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SYSTEMATIC REVIEW

The impact of Option B+ on mother-to-child transmission of HIV in Africa: A systematic review

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Abstract

Objective: In 2015, the WHO released new guidelines to reduce mother-to-child transmission (MTCT) of HIV. The recommendations, known as Option B+, included initiation of lifelong highly active antiretroviral therapy regardless of CD4 count for all HIV-positive pregnant and breastfeeding mothers. For infants, exclusive breastfeeding for 6 months and antiviral therapy were sanctioned. Targets of <5% transmission in breastfeeding populations and <2% in non-breastfeeding populations were set. This review evaluated the impact of Option B+ on MTCT in African countries.

Methods: Using the PRISMA guidelines, a systematic search of PubMed and Google Scholar databases was conducted to identify relevant studies published between 2015 and 2021. All studies meeting inclusion criteria were evaluated.

Results: Of the 687 references screened, 22 studies from 11 countries (Cameroon, Ethiopia, Lesotho, Malawi, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe) met inclusion criteria. Six studies reported MTCT rates of <2%, 16 studies reported rates of 2–5% and two studies (Uganda and Zambia) reported 6% or more. Rates varied within the same study at different time points post-partum and amongst studies from the same country. Overall, reported MTCT rates appear to be close to WHO targets. However, diverse study designs, selection bias, extensive loss to follow-up and undocumented adherence rates to Option B+ protocols may significantly underestimate MTCT rates of HIV in Africa.

Conclusions: Standardised protocols for impact evaluation must be established to provide evidenced-based data on the efficacy of Option B+ in Africa.

KEYWORDS
highly active antiretroviral therapy, mother-to-child transmission, option B +

INTRODUCTION

The Joint United Nations Programme on HIV& AIDS (UNAIDS) estimates that globally, there are approximately 37 million people living with HIV/AIDS, with women and girls accounting for 53% of the infections.[1] The majority of these females live in Sub-Saharan Africa.[2] In 2014, it was estimated that globally, 1.5 million HIV-infected women become pregnant every year, resulting in 240,000 (210,00–280,000) mother-to-child transmissions (MTCT) of HIV.[3] Sub-Saharan Africa accounted for 85% of the cases. These grim statistics led the WHO to release new guidelines in September 2015. They recommended that all pregnant and breastfeeding mothers diagnosed with HIV, regardless of CD4 count, be enrolled in lifelong High Active Antiretroviral Treatment (HAART) or simply, antiretroviral therapy (ART).[4] This is commonly referred to as Option B+, a revision of earlier approaches (Option A and Option B), all aimed at improving the efficacy of preventing mother-to-child HIV transmission.[5] Moreover, the WHO recommends that HIV-infected women on lifelong treatment (Option B+) exclusively breastfeed for 6 months and continue breastfeeding in combination with complementary

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foods to 24 months or longer.[6] The current WHO recommendation was successfully implemented in Malawi in 2010.[7,8] The Option B+ recommendation including exclusive breastfeeding was formally recommended to countries with generalised HIV epidemics, limited access to CD4 testing, breastfeeding duration exceeding 12 months and high fertility rates.[8–12]

In the developed world, recommendations differ from those of the WHO. Infant formula is safe and readily available; therefore, breastfeeding should be avoided by HIV-positive mothers.[13] Following these current guidelines, the risk of transmission to infants is less than 1%. In contrast, many poorer countries have adopted Option B+ as the standard approach in the Prevention of Mother-to-Child Transmission of HIV (PMTCT), particularly in Sub-Saharan Africa.[14] Implementation of Option B+ raises numerous public health concerns including the acceptability of lifelong HIV treatment impact on growth and development in children and overall adherence rates.[14–16] The primary goal of Option B+ is to prevent vertical transmission of HIV from mother to child. So far, 80% of low- and middle-income countries and over 90% of African countries are implementing Option B+ with scale-up still ongoing in some areas.[17]

Options for prevention of mother-to-child transmission of HIV: Option A, Option B and Option B+

Before 2010, most countries implemented Option A and/or Option B as the PMTCT for HIV-positive pregnant and breastfeeding women. In Option A, a single antiretroviral treatment (Zidovudine) was administered to HIV-positive women during pregnancy. This was then followed by HAART (a combination of Zidovudine, Lamivudine and Nevirapine) at the onset of labour until 1 week after delivery. Under Option B, HAART was administered during pregnancy until 1 week after cessation of breastfeeding. In both Options A and B, the infant would also receive daily oral antiretroviral treatment (Nevirapine or Zidovudine) from birth to cessation of breastfeeding and to 6 weeks if not breastfeeding.[6] However, most resource-limited countries faced numerous challenges for the implementation of Options A and B. Problems included lack of routine CD4 monitoring, long distances to health facilities, expensive transport and long waiting time for services at health facilities. In response to these problems, Option B+ was introduced and first implemented in Malawi in 2010.[18]

In Option B+, lifelong HAART from pregnancy is administered to HIV-positive mothers irrespective of CD4 count levels or clinical stage of the disease. It eliminates the need for continuous monitoring of CD4 status, therefore reducing frequent visits to health facilities. Breastfeeding is recommended, thus reducing stigma. Previously, it was common to restrict breastfeeding in HIV-positive mothers to prevent transmission to the infant (19). Under Option B+, the infant also receives daily oral antiretroviral treatment (Nevirapine or Zidovudine) from birth to cessation of breastfeeding. Evidence from Malawi on the high efficacy of Option B+ for preventing HIV transmission to children, PMTCT led to the current WHO Option B+ recommendation.[4]

Option B+ took the spotlight after the launch of the 'Global plan towards elimination of new HIV infections among children' by UNAIDS in 2011.[20] The aim was to reduce mother-to-child transmission of HIV (MTCT) to zero and raise an AIDS-free generation. The transitions from Option A to Option B and finally to the current Option B+ were based on new evidence supporting the reduction in maternal-to-child transmissions of HIV.[21] The regimens administered to the mothers and their HIV-exposed infants in the three options are described in Table 1.

Despite widespread initiation of Option B+ throughout Africa, definitive evidence of its effectiveness in reducing MTCT has yet to be demonstrated. It was hoped that transmission rates would be 2%–5% or lower.[22] However, the rates of MTCT as determined in routine maternal and infant health-care settings have yet to be rigorously evaluated. The question is repeatedly asked whether Option B+, with lifelong antiviral therapy and exclusive breastfeeding for 6 months, is the best approach for the reduction of HIV/AIDS transmission to infants. No randomised controlled trials exist to help resolve this issue. Therefore, it is timely to review the available literature assessing the impact of option B+ on MTCT rates following widespread implementation throughout Africa. The aim of this paper was to critically review published studies on the efficacy of Option B+ on limiting mother-to-child transmission of HIV in Africa and to assess the strength of the evidence.

METHODS

This review examined published data reporting MTCT rates of HIV in African countries that have adopted the Option B+ protocols. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was used to conduct the review.[23]

A thorough search on PubMed and Google Scholar databases was conducted to identify relevant studies published between 2015 and 2021. The rationale for limiting the year of publication was that Option B+ was officially mandated in 2015 by the WHO. Earlier studies commonly reported results from Option A or Option B or a mixture of protocols making it difficult to extract data specifically for Option B+. Reference lists in the identified papers were also screened.

Search terms used included 'Option B+', 'Option B+ and mother to child transmission of HIV', 'MTCT' and 'Africa'. Results were exported to an electronic spreadsheet and duplicates were removed. Article titles and abstracts of all potentially relevant studies were reviewed by at least two authors. Full texts were accessed when necessary to determine eligibility.

Inclusion criteria were set and specifically included full-text articles in English with data on mother-to-child transmission rates of HIV following WHO Option B+ implementation in African countries. The review excluded

TABLE 1 Options A, B and B+ for prevention of mother-to-child transmission of HIV

	Woman receives Treatment (CD4count: <350 cells/mm3)	Treatment (CD4count: >350 cells/mm3)	Infant receives
Option A	HAART[a] for life	*Antepartum*: Zidovudine (AZT) starting as early as 14 weeks of gestation. *Intrapartum*: HAART continued through childbirth. *Postpartum*: HAART through 7 days postpartum.	Daily Nevirapine (NVP) or Zidovudine (AZT) from birth through age 4–6 weeks regardless of infant feeding method.
Option B	HAART for life	*Antepartum*: HAART (triple dose regimen) starting as early as 14 weeks gestation. *Intrapartum*: HAART continued through childbirth. *Postpartum*: HAART if breastfeeding, until 1 week after cessation of breastfeeding.	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method.
Option B+	HAART for life	HAART for life.	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method.

Note: UNICEF, 2012: Options B and B+: Key Considerations for Countries.[6]
[a]HAART - High Active Antiretroviral Treatment; NVP- Nevirapine; AZT- Zidovudine.

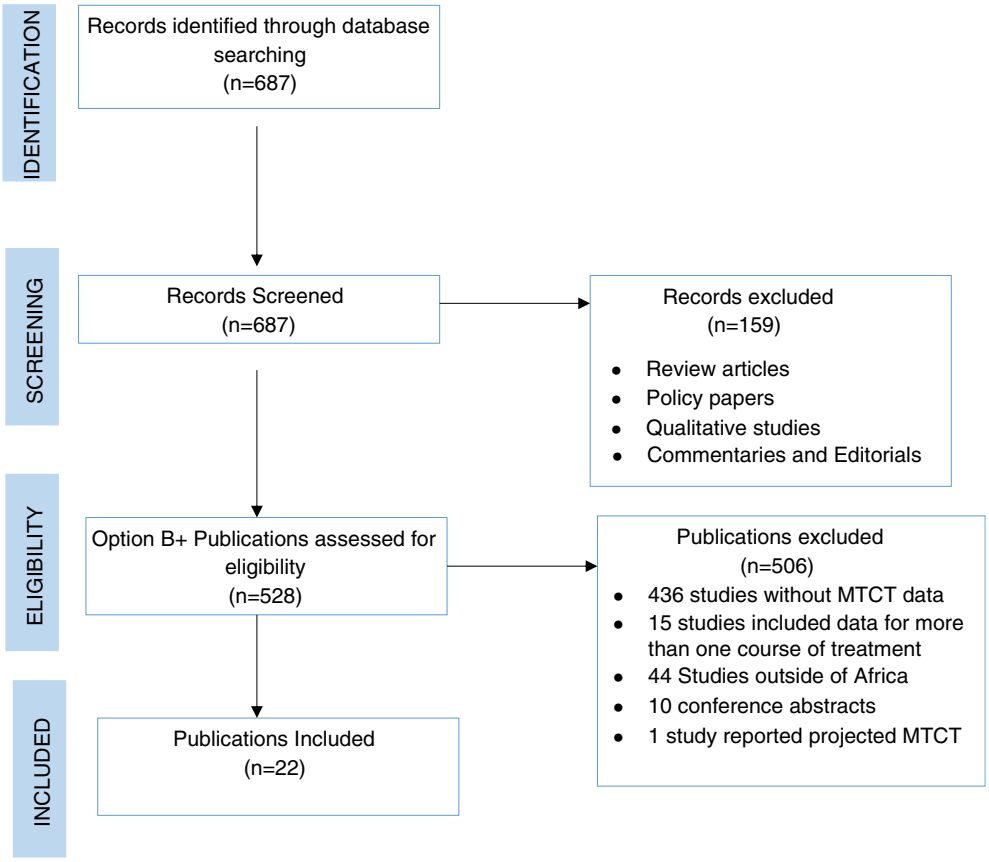

FIGURE 1 Review flow chart

studies where the MTCT was not reported, studies outside Africa, studies published before 2015 and studies where data were unclear as to the exact course of treatment (Option A, Option B or Option B +). Qualitative studies, adherence studies, reviews, commentaries and editorials were excluded. The process of selection of articles that met inclusion criteria using the PRISMA protocol is summarised in a flow chart (Figure 1).

Data were extracted and summarised in an electronic spreadsheet and included relevant information from eligible studies. The following information was extracted: Study design; sample size of HIV-positive women; reported MTCT

including time testing was carried out; lost to follow-up including not tested or dead; site of data collection; reporting of adherence during pregnancy; breastfeeding status and infant treatment with ART. Results were evaluated to assess the strength of the body of evidence. This was based on targets set for Option B+ implementation by the WHO.[22] Success was defined by the WHO as mother-to-child transmission (MTCT) of HIV of less than 5% in breastfeeding populations or less than 2% in non-breastfeeding populations. Data were assessed by all study authors.

RESULTS

The search across databases generated a total of 687 studies, out of which 22 studies met the specified inclusion criteria (Figure 1).

Data collected for this review were summarised in Table 2, which identified 22 studies from 11 African Countries that met inclusion criteria (Cameroon, Ethiopia, Lesotho, Malawi, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe). Study designs varied as follows: there were 13 retrospective cohort studies[23–36]; five prospective cohort studies[37–40,45]; two cross-sectional studies[41,42] and one randomised control trial (RCT).[43] Sample sizes ranged from 124[13,15] to 2505 women.[42] The time of testing infants for HIV was not standardised. One study reported HIV status immediately after birth, with no further follow-up.[26] More commonly, infant HIV status was determined at an older age or whenever the infant was brought to the clinic. Loss to follow-up (LTFU) was addressed in only 14 of the 22 studies and varied from 3%[24] to 47%.[37] Studies were carried out in many settings ranging from urban hospitals and clinics (13 studies) to rural clinics (3 studies). Several studies reported data from combined rural and urban locations (6 studies).

The Option B+ protocol includes lifelong ART for HIV-positive women. It was hard to establish adherence rates during pregnancy as the data presented in most of the studies were incomplete. If the diagnosis of HIV occurred during prenatal care, ART was begun mid-pregnancy. In other cases, adherence with Option B+ was determined at the time of birth or presented as a median number of days medication was taken. Methods of measuring adherence were not consistent and often not fully defined. Adherence was self-reported, and there were significant problems with the retention of mothers if they were diagnosed during pregnancy.[42,43] In some studies, HIV-positive mothers were not on ART or refused treatment.

The breastfeeding status of mothers was not presented in 8 of the 22 studies included in this review. Very high rates of exclusive breastfeeding for 6 months were reported in more than a few studies, but others reported much lower rates and mixed feeding practices. The Option B+ protocol also calls for providing prophylactic ART therapy to infants born to HIV-positive mothers. Approximately half of the studies did not clearly present this information. Where data were available, high rates of over 90% were commonly reported with two exceptions, Malawi at ~77%[28] and Zambia at 76%.[33]

Mother-to-child transmission of HIV in Option B+

The primary outcome of this review was to evaluate the success of Option B+ in eliminating vertical transmission of HIV infections from mother to child. The findings presented here indicate a wide range of MTCT in African countries following Option B+ implementation.

Of the studies presented in Table 2, six studies provided data that MTCT rates in Africa are very low. Rates of MTCT of <2% were reported in Ethiopia,[26] Lesotho at birth,[44] Rwanda,[31] South Africa,[43] Uganda[39] and Zimbabwe.[45] These studies suggest that the WHO targets for eliminating MTCT of HIV are being met in areas where Option B+ is implemented.

A total of 16 studies reported MCTC rates of >2% to 5% with Option B+ implementation. Studies were from Cameroon,[24] Ethiopia at 2 years,[25,27] Lesotho at 2 years,[44] Malawi,[28,29,30,41,42] Rwanda at 2 years,[31] Swaziland,[37] Tanzania,[42] Zambia[33,34,40] and Zimbabwe.[36] A study from Uganda[32] and a study from Zambia[34] reported MTCT rates of above 5%, surpassing the WHO target for elimination of HIV transmissions from mother to child. Two studies, the Rwandan study[31] and Lesotho study,[44] reported different MTCT rates at different age categories (at birth, 6 weeks, 9 months and at 2 years of age).

Reported vertical transmission rates from mother to child were not consistent. For example, significantly different rates were reported in a single country. Two studies, both from Uganda and published in the same year, differed widely in reported results. One small study looking at drug-resistant mutations of HIV found that in mothers following Option B+ with low viral counts, MTCT was eliminated.[39] A second study in health-care facilities across 62 districts reported the highest rates found in this review of 6.5% at 18 weeks of age.[32] Notable differences were also found for MTCT in Ethiopia with data ranging from 0.4%[26] to 3.7%.[27] In Zambia, rates of 2.9% were reported by Muyunda et al.[35] whilst more than twice that rate (6%) was documented by Hanunka.[34]

The timing of HIV testing to determine MTCT rates is an important variable to assess the effectiveness of Option B+. Variability in these data appears to be related to different epidemiology approaches and study designs. Reported MTCT for infants covered a wide range of ages from immediately after birth, at 6 weeks, 4–12 weeks and 6–12 weeks, at 6, 9, 12 and 24 months. In one case, no set age was reported for determining MTCT, rather, data were collected whenever the mother came to the clinic and blood tests were performed.[41] Information that is more accurate can be obtained if HIV status is established at birth, followed by a second test preferably at 12–24 months (most infants are weaned). Tukei et al.[44] in Lesotho reported in this manner, which allows for differentiating the time of infection, but requires resource allocation for long-term follow-up.

Other challenges in presenting results included inconsistent protocols for determining LTFU. For example, LTFU either was not documented in the study or was not calculated in a systematic method. Data from retrospective

TABLE 2 Studies evaluating option B+ and its impact on mother-to-child transmission (MTCT) of HIV

S/no	Study authors	Year	Country	Study design	Sample size (HIV+ women)	MTCT & Timing of test	% lost to follow-up, not tested or died	Site of data collection urban or rural	Adherence to ART during pregnancy	Breastfeeding status	Infant treatment with ART first 4–6 weeks
1	Valère et al,[24]	2018	Cameroon	Retrospective, cross sectional	179	2.2% at 2–5 months	5/179 3%	Yaounde 3 Hospitals Urban	Started anytime during pregnancy, At least 4 weeks on treatment	~50% EBF for up to 6 months	Yes
2	Moges et al,[25]	2017	Ethiopia	Retrospective cohort study	169	2.37% at 24 months	Only included cases with complete medical records	Northwest Ethiopia Rural	Yes (mixed with data prior to Option B+)	96% EBF for first 6 months	Yes 92% (mixed with data prior to Option B+)
3	Chaka et al[26]	2019	Ethiopia	Retrospective study	248	0.4% at birth	25/248 10%	3 Public Health Clinics Urban	51% were on ART by weeks 13–24 of pregnancy	93.5% EBF for 6 months	98%
4	Kassaw et al,[27]	2020	Ethiopia	Retrospective cohort	217	3.7% at 24 months	Only included cases with complete medical records	Five regional referral hospitals Northern Ethiopia	Data not presented	62% EBF first 6 months	Data not presented
5	Tukei et al,[44]	2020	Lesotho	Observational cohort	631 652 (+ sero-converted)	0.9% at birth 2.9% at 2 years	431/631 32% 463/652 29% at 2 years	National data Mixed Urban and Rural	97% on ART at the time of delivery	~50% EBF ~39% some BF	97% of infants treated
6	Herce et al,[41]	2015	Malawi	Serial cross-sectional study	608 infants	3.6% at first testing	No LTFU in this design	Central Districts Mixed Urban and Rural	Data not presented	Data not presented	In 2013, 100% of infants treated
7	Kim et al,[28]	2015	Malawi	Retrospective cohort	998	2.6% at 6–12 weeks	134/998 13.5%	Lilongwe Urban	Median 95 days on ART	Data not presented	77.3% of infants treated
8	Barr et al,[42]	2018	Malawi	Cross-sectional analysis	2505	3.7% at 4–12 weeks	No LTFU in this design	National data Mixed Urban and Rural	91.3% on ART during pregnancy	Data not presented	98% of infants treated
9	Fokam et al,[29]	2019	Malawi	Retrospective cohort	199	2.8% at 6 weeks	40.8% at 6 months 55.1% at 1 year	Hospital Urban	82.5% on ART 4 weeks prior to birth	90.8% EBF	91.2% infants treated
10	Harrington et al,[30]	2019	Malawi	Retrospective cohort	299	2.0% at 6 weeks	32/299 11%	Hospital in Lilongwe Urban	Data not presented	Data not presented	Data not presented
11	Gill et al,[31]	2017	Rwanda	Prospective cohort	608	0.5% at 6 weeks 0.9% at 9 months 2.2% at 24 months	155/608 25% at 24 months	Clinics in Kigali Urban	14 women were not on ART at study entry, 3 of whom enrolled postpartum	97.6% were breastfed; EBF was reported by 88.0% at 1 month and 61.2% at 5–6 months	Yes
12	Myer et al,[43]	2018	South Africa	Randomised Control Trial	381 Option B+	1.2% at 1 year 1.9% mortality	95/381 25%	Large health-care facility in Cape Town Urban	Problems with retention when diagnosed during pregnancy	EBT was inclusion criteria for RCT	Data not presented
13	Etoori et al,[37]	2018	Swaziland	Prospective Cohort	496/660 (75%) initiated ART	7/320 2.2% at 6 weeks	47% at 2 years	8 primary clinics in the South Majority rural	75% initiated 50% at 2 years	Data not presented	Data not presented

(Continues)

TABLE 2 (Continued)

S/no	Study authors	Year	Country	Study design	Sample size (HIV+ women)	MTCT & Timing of test	% lost to follow-up, not tested or died	Site of data collection urban or rural	Adherence to ART during pregnancy	Breastfeeding status	Infant treatment with ART first 4–6 weeks
14	Gamell et al,[38]	2017	Tanzania	Prospective cohort	124	2.2% median follow-up time of 19 months	32/124 25%	Large clinic Kilombero District Rural	Problems with retention when diagnosed during pregnancy	91% EBF	Inconclusive data
15	Baryamutuma et al,[32]	2017	Uganda	Retrospective Cohort	283	6.5% at 18 weeks	53.7%	505 clinics in 62 districts Mixed Urban and Rural	Data not presented	Data not presented	Data not presented
16	Machnowska et al,[39]	2017	Uganda	Prospective Cohort	124	0.0% at 18 months	49/124 40%	ANC clinic Fort Portal Urban	Data not presented	Data not presented	Yes
17	Ngoma et al,[40]	2015	Zambia	Prospective cohort	219	4.1% at 18 months or before death	188/279 33%	Public Clinic in Lusaka, Zambia Urban	Self-reported adherence considered unreliable	92.8% EBF for 6 months	Data not presented
18	Bonawitz et al,[33]	2016	Zambia	Retrospective Cohort	459	3.7% variable	Only included cases with complete medical records	Five clinics: in Mazabuka & Livingstone Districts Southern Zambia	4/459 declined treatment	No data on cohort 11/17 HIV+ EBF 2/17 mixed	76% at birth
19	Hanunka,[34]	2018	Zambia	Retrospective cohort	793	6.0% at 6 weeks	At 3 months 39.6% of mothers transferred 37% had died	Clinics in Lusaka Urban	Data not presented	Data not presented	Data not presented
20	Muyunda et al,[35]	2020	Zambia	Retrospective cohort	580	2.9% variable	Only included cases with complete medical records	~600 government health facilities Mixed Urban and Rural	Data not presented	Data not presented	Unclear
21	Ndarukwa et al,[36]	2019	Zimbabwe	Retrospective cohort	1204	2.5% at 6 weeks	Only included cases with complete medical records	Clinics in Harare Urban	2% were not on ART	94% EBF at 6 weeks	Unclear
22	Zijenah et al.[45]	2021	Zimbabwe	Prospective cohort	502 HIV + mothers 492 live births	1.6% at 6 months	453/492 8%	Clinic in Harare Urban	Data not presented	99% EBF for 6 months	Yes

Abbreviations: ANC, Antenatal care; ART, Antiretroviral therapy; EBF, Exclusive breastfeeding; MTCT, Mother-to-child transmission.

studies commonly included only women and infants with full data sets. Kassaw et al., 2020, in an Ethiopian study excluded exposed infants because birth dates were missing from the documentation, test results were missing or HIV testing dates were not on file. A 'representative' sample was taken only from exposed infants with complete medical records of both mothers and infants.[27] If a study design was cross sectional, by definition, data were collected at a single time point without follow-up. One of the newer studies from Zimbabwe used a prospective design and accurately reported lost to follow-up and overall mortality rates. These data appear to be more reliable and complete than in most previous studies. Results documented a 1.6% MTCT rate at age 6 months with approximately 8% LTFU.[45]

Times of data collection amongst studies describing breastfeeding practices were also not standardised. Data were collected at birth, at 6 weeks or at 6 months. Differentiation between exclusive breastfeeding (EBF) and mixed feeding practices was not always defined. Here, data sets were often incomplete and were impacted by LTFU.

Variability in study designs made it hard to make comparisons and evaluate the efficacy of Option B+. Thirteen studies were designed as retrospective cohorts, which exclude exposed infants when documentation was missing. Five studies were prospective cohorts which can more distinctly indicate the temporal sequence between an exposure and an outcome. However, in these studies, a major challenge was LTFU, particularly in the exposure group. Two studies were cross sectional with data collected at a single point in time. This design provides correlated data but does not allow for causal inference.

The gold standard of epidemiological research, the randomised control trial (RCT), was used in a single study from Cape Town, South Africa.[43] The study was designed to determine if the location for postpartum ART treatment for HIV-positive mothers (providing services within maternal and child health clinics vs. general adult HIV clinics) would improve retention and adherence rates amongst new mothers. The study period included both Option A and Option B+; however, results were reported separately for women who received Option B+ treatment. Secondary outcomes of the study included mother-to-child HIV transmission rates. Combined transmission and mortality rates were less than 3%, but LTFU was high at ~25%. Randomisation was not for Option B+.

DISCUSSION

This systematic review identified studies that reported vertical MTCT of HIV in African countries after implementation of Option B+. These data are crucial for determining optimal health policy and recommendations. The available publications demonstrated a genuine effort to present the efficacy of Option B+. Despite hundreds of publications that discuss Option B+, only 22 studies met inclusion criteria. The identified studies used diverse epidemiological approaches, demonstrated substantial bias in reporting data and had methodological limitations. This made it difficult to assess and compare results. With the currently available publications, it was considered unsuitable to integrate and pool data or carry out any advanced data analyses, essential for arriving at definitive conclusions. Despite goals set by the WHO for MTCT of HIV, no uniform standard has been employed for evaluating this parameter following the implementation of Option B+.

Studies commonly did not address confounding factors and suffered from potential biases. Rarely were confounders like maternal age and education, family size, access to care, access to safe water, socioeconomic standing or marital status taken into consideration. There were also numerous sources of bias. For example, studies used inconsistent definitions for LTFU. In some cases, LTFU included infant death, but in other situations, mortality rates were reported separately. This led to difficulty in determining accurate retention rates, and in some cases, attrition rates or LTFU was not reported at all. It was also impossible to differentiate between women who discontinued treatment or relocated. Women/infants that were not lost to follow-up but had missing data were not included. The study design accounted for some of the incomplete information. Retrospective studies used data collected in routine visits in clinical settings. Although this is a practical and cost-effective solution for evaluation purposes, it induces a *selection bias* that cannot be ignored. Commonly, only women who had complete data sets were included for evaluation. Therefore, there was no way to accurately determine how many women were lost to follow-up. Assuming that those lost to follow-up were more likely to have poorer adherence to protocols, there is potential for a substantial underestimation of MTCT rates.

Adherence

Potential bias also arises from the participants' level of adherence to the Option B+ protocols. Adherence to treatment in the Option B+ programme is a major indicator of effectiveness and predictor of successful outcomes. Following recommended protocols promotes viral suppression and prevents drug resistance.[19] However, low adherence rates have been recorded in African populations where Option B+ has been implemented.[46] Studies in this review either did not report or reported high variability in pre-pregnancy ART treatment. In most cases, it was impossible to determine if study participants were following the Option B+ protocols of lifelong ART therapy. Data were rarely provided for adherence to drug treatment during pregnancy and lactation. If a mother arrived at a clinic during pregnancy and was HIV positive, Option B+ was initiated at that time. It was noted that in these situations, adherence was particularly challenging.[42] Lack of consistency of time of implementation of Option B+ along with limited data if medications were taken regularly and in a timely manner were additional limitations of these studies. Results from a meta-analysis indicated

relatively good retention rates for African women in Option B+ programmes, 72.9% at 6 months and 76.4% at 12 months.[47] However, retention rates do not accurately measure adherence to protocols. Results regarding compliance with protocols for the administration of antiviral medications for newborn and breastfeeding infants were also not routinely presented. Because adherence/compliance was not properly addressed in most of the studies, a notable *compliance bias* was introduced. It was also questionable if self-reported adherence rates truly reflected recommended implementation of Option B+ protocols.

Breastfeeding

Exclusive breastfeeding in HIV-positive mothers is associated with decreased infant mortality in the developing world.[5] It is the recommended feeding method for infants in resource-limited settings. However, it can also be the source of vertical transmission of HIV to the infant. Results from this review indicate that when reported, exclusive breastfeeding was widespread. To maximise the benefits of following the Option B+ protocols, adhering to lifelong ART treatment and EBF for the first 6 months must be routine components of care.[33]

Infant treatment and timing of HIV testing

All infants born to HIV-positive mothers should be receiving daily NVP or AZT up to 4–6 weeks.[6] Therefore, if MTCT is to be accurately determined, testing for HIV should be carried out after 6 weeks and preferably at the time of weaning. Because vertical transmission of HIV occurs during pregnancy, childbirth and breastfeeding, presenting results at the time of birth[26] or at any time earlier than weaning is misrepresentative. Two studies reported MTCT data at more than one time point and provided a cumulative rate at the age of 24 months.[31,44] This appears to be an optimal approach for establishing reliable data for MTCT based on the assumption that at 2 years; most young children have stopped breastfeeding. In the absence of standardised protocols, every study in this review presented data for infants tested for HIV at different time points.

Challenges of implementation

Under real-world conditions, where resources are limited, a long list of factors appears to attenuate the effectiveness of reducing MTCT of HIV through Option B+. In a cross-sectional study in 505 health-care facilities throughout Uganda, about half consistently fully monitored HIV patients at routine visits.[32] Lack of medications and HIV test kits were reported in 20%–46% of locations. These facts help in understanding the difficulty in accurately evaluating the success of Option B+. Without critical supplies, the programme cannot be implemented as recommended. These problems were not restricted to Uganda. Countries like Tanzania are struggling to provide universal HIV testing for pregnant women, rescreening during late pregnancy and following delivery.[42] Furthermore, diagnosis is not sufficient to reduce the MTCT of HIV. Positive results must be linked to care, and active follow-up must be carried out. Work from Lesotho also documented numerous challenges and reported that programmes were seldom fully implemented.[44] Interestingly, these challenges were reported in both urban and rural settings and in variable health-care settings (clinics and hospitals).

Malawi was one of the first countries to adopt Option B+, the lifelong treatment approach for combating the AIDS epidemic.[7] It was preferred over Option A and B because it does not depend on CD4 counts or the availability of laboratory services. This is reflected in the high number of published studies from this country. However, retention rates over time appear to be low.[29] The most current available national data indicate LTFU rates as high as 26.2%.[48] Explanations provided for high rates of lost-to-follow-up and discontinued treatment included fear of HIV disclosure, anticipated or experienced stigma and insufficient social support. Other issues included non-acceptance of HIV status, ART side effects, lack of funds for transport and negative experiences with clinic staff.[29,49]

Many studies have been published looking at African populations and report national data on MTCT of HIV over the past 10–15 years. However, it is hard to establish that the data are referring specifically to the implementation of Option B+. Data from Kenya during 2007–2015 showed that the number of infants testing HIV positive had gone down from 11.1% to 6.9%.[50] This is encouraging and ART therapy in mothers was found to reduce the odds of infection in infants (OR: 1.92; 95% CI: 1.79–2.06). However, the reduction in MTCT cannot be specifically attributed to the implementation of Option B+. Many HIV-positive mothers did not receive treatment during pregnancy, infants did not receive prophylaxis therapy and prevention programmes (PMTCT) were not uniformly implemented countrywide. Data from Mashonaland East, Zimbabwe, were similar, with an overall reduction of MTCT following the implementation of Option B+ from 5.3% in 2014 to 4.0% in 2016.[51] Here too, many women included in the data did not follow the specific protocols of Option B+. Reports from Ethiopia also reflected improved rates of MTCT following a programme shift from Option A to Option B+. A reduction from 10.29% transmission to 2.37% was documented.[25] A large retrospective cohort study in Soweto, South Africa, also found a marked decline in MTCT rates; 6.9% in 2007 before Option B+ to 0.9% in 2014 and 0.8% in 2015 after the implementation of Option B+.[52] Data were collected from routine district reporting in a national database. Although a statistical association exists between the official implementation of Option B+ and reduced rates of MTCT, this does not confirm causality.

Nigeria is the country with the largest population in Africa and is thought to have one of the highest rates of HIV-infected babies in the world.[53] Data published in a retrospective review did not specifically identify the protocols used in Nigeria as being Option B+. Regardless, a marked decrease in MTCT from 2008 (14.3%) to 2014 (4.9%) was reported.[54] More recent data from the north central zone reported an MTCT rate of 11.4% in infants at age 20 months or older. Only 54.5% of mothers received ART medication prior to pregnancy.[55]

It is assumed that data comparing MTCT of HIV in African countries over time reflect the implementation of Option A or B in earlier years with more recent studies reflecting results from the adoption of Option B+. Consistently, the data reflect a reduction of MTCT of the virus.[4]

The overall impression is that the lifelong approach of antiviral therapy recommended in Option B+ is helping to eliminate MTCT and reduce AIDS in Africa. However, poor documentation of routine services, lack of sufficient resources to provide every HIV-positive mother with counselling and treatment and the inability to accurately monitor adherence inhibit assessment of the actual transmission rates in African countries.

In more than one case, reported improvement in preventing MTCT was attributed to integrated service delivery models and not necessarily the implementation of Option B+. In Tanzania, antenatal and HIV services with specialised counselling were delivered in a single clinic which appeared to be the cause of reduced transmission rates.[42] A study in South Africa reported similar findings[43] and suggested that integration of Mother and Child Health programmes with HIV services may be a simple way to improve the health outcomes of both women and children.

Scale-up and implementation of Option B+ should include intense measures to increase adherence to ART during pregnancy, during breastfeeding and after breastfeeding. Encouragement to provide antiviral treatments to infants and children is also a key to reducing vertical transmission. A re-evaluation of delivery models may be critical for reaching these goals. there is a need for more rigorous large-scale prospective research on MTCT in countries implementing the Option B+ programme.

CONCLUSIONS

Global interest is high for achieving the ambitious goal of virtual elimination of mother-to-child HIV transmissions. Reports show an impressive decline of approximately 52% in new HIV infections amongst children aged 0–9 years since 2010.[56] However, it remains to be shown that the implementation of Option B+ is the cause of this improvement. The currently available literature is hampered by severe methodological limitations and numerous barriers to programme execution. Standardised protocols for impact evaluation must be implemented to provide evidenced-based data on the efficacy of Option B+ in Africa and worldwide.

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