

**T8.7: Paediatric HIV Disease Under Different
Intervention Scenarios**

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Abstract:

There are about 2,000 new cases of paediatric HIV transmission per day, occurring during pregnancy, childbirth or in the early months of life. 90% of them are in Africa. A range of interventions have been shown to be effective against such transmission, including antiretroviral drugs, cessation of breast-feeding at six months, and elective Caesarean delivery, which is often impractical in Africa. ARV drugs are effective in adults and apparently in children, although it is necessary for the drugs to be given to all at-risk newborns as HIV cannot be identified with certainty in this group. However, this modelling study shows that reducing HIV among women of childbearing age cuts both adult and child deaths most effectively. A combination of such approaches could lead to an 80% reduction in new infections by 2030. HIV prevention in women of childbearing age could save 80,000 new infections in Nigeria by 2030 and 44,000 in Ethiopia.

This review has been commissioned as part of the UK Government's Foresight project, Infectious Diseases: preparing for the future. The views expressed do not represent the policy of any Government or organisation.

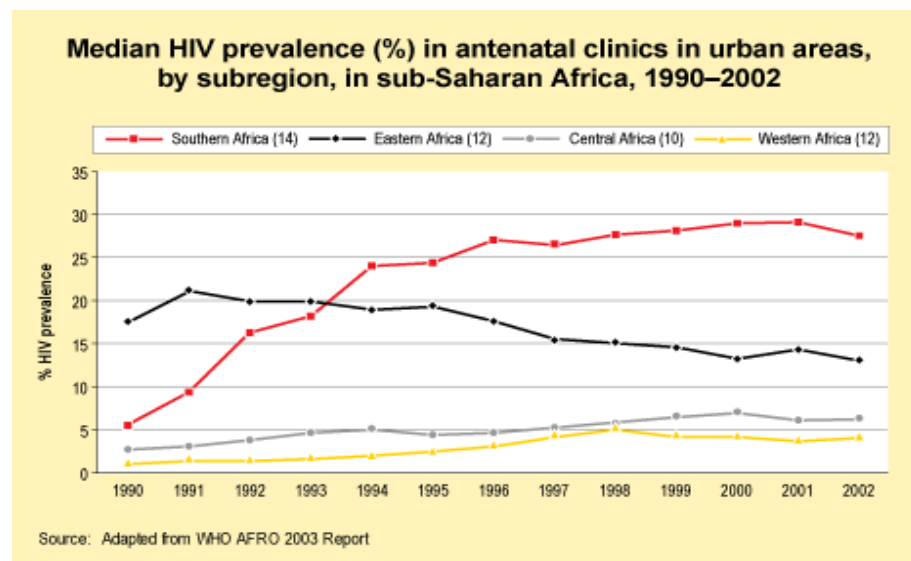
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Introduction

Currently, an estimated 2000 new paediatric HIV infections occur each day, nearly all through mother-to-child transmission (MTCT) occurring before and during delivery and afterwards through breast-feeding [1]. Close to 90% of paediatric infections occur in sub-Saharan Africa where the prevalence of HIV infection among women of childbearing age reaches 40% or more in some parts of the southern end of the continent [2,3].

Figure 1.



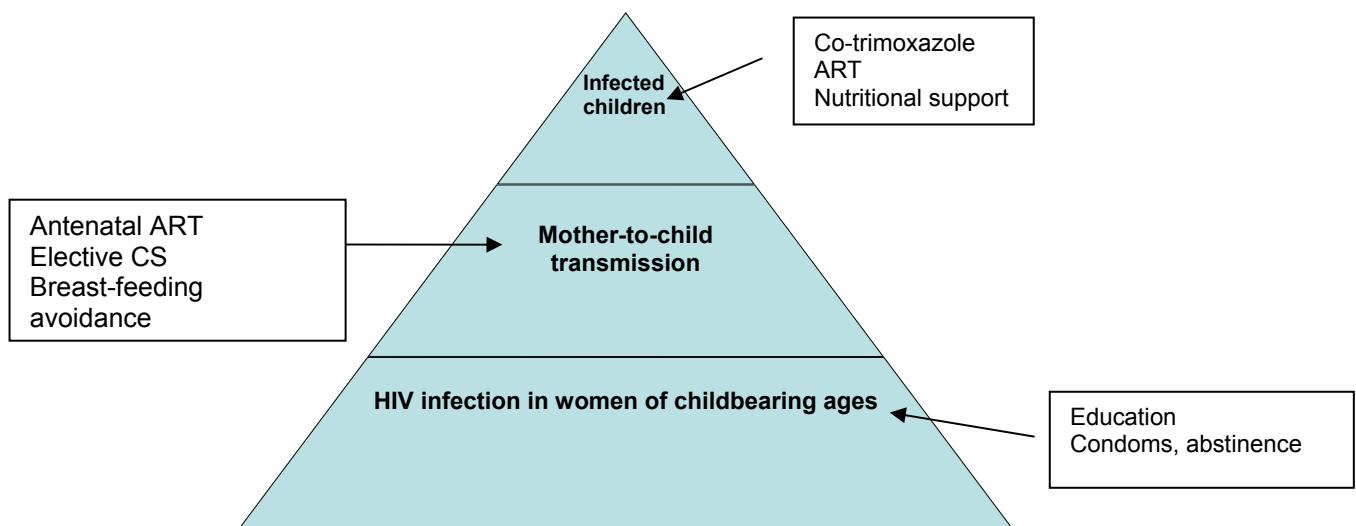
Mother-to-child transmission of HIV infection

Without specific interventions, between 15% and 40% of children born to HIV-infected women will acquire the virus through mother-to-child transmission (MTCT) [1]. The risk of MTCT is associated with maternal HIV disease progression, in particular HIV RNA viral load in plasma, and with the circumstances surrounding delivery and breast-feeding. Elective caesarean section delivery, before rupture of membranes and before onset of labour, has been shown to reduce the risk of MTCT by 50% to 80% compared to normal vaginal delivery. Prolonged breast-feeding, which is common in many parts of the world with high HIV prevalence, doubles the overall MTCT rate.

When it is safe, feasible and affordable, HIV-infected women are advised to refrain from breast-feeding, but where this is not possible, they are advised to exclusively breast-feed for 6 months, ceasing as soon as possible thereafter [4]. Although European guidelines recommend that HIV-infected women are offered an elective caesarean section, carried out before labour and before membrane rupture [5], this is not appropriate in developing country settings, where operative deliveries are neither safe nor affordable.

A number of interventions are available to prevent the acquisition of infection in young adults, to block mother-to-child transmission and to delay disease progression in infected children. MTCT, for example, can be prevented by: lowering maternal HIV viral load through the use of antiretroviral therapy during pregnancy, delivery and the breast-feeding period; avoiding exposure to infected maternal secretions through elective caesarean section delivery before the onset of labour and before rupture of the membranes; and by avoiding breast-feeding (Figure 2) [1,6]. Virtual elimination of MTCT is now a possibility in some areas of the world where transmission rates can be reduced to about 1% with prolonged (from early pregnancy) combination antenatal therapy, elective CS delivery before onset of labour and before rupture of the membranes, and by avoiding breast-feeding.

Figure 2. Stages relating to the acquisition of HIV infection in children, and points for intervention



However, in resource-limited settings, elective CS and refraining from breast-feeding are usually not feasible, safe, acceptable or affordable. In this context the major contribution to reducing the risk of MTCT comes from the use of antiretroviral therapy in the peripartum period [1,7]. In many cases this consists of zidovudine monotherapy given for the last few weeks of pregnancy, or single dose NVP given to the mother at the onset of labour and to the infant within a few days of birth. Although both these relatively simple regimens are known to significantly reduce the risk of MTCT, longer and/or combination ART has been shown to be more effective. This may be feasible in some resource-limited settings.

With short course antenatal ART from 36 weeks of pregnancy, vaginal delivery and only 6 months breast-feeding, rates can be reduced to 15%-20%, which is still an improvement on previous rates of 30% or more. A combination of ZDV from 32 weeks gestation and sdNVP, which could reduce the rate of MTCT at about 6 weeks to 7% or less, is now recommended as

one of the simplest, highly efficacious regimens, but its large scale introduction has been problematic. It should be noted that, even where peripartum transmission is prevented through the use of antiretroviral therapy for a limited period, infants who are breast-fed remain at risk of acquiring infection as long as breast-feeding continues.

Progression of disease in vertically infected children

Despite efforts in many programmes aimed at preventing MTCT, the number of children acquiring infection continues to be high. The most detailed picture of disease progression comes from resource-rich countries, while information from sub-Saharan Africa is sparse and incomplete. Most studies show fast progression rate in infants and young children, and a slower rate of progression in older, surviving children

Across Africa, HIV accounts for close to 10% of all child mortality, ranging from up to 50% in some areas of southern Africa to less than 5% in areas of west Africa. In six sub-Saharan African countries - Botswana, Lesotho, South Africa, Namibia, Swaziland and Zimbabwe - AIDS is responsible for one-third to two-thirds of all under-five deaths. Therefore, the UN Millennium goals to reduce child mortality will not be achieved in those countries without adequately tackling HIV/AIDS, and the response to the prevention of MTCT needs integrated approaches that include HIV prevention as well as care, support and treatment for women and children.

The need to focus on preventing HIV infection in women of childbearing age is highlighted by the finding that all children born to HIV-infected mothers are at increased mortality risk, irrespective of their own infection status. In a pooled analysis of data taken from three demographic studies in Uganda, Tanzania and Malawi, the excess risk of death for children of HIV-infected mothers was 3.3, with the effect continuing throughout childhood [8]. In agreement with a previous Ugandan study, the excess risk of child mortality associated with maternal death was 2.9 in the year preceding the death and 4.9 in the year following. These risks were independent of maternal HIV status. In a large, pooled meta-analysis of data from seven PMTCT trials in sub-Saharan Africa which looked at a total of 3468 children born to HIV-infected mothers, mortality in HIV-infected infants was significantly higher than in their uninfected counterparts [9]. Overall mortality was associated with maternal illness and death.

Young children are at a particularly high risk of death, and it is difficult to identify those at highest risk. With the difficulty of diagnosing HIV infection in the first year of life due to a lack of virological tests in many settings, many children die before they are recognised as HIV-infected.

ART, initiated at an appropriate time, has been shown in adults, and in a few trials in children, to substantially reduce the risk of mortality. Without antiretroviral therapy, a substantial proportion of infected children progress rapidly to serious disease and death, and, by the age of one year, only about 65% of infected children will still be alive [10]. Eligibility for antiretroviral

treatment is currently assessed on either clinical or immunological grounds. Treatment is started *either* when an individual's clinical condition deteriorates to moderate or severe disease *or* when immunological levels drop to a status indicating severe immune deficiency. In developed countries, the decision when to initiate ART in HIV-infected children is based on clinical symptoms, an assessment of CD4 T-cell count or percentage and HIV RNA viral load. However, in many resource-limited settings, these laboratory tests are not available. Here eligibility depends on clinical symptoms alone.

Co-trimoxazole as *Pneumocystis Carinii* Pneumonia (PCP) prophylaxis should be given from 6 weeks of age to all infants born to HIV-infected mothers until HIV infection in the child has been excluded, and to all symptomatic infected children, including those after PCP. In a trial in Zambia, co-trimoxazole was shown to be highly efficacious in reducing morbidity and mortality caused by bacterial infections in children older than one year of age.

Methods

A simple model was developed to forecast the number of HIV-infected children born and the number eligible for ART in the years 2015 and 2030 on the basis of clinical disease progression at yearly age intervals, allowing for antenatal HIV prevalence, use of PMTCT interventions, infant feeding policies, and the availability of co-trimoxazole (which can delay progression to serious disease and death). This model can also be used to assess the effect of policy decisions on the prevention and management of HIV infection in young women and children in sub-Saharan countries.

The model was developed as a set of Excel spreadsheets, which allowed the input of a number of pertinent values relating to a particular setting in a flexible manner. These included birth rate, population size, antenatal prevalence (published data in UN yearbooks and/or World Bank annual reports), prevention of MTCT programme coverage, breast-feeding policies and practices, availability of co-trimoxazole, early diagnosis of infection in infants of HIV-infected mothers, and antiretroviral therapy to delay disease progression in either women and/or children (paper submitted for publication). Input information is ideally locally or nationally sourced, but if there is no data available then various appropriate assumptions can be used repeatedly to arrive at a range of estimated numbers.

The number of vertically-exposed children born annually is estimated on the basis of information on population size, birth rates and antenatal HIV prevalence, which is used to calculate the number of pregnant women likely to be HIV-infected. The proportion of children born to HIV-infected women who acquire HIV infection themselves depends on the coverage and type of interventions to prevent mother-to-child transmission as well as the extent and duration of breast-feeding. Applying a transmission rate appropriate to the population and to the number of exposed children provides the estimated number of vertically-infected children. To calculate the proportion of infected children alive at each age, a cumulative mortality rate is applied. These mortality rates are based on a pooled analysis of data from sub-Saharan

Africa [9] and have been extrapolated to cover all ages from birth to 10. Where appropriate, the mortality rate is modified to take account of current and past coverage with co-trimoxazole and ART.

The countries chosen as examples are Nigeria, Zambia and Ethiopia. Nigeria has a relatively modest antenatal HIV prevalence currently, but a very large population, Zambia has a higher and longer-established HIV epidemic, and Ethiopia a large population and a modest HIV prevalence.

Number of children vertically acquiring HIV for 2015 and 2030: effect of changing antenatal prevalence

Most women access antenatal services at least once during pregnancy, which provides an opportunity for offering both an HIV test to diagnose infection, and interventions to prevent mother-to-child transmission for those women found to be infected. At a population level, the antenatal prevalence is used to monitor the spread of the epidemic and to look at trends over time. The prevalence among pregnant women in some settings is far higher than the overall prevalence among the adult population. For example, in sub-Saharan Africa, the antenatal prevalence among pregnant women is about 30% in southern Africa, about 13% in eastern, 7% in central and 4% in western Africa (Figure 1). Of particular concern is the high prevalence among younger women. In South Africa, antenatal prevalence among the under-20s is now 15%, rising to 30% among 20-24 year olds and 35% in 25-29 year olds.

From these antenatal prevalence estimates, it can be calculated that, globally, each year, more than 2.8 million HIV-infected women give birth, 80% of them in sub-Saharan Africa.

The model presented here reflects the changing birth rates estimated for the years 2015-2030, as follows:

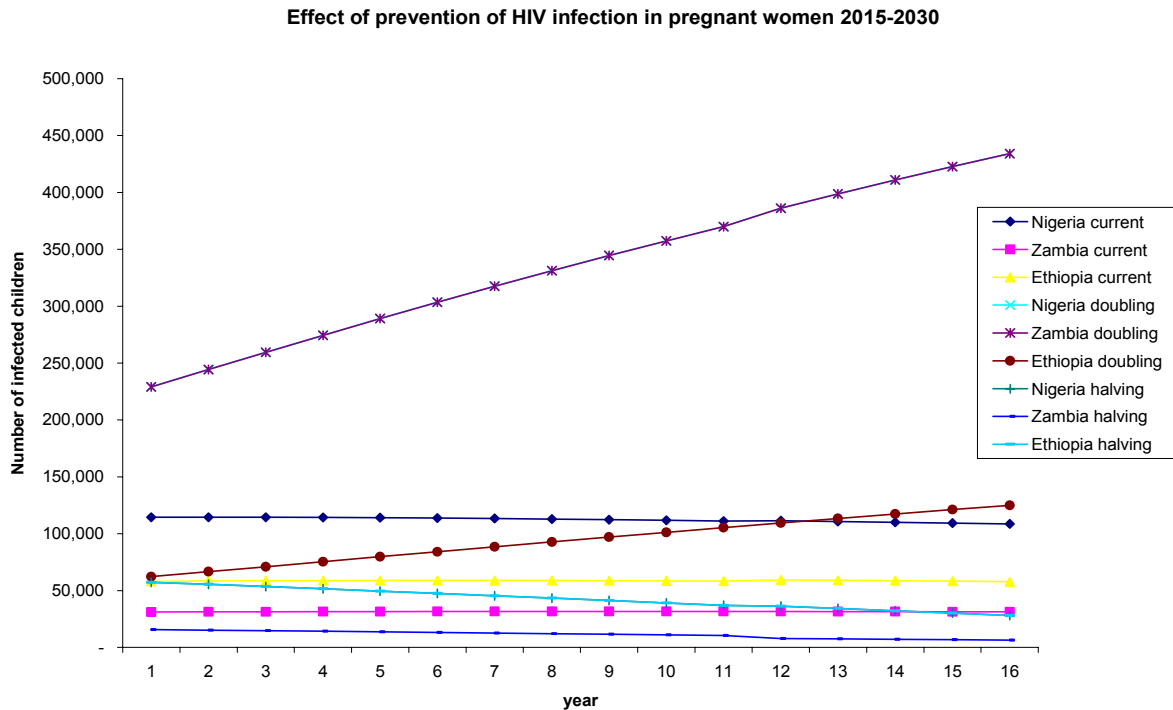
	Indicator	2005-2010	2010-2015	2015-2020	2020-2025	2025-2030
Nigeria	Crude birth rate (per 1,000 population)	39.5	36.6	33.2	30.0	27.3
Zambia	Crude birth rate (per 1,000 population)	39.6	37.8	35.3	32.4	29.7
Ethiopia	Crude birth rate (per 1,000 population)	38.9	36.6	34	31.1	28.3

In addition, the example assumes:

- a. Stable antenatal prevalence at current levels over the whole of the period 2005-2030 at 5.4% in Nigeria, 16.5% in Zambia and 4.4% in Ethiopia.
- b. Increasing antenatal prevalence doubling from 2005 levels by 2015 and doubling again by 2030.

- c. Decreasing antenatal prevalence to half 2005 levels by 2015 and a further half by 2030.

The results of this exercise for 2015-2030 are shown in Figure 3.



Preventing infection in women of childbearing age is an effective way of preventing infection in children. Every reduction in the number of women infected brings a similar size reduction in children infected – and the implications are even wider, as prevention of infection in mothers also has benefits in terms of reduced mortality for all their children, not just for infected children. The model here assumes a halving in the antenatal prevalence by 2015 and again by 2030 – that is 50% of current levels by 2015. Figure 3 above suggests that a strenuous effort in preventing women of childbearing age from becoming infected in Nigeria could prevent about 56,000 new infections in infants in 2015 and about 80,000 in 2030. Comparable figures for Zambia would be about 15,500 in 2015 and 23,500 in 2030, and for Ethiopia nearly 30,000 and 44,000 in 2015 and 2030 respectively.

Numbers of infected children born annually, 2015-2030: effect of changing coverage of the prevention of mother-to-child transmission programme

All approaches to preventing MTCT depend on identifying HIV infection in pregnant women. But experience from many countries suggests that that is not an easy task. An offer of HIV testing is more likely to be taken up if the test used provides a result on the same day. Even then, many women may not want to know their results, may not come back to the services and will not

have access to MTCT interventions or any care they may need for their own HIV infection.

Despite reported successes in some settings, worldwide, fewer than 10% of HIV-infected women are estimated to benefit from services designed to prevent MTCT, resulting in continued substantial numbers of infected children each year. Also, even with complete coverage of effective peripartum ART interventions, an estimated 300,000 children in the world will acquire HIV through breast-feeding, unless the common, prolonged duration of breast-feeding is substantially curtailed. WHO guidelines recommend that, where refraining from breast-feeding is not feasible, HIV-infected women should be advised to exclusively breast-feed for 6 months, with rapid cessation as soon as possible thereafter [4].

Currently, commonly used MTCT interventions include monotherapy with zidovudine (ZDV) from 32 or 34 weeks of pregnancy, and/or single dose

nevirapine (NVP) at the time of delivery, with another single dose given to the neonates within days of being born [1]. Single dose NVP has been shown to reduce the risk of MTCT by about 40%, to 12% at 6 weeks of age. Short course ZDV has been associated with a similar reduction in risk, while a combination of the two could reduce the risk to about 6% or 7% at 6 weeks of age. However there is a continuing potential risk of acquisition of infection through breast-feeding.

In calculating the number of infected children born each year in Nigeria, Zambia and Ethiopia, the following assumptions have been made: Nigeria, antenatal prevalence currently 5.4%, with a PMTCT programme coverage of 0%; Zambia, 16.5% prevalence and 6% PMTCT programme coverage; and Ethiopia 4.4% and 0% respectively. It is also assumed that programme coverage also implies adherence to the intervention offered. Changes in birth rates in this period are allowed for.

The overall risk of MTCT without interventions is assumed to be 36%, with single dose NVP 26% and with ZDV plus single dose NVP 21%, with the high rates reflecting prolonged breast-feeding. It is further assumed that there will not be any significant advances in rolling out more effective PMTCT. Although this may be a theoretical possibility, cost, logistics and potential adverse effects will hinder the widespread application of such PMTCT approaches.

- a. Antenatal HIV prevalence at current levels, PMTCT at current coverage (2005 levels)
- b. Antenatal prevalence at current levels, PMTCT with ZDV from 34 weeks coverage up to 50% by 2015 and
- c. 100% by 2030

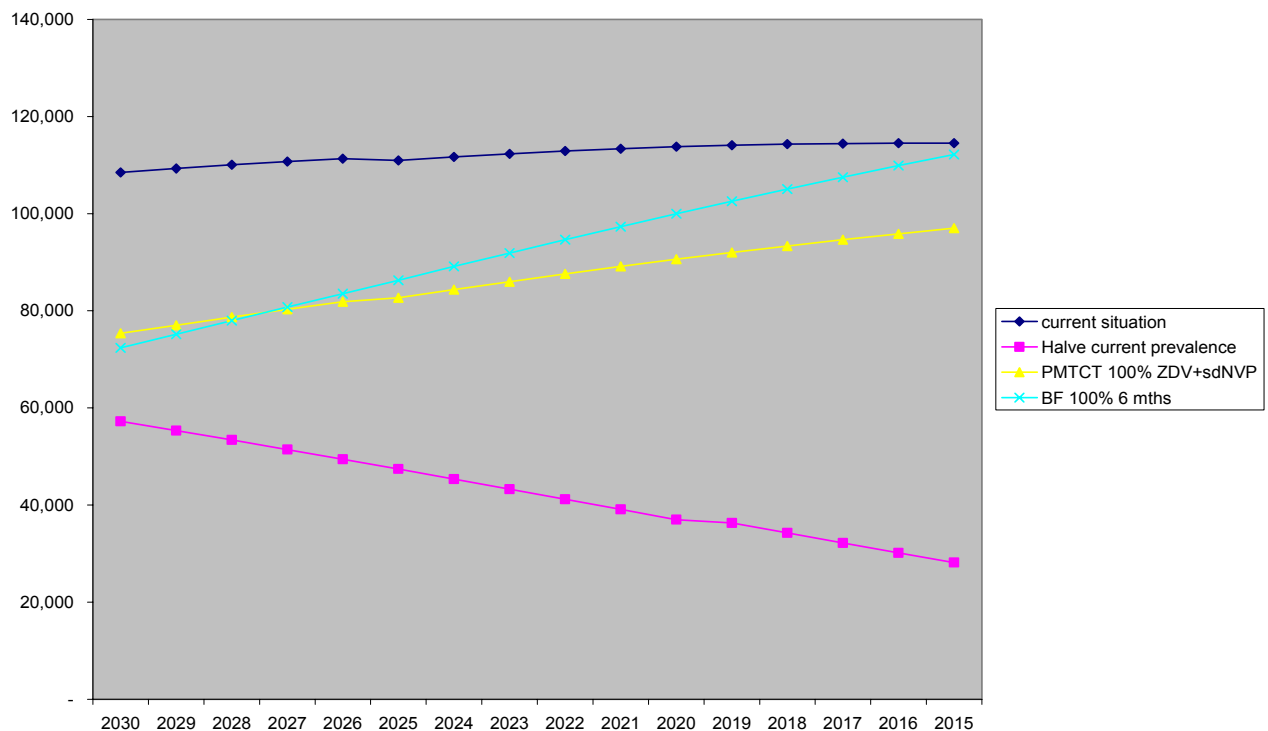
Table 1 *Estimated number of infected children born each year by country*

Year	Current levels of PMTCT coverage			PMTCT up to 50% by 2015 and 100% by 2030			100% < 6 mths breast-feeding by 2030 starting in 2015		
	Nigeria	Zambia	Ethiopia	Nigeria	Zambia	Ethiopia	Nigeria	Zambia	Ethiopia
2015	114,503	30,508	58,172	97,010	26,330	49,284	112,189	30,449	56,996
2016	114,516	30,632	58,387	95,852	26,118	48,871	109,886	29,943	56,027
2017	114,452	30,740	58,558	94,630	25,891	48,417	107,512	29,415	55,007
2018	114,312	30,832	58,684	93,348	25,648	47,922	105,070	28,868	53,939
2019	114,096	30,907	58,765	92,007	25,389	47,388	102,565	28,303	52,826
2020	113,803	30,967	58,800	90,609	25,116	46,817	100,002	27,720	51,669
2021	113,386	31,010	58,791	89,120	24,829	46,209	97,344	27,120	50,473
2022	112,895	31,037	58,737	87,582	24,528	45,567	94,640	26,504	49,239
2023	112,330	31,047	58,638	85,997	24,213	44,892	91,896	25,874	47,971
2024	111,690	31,042	58,493	84,367	23,886	44,184	89,115	25,230	46,671
2025	110,975	31,020	58,304	82,695	23,547	43,446	86,302	24,574	45,341
2026	111,353	31,560	59,341	81,860	23,201	43,624	83,514	23,670	44,506
2027	110,740	31,504	59,031	80,283	22,839	42,796	80,748	22,972	43,044
2028	110,062	31,431	58,674	78,672	22,467	41,940	77,961	22,264	41,561
2029	109,320	31,342	58,269	77,029	22,084	41,058	75,157	21,548	40,060
2030	108,512	31,237	57,818	75,356	21,692	40,151	72,341	20,824	38,545

The example presented in Table 2 shows the separate effects of either antiretroviral prophylaxis or shorter breast-feeding and highlights the effect of a reasonably efficacious PMTCT antiretroviral prophylaxis regimen as well as the effect of a policy of exclusive breast-feeding for six months, with abrupt cessation. If all women followed these WHO guidelines for infant feeding about one-third fewer children would acquire infection each year. Increasing PMTCT coverage to half of all infected pregnant women in 2015 and all women by 2030, would reduce the number of infected children in 2015 by about 16% and in 2030 by about 31%.

These preventive intervention policies are multiplicative, so that extending both the PMTCT programme coverage to 100% ZDV plus single dose NVP and to 100% exclusive breast-feeding for 6 months would reduce the number of new infections by 61%. If, in addition, the antenatal prevalence was halved, the resulting reduction would be 80% (Figure 4).

Figure 4. Number of children infected per year, currently, with 100% PMTCT coverage, with all women breast-feeding for 6 months, with halving of the current antenatal prevalence, with 2 of the 3 and with all 3: Nigeria



Antiretroviral treatment for eligible infected children

Whether or not infected children need antiretroviral treatment depends on their clinical condition. The model predicts disease progression to moderate or severe levels. Table 2 provides the total number of infected children alive in each of the three countries at selected time points. Without any available treatment for infected children, or prophylaxis to delay disease progression,

about 14% of infected children alive would be sufficiently seriously ill to be eligible for antiretroviral treatment. These numbers then pose a considerable burden for the healthcare system.

If co-trimoxazole is provided for half the infected children by 2025 and for all infected children by 2030, disease progression is substantially delayed and the overall number of infected children in each year therefore increases (Table 2). With such prophylaxis, about 11.5% of infected children alive in 2015 would require antiretroviral therapy, and just over 9% in 2030.

Where co-trimoxazole prophylaxis is combined with antiretroviral therapy for all infected children from birth, there is a substantial increase in the number of children alive at each of the selected time points, with both treatment approaches being beneficial in terms of keeping children alive. With children on antiretroviral treatment living longer there is some accumulation of children on ART (Table 2). In 2015, when coverage with both is only 50%, about 15% of infected children would be on antiretroviral treatment, and by 2030 when coverage reaches all eligible children this would be about 21%.

Table 2. Projected numbers of HIV-infected children alive, at selected time points, for the three countries considered, allowing for changes in birth rate over time

	Total infected alive								
	No treatment			Cotrim prophylaxis			Cotrim and ART		
	Nigeria	Zambia	Ethiopia	Nigeria	Zambia	Ethiopia	Nigeria	Zambia	Ethiopia
2015	421,093	552,085	203,441	534,178	144,884	260,136	594,632	161,282	289,522
2020	431,769	576,484	205,652	615,138	167,847	306,852	707,951	193,063	352,976
2025	430,486	591,859	218,509	661,964	185,868	346,183	792,358	219,608	409,089
2030	411,578	575,912	216,474	708,432	200,649	377,150	854,601	241,966	454,942

Conclusion

By quantifying the effect of changes in HIV prevalence among pregnant women, population coverage of prevention of mother-to-child transmission programmes, including infant feeding policies, and of paediatric treatment scenarios, this modelling exercise highlights not only the importance of preventing infection in young people as a means of risk reduction in young infants, but also the importance of preventing transmission of infection from an already HIV-infected mother to her unborn or young infant. HIV is a sexually transmitted disease with prevention depending on three behaviours: abstinence, being faithful to one partner, and safe sex using condoms. Control of infection at population levels is dependent on understanding social factors, including internal and external migration. In addition, political will and international economic ties play an important role.

It is clear that, unless the risk of young people acquiring HIV infection is substantially reduced, the UN targets of a 50% reduction in newly-acquired infection in children is not going to be met, nor will the Millennium goal of a reduction in child mortality be achieved. Across Africa, HIV accounts for close to 10% of all child mortality, ranging from up to 50% in some areas of southern Africa to less than 5% in areas of west Africa. In six sub-Saharan African countries, namely Botswana, Lesotho, South Africa, Namibia, Swaziland and Zimbabwe, AIDS accounts for one- to two- thirds of all under-five deaths. Therefore, a reduction in child mortality will not be achieved in those countries without adequately tackling HIV, and the response to the prevention of mother-to-child transmission requires integrated approaches which include HIV prevention as well as care, support and treatment for women and children.

Although the simplicity of the model and ease of use make it attractive for programmatic purposes, dependence on various assumptions and the possibility of less reliable data limits the accuracy of the estimates. Therefore the projections should be used as illustrative only, to be taken as indicative of the changes that could occur if certain policy and practices were applied at a population level. Not doing anything in terms of preventing HIV in either mothers or the infants of HIV-infected mothers means maintaining the status quo. The examples provided here clearly show that this is unacceptable.

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