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REVIEW

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Advances in therapy for the prevention of HIV transmission from mother to child

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ABSTRACT

Introduction: Actually, ~17.8 million women and 1.8 million children (<15 years) are currently infected with the Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS). Particularly, the majority of pediatric infections (>90%) resulted from 'HIV mother-to-child transmission' (MTCT), both in pregnancy, labour, delivery and later by breastfeeding. Due to its high pediatric incidence, MTCT represents a public health concern.

Areas covered: In this review, we focus on available treatments and antiretroviral drugs recommended by the World Health Organization, and the main clinical investigations in antiretroviral pharmacotherapy to prevent the MTCT.

Expert opinion: The MTCT has been improved dramatically in the last few years mainly due to prophylactic perinatal antiretroviral therapy for pregnant women living with HIV. However, there is still a milestone to reach since HIV MTCT remains as a public health challenge associated with MTCT though breastfeeding (post-natal transmission). In this context, different strategies could be employed as an attempt to reduce pediatric HIV infections. One of them involves the improvement of patient adherence to the HIV therapy. One possible solution is the development of novel long-acting formulations for prophylaxis of mothers and children, and a second possible solution is increase the inclusion of mothers and infants in care programs to more effectively prevent the vertical transmission.

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HIV mother-to-child transmission; antiretroviral pharmacotherapy; prevention; pregnancy; breastfeeding

1. Introduction

According to the 2015 World Health Organization (WHO) latest statics, approximately 36.7 million people live with the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), accounting 2.1 million newly HIV infections worldwide. Among them, 17.8 million women and 1.8 million children (<15 years) are currently infected with HIV [1]. The same year, ~150,000 children became infected with HIV (~410 new infections per day) and an estimated 110,000 died from AIDS. Particularly, the majority of these pediatric infections (>90%) resulted from 'HIV mother-to-child transmission' (MTCT), in pregnancy, labor, and delivery and later by breastfeeding [2]. Due to its high pediatric incidence, MTCT represents a public health concern. In high-income countries, maternal and child deaths related to HIV infection were almost zero in 2009. However, a clear different situation was observed in middle–low-income regions, where only a few HIV-infected pregnant women received an appropriate HIV treatment for themselves and for preventing their children from became infected. In this context, the application of comprehensive interventions should be priority in developing countries in order to achieve the eradication of HIV pediatric infections due to MTCT [3].

Different strategies have been developed in recent years to reduce the number of new HIV infections in newborns. One of them was the development of the Inter-Agency Task Team for the elimination of MTCT co-convened by the WHO and the United Nations Children's Fund toward the elimination of HIV-infected newborns and for keeping their mothers alive (*Global Plan toward the elimination of new HIV infections among children and keeping their mothers alive* – 2015 Global Plan) [4]. In this way, two main targets could be achieved: the reduction of the number of both newborn HIV infections (~90%) and HIV-related maternal deaths (~50%). Prevention of mother-to-child transmission (PMTCT) represents a key factor to ensure a new generation free from AIDS, being a unique opportunity to eradicate HIV infections among children worldwide [5].

There are a series of effective interventions that could successfully reduce the transmission rate from 15–45% to 5–2% at the different transmission stages [6,7]. In this framework, not also an early start of the antiretroviral (ARV) therapy for HIV-infected pregnant women (regardless of their CD4 count) but also a short course of ARV drugs for the newborn appears as the primary intervention to effectively reduce MTCT. High patience adherence to ARV therapy results crucial to reach undetectable viral levels for PMTCT. However, many women leave ARV therapy after their children are born,

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Article highlights

- Pediatric HIV remains as a public health challenge were the major of these pediatric infections resulted from 'mother-to-child transmission' (MTCT).
- Guidelines to promote the prevention of MTCT (PMTCT) (options: A, B and B+) represent a key intervention for the reduction of pediatric HIV infections due to MTCT.
- PMTCT requires ARVs-based therapy for all HIV-infected pregnant women since ARV drugs reduce maternal viral load in blood and genital secretions.
- Despite the benefits of the combined ARVs therapy for both, mother and child, risks associated with the pharmacotherapy should be considered.
- PMTCT during the postnatal period requires pharmacotherapy interventions including children treatment with different ARVs regimens and ARVs prophylaxis to lactating women.

This box summarizes key points contained in the article.

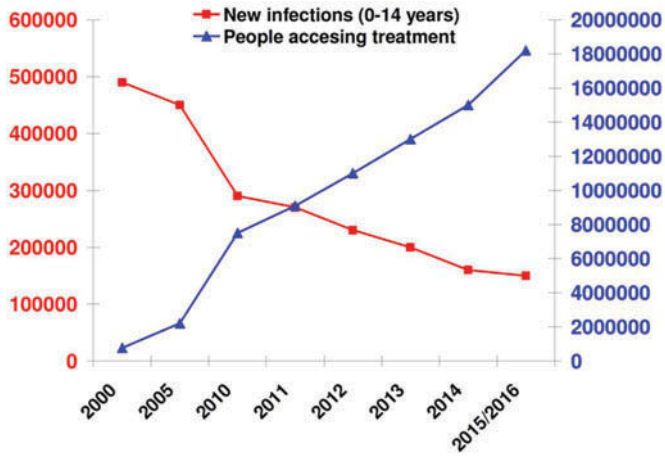

Figure 1. Number of new infections (aged 0–14) (red) and number of people accessing treatment (blue). Full color available online. AQ3

increasing the possibilities of children HIV infection during breastfeeding. Hence, women must be educated about the benefits of an adequate adherence to ARV medicines and also appropriate breastfeeding practices should be employed for women living with HIV. Furthermore, other ways to avoid MTCT are related with the prevention of HIV infection during pregnancy [8,9].

In 2015, 77% of pregnant women living with HIV received effective ARV therapy. Different ARV regimen choices have been recommended for those patients who have never received ARVs previously. Among them, abacavir plus lamivudine and tenofovir plus emtricitabine or lamivudine in addition to zidovudine plus lamivudine have been selected as the preferred dual nucleoside analog reverse-transcriptase inhibitors. Furthermore, efavirenz has been selected as the preferred non-nucleoside reverse-transcriptase inhibitor, according to Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women [10]. Nevertheless, regulatory authorities recommend against the use of efavirenz during the first trimester of pregnancy due to greater risk of neural tube defects in nonhuman primates [11]. Despite this consideration, updated meta-analysis of clinical trials has demonstrated the absence of an increased risk of central nervous system congenital anomalies associated with exposure to efavirenz during the first trimester of pregnancy [12].

AQ2 With regard to pediatric HIV, it remains as a public health challenge where ARV drugs allowed to reduce new HIV infections among children (~1.6 million) and AIDS-related pediatric deaths since 2000 (Figure 1). Without an ARV therapy, the life expectancy of those HIV-infected infants (aged 2 years) is of only 2–5 years [9,13]. Fortunately, some middle–low-income regions (known as priority regions) such as Uganda, Botswana, Swaziland, Namibia, and South Africa could meet the Global Plan target of reducing MTCT to ~2% between 2009 and 2015, representing a major advance in the reduction of pediatric HIV, being these nations really close to eradicate MTCT [7].

AQ4 There by the question is: what is next in PMTCT facing pediatric HIV eradication worldwide? Although the 2015 Global Plan has demonstrated high progress in reducing new HIV infections among children, almost 150,000 pediatric new infections (2800 per week) were accounted worldwide only in 2015 [9,13].

Recently, the United States President's Emergency Plan for AIDS Relief and the Joint United Nations Program on HIV/AIDS (UNAIDS) have developed a novel initiative denoted as '*Start Free, Stay Free, AIDS Free*' with different targets by 2018 and 2020 included in the 2016 United Nations Political Declaration on Ending. '*Start Free, Stay Free, AIDS Free*' aims to meet the pending agenda of the 2015 Global Plan and give the main challenging strategies to end HIV epidemic in children, adolescents, and young women [13]. Some of the key strategies are related with the access of pregnant and breastfeeding women to lifelong ARV therapy (95%), the annual reduction in new HIV pediatric infections (0–14 years old) (less than 40,000), and the access of HIV-infected children (~1.8 million, 0–14 years old) to an adequate anti-HIV therapy.

Furthermore, this initiative also includes adolescents (15–19 years old) living with HIV. It is estimated that approximately 390,000 adolescent girls and young women are infected with HIV per year. Then, '*Start Free, Stay Free, AIDS Free*' initiative promotes main goals related with the reduction of new HIV infections (<100,000) and the access to ARV medicines for 1.5 million adolescents over 2020, as an attempt to promote adolescents to stay free from HIV and to guarantee the free access to the anti-HIV therapy for those adolescents and young adults living with HIV [9,13]. Table 1 shows the commonly used ARV drugs in the PMTCT.

In this framework, the present review toughly revised the main clinical investigations in ARV therapy to PMTCT and the recommended perinatal/pediatric guidelines for HIV treatment. Moreover, an update of the new ARV combinations recommended for pregnant women living with HIV and newborn will be fully discussed.

2. Programs to prevent HIV MTCT

Guidelines to promote the PMTCT (employing ARVs) constitute one of the first interventions to reduce pediatric HIV due to transmission from mothers to their babies. First, according to the WHO 2006 guidelines, it was recommended an ARV therapy

Table 1. List of antiretroviral drugs used for prevention of mother-to-child transmission and that have been approved by the US Food and Drug Administration (FDA).

Drug class	Generic name	Abbreviation	Brand name	FDA approval date	Adult dosage forms	Pediatric formulation available	Age recommended	For infants
Nucleoside reverse-transcriptase inhibitors (NRTIs)	Abacavir	ABC	Ziagen	December 1998	Tablet	Oral solution (20 mg/mL)	>3 months	☺
	Emtricitabine	FTC	Emtriva	July 2003	Capsule	Oral solution (10 mg/mL)	0 week	☺☺
	Lamivudine	3TC	Epivir	November 1995	Tablet	Oral solution (10 mg/mL)	0 week	☺☺
	Tenofovir disoproxil fumarate	TDF	Viread	October 2001	Tablet	Oral powder for be mixed with soft food (40 mg/g)	>2 years	☹
	Zidovudine	AZT	Retrovir	March 1987	Capsule	Syrup (10 mg/mL)	0 week	☺☺
Non-nucleoside reverse-transcriptase inhibitors	Efavirenz	EFV	Sustiva (US) Stocrin (Europe)	September 1998	Tablet, capsule	Oral solution (30 mg/mL)[a]	>3 years	☺☹
	Nevirapine[b]	NVP	Viramune	June 1996	Tablet	Syrup (10 mg/mL)	0 week	☺☺
			Viramune XR	March 2011				
Protease inhibitors	Ritonavir[c]	RTV	Norvir	March 1996	Tablet, capsule	Oral solution (80 mg/mL)	>1 month	☺☺
	Lopinavir and ritonavir	LPV/RTV	Kaletra	September 2000	Tablet	Oral solution (LPV 80 mg/mL – RTV 20 mg/mL)	>1 month	

[a]Oral solution formulation was discontinued in October 2015.
[b]Viramune XR is the extended-release dosage form of nevirapine.
[c]RTV solution contains 43% v/v of ethanol.

AQ5

(starting at 28-weeks of pregnancy) of a daily zidovudine regimen along with a single administration of nevirapine (one dose) for pregnant women during labor and for the newborns during their first few days of life [14]. Then, the WHO's 2010 PMTCT ARV guidance provided two different options for short-term ARV prophylaxis, known as Option A and Option B, for those HIV-positive pregnant women with CD4 T cell (CD4) greater than 350 cells/mm^3 who did not need ARV medicines for their health. Patients were encouraged for an earlier start of any option (before 14 weeks of pregnancy) for a significant reduction of MTCT.

On one hand, Option A involved the administration of ARVs during pregnancy and labor with an ARV postpartum 'tail' regimen to avoid drug resistance. Furthermore, newborns received ARV medicines thought the breastfeeding stage. On the other hand, Option B involved the ARV administration for all pregnant and breastfeeding women living with HIV. After the lactating period, women could chose to discontinue the ARV therapy, according to their CD4 count (>350 cells/mm^3) [15–17].

Recently, a new approach was developed taking into account the poor accessibility to the CD4 testing in some low–middle-income regions. This novel option, known as Option B+, was first implemented in Malawi (2011) as an attempt to design an easiest program for PMTCT, regardless of the CD4 count of the pregnant women living with HIV. This simple 'one-size-fits-all' strategy envisioned the lifelong ARV access of pregnant/breastfeeding women in high scale even though they had poor access to CD4 testing. With respect to HIV-exposed children, Option B+ also involved the administration of an ARV regimen along with an early infant diagnosis of HIV infection [15–17].

Encouraging results were observed in Malawi experience with Option B+ where there was a great increment in the number of pregnant/breastfeeding women living with HIV who had access to ARV medicines (700%) [7]. Furthermore, Malawi aimed to expand the ARV therapy to those women living in hard-to-reach areas for an equal ARV access along the country. Then, an integrated program was developed, involving Option B+, to further expand PMTCT. In this way, nurses were trained to administer ARV at primary care facilities where pregnant women and children access for medical services near their homes [17]. Due to its high success, all priority regions (with exception of Nigeria) had adopted Option B+ by the end of 2015 [2]. The three options mentioned are summarized in Table 2.

2.1. Conditions for the beginning of ARV pharmacotherapy

Actually, the MTCT rate has declined substantially in those countries where interventions aimed at reducing the risk have been implemented [18–25].

In the case of HIV-infected pregnant women, an evaluation of HIV disease status should be done to start an adequate ARV therapy. This initial assessment should focus on a review of previous HIV-related diseases; recent CD4 counts (as described in Section 2), plasma HIV RNA levels, and the possibility of prophylaxis against opportunistic infections. On the other hand, the complete blood cell count and renal and hepatic function should be known and, if necessary, the results of previous and current studies of resistance to HIV drugs [19–30].

Table 2. The three options recommended by the World Health Organization for the prevention of mother-to-child transmission (PMTCT).

		Options for PMTCT		
		A	B	B+
Mother receive	Treatment (with CD4 count <350 cells/mm^3)	Triple antiretroviral (ARV) starting as soon as diagnosed and continued for life.	Same as Option A	Same as Option A
	Prophylaxis (with CD4 count >350 cells/mm^3)	Antepartum: AZT starting as early as 14 weeks of gestation. Intrapartum: at onset of labor, sd-NVP and first dose of AZT/3TC. Postpartum: daily AZT/3TC through 7 days postpartum.	Triple ARVs starting as early as 14 weeks of gestation and continued intrapartum and through childbirth if not breastfeeding or until 1 week after cessation of all breastfeeding.	For this option, treatment and prophylaxis are the same.
Infant receive		Daily NVP from birth until 1 week after cessation of all breastfeeding; or if not breastfeeding or if mother is on treatment, through age 4–6 weeks.	Daily NVP or AZT from birth through age 4–6 weeks regardless of infant feeding method.	Same as Option B

Prevention of perinatal transmission of HIV through ARV treatment is recommended for all pregnant women. ARV drugs reduce perinatal transmission, through decreases in maternal viral load in blood and genital secretions [20,30–32].

2.2. Advantages and disadvantages of ARV pharmacotherapy in the PMTCT

Although there is vast evidence supporting the benefits of combination ARV drugs for both mother and child, they are not without risk. In relation to this, some studies have demonstrated higher rates of complications in pregnancy with combined ARV therapy than with regimens containing fewer agents while these concerns may be in fact due to the severity of the disease, rather than the association with ARV [21–34]. For instance, combined ARV regimens based on zidovudine or tenofovir are associated with a greater risk of preterm delivery before 34 weeks and birth weight of less than 2500 g when compared with zidovudine alone [21]. Other studies have estimated the use of protease inhibitors (PIs) and the risk of preterm partum, as well as the use of zidovudine and the risk of congenital cardiac defects or the use of tenofovir and the risk of lower postnatal infant growth [22,35].

In 2013, with the arrival of the Option B+, the WHO recommended triple ARV pharmacotherapy for all HIV-infected pregnant and breastfeeding women, regardless of the CD4+ cell count of the woman [23,24,31]. The aim was to increase ARV coverage during pregnancy and breastfeeding, thereby ensuring that all women eligible for ARV treatment initiate treatment and further reduce vertical transmission [23,30–33]. With the objective of choosing the most effective ARV combination to reduce vertical transmission, with the lower frequency and severity of adverse events, different clinical studies have been performed. The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial, in 2011, compared the relative efficacy and safety of various proven ARV strategies for the prevention of vertical transmission during pregnancy among asymptomatic HIV-infected pregnant women with high CD4 counts [21]. In this trial, three regimens were compared: zidovudine plus intrapartum single-dose nevirapine with 6–14 days of tenofovir and emtricitabine postpartum (zidovudine alone); zidovudine, lamivudine, and lopinavir–ritonavir (zidovudine-based ARV therapy); and tenofovir, emtricitabine, and lopinavir–ritonavir (tenofovir-based ARV therapy). The results demonstrated that the rate of early transmission was significantly lower in the combined maternal ARV therapy groups than in the zidovudine-alone group. In terms of adverse events, women receiving zidovudine-based or tenofovir-based ARV therapy had a significantly higher rate of adverse event than those receiving zidovudine alone and a higher rate of abnormal blood chemical values, without significant difference between the two ARV therapy groups. The same situation was observed when analyzing adverse pregnancy outcomes, a low birth weight and preterm delivery [21].

In 2011, a retrospective cohort trial performed in Jimma University Specialized Hospital (JUSH), in Ethiopia, was demonstrated that triple therapy consisting of zidovudine, lamivudine, and nevirapine administered during pregnancy significantly reduced the percentage of MTCT, compared to monotherapy (zidovudine) and a regimen consisting of lamivudine, zidovudine, and a single dose of nevirapine at the time of delivery [25]. With regard to the use of zidovudine as monotherapy, it should be noted that studies evaluating longer periods of that regimen have reported a wide range of detected resistance [26]. In relation to PIs, atazanavir/ritonavir and darunavir/ritonavir are the preferred PI drugs for use in ARV therapy-naive pregnant women, based on efficacy studies in adults and experience with use in pregnancy [19]; nevertheless, a retrospective trial performed at 10 London HIV centers compared several key pregnancy outcomes among women receiving one lopinavir/ritonavir or atazanavir/ritonavir combined with fixed doses of nucleoside reverse-transcriptase inhibitors, during pregnancy, between 2007 and 2012. In both regimens, the rate of viral suppression, the median times to first undetectable HIV viral load, and preterm delivery rates did not differ [27].

On the other hand, in the case of non-nucleoside reverse-transcriptase inhibitors, although it is a first-line drug, efavirenz has been intensely followed because of the results of a small study in nonhuman primates where malformations were observed significant in infant cynomolgus monkeys receiving efavirenz from gestational days 20–150. Anyway, a meta-analysis including data from 23 studies reporting on 2026 first trimester exposures found no increased risk of overall birth defects in infants born to women on efavirenz during the first trimester compared with those on other ARV drugs during the same trimester [12,19–27].

The integrase inhibitor raltegravir is recommended in late stages of pregnancy in women with a high viral load. This

recommendation is due to the agent's ability to decrease it in a short period (approximately 2-log copies/mL decrease by week 2 of therapy). In a twice-daily, multicenter, triple-blind, dose-ranging, randomized study, HIV-infected patients with a genotypic and phenotypic resistance to at least one nucleoside reverse-transcriptase inhibitor, one non-nucleoside reverse-transcriptase inhibitor, and one PI were randomly assigned to receive raltegravir (200, 400, or 600 mg) or placebo orally twice a day. The results showed that in all raltegravir groups, there was a decrease of about 2 $\log^{10}$ copies per mL in HIV-1 RNA from baseline noted as early as 2 weeks after initiation of treatment, with a significant difference in change in viral load from baseline between the raltegravir and placebo groups [28].

Finally, efficacy and safety studies in pregnant women are still lacking to recommend ARV therapy entry and fusion inhibitors, such as maraviroc and enfuvirtide, respectively. Preferred regimens for ARV therapy initiation in pregnancy are shown in Table 3.

3. Prevention of MTCT of HIV-1 through breastfeeding

In breastfed infants, the postpartum period accounts for 25–45% of the total cases of HIV-1 MTCT [36]. In the absence of ARV therapy, the overall absolute risk of transmission increased from 15–25% in formula-fed infants to 25–40% in breast-fed infants [36]. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that transmission of HIV-1 during breastfeeding contributes to half the cases of infant infections [36]. In the absence of treatment, nearly 50% of the infected infants will die before their second year of life [37]. Although infant feeding with formula decreases the risk of postnatal HIV infection, this strategy is associated with an increased rate of early death in families of low socioeconomic status [38]. Moreover, clinical trials have shown that early cessation of breastfeeding in HIV-1-exposed uninfected children is associated with an increase in acute morbidity events and cumulative mortality [39]. Therefore, the WHO recommends exclusive breastfeeding of infants born to mothers known to be infected with HIV during the first 6 months of life, introducing appropriate complementary foods thereafter with continuation of lactation for the first 12 months of life [40].

In order to prevent MTCT during postnatal period, two strategies of ARV treatment interventions have been evaluated in clinical trials, including the treatment of infants with different ARV regimens and the provision of combination ARV prophylaxis to lactating women [41]. Several studies evaluated administration of maternal ARV regimens for the prevention of MTCT infections during breastfeeding. The Kisumu Breastfeeding Study – a single-arm, open-label trial conducted between 2003 and 2009 – has assessed the efficacy and safety of maternal triple ARV regimen based on zidovudine/lamivudine plus nevirapine or zidovudine/lamivudine plus nelfinavir beginning at 34 weeks of gestation and continuing for up to 6-month postpartum while exclusively breastfeeding [42]. The primary objectives of the study were to detect a 50% reduction in the HIV MTCT rate and a 50% improvement in the infant HIV-free survival rate at 18 months compared to the corresponding rate using the single-dose nevirapine regimen in the HIVNET 012 study [42]. Triple ARV therapy with zidovudine/lamivudine plus nevirapine or nelfinavir has reduced the 18-month transmission rate from 15.7% reported in the HIVNET 012 study to 6.7% [42]. Nevertheless, the study has failed to demonstrate the objective of a 50% reduction in transmission compared to HIVNET 012 historic data (15.3% vs. 20.7%) [42]. Triple ARV regimen based on zidovudine/lamivudine plus nevirapine or nelfinavir was well tolerated and safe, as there were no unexpected drug-related serious adverse events, and the rates of nevirapine- and zidovudine-related adverse events were consistent with those reported in the prescribing information [42].

The open-label, nonrandomized, prospective cohort study Mitra Plus assessed the ability to reduce breastfeeding MTCT by treating HIV-infected women with triple therapy with zidovudine/lamivudine plus nevirapine or nelfinavir initiated during late pregnancy and continued for 6 months during breastfeeding [43]. The analysis has included 441 infants reporting a cumulative HIV-1 transmission rate of 5.0% at 6 months [43]. The comparison of the transmission rate at 6 months reported in the Mitra Plus trial with the results of the Petra trial arm A, in which only short-course treatment with zidovudine + lamivudine was given to the women for 2 weeks before and 1 week after delivery and to the infants for 1 week after birth, has demonstrated a 50% reduction in breastfeeding HIV-1 transmission [43].

Table 3. Preferred regimens for antiretroviral pharmacotherapy initiation in pregnancy.

Guideline	DHHS	EACS	WHO
	NRTI backbones: • ABC/3TC • TDF/FTC • AZT/3TC Third agent: • ATV/r • DRV/r • EFV • RAL	Generally the same as for nonpregnant women but: • Do not initiate NVP • EFV can be started in pregnancy or continued in women who are already on therapy with HIV control • LPV/r and ATV/r are preferred PIs • Do not use d4T + ddI or triple NRTI • combinations	Same as for nonpregnant adults: • TDF/FTC/EFV • AZT/3TC/EFV • TDF/FTC/NVP • AZT/3TC/NVP

DHHS: Department of Health and Human Services; EACS: European AIDS Clinical Society; ATV/r: ritonavir-boosted atazanavir; DRV/r: ritonavir-boosted darunavir; RAL: raltegravir; LPV/r: ritonavir-boosted lopinavir; d4T: stavudine; ddI: didanosine; WHO: World Health Organization; NRTI: nucleoside reverse-transcriptase inhibitor; HIV: human immunodeficiency virus; PI: protease inhibitor.

The Kesho Bora study was designed to assess the efficacy and safety of triple ARVs (zidovudine, lamivudine, and lopinavir/ritonavir) until cessation of breastfeeding to a maximum of 6.5 months postpartum compared with zidovudine and single-dose nevirapine prophylaxis in pregnant women infected with HIV [44]. In addition to maternal prophylaxis, all infants received a 0.6 mL dose of nevirapine at birth and zidovudine during 1 week after birth [44]. The authors have found that maternal triple ARV prophylaxis with zidovudine lamivudine and lopinavir/ritonavir reduced the risk of MTCT rate by 43% at 12 months compared with zidovudine and single-dose nevirapine regimen (5.4% vs. 9.5%; $P = 0.029$) [44]. Regarding the safety of maternal prophylaxis with this triple ARV regimen, the rate of drug-related serious adverse events in mothers or infants was not increase with regard to zidovudine and single-dose nevirapine prophylaxis [44].

In another controlled clinical trial, Shapiro et al. [45] evaluated the efficacy of ARV treatment with abacavir, zidovudine, and lamivudine or lopinavir–ritonavir, zidovudine, and lamivudine for PMTCT in HIV-infected pregnant women with CD4 ≥200 cells/mm^3. Both groups have received triple therapy from week 26 to 34 gestation through planned weaning of breastfeeding by 6 months postpartum. The trial also included an observational group composed of women with baseline CD4 <200, which received nevirapine–zidovudine–lamivudine indefinitely. During a follow-up period of 24 months, only eight children were HIV infected during the breastfeeding period, resulting in an MTCT rate of 2.1% with abacavir, zidovudine, and lamivudine, 0.3% with lopinavir–ritonavir, zidovudine, and lamivudine, and 0.6% with nevirapine–zidovudine–lamivudine indefinitely [45].

More recently, the PROMOTE-Pregnant Women and Infants study has evaluated the efficacy and safety of lopinavir/ritonavir versus efavirenz-based ARV therapy in pregnant and breastfeeding women. The trial included HIV-infected, ARV therapy-naive pregnant women at 12–28 weeks of gestation and having any CD4 count, which were randomized to lopinavir/ritonavir plus lamivudine/zidovudine or efavirenz plus lamivudine/zidovudine and were counseled to breastfeed for 1-year postpartum [46]. Although efavirenz-based ARV regimen provided greater virologic suppression than lopinavir/ritonavir-based therapy at delivery (97.6% vs. 86.0%; $P < 0.001$), at 48 weeks postpartum, the rate of viral suppression was similar between efavirenz and lopinavir/ritonavir arm (91.0% vs. 88.4%) [46]. In terms of vertical HIV-1 transmission, both regimens were highly effective providing an HIV-free infant survival of 92.9% (lopinavir/ritonavir) and 97.2% (efavirenz). The incidence of grade 1 or 2 gastrointestinal adverse events was higher among women on lopinavir/ritonavir-based ARV regimen compared with efavirenz-based ARV therapy [46].

AQ8 The importance of ART in reducing the postnatal risk of MTCT was highlighted by a meta-analysis of controlled clinical trials [47]. Specifically, Chikhungu et al. compared the HIV-free survival rate at 12 and 18 months in breastfed infant by duration of maternal ARV therapy (6 months or lifelong). The analysis included 18 studies (published between 2005 and 2015), and the pooled estimates for 12-month HIV-free survival rate were 89.8% for infants of mothers on ARV therapy for 6 months postpartum and 91.4% for infants of mothers on lifelong therapy [47]. At 18 months, the estimated HIV-free survival rate was 89% when mothers stopped ARV therapy at 6 months and increased to 96% on lifelong treatment [47], suggesting that the risk of transmission through breastfeeding continued beyond 6 months and after cessation of maternal ARV therapy. These findings suggest that continuation of maternal ARV therapy during postpartum and breastfeeding represents an essential component of the PMTCT program [47].

On the other hand, infant ARV therapy represents an alternative intervention to PMTCT during breastfeeding when maternal therapy is not possible or not being adhered to [47]. According to 2016 WHO recommendations, infants born to mothers with HIV who are at high risk of acquiring HIV should receive infant prophylaxis with zidovudine and nevirapine during the first 6 weeks of life, whether they are breastfed or formula fed [40]. In addition, breastfed infants who are at high risk of acquiring HIV, including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks using either zidovudine plus nevirapine or nelfinavir alone [40]. Infants of mothers treated with ARV therapy that are breastfeeding should receive 6 weeks of infant prophylaxis with daily nevirapine [40].

Several ARV regimens have proved to be effective and safe for infant preexposure prophylaxis to prevent HIV-1 transmission through breastfeeding. Early clinical studies have demonstrated that nevirapine given once-daily for the first 6 weeks of life to infants exposed to HIV-1 by breastfeeding attenuates MTCT compared with single-dose administration of the drug at birth or neonatally [48]. The clinical trial HPTN 046 has evaluated the benefits and safety of the extension of infant nevirapine regimen during the whole lactation period. The study enrolled breastfeeding infants born to mothers with HIV-1 that receive nevirapine from birth to 6 weeks and were further randomized to continue extended nevirapine prophylaxis or placebo until 6 months or until breastfeeding cessation [48]. Between 6 weeks and 6 months, the rate of HIV-1 infection was 1.1% in infants who received extended nevirapine and 2.4% of controls treated with placebo, equating to a 54% reduction in MTCT [48]. The report of adverse events has demonstrated that the extended nevirapine prophylaxis is safe for the infant, considering that the rate of serious adverse events, rash,and abnormal laboratory values was not different between study arms [48].

The importance of extended infant prophylaxis with nevirapine alone or in combination with zidovudine was confirmed by the pooled analysis of five clinical trials including data from 5396 mother–infant pairs treated with different infant ARV regimen [49]. Cox regression models revealed that treatment of breasted infant with nevirapine attenuates the rate of HIV-1 infection by 71% and the rate of HIV infection or death by 71% and 58%, respectively [49]. The analysis also showed a greater reduction in the risk of breast milk HIV-1 transmission with the prolongation of nevirapine prophylaxis (Figure 2) [49].

More recently, the randomized controlled trial ANRS 12174 was designed to compare the efficacy and safety of infant prophylaxis with lamivudine or lopinavir/ritonavir in breastfed

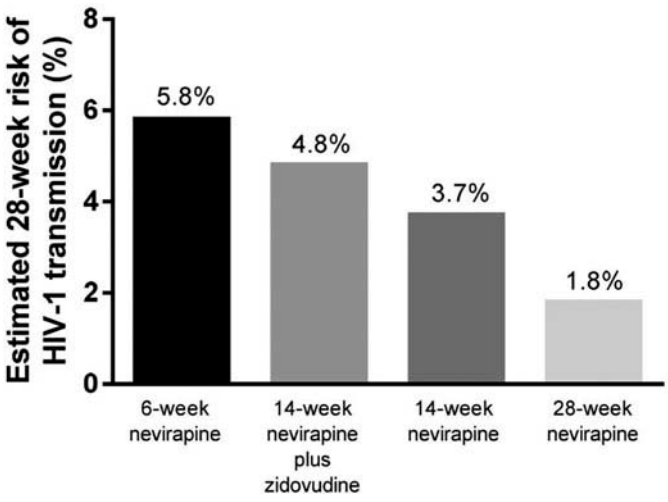

Figure 2. Rate of 28-week HIV-1 transmission in infant that received different nevirapine prophylaxis regimens.

children born to HIV-1-infected mothers not eligible for ARV therapy [50]. Both lamivudine and lopinavir/ritonavir regimens were associated with very low rates of HIV-1 postnatal transmission for up to 50 weeks of breastfeeding (1.5% vs. 1.4%), confirming the importance to extend infant prophylaxis until the end of HIV-1 exposure [50]. Lamivudine and lopinavir/ritonavir were equally well tolerated with a similar rate of grade 3 to 4 adverse event.

Infant prophylaxis has also been effective in the prevention of intrapartum HIV infection in children born to HIV-infected mothers who did not receive antenatal ARV therapy because of late identification [51]. Nielsen-Saines et al. randomly assigned formula-fed infants born to women with a peripartum diagnosis of HIV-1 infection to zidovudine for 6 weeks, zidovudine for 6 weeks plus three doses of nevirapine during the first 8 days of life, or zidovudine for 6 weeks plus nelfinavir and lamivudine for 2 weeks [51]. Intrapartum transmission of HIV-1 was significantly lower in infants treated with zidovudine plus nevirapine (2.2%) or zidovudine plus nelfinavir and lamivudine (2.4%) when compared with oral administration of zidovudine alone (4.8%) [51]. In addition, the three-drug regimen based on zidovudine plus nelfinavir and lamivudine was associated with a greater risk of neutropenia with regard to the other infant ARV regimens, suggesting that zidovudine for 6 weeks plus three doses of nevirapine during the first 8 days of life is an attractive option for prophylaxis in infants at high risk for perinatal HIV-1 infection [51].

Although the clinical trial was not specifically designed to compare maternal or infant ARV to reduce HIV-1 transmission, the BAN Study Group evaluated the efficacy of a maternal triple-drug ARV regimen (zidovudine/lamivudine plus nelfinavir or lopinavir/ritonavir) or infant nevirapine prophylaxis for 28 weeks during breastfeeding to reduce postnatal transmission of HIV-1 in Malawi [52]. Compared with a control group that not receive extended postnatal ARV regimen, the protective efficacy against HIV-1 transmission from 2–28 weeks was 74% for infant nevirapine and 53% for the maternal triple ARV regimen. Infants also showed a significantly increased HIV-1-negative survival with either infant or maternal regimens, with a trend toward increased benefit when the ARVs were administered directly to the infant [52]. In terms of safety, triple maternal ARV regimen was associated with a greater risk of neutropenia than infant nevirapine prophylaxis, but 1.9% of the infants that receive nevirapine had a hypersensitivity reaction [52].

Taking together, the results of large clinical trials revealed the importance of infant or maternal ARV interventions during the complete period of HIV-1 exposure by breastfeeding in order to prevent MTCT during postnatal period.

4. Conclusion

The present manuscript reviews the latest strategies to improve PMTCT, including the different ARV regimens for HIV-infected pregnant women and the different options that could be achieved as an attempt to improve PMTCT during pregnancy, labor, and breastfeeding. It is worth stressing that MTCT remains as a public health challenge where efforts are directed to warrant the complete accesses (along with the earliest start) to the anti-HIV pharmacotherapy for every HIV-infected pregnant woman and newborn.

5. Expert opinion

The PMTCT has been improved dramatically in the last few years mainly due to prophylactic perinatal ARV-based therapy for pregnant and breastfeeding women living with HIV. However, there is still a milestone to reach since HIV MTCT remains as a public health challenge associated with MTCT through breastfeeding (postnatal transmission). It has been estimated that new 400,000 pediatric infections accounted due to breastfeeding worldwide since prophylactic prevention of HIV MTCT is not 100% effective [53]. Different reasons have been proposed as an explanation of why the PMTCT has not reached a 100% of effectiveness. Indeed, postnatal HIV transmission results mainly from (i) HIV-infected women who never have been diagnosed with the infection, (ii) acute HIV infection during pregnancy or breastfeeding, and (iii) the lack of access/adherence to the ARV therapy during pregnancy and/or breastfeeding.

In this context, different strategies could be employed as an attempt to reduce pediatric HIV infections. In the first place, HIV test should be offered to every pregnant woman in the first prenatal medical visit (universal HIV screening for pregnant women) and the possibility of retesting during the third trimester and breastfeeding to minimize HIV pediatric infections, improving PMTCT. Particularly, the immunoassay of fourth generation is recommended for the HIV test [54]

Other strategy involves the improvement of patient adherence to the HIV therapy. Approximately, 70% of adherence to ARV treatment has been estimated over time for patients living with HIV. When treatment adherence results suboptimal, HIV can replicate, increasing the risk of MTCT and drug resistance. In case of breastfeeding mothers, this represents a major risk for newborns to become infected with HIV (30–40%) [53].

One possible solution for this issue is related with the development of novel long-acting ARVs for prophylaxis of both mothers and children. Injectable long-acting

formulations could be administered once or twice a month replacing the oral daily administration of conventional ARV tablets. Patient adherence to ARV therapy for prophylaxis or therapeutic interventions could be enhanced due to a 'more patient-friendly ARV therapy' [53,55,56]. This strategy is being currently employed for chronic therapies such as psychiatric disorders, contraception, or prostate cancer (Lupron depot®). Until now, there are no commercially available injectable long-acting ARV formulations, and only a few approaches have reached clinical trials recently. The main reason for this might be related with the physicochemical limitations of the current ARV medicines, as non-adequate antiviral potency and drug–drug interactions, that could be overcome with micro- and nanotechnological platforms. For instance, a nanocrystal-based formulation of rilpivirine (phase I) and cabotegravir (phase IIa) have been evaluated for subcutaneous and intramuscular routes. Furthermore, a combination of both ARVs is being evaluated for HIV therapy as a long-acting formulation for maintenance of HIV suppression [55,56].

On the other hand, there is a need to increase the inclusion and retention of mothers and infants in preventive care programs. Statistics from the WHO for the 22 designated priority countries revealed that only 44% of pregnant women were tested for HIV-1 and received results in 2013 [36]. Moreover, only 73% of the pregnant women with known HIV-1 infection received effective ARVs to prevent vertical transmission, and the percentage of treated mothers further decreased to 61% during breastfeeding [36]. Only half of the infants born to HIV-infected mothers were reported to have received postnatal ARV prophylaxis [36], suggesting that the postnatal care is largely suboptimal.

Considering that the success of PMTCT largely depends on adherence, it remains to be established if dual maternal and infant ARV treatment represents an effective strategy to reduce HIV-1 transmission during lactation. Nowadays, extended infant ARV prophylaxis is indicated in mothers who do not register, present late for antenatal care, or in whom HIV infection is diagnosed postpartum. Nevertheless, there are no studies that evaluate the benefits to added infant ARV treatment during the whole breastfeeding period to the Option B or Option B+ strategy [57].

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Declaration of interest

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