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Steep Declines in Pediatric AIDS Mortality in South Africa, Despite Poor Progress Toward Pediatric Diagnosis and Treatment Targets

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Background: Few attempts have been made to monitor progress toward HIV diagnosis and antiretroviral treatment (ART) coverage targets in children, and the impact that ART and prevention of mother-to-child transmission (PMTCT) programs have had on pediatric HIV incidence and mortality.

Methods: A multiparameter evidence synthesis approach was adopted to integrate South African pediatric HIV data sources. A previously developed model of HIV in South Africa was calibrated to household survey HIV prevalence data, routine antibody testing data, data on numbers and ages of children on ART, vital registration data and data on HIV diagnosis at death. The impact of ART and PMTCT was estimated by comparing validated model outputs against model predictions of the trends that would have been expected in the absence of ART and PMTCT.

Results: By mid-2018, the model estimated that 75.2% (95% CI: 73.9%–76.8%) of HIV-positive children were diagnosed, substantially lower than the corresponding estimates in HIV-positive adults (91.0%). ART coverage in children in 2018 (51.2%, 95% CI: 49.4%–52.7%) was also lower than that in adults (62.0%). In 2017–2018, the numbers of new cases of mother-to-child transmission and pediatric AIDS deaths were reduced by 84% and 94%, respectively, relative to what would have been expected in the absence of interventions, but reductions in mortality were driven largely by PMTCT.

Conclusions: Although levels of AIDS mortality in children have declined dramatically in South Africa, this has mostly been due to successful PMTCT programs, and progress toward the 90-90-90 targets appears relatively poor when compared with that in adults.

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The number of AIDS deaths in children globally is estimated to have declined from a peak of 300,000 in 2003 to 100,000 in 2018, while the number of HIV infections in children has declined from 2.2 million in 2007 to 1.7 million in 2018.[1] These reductions are often attributed to the success of HIV interventions, specifically prevention of mother-to-child transmission (PMTCT) and pediatric antiretroviral treatment (ART).[2] However, poor reporting of cause of death information and weak monitoring of pediatric HIV in many countries means that these estimates are determined largely by mathematical models, rather than direct measurement. In most countries, model-based estimates of pediatric HIV burden are derived from estimates of HIV prevalence in women of reproductive age, together with assumptions about their fertility rates and risk of mother-to-child transmission, pediatric HIV survival and the efficacy of different PMTCT and pediatric ART strategies. In the absence of validation against pediatric HIV data, these model estimates are highly uncertain and susceptible to changes in model assumptions—a concern that has been raised in relation to estimates of the pediatric HIV burden published previously by the Joint United Nations Program on HIV/AIDS (UNAIDS).[3]

UNAIDS has specified ambitious targets to reduce HIV incidence by 2020. The "90-90-90" targets aim for a 90% level of HIV diagnosis among all people living with HIV, a 90% ART coverage among all HIV-diagnosed individuals, and a 90% viral suppression among all ART patients.[4] Although much work has focused on estimating progress toward the 90-90-90 targets in HIV-positive adults, there is a lack of comparable statistics for HIV-positive children globally.[5] The estimation of levels of HIV diagnosis in HIV-positive children is particularly challenging, as children are often not able to report whether they know their HIV status, and caregivers may be reluctant to disclose a child's HIV-positive status. However, through a combination of routine HIV testing data and mathematical modeling, it is possible to estimate the fraction of HIV-positive adults who are diagnosed,[6] and the same methods can be applied in children.

Given the many uncertainties that exist around the epidemiology of pediatric HIV, it is critical that tools be developed to better harmonize available pediatric HIV data sources. Multiparameter evidence synthesis is a formal Bayesian approach to integrating different types of data within a mathematical model.[7] South Africa is a country in which such an approach would be particularly valuable, given the severity of its HIV epidemic, and the wealth of pediatric HIV data available.[2] Under-5 mortality rates in South Africa have dropped dramatically since 2003, from a rate of around 80 per 1000 births in 2003 to 32 per 1000 births in 2017.[8] However, there has been no formal assessment of the extent to which these

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declines can be attributed to the success of PMTCT and pediatric ART programs.

This study aims to demonstrate how multiparameter evidence synthesis can be used to produce improved pediatric HIV estimates, using South Africa as a case study. We also aim to assess the extent to which the 90-90-90 targets have been met in South African children and to compare these to estimates for adults. Finally, we aim to assess the impact that PMTCT and pediatric ART programs have had on pediatric HIV incidence and mortality in South Africa.

MATERIALS AND METHODS

This analysis is based on the Thembisa model, a combined demographic and HIV model developed for South Africa. A full description of the pediatric component of the model is provided in Supplemental Digital Content 1, http://links.lww.com/INF/D909. The numbers of births to HIV-positive women are estimated based on national fertility rates and observed relative rates of pregnancy in HIV-negative and diagnosed HIV-positive women in different HIV stages.[9] The model allows for 2 types of mother-to-child transmission: perinatal (at or before birth) and postnatal (due to breast-feeding). The model also allows for possible sexual acquisition of HIV in children 10 years of age and older. Probabilities of mother-to-child transmission are assumed to depend on the mother's stage of HIV infection and her receipt of ART or other forms of antiretroviral prophylaxis.[10] Uptake of maternal HIV testing during pregnancy and different forms of ART/prophylaxis after diagnosis are assumed to change over time, based on routine data, PMTCT guidelines and surveys of women attending immunization clinics.[11] HIV-diagnosed mothers are also assumed to breastfeed for shorter durations, on average, than HIV-negative mothers. The model also allows for maternal HIV acquisition during pregnancy and breast-feeding, with high mother-to-child transmission risks being assumed in the acute phase of maternal HIV infection.[12]

Figure S2 in Supplemental Digital Content 1, http://links.lww.com/INF/D909, illustrates the structure of the HIV disease progression model in HIV-positive children. In the absence of ART, children are assumed to progress through 2 disease stages: early and late disease, defined in terms of clinical and immunologic criteria.[13] Children who acquire HIV perinatally are assumed to progress to late disease more rapidly than children who acquire HIV postnatally.[14] Rates of progression from early to late HIV infection and rates of mortality in untreated late disease are assumed to be related to age, being highest in neonates and declining to lower rates in older children.[15]

Two types of pediatric HIV diagnosis are modeled. Polymerase chain reaction (PCR) testing is assumed to be conducted in early infancy: at 6 weeks in the 2006–2014 period and at birth and at 10 weeks after 2014. Antibody testing is assumed to be conducted at 18-month immunization visits and, after 18 months of age, at an annual rate that depends on the child's age, HIV disease stage and sexual experience (higher in the 19–59 month age group, in late HIV disease, and in sexually experienced children). Rates of HIV testing are assumed to change over time, based on testing guidelines and routine HIV testing data. After diagnosis, HIV-positive children are assumed to either start ART immediately or delay ART initiation, with the average duration of the delay being calculated such that the model matches total reported numbers of children on ART. Mortality rates in treated children are estimated from South African cohorts participating in the International epidemiology Databases to Evaluate AIDS collaboration,[16] adjusting to allow for changes in mortality over time as fewer children have delayed ART until the very advanced stages of late disease. Children are also assumed to discontinue ART at a constant rate and can also resume ART after an interruption.

A Bayesian approach was adopted in the calibration of the pediatric HIV model. Prior distributions were assigned to represent uncertainty regarding 17 of the parameters that are most difficult to quantify precisely: relative rates of fertility in HIV-positive undiagnosed women, postnatal transmission probabilities, rates of progression from early to late disease, untreated mortality rates, relative rates of testing in late disease and sexually experienced children and rates of mortality after ART initiation (Table S6, Supplemental Digital Content 1, http://links.lww.com/INF/D909). These prior distributions, which represent prior beliefs about plausible parameter ranges, were set with reference to reviews of the HIV literature. A likelihood function was specified to represent the goodness of model fit to several pediatric HIV data sources (summarized in Table S7, Supplemental Digital Content 1, http://links.lww.com/INF/D909). Finally, posterior distributions (representing the parameter combinations most consistent with both the prior distributions and the likelihood function) were estimated numerically, using Incremental Mixture Importance Sampling.[17]

Posterior estimates of progress toward the 90-90-90 targets in children were calculated and compared against recently published estimates for South African adults, based on the same model.[18] To assess the effect that ART and PMTCT programs have had on pediatric HIV incidence and mortality, we compared model estimates of actual incidence and mortality trends ("ART and PMTCT" scenario) to model estimates in 3 counterfactual scenarios: a scenario in which there was no ART or PMTCT ("No ART or PMTCT"), a scenario in which there was only PMTCT (short-course antiretroviral prophylaxis) but no ART ("PMTCT only"), and a scenario in which there was PMTCT and adult ART but no pediatric ART ("No pediatric ART").

RESULTS

The posterior model estimates were generally in good agreement with the calibration and validation data sets (Fig. 1). However, the model yielded a lower estimate of pediatric HIV prevalence in 2017 (2.1%, 95% CI: 2.0%–2.2%) than was measured in the national household survey in 2017 (2.7%, 95% CI: 2.2%–3.3%) (Fig. 1A). Although routine reporting of HIV antibody testing in children only started in 2015, the limited data suggest a more rapid decline in positive test results than predicted by the model over 2015–2017 (Fig. 1B). In the period up to 2009, public ART programs reported cumulative ART enrolment, but thereafter health facilities switched to reporting current ART enrolment, and the model estimates of cumulative and current enrolment were roughly comparable to the reported totals in the 2001–2009 and post-2010 periods, respectively (Fig. 1C). The model was also in reasonably good agreement with observed age distributions in ART patients, recorded death data and proportions of deaths with HIV-positive diagnoses (Fig. 1D–F). Although model estimates of perinatal transmission rates from HIV-diagnosed mothers were in good agreement with routine PCR testing data in 2008 and subsequent years, the model was less consistent with the PCR data before 2008, when PCR testing was less routine and probably biased toward sicker children who were more likely to be HIV infected (Fig. 1G). The model was also validated by the estimates of numbers of pediatric AIDS deaths from the National Burden of Disease study, which showed a steep decline after 2005 (Fig. 1H). More detailed model fits to age-specific mortality data are shown in Figure S6, Supplemental Digital Content 1, http://links.lww.com/INF/D909, and the posterior estimates of the key model parameters are shown in Table S13, Supplemental Digital Content 1, http://links.lww.com/INF/D909.

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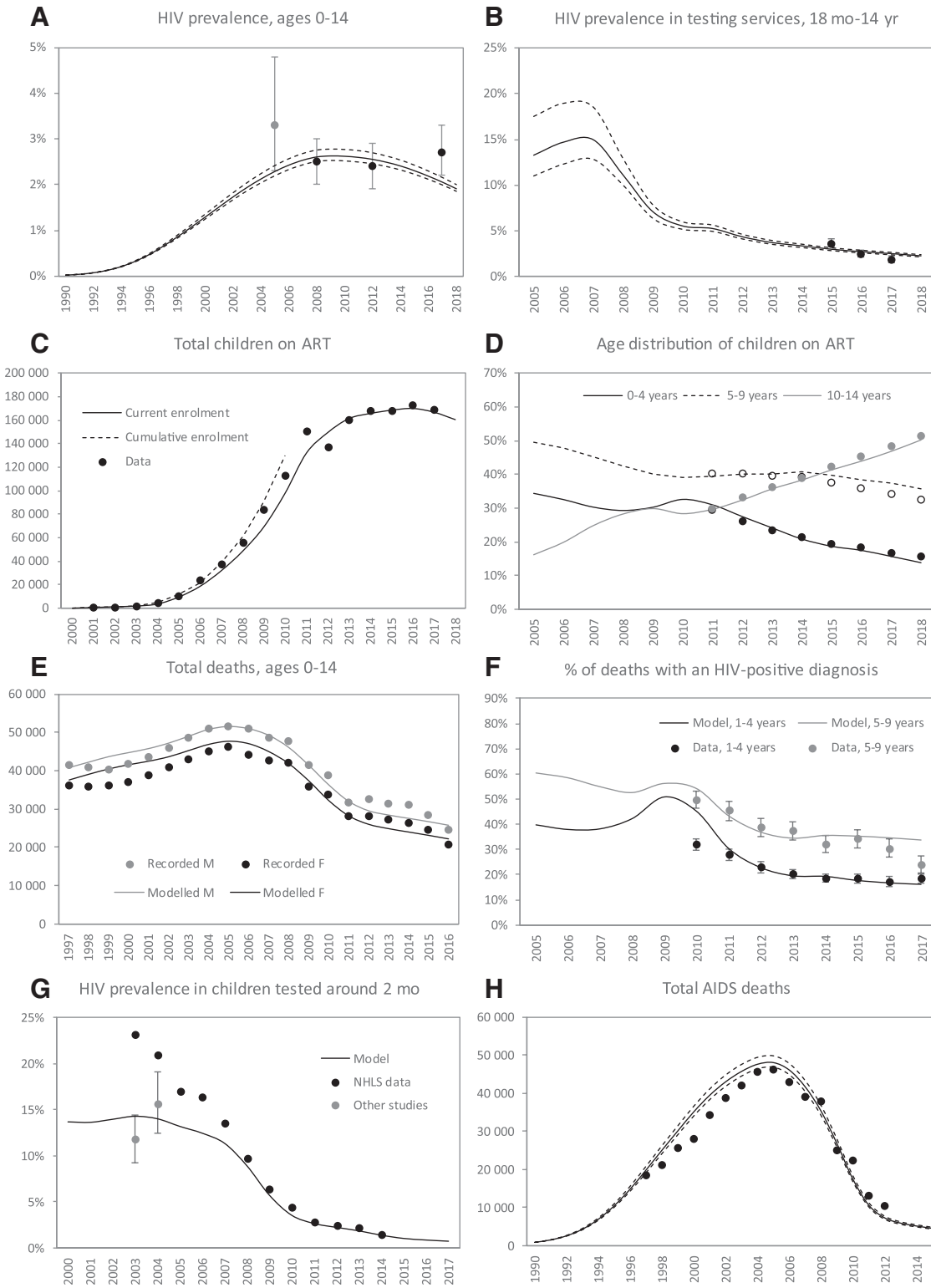


FIGURE 1. Model comparisons with calibration and validation datasets. A–F: Model calibration; G and H: model validation. Unless stated otherwise in the figure legend, solid lines represent posterior means of the model outputs, dashed lines represent 95% confidence intervals around the posterior means, and dots represent data points used in calibration/validation. A: The grey dot represents an estimate of HIV prevalence in 2–14 years old, and the black dots represent prevalence in 0–14 years old. G: The model estimate of HIV prevalence is calculated only for children born to mothers who were diagnosed positive antenatally.

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The model estimates the fraction of HIV-positive children who were diagnosed in 2018 to be 75.2% (95% CI: 73.9%–76.8%)—substantially lower than the corresponding estimates in adults (91.0%, 95% CI: 90.6%–91.5%).[18] The model estimate of ART coverage in children in 2018 (51.2%, 95% CI: 49.4%–52.7%) is also lower than that in adults (62.0%, 95% CI: 60.2%–64.3%). When stratified by age, levels of HIV diagnosis and ART coverage are substantially higher in older children than in younger children (Fig. 2B), reflecting the delay between transmission (at or soon after birth) and diagnosis and subsequent treatment. The numbers of HIV-positive children are higher at older ages than at younger ages (Fig. 2A), due to the success of PMTCT programs in reducing vertical transmission in recent years.

The model estimates that pediatric AIDS deaths peaked in 2004–2005, at 48,000 per annum (95% CI: 47,000–50,000) and declined to 3800 (95% CI: 3600–4100) in 2016–2017, the most recent year for which mortality data are available (Fig. 3A). Cumulatively, 584,000 children had died from AIDS by mid-2017. In the absence of any PMTCT or ART program, the situation would have been substantially worse, with annual AIDS deaths peaking at 66,000 in 2008–2009, and cumulative AIDS deaths reaching 1.127 million by mid-2017. This implies a cumulative reduction of 543,000 (95% CI: 530,000–560,000) in the number of AIDS deaths, as a result of PMTCT and ART programs (or a 48% reduction). Figure 3A shows that although most of this reduction was due to short-course PMTCT, the effect of longer-term adult ART was also substantial (reducing both vertical and sexual transmission), as was the effect of pediatric ART. PMTCT and ART programs together reduced the number of pediatric AIDS deaths in 2017–2018 by 94.1% (95% CI: 93.8%–94.4%), relative to the "No ART or PMTCT" scenario.

In the absence of any PMTCT or ART intervention, the mother-to-child transmission rate would have stabilized at around 38% (Fig. 3B). However, the combined effect of the short-course PMTCT and adult ART programs has been a reduction in the mother-to-child transmission rate to 4.1% in 2017–2018, equivalent to 12,500 (95% CI: 12,100–13,000) new infections (including perinatal and postnatal transmission, and transmission from women who seroconverted after delivery). A further 1500 new infections in children less than 15 years of age are estimated to have resulted from sexual transmission in 2017–2018 (11% of all new infections in children). The total number of mother-to-child transmission cases averted by the PMTCT and ART programs, over the period up to mid-2018, is 719,000 (95% CI: 701,000–740,000). Interventions reduced the number of mother-to-child transmissions in 2017–2018 by 83.7% (95% CI: 83.4%–84.3%), relative to the "No ART or PMTCT" scenario. Reductions in perinatal transmission are estimated to have been substantially greater than reductions in postnatal transmission: in 2004–2005, perinatal transmission accounted for 60% of all mother-to-child transmission, but by 2017–18, it accounted for only 25% of transmission.

DISCUSSION

This analysis demonstrates that PMTCT and ART programs in South Africa have had a dramatic impact, reducing the numbers of mother-to-child transmissions and pediatric AIDS deaths by 84% and 94%, respectively, in 2017–2018. Most of this reduction has been attributable to short-course antiretroviral prophylaxis (PMTCT) and maternal ART, although over the last decade the scale-up of ART in children has also contributed substantially to the reduction in pediatric HIV mortality.

The relatively low proportions of HIV-positive children who are diagnosed and on ART might be considered disappointing when compared with those in adults. However, age-specific results suggest that the problem of undiagnosed and untreated HIV is most serious in younger children, that is, children who have acquired HIV recently, and by age 14, levels of diagnosis and ART coverage are similar to those in adults (Fig. 2B). The same dynamic is often observed in adults, with younger adults (who are more likely to be recently infected) having much lower levels of diagnosis and ART coverage than older adults.[19–21] Recently acquired HIV infections are less likely to have been diagnosed and treated than infections of longer duration, and thus without appropriate control for differences in the average duration of infection, cross-sectional "cascade" measures of diagnosis and ART coverage tell us little about rates at which HIV is being newly diagnosed and treated. Longitudinal cascade measures are likely to be more appropriate for comparing rates of testing and treatment across different age groups.[22]

Our previous modeling work demonstrates that an increasingly high proportion of new HIV infections in South African children are the result of vertical transmission from mothers who acquire HIV while breast-feeding.[23] This explains why we find

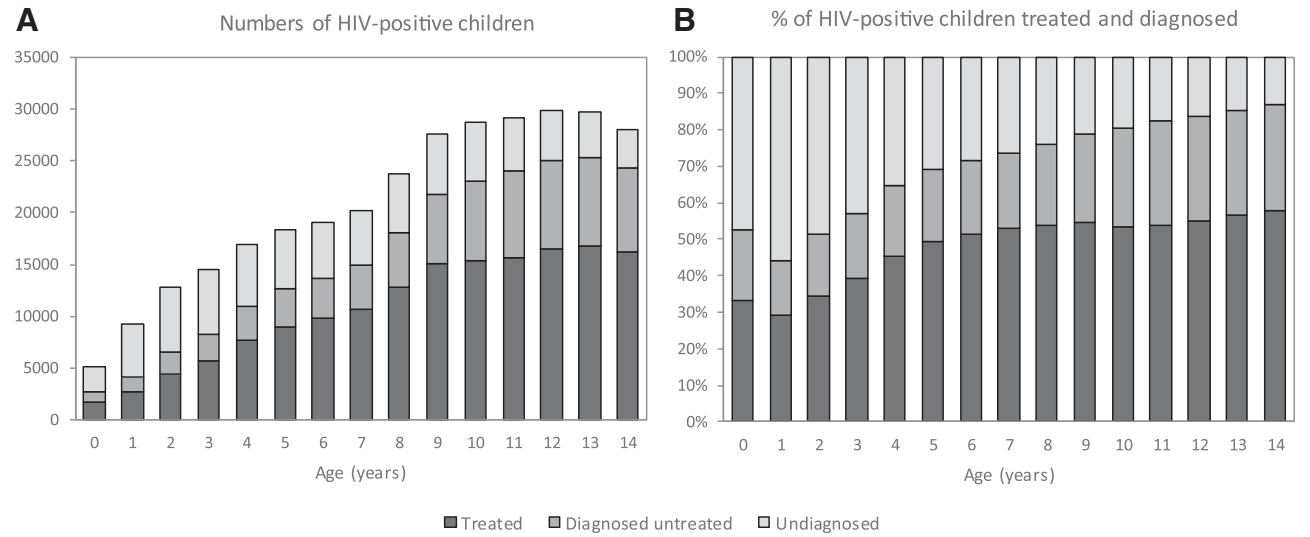


FIGURE 2. HIV diagnosis and treatment coverage by age, in 2018.

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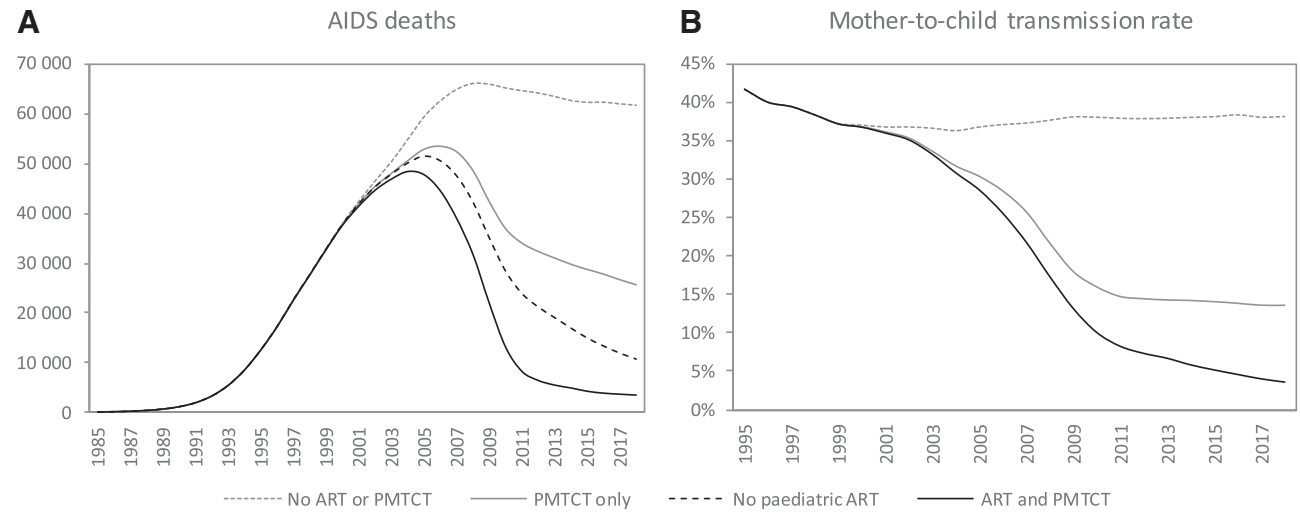


FIGURE 3. Impact of ART and PMTCT on pediatric AIDS mortality and mother-to-child transmission. The mother-to-child transmission rate is calculated by dividing total cases of mother-to-child transmission (including perinatal and postnatal transmission, and transmission from mothers who seroconvert after delivery) by the number of births to mothers who were HIV positive at the time of delivery.

slower declines in postnatal transmission than in perinatal transmission since 2004. It also explains why the fraction of HIV-positive children who are undiagnosed is high in the first 2 years of life (Fig. 2B), as it is challenging to identify mothers who seroconvert while breast-feeding and to then test their infants. Further effort is required to prevent and diagnose maternal seroconversion during the breast-feeding period, for example, through the promotion of pre-exposure prophylaxis to breast-feeding women at high risk of HIV acquisition.[24]

We estimate that a substantial fraction of children who have been diagnosed positive are not currently receiving ART (32% in 2018). This differs from the results of household surveys in Kenya[25] and Zimbabwe,[26] in which almost all children who were known to be HIV positive were also on ART. It is possible that caregivers interviewed in household surveys may be reluctant to disclose knowledge of a child's HIV-positive status when the child is not on ART, and there is substantial evidence of underreporting of knowledge of HIV status in HIV-positive adults, especially in those who are untreated.[27] Local evidence suggests that a substantial fraction of children who test positive do not subsequently start ART,[28,29] potentially due to lack of awareness of the importance of early ART initiation.[30] High rates of ART interruption have also been noted in treated children in Europe and Thailand,[31] and it is likely that a substantial fraction of the diagnosed untreated children are ART-experienced children who have dropped out of care. Further research is required to identify the reasons why diagnosed HIV-positive children are often untreated.

A strength of this analysis is that it systematically combines different pediatric HIV data sources, to produce more reliable pediatric HIV estimates for South Africa. The previous version of Thembisa (version 4.1) did not include a number of the data sources included in this analysis (the mortality data and the proportions of deaths with an HIV-positive diagnosis) and hence produced less accurate estimates. For example, the estimated number of AIDS deaths in children in 2012 was estimated to be 18,200 (95% CI: 13,300–22,900) in Thembisa version 4.1, in comparison to 7300 (95% CI: 6900–7800) in the current analysis. The latter is much more consistent with the number estimated in the National Burden of Disease study (10,300), based on analyses of vital registration data.[32] Greater efforts are required to improve vital registration in the countries most severely affected by HIV, to improve model estimates. However, even in the absence of such data, there are many opportunities to integrate existing pediatric HIV data sources into models, through the multiparameter evidence synthesis approach. Most sub-Saharan African countries have data on numbers of children on ART and their age distribution, numbers of children tested for HIV and numbers testing positive and household survey estimates of the numbers of children who are HIV positive, but these data are not currently being integrated into the process of producing estimates of pediatric HIV incidence and prevalence. Challenges to including these data include potential concerns regarding data quality (especially in the context of routine testing, which may be affected by misreporting), poor antibody test sensitivity in children who start ART soon after birth[33] and the underrepresentation of infants born to undiagnosed and high-risk HIV-positive mothers in early infant testing data.

Achieving greater levels of HIV diagnosis and ART coverage in children will require innovations in HIV testing, such as testing targeted to orphans, children of HIV-positive parents and adolescents in clinics.[34] It will also require better return of PCR results to caregivers,[28] improved counseling on the importance of early ART initiation and greater efforts to retain children in ART programs, particularly as they enter adolescence and become increasingly independent of their caregivers. Mathematical models, when appropriately calibrated to available data, have an important role to play in identifying where current programs are failing, and how new programs can further reduce the pediatric HIV burden.

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