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Objectives: Using published, nationally-representative estimates, we calculated the total number of perinatally HIV-exposed and HIV-infected infants born during 1978–2010, the number of perinatal HIV cases prevented by interventions designed for the prevention of mother-to-child transmission (PMTCT), and the number of infants exposed to antiretroviral (ARV) drugs during the prenatal and intrapartum periods.

Design: We calculated the number of infants exposed to ARV drugs since 1994, and the number of cases of mother-to-child HIV transmission prevented from 1994 to 2010 using published data. We generated confidence limits for our estimates by performing a simulation study.

Methods: Data were obtained from published, nationally-representative estimates from the Centers for Disease Control and Prevention. Model parameters included the annual numbers of HIV-infected pregnant women, the annual numbers of perinatally infected infants, the annual proportions of infants exposed to ARV drugs during the prenatal and intrapartum period, and the estimated MTCT rate in the absence of preventive interventions. For the simulation study, model parameters were assigned distributions and we performed 1,000,000 repetitions.

Results: Between 1978 and 2010, an estimated 186,157 (95% CI: 185,312–187,003) HIV-exposed infants and approximately 21,003 (95% CI: 20,179–21,288) HIV-infected infants were born in the United States. Between 1994 and 2010, an estimated 124,342 (95% CI: 123,651–125,034) HIV-exposed infants were born in the US, and approximately 6083 (95% CI: 5931–6236) infants were perinatally infected with HIV. During this same period, about 100,207 (95% CI: 99,374–101,028) infants were perinatally exposed to ARV drugs. As a result of PMTCT interventions, an estimated 21,956 (95% CI: 20,191–23,759) MTCT HIV cases have been prevented in the United States since 1994.

Conclusion: Although continued vigilance is needed to eliminate mother-to-child HIV transmission, PMTCT interventions have prevented nearly 22,000 cases of perinatal HIV transmission in the United States since 1994.

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(Te)he first cases of perinatally acquired human immunodeficiency virus 1 (HIV) in the United States probably occurred in 1978.1 In 1994, the United States Public Health Service Task Force (USPHS) recommended the use of zidovudine to reduce perinatal transmission of HIV,2 based on clinical trial results.3 In subsequent years, other interventions for prevention of mother-to-child transmission (PMTCT) were recommended, including use of combination antiretroviral (ARV) treatment in 1997,4 and elective cesarean section delivery for women with HIV viral loads greater than 1000 copies/mL.5 The recommendation of opt-out HIV testing for pregnant women was introduced in 19996 with the goal of increasing the proportion of women whose HIV status was known before delivery, allowing more HIV-infected pregnant women to receive preventive interventions during pregnancy.7 Avoidance of breastfeeding by HIV-infected women has been recommended in high-resource settings since 1985;8 breastfeeding by HIV-infected women has been estimated to increase the risk of mother-to-child HIV transmission by an additional 14%.9 The Enhanced Perinatal Surveillance system of the US Centers for Disease Control and Prevention (CDC) estimated the rate of MTCT in the United States as 1.7%–2.9% during 2005–2008,10 although by 2003 MTCT rates of less than 1% had been reported in a large European cohort.2

HIV case reporting to state surveillance systems has been conducted in some states since 1985,12 although confidential name-based HIV infection reporting was not implemented in all US states and territories until 2008.13 At present, perinatal HIV exposure reporting is conducted in only a subset of these jurisdictions. It has, therefore, been difficult to determine the annual numbers of HIV-infected women delivering infants and of perinatally infected infants.7 Reports of perinatally acquired AIDS cases have been the only data that have been consistently available from all US jurisdictions over time, from the early years of the epidemic. However, using these data to estimate the incidence of perinatal HIV infection is challenging and requires indirect estimation through statistical methods.14,15 Nevertheless, there have been several national estimates of the annual numbers of HIV-infected infants,15–19 and the annual numbers of infants born to HIV-infected women (HIV-exposed infants), as well as national estimates for the annual proportions of HIV-infected pregnant women prescribed ARVs during the prenatal and intrapartum periods.7,10,20,21 Neither the annual numbers of perinatal HIV cases prevented by PMTCT interventions nor the annual numbers of infants perinatally exposed to ARV have previously been estimated for the entire United States. The latter figure is significant because it reflects the population of infants and children who may be at risk for toxicities from ARV use, perinatal ARV use in particular. Although several studies have indicated
very low rates of birth defects or carcinogenicity,22–25 the possible increased risk of mitochondrial and other toxicities in infants and children who were perinatally exposed to ARV drugs26,27 warrants long-term follow-up of these infants.

The objectives of the present study were to use national estimates previously published by CDC to estimate the number of perinatally HIV-exposed and HIV-infected infants in the United States since the beginning of the HIV epidemic, the number of perinatal HIV infections prevented and the number of HIV-exposed infants perinatally exposed to ARVs in the United States during 1994–2010, a period of increasing ARV use.

MATERIALS AND METHODS

We identified data from several published sources (Table 1, columns 1b, 1f) for the annual numbers of HIV-infected pregnant women who delivered (column 1e) and the annual numbers of HIV-infected infants born (column 1g) for 1978–2010. When available, we used published point estimates or, if only ranges were given, the midpoints of those ranges, as the best estimates of these annual numbers. When data were not available, we linearly interpolated or extrapolated the available data to obtain estimated numbers for each year (columns 1d, 1h). For the years 2007–2010, data were not available on the numbers of births to HIV-infected women, so the 2006 estimate was carried forward to be conservative in our final estimate of the number of perinatal HIV infections averted. For 1978–1987, we estimated the annual numbers of HIV-infected women (column 1d) as 4.4346 times the annual numbers of HIV-infected infants estimated by Davis et al1 (column 1g), where 4.4346 = 1/0.2255 is the reciprocal of the HIV MTCT transmission rate in the absence of ARV prophylaxis, estimated from the placebo arm of the completed ACTG 076 trial.3 Note that 1978 is the first year in which HIV-infected infants were born in the United States, according the AIDS-based back-calculation.1

In the absence of variance estimates, we assumed that the estimated annual numbers (columns 1d, 1h) represented count data and calculated exact 95% confidence intervals (CIs) using the Poisson distribution (columns 1e, 1i). We then estimated the annual numbers of HIV MTCT cases that would have occurred in the absence of ARVs as the product of the annual numbers of HIV-infected women (column 1d) times the HIV MTCT rate of 0.2255.3 In turn, we estimated the annual numbers of perinatal HIV cases prevented (column 1j) after the introduction of ARV prophylaxis, estimated from the placebo arm of the completed AIDS clinical trials group (ACTG) 076 trial.1 Note that 1978 is the first year in which HIV-infected infants were born in the United States, according the AIDS-based back-calculation.1

We performed a simulation study with 1,000,000 repetitions to obtain 95% CIs for the annual numbers of perinatal HIV infections peaked in 1991 at 17601 and declined over time. A separate term was fit for 1994, the first year ARVs were available, because the proportions for this year was so much lower than for the other years. We obtained smoothed proportions of infants exposed to perinatal and intrapartum ARVs (columns 2f, 2l). Fitting these logistic regression models allowed us to interpolate and extrapolate to years for which data were not available and gave tighter estimates of the true proportions for each year. In turn, we estimated the annual numbers of infants exposed to perinatal and intrapartum ARVs (columns 2g, 2m) as the product of the annual numbers of HIV-infected pregnant women who delivered (column 1d) and the annual smoothed proportions of infants exposed to perinatal and intrapartum ARVs (columns 2f, 2l), respectively.

We also used the above simulation study with 1,000,000 repetitions to obtain 95% CIs for the annual numbers of infants exposed to perinatal and intrapartum ARVs (columns 2h, 2n) for 1994–2010. First, for each repetition, we estimated the annual numbers of HIV-infected women from a Poisson distribution with mean parameter equal to (column 1d). Second, we estimated the annual numbers of infants exposed to intrapartum ARVs as binomial variables with proportion parameters equal to the simulated annual numbers of HIV-infected infants born to HIV-infected women (columns 2d, 2j) for the annual numbers of infants exposed to perinatal and intrapartum ARVs, respectively, and sizes equal to the simulated number of HIV-infected women. Finally, we computed the 0.025 and the 0.975 percentiles over all 1,000,000 repetitions to obtain the bounds of the 95% CIs for the annual numbers of infants exposed to perinatal and intrapartum ARVs (columns 2h, 2n).

RESULTS

Using the data sources listed in the Tables 1 and 2, we estimated that between 1978 and 2010 approximately 186,157 (95% CI: 185,312–187,003) HIV-infected women gave birth in the United States (Table 1). The annual number of HIV-infected women giving birth increased approximately 28-fold during this period, from 310 in 1978 at the start of the epidemic to 8700 in 2006.30 During this period, approximately 21,003 (95% CI: 20,719–21,288) infants were perinatally infected with HIV. The estimated annual number of perinatal HIV infections peaked in 1991 at 17601 and declined...
steadily after 1993 to 151 (95% CI: 127–176) in 2010. The annual MTCT rate dropped from a high of 6145 in 1994 to 8700 in 2010. Dur-

Both prenatal and intrapartum ARV use increased from 1994 to 2010 (Table 2). In 1994, approximately 54% of women received prenatal ARVs, resulting in 3293 (95% CI: 2794–3784) infant ARV exposures. By 2010, the proportion of HIV-infected pregnant women receiving ARVs during the prenatal period had risen to 87%, and 7558 (95% CI: 7366–7749) infants were exposed to ARVs that year. Altogether, an estimated 100,207 (95% CI: 99,374–101,028) infants were exposed to ARV drugs during the prenatal period.

The proportion of women receiving ARVs during the intra-
partment period increased substantially during this period, from 32% in 1994 to 87% in 2010 (Table 2). The estimated annual number of infants exposed to ARVs during the intrapartum period grew from 20.6% in 1994 to a low of 1.7% in 2010. In total, approximately 6083 (95% CI: 5931–6236) infants were infected with HIV perinatally during this period. As a result of PMTCT interventions, an estimated 21,956 (95% CI: 20,191–23,759) cases of perinatal HIV were prevented between 1994 and 2010. In addition, after the introduction of ARVs, an increasing proportion of expected cases of MTCT were prevented each year; only about 9% of expected cases of MTCT were prevented in 1994, compared with 92% in 2010 (data not shown).

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DISCUSSION

PMTCT interventions—including HIV testing for pregnant women, ARV prophylaxis, avoidance of breastfeeding and elective cesarean section—have dramatically reduced the rates of MTCT of HIV in the United States. However, during the years of this study, a lack of national HIV infection and perinatal HIV exposure reporting has made it difficult to determine the full impact of these interventions. Strategies such as opt-out HIV testing for pregnant women, rapid testing at labor and delivery and improved ARV prophylaxis have played significant roles in identifying HIV infections and providing timely treatment for women before or early in pregnancy need continued support.

Other studies have highlighted the role of missed HIV prevention opportunities, including late or no maternal HIV testing, inadequate ARV prophylaxis, breastfeeding or low maternal CD4 cell counts. Addressing these missed prevention opportunities is crucial to the elimination of perinatal HIV transmission. Efforts to identify HIV infections and provide timely treatment for women before or early in pregnancy need continued support.

Whereas ARV drugs have played an important role in reducing the MTCT rate, recent research has also explored potential toxicities associated with fetal/infant ARV drug exposure, including low birth weight, congenital abnormalities, childhood cancers and mitochondrial dysfunction. While a number of observational studies have found an association between maternal combination ARV therapy and childhood cancers and mitochondrial dysfunction, this relationship has not been consistently observed.

A recent meta-analysis (including studies from the United States), however, found that exposure to ARV therapy during pregnancy did not increase the odds of premature birth. Preventing cases of MTCT directly through ARV prophylaxis has increased annually, the proportion of women receiving ARVs during the prenatal period appears to have remained relatively stable since 2004, when an estimated 83% received prenatal ARVs. We estimated that approximately 87% of HIV-infected pregnant women received prenatal ARV prophylaxis in 2010.

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HIV-associated morbidity and mortality. Reducing rates of perinatal HIV transmission likely also leads to decreased healthcare utilization costs that are associated with HIV testing, treatment, in-patient care and outpatient care, and laboratory monitoring, and reductions in the levels of overall HIV-associated health system spending. In addition to health system costs, perinatal HIV infections also have economic ramifications for individuals, families and society. Preventing perinatal HIV reduces annual expenditures on HIV care and treatment for people living with HIV, their families and the wider US healthcare system. Calculating the cost-effectiveness of perinatal HIV transmission prevention interventions may be an avenue for future research.

**Limitations**

This analysis was based on the best available nationally representative estimates. However, a lack of national, HIV infection (during the time of the study) and perinatal HIV exposure reporting made the annual numbers of HIV-infected pregnant women and infants difficult to determine with precision. Several of the published estimates by CDC involved modeling, including “back-calculations” from numbers of AIDS cases. The modeled data were limited to numbers of HIV-infected women delivering, and the numbers of HIV-exposed and HIV-infected infants. This analysis was limited by missing data for several years during our period of interest. Our method of estimation assumed a constant rate of change for unknown years, when the actual rate of change may have been substantially more variable. Notably, we assumed no change in the annual number of HIV-infected women delivering after 2006, whereas that number might have increased in that period. The annual number of infected infants was last modeled for 2009, and we assumed that the number did not change in 2010. Estimates for the annual number of HIV-infected pregnant women and their infants who were exposed to ARV drugs are subject to the same limitations. For several years of ARV data, we had to use raw data, as opposed to that which was published. In the absence of consistent nationwide data on the number of HIV-infected infants, we relied on published numbers derived from models; for consistency’s sake, we used only CDC data.

**CONCLUSION**

This study provides the first national estimates of the number of HIV-infected pregnant women, HIV-infected infants and the number of perinatal HIV cases prevented by PMTCT interventions in the United States. Using these estimates, we calculated the number of prenatal and intrapartum ARV exposures among infants born to HIV-infected mothers. These estimates will be important for policy-making and provide reference data for future studies, including those on ARV toxicities and those on net-savings associated with PMTCT programs. Great progress has been made in the prevention of MTCT of HIV since the introduction of ARVs and other preventive interventions; PMTCT interventions have prevented nearly 22,000 cases of MTCT of HIV between 1994 and 2010. However, continued vigilance to prevent, identify and treat HIV infections in women must be undertaken to eliminate perinatal HIV in the United States.
REFERENCES


