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

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

3

4

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26

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31

32 **Summary**

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

46

## 47 **Introduction**

48 In the last twenty years, considerable progress has been achieved to improve policies and  
49 scale up the roll out of strategies to prevent mother-to-child transmission of HIV (PMTCT)  
50 globally. Between 2000 and 2015, an estimated 1.4 million paediatric infections have thus  
51 been averted, a 70% decrease in new paediatric HIV infections compared to the previous  
52 fifteen-year period when the epidemic peaked.<sup>1</sup> In 2015, it was estimated that 80% of HIV-  
53 infected pregnant women worldwide had received antiretroviral drugs (ARV) for PMTCT.  
54 Attaining the elimination of mother-to-child transmission of HIV (eMTCT) hence became an  
55 achievable goal.<sup>2</sup> In 2012 the World Health Organization (WHO) recommended PMTCT  
56 based on lifelong triple antiretroviral therapy (ART) for pregnant and lactating women living  
57 with HIV with short course ARV prophylaxis in HIV-exposed neonates. Since 2016 the WHO  
58 recommends the Universal test and treat (UTT) strategy including for PMTCT with, exclusive  
59 breastfeeding during the first six months and continued breastfeeding for at least 12 months  
60 up to 24 months or longer while being fully supported for maternal triple ART adherence.<sup>3</sup>  
61 The combination of these preventive measures, together with reducing HIV acquisition in  
62 women of childbearing age are considered sufficient to reach eMTCT. By 2016 all twenty-two  
63 Global Plan priority countries (where 90% of the world's HIV positive pregnant women live)  
64 had scaled up UTT-based PMTCT. However, in 2018, six years after the WHO introduced  
65 triple ART for PMTCT globally 160,000 new paediatric HIV infections were diagnosed, far  
66 above the target of less than 40,000 new infections set for 2015 onwards.<sup>4</sup> With early and  
67 more efficacious pre-conception and antenatal ART access, the proportion of mother-to-child  
68 transmission of HIV (MTCT) attributable to intrauterine or intrapartum HIV transmission is  
69 decreasing. However, women and their infants may slip through the net of UTT-based  
70 PMTCT. Maternal HIV acquisition during late pregnancy or postpartum, chronic untreated  
71 maternal HIV infection or sub-optimal adherence to maternal ART postnatally are increasing  
72 the relative contribution of breastfeeding to overall MTCT. In South African infants, according  
73 to the Thembisa model, v4.1, from 2010 onwards, postnatal HIV acquisition is outweighing  
74 perinatal acquisition and the gap between the two modes of acquisition is still widening  
75 (Figure 1).<sup>5,6</sup> The Thembisa model estimates that postnatal HIV acquisition accounted for  
76 40% of total MTCTs in 2004-2005, increasing to 75% in 2017-2018.<sup>5,6</sup>

77 In 2017, breastfeeding contributed to more than 50% of MTCT in 15 of the 21 global priority  
78 countries in sub-Saharan Africa.<sup>7</sup> This suggests that current application of PMTCT policy will  
79 be insufficient to eliminate MTCT, and postnatal MTCT in particular.

80 This paper summarizes the rationale for continuing to seek complementary biomedical  
81 interventions to prevent postnatal MTCT. We discuss each complementary intervention,

82 differentiating between those currently available and those under investigation. Finally, we  
83 end by a call for urgent action to evaluate and implement the operational ('real-life')  
84 effectiveness of complementary biomedical preventive strategies to eliminate postnatal  
85 MTCT.

86

### 87 ***Why postnatal MTCT is declining slower than expected?***

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

91

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

95 Health system circumstances include that antenatal clinics (ANC)-centred PMTCT programs  
96 experience difficulties with screening pregnant women, early triaging and retaining HIV  
97 infected women in treatment and care to render them aviraemic. At population level in high  
98 HIV prevalence settings, weak PMTCT program monitoring and evaluation systems hinder  
99 programme managers from enforcing appropriate corrective actions. At the individual level,  
100 breastmilk transmission of HIV-1 is more likely to occur when women interrupt ART during  
101 lactation, due to viral rebound in breast milk.<sup>8</sup> Furthermore, many HIV-exposed children are  
102 breastfed for prolonged periods, without clear monitoring of maternal viral load. As HIV  
103 transmission does not stop abruptly at 18 months, and as many countries do not adequately  
104 implement the last infant HIV test at 6-weeks post breastfeeding cessation, a significant  
105 proportion of HIV exposed children get infected through breastfeeding after the last negative  
106 HIV test. A recent study conducted in 562 children from four African countries, Burkina Faso,  
107 Uganda, South Africa and Zambia, who had been HIV-exposed during previous  
108 breastfeeding and tested HIV-negative at 12 months, demonstrated that at age 5-6 years,  
109 residual HIV transmission is 1.4%, most likely due to prolonged breastfeeding without  
110 maternal viral load suppression.<sup>9</sup>

111

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

113 A considerable number of women do not access appropriate PMTCT-related care: A study  
114 conducted in Kenya, Malawi and South Africa, demonstrated that among 11,000 HIV-1-  
115 infected pregnant or breastfeeding women, 27 to 73% had a plasma HIV RNA >1000  
116 copies/mL.<sup>10,11</sup> These women with unsuppressed viraemia were either undiagnosed for HIV,

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

119 Some women do not access even one ANC visit due to geographic, cultural (including  
120 discriminatory attitudes), or logistic challenges. In 2016 in sub-Saharan Africa, more than  
121 20% of women never attended ANC before delivery (UNICEF global databases 2017 based  
122 on Multiple Indicator Cluster Surveys and Demographic and Health Surveys) and could  
123 therefore not benefit from HIV testing and care at that point. In contrast, approximately 90%  
124 of children are brought to a health facility for their third postnatal immunisation vaccines,  
125 making postnatal infant reinforcement interventions feasible.

126 Estimates of community-level HIV incidence amongst pregnant and lactating women are not  
127 routinely available as few women are re-tested. A sub study of the recent ECHO trial, South  
128 Africa, estimated annual HIV incidence in 5768 sexually active, non-pregnant, HIV-uninfected  
129 women (16-35 years) from nine South African communities.<sup>12</sup> The estimated HIV incidence  
130 was 4.51 per 100 woman-years of follow up (95% confidence interval (CI): 4.05-5.01), with  
131 wide discrepancies across communities and a much higher risk in women below 24 years.<sup>13</sup>  
132 Late pregnancy and postpartum seem to be particularly risky periods for HIV acquisition by  
133 women of childbearing age: A study of 686 pregnancies in seven African countries  
134 (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia) measured a per-  
135 coital act risk of HIV acquisition three to four times higher during late pregnancy and  
136 postpartum respectively, compared with the nonpregnant period.<sup>14</sup> The biological reasons for  
137 this are still under investigation. An alarming consequence of this is the very high risk of  
138 postnatal HIV transmission (due to high HIV replication during acute infection) if maternal  
139 HIV is acquired during the last trimester of pregnancy or while breastfeeding: approximately  
140 30% of breastfed infants will acquire HIV infection – usually rapidly (within weeks) of their  
141 mother's acquisition of the virus.<sup>15,16</sup> There is a consistent lack of surveillance data  
142 quantifying paediatric HIV infection following maternal postnatal HIV acquisition. It has,  
143 however, been estimated to account for more than 40% of new paediatric infections in  
144 Botswana and 18 to 24% in Zimbabwe.<sup>16,17</sup>

145 Given the substantial variation of HIV prevalence and incidence within countries, a fine-tuned  
146 system is needed to capture hot spots of high HIV burden and transmission, identify local  
147 drivers of MTCT and implement appropriate solutions.<sup>18,19</sup> For example, in South Africa  
148 during 2017-2018 MTCT ranged between 0% and 3.6% at district level, with a national  
149 average of 0.9%.<sup>20</sup> Intra-uterine case rates ranged from 72 to 360 HIV infections per 100 000  
150 live births at district level.<sup>21</sup> Nine districts had an antenatal HIV prevalence of at least 35%  
151 plus an intra-uterine case rate above 200 per 100,000 live births.<sup>21,22</sup> A rapid roll-out of new

152 recency infection testing would help to prioritise eMTCT interventions hot spots with the  
153 highest maternal HIV prevalence and incidence - this could be a winning strategy.<sup>22 23</sup>

154

## 155 **Complementary biomedical strategies to reduce postnatal MTCT**

156 Interventions to reduce postnatal MTCT need to recognise pathophysiologic mechanisms  
157 specific to breastfeeding. First, HIV transmission can occur even during very late stages of  
158 breastfeeding: transmission events have been documented long after the last 12 to 18  
159 months HIV test in breastfeeding infants.<sup>9</sup> Second, both cell-free and cell-associated HIV  
160 from breast milk have been associated with transmission events.<sup>24-26</sup> Transmission has  
161 occurred despite undetectable viral load in breast milk and/or maternal blood.<sup>27-30</sup> Residual  
162 breastfeeding HIV transmission from a mother prescribed ART for approximately 6 months  
163 has been estimated at around 2.4-2.9% at 12 months.<sup>31,32</sup> Third, a very narrow bottleneck of  
164 transmitted/founder viruses operate in HIV transmission by breastfeeding.<sup>26,33</sup> The latter  
165 implies that a single or a combination of a small number of compounds – ARV drugs and/or  
166 broadly neutralizing antibodies (bNAbs) and/or a vaccine – administered to the exposed  
167 infant may be sufficient to block transmission of this limited population of diverging viruses.

168 Complementary strategies to reduce postnatal MTCT should include strategies that are  
169 currently acceptable and feasible, while working on testing new innovative approaches under  
170 investigation to further improve our ability to reduce postnatal MTCT (Figure 2). The former  
171 includes PrEP for pregnant or lactating uninfected women to prevent HIV acquisition, and  
172 reinforcement approaches such as repeat HIV testing, adapted maternal care and extended  
173 post-exposure prophylaxis for infants whose mothers have a detectable viral load. These  
174 strategies are discussed in detail below.

175

### 176 ***Improving existing policies that are not optimally implemented***

#### 177 **PrEP for high risk HIV uninfected pregnant/lactating women**

178 The high incidence of maternal HIV infections during pregnancy and more significantly during  
179 breastfeeding remains a major hurdle to achieving eMTCT.<sup>34,35</sup> In 2017, WHO released  
180 guidance and a policy brief recommending tenofovir-disoproxil fumarate (TDF)-containing  
181 PrEP for pregnant and lactating women at substantial risk of acquiring HIV infection,<sup>36</sup>  
182 coupled with adherence support and continued monitoring of antiretroviral toxicity, pregnancy  
183 outcomes and child growth. Despite a relatively high foetal transplacental exposure to TDF,  
184 there may be limited safety concerns specifically relating to pregnancy.<sup>37,38</sup> There is even

185 less evidence of TDF/emtricitabine (FTC) toxicity in breastfed infants because exposure to  
186 TDF in breast milk is minimal and estimated to be 0.5% to 16% of foetal exposure via  
187 placental transfer.<sup>30,39-41</sup> Breast milk exposure to TDF is estimated to be between 0.01% and  
188 0.04% of the recommended therapeutic dose.<sup>42</sup> Although FTC absorption into breast milk is  
189 higher than TDF, infant exposure to FTC via breast milk remains negligible at 0.5% of the  
190 recommended therapeutic dose (6 mg/kg).<sup>39</sup> Overall, there is limited evidence of safety  
191 concerns for TDF/FTC PrEP use during breastfeeding because of the negligible exposure to  
192 TDF and FTC in breast milk.

193 Efficacy of PrEP in HIV prevention is highly dependent on adherence and consistent use.<sup>43</sup>  
194 Although there are no studies to-date that evaluate adherence to PrEP in the postnatal  
195 period, reasons for poor adherence or early discontinuation of PrEP are expected to be  
196 similar among nursing mothers, as they are among non-pregnant women. Women may be  
197 more motivated to adhere to PrEP during postpartum if they are clearly informed that the risk  
198 of MTCT through breastfeeding in acute infection is extremely high. In PrEP clinical trials,  
199 adherence and consistent use of PrEP are reportedly high in the first three months (84%) but  
200 generally wane at subsequent visits.<sup>44</sup> At six and 12 months, women with detectable levels of  
201 TDF declined to 57% and 31%, respectively. Recent experience with implementing PrEP in  
202 family planning clinics in Kenya amongst non-pregnant women underscores the challenge of  
203 poor uptake and retention of women on PrEP at programmatic level.<sup>45</sup> Continuation of PrEP  
204 use at one, three and six months post initiation was 41%, 24% and 15%, respectively.<sup>45</sup> Pill  
205 burden was a common reason for women who declined PrEP and contributed to 17% of  
206 women discontinuing PrEP in the first month post-initiation. In a systematic review of  
207 adherence to daily oral PrEP for HIV prevention in several studies, common reasons for poor  
208 adherence and early discontinuation were stigma, low risk perception, low decision-making  
209 power, side effects and logistics of daily life.<sup>46</sup>

210 To address poor adherence to the daily PrEP regimen, two new modalities delivering long-  
211 acting antiretroviral regimens for PrEP have progressed to Phase III clinical trials in non-  
212 pregnant and non-lactating women. Intramuscular injections of Long Acting (LA)  
213 Cabotegravir (CAB)(CAB-LA), a strand transfer integrase inhibitor, every eight to 12 weeks  
214 was evaluated for its safety, tolerability and pharmacokinetics in low-risk HIV-uninfected  
215 adults.<sup>47</sup> In this HPTN077 study, the only adverse events more common in the CAB-LA group  
216 than the placebo group were Grade 2 or higher injection site reactions. The authors  
217 concluded that CAB-LA was well tolerated in this healthy population and recommended 600  
218 mg every eight weeks. This regimen is currently being evaluated for safety and efficacy (HIV  
219 prevention) among young non-pregnant and non-lactating women in Botswana, Kenya,  
220 Malawi, South Africa, Swaziland, Uganda and Zimbabwe (HPTN 084 study, clinicaltrials.gov

221 NCT 03164564); results are expected in 2022. Further studies are required to evaluate the  
222 safety of infant exposure to CAB-LA via breastmilk. The IMPAACT 2026 study is in  
223 development to evaluate LA ARV concentrations in breastmilk including CAB-LA exposure to  
224 breastfed infants.<sup>48</sup>

225 Rilpivirine (RPV, TMC278), the only other LA injectable non-nucleoside reverse transcriptase  
226 inhibitor (NNRTI), was well tolerated in healthy male and female HIV-uninfected non-  
227 pregnant volunteers with no serious adverse events.<sup>49</sup> Lower peak concentration in the  
228 female genital tract in association with increased body mass index has cast some uncertainty  
229 on the role of RPV LA as PrEP.<sup>50</sup>

230 Providing women with another HIV prevention option, namely monthly self-insertion of a  
231 vaginal ring containing 25 mg Dapivirine (DPV), a NNRTI in two phase III clinical trials (MTN  
232 020/Aspire study and Ring Study) over a 2-year period resulted in 30% lower HIV incidence  
233 in non-pregnant women.<sup>51,52</sup> While DPV was well tolerated with no serious adverse events in  
234 women, protective efficacy was again limited by poor adherence to the self-insertion of the  
235 vaginal ring. Pregnant and lactating women were excluded from participating in both trials.  
236 However, 169 women became pregnant during the course of the trial.<sup>53</sup> Although study  
237 product was withheld soon after diagnosis of pregnancy, a *post hoc* analysis revealed no  
238 association between periconception DPV ring and adverse pregnancy and infant outcomes.<sup>53</sup>

239 A subsequent study (MTN-029/IPM 039 study) enrolled 16 women who had stopped  
240 breastfeeding but could still express breastmilk.<sup>54</sup> Following DPV vaginal ring insertion, the  
241 median concentration of DPV in breastmilk and plasma were 676 pg/mL and 327 pg/mL,  
242 respectively and 36.25 ng/mg cervical fluid.<sup>54</sup> The estimated mean daily infant dosage was  
243 74.3 ng/kg/day – much lower than infant exposure to TDF/FTC in mothers taking TDF/FTC  
244 These findings suggest low infant exposure to DPV during breastfeeding.

245

## 246 **Reinforcement approaches**

247 Oral ARV administration to an HIV-exposed uninfected infant was shown to be safe and  
248 remarkably effective in preventing breastfeeding transmission of HIV, both during short  
249 periods of six weeks to six months or throughout breastfeeding.<sup>55-58</sup> Two drugs do not seem  
250 to be more effective than one, suggesting again that infant cells can be simply protected from  
251 acquisition of cell-free and cell-associated HIV from a very small population of founder  
252 viruses present at transmission. This strategy is very similar to PrEP in HIV-exposed adults –  
253 which is recommended by WHO to any population exposed to HIV having an expected

254 incidence of HIV infection above 3 per 100 person-years – and can be qualified as infant  
255 PrEP.

256 Reinforcement approaches are meant to improve and/or simplify the operational application  
257 of existing policies. These are based on maternal HIV retesting during late pregnancy or  
258 breastfeeding, and need concomitant support by means of high-performance point of care  
259 (POC) qualitative and quantitative molecular HIV tests.<sup>59-61</sup> The latter will diagnose infant  
260 HIV infection and determine maternal HIV viral load, thus differentiating between two groups  
261 of infants. The first group is HIV infected infants who need prompt ART initiation; the second  
262 group is HIV uninfected infants whose mothers have detectable HIV in blood and/or breast  
263 milk. In the latter infant PrEP, together with reinforcement of maternal ART may be a safe  
264 intervention to protect the infant against HIV acquisition during the breastfeeding period.

265 For optimal effectiveness of reinforcement approaches, we need to identify the best timing to  
266 retest women for HIV. The ongoing PROMISE-EPI trial (NCT03870438), currently underway  
267 in Zambia and Burkina Faso has chosen the 6-8 week Expanded Program on Immunization  
268 (EPI) visit. After maternal HIV (re)testing, a molecular POC test is offered to all infants of  
269 HIV-infected mothers and ART is initiated immediately in HIV-infected infants. Then, a POC  
270 viral load is performed in all mothers living with HIV and those not virally suppressed receive  
271 reinforced counselling on ART treatment and adherence, while the HIV-exposed uninfected  
272 infant receives daily oral lamivudine (as PrEP) until the end of breastfeeding. Results on  
273 efficacy and safety of this strategy should be available by the end of 2021.

274 Other reinforcement approaches may include introducing alternative infant PrEP regimens  
275 such as long acting ARV or bNABs in well- baby clinics or outpatient paediatric clinics.

276

## 277 ***New preventive strategies***

### 278 **Passive immunoprophylaxis by means of long acting bNABs**

279 Worldwide, more than 40 human monoclonal antibodies with broadly neutralizing properties  
280 directed at HIV have been developed and characterized.<sup>62</sup> These are directed toward  
281 different neutralizing epitopes of the HIV envelope, such as the V1V2 glycan, high mannose  
282 V3 supersite, CD4 binding site, g120-gp41 interface or membrane-proximal external regions  
283 (MPER).

284

285 These bNABs can display different immune effector functions for inhibiting HIV.<sup>63</sup> Firstly, they  
286 can directly neutralize cell-free virions by attaching to HIV and providing immune exclusion,

287 and antibody-mediated viral clearance. Secondly, they can bind to infected cells and mediate  
288 either antibody-dependent cell cytotoxicity (ADCC) through Fc-FcR interactions or through  
289 macrophage's phagocytosis and cellular destruction. Finally, bNAbs and viral antigens can  
290 form immune complexes which can be taken by dendritic cells and may stimulate adaptive  
291 cytotoxic T-cell activity and B-cell maturation.<sup>64</sup> The ability to kill latently HIV-infected T-cells  
292 has been demonstrated *in vivo* for the bNAb 3BNC117 and, in simian-human  
293 immunodeficiency virus (SHIV)-infected rhesus monkeys, PGT121 bNAb infusion was  
294 associated with a depletion of proviral DNA.<sup>65</sup> Furthermore, 3BNC117 infusion has been  
295 associated with a significant delay in viral rebound in humans after analytical ART  
296 interruption.<sup>66</sup> All these properties make these bNAbs attractive candidates for HIV  
297 therapeutics but also for new preventive tools.<sup>67-69</sup>

298  
299 The bNAb VRC01 developed by the US Vaccine Research Centre (VRC) has been the most  
300 largely studied in humans and the only monoclonal antibody to date being evaluated in  
301 efficacy trials. VRC01, directed against the CD4 binding site of HIV-1 gp120 and formulated  
302 at 100 mg/mL for intravenous (IV) or subcutaneous (SC) administration, is actively  
303 transported to mucosal tissues.<sup>70</sup> A lysine-serine (LS) mutation in the Fc fragment has been  
304 found to extend the half-life of VRC01 and other bNAbs, by allowing them to escape  
305 proteasome catabolism and to recycling in the extracellular compartment.<sup>71</sup>  
306 VRC07-523 is a related clone of VRC01, engineered for increased neutralising potency and  
307 breadth, covering *in vitro* 96% of HIV strains at an almost 10-fold lower concentration. In  
308 particular, VRC07-523 is most active against HIV-1 clade C rendering it an ideal bNAb  
309 intervention for infants in Southern Africa where clade C largely predominates.<sup>72</sup>

310  
311 Two phase 2 trials using VRC01 or the closely related VRC07523LS subcutaneously are  
312 ongoing in HIV-exposed infants (NCT02256631) and in HIV-infected infants receiving ART  
313 (NCT03208231). Preliminary results from the IMPAACT P1112 trial suggest that VRC01 is  
314 well tolerated at the dose of 20-40 mg/kg (approximately 1mL) but that the long-acting  
315 formulation of VRC01, VRC01LS has a shorter half-life in infants than predicted.<sup>73</sup> A  
316 modelling exercise derived from data in animal models allows predicting a high protective  
317 efficacy and a good tolerance in humans.<sup>74</sup> In neonatal macaque model, administration of a  
318 PGT121 and VRC07-523 combination mediated effective post-exposure prophylaxis in  
319 infants within 30 to 48 hours of oral SHIV exposure.<sup>75,76</sup>

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

324 dose. It is likely that these bNAbs could be produced at large scale in countries such as  
325 South Africa where 120 kg could suffice to cover the needs of the 1.2 million new-borns per  
326 year.

327  
328 The principle of using monoclonal antibodies in paediatrics for prophylaxis has existed for  
329 decades to prevent vertical transmission of hepatitis B (polyclonal hepatitis B  
330 immunoglobulins HBIG) or to prevent respiratory syncytial virus (RSV) infections in children  
331 (monoclonal antibodies against RSV). Despite differences (neither hepatitis B nor RSV  
332 infections have a definitive medical treatment, whilst HIV infection has ART), hard to reach or  
333 at risk populations with poor access or adherence to ART may benefit from the principle of  
334 using monoclonal antibody as a universal intervention to prevent vertical transmission of HIV.  
335 If shown to be well tolerated in neonates in phase 1 and 2a trials, a first dose of long acting  
336 bNAbs (one antibody or a combination, less than 1ml subcutaneously) could be administered  
337 to all neonates in high HIV prevalence/incidence settings, with a repeated dose, eventually  
338 integrated in the EPI program, every three to four months as long as the infant is still  
339 breastfed. This strategy has the theoretical potential to prevent residual MTCT in the  
340 postnatal period and to prevent infant HIV acquisition from mothers with acute infection while  
341 breastfeeding.

342  
343 HIV transmission by breastfeeding is the result of a narrow bottleneck of transmitted/founder  
344 viruses; thus, it is neither proven nor obvious that a combination of bNAbs would do better to  
345 prevent immune escape than a single antibody. Clearly, the potency and also the breadth of  
346 these antibodies are crucial criteria to consider. If the intervention has to be conducted in  
347 Southern Africa, a bNAb covering clade C neutralization would be an important advantage.  
348 As viruses can be either cell-free or cell-associated, including in a combination, a bNAb with  
349 demonstrated effects on cellular reservoirs may be indicated, since HIV antibodies are able  
350 to neutralize HIV in endosomes and transcytosis vesicles.<sup>24,77,78</sup> VRC01-LS, displayed  
351 increased transcytosis across human FcRn-expressing cellular monolayers *in vitro* while  
352 retaining FcγRIIIa binding and function, including ADCC activity, at levels similar to VRC01. It  
353 persisted in the rectal mucosa of adult macaques even when it was no longer detectable in  
354 the serum.<sup>70</sup> Therefore, the closely related VRC07-523-LS, as well as 3BNC117-LS (for its  
355 potency on cell-associated viruses), CAP256-LS (an antibody developed in South Africa with  
356 exquisite breadth on clade C viruses), 10-1074-LS, PGT121 or PGDM1400 may be potential  
357 candidates, and need further investigation. The very first step should be to evaluate safety  
358 and pharmacokinetics of these products in phase 1/2 trials in new-borns and infants.

359

360 A potential beneficial effect of using bNAbs for preventing breastfeeding transmission of HIV  
361 may be the induction of a prolonged endogenous protective immunity against HIV. This  
362 possibility was raised from the observation of an active life-long protection in a mouse model  
363 of murine retroviral infection treated by monoclonal antibody immunotherapy.<sup>79</sup> This adaptive  
364 immune response involves multiple cellular and molecular actors of the immune system  
365 triggered by immune complexes including bNAbs. If reproduced in the human through the  
366 “vaccine-like” bNAb(s) intervention in breastfed infants, this vaccine effect of “passive”  
367 immunoprophylaxis may prove to be somewhat “active” and may represent a completely  
368 novel approach in human vaccinology to be explored.

369

### 370 **Active vaccination to induce neutralizing or non-neutralising antibodies to protect** 371 **breastfed infants**

372 An effective HIV vaccine inducing non-neutralizing antibodies administered during the  
373 neonatal period has the potential to be a critical component in the strategy to achieve  
374 paediatric HIV elimination. Several antibody mediated immune responses such as antibody-  
375 dependent cellular phagocytosis (ADCP) and ADCC have been correlated with reduced  
376 acquisition of infection in both non-human primates (NHP) and humans (RV144 trial).<sup>80</sup> Two  
377 such approaches are being evaluated in efficacy trials in Southern and East Africa for the  
378 prevention of sexual acquisition. Unfortunately, one of these studies, the HVTN 702 phase  
379 2b/3 study, an adaptation of the RV144/Thai trial found to be efficacious in Thailand,  
380 modified to be clade C specific, did not demonstrate efficacy when evaluating whether the  
381 heterologous prime-boost ALVAC/glycoprotein 120 aimed at eliciting non-neutralizing  
382 immune responses such as binding antibodies, ADCC, ADCP and polyfunctional T-cell  
383 responses could prevent sexual transmission of HIV.<sup>81</sup> The second study, HVTN 705  
384 (Imbokodo), a proof-of-concept efficacy study is still underway in sub-Saharan Africa. It uses  
385 a heterologous prime boost HIV vaccine regimen evaluating a mosaic adenovirus-26 vector  
386 and clade C HIV-1 env gp140 trimers. Safety and immunogenicity studies demonstrated the  
387 induction of robust immune responses such as non-neutralizing antibodies binding to HIV-  
388 envelope, ELISPOT T-cell responses and ADCP which were associated with reduced HIV  
389 acquisition in NHP challenge studies. Should HVTN 705 be efficacious, there is biological  
390 plausibility to evaluate this approach in children to prevent MTCT. Identifying correlates of  
391 protection in efficacy studies could pave a way for their rapid evaluation in infants.

392

393 Active vaccination strategies aimed at inducing bNAbs, utilizing strategies such as B-cell  
394 immunogen lineage vaccine design, germline targeting vaccine design or epitope-based  
395 vaccine SOSIP trimers or fusion peptides have the potential to be cost-effective strategies

396 that could be employed at the time of EPI vaccination.<sup>82</sup> The enhancement of B-cell  
397 responses to bNAb-directed immunogens has been observed in infant rhesus macaques,  
398 and provides justification to evaluate this concept in infants.<sup>83-85</sup> HVTN 135 is a phase I proof-  
399 of-concept study to evaluate the safety, tolerability and immunogenicity of CH505TF gp120  
400 adjuvanted with GLA-SE in healthy HIV exposed uninfected infants in Soweto, South Africa.  
401 HVTN 135 will evaluate the ability of the vaccine regimen to initiate both CD4 binding site  
402 and V1V2 lineage-specific antibodies with the potential to develop neutralization capacity in  
403 an infant population. Expansion of this approach, evident by the several vaccine studies, is  
404 underway exploring the safety, immunogenicity and pharmacokinetics of these vaccines that  
405 aim to induce bNAb responses to HIV. The results of these, and their applicability to reducing  
406 breastmilk MTCT on a large scale, in high HIV prevalence / incidence settings need to be  
407 investigated.

408

## 409 **Conclusion**

410 The contribution of breastmilk HIV transmission to overall MTCT is increasing, given our  
411 success in the use of early and more efficacious pre-conception and antenatal ART in  
412 women living with HIV. Consequently, breastmilk transmission will continue to negatively  
413 impact on paediatric HIV because of maternal HIV acquisition during late pregnancy or  
414 postpartum, chronic untreated HIV infection or sub-optimal adherence to maternal ART  
415 postnatally. It is evident that in high burden countries with poor health systems, current  
416 application of PMTCT policy will not be sufficient to eliminate MTCT. In areas with high HIV  
417 prevalence and incidence, urgent action is required to reinforce and scale-up existing  
418 policies, to implement new biomedical preventive strategies and to evaluate the operational  
419 effectiveness of existing and new strategies. The effect of primary HIV prevention in at risk  
420 lactating women using PrEP, maternal re-testing strategies amongst HIV negative mothers,  
421 and extended infant post-exposure prophylaxis in exposed breastfed infants can be  
422 evaluated immediately: they form part of current policy, but are sub-optimally implemented.  
423 However, they rely on adherence to medication, or provider-initiated repeat HIV testing. We  
424 strongly believe that ethically-sound research protocols aiming to test new complementary  
425 strategies such as vaccines or bNAbs, that are independent of daily adherence or provider-  
426 initiated testing, need to be urgently approved by Human Research Ethics Committees, and  
427 tested. These strategies may have wide-ranging impact in high HIV prevalence / incidence  
428 breastfeeding settings.

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435 **Contribution of each author:**

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

440 ***In detail:***

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446 reviewing and approving the final version
- 447 • Nicolas Nagot: contributed to reviewing the evidence around PMTCT effectiveness  
448 using current strategies, and to all drafts, reviewing and approving the final version
- 449 • Dhayendre Moodley: wrote the initial draft of the PrEP section; contributed to all  
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726 **Figure 1.** Relative contribution of breastfeeding to perinatal MTCT in South Africa

727 Source: Thembisa model v4.1; available on

728 [https://thembisa.org/content/downloadPage/Thembisa4\\_1report](https://thembisa.org/content/downloadPage/Thembisa4_1report)

729 Y axis represents the number of new HIV-infected infants recorded in the South African  
730 paediatric data sources, X axis the year of occurrence.

731 Dashed lines represent 95% confidence intervals.

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

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