HIV and the Millennium Development Goals

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ABSTRACT

Millennium Development Goal (MDG) 6 has two HIV/AIDS commitments: to have halted and begun to reverse the spread of HIV/AIDS by 2015 and to ensure access to treatment among all those in need by 2010. Given the almost universal lack of access to HIV testing, prevention and treatment for children in high prevalence countries in 2000, the achievements of the past 15 years have been extraordinary, fuelled by massive donor investment, strong political commitment and ambitious global targets; however, MDG 6 is some way from being attained. Prevention of mother-to-child transmission (PMTCT) services have expanded enormously, with new infections among children falling by 58% between 2002 and 2013. There has been a shift towards initiation of lifelong antiretroviral therapy (ART) for pregnant and breastfeeding women, although low HIV testing rates in pregnancy, suboptimal PMTCT coverage and poor retention in care remain barriers to achieving HIV elimination among children. Early infant diagnosis has expanded substantially but, in 2013, only 44% of all HIV-exposed infants were tested before 2 months of age. Diagnosis of HIV, therefore, frequently occurs late, leading to delays in ART initiation. By the end of 2013, approximately 760 000 children were receiving ART, leading to 40% decline in AIDS-related mortality. However, only 24% of HIV-infected children were receiving ART, compared with 36% of adults, leading to a 'treatment gap'. In this review, we summarise progress and remaining challenges in reaching MDG 6 and discuss future strategies to achieve the ambitious goals of paediatric HIV elimination and universal access to treatment.

INTRODUCTION

One of the most devastating consequences of the global HIV pandemic has been the impact on children, particularly in sub-Saharan Africa. In the absence of prevention of mother-to-child transmission (PMTCT) interventions, up to 40% of infants born to HIV-infected mothers acquire the infection, either *in utero*, at delivery or during breastfeeding.[1] Disease progression in HIV-infected children is more rapid than in adults, with over half dying by 2 years of age without treatment.[2] Even those who remain uninfected are, nonetheless, affected by HIV, with increased mortality and poor growth among HIV-exposed infants,[3] and orphanhood due to parental HIV creating child-headed households in many parts of sub-Saharan Africa.

In 2000, when the United Nations Millennium Declaration was made, there were an estimated 36 million adults and 1.4 million children living with HIV; few countries had effective PMTCT interventions or antiretroviral therapy (ART) treatment programmes, and there were an estimated 500 000 AIDS-related deaths per year in those aged <15 years[4] (although advances in methodology led to somewhat lower estimates subsequently[5]). Millennium Development Goal (MDG) 6, therefore, focused on HIV/AIDS, among other infectious diseases, and had two principal commitments: first, to have halted and begun to reverse the spread of HIV/AIDS by 2015; and, second, to achieve universal access to treatment for HIV/AIDS among all those in need by 2010. MDG 6 emerged from the extraordinary successes being witnessed at that time in developed countries, where the advent of combination ART was leading to reductions in mother-to-child transmission (MTCT) and HIV-related mortality, transforming HIV from a rapidly fatal infection to a long-term chronic disease.[6]

Enormous progress has been made in reducing the impact of HIV on children globally, although the MDG 6 targets are some way from being attained. Although 26 countries reported in 2013 that they had succeeded in reducing by half the number of new HIV infections since 2001, in other countries, urgent action is still required to halt and reverse the spread of HIV[7] as 90% of new infections occur in 22 priority countries, 21 of which are in sub-Saharan Africa.[8] While the number of new infections among children has fallen by 58% since its peak in 2002, mortality from HIV among children has declined by only 40% due to persistently low coverage of ART in children compared with adults.[9]

There is, however, a great sense of optimism that much has been achieved and that more can be done to consolidate and accelerate progress by refining the approach. The *Double Dividend*,[10] a joint initiative between Unicef, the Elizabeth Glaser Pediatric AIDS Foundation and WHO, considers the dual goals of ending paediatric HIV/AIDS and improving child survival together, highlighting the need for an integrated approach to MDG 4 (child survival), MDG 5 (maternal health) and MDG 6. Current priorities are, therefore, focused on embedding HIV prevention and treatment within broader Maternal, Newborn and Child Health (MNCH) services and strengthening systems for provision of more comprehensive, effective and efficient care. This approach is also endorsed in other high-level initiatives,[8 10 11] which together could substantially improve survival and health of women and children.

This review will summarise progress and remaining challenges within the three principal domains of the paediatric HIV prevention and treatment continuum: PMTCT to prevent HIV infection among children; early infant diagnosis (EID) and provider-initiated testing and counselling (PITC) to identify new infections; and linkage to HIV care and treatment to ensure long-term health and survival of infected children (figure 1).

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Figure 1 The paediatric HIV cascade. A continuum of care is required to connect prevention of mother-to-child transmission (PMTCT) of HIV infection with early infant diagnosis and to ensure linkage of infected children into HIV care and treatment.

PMTCT OF HIV

The generalised nature of the HIV epidemic in sub-Saharan Africa has resulted in high HIV prevalence among reproductive-aged women: by 2000, one-quarter of women presenting for antenatal care in parts of sub-Saharan Africa were HIV-infected.[4] Between 2000 and 2010, HIV prevalence continued to rise in several countries, to reach a plateau of over 30% among antenatal attendees in countries such as South Africa.[12] While in Europe/USA, universal HIV testing in pregnancy combined with a package of PMTCT interventions (antenatal and postnatal ART, prelabour Caesarean section and avoidance of breastfeeding) can reduce transmission to <1%,[13] this approach is not feasible in sub-Saharan Africa, where Caesarean section is frequently unavailable or unsafe, and breastfeeding is essential for infant survival.

A public health approach to HIV prevention and treatment in sub-Saharan Africa has, therefore, been endorsed by WHO since 2001. Following the HIVNET 012 trial,[14] which reported that a single dose of nevirapine to the mother and infant could reduce HIV transmission by almost 50%, this became the most widely used intervention across sub-Saharan Africa, because of its feasibility and low cost. As subsequent trials reported reduced MTCT and drug resistance with combination ART regimens, the imperative to scale up more effective PMTCT interventions emerged[15 16]; however, the combination of high HIV prevalence, high fertility, late or incomplete antenatal care, inadequate HIV testing rates and widespread adoption of less effective PMTCT regimens meant that by the halfway point of MDG 6, an estimated 370 000 children per year were still becoming infected with HIV.[17]

From 2010, WHO recommended ART initiation from 14 gestational weeks, with lifelong treatment for women with CD4 counts <350 cells/μL and two antiretroviral options for those with CD4 >350 cells/μL to cover the entire period of transmission risk during pregnancy and breastfeeding: zidovudine monotherapy (Option A) or combination ART (Option B).[18] In 2011, a high-profile commitment[19] was made to eliminate new HIV infections among children by 2015 (defined as 90% reduction in the number of infected children from 2009 figures, ie, to around 40 000 per year) and to reduce HIV-related maternal mortality by 50%. In 2013, WHO guidelines were updated to include an option for lifelong ART in pregnant and breastfeeding women regardless of clinical stage or CD4 count (Option B+), with the aim of simplifying PMTCT implementation; harmonising drug regimens used for pregnant and non-pregnant populations; avoiding treatment interruption, which risks selecting drug resistance and covering future pregnancies.[20]

By 2012, there were an estimated 1.5 million HIV-infected pregnant women globally, and PMTCT services were reaching 65% of women in the 21 priority countries in sub-Saharan Africa.[21] This expansion of effective PMTCT coverage led to new infections among children falling to 240 000 in 2013, a decline of 52% from 2001 (figure 2).[22] Globally, almost 80% of countries had adopted either Option B or Option B+ regimens by 2013[22]; however, by current projections, the ambitious target of HIV elimination is unlikely to be met, because of several remaining barriers. In 2013, for example, 54% of pregnant women in low-income and middle-income countries did not receive an HIV test.[22] Among the 22 priority countries, several still have PMTCT coverage rates below 50% (figure 3). Further efforts are, therefore, needed to ensure that HIV testing occurs during pregnancy, to increase the pace of implementation of Option B or B+ PMTCT regimens within antenatal care services and to retain women in care throughout pregnancy and breastfeeding. As use of lifelong ART regimens for pregnant and breastfeeding women increases, the impact of PMTCT expansion on broader health services delivery will require careful evaluation.[23]

DIAGNOSIS OF HIV INFECTION IN CHILDREN

Diagnosis of HIV is a prerequisite for ART initiation, but serological testing in children under 18 months of age is complicated by the presence of maternal anti-HIV antibodies. Diagnosis in young children, therefore, requires nucleic acid testing, which is approximately 10-fold more expensive, technically demanding and inaccessible in many settings. EID, together with initiation of cotrimoxazole prophylaxis for all

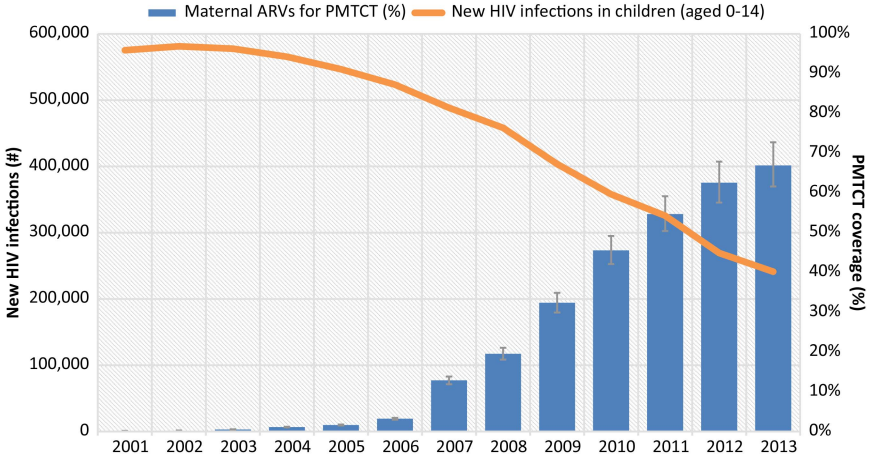

Figure 2 Trends in new HIV infections among children (aged 0–14) and coverage of maternal ART for PMTCT in all low-income and middle-income countries, 2001–2013. (*Source*: UNAIDS 2014 HIV and AIDS estimates, August 2014).

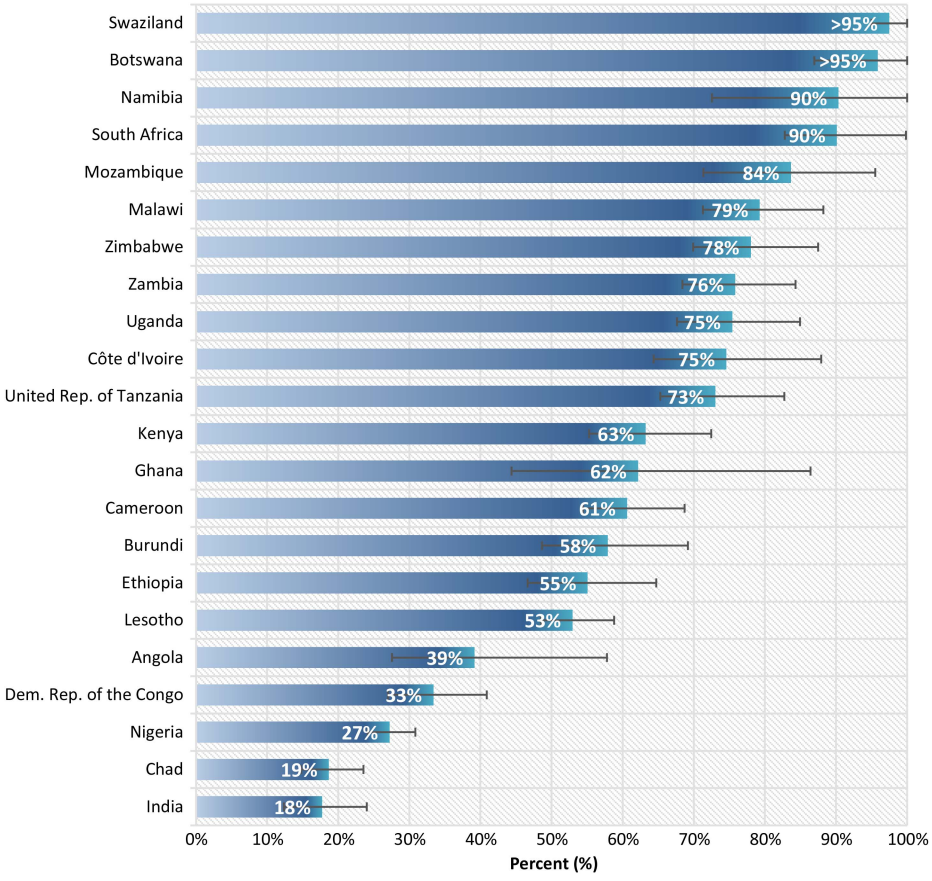

Figure 3 Global Prevention of mother-to-child transmission (PMTCT) coverage in 2013. Percentage of HIV-infected pregnant women within the 22 Global Plan priority countries[8] receiving most effective regimens of antiretroviral medicines for PMTCT in 2013. (*Source*: Joint United Nations Programme on HIV/AIDS, The Gap Report, Geneva, July 2014[9])

HIV-exposed infants, is recommended at 4–6 weeks of age, or at the earliest opportunity thereafter[20] (although there is an emerging argument for moving the first virological test closer to birth[24 25]). EID coverage has expanded substantially over the last 5 years, but in 2013, only 44% of all HIV-exposed infants received a test before 2 months of age. Among the 22 priority countries, only 6 (South Africa, Swaziland, Botswana, Namibia, Zambia and Zimbabwe) reported coverage above 50%, and in 5 countries (Angola, Chad, Nigeria, Malawi and Democratic Republic of Congo) coverage was still below 6%.[26]

Decentralisation of EID to rural health clinics is essential to enable integration of HIV diagnosis into a wider range of child health services, and this has been facilitated by use of dried blood spots, which simplifies collection, storage and transportation of filter paper specimens to central laboratories; however, long turnaround times and loss to follow-up remain major problems in many programmes.[27 28] Point-of-care virological testing may help to overcome these problems and improve retention in care, particularly if combined with strong referral systems, but although several platforms are in development, none has yet been rolled out.[29] Diagnosis of HIV, therefore, frequently occurs late, leading to delays in ART initiation and unacceptably high infant mortality.[30] An analysis of data from national programmes in Namibia, Uganda, Cambodia and Senegal showed that, despite rapid expansion of EID services, the overall effect on health remained small because in three of the four countries, fewer than 40% of HIV-infected infants actually started treatment.[27]

Although EID is an essential component of the PMTCT cascade, it has been argued that, in the context of limited healthcare budgets, other entry points to HIV testing are more cost-effective.[31] Outside PMTCT settings, PITC in high HIV prevalence sites, such as malnutrition units, inpatient wards or within routine MNCH services, enables diagnosis of HIV-infected children born to previously undiagnosed women; however, opportunities for PITC are frequently missed.[32] Infant diagnosis needs to be tailored to the context of an individual country, depending on available health budgets and HIV prevalence.[31] To be effective, however, EID must be linked to HIV treatment and care so that children can initiate ART promptly following diagnosis.[33]

PAEDIATRIC TREATMENT AND CARE

HIV treatment has been one of the unprecedented success stories of recent years. A repertoire of over 25 antiretroviral drugs is now available for adults, although establishing a similar range for children has been slower. When MDG 6 was launched, there was only sporadic access to ART in sub-Saharan Africa, and the notion of universal access by 2010 seemed a highly aspirational target. Scale-up of ART provision was driven initially by the UNAIDS goal of 3 million people accessing treatment by 2005 ('3 by 5'), and the subsequent goal of '5 by 10', and ART roll-out was accelerated considerably by establishment of the Global Fund To Fight AIDS, Tuberculosis and Malaria, and the US President's Emergency Plan For AIDS Relief. Although universal access to treatment remains some way off, there has, nevertheless, been an enormous expansion of ART provision: by the end of 2013, 12.9 million people globally were receiving ART.[9]

The first WHO guidelines for HIV-infected children were issued in 2006,[34] although treatment of children was included in 2003 adult guidelines.[35] For many years, there was a paucity of evidence to guide management of the youngest children, but now randomised clinical trial data are available to inform

treatment guidelines.[36] In particular, the children with HIV early antiretroviral (CHER) trial in South Africa[37] demonstrated the mortality reduction associated with early treatment in infancy, which led to global adoption of guidelines in 2008 recommending universal ART for HIV-infected infants. Since then, there has been a gradual shift towards earlier treatment initiation in older age groups, with 2013 guidelines advocating universal treatment of children under 5 years of age.[20]

By the end of 2013, an estimated 760 000 children were receiving ART, leading to a 40% decline in AIDS-related mortality from its peak in 2005.[22] However, only 24% of HIV-infected children were receiving ART, compared with 36% of adults, leading to a treatment 'gap' between adult and paediatric coverage (figure 4).[9] Treatment of young children is more challenging compared with adults because of high viral loads, rapid disease progression, need for appropriate formulations and reliance on caregivers, who may themselves be ill.[38] Initially, liquid ART formulations were developed, but these tended to have a short shelf life and were often expensive and unpalatable. As fixed-dose combination (FDC) tablets began to be used in adults, clinicians took the opportunity to evaluate halved FDC tablets for children as an alternative to liquids, leading eventually to the development of paediatric FDCs, granules and sprinkles, which are now considered the most appropriate formulations for children.

The current focus is on treatment simplification, with increasing harmonisation across paediatric and adult guidelines; decentralisation of HIV care and treatment, with task-shifting to lower-level health facilities; and greater integration within broader MNCH services to enable the ultimate goal of universal treatment access to be achieved.[20]

REMAINING BARRIERS TO MDG 6

Given the almost universal lack of access to HIV testing, prevention and treatment for children in high prevalence countries in 2000, the achievements of the past 15 years have been extraordinary, fuelled by massive donor investment, strong political commitment and ambitious global targets. Despite these successes, there remain substantial barriers to achieving the goals of eliminating new HIV infections among children and ensuring universal access to treatment. Policymakers and clinicians have tended to ignore women and children outside PMTCT settings. Even within the PMTCT cascade, there are challenges: repeat testing, counselling and access to contraception for HIV-negative women are frequently unavailable; among HIV-infected women, retention in care and adherence to ART during the postnatal period are often poor and final ascertainment of infant HIV status frequently does not occur. Scale-up of paediatric ART still lags behind that of adults[9] for multiple reasons, including low EID coverage, weak linkages to care, lack of trained staff and poor decentralisation of services[10]; despite availability of effective ART, therefore, three-quarters of children are not enrolled into HIV care and treatment. Among children who do initiate ART, there are limited data from many settings on ART adherence, retention within programmes and long-term outcomes. Despite simplification over time, guidelines for children remain more complex than those for adults because of differences in initiation criteria, treatment regimens and dosing across ages, leading to a perception among clinicians that treatment of children is challenging, time consuming and of low priority. Although there has been huge progress in the availability of appropriate ART formulations for children, there is need to develop more FDCs and granules, particularly for protease inhibitor-based regimens, which are now recommended first-line in young children. Finally, as HIV-infected children survive on treatment, greater attention needs to be paid to providing family centred care, addressing chronic complications of HIV infection and treatment, ensuring long-term immunological health and providing better adherence support, particularly for adolescents.

THE POST-2015 LANDSCAPE

There will continue to be a shift away from 'verticalisation' of HIV prevention and treatment programmes towards a fully integrated service delivery model, in line with the *Double Dividend*[10] goal of supporting wider child survival efforts. This will require task-shifting of HIV diagnosis and ART provision to lower-level health facilities which, to date, has been slow to occur for paediatric care, further training of health workers, and mobilisation of communities to create a demand for services. Development of affordable and feasible point-of-care technologies (for DNA PCR, viral load and CD4 counts) for rural health clinics would ensure more timely HIV diagnosis and treatment initiation, allow monitoring of ART efficacy and reduce loss to follow-up. There will be an ongoing incentive to evaluate new antiretroviral drugs in children, particularly those from newer classes (such as the integrase inhibitors) that have no cross-resistance to existing agents and would provide the opportunity to harmonise drug choices across ages. Alternative approaches to management of paediatric HIV, such as ART initiation closer to birth,[39] intensification followed by maintenance ART, early treatment initiation followed by interruption[40] or short-cycle therapy (enabling time off ART during weekends), may provide clinical benefits and still be feasible within a public health approach.

New HIV infections among children continue to decline, and gradual expansion of treatment coverage is allowing more children to survive on long-term ART. The UNAIDS aspiration is for zero new HIV infections, zero discrimination and zero AIDS-related deaths.[21] To this end, the UNAIDS post-2015

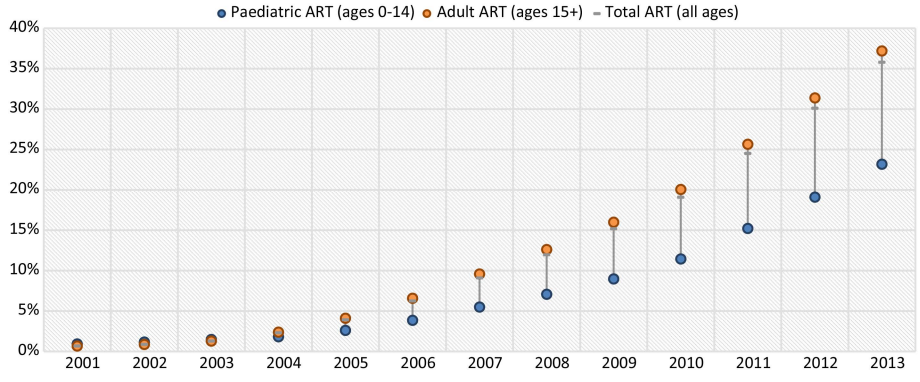

Figure 4 The Treatment Gap between adults and children. Percentage of adults (aged 15+) and children (aged 0–14) living with HIV receiving antiretroviral therapy in all low-income and middle-income countries, 2001–2013. UNAIDS recommends using the denominator of all adults and children living with HIV and not just those eligible for ART based on 2013 WHO eligibility treatment criteria. (*Source*: UNAIDS 2014 HIV and AIDS estimates, August 2014).

target has been labelled '90-90-90': that 90% of HIV-infected people will know their status, 90% of those diagnosed will be on ART and 90% of those treated will have an undetectable viral load.[41] Based on modelling, UNAIDS has estimated that achieving these benchmarks by 2020 could end the AIDS epidemic by 2030.[41] Although HIV/AIDS currently remains an unfinished MDG,[21] the progress achieved in the past 15 years should galvanise the global community to capitalise on these successes and strive towards the goal of elimination.

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