Eliminating postnatal HIV transmission in high incidence areas: need for complementary biomedical interventions

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Summary

The rate of mother-to-child transmission (MTCT) of HIV from breastfeeding is increasing relative to other causes of MTCT. Early effective preconception and antenatal antiretroviral therapy (ART) reduces intrauterine and intrapartum MTCT, whereas maternal post-partum HIV acquisition, untreated maternal HIV, and suboptimal postnatal maternal ART adherence increase the risk of MTCT through breastfeeding. Although the absolute number of cases of MTCT acquired through breastfeeding is decreasing, the rate of decrease is less than the decrease in intrauterine and intrapartum MTCT. Unless current strategies are universally applied, they might not be sufficient to eliminate MTCT due to breastfeeding. Urgent action is needed to evaluate and implement additional preventive biomedical strategies in high HIV prevalence and incidence settings to eliminate MTCT from breastfeeding. Preventive strategies include: pre-exposure prophylaxis in breastfeeding women who have an increased risk of acquiring HIV; postnatal reinforcement strategies, such as maternal retesting for HIV, maternal care reinforcement, and prophylaxis in infants exposed to HIV via

breastmilk; and active (vaccine) or passive immunoprophylaxis with long-acting broadly neutralising antibodies.

Introduction

In the past 20 years, considerable progress has been made to improve policies and scale up the roll-out of strategies to prevent mother-to-child transmission of HIV (PMTCT) globally. Between 2000 and 2015, an estimated 1·4 million paediatric HIV infections have been averted, which is a 70% decrease in new paediatric HIV infections compared with the epidemic's peak in the previous 15-year period.[1] In 2015, UNAIDS estimated that 80% of pregnant women with HIV worldwide had received antiretroviral therapy (ART) as part of PMTCT. Considering the successful uptake of ART in pregnant women, the elimination of mother-to-child transmission of HIV (EMTCT) became an achievable goal. [2] In 2012, WHO first recommended lifelong triple ART for pregnant women and for breastfeeding women living with HIV alongside short-course antiretroviral prophylaxis for neonates who are exposed to HIV. Since 2016, WHO recommends the universal test and treat (UTT) strategy for PMTCT. WHO also recommends providing access to maternal ART (a triple therapy combination) and adherence support for women with HIV who are exclusively breastfeeding during the first 6 months and continue to breastfeed for at least 12 months. [3] The combination of these preventive measures together with reducing HIV acquisition in women who are of childbearing age is considered sufficient to achieve EMTCT. By 2016, all 22 of the UNAIDS Global Plan priority countries (where 90% of the world's pregnant women who have HIV live) had increased UTT-based PMTCT. Despite this effort, in 2018 (6 years after WHO introduced triple ART for PMTCT globally), 160 000 new paediatric HIV infections were diagnosed, which is more than the target for 2015 onwards of less than 40 000 new paediatric HIV infections. [4] With early and effective preconception and antenatal ART access, the proportion of intrauterine and intrapartum mother-to-child transmission (MTCT) is decreasing relative to overall MTCT. However, women and infants can still acquire HIV even with UTT-based PMTCT in place. Due to factors such as maternal HIV acquisition late in the third trimester of pregnancy or post-partum, chronic untreated maternal HIV infection, and suboptimal postnatal adherence to maternal ART, the relative contribution of breastfeeding to the overall MTCT rate is increasing. According to the University of Cape Town's Thembisa model (version 4·1), from 2010 onwards in South Africa, postnatal HIV acquisition in infants has become more common than perinatal acquisition in infants, and the gap between the two modes of acquisition is still widening (figure 1).[5, 6] The Thembisa model estimates that postnatal HIV acquisition accounted for 40% of all cases of MTCT in 2004–05, increasing to 75% of total MTCTs in 2017–18.[5, 6]

In 2017, breastfeeding contributed to more than 50% of MTCT cases in 15 of the 21 UNAIDS Global Plan priority countries in sub-Saharan Africa.[7] These data suggest that current application of PMTCT policy will not be sufficient to eliminate MTCT, particularly postnatal MTCT.

This Health Policy paper summarises the rationale for continuing to seek complementary biomedical interventions to prevent postnatal MTCT. We discuss each complementary intervention, differentiating between those currently available and those under investigation. Finally, we finish with a call for urgent action to evaluate and implement the operational (real life) effectiveness of complementary biomedical preventive strategies to eliminate postnatal MTCT.
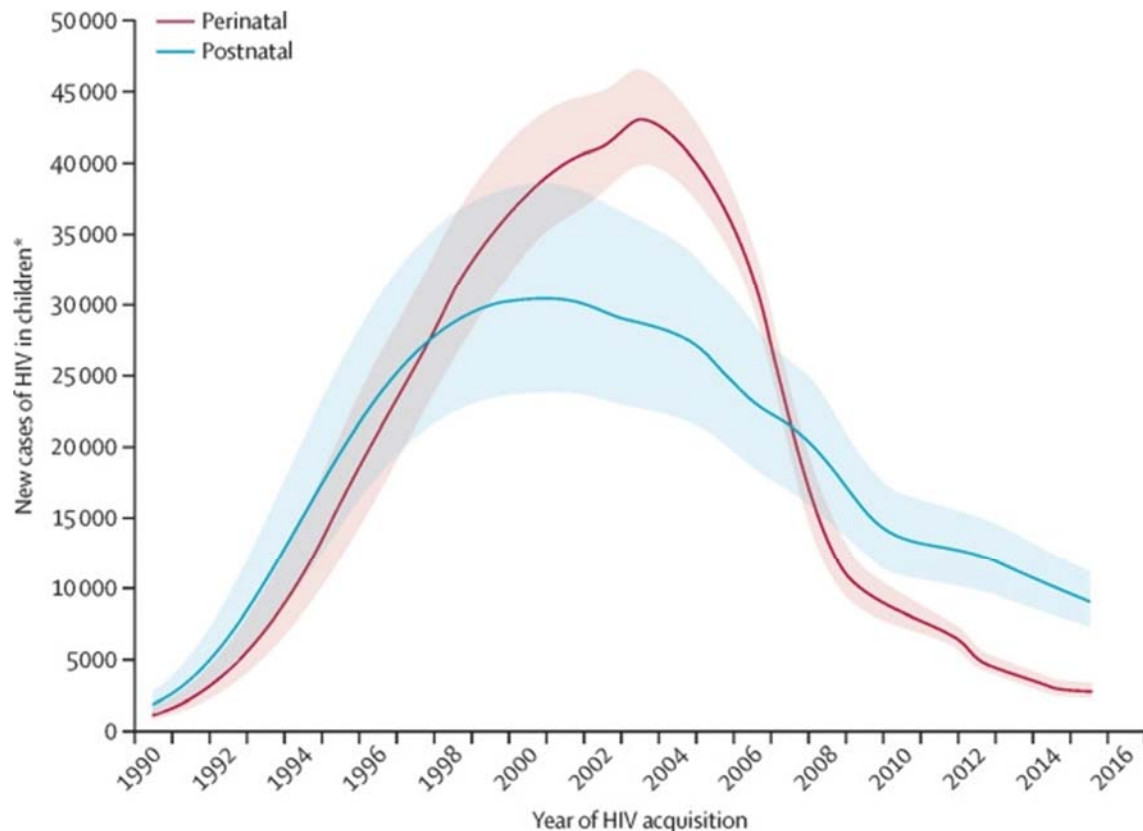
Figure 1. Relative contribution of breastfeeding to perinatal mother-to-child transmission of HIV in South Africa

Reasons for the slower than expected decline in postnatal MTCT

The current PMTCT focuses on the antenatal and intrapartum period, and relies on identifying women who are living with HIV, recommending that they begin ART, and following up with mothers and their children post partum to increase ART adherence and to diagnose HIV in infants at an early stage.

In women who are accessing PMTCT-related care antenatally, most residual HIV transmission occurs because of one or a combination of circumstances at the health system, population, and individual level.

In health systems, antenatal-clinic-centred PMTCT programmes have difficulties with screening pregnant women, early triaging, and retaining women living with HIV in treatment and care to render them aviraemic. At the population level, weak PMTCT programme monitoring and evaluation systems make enforcing appropriate corrective actions challenging in settings with a high HIV prevalence. At the individual level, transmission of HIV-1 through breastfeeding is likely to occur if women stop ART during lactation, leading to viral rebound.[8] Furthermore, many children who are exposed to HIV are breastfed well beyond 12–18 months without recommended monitoring of maternal viral load. HIV transmission does not stop abruptly at 18 months when the last HIV test is usually recommended and, as many countries do not adequately implement the final infant HIV test 6 weeks after breastfeeding cessation, many children who have been exposed to HIV are

not diagnosed at that time. A study of 562 children from four African countries (Burkina Faso, Uganda, South Africa, and Zambia) who had been exposed to HIV during breastfeeding and received a negative HIV test at 12 months showed that residual HIV transmission occurred at a rate of 1·4% between the ages of 12 months and 5–6 years. This residual transmission is most likely due to extended and unreported breastfeeding without maternal viral load suppression.[9]

Health system access, HIV acquisition, viral load monitoring, and postnatal MTCT

A considerable number of women have no access to appropriate PMTCT-related care. A study done in Kenya, Malawi, and South Africa showed that, among 11 000 pregnant or breastfeeding women who were HIV-1 positive, 27–73% had a plasma HIV RNA count of more than 1000 copies per mL.[10, 11] The women with unsuppressed viraemia were either undiagnosed or had acquired HIV after the initial antenatal clinic screening, and had not started ART or had not been able to be adherent.

Some women do not have access or sufficient access to antenatal clinics due to geographical, cultural (including discriminatory attitudes), or logistical challenges. Between 2014 and 2019 in eastern and southern Africa, 86% of women had visited antenatal clinics at least once, and 54% visited antenatal clinics at least four times, showing that continued PMTCT-related monitoring and antenatal care can be challenging.[12] In contrast, coverage of immunisation when infants are at age 6 weeks is 88%, 81% at age 10 weeks, and 78% at age 14 weeks in eastern Africa and southern Africa, making postnatal infant reinforcement interventions feasible.[13]

Community-level HIV incidence among pregnant and breastfeeding women is not routinely estimated as few women are retested. A substudy of the ECHO trial estimated annual HIV incidence in 5768 sexually active women, aged 16–35 years, who were not pregnant or living with HIV from nine South African communities. [14] The estimated HIV incidence was 4·51 (95% CI 4·05–5·01) per 100 woman-years of follow-up, with wide discrepancies across communities, and the highest incidence was in women younger than 24 years.[15] Women in late pregnancy and post-partum periods (up to 6 weeks after delivery) are at particularly high risk for HIV acquisition compared with all women of childbearing age; a study of 686 pregnancies in seven African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) measured a risk of HIV acquisition per coital act that was 3–4 times higher during the late pregnancy and post-partum periods than when not pregnant.[16] The biological reasons for the high risk of HIV acquisition during late pregnancy and the post-partum periods are still being investigated. Because of this high per-coital-act risk, there is also a high risk of postnatal HIV MTCT (due to high HIV replication during acute infection) if maternal HIV is acquired during the final trimester of pregnancy or while breastfeeding. Approximately 30% of infants breastfed by women who have newly acquired HIV will acquire HIV, usually within weeks of their mother's acquisition of HIV.[17, 18] There is a scarcity of surveillance data that quantify paediatric HIV infections after postnatal maternal HIV acquisition. However, MTCT after postnatal HIV acquisition is estimated to account for more than 40% of new paediatric infections in Botswana and 18–24% of new paediatric infections in Zimbabwe.[18, 19]

Given the substantial variation of HIV prevalence and incidence within countries, a fine-tuned system is needed to identify areas of high HIV burden and transmission, identify local drivers of MTCT, and implement appropriate solutions.[20, 21] vFor example, in South

Africa during 2017–18, rates of MTCT at age 10 weeks ranged from 0% to 3·6% at district level, with a national average of 0·9%.[22] Intrauterine HIV infection rates ranged from 72 to 360 infections per 100 000 livebirths at district level.[23] Nine districts in South Africa had an antenatal HIV prevalence of at least 35% and an intrauterine MTCT case rate of more than 200 per 100 000 livebirths.[24, 25] A successful strategy against MTCT might be a rapid roll-out of new recency infection testing (for diagnosis of new HIV infections) to help to prioritise EMTCT interventions in areas with the highest maternal HIV prevalence and incidence.[24, 25]

Complementary biomedical strategies to reduce postnatal MTCT

Interventions to reduce postnatal MTCT need to take the pathophysiological mechanisms that are specific to breastfeeding into account. First, HIV transmission can occur during the late stages of breastfeeding, and transmission events have been documented long after the final 12–18-month HIV test in breastfeeding infants.[9] Second, both cell-free and cell-associated HIV from breastmilk have been associated with transmission events.[26, 27, 28] Transmission has occurred despite undetectable viral load in breastmilk and maternal blood.[29, 30, 31, 32] HIV transmission through breastfeeding from a mother taking ART for approximately 6 months has been estimated to occur in 2·4–2·9% of cases by 12 months.[33, 34] Third, a very narrow genetic bottleneck of transmitted or founder virus exists in breastmilk, which is responsible for HIV transmission by breastfeeding.[28, 35] This genetic bottleneck implies that a single or a combination of compounds (antiretroviral drugs, broadly neutralising antibodies [bNAbs], or a vaccine) administered to the exposed infant might be sufficient to block the transmission of this small population of diverging viruses.
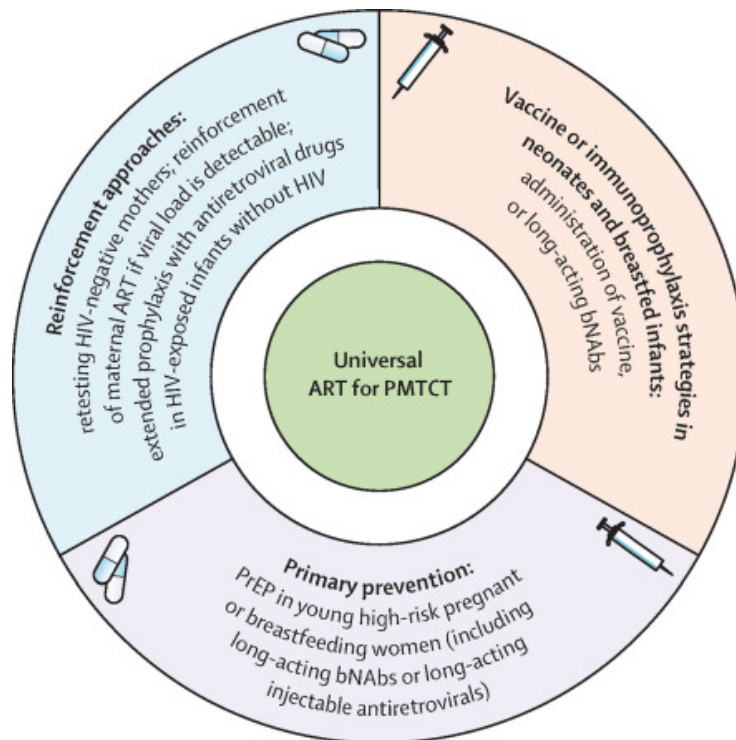
Figure 2. Combining strategies for preventing HIV transmission from breastfeeding in high HIV prevalence and incidence settings

Complementary strategies to PMTCT to reduce postnatal MTCT should be acceptable and feasible, and new and innovative approaches that reduce postnatal MTCT should be tested (figure 2). Currently accepted and feasible strategies include pre-exposure prophylaxis (PrEP) for pregnant or breastfeeding women without HIV to prevent HIV acquisition, and reinforcement approaches such as repeat HIV testing, adapted maternal care, and extended post-exposure prophylaxis for infants whose mothers have a detectable viral load.

Improving existing policies that are not optimally implemented

PrEP for pregnant or breastfeeding women at high risk of acquiring HIV infection

The high incidence of maternal HIV infections during pregnancy and, more importantly, during breastfeeding is a major hurdle to achieving EMTCT.[36, 37] In 2017, WHO released guidance and a policy brief recommending PrEP containing tenofovir disoproxil fumarate for pregnant and breastfeeding women at substantial risk of acquiring HIV,[38] coupled with adherence support and continued monitoring of antiretroviral toxicity, pregnancy outcomes, and child growth. Despite a high fetal transplacental exposure to tenofovir disoproxil fumarate in pregnant women undergoing PrEP, there are likely to be few safety concerns relating to pregnancy.[39, 40] Because exposure to tenofovir disoproxil fumarate from breastmilk is low, estimated to be 0·5–16% of fetal exposure from placental transfer, there is very low evidence of tenofovir disoproxil fumarate plus emtricitabine toxicity in breastfed infants.[32, 41, 42, 43] Exposure to tenofovir disoproxil fumarate from breastmilk is estimated to be between 0·01% and 0·04% of the recommended therapeutic dose adjusted to infants.[44] Although emtricitabine absorbs into breastmilk more readily than tenofovir disoproxil fumarate, infant exposure to emtricitabine from breastmilk is negligible at 0·5% of the recommended therapeutic dose in children (6 mg/kg). [41] Overall, research shows that there are few safety concerns for tenofovir disoproxil fumarate plus emtricitabine PrEP use during breastfeeding because of the negligible amount of tenofovir disoproxil fumarate and emtricitabine that infants are exposed to in breastmilk.

Effectiveness of PrEP in preventing HIV is highly dependent on adherence and consistent use. [45] WHO recommends daily PrEP for women who are at high risk of HIV transmission and are having unprotected sex during pregnancy. Although there are no studies that have evaluated adherence to PrEP during the postnatal period, the reasons for poor adherence or early discontinuation of PrEP among breastfeeding mothers are expected to be similar to the reasons given by women who are not pregnant. Women might be more likely to adhere to PrEP during the post-partum periods if they are clearly informed about the risk of MTCT through breastfeeding during acute infection, than if they are not informed of this risk. In PrEP clinical trials, adherence and consistent use of PrEP among women are reportedly high in the first 3 months (at 84%) but generally decrease thereafter.[46] In a clinical trial by Celum and colleagues, [46] the proportion of women who had detectable concentrations of tenofovir disoproxil fumarate declined to 57% at 6 months and to 31% at 12 months. An attempt to administer PrEP in family planning clinics in Kenya to non-pregnant women highlights the challenge of increasing uptake of and retention on PrEP at the programmatic level. During this attempt to implement PrEP in family planning, the proportion of women who were continuing to use PrEP was 41% at 1 month, 24% at 3 months, and 15% at 6 months after initiation.[47] The pill burden of PrEP was a common

reason given by women for declining treatment and contributed to 17% of women discontinuing PrEP in the first month of treatment. In a systematic review of adherence rates for daily oral PrEP for HIV prevention in several studies, the common reasons for poor adherence and early discontinuation were the stigma of PrEP treatment, perception that they were not at risk for HIV, not having enough power to make decisions, the side-effects of PrEP, and difficulty in taking PrEP due to the logistics of their daily life.[48]

To address poor adherence to the daily PrEP regimen, two new modalities delivering long-acting antiretroviral regimens for PrEP are in phase 3 clinical trials for women who are not pregnant or breastfeeding. Long-acting cabotegravir, a strand transfer integrase inhibitor, given by intramuscular injections every 8–12 weeks, was evaluated for its safety, tolerability, and pharmacokinetics in adults without HIV at low risk of infection.[49]

In this study (HPTN077), the only adverse events more common in the long-acting cabotegravir group than in the placebo group were grade 2 or higher injection site reactions. The authors concluded that long-acting cabotegravir was well tolerated in the tested population and recommended 600 mg every 8 weeks. The regimen of 600 mg of long-acting cabotegravir every 8 weeks (vs daily oral tenofovir disoproxil fumarate plus emtricitabine) is being evaluated for safety and efficacy for HIV prevention among women aged 18–45 years in Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda, and Zimbabwe (HPTN084 study; NCT03164564). A planned review of study data in November 2020, showed that the prevalence of HIV infections was 0·21% for women given long-acting cabotegravir and 1·79% for women given tenofovir disoproxil fumarate plus emtricitabine.[50] The hazard ratio in the group given long-acting cabotegravir versus the group given tenofovir disoproxil fumarate plus emtricitabine was 0·11 (95% CI 0·04–0·32), showing the effectiveness of long-acting cabotegravir in the HPTN084 study population. [50] Additional studies are required to evaluate the safety of exposure to long-acting cabotegravir in infants via breastmilk. The IMPAACT 2026 study is in development to evaluate concentrations of long-acting antivirals, including long-acting cabotegravir, in breastmilk, and the level of exposure in breastfed infants.[51]

Rilpivirine, the only other long-acting injectable non-nucleoside reverse transcriptase inhibitor, was well tolerated in healthy people who were not pregnant and were not living with HIV with no serious adverse events.[52] The finding that lower peak concentration of long-acting rilpivirine in the female genital tract is associated with increased body-mass index has cast some uncertainty on the role of long-acting rilpivirine as PrEP.[53]

In two phase 3 clinical trials (MTN 020/Aspire study and Ring Study), monthly self-insertion of a vaginal ring containing 25 mg dapivirine (a non-nucleoside reverse transcriptase inhibitor) during a 2-year period resulted in a 30% lower HIV incidence in pregnant women than in pregnant women who received a placebo.[54, 55] Although vaginal rings containing dapivirine were well tolerated with no serious side-effects in women, protective efficacy was again limited by poor adherence to the self-insertion of the vaginal ring. Pregnant and breastfeeding women were excluded from participating in both previously mentioned trials. However, 169 women became pregnant during the trial.[56] Although study product was withheld soon after confirmation of pregnancy, a post-hoc analysis revealed no association between dapivirine ring use during periconception and adverse pregnancy and infant outcomes.[56]

A subsequent study (MTN-029/IPM 039) enrolled 16 women who had stopped breastfeeding but could still express breastmilk.[57] Following insertion of the dapivirine

vaginal ring, the median concentration of dapivirine in breastmilk was 676 pg/mL, 327 pg/mL in plasma, and 36·25 ng/mg in cervical fluid. [57] The estimated mean daily infant exposure was 74·3 ng/kg per day, which was much lower than infant exposure to tenofovir disoproxil fumarate plus emtricitabine in mothers taking tenofovir disoproxil fumarate plus emtricitabine. These findings suggest that infant exposure to dapivirine while breastfeeding is low.

Reinforcement approaches

Oral antiretroviral administration to infants who had been exposed to HIV (but had not acquired HIV) was shown to be safe and remarkably effective in preventing MTCT from breastfeeding when taken during 6 week to 6 month periods or for the duration of the breastfeeding period.[58, 59, 60, 61] Two drugs do not seem to be more effective than one, which suggests that infant cells can be protected from acquisition of cell-free and cell-associated HIV from a very small population of founder viruses present at transmission. Oral antiviral administration to infants is similar to PrEP in adults who are exposed to HIV, a strategy that is recommended by WHO to any population with an expected incidence of HIV infection above 3 per 100 person-years, and can be considered as infant PrEP.

Reinforcement approaches are intended to improve or simplify the operational application of existing policies. These approaches are based on maternal HIV retesting during late pregnancy or breastfeeding, and need to be supported by high-performance point-of-care (POC) qualitative and quantitative molecular HIV tests.[62, 63, 64] The POC testing will diagnose infant HIV infection and determine maternal HIV viral load. Through diagnosing HIV infection in infants and determining HIV viral load in the mothers, two groups could be established: infants who have HIV and need prompt ART initiation; and infants without HIV whose mothers have detectable HIV in blood or breastmilk. In the latter group, infant PrEP reinforced with maternal ART might be a safe intervention to protect the infant against HIV acquisition during the breastfeeding period.

For optimal effectiveness of reinforcement approaches, the best time to retest women for HIV needs to be identified. The current WHO guidelines recommend that women with HIV are tested every 3 months, starting at the last trimester of pregnancy until the end of breastfeeding.[65] The ongoing PROMISE-EPI trial (NCT03870438), which is underway in Zambia and Burkina Faso, has chosen the 6–8 week Expanded Programme on Immunization visit. After maternal HIV testing or retesting, a molecular POC test is offered to all infants of mothers who have HIV, and ART is initiated immediately in infants who are diagnosed with HIV. HIV viral load is tested at POC in all mothers living with HIV, and those who are not virally suppressed receive reinforced counselling on ART treatment and adherence and their infant receives daily oral lamivudine (as PrEP) until the end of breastfeeding. Results on efficacy and safety of this strategy should be available by the end of 2021.

Other reinforcement approaches might include introducing alternative infant PrEP regimens, such as prescribing long-acting antiretrovirals or bNAbs in well-baby clinics or outpatient paediatric clinics.

New preventive strategies

Passive immunoprophylaxis by means of long-acting bNAbs

Worldwide, more than 40 human monoclonal bNAbs have been developed and characterised for HIV.[66] These antibodies target different neutralising epitopes of the HIV envelope, such as the V1V2 glycan, high mannose V3 supersite, CD4 binding site, gp120-gp41 interface, or the membrane-proximal external regions.

These bNAbs can have different immune effector functions for inhibiting HIV.[67] First, they can directly neutralise cell-free virions by attaching to the HIV virion and promoting immune exclusion and antibody-mediated viral clearance. Second, bNAbs can bind to infected cells and mediate either antibody-dependent cell cytotoxicity (ADCC) through Fc–FcR interactions or through phagocytosis by macrophages and cellular destruction. Finally, bNAbs and viral antigens can form immune complexes that can be taken by dendritic cells and can stimulate adaptive cytotoxic T-cell activity and B-cell maturation.[68] For the bNAb 3BNC117, the ability to kill latently HIV-infected T cells has been shown in vivo and, in rhesus monkeys infected with simian-human immunodeficiency virus (SHIV), infusion of PGT121 bNAb was associated with a depletion of proviral DNA.[69] Furthermore, 3BNC117 infusion in humans has been associated with a substantial delay in viral rebound after analytical ART interruption.[70] All these properties make these bNAbs attractive candidates for HIV therapeutics and for new preventive tools.[71, 72, 73]

The VRC01 bNAb, developed by the US Vaccine Research Centre, has been the most studied bNAb in humans and the only monoclonal antibody to be evaluated in efficacy trials. VRC01, which is directed against the CD4 binding site of HIV-1 gp120 and is formulated at 100 mg/mL for intravenous or subcutaneous administration, is actively transported to mucosal tissues.[74] A lysine to serine mutation in the Fc fragment has been found to extend the half-life of VRC01 and of other bNAbs by allowing them to escape proteasome catabolism and recycling in the extracellular compartment.[75]

VRC07-523 is a clone of VRC01, engineered for increased neutralising potency and breadth, and has specificity for 96% of HIV strains in vitro at a concentration almost ten times lower than VRC01. In particular, VRC07-523 is most active against HIV-1 subtype C rendering it an ideal bNAb intervention for infants in southern Africa where subtype C predominates.[76]

Two phase 2 trials using VRC01 or the closely related VRC07-523LS subcutaneously are ongoing in infants exposed to HIV (NCT02256631) and in infants who have HIV and are receiving ART (NCT03208231). Preliminary results from the IMPAACT P1112 trial suggest that VRC01 is well tolerated at a dose of 20–40 mg/kg (approximately 1 mL in infants) but that the long-acting formulation of VRC01, VRC01-LS, has a shorter half-life in infants than predicted.[77] A modelling exercise derived from data in animal models predicts high protective efficacy for VRC01 and good tolerance in humans.[78] In a neonatal macaque model, administration of PGT121 and VRC07-523 in combination mediated effective post-exposure prophylaxis in infants within 30–48 h of oral SHIV exposure.[79, 80]

There is also an exciting prospect of bNAbs, especially in their long-acting formulation, as an innovative passive immune prophylaxis strategy to prevent HIV transmission from breastfeeding and to finally reach EMTCT in high incidence and high prevalence areas. The production cost of long-acting bNAbs could be fairly low, at less than US$5 for a perinatal dose. It is likely that these bNAbs could be produced at large scale in

countries such as South Africa where 120 kg could suffice to cover the needs of the 1·2 million newborn babies per year.

The principle of using monoclonal antibodies in paediatrics for prophylaxis has existed for decades to prevent vertical transmission of hepatitis B (eg, polyclonal hepatitis B immunoglobulins) or to prevent respiratory syncytial virus infections in children (eg, monoclonal antibodies against respiratory syncytial virus). Despite differences between the infection control of these viruses (neither hepatitis B nor respiratory syncytial virus infections have a definitive medical treatment, whereas HIV infection has ART), key populations that are hard to reach or are at risk of HIV infection with poor access or difficulty with adherence to ART could benefit from use of monoclonal antibodies as a universal intervention to prevent vertical transmission of HIV. If shown to be well tolerated in neonates in phase 1 and 2a trials, a first dose of long-acting bNAbs (one or a combination of antibodies), less than 1 mL subcutaneously, could be administered to all neonates in high HIV prevalence and incidence settings. This dose could be repeated every 3–4 months as long as the infant is still breastfed and eventually integrated into the WHO's Expanded Programme on Immunization. Use of monoclonal antibodies in this way has the theoretical potential to prevent residual MTCT in the postnatal period and to prevent infant HIV acquisition from mothers with acute infection while breastfeeding.

HIV transmission by breastfeeding is the result of a narrow genetic bottleneck of transmitted or founder viruses; therefore, it is not proven or obvious that a combination of bNAbs would do better to prevent immune escape than a single antibody. Clearly, the potency and breadth of these antibodies are crucial to consider. If interventions with bNAbs take place in southern Africa, a bNAb that neutralises subtype C would be an important advantage in reducing MTCT during the postnatal period. As viruses can be either cell free or cell associated, including in a combination, a bNAb with effects on cellular reservoirs could be indicated since HIV antibodies are able to neutralise HIV in endosomes and transcytosis vesicles.[26, 81, 82] In vitro, VRC01-LS displayed increased transcytosis across human FcRn-expressing cellular monolayers while retaining FcγRIIIa binding and function, including ADCC activity, at a level that was similar to VRC01. VRC01-LS persisted in the rectal mucosa of adult macaques even when it was no longer detectable in the serum.[74] Potential bNAb candidates against MTCT that need further investigation include: VRC07-523-LS (which is closely related to VRC01-LS); 3BNC117-LS (for its potency against cell-associated viruses); CAP256-LS (an antibody developed in South Africa with specificity for a large number of subtype C viruses); 10-1074-LS; PGT121; and PGDM1400. The first step to investigate bNAbs as therapies to prevent MTCT should be to evaluate safety and pharmacokinetics of these potential candidates in phase 1 and phase 2 trials in neonates and infants.

A potential and beneficial effect of bNAbs for preventing MTCT from breastfeeding could be the induction of a prolonged endogenous protective immunity against HIV. The possibility of prolonged endogenous protective immunity against HIV was raised from the observation of an active lifelong protection in a mouse model of murine retroviral infection treated by monoclonal antibody immunotherapy.[83]

This adaptive immune response involves multiple cellular and molecular actors of the immune system triggered by immune complexes that include bNAbs. If reproduced in humans through the vaccine-like intervention of bNAbs in breastfed infants, this effect of so-called passive immunoprophylaxis could prove to be somewhat active and might represent a completely new approach in human vaccinology.

Active vaccination to induce neutralising or non-neutralising antibodies to protect breastfed infants

An effective HIV vaccine inducing non-neutralising antibodies that is administered to infants during the neonatal period could be a crucial component in the strategy to achieve paediatric HIV elimination. Several antibody-mediated immune responses, such as antibody-dependent cellular phagocytosis (ADCP) and ADCC, have been correlated with reduced HIV infection in non-human primates and in humans (eg, the RV144 trial).[84] Approaches to trigger antibody-mediated immune responses are being evaluated in efficacy trials in southern and eastern Africa to prevent HIV acquisition through sexual intercourse. HVTN 702, a phase 2b and phase 3 trial, modified the heterologous prime-boost ALVAC and p120 vaccine that had already shown efficacy in a trial in Thailand (RV144) to be subtype C specific.[85] Although the vaccine was intended to elicit non-neutralising immune responses (such as binding antibodies, ADCC, ADCP, and polyfunctional T-cell responses), HVTN 702 did not show efficacy for preventing sexual transmission of HIV.[85] Another study, a proof-of-concept efficacy study named HVTN 705 (Imbokodo), is still underway in sub-Saharan Africa. The study uses a heterologous prime-boost HIV vaccine regimen to evaluate a mosaic adenovirus-26 vector and subtype C HIV-1 Env gp140 trimers. Safety and immunogenicity studies have shown that the vaccine regimen used in HVTN 705 induces robust immune responses that were also associated with reduced HIV acquisition in challenge studies in non-human primates, including non-neutralising antibodies binding to the HIV envelope, T-cell responses assessed with enzyme-linked immuno absorbent spot assays, and ADCP. Depending on the efficacy of the vaccine used in HVTN 705, there is biological plausibility that this approach will prevent MTCT, and therefore there is a need to evaluate it in children. Identifying correlates of protection in efficacy studies of HIV vaccines that induce non-neutralising antibodies could pave a way for the treatment's rapid evaluation in infants.

Active vaccination strategies aimed at inducing bNAbs that use approaches such as B-cell immunogen lineage vaccine design, germline targeting vaccine design, and epitope-based vaccine SOSIP (ie, a disulfide bond [SOS] linking the gp120 and gp41 subunits in combination with Ile559Pro [IP]) trimers or fusion peptides have the potential to be cost-effective and could be used alongside Expanded Programme on Immunization vaccinations.[86] The enhancement of B-cell responses to bNAb-directed immunogens has been observed in infant rhesus macaques, which provides justification to evaluate use of bNAb-directed immunogens in infants.[87, 88, 89] HVTN 135 is a phase 1 proof-of-concept study to evaluate the safety, tolerability, and immunogenicity of CH505TF gp120 adjuvanted with GLA-SE (a synthetic TLR4 agonist) in healthy infants who do not have HIV but have been exposed to HIV in Soweto, South Africa. HVTN 135 will evaluate whether the vaccine regimen increases CD4 binding site and V1V2 lineage-specific antibodies with the potential to develop neutralisation capacity in an infant population. Expansion of approaches aimed at inducing bNAb responses to HIV are underway, exploring the safety, immunogenicity, and pharmacokinetics of these vaccines. The results of these studies and their applicability to reducing MTCT from breastmilk on a large scale in high HIV prevalence and incidence settings need to be investigated.

Conclusion

Partly due to the use of early and more efficacious preconception and antenatal ART in women living with HIV, the contribution of HIV transmission from breastfeeding to overall MTCT rates is increasing. Consequently, HIV transmission from breastfeeding will continue to contribute to paediatric HIV incidence because of maternal HIV acquisition during late pregnancy or the post-partum periods, chronic untreated HIV infection, or suboptimal adherence to maternal ART during the postnatal periods. It is clear that in high-burden countries with poor health systems, current application of PMTCT policies will not be sufficient to eliminate MTCT. In areas with high HIV prevalence and incidence, urgent action is required to reinforce and scale up existing policies, to implement new biomedical preventive strategies, and to evaluate the operational effectiveness of existing and new strategies. The effect of primary HIV prevention in at-risk breastfeeding women using PrEP, maternal retesting strategies among mothers who do not have HIV, and extended infant post-exposure prophylaxis in breastfed infants who are exposed to HIV can be evaluated immediately. These strategies form part of current policy but are suboptimally implemented, relying on adherence to medication or provider-initiated repeat HIV testing. We believe that ethical research protocols aiming to test new complementary strategies (such as vaccines or bNAbs) that do not rely on daily adherence or provider-initiated testing need to be urgently approved by human research ethics committees and tested. These new complementary strategies could have wide-ranging effects for breastfeeding mothers and infants in high HIV prevalence and incidence settings.

Search strategy and selection criteria

We searched MEDLINE, PubMed, and references from relevant articles, textbooks, and conference abstract or proceedings. We used the search terms "HIV", "breastfeeding", "breast milk", "prevention of mother to child transmission", "PMTCT cascade", "Pre-exposure prophylaxis", "broadly neutralizing antibodies", "HIV vaccine", "pregnancy", "high risk lactating women", and "HIV acquisition", searching for articles published from Jan 1, 1970, to March 19, 2021. Only publications in English language were reviewed. WHO and UNAIDS publications were searched for using the WHO and UNAIDS websites.

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