection reside[17] and from the response of the global health sector to HIV-1.[24] NA denotes not available.

all countries would achieve 95% coverage of infected mothers and their infants, it is estimated that 1.94 million children will be living with HIV-1 in 2020.[28]

EARLY COMBINATION THERAPY TO REDUCE INFANT MORTALITY

Untreated children have more rapid progression of HIV-1 infection than do untreated adults; in sub-Saharan Africa, 53% of children infected with HIV-1 die before the age of 2 years and 75% before the age of 3 years.[29] An analysis with adjustment for the timing of infection showed a significantly higher risk of death by 18 months among infants infected perinatally (in utero or intrapartum) (60%) than in those infected through breast-feeding (36%).[30]

The detection and measurement of HIV-1 nucleic acids in relatively small volumes of blood has improved understanding of the pathogenesis of pediatric HIV-1 and has advanced its diagnosis and treatment. Since maternal HIV-1 antibodies are passively transferred in the third trimester of pregnancy, all children born at term to HIV-1–infected women are seropositive. For HIV-1 infection to be diagnosed in children before the age of 18 months, current guidelines require that HIV-1 nucleic acid be detected in two separate blood samples.[31] Rapid progression of disease in children is associated with robust HIV-1 replication[32,33] and delayed generation of HIV-1–specific immune responses.[34,35] In the absence of antiretroviral therapy, plasma HIV-1 RNA levels increase rapidly after birth, peak at 1.0×10^5 to 1.0×10^7 RNA copies per milliliter of plasma within a few months, and remain high during the first 2 years of life.[36,37]

In the mid-1990s, given the rapid progression of the disease in children, clinical trials began to focus on early diagnosis and the use of combination antiretroviral therapy during the first 3 months of life, with the goals of minimizing

exposure to viral replication and preserving immune function. These trials showed that antiretroviral therapy initiated within 12 weeks after birth results in the rapid suppression (following a median of 8 to 12 weeks of therapy) of plasma HIV-1 RNA levels to below the limit of detection of both routine assays (<400 HIV-1 RNA copies per milliliter of plasma) and ultrasensitive assays (<20 or <40 HIV-1 RNA copies per milliliter of plasma, depending on the assay).[38-40] Control of HIV-1 replication within the first 6 months of life was associated with normal CD4+ cell counts and intact antibody and cell-mediated immunity in response to childhood vaccines. However, a persistent lack of HIV-1–specific antibodies and T-cell responses was noted in infants in whom antiretroviral therapy resulted in early control of HIV-1 replication.[41,42] After the 2008 publication of the results of a randomized clinical trial showing that early antiretroviral therapy markedly reduced mortality in HIV-1–infected infants,[43] the WHO and United States guidelines were modified to recommend early diagnosis and immediate initiation of antiretroviral therapy for all HIV-1–infected children under the age of 12 months.

LIMITING HIV-1 PERSISTENCE WITH EARLY THERAPY

Although plasma HIV-1 RNA is undetectable after viral replication is suppressed by early antiretroviral therapy, circulating HIV-1 DNA can still be detected in most children. When activated CD4+ cells are infected, viral enzymes mediate the transcription of HIV-1 RNA into double-stranded DNA and the integration of double-stranded DNA (provirus) into the host genome. Reversion of activated CD4+ cells to a resting memory state, in which HIV-1 gene expression is limited, generates a pool of potentially long-lived cells with integrated HIV-1 provirus that are not susceptible to control by antiretroviral therapy or by the immune system. CD4+ T cells with replication-competent HIV-1 provirus (latent reservoir) serve as the barrier to cure.

Recent longitudinal studies have shown a marked reduction in cell-associated HIV-1 DNA levels and in the size of the latent reservoir immediately after early therapy; lower cell-associated HIV-1 DNA levels and a smaller latent reservoir have also been noted in children in whom antiretroviral therapy is initiated in the first 3 months of life than in those in whom therapy begins after 3 months (Fig. 3).[44-51] These studies show a relationship between a younger age when antiretroviral therapy or virologic control begins and lower HIV-1 DNA levels in peripheral-blood mononuclear cells (PBMCs) after 1 to 4 years of treatment; they also show that early antiretroviral therapy reduces but does not eliminate the latent reservoir.[51] HIV-1 DNA levels that are measured directly in peripheral blood are estimated to be at least 100 to 150 times as high as levels of replication-competent virus measured by in vitro viral-outgrowth assays.[45] The ready detection of replication-competent HIV-1 5 years after virologic suppression is compatible with the clinical observation that viral replication rebounds within weeks after antiretroviral therapy is discontinued in the majority of young children who have received early treatment.[46,47]

Remarkably low circulating levels of HIV-1 DNA have been reported in children with prolonged suppression of viral replication (6 to 10 years or more) after antiretroviral therapy initi-

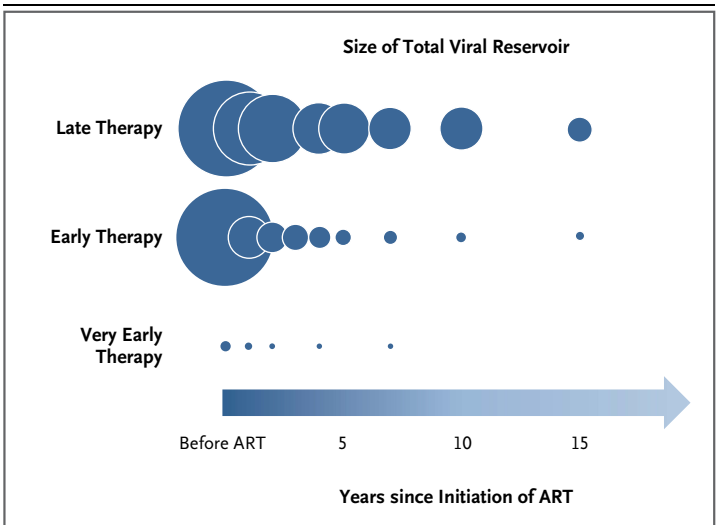

Figure 3. Effects of Timing of Antiretroviral Therapy (ART) on the Persistence of HIV-1–Infected CD4+ T Cells in Children.

Levels of CD4+ T-cell infection are lower after the suppression of HIV-1 replication following early treatment (initiated when the infant is <3 mo of age) and very early treatment (initiated <48 hr after birth) than following late treatment (initiated when the infant is >3 mo of age).[2,44-52] Available data suggest that cell-associated HIV-1 DNA levels continue to decay over many years.[48]

ated in early infancy.[48-50,52] In a cross-sectional study of children with HIV-1 suppression who had received therapy for at least a decade, extremely low levels of circulating HIV-1 DNA (<10 DNA copies per million PBMCs) were detected in most children in whom HIV-1 replication was suppressed before the age of 1 year — a significantly lower level than in children in whom replication was suppressed at 1 year of age or older.[52] HIV-1 DNA levels that were measured in children with indeterminate or negative results on Western blots for HIV-1 were lower than those in HIV-1–seropositive children, indicating that low or absent levels of HIV-1 antibodies in children more than 2 years of age who were treated early may serve as a marker to identify those with the lowest levels of cell-associated HIV-1 DNA.

The presence of very low levels of circulating HIV-1 DNA and the absence of replication-competent virus in children who have prolonged virologic suppression after early antiretroviral therapy raise the question of whether long-term therapy restricts the persistence of HIV-1 over time. After the initial rapid decline in circulating HIV-1 DNA levels during the first 1 to 2 years of therapy, a continued, slower decline in HIV-1 DNA levels in PBMCs was observed in children in whom therapy was initiated within 3 months after birth and in whom plasma HIV-1 RNA levels were consistently below the detection limits of ultrasensitive RNA assays for at least a decade.[48] This decline occurs in the absence of detectable HIV-1–specific immune responses, suggesting that antiretroviral therapy in early infancy reduces the seeding of long-lived cells harboring HIV-1 DNA and the latent reservoir. In adults and children who have received early treatment, the proportion of the total number of CD4+ cells containing HIV-1 DNA in transitional memory CD4+ cells appears to exceed that in longer-lived central memory or stem memory CD4+ cells.[48,53]

The decay in viral reservoirs over time after viral suppression in children who receive early treatment contrasts with the reported stability of HIV-1 DNA levels in PBMCs and the latent reservoir in adults treated either early or late who have viral suppression during antiretroviral therapy. In adults, studies have shown a half-life of 43 to 44 months for the latent viral reservoir, which suggests that clearance of this reservoir would take a minimum of 73 years of therapy.[54] Additional research is necessary to clarify the size and stability of the latent reservoir in children who have virologic suppression after receiving early antiretroviral therapy.

Studies indicate a relationship between the duration of exposure to viral replication and the size of the residual HIV-1 reservoir after viral suppression is achieved in children receiving antiretroviral therapy.[44-46] This finding suggests that initiating therapy even earlier — within the first days of life — may reduce long-lasting HIV-1 reservoirs even further. Low HIV-1 DNA levels in PBMCs and a small latent reservoir are associated with an increased likelihood and duration of remission after therapy is discontinued.[53,55] The recently described case of the child referred to as the Mississippi Baby suggests that very early antiretroviral therapy can reduce the latent reservoir sufficiently to permit a period of virologic control without therapy.[56] In this case, therapy consisting of one non-nucleoside and two nucleoside reverse-transcriptase inhibitors was initiated 30 hours after birth in an infant at high risk for perinatal infection from her HIV-1–infected mother, owing to a lack of maternal prenatal care and the absence of antenatal antiretroviral therapy. HIV-1 infection was confirmed in the infant at 1 week of age, and therapy was continued through the age of 18 months. Although virologic rebound was observed at 45 months of age, early antiretroviral therapy probably reduced the HIV-1 reservoirs sufficiently to make possible 27 months of virologic control without treatment.[57]

A clinical trial funded by the National Institutes of Health (International Maternal Pediatric Adolescent AIDS Clinical Trials Network Protocol 1115; ClinicalTrials.gov number, NCT02140255) recently began enrollment to evaluate whether antiretroviral therapy initiated within 48 hours after birth in infants infected in utero and continued through the age of 2 years reduces the size of the latent reservoir sufficiently to allow a period of remission after antiretroviral therapy is discontinued. Outside the research setting, it is not recommended that such therapy be discontinued in children who have prolonged viral suppression after early treatment, since cases of rapid viral rebound after the in-

terruption of antiretroviral therapy have been described.[58]

CHALLENGES IN ACHIEVING HIV-1 REMISSION IN CHILDREN

Current nucleic acid–based methods for diagnosing HIV-1 require sophisticated laboratory equipment and technical expertise; point-of-care testing devices that are currently in development could greatly aid in the rapid identification of HIV-1–infected infants. Circulating levels of HIV-1 DNA and the latent viral reservoir may fall below the limits of detection of currently available assays in infants treated early (<3 months of age) or very early (<48 hours after birth). More sensitive assays to detect replication-competent HIV-1 in diverse types of small-volume specimens, such as blood and cerebrospinal fluid, will help to define the size and anatomical distribution of the latent reservoir in children who have virologic suppression after early or very early antiretroviral therapy; such assays may also lead to a better understanding of the relationship between the size of the latent reservoir and the durability of remission once antiretroviral therapy is discontinued. Noninvasive techniques for measuring tissue reservoirs of the virus and the discovery of biomarkers that can be used to predict the likelihood of remission if antiretroviral therapy is discontinued would greatly facilitate research into the pathogenesis of HIV-1 and related clinical trials.

At present, only a very limited number of antiretroviral drugs are available for use in young infants; several of these overlap with the antiretroviral agents used to prevent mother-to-child transmission of HIV-1 and have low resistance thresholds. Thus, there is a pressing need to develop additional drugs appropriate for use in young infants. Because only 32% of children with HIV-1 infection who need treatment are receiving antiretroviral therapy, additional efforts are necessary to improve their access to care.[17]

An important question is whether antiretroviral therapy alone will reduce the latent reservoir of virus sufficiently to permit remission to last for years. Regimens combining antiretroviral agents with those that activate viral genomes integrated into the host genome (latency-reversing agents) of resting memory CD4+ cells might reduce or clear the latent reservoir of HIV-1; a combination of these agents with a therapeutic vaccine that induces HIV-1–specific CD8+ cells might enhance the clearance of HIV-1–infected cells. The addition of neutralizing antibodies to early or very early antiretroviral regimens might enhance the control of HIV-1 replication after antiretroviral therapy is discontinued. In the future, gene-editing techniques may be developed that can be used to reduce the susceptibility of CD4+ cells to HIV-1 infection or to remove integrated HIV-1 provirus from infected cells.

CONCLUSIONS

The prevention of new infections in children and control of HIV-1 in children who become infected are essential elements in attaining the goal of eliminating pediatric HIV-1 infection. There has been considerable progress toward the prevention of new pediatric HIV-1 infections in recent years because of the global implementation of highly effective antiretroviral treatments to prevent mother-to-child transmission of HIV-1. With the increasing global availability of antiretroviral drugs, there has also been a convergence of guidelines for prevention and treatment in resource-rich countries and the WHO guidelines for resource-limited countries (Fig. 4).[15,59] Moreover, recent studies have shown that it is possible to substantially reduce the size of the latent reservoir in infected children with very early treatment.

Continued progress towards eliminating pediatric HIV-1 infection requires finding solutions to long-standing problems in maternal and child health systems in countries with limited resources so as to improve the delivery of preventive health care services at each stage of gestation, delivery, and breast-feeding during which transmission from mother to child may occur (Fig. 2). These problems include inadequate access to early antenatal care, poor linkage between mother–child pairs and postnatal health services, and a lack of systems to ensure long-term retention in care and continued provision of and adherence to maternal antiretroviral therapy. The achievement of remission, and potentially the cure, of pediatric HIV-1 infection will require additional research to improve both

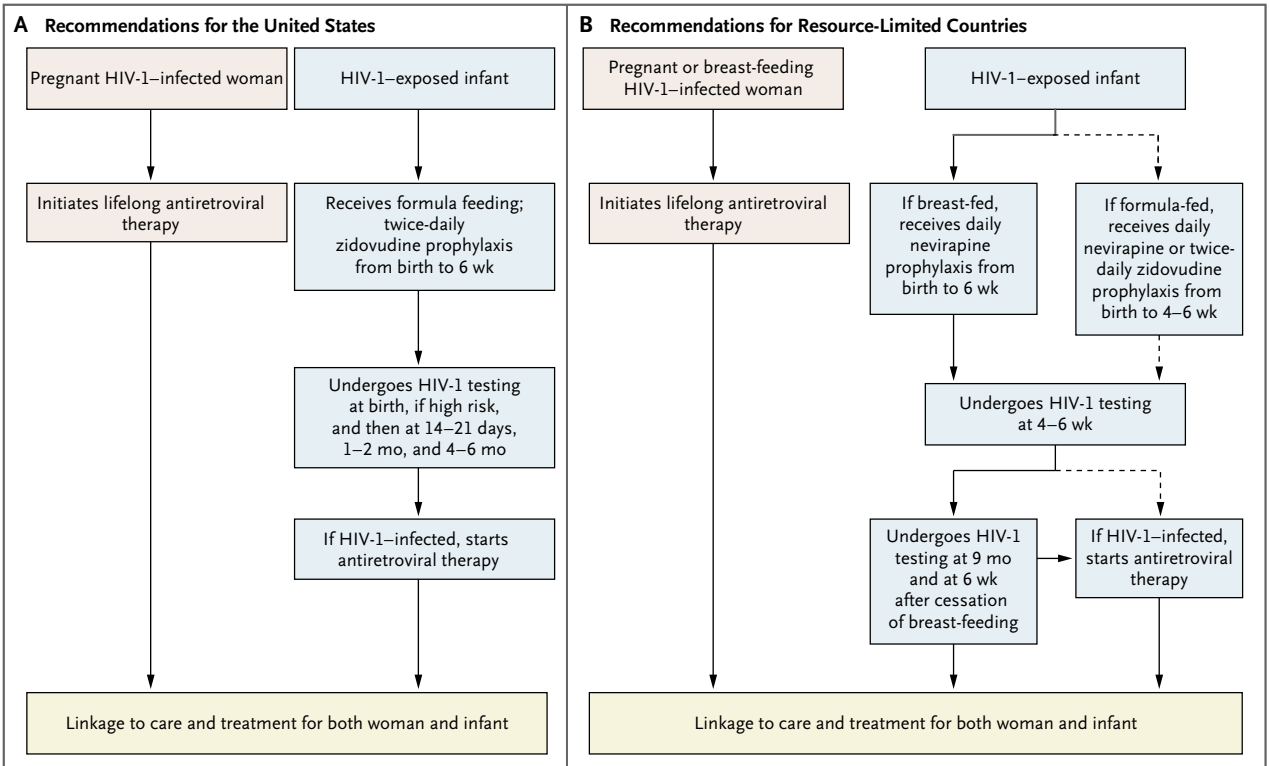

Figure 4. Current Guidelines for the Prevention of Mother-to-Child HIV-1 Transmission and Treatment of HIV-1–Infected Women and Infants in the United States and Resource-Limited Countries.

Among pregnant HIV-1–infected women in the United States, the preferred antiretroviral regimen is a combination of two nucleoside reverse-transcriptase inhibitors plus atazanavir–ritonavir, darunavir–ritonavir, efavirenz, or raltegravir. Among pregnant and breast-feeding women with HIV-1 infection in resource-limited countries, the preferred regimen is tenofovir plus either lamivudine or emtricitabine plus efavirenz. Recommendations for the United States are from the Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission.[59] Recommendations for resource-limited countries are from the WHO.[15]

methods of early diagnosis in resource-limited settings and methods to define the size and distribution of the latent HIV-1 reservoir in children more accurately. New antiretroviral drugs that are highly active, palatable, and inexpensive are needed for pediatric treatment, as are improved systems for providing children with access to lifesaving antiretroviral therapies.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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SHARING DATA IN A PUBLIC HEALTH EMERGENCY

The case for sharing data, and the consequences of not doing so, have been brought into stark relief by the Ebola and Zika outbreaks. In response, the *New England Journal of Medicine* has become a journal signatory to the following statement.

"In the context of a public health emergency of international concern, it is imperative that all parties make available any information that might have value in combatting the crisis. As research funders and journals, we are committed to working in partnership to ensure that the global response to public health emergencies is informed by the best available research evidence and data.

Journal signatories will make all content concerning the Zika virus free access. Any data or preprint deposited for unrestricted dissemination ahead of submission of any paper will not preempt later publication in these journals.

Funder signatories will require researchers undertaking work relevant to public health emergencies to establish mechanisms to share quality-assured interim and final data as rapidly and widely as possible, including with public health and research communities and the World Health Organization.

We urge other journals and research funders to make the same commitments."