



HAL
open science

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

Philippe van de Perre, Ameena Goga, Nobubelo Ngandu, Nicolas Nagot, Dhayendre Moodley, Rachel King, Jean-Pierre Moles, Beatriz Mosqueira, Witness Chirinda, Gabriella Scarlatti, et al.

► To cite this version:

Philippe van de Perre, Ameena Goga, Nobubelo Ngandu, Nicolas Nagot, Dhayendre Moodley, et al.. Eliminating postnatal HIV transmission in high incidence areas: need for complementary biomedical interventions. *The Lancet*, 2021, 397 (10281), pp.1316-1324. 10.1016/s0140-6736(21)00570-5 . hal-03274638

HAL Id: hal-03274638

<https://hal.science/hal-03274638>

Submitted on 24 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

3

4

5 Philippe Van de Perre, Professor, PhD ^{1*}, Ameena Goga, Professor, PhD ^{2,3*}, Nobubelo
6 Ngandu, PhD ², Nicolas Nagot, Professor, PhD ¹, Dhayendre Moodley, PhD⁴, Rachel King,
7 PhD⁵, Jean-Pierre Molès, PhD ¹, Beatriz Mosqueira, PhD ¹, Witness Chirinda PhD ²,
8 Gabriella Scarlatti, MD, PhD⁶, Thorkild Tylleskär, Professor, PhD⁶, François Dabis,
9 Professor, PhD^{8,9**} and Glenda Gray, Professor, DSc^{2**}.

10 * these authors equally contributed to this manuscript

11 ** these authors equally contributed to this manuscript

12

13 ¹ Pathogenesis and control of chronic infections, INSERM, Etablissement Français du Sang,
14 University of Montpellier; CHU Montpellier, Montpellier, France

15 ² South African Medical Research Council, Pretoria and Cape Town, South Africa

16 ³ University of Pretoria, Pretoria, South Africa

17 ⁴ Centre for AIDS Research in South Africa and Department of Obstetrics and Gynaecology,
18 School of Clinical Medicine, University of KwaZulu Natal, Durban, South Africa

19 ⁵ UCSF, San Francisco, CA, USA

20 ⁶ Viral Evolution and Transmission Unit, Division of Immunology, Transplantation and
21 Infectious Diseases, IRCCS Ospedale San Raffaele,, Milano, Italy

22 ⁷ Centre for International Health, University of Bergen, Bergen, Norway

23 ⁸ Agence Nationale de Recherche sur le Sida et les hépatites virales (ANRS), Paris, France

24 ⁹ Université Bordeaux, ISPED, Centre INSERM U1219 – Bordeaux Population Health,
25 Bordeaux, France

26

27 Summary: 150 words

28 Text: 4500 words

29 Figure: 2

30 References: 85

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.¹ 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.² 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.³
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.⁴ 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).^{5,6} The Thembisa model estimates that postnatal HIV acquisition accounted for
76 40% of total MTCTs in 2004-2005, increasing to 75% in 2017-2018.^{5,6}

77 In 2017, breastfeeding contributed to more than 50% of MTCT in 15 of the 21 global priority
78 countries in sub-Saharan Africa.⁷ 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.⁸ 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.⁹

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.^{10,11} 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.¹² 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.¹³
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.¹⁴ 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.^{15,16} 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.^{16,17}

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.^{18,19} 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%.²⁰ Intra-uterine case rates ranged from 72 to 360 HIV infections per 100 000
150 live births at district level.²¹ 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.^{21,22} 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.^{22 23}

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.⁹ Second, both cell-free and cell-associated HIV
160 from breast milk have been associated with transmission events.²⁴⁻²⁶ Transmission has
161 occurred despite undetectable viral load in breast milk and/or maternal blood.²⁷⁻³⁰ 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.^{31,32} Third, a very narrow bottleneck of
164 transmitted/founder viruses operate in HIV transmission by breastfeeding.^{26,33} 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.^{34,35} 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,³⁶
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.^{37,38} 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.^{30,39-41} Breast milk exposure to TDF is estimated to be between 0.01% and
188 0.04% of the recommended therapeutic dose.⁴² 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).³⁹ 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.⁴³
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.⁴⁴ 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.⁴⁵ Continuation of PrEP
204 use at one, three and six months post initiation was 41%, 24% and 15%, respectively.⁴⁵ 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.⁴⁶

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.⁴⁷ 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.⁴⁸

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.⁴⁹ 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.⁵⁰

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.^{51,52} 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.⁵³ 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.⁵³

239 A subsequent study (MTN-029/IPM 039 study) enrolled 16 women who had stopped
240 breastfeeding but could still express breastmilk.⁵⁴ 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.⁵⁴ 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.⁵⁵⁻⁵⁸ 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.⁵⁹⁻⁶¹ 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.⁶² 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.⁶³ 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.⁶⁴ 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.⁶⁵ Furthermore, 3BNC117 infusion has been
295 associated with a significant delay in viral rebound in humans after analytical ART
296 interruption.⁶⁶ All these properties make these bNAbs attractive candidates for HIV
297 therapeutics but also for new preventive tools.⁶⁷⁻⁶⁹

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.⁷⁰ 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.⁷¹

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.⁷²

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.⁷³ A
316 modelling exercise derived from data in animal models allows predicting a high protective
317 efficacy and a good tolerance in humans.⁷⁴ 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.^{75,76}

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.^{24,77,78} 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.⁷⁰ 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.⁷⁹ 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).⁸⁰ 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.⁸¹ 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.⁸² 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.⁸³⁻⁸⁵ 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.

429

430

431

432

433

434

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:***

- 441 • Philippe Van de Perre: put together first draft with A Goga, collated co-authors
442 comments and put together final version. Led the response to comments.
- 443 • Ameena Goga: put together first draft with P VdP, collated co-authors comments and
444 put together final version. Led the response to comments.,
- 445 • Nobubelo Ngandu: contributed especially to the introduction; contributed to all drafts,
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
450 drafts, reviewing and approving the final version
- 451 • Rachel King: contributed to all drafts from a social science perspective, reviewing and
452 approving the final version
- 453 • Jean-Pierre Molès: contributed to all drafts from a laboratory perspective, reviewing
454 and approving the final version
- 455 • Beatriz Mosqueira: contributed to all drafts, using her experience as a PMTCT project
456 manager, reviewing and approving the final version
- 457 • Witness Chirinda: contributed to all drafts from a public health perspective, reviewing
458 and approving the final version
- 459 • Gabriella Scarlatti: contributed to all drafts from a paediatric immunology perspective,
460 reviewing and approving the final version

- 461 • Thorkild Tylleskär: contributed to all drafts from a global child health perspective,
462 reviewing and approving the final version
- 463 • François Dabis: contributed to all drafts from a global PTCT perspective, reviewing
464 and approving the final version
- 465 • Glenda Gray: wrote the initial draft of the vaccine section and contributed to all drafts,
466 reviewing and approving the final version

467

468 Declaration of interest of each author: None of the authors have declared any conflict of
469 interest

470 References

- 471 1. UNAIDS (2018). UNAIDS Data 2018.
472 <http://www.unaids.org/en/resources/documents/2018/unaids-data-2018>
- 473 2. World Health Organization (2017). Global guidance on processes and criteria for
474 validation: Elimination of mother-to-child transmission of HIV and syphilis: second edition.
475 2017. Geneva; 2017. Available from
476 <https://apps.who.int/iris/bitstream/handle/10665/259517/9789241513272-eng.pdf> Date
477 accessed 22/07/2019.
- 478 3. World Health Organization (2016) Consolidated guidelines on the use of antiretroviral
479 drugs for treating and preventing HIV infection: recommendations for a public health
480 approach. Second edition.
481 http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf Date
482 accessed 04/24/2019.
- 483 4. UNAIDS (2019). UNAIDS Data 2019.
484 https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf
- 485 5. Johnson L. and Dorrington R. (2018) Thembisa version 4.1: A model for evaluating the
486 impact of HIV/AIDS in South Africa.
487 Available on: https://thembisa.org/content/downloadPage/Thembisa4_1report
- 488 6. Johnson LF, Patrick M, Stephen C, Patten G, Dorrington RE, Maskew M, Jamieson L,
489 Davies MA. Steep decline in pediatric AIDS mortality in South Africa, despite poor
490 progress toward pediatric diagnosis and treatment targets. *Pediatr Infect Dis J* 2020; in
491 press.
- 492 7. UNAIDS (2016). On the fast track to an AIDS free generation: The incredible journey of
493 the global plan towards the elimination of new HIV infections among children by 2015 and
494 keeping their mothers alive. UNAIDS 2016. Available from
495 <http://www.aidsdatahub.org/fast-track-aids-free-generation-unaids-2016> .
- 496 8. Manigart O, Crepin M, Leroy V, et al. Effect of perinatal zidovudine prophylaxis on the
497 evolution of cell-free HIV-1 RNA in breast milk and on postnatal transmission. *J Infect Dis*
498 2004; **190**: 1422-28.
- 499 9. Molès JP, Meda N, Kankasa C, et al. A new plan for extended paediatric HIV testing is
500 needed in Africa. *Lancet Global Health* 2019; **7**: e1603-e1604.
- 501 10. Maman D, Huerga H, Mukuil, et al. Chilima B, Kirubi B , Van Cutsem G, Masiku C,
502 SzumilinE, Ellman T, Etard JF. Most breastfeeding women with high viral load are still
503 undiagnosed in sub Saharan Africa. Abstract 32. Conference on Retroviruses and
504 Opportunistic Infections; February 23-26, 2015, Seattle, Washington.

- 505 11. Maman D, Zeh C, Mukui I, et al. Cascade of HIV care and population viral suppression in
506 a high-burden region of Kenya. *AIDS* 2015; **29**: 1557-65.
- 507 12. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV
508 incidence among women using intramuscular depot medroxyprogesterone acetate, a
509 copper intrauterine device, or a levonorgestrel implant for contraception: a randomised,
510 multicentre, open-label trial. *Lancet* 2019; pii: S0140-6736(19)31288-7.
- 511 13. Palanee-Phillips T, Baeten J, Heller K, Ahmed K, Batting J, Beesham I, Heffron R,
512 Justman J, Makkan H, Mastro T, Morrison S, Mugo N, Nair G, Philip N, Pleaner M, Reddy
513 K, Selepe P, Scoville C, Smit J, Thomas K, Donnell D, Rees H, ECHO Trial Consortium.
514 High HIV incidence among young women in South Africa: data from the ECHO trial.
515 Abstract LBPEC23. 10th IAS Conference on HIV Science, Mexico City, Mexico, 21-24 July
516 2019.
- 517 14. Thomson KA, Hughes J, Baeten JM, et al. Increased Risk of HIV Acquisition Among
518 Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-
519 Coital-Act Analysis Among Women With HIV-Infected Partners. *J Infect Dis* 2018; **218**: 16-
520 25.
- 521 15. Van de Perre P, Simonon A, Msellati P, et al. Postnatal transmission of human
522 immunodeficiency virus type 1 from mother to child. A prospective cohort study in Kigali,
523 Rwanda. *New Engl J Med* 1991; **325**: 593-598.
- 524 16. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among
525 Zimbabwean women who seroconverted postnatally: prospective cohort study. *Brit Med J*
526 2010; **341**: c6580.
- 527 17. Lockman S, Creek T. Acute maternal HIV infection during pregnancy and breast-feeding:
528 substantial risk to infants. *J Infect Dis* 2009; **200**: 667-9.
- 529 18. Dwyer-Lindgren L, Cork MA, Sligar A, et al. Mapping HIV prevalence in sub-Saharan
530 Africa between 2000 and 2017. *Nature* 2019; **570**: 189-193.
- 531 19. Goga A, Sherman G, Chirinda W, et al. Eliminating mother-to-child transmission of HIV in
532 South Africa, 2002-2016: progress, challenges and the last mile plan. *South Africa Health*
533 *Reviews*. 2017. Available from
534 [https://www.hst.org.za/publications/South%20African%20Health%20Reviews/13_Eliminati](https://www.hst.org.za/publications/South%20African%20Health%20Reviews/13_Eliminating%20mother%20to%20child%20transmission%20of%20HIV%20in%20South%20Africa_2002%20to%202016_progress_challenges%20and%20the%20Last%20Mile%20Plan.pdf)
535 [ng%20mother%20to%20child%20transmission%20of%20HIV%20in%20South%20Africa_](https://www.hst.org.za/publications/South%20African%20Health%20Reviews/13_Eliminating%20mother%20to%20child%20transmission%20of%20HIV%20in%20South%20Africa_2002%20to%202016_progress_challenges%20and%20the%20Last%20Mile%20Plan.pdf)
536 [2002%20to%202016_progress_challenges%20](https://www.hst.org.za/publications/South%20African%20Health%20Reviews/13_Eliminating%20mother%20to%20child%20transmission%20of%20HIV%20in%20South%20Africa_2002%20to%202016_progress_challenges%20and%20the%20Last%20Mile%20Plan.pdf)
537 [and%20the%20Last%20Mile%20Plan.pdf](https://www.hst.org.za/publications/South%20African%20Health%20Reviews/13_Eliminating%20mother%20to%20child%20transmission%20of%20HIV%20in%20South%20Africa_2002%20to%202016_progress_challenges%20and%20the%20Last%20Mile%20Plan.pdf). Accessed 7 October 2019.
- 538 20. Massyn N, Pillay Y, Padarath A, editors. District Health Barometer 2017/18. Durban:
539 Health Systems Trust; January 2019 (Chapter 5- section A- Prevention of mother-to-child
540 transmission by Makua A, Mazanderani AH, Sherman G, Massyn N).

- 541 21. Goga A, Chirinda W, Ngandu NK, et al. Closing the gaps to eliminate mother-to-child
542 transmission of HIV (MTCT) in South Africa: Understanding MTCT case rates, factors that
543 hinder the monitoring and attainment of targets, and potential game changers. *S Afr Med J*
544 2018; **108** (3 Suppl 1): S17-S24.
- 545 22. Woldesenbet S.A., Kufa T., Lombard C., Manda S., Ayalew K., Cheyip M., Puren A. The
546 2017 National Antenatal Sentinel HIV Survey, South Africa, National Department of
547 Health. 2019.
- 548 23. The Trace Initiative. Available at <https://trace-recency.org/about-recency/>. Accessed 10
549 April 2020.
- 550 24. Van de Perre P, Rubbo PA, Viljoen J, et al. HIV-1 reservoirs in breast milk and
551 Translational Challenges in Eliminating HIV-1 transmission through breastfeeding. *Sci*
552 *Transl Med* 2012; **4**: 143sr3.
- 553 25. Koulinska IN, Villamor E, Chaplin B, et al. Transmission of cell-free and cell-associated
554 HIV-1 through breast-feeding. *J Acquir Immune Defic Syndr* 2006; **41**: 93-99.
- 555 26. Danaviah S, de Oliveira T, Bland R, et al. Evidence of Long-Lived Founder Virus in
556 Mother-to-Child HIV Transmission. *PLOS One* 2015; **10**: e0120389.
- 557 27. Giuliano M, Andreotti M, Liotta G, et al. Maternal antiretroviral therapy for the prevention
558 of mother-to-child transmission of HIV in Malawi: maternal and infant outcomes two years
559 after delivery. *PLoS One* 2013; **8**: e68950.
- 560 28. Davis NL, Miller WC, Hudgens MG, et al. Maternal and breastmilk viral load: impacts of
561 adherence on peripartum HIV infections averted-the breastfeeding, antiretrovirals, and
562 nutrition study. *J Acquir Immune Defic Syndr* 2016; **73**: 572–80.
- 563 29. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-
564 feeding in Botswana. *N Engl J Med* 2010; **362**: 2282–94.
- 565 30. Waitt C, Low N, Van de Perre P, et al. Does U=U for breastfeeding mother-infant pairs?
566 Breastfeeding for mothers on effective treatment for HIV infection in high-income settings.
567 *Lancet HIV* 2018; pii: S2352-3018(18)30098-5.
- 568 31. Rollins N, Mahy M, Becquet R, Kuhn L, Creek T, Mofenson L. Estimates of peripartum
569 and postnatal mother-to-child transmission probabilities of HIV for use in Spectrum and
570 other population-based models. *Sex Transm Infect* 2012; **88**: i44-i51.
- 571 32. Bispo S, Chikhungu L, Rollins N, Siegfried N, Newell ML. Postnatal HIV transmission in
572 breastfed infants of HIV-infected women on ART: a systematic review and meta- analysis.
573 *J Int AIDS Soc* 2017; **20**: 21251.
- 574 33. Salazar-Gonzalez JF, Salazar MG, Learn GH, et al. Origin and evolution of HIV-1 in
575 breast milk determined by single-genome amplification and sequencing. *J Virol* 2011; **85**:
576 2751–63.

- 577 34. Moodley D, Esterhuizen T, Reddy L, et al. Incident HIV infection in pregnant and lactating
578 women and its effect on mother-to-child transmission in South Africa. *J Infect Dis* 2011;
579 **203**: 1231-4.
- 580 35. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and
581 postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-
582 analysis. *PLoS Med*. 2014; **11**: e1001608.
- 583 36. WHO Technical Brief: Preventing HIV during pregnancy and breastfeeding in the context
584 of pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2017. Licence:
585 CC BY-NC-SA 3.0 IGO.
- 586 37. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of Tenofovir Disoproxil Fumarate-
587 Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their
588 Infants: A Systematic Review and Meta-Analysis. *J Acquir Immune Defic Syndr* 2017; **76**:
589 1-12.
- 590 38. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for
591 women and their infants during pregnancy and breastfeeding. *AIDS* 2017; **31**: 213-32.
- 592 39. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure Prophylaxis Use by
593 Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral
594 Excretion in Breast Milk and Infant Absorption. *PLoS Med* 2016; **13**: e1002132.
- 595 40. Benaboud S, Pruvost A, Coffie PA, et al. Concentrations of tenofovir and emtricitabine in
596 breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA
597 Study, Step 2. *Antimicrob Agents Chemother* 2011; **55**: 1315-7.
- 598 41. Palombi L, Pirillo MF, Marchei E, et al. Concentrations of tenofovir, lamivudine and
599 efavirenz in mothers and children enrolled under the Option B-Plus approach in Malawi. *J*
600 *Antimicrob Chemother* 2016; **71**: 1027-30.
- 601 42. Hu X, Wang L, Xu F. Guides concerning tenofovir exposure via breastfeeding: A
602 comparison of drug dosages by developmental stage. *Int J Infect Dis* 2019; **87**: 8-12.
- 603 43. Chou R, Evans C, Hoverman A, et al. Preexposure Prophylaxis for the Prevention of HIV
604 Infection: Evidence Report and Systematic Review for the US Preventive Services Task
605 Force. *JAMA* 2019; **321**: 2214-30.
- 606 44. Celum C, Mgodhi N, Bekker LG, Hosek S, Donnell D, Anderson PL, Dye BJ, Pathak S,
607 Agyei Y, Fogel JM, Marzinke MA, Makgamathe K, Kassim S, Mukaka S, Noble H,
608 Adeyeye A, Delany-Moretlwe S, on behalf of the HPTN 082 Study Team. PrEP Adherence
609 and Effect of Drug Level Feedback Among Young African Women in HPTN 082. 10th IAS
610 Conference on HIV Science, Mexico City (2019).
- 611 45. Mugwanya KK, Pintye J, Kinuthia J, et al. PrEP Implementation for Young Women and
612 Adolescents (PriYA) Program. Integrating preexposure prophylaxis delivery in routine

- 613 family planning clinics: A feasibility programmatic evaluation in Kenya. *PLoS Med* 2019;
614 **16**: e1002885.
- 615 46. Sidebottom D, Ekström AM, Strömdahl S. A systematic review of adherence to oral pre-
616 exposure prophylaxis for HIV - how can we improve uptake and adherence? *BMC Infect*
617 *Dis* 2018; **18**: 581.
- 618 47. Landovitz RJ, Li S, Grinsztejn B, et al. Safety, tolerability, and pharmacokinetics of long-
619 acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase
620 2a randomized controlled trial. *PLoS Med* 2018; **15**: e1002690.
- 621 48. IMPAACT Network. Pharmacokinetic Properties of Antiretroviral, Anti-Tuberculosis,
622 Contraceptive and Related Drugs During Pregnancy and Postpartum.
623 https://www.impaactnetwork.org/studies/IMPAACT2026.asp_
- 624 49. Verloes R, Deleu S, Niemeijer N, Crauwels H, Meyvisch P, Williams P. Safety,
625 tolerability and pharmacokinetics of rilpivirine following administration of a long-acting
626 formulation in healthy volunteers. *HIV Med* 2015; **16**: 477-84.
- 627 50. Jackson AG, Else LJ, Mesquita PM, et al. A compartmental pharmacokinetic evaluation
628 of long-acting rilpivirine in HIV-negative volunteers for pre-exposure prophylaxis. *Clin*
629 *Pharmacol Ther* 2014; **96**: 314-23.
- 630 51. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing
631 Dapivirine for HIV-1 Prevention in Women. *N Engl J Med* 2016; **375**: 2121-32.
- 632 52. Nel A, van Niekerk N, Kapiga S, et al. Ring Study Team. Safety and Efficacy of a
633 Dapivirine Vaginal Ring for HIV Prevention in Women. *N Engl J Med* 2016; **375**: 2133-43.
- 634 53. Makanani B, Balkus JE, Jiao Y, et al. Pregnancy and Infant Outcomes Among Women
635 Using the Dapivirine Vaginal Ring in Early Pregnancy. *J Acquir Immune Defic Syndr* 2018;
636 **79**: 566-572.
- 637 54. Noguchi LM, Hoesley C, Kelly C, et al. Pharmacokinetics of Dapivirine Transfer into
638 Blood Plasma, Breast Milk, and Cervicovaginal Fluid of Lactating Women Using the
639 Dapivirine Vaginal Ring. *Antimicrob Agents Chemother* 2019; **63 pii**: e01930-18.
- 640 55. SWEN Study group. Extended-dose nevirapine to 6 weeks of age for infants to prevent
641 HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three
642 randomised controlled trials. *Lancet* 2008; **372**: 300-13.
- 643 56. Jamieson DJ, Chasela CS, Hudgens MG, et al. Maternal and infant antiretroviral
644 regimens to prevent postnatal HIV-1 transmission: 48-week follow-up of the BAN
645 randomised controlled trial. *Lancet* 2012; **379**: 2449-58.
- 646 57. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to
647 reduce breast-milk HIV-1 transmission. *N Engl J Med* 2008; **359**: 119-29.

- 648 58. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with
649 lopinavir–ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding
650 up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*
651 2016; **387**: 566-73.
- 652 59. Technau KG, Kuhn L, Coovadia A, Murnane PM, Sherman G. Xpert HIV-1 point-of-care
653 test for neonatal diagnosis of HIV in the birth testing programme of a maternity hospital: A
654 field evaluation study. *Lancet HIV* 2017; **4**: e442–e448.
- 655 60. Agutu CA, Ngetsu CJ, Price MA, et al. Systematic review of the performance and clinical
656 utility of point of care HIV-1 RNA testing for diagnosis and care. *PLoS One* 2019; **14**:
657 e0218369.
- 658 61. Jani I, Meggi B, Loquiha O, Tobaiwa O, Mudenyanga C, Mutsaka D, Mabunda N, Vubil
659 A, Vojnov L, Peter T. Effect of point-of-care testing on antiretroviral therapy initiation rates
660 in infants. Abstract 26. Conference on Retroviruses and Opportunistic Infections; February
661 13-16, 2017, Seattle, Washington.
- 662 62. Gruell H, Klein F. Antibody-mediated prevention and treatment of HIV-1 infection.
663 *Retrovirology* 2018; **15**: 73.
- 664 63. Halper-Stromberg A, Nussenzweig MC. Towards HIV-1 remission: potential roles for
665 broadly neutralizing antibodies. *J Clin Invest* 2016; **126**: 415-23.
- 666 64. Bruel T, Guivel-Benhassine F, Amraoui S, et al. Elimination of HIV-1-infected cells by
667 broadly neutralizing antibodies. *Nat Commun* 2016; **7**: 10844.
- 668 65. Barouch DH, Whitney JB, Moldt B, et al. Therapeutic efficacy of potent neutralizing HIV-
669 1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. *Nature* 2013; **503**:
670 224-8.
- 671 66. Scheid JF, Horwitz JA, Bar-On Y, et al. HIV-1 antibody 3BNC117 suppresses viral
672 rebound in humans during treatment interruption. *Nature* 2016; **535**: 556-60.
- 673 67. Mendoza P, Gruell H, Nogueira L, et al. Combination therapy with anti-HIV-1 antibodies
674 maintains viral suppression. *Nature* 2018; **561**: 479-84.
- 675 68. Caskey M, Klein F, Nussenzweig MC. Broadly neutralizing anti-HIV-1 monoclonal
676 antibodies in the clinic. *Nat Med* 2019; **25**: 547-53.
- 677 69. Barin F, Braibant M. HIV-1 antibodies in prevention of transmission. *Curr Opin HIV AIDS*
678 2019; **14**: 273-8.
- 679 70. Ko SY, Pegu A, Rudicell RS, et al. Enhanced neonatal Fc receptor function improves
680 protection against primate SHIV infection. *Nature* 2014; **514**: 642-5.
- 681 71. Mascola JR. VRC01-LS and new HIV Antibody Combinations 2nd Workshop on
682 Prevention Trials in Infants Born to HIV-Positive Mothers, Maputo, Mozambique, 6-7
683 February 2017.

- 684 72. Rademeyer C, Korber B, Seaman MS, et al. Features of Recently Transmitted HIV-1
685 Clade C Viruses that Impact Antibody Recognition: Implications for Active and Passive
686 Immunization. *PLoS Pathog* 2016; **12**: e1005742.
- 687 73. Cunningham CK, McFarland EJ, Morrison RL, Capparelli EV, Safrit JT, Mofenson LM,
688 Mathieson B, Valentine ME, Perlowski C, Smith B, Hazra R, Purdue L, Muresan P,
689 Harding PA, Mbengeranwa T, Robinson LG, Wiznia A, Theron G, Lin B, Bailer RT,
690 Mascola JR, Graham BS; IMPAACT P1112 team. Safety, Tolerability, and
691 Pharmacokinetics of the Broadly Neutralizing HIV-1 Monoclonal Antibody VRC01 in HIV-
692 Exposed Newborn Infants. *J Infect Dis* 2019 ; pii: jiz532.
- 693 74. Huang Y, Karuna S, Carpp LN, et al. Modeling cumulative overall prevention efficacy for
694 the VRC01 phase 2b efficacy trials. *Hum Vaccin Immunother* 2018; **23**: 1-12.
- 695 75. Hessel AJ, Jaworski JP, Epton E, et al. Early short term treatment with neutralizing
696 human monoclonal antibodies halts SHIV infection in infant macaque. *Nat Med* 2016; **22**:
697 362-8.
- 698 76. Shapiro MB, Cheever T, Malherbe DC, Pandey S, Reed J, Yang ES, Wang K, Pegu A,
699 Chen X, Siess D, Burke D, Henderson H, Lewinsohn R, Fischer M, Stanton JJ, Axthelm
700 MK, Kahl C, Park B, Lewis AD, Sacha JB, Mascola JR, Hessel AJ, Haigwood NL. Single-
701 dose bNAb cocktail or abbreviated ART post-exposure regimens achieve tight SHIV
702 control without adaptive immunity. *Nat Commun* 2020; 11: 70.
- 703 77. Abela IA, Berlinger L, Schanz M, et al. Cell-cell transmission enables HIV-1 to evade
704 inhibition by potent CD4bs directed antibodies. *PLoS Pathog* 2012; **8**: e1002634.
- 705 78. Bomsel M, Heyman M, Hocini H, et al. Intracellular neutralization of HIV transcytosis
706 across tight epithelial barriers by anti-HIV envelope protein dIlgA or IgM. *Immunity* 1998; **9**:
707 277-87.
- 708 79. Naranjo-Gomez M, Pelegrin M. Vaccinal effect of HIV-1 antibody therapy. *Curr Opin HIV*
709 *AIDS* 2019; **14**: 325-333.
- 710 80. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and
711 AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; **361**: 2209-20.
- 712 81. Bekker LG, Moodie Z, Grunenberg N, et al. Subtype C ALVAC-HIV and bivalent subtype
713 C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase
714 1/2 trial. *Lancet HIV* 2018; **5**: e366-e378.
- 715 82. Williams WB, Zhang J, Jiang C, et al. Initiation of HIV neutralizing B cell lineages with
716 sequential envelope immunizations. *Nat Commun* 2017; **8**: 1732.
- 717 83. Milligan C, Slyker JA, Overbaugh J. The Role of Immune Responses in HIV Mother-to-
718 Child Transmission. *Adv Virus Res* 2018; **100**: 19-40.
- 719 84. Goo L, Chohan V, Nduati R, Overbaugh J. Early development of broadly neutralizing
720 antibodies in HIV-1-infected infants. *Nature medicine* 2014; **20**: 655-658.

721 85. Phillips B, Van Rompay KKA, Rodriguez-Nieves J, et al. Adjuvant-Dependent
722 Enhancement of HIV Env-Specific Antibody Responses in Infant Rhesus Macaques. *J Virol*
723 2018; **92**: e01051-18.

724 .

725

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

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.

732

733

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

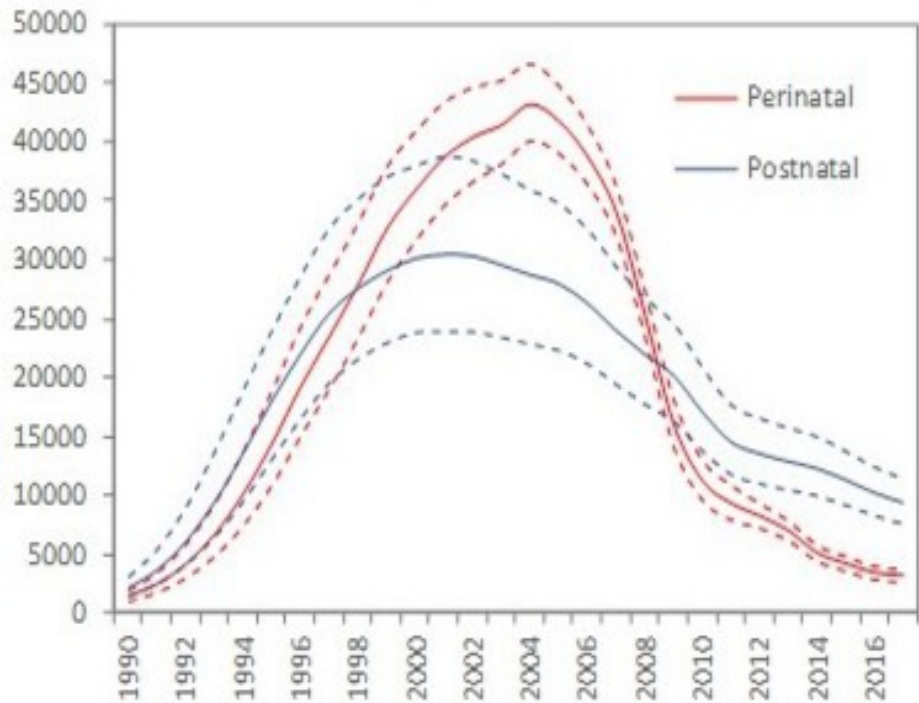
736

737

738

739

740



REINFORCEMENT APPROACHES:

- I. Retesting HIV negative mothers
- II. If VL detectable, reinforcement of maternal ART
- III. In HIV exposed uninfected infants, extended prophylaxis with ARV drug



Universal
ART for
PMTCT

**IMMUNOPROPHYLAXIS STRATEGIES
IN ALL NEWBORNS
AND/OR BREASTFED INFANTS:**
Administration of vaccine
or long-acting bNAbs



PrEP in young high risk pregnant
or lactating women (including
long-acting bNAbs or long-acting
injectable ARV drug)



PRIMARY PREVENTION: