Eliminating post-natal HIV transmission in high incidence areas: need for complementary biomedical interventions

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Summary

The relative contribution of breastfeeding to mother-to-child transmission of HIV (MTCT) is increasing: early, effective pre-conception and antenatal antiretroviral therapy (ART) reduces intrauterine and intrapartum MTCT, whilst maternal postpartum HIV acquisition, untreated maternal HIV infection, or sub-optimal postnatal maternal ART adherence increase the proportion of MTCT through breastfeeding. Although absolute MTCT through breastmilk is decreasing, this decrease occurs at a slower rate compared with intrauterine and intrapartum MTCT. Unless universally applied, current strategies may not be sufficient to eliminate MTCT through breastmilk. In high HIV prevalence and incidence settings, urgent action is needed to evaluate and implement additional preventive biomedical strategies to eliminate breastmilk MTCT. These include pre exposure prophylaxis (PrEP) in at risk HIV negative lactating women, postnatal rescue strategies such as maternal retesting for HIV, maternal care reinforcement and infant prophylaxis in HIV exposed breastfed infants, and active (vaccine) or passive immunoprophylaxis with long acting broadly neutralizing antibodies.

Introduction

In the last twenty years, considerable progress has been achieved 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 infections have thus been averted, a 70% decrease in new paediatric HIV infections compared to the previous fifteen year period when the epidemic peaked.[1] In 2015, it was estimated that 80% of HIV-infected pregnant women worldwide had received antiretroviral drugs (ARV) for PMTCT. Attaining the elimination of mother-to-child transmission of HIV (eMTCT) hence became an achievable goal.[2] In 2012, the World Health Organization (WHO) recommended PMTCT based on lifelong triple antiretroviral therapy (ART) for pregnant and lactating women living with HIV with short course ARV prophylaxis in HIV-exposed neonates. Since 2016, the WHO recommends the Universal test and treat (UTT) strategy including for PMTCT with, exclusive breastfeeding during the first six months and continued breastfeeding for at least 12 months up to 24 months or longer while being fully supported for maternal triple ART adherence.[3] The combination of these preventive measures, together with reducing HIV acquisition in women of childbearing age, are considered sufficient to reach eMTCT. By 2016, all twenty-two Global Plan priority countries (where 90% of the world's HIV positive pregnant women live) had scaled up UTT-based PMTCT. However, in 2018, six years after the WHO introduced triple ART for PMTCT globally 160,000 new paediatric HIV infections were diagnosed, far above the target of less than 40,000 new infections set for 2015 onwards.[4] With early and more efficacious pre-conception and antenatal ART access, the proportion of mother-to-child transmission of HIV (MTCT) attributable to intrauterine or intrapartum HIV transmission is decreasing. However, women and their infants may slip through the net of UTT-based PMTCT. With maternal HIV acquisition during late pregnancy or postpartum, chronic untreated maternal HIV infection or sub-optimal adherence to maternal ART postnatally the relative contribution of breastfeeding to overall MTCT is increasing. In South African infants, according to the Thembisa model, v4.1, data collected since 1996 shows that, from 2010 onwards, postnatal HIV acquisition is outweighing perinatal acquisition and the gap between the two modes of acquisition keeps widening (Figure 1). The Thembisa model estimates that postnatal HIV acquisition accounted for 40% of total MTCTs in 2004-2005, increasing to 75% in 2017-18 (Leigh Johnson – personal communication).

In 2017, breastfeeding contributed to more than 50% of MTCT in 15 of the 21 global priority countries in sub-Saharan Africa.[5] This suggests that current application of PMTCT policy will be insufficient to eliminate MTCT, and postnatal MTCT in particular.

This paper summarizes 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 end by a call for urgent action to evaluate and implement the operational ('real-life') effectiveness of complementary biomedical preventive strategies to eliminate postnatal MTCT.

Why postnatal MTCT is declining slower than expected?

The current PMTCT strategy focuses heavily on the antenatal and intrapartum period, and relies on identifying HIV-infected women, offering them ART and following up mother-baby pairs post-partum to optimize ART adherence and encourage early infant HIV diagnosis.

In mothers accessing PMTCT-related care antenatally, most residual transmission occurs secondary to one or a combination of health system, population and individual level circumstances.

Health system barriers? include that antenatal clinic (ANC)-centred PMTCT programs experience difficulties with screening pregnant women, early triaging and retaining HIV infected women in treatment and care to render them aviraemic. At population level in high HIV prevalence settings, weak PMTCT program monitoring and evaluation systems hinder programme managers from enforcing appropriate corrective actions. At the individual level, breastmilk transmission of HIV-1 is more likely to occur when women interrupt ART during lactation, due to viral rebound in breast milk.[6] Furthermore, many HIV-exposed infants are breastfed for prolonged periods, without clear monitoring of maternal viral load. As HIV transmission does not stop abruptly at 18 months, and as many countries do not adequately implement the last infant HIV test at 6-weeks post breastfeeding cessation, a significant proportion of HIV exposed infants get infected through breastfeeding after the last negative HIV test. A recent study conducted in 562 children from four African countries, Burkina Faso, Uganda, South Africa and Zambia, who had been HIV-exposed during previous breastfeeding and tested HIV-negative at 12 months, demonstrated that at age 5-6 years, residual HIV transmission is 1.4%, most likely due to prolonged breastfeeding without maternal viral load suppression.[7]

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

A considerable number of women do not access appropriate PMTCT-related care. A study conducted in Kenya, Malawi and South Africa, demonstrated that among 11,000 HIV-1-infected pregnant or breastfeeding women, 27 to 73% had a plasma HIV RNA >1000 copies/mL.[8,9] These women with unsuppressed viraemia were either undiagnosed for HIV, or

had recent infections (after initial ANC screening), were not initiated on ART or were non-adherent to ART.

Some women do not access even one ANC visit due to geographic, cultural (including discriminatory attitudes), or logistic challenges. In 2016 in sub-Saharan Africa, more than 20% of women never attended ANC before delivery (UNICEF global databases 2017 based on Multiple Indicator Cluster Surveys and Demographic and Health Surveys) and could therefore not benefit from HIV testing and care at that point. In contrast, approximately 90% of children are brought to a health facility for their third postnatal immunisation vaccines, making postnatal infant rescue interventions feasible.

Estimates of community-level HIV incidence amongst pregnant and lactating women are not routinely available as few women are re-tested. A sub study of the large, recent ECHO trial, South Africa, estimated annual HIV incidence in 5768 sexually active, non-pregnant, HIV-uninfected women (16-35 years) from nine South African communities.[10] The estimated HIV incidence was 4.51 per 100 woman-years of follow up (95% confidence interval (CI): 4.05-5.01), with wide discrepancies across communities and a much higher risk in women below 24 years.[11] Late pregnancy and postpartum seem to be particularly risky periods for HIV acquisition by women of childbearing age: A study of 686 pregnancies in seven African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia) measured a per-coital act risk of HIV acquisition three to four times higher during late pregnancy and *postpartum* respectively, compared with the nonpregnant period.[12] The biological reasons for this are still under investigation. An alarming consequence of this is the very high risk of postnatal HIV transmission (due to high HIV replication during acute infection) if maternal HIV is acquired during the last trimester of pregnancy or while breastfeeding: approximately 30% of breastfed infants will acquire HIV infection – usually rapidly (within weeks) of their mother's acquisition of the virus.[13,14] There is a consistent lack of surveillance data quantifying paediatric HIV infection following maternal postnatal HIV acquisition. It has, however, been estimated to account for more than 40% of new paediatric infections in Botswana and 18 to 24% in Zimbabwe.[14,15]

Given the substantial variation of HIV prevalence and incidence within countries, a fine-tuned system is needed to capture hot spots of high HIV burden and transmission, identify local drivers of MTCT and implement appropriate solutions.[16,17] For example, in South Africa during 2017-2018 MTCT ranged between 0% and 3.6% at district level, with a national average of 0.9%.[18] Intra-uterine case rates ranged from 72 to 360 HIV infections per 100 000 live births at district level.[19] Nine districts had an antenatal HIV prevalence of at least 35% plus an intra-uterine case rate above 200 per 100,000 live births.[19,20] A rapid roll-out of new recency infection

testing would help to prioritise eMTCT interventions hot spots with the highest maternal HIV prevalence and incidence - this could be a winning strategy.[20, 21]

Complementary biomedical strategies to reduce postnatal MTCT

Interventions to reduce postnatal MTCT need to recognise pathophysiologic mechanisms specific to breastfeeding. First, HIV transmission can occur even during very late stages of breastfeeding: transmission events have been documented long after the last 12 to 18 months HIV test in breastfeeding infants.[7] Second, both cell-free and cell-associated HIV from breast milk have been associated with transmission events:[22-24] Transmission has occurred despite undetectable viral load in breast milk and/or maternal blood.[25-28] Residual breastfeeding HIV transmission from a mother prescribed ART for approximately 6 months has been estimated at around 2.4-2.9% at 12 months. [29, 30] Third, a very narrow bottleneck of transmitted/founder viruses operate in HIV transmission by breastfeeding.[24, 31] The latter implies that a single or a combination of a small number of compounds – ARV drugs and/or broadly neutralizing antibodies (bNAbs) and/or a vaccine – administered to the exposed infant may be sufficient to block transmission of this limited population of diverging viruses.

Complementary strategies to reduce postnatal MTCT should include strategies that are currently acceptable and feasible, while working on testing new innovations under investigation to further improve our ability to reduce postnatal MTCT (Figure 2). Currently acceptable and feasible strategies include ART as the cornerstone as well as PrEP for pregnant or lactating uninfected women 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. These strategies are discussed in detail below. Innovative strategies under investigation include vaccines and bNAbs.

Improving existing policies that are not optimally implemented

PrEP for high risk HIV uninfected pregnant/lactating women

The high incidence of maternal HIV infections during pregnancy and more significantly during breastfeeding remains a major hurdle to achieving eMTCT.[32, 33] In 2017, WHO released guidance and a policy brief recommending tenofovir-disoproxil fumarate (TDF)-containing PrEP for pregnant and lactating women at substantial risk of acquiring HIV infection,[34] coupled with adherence support and continued monitoring of antiretroviral toxicity, pregnancy outcomes and child growth. Despite a relatively high foetal transplacental exposure to TDF,

there may be limited safety concerns specifically relating to pregnancy.[35,36] There is even less evidence of TDF/emtricitabine (FTC) toxicity in breastfed infants because exposure to TDF in breast milk is minimal and estimated to be 0.5% to 16% of foetal exposure via placental transfer.[28,37-39] Breast milk exposure to TDF is estimated to be between 0.01% and 0.04% of the recommended therapeutic dose.[40] Although FTC absorption into breast milk is higher than TDF, infant exposure to FTC via breast milk remains negligible at 0.5% of the recommended therapeutic dose (6 mg/kg).[37] Overall, there is limited evidence of safety concerns for TDF/FTC PrEP use during breastfeeding because of the negligible exposure to TDF and FTC in breast milk.

Efficacy of PrEP in HIV prevention is highly dependent on adherence and consistent use.[41] Although there are no studies to-date that evaluate adherence to PrEP in the postnatal period, reasons for poor adherence or early discontinuation of PrEP are expected to be similar among nursing mothers, as they are among non-pregnant women. Postpartum women may be more motivated to adhere to PrEP if it is made clear to them that the risk of MTCT through breastfeeding in acute infection is extremely high. In PrEP clinical trials, adherence and consistent use of PrEP are reportedly high in the first three months (84%) but generally wane at subsequent visits.[42] At six and 12 months, women with detectable levels of TDF declined to 57% and 31%, respectively. Recent experience with implementing PrEP in family planning clinics in Kenya amongst non-pregnant women underscores the challenge of poor uptake and retention of women on PrEP at programmatic level.[43] Continuation of PrEP use at one, three and six months post initiation was 41%, 24% and 15%, respectively.[43] Pill burden was a common reason for women who declined PrEP and contributed to 17% of women discontinuing PrEP in the first month post-initiation. In a systematic review of adherence to daily oral PrEP for HIV prevention in several studies, common reasons for poor adherence and early discontinuation were stigma, low risk perception, low decision-making power, side effects and logistics of daily life.[44]

To address poor adherence to the daily PrEP regimen, two new modalities delivering long-acting antiretroviral regimens for PrEP have progressed to Phase III clinical trials in non-pregnant and non-lactating women. Intramuscular injections of Long Acting (LA) Cabotegravir (CAB)(CAB-LA), a strand transfer integrase inhibitor, every eight to 12 weeks was evaluated for its safety, tolerability and pharmacokinetics in low-risk HIV-uninfected adults.[45] In this HPTN077 study, the only adverse events more common in the CAB-LA group than the placebo group were Grade 2 or higher injection site reactions. The authors concluded that CAB-LA was well tolerated in this healthy population and recommended 600 mg every eight weeks. This regimen is currently being evaluated for safety and efficacy (HIV prevention) among young non-pregnant and non-lactating women in Botswana, Kenya, Malawi, South Africa, Swaziland,

Uganda and Zimbabwe (HPTN 084 study, clinicaltrials.gov NCT 03164564); results are expected in 2022. Further studies are required to evaluate the safety of infant exposure to CAB-LA via breastmilk. The IMPAACT 2026 study is in development to evaluate LA ARV concentrations in breastmilk including CAB exposure to breastfed infants.[46]

Rilpivirine (RPV, TMC278), the only other LA injectable non-nucleoside reverse transcriptase inhibitor (NNRTI), was well tolerated in healthy male and female HIV-uninfected non-pregnant volunteers with no serious adverse events.[47] Lower peak concentration in the female genital tract in association with increased body mass index has cast some uncertainty on the role of RPV-LA as PrEP.[48]

Providing women with another HIV prevention option, namely monthly self-insertion of a vaginal ring containing 25 mg Dapivirine (DPV), a NNRTI in two phase III clinical trials (MTN 020/Aspire study and Ring Study) over a 2-year period resulted in 30% lower HIV incidence in non-pregnant women.[49,50] While DPV was well tolerated with no serious adverse events in women, protective efficacy was again limited by poor adherence to the self-insertion of the vaginal ring. Pregnant and lactating women were excluded from participating in both trials. However, 169 women became pregnant during the course of the trial.[51] Although study product was withheld soon after diagnosis of pregnancy, a *post hoc* analysis revealed no association between periconception DPV ring and adverse pregnancy and infant outcomes.[51]

A subsequent study (MTN-029/IPM 039 study) enrolled 16 women who had stopped breastfeeding but could still express breastmilk.[52] Following DPV vaginal ring insertion, the median concentration of DPV in breastmilk and plasma were 676 pg/mL and 327 pg/mL, respectively and 36 ng/mg cervical fluid.[52] The estimated mean daily infant dosage was 74.3 ng/kg/day – much lower than infant exposure to TDF/FTC in mothers taking TDF/FTC These findings suggest low infant exposure to DPV during breastfeeding.

Reinforcement approaches

Oral antiretroviral administration to an HIV-exposed uninfected infant was shown to be safe and remarkably effective in preventing breastfeeding transmission of HIV, both during short periods of six weeks to six months or throughout breastfeeding.[53-56] Two drugs do not seem to be more effective than one, suggesting again that infant cells can be simply protected from acquisition of cell-free and cell-associated HIV from a very small population of founder viruses present in the inoculum. This strategy is very similar to PrEP in HIV-exposed adults – which is recommended by WHO to any population exposed to HIV having an expected incidence of HIV infection above 3 per 100 person-years – and can be qualified as infant PrEP.

Reinforcement approaches are meant to improve and/or simplify the operational application of existing policies. These are based on maternal HIV retesting during late pregnancy or breastfeeding, and need concomitant support by means of high-performance point of care (POC) qualitative and quantitative molecular HIV tests. [57-59] The latter will diagnose infant HIV infection and determine maternal HIV viral load, thus differentiating between two groups of infants. The first group is HIV infected infants who need prompt ART initiation; the second group is HIV uninfected infants whose mothers have detectable HIV in blood and/or breastmilk. In the latter infant, PrEP together with reinforcement of maternal ART may be a safe intervention to protect the infant against HIV acquisition during the breastfeeding period.

For optimal effectiveness of reinforcement approaches, we need to identify the best timing to retest women for HIV. The ongoing PROMISE-EPI trial (NCT03870438), currently underway in Zambia and Burkina Faso has chosen the 6-8 week Expanded Program on Immunization (EPI) visit. After maternal HIV (re)testing, a molecular POC test is offered to all infants of HIV-infected mothers and ART is initiated immediately in HIV-infected infants. Then, a POC viral load is performed in all mothers living with HIV and those not virally suppressed receive reinforced counselling on ART treatment and adherence, while the HIV-exposed uninfected 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 may include introducing alternative infant PrEP regimens such as long acting ARV 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 antibodies with broadly neutralizing properties directed at HIV have been developed and characterized.[60] These are directed toward different neutralizing epitopes of the HIV envelope, such as the V1V2 glycan, high mannose V3 supersite, CD4 binding site, g120-gp41 interface or membrane-proximal external regions (MPER).

These bNAbs can display different immune effector functions for inhibiting HIV.[61] Firstly, they can directly neutralize cell-free virions by attaching to HIV and providing immune exclusion, and antibody-mediated viral clearance. Secondly, they can bind to infected cells and mediate either antibody-dependent cell cytotoxicity (ADCC) through Fc-FcR interactions or through macrophage‘s phagocytosis and cellular destruction. Finally, bNAbs and viral antigens can

form immune complexes which can be taken by dendritic cells and may stimulate adaptive cytotoxic T-cell activity and B-cell maturation.[62] The ability to kill latently HIV-infected T-cells has been demonstrated *in vivo* for the bNAb 3BNC117 and, in simian-human immunodeficiency virus (SHIV)-infected rhesus monkeys, PGT121 bNAb infusion was associated with a depletion of proviral DNA.[63] Furthermore, 3BNC117 infusion has been associated with a significant delay in viral rebound in humans after analytical ART interruption.[64] All these properties make these bNAbs attractive candidates for HIV therapeutics but also for new preventive tools.[65-67]

The bNAb VRC01 developed by the US Vaccine Research Centre (VRC) has been the most largely studied in humans and the only monoclonal antibody to date being evaluated in efficacy trials. VRC01, directed against the CD4 binding site of HIV-1 gp120 and formulated at 100 mg/mL for intravenous (IV) or subcutaneous (SC) administration, is actively transported to mucosal tissues.[68] A lysine-serine (LS) mutation in the Fc fragment has been found to extend the half-life of VRC01 and other bNAbs, by allowing them to escape proteasome catabolism and to recycling in the extracellular compartment.[69]

VRC07-523 is a related clone of VRC01, engineered for increased neutralising potency and breadth, covering *in vitro* 96% of HIV strains at an almost 10-fold lower concentration. In particular, VRC07-523 is most active against HIV-1 clade C rendering it an ideal bNAb intervention for infants in Southern Africa where clade C largely predominates.[70]

Two phase 2 trials using VRC01 or the closely related VRC07-523-LS subcutaneously are ongoing in HIV-exposed infants (NCT02256631) and in HIV-infected infants receiving ART (NCT03208231). Preliminary results from the IMPAACT P1112 trial suggest that VRC01 is well tolerated at the dose of 20-40 mg/kg (approximately 1mL) but that the long-acting formulation of VRC01, VRC01-LS has a shorter half-life in infants than predicted.[71] A modelling exercise derived from data in animal models allows predicting a high protective efficacy and a good tolerance in humans.[72] In neonatal macaque model, administration of a PGT121 and VRC07-523 combination mediated effective post-exposure prophylaxis in infant macaques within 30 to 48 hours of oral SHIV exposure.[73,74]

There is also an exciting prospect of using bNAbs, especially in their long-acting formulation, as an innovative passive immune prophylaxis strategy to preventing breastfeeding HIV transmission and finally reaching eMTCT in high incidence/prevalence breastfeeding areas. The production cost of long-acting bNAbs could be fairly low, less than 5US$ 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 new-borns per year.

The principle of using monoclonal antibodies in paediatrics for prophylaxis has existed for decades to prevent vertical transmission of hepatitis B (polyclonal hepatitis B immunoglobulins HBIG) or to prevent respiratory syncytial virus (RSV) infections in children (monoclonal antibodies against RSV). Despite differences (neither hepatitis B nor RSV infections have a definitive medical treatment, whilst HIV infection has ART), hard to reach or at risk populations with poor access or adherence to ART may benefit from the principle of using monoclonal antibody 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 antibody or a combination, less than 1ml subcutaneously) could be administered to all neonates in high HIV prevalence / incidence settings, with a repeated dose, eventually integrated in the EPI program, every three to four months as long as the infant is still breastfed. This strategy 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 bottleneck of transmitted/founder viruses; thus, it is neither proven nor obvious that a combination of bNAbs would do better to prevent immune escape than a single antibody. Clearly, the potency and also the breadth of these antibodies are crucial criteria to consider. If the intervention has to be conducted in Southern Africa, a bNAb covering clade C neutralization would be an important advantage. As viruses can be either cell-free or cell-associated, including in a combination, a bNAb with demonstrated effects on cellular reservoirs may be indicated, since HIV antibodies are able to neutralize HIV in endosomes and transcytosis vesicles.[22,75,76] VRC01-LS, displayed increased transcytosis across human FcRn-expressing cellular monolayers *in vitro* while retaining FcγRIIIa binding and function, including ADCC activity, at levels similar to VRC01. It persisted in the rectal mucosa of adult macaques even when it was no longer detectable in the serum.[68] Therefore, the closely related VRC07-523-LS, as well as 3BNC117-LS (for its potency on cell-associated viruses), CAP256-LS (an antibody developed in South Africa with exquisite breadth on clade C viruses), 10-1074-LS, PGT121 or PGDM1400 may be potential candidates, and need further investigation. The very first step should be to evaluate safety and pharmacokinetics of these products in phase 1/2 trials in new-borns and infants.

Finally, a potential beneficial effect of using bNAbs for preventing breastfeeding transmission of HIV may be the induction of a life-long endogenous protective immunity against HIV. This possibility was raised from the observation of an active life-long protection in a mouse model of murine retroviral infection treated by monoclonal antibody immunotherapy.[77] This adaptive immune response involves multiple cellular and molecular actors of the immune system triggered by immune complexes including bNAbs. If reproduced in the human through the

"vaccine-like" bNAb(s) intervention in breastfed infants, this vaccine effect of "passive" immunoprophylaxis may prove to be somewhat "active" and may represent a completely novel approach in human vaccinology to be explored.

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

An effective HIV vaccine inducing non-neutralizing antibodies administered during the neonatal period has the potential to be a critical component in the strategy to achieve paediatric HIV elimination. Several antibody assays such as antibody-dependent cellular phagocytosis (ADCP) and ADCC have been correlated with reduced acquisition of infection in both non-human primates (NHP) and humans (RV144 trial).[78] Two such approaches are being evaluated in efficacy trials in Southern and East Africa for the prevention of sexual acquisition. Unfortunately, one of these studies, the HVTN 702 phase 2b/3 study, an adaptation of the RV144/Thai trial found to be efficacious in Thailand, modified to be clade C specific, did not demonstrate efficacy when evaluating whether the heterologous prime-boost ALVAC/glycoprotein 120 aimed at eliciting non-neutralizing immune responses such as binding antibodies, ADCC, ADCP and polyfunctional T-cell responses could prevent sexual transmission of HIV.[79] The second study, HVTN 705 (Imbokodo), a proof-of-concept efficacy study is still underway in sub-Saharan Africa. It uses a heterologous prime boost HIV vaccine regimen evaluating a mosaic adenovirus-26 vector and clade C HIV-1 env gp140 trimers. Safety and immunogenicity studies demonstrated the induction of robust immune responses such as non-neutralizing binding antibodies to HIV-envelope, ELISPOT T-cell responses and ADCP antibodies which were associated with reduced HIV acquisition in NHP challenge studies. Should HVTN 705 be efficacious, there is biological plausibility to evaluate this approach in children to prevent MTCT. Identifying correlates of protection in efficacy studies could pave a way for their rapid evaluation in infants.

Active vaccination strategies aimed at inducing bNAbs, utilizing strategies such as B-cell immunogen lineage vaccine design, germline targeting vaccine design or epitope-based vaccine SOSIP trimers or fusion peptides have the potential to be cost-effective strategies that could be employed at the time of EPI vaccination.[80] The enhancement of B-cell responses to bNAb-directed immunogens has been observed in infant rhesus macaques, and provides justification to evaluate this concept in infants.[81-83] HVTN 135 is a phase I proof-of-concept study to evaluate the safety, tolerability and immunogenicity of CH505TF gp120 adjuvanted with GLA-SE in healthy HIV exposed uninfected infants in Soweto, South Africa. HVTN 135 will evaluate the ability of the vaccine regimen to initiate both CD4bs and V1V2 lineage-specific

antibodies with the potential to develop neutralization capacity in an infant population. Expansion of this approach, evident by the several vaccine studies, is underway exploring the safety, immunogenicity and pharmacokinetics of these vaccines that aim to induce bNAb responses to HIV. The results of these, and their applicability to reducing breastmilk MTCT on a large scale, in high HIV prevalence / incidence settings need to be investigated.

Conclusion

The contribution of breastmilk HIV transmission to total MTCT is increasing, given our success in the use of early and more efficacious pre-conception and antenatal ART in women living with HIV. Consequently, breastmilk transmission will continue to negatively impact on paediatric HIV because of maternal HIV acquisition during late pregnancy or postpartum, chronic untreated HIV infection or sub-optimal adherence to maternal ART postnatally. It is evident that in high burden countries with poor health systems, current application of the PMTCT policy 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 lactating women using PrEP, maternal re-testing strategies amongst HIV negative mothers, and extended infant post-exposure prophylaxis in exposed breastfed infants can be evaluated immediately: they form part of current policy, but are sub-optimally implemented. However, they rely on adherence to medication, or provider-initiated repeat HIV testing. We strongly believe that ethically-sound research protocols aiming to test new complementary strategies such as vaccines or bNAbs, that do not rely on optimal adherence or provider-initiated testing, need to be urgently approved by Human Research Ethics Committees, and tested. These strategies may have wide-ranging impact in high HIV prevalence / incidence breastfeeding settings.

Contribution of each author:

PV and AG conceptualised the framework of the manuscript and drafted and circulated the first version. All invited co-authors contributed to the conceptualisation, literature search, drafting, and final editing process according to their expertise. All authors contributed to the final version of the manuscript and approved the revised version.

In detail:

- Philippe Van de Perre: put together first draft with A Goga, collated co-authors comments and put together final version. Led the response to comments.
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- Nobubelo Ngandu: contributed especially to the introduction; contributed to all drafts, reviewing and approving the final version
- Nicolas Nagot: contributed to reviewing the evidence around PMTCT effectiveness using current strategies, and to all drafts, reviewing and approving the final version
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709 **Figure 1.** Relative contribution of breastfeeding to perinatal MTCT in South Africa (Thembisa
710 model v4.1, permission from Dr Leigh F. Johnson)

711 Y axis represents the number of new HIV-infected infants recorded in the South African
712 paediatric data sources, X axis the year of occurrence. Dashed lines correspond to the upper
713 and lower bound estimates.

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716 **Figure 2.** Combining strategies for preventing breastfeeding HIV transmission in high HIV
717 prevalence / incidence settings

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