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Antiretroviral drug regimens to prevent mother-to-child transmission of HIV: a review of scientific, program, and policy advances for sub-Saharan Africa

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Abstract

Considerable advances have been made in the effort to prevent mother-to-child HIV transmission (PMTCT) in sub-Saharan Africa. Clinical trials have demonstrated the efficacy of antiretroviral regimens to interrupt HIV transmission through the antenatal, intrapartum, and postnatal periods. Scientific discoveries have been rapidly translated into health policy, bolstered by substantial investment in health infrastructure capable of delivering increasingly complex services. A new scientific agenda is also emerging, one that is focused on the challenges of effective and sustainable program implementation. Finally, global campaigns to "virtually eliminate" pediatric HIV and dramatically reduce HIV-related maternal mortality have mobilized new resources and renewed political will. Each of these developments marks a major step in regional PMTCT efforts; their convergence signals a time of rapid progress in the field, characterized by an increased interdependency between clinical research, program implementation, and policy. In this review, we take stock of recent advances across each of these areas, highlighting the challenges – and opportunities – of improving health services for HIV-infected mothers and their children across the region.

Keywords

prevention of mother-to-child HIV transmission; PMTCT; HIV; antiretroviral prophylaxis; sub-Saharan Africa; global epidemic

Introduction

Tremendous gains have been made to prevent mother-to-child HIV transmission (PMTCT) worldwide. Since the peak of the global HIV epidemic in 2003, we have witnessed a greater than 40% decline in new pediatric HIV infections annually [1]. In sub-Saharan Africa, where an estimated 1.5 million HIV-infected women become pregnant each year, incident HIV infections among infants and children has dropped by 24% in two years. Despite these substantial gains, however, the absolute numbers of HIV-infected children remains staggering. In 2011 alone, more than 330,000 children were newly infected and in need of lifelong HIV treatment [2].

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Efficacious antiretroviral drug regimens have been the cornerstone of PMTCT programs. The virtual eradication of pediatric HIV in North America and Europe was due in large part to the highly effective combination maternal antiretroviral regimens available to HIV-infected pregnant women [3, 4]. The path toward progress has been slower in sub-Saharan Africa. Because of limited health infrastructure and high disease burden, early PMTCT programs relied heavily on simple interventions such as peripartum single-dose nevirapine (NVP) [5]. However, the need for effective yet scalable regimens, particularly those targeting breastfeeding populations, has led to a series of remarkable scientific discoveries. Recommended drug interventions have rapidly incorporated more effective (and often more complex) regimens, while their implementation has been made possible by huge external investment in health systems infrastructure [6, 7]. The 2010 World Health Organization (WHO) guidelines for PMTCT represented a culmination of those efforts [8], as global recommendations became closely aligned to those of industrialized countries.

In June 2011, the Joint United Nations Programme on HIV/AIDS (UNAIDS) introduced the *Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive*, which called for a 90% reduction in new childhood HIV infections and a 50% reduction in HIV-related maternal deaths by 2015 [9]. Endorsed by 22 governments and numerous international agencies, this initiative has reframed the policy discussion around PMTCT away from prevention to the “virtual elimination” of pediatric HIV. To reach these highly ambitious targets, however, coordinated efforts will be needed, so that recent advances in clinical research can be quickly translated to policy and effective program implementation. In this report, we review the substantial progress that has been made since 2010, when the WHO issued its most recent recommendations for PMTCT.

New clinical evidence

The 2010 WHO recommendations for PMTCT emphasized early triage for HIV eligibility, lengthier durations of antenatal prophylaxis, and antiretroviral coverage during the breastfeeding period [8]. Women who met immunologic and/or clinical criteria for lifelong antiretroviral therapy (ART) were to initiate as soon as possible; those who did not were prescribed antenatal prophylaxis from 14 weeks gestation onward. The WHO recommended two approaches (also called “options”) for PMTCT prophylaxis. With “Option A,” pregnant women were to start zidovudine (ZDV) monotherapy during the antenatal period and, around delivery, take a single-dose of NVP with a week-long “tail” of zidovudine-lamivudine (ZDV-3TC). HIV-exposed infants were prescribed continuous daily nevirapine (NVP) from birth until the cessation of breastfeeding. In the “Option B” strategy, women not yet eligible for ART were to initiate three-drug combination antiretroviral prophylaxis during the antenatal period and continue until the cessation of breastfeeding. During the first six weeks of life, their HIV-exposed newborns were to receive daily NVP or ZDV prophylaxis. Strong scientific evidence supported these two comprehensive prophylaxis regimens (Table 1); however, because of the lack of head-to-head comparisons, Ministries of Health were encouraged to consider the relative risks and benefits of each approach and select the most feasible policy for nationwide implementation.

Reducing risk of HIV transmission during breastfeeding

To promote infant HIV-free survival, the 2010 WHO guidelines promoted 6 months of exclusive breastfeeding, followed by 6 months of complementary feeding, for HIV-infected mothers without safe and reliable alternatives for infant nutrition [8]. Antiretroviral regimens were to be prescribed to either mother or infant, to provide prophylaxis during breastfeeding. Since 2010, new reports have emerged to further support the postpartum components of Option A and Option B. Hudgens and colleagues pooled data from five randomized trials of extended infant NVP prophylaxis: Post-Exposure Prophylaxis of

Infants (PEPI-Malawi), the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study, and the 3 parallel randomized trials of Six Weeks Extended Nevirapine (SWEN). They found that the 28-week efficacy increased with the duration of infant NVP prophylaxis, when compared to those receiving single-dose NVP with up to one week of ZDV or ZDV-3TC: 6-week regimen (adjusted hazard ratio [HR]: 0.80; 95%CI: 0.53–1.21), 14-week regimen (adjusted HR: 0.36; 95%CI: 0.23–0.57); and 28-week regimen (adjusted HR: 0.28; 95%CI: 0.15–0.54) [22].

Similar trends were observed in longer-term follow-up of the individual studies. By 12 months of life, differences in HIV transmission were no longer detectable between 6 weeks of extended infant NVP and peripartum nevirapine (risk ratio: 0.87; 95%CI: 0.56–1.15) [23]. However, when infant NVP was provided for 14 weeks (6% vs. 12%; $p<0.05$) and 28 weeks (4% vs. 7%; $p=0.003$), the risk of HIV transmission at 12 months postpartum was significantly lower than in the control arm [24, 25]. In the HIV Prevention Trials Network (HPTN) 046 protocol, at 6 months of follow-up, infant NVP prophylaxis for 6 months was also shown to be superior to a shorter regimen of 6 weeks (1.1% vs. 2.4%; $p=0.05$). However, differences in HIV transmission were not sustained and, by 12 months of life, differences were no longer observed (2.1% vs. 3.0%; 0.27). In a subgroup analysis, there were also no detectable differences in breastfeeding transmission between the intervention and control arms among women with CD4 <350 cells/μL but not receiving ART [21].

Provision of continuous maternal combination prophylaxis – from pregnancy until breastfeeding cessation – has also shown to be efficacious. In Kenya, the single-arm Kisumu Breastfeeding Study demonstrated low rates of drug toxicity and HIV transmission when three-drug regimens were prescribed from 34–36 weeks gestation to 6 months postpartum. Among the 487 mother-infant pairs, HIV transmission was 2.5% at birth, 4.2% at 6 weeks, 5.0% at 6 months, 5.7% at 12 months, and 7.0% at 24 months [14]. A similar sustained protective effect was also observed in the maternal prophylaxis arm of the BAN study, which started maternal combination regimens after delivery and provided them for only the first 28 weeks postpartum: 4% of infants in the experimental arm were infected at 12 months of life versus 7% in the control arm ($p=0.03$) [25]. Across multiple sites in South Africa, Kenya, and Burkina Faso, the Kesho Bora study showed that lower rates of HIV transmission at 12 months when combination maternal regimens (antenatal, intrapartum, postpartum through 6 months of breastfeeding) were compared to antenatal ZDV and peripartum NVP (5.4% vs. 9.5%; log-rank $p=0.029$). Interestingly, the transmission rates between the two arms were comparable at birth (1.8% vs. 2.5%), suggesting similar efficacy between the antenatal components of Option A and Option B among women who are not eligible for ART [26]. In their comparison of three combination antiretroviral regimens, Shapiro and colleagues demonstrated high rates of virologic suppression (defined as < 400 copies/mL) at delivery and throughout breastfeeding period (>92%). Only 8 of 709 (1.1%; 95% CI: 0.5–2.2) of infants were infected – among the lowest transmission rate ever reported in breastfeeding infants – with the majority acquiring HIV *in utero* [16].

To date, there have been no studies comparing the full Option A and Option B regimens described by the WHO in 2010 [8]. The only head-to-head comparison thus far has been of the postpartum components in the BAN study, where no differences were noted between maternal and infant prophylaxis regimens at 28 weeks of life (2.9% vs. 1.7%; $p=0.10$) [13]. The 1077 PROMISE study (NCT01061151), funded by the U.S. National Institutes of Health, will directly compare the antenatal/intrapartum and postpartum components of Option A and Option B. Enrollment commenced in 2011 and is ongoing.

Impact of antiretroviral regimens on maternal and infant health

The risk of maternal mortality among HIV-infected women remains high in the 24 months following delivery, even among those with CD4 counts as high as 1000 cells/μL [27]. Because many of the observed co-morbidities may be HIV-related (e.g., tuberculosis), early initiation of three-drug combination ART could reduce the number of deaths around time of delivery. In the HPTN 052 study, which enrolled non-pregnant adults, immediate ART initiation at CD4 counts of 350–550 cells/μL led to fewer clinical events and greater time to first AIDS-defining diagnosis when compared to a strategy of waiting until the CD4 count fell below 350 cells/μL [28]. In the Kesho Bora study, combination triple antiretroviral regimens resulted in a lower incidence of HIV disease progression during its use, but this effect waned once the drugs were discontinued [26].

Early data from the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) cohort suggested reduced maternal mortality, stillbirth, and prematurity with provision of ART [29]. More recent studies from Botswana are less reassuring. In an observational analysis of over 9,500 HIV-infected pregnant women, ART prior to conception was associated with higher risk for preterm delivery (adjusted odds ratio [OR]: 1.2, 95%CI: 1.1–1.4), small for gestation age (adjusted OR: 1.8, 95%CI: 1.6–2.1), and stillbirth (adjusted OR: 1.5, 95%CI: 1.2–1.8), when compared to all other HIV-infected women. Similar observations were made when women initiating ART in pregnancy were compared to those starting ZDV prophylaxis [30]. In a study of 99 stillbirths at Princess Marina Hospital (Gaborone, Botswana), a large proportion had placental pathology suggestive of chronic hypertensive damage. This finding was similar between HIV-infected women on ART and HIV-uninfected women (65% vs. 54%, p=0.37); however, it was less frequently observed among HIV-infected women not on ART (28%; p= 0.003 when compared to women on ART) [31].

There is growing literature about the safety of antiretroviral exposure to the fetus and infant in the antenatal, intrapartum, and postpartum periods. Despite concerning animal data around first-trimester efavirenz exposure and embryopathy, particularly neural tube defects, a meta-analysis of 21 human studies suggests only rare incidence of myelomeningocele (0.07%) overall and no difference between efavirenz and non-efavirenz-containing antiretroviral regimens [32, 33]. In a cohort of U.S. infants, exposure to tenofovir-based ART *in utero* was associated with reduced head circumference and length-for-age *z*-scores at one year of age (when compared to exposure to non-tenofovir-based regimens), but the long-term significance of these findings is yet unknown [34]. In follow-up of 219 children born to women in the Development of Antiretroviral Therapy in Africa (DART) trial, *in utero* tenofovir exposure did not seem to increase birth defects or growth abnormalities. Height- and weight-for-age at two years were similar to HIV-uninfected Ugandan populations [35]. Maternal ART has been associated with an increased risk for severe infant anemia compared to maternal and infant ZDV regimens [36]. Combination maternal regimens have also been associated with lower weight-for-age, length-for-age, and weight-for length at birth; however, due to rapid growth observed in ART-exposed children, most abnormalities had corrected by 3 months of age [37].

The risk of antiretroviral drug resistance is increased among failed cases of prophylaxis. In studies of extended infant NVP prophylaxis, for example, genotypic resistance to non-nucleotide reverse transcriptase inhibitor agents (NNRTI) was detectable in 75–92% of HIV-infected infants [38, 39]. The highest risk of drug resistance appeared to be among infants acquiring HIV in the antenatal, intrapartum, or early breastfeeding period in the HPTN 046 study. Twelve of 13 (92%) infants infected by 6 weeks of age had detectable NNRTI resistance, while 7 of 25 (28%) infants infected between 6 weeks and 6 months of age had detectable resistance [40]. HIV-infected infants demonstrated slower “clearance” of

NVP-resistant virus (the time until resistance can no longer be detected by conventional genotyping), with over half persisting past one year of age [41]. Infant antiretroviral drug resistance has also been associated with maternal combination maternal prophylaxis or treatment, presumably due to sub-therapeutic drug levels in breast milk. In the Kisumu Breastfeeding Study, 16 of 24 (67%) infected infants had detectable resistance mutations, most commonly to NVP and 3TC [42]. Perhaps more alarming was the finding among HIV-infected infants from the PEPI-Malawi study, whose mothers had initiated HIV treatment in the first year following delivery. Of 37 infected infants and children, 11 (30%) were found to have multi-class drug resistance [43].

From research to policy to practice

While the science behind global PMTCT policy is robust, key challenges hinder in its effective implementation. By the end of 2011, 57% of HIV-infected women worldwide were estimated to have received an antiretroviral regimen during pregnancy; only 30% of those who were treatment-eligible had initiated ART [1]. These estimates fall well short of the thresholds needed to achieve the 90% reduction of new pediatric HIV cases or the "virtual elimination" target of <5% transmission [44, 45].

Missed opportunities along the PMTCT cascade

The "PMTCT cascade" represents the critical pathway pregnant women and their infants must successfully navigate to receive the full benefit of PMTCT services. These steps include (but are not limited to) women agreeing to HIV testing, receiving their results, undergoing ART eligibility screening, initiating treatment or prophylaxis, and adhering to the prescribed regimens [46]. Infants must also adhere to antiretroviral prophylaxis regimens and undergo appropriately timed HIV testing; those who are infected must urgently initiate antiretroviral therapy [47]. Attrition at each point can be thought of as system inefficiency that limits program impact, reduces overall coverage, and leads to more infant HIV infection [48]. Wettstein, et al. highlighted the magnitude of these missed opportunities. In their meta-analysis of 44 studies and 75,172 HIV-infected pregnant women, 94% of pregnant women accepted HIV testing when an opt-out approach was used (compared to 58% when women had to actively request testing services); 70% of those identified as HIV-infected initiated any antiretroviral prophylaxis; 62% who were found eligible for lifelong HIV treatment actually initiated ART; and 64% of HIV-exposed newborns had early infant testing performed around six weeks of life [49].

Once characterized, the PMTCT cascade can be used to identify key gaps in service provision. Program interventions can then be designed, implemented, and evaluated to optimize performance. One area that has received great attention, for example, has been the early triage of HIV-infected pregnant women who require lifelong HIV treatment. According to the 2010 WHO guidelines, providers should conduct immunologic and clinical screening for ART as early as possible in pregnancy; however, in many settings, determining eligibility can take weeks to months. In a study in South Africa's Western Cape, for example, only 51% of women who required ART started it during pregnancy; 27% remained on alternative prophylaxis regimens; and 22% did not receive any antiretroviral intervention prior to delivery [50]. In Durban, South Africa, Hussain and colleagues found that 31% of HIV-infected pregnant women undergoing CD4 screening never received their results [51]. Several strategies have been shown to improve services at this bottleneck. A pilot program comprising point-of-care CD4 testing, same-day initiation, and intensive support early in the course of therapy led to near universal (97%) ART initiation during pregnancy [52]. In Zambia, integration of HIV services within antenatal care clinics resulted in a two-fold increase (14% vs. 33%; adjusted hazard ratio: 2.01, 95%CI: 1.37–2.95) in timely ART initiation, defined as 60 days from initial HIV diagnosis [53]. Even the

innovative Option B+ approach (see below) was originally designed to address the limited availability of CD4 count testing across Malawi [54]. Other successful strategies have included combined mother-infant clinics, active peer follow-up for missed appointments, cellular phone-based reminders, short message service (SMS) results reporting, and ongoing supportive supervision and clinical mentorship [55–58].

As strategies for PMTCT in resource-constrained settings have evolved in complexity, the measurement of attrition along the cascade has presented new challenges. HIV testing and ART initiation are single events that can be easily documented; however, the monitoring of longer term health behaviors may not be so straightforward. Adherence to prescribed antiretroviral regimens, for example, has been notoriously difficult to measure in program settings. Self-reported adherence is prone to reporting biases and more intensive measures such as pill counts, electronic tracking devices, and serum drug levels require resources often unavailable for broad implementation. Yet, the role of careful adherence monitoring cannot be overstated. In a meta-analysis of 51 studies, Nachega and colleagues found that the proportion of HIV-infected pregnant women with adequate adherence (≥80%) fell significantly from the antenatal to the postpartum periods (76% vs. 53%; p=0.005) [59]. Loss to follow-up, a commonly used proxy for non-adherence, was seen at higher rates among pregnant versus non-pregnant women in South African cohorts (19% vs. 11%; adjusted HR: 1.54; 95%CI: 1.38–1.72) [60].

Option A vs. Option B

Because of their similar reported efficacy and the few direct comparisons to date, preferences for the WHO's Option A and Option B have been based largely on operational and programmatic factors [8]. Early country adaptation of the 2010 WHO guidelines in Africa favored Option A for reasons of cost and feasibility [61]. By 2012, however, many Ministries of Health had moved away from this policy, instead endorsing universal antiretroviral treatment or prophylaxis for HIV-infected pregnant women. Even in countries like South Africa, which were thought to have robust Option A-based PMTCT programs, policymakers had reversed course in support of Option B [62]. Such policy changes have been supported by the WHO and UNICEF, endorsements which have undoubtedly facilitated the transition regionally [63, 64].

This shift in PMTCT policy has been driven by at least three important considerations. First, although Option A has been shown to be effective in early (i.e., 6–12 weeks postpartum) and longer term (i.e. 12 months postpartum) program evaluations [65–68], there have been growing concerns about its operational feasibility, particularly after delivery. The complexity of regimen changes for mother and child, the need for regular clinic visits in early infancy, and the supply chain demands of NVP syrup have all dampened the initial enthusiasm surrounding this approach. In Uganda, for example, Walakira and colleagues observed high program attrition among infant on postpartum NVP. Only approximately 10% of mother-infant pairs completed the recommended five-visit postpartum schedule [69]. Ishikawa et al. reported low uptake (57%) and poor adherence (50%) to extended infant NVP in rural Zambia [70]. In patient interviews, investigators also found high rates of improper infant dosing, with less than half of HIV-exposed infants receiving the prescribed amounts of daily NVP [71]. In contrast, field reports of Option B have been generally encouraging [72–75]. While the broad implementation of maternal prophylaxis presents its own operational issues – including the expansion of treatment services, the need for trained providers at primary health centers, and the threat of attrition over time – these challenges appear well-aligned to current priorities of general HIV treatment programs.

Second, there are clear benefits to a PMTCT model that emphasizes the expansion of HIV treatment and increases access to such services at the primary care level. In this broader

context of program implementation, Option B holds a clear advantage over Option A, which is inherently less integrated in its approach. As countries explore innovative strategies to initiate ART earlier in the course of disease – both for its treatment and prevention benefits – the Option B model sets the stage for a transition to the Option B+ strategy (i.e., lifelong ART for all HIV-infected pregnant women), which in turn prepares national programs for broader "universal access" or "test and treat" initiatives [76, 77]. Such considerations are not based in scientific evidence; however, the importance of forward strategic planning in health policy cannot be overlooked.

Lastly, an evolving understanding of Option B's cost and projected cost-effectiveness has contributed to shifts in regional policy. Early multi-country modeling suggested that Option A may result in greater numbers of infant infections averted and life-years gained [78]; work from Malawi and Tanzania demonstrated a lower cost-effective ratio associated with the strategy [79, 80]. More recent work indicates that, when both maternal and infant outcomes are considered, maternal combination prophylaxis may be the preferred strategy. Using program data from Zimbabwe, Ciaranello et al estimated that all three WHO-endorsed approaches (Option A, B, or B+) would result in significant gains in combined maternal and child life expectancy when compared to single-dose NVP. However, Option A was projected to be more costly and less effective than Option B, and Option B actually became cost-saving after four years of implementation. Additionally, Option B+ had a favorable incremental cost-effectiveness ratio of $1,370 per year of life saved (combining maternal and infant life expectancy), compared with Option B [81]. Current trends in global antiretroviral drug pricing should only favor the cost-effectiveness of full ART regimens for PMTCT over time. Between 2009 and 2011, the cost for the tenofovir + lamivudine + efavirenz combination dropped by 33%. Over the same period, drug costs for Option A decreased only marginally, by 3% [82].

PMTCT in the broader context of maternal-child health: Option B+

The Option B+ approach, in which all HIV-infected pregnant women initiate lifelong ART irrespective of clinical or immunologic status, represents a paradigm shift in the field of PMTCT. First introduced and implemented by the Malawian government [54], this policy has garnered enthusiasm globally and helped to renew focus upon maternal and child health. The justifications behind Option B+ are highly compelling, particularly in light of global initiatives to eliminate new pediatric HIV infections and to dramatically reduce maternal mortality [9]. However, a critical examination is needed to better understand its opportunities, limitations, and potential pitfalls.

By eliminating CD4 testing from the critical pathway of eligibility screening – a step associated considerable delay in many settings [83] – the Option B+ strategy allows earlier initiation of ART in the index pregnancy. Earlier ART initiation increases the likelihood that maternal viral suppression is achieved and maintained in the antenatal period, which in turn reduces risk for later vertical transmission [84, 85]. However, the incremental PMTCT gains of Option B+ depend on local circumstances. In settings where CD4 capacity is extremely limited or altogether unavailable, initiation of lifelong ART for all pregnant women will ensure that those at highest risk for transmission (i.e., women with CD4 <350 cells/μL) receive suppressive antiretroviral treatment in a timely fashion. In contrast, gains will be more modest in where health systems function reasonably. The additional time on ART for a pregnant woman may represent only days to weeks in such settings [86]. Whether this will result in appreciable reductions in new pediatric HIV cases depends upon how early women come in for their first antenatal visit. The continuation of ART following breastfeeding also has implications for PMTCT in subsequent pregnancies. Chibwesha and colleagues observed a 2% transmission rate among mothers on ART for greater than 13 weeks during pregnancy, compared to 9% transmission among those on ART for less than 4 weeks [87].

The Option B+ approach imparts other important health benefits. Early initiation of ART has been shown to slow HIV disease progression and reduce the incidence of HIV-related conditions [26, 28]. The continuation of ART after breastfeeding in Option B+ mitigates concerns about treatment interruption between pregnancies. Although large adult treatment trials have demonstrated the inferiority of CD4-guided episodic therapy [88], it is yet unclear how these results apply to pregnant and postpartum women who likely face different circumstances. The early initiation of ART would also provide significant secondary HIV prevention benefits. In the landmark HPTN 052 trial, Cohen et al. reported a 96% reduction in horizontal HIV transmission to serodiscordant, HIV-negative partners when individuals with 350–550 cells/μL started ART [89].

The Malawi national program began implementation of Option B+ in July 2011 and, to date, over 45,000 pregnant women have started lifelong ART under these guidelines [90]. At the time of this writing, several other Ministries of Health in sub-Saharan Africa had endorsed Option B+ and were preparing to bring services to scale. While these early reports are encouraging, ongoing program evaluation is needed to ensure the current and future success of such programs. Health system demands must be critically appraised and, when needed, appropriate action must be taken to prevent overload of the existing infrastructure. The Malawian government made significant investments to prepare for the Option B+ roll-out, including the establishment of some 640 sites and the training of over 4,000 providers in HIV care and treatment [91]. Although this decentralized model is sure to improve access, quality health services cannot be assured without ongoing assessment and supervisory support [92].

It is also important to recognize at this early stage that the individual and population effectiveness of Option B+ are yet unknown. Because of the lengthy breastfeeding duration common in Malawi [93], the first cohorts of women enrolled in the Option B+ national program are only beginning to complete that stage. The success of this approach hinges on patient uptake of services, adherence to antiretroviral regimens, and continued retention in care, but these characteristics that have varied greatly from setting to setting [94–96]. To better understand the downstream impact of the Option B+ approach, “real world” program data are needed and must be carefully evaluated. Alongside the aggregate tallies routinely available in most African health information systems, longitudinal patient-level data should be collected at representative sites, ideally linked between programs (i.e., PMTCT, ART) and between mother and child.

Conclusion

With an ever-growing armamentarium of highly efficacious PMTCT interventions and unprecedented resources available to implement new interventions across the continent, it is now possible to envision the virtual elimination of pediatric HIV in sub-Saharan Africa. We know how to prevent the mother-to-child transmission of HIV. In the coming years, the challenges of PMTCT will likely lay less in scientific discovery than in the implementation of sustainable and effective programs. These shifting priorities are reflected in the recent advances in the field, which have been driven by high quality clinical trials, innovative policy-making, and critical implementation research. Although we have focused on only one aspect of PMTCT in this review, we recognize the importance of other key areas to curbing the pediatric HIV epidemic: the prevention of primary HIV infections among women of child-bearing age, the prevention of unintended pregnancies among HIV-infected women, and the linkage of HIV-infected women and children into long-term care. A broad scientific agenda that encompass all these components will be essential to guide new innovations in the field and to improve health services for HIV-infected mothers and their children.

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Table 1

Clinical evidence in support of the World Health Organization's Option A and Option B approaches for the prevention of mother-to-child HIV transmission among women who are yet ineligible for antiretroviral therapy

	Option A		Option B	
	Mother	**Infant**	**Mother**	**Infant**
Antenatal	ZDV from 14 onward [10–12]	–	Three-drug combination antiretroviral regimen from 14 weeks until breastfeeding cessation [13–16]	-
Intrapartum	Single-dose NVP and 1-week ZDV+3TC [5, 17, 18]	–		-
Postpartum	–	NVP for 6 weeks or until the end of breastfeeding [13, 19–21]		NVP or ZDV for 6 weeks [19]

ZDV = zidovudine; 3TC = lamivudine; NVP = nevirapine