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1 CONTEMPORARY CLINICAL TRIALS

2 **Design and challenges of a large HIV prevention clinical study on mother-to-child transmission:**
3 **ANRS 12397 PROMISE-EPI study in Zambia and Burkina Faso**

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8
9 **Abstract**

10 Post-natal HIV infection through breastfeeding remains a challenge in many low and middle-income
11 countries, particularly due to non-availability of alternative infant feeding options and the suboptimal
12 Prevention of Mother to Child Transmission of HIV-1 (PMTCT) cascade implementation and
13 monitoring. The PROMISE-EPI study aims to address the latter by identifying HIV infected mothers
14 during an almost never-missed visit for their infant, the second extended program on immunization
15 visit at 6-8 weeks of age (EPI-2). The study is divided into 3 components inclusive of an open-label
16 randomized controlled trial aiming to assess the efficacy of a responsive preventive intervention
17 compared to routine intervention based on the national PMTCT guidelines for HIV-1 uninfected
18 exposed breastfeeding infants. The preventive intervention includes: a) Point of care testing for early
19 infant HIV diagnosis and maternal viral load; b) infant, single-drug Pre-Exposure Prophylaxis (PrEP)
20 (lamivudine) if mothers are virally unsuppressed.

21 The primary outcome is HIV-transmission rate from EPI-2 to 12 months. The study targets to screen
22 37 000 mother/infant pairs in Zambia and Burkina Faso to identify 2000 mother/infant pairs for the
23 clinical trial.

24 The study design and challenges faced during study implementation are described, including the
25 COVID-19 pandemic and the amended HIV guidelines in Zambia in 2020 (triple-drug PrEP in HIV
26 exposed infants guided by quarterly maternal viral load). The changes in the Zambian guidelines
27 raised several questions including the equipoise of PrEP options, the standard of care-triple-drug
28 (control arm in Zambia) versus the study-single-drug (intervention arm).

29
30 **Trial registration number** (www.clinicaltrials.gov): NCT03869944

31
32 **Keywords:** HIV, mother-to-child transmission, randomized controlled trial, design, pre-exposure
33 prophylaxis, Africa

34 **Submission category:** Study Design, Statistical Design, Study Protocols

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37 **1 Introduction**

38 World Health Organization (WHO) recommendation for the prevention of mother-to-child
39 transmission (MTCT) of HIV in 2013 (1), notably, includes a lifelong antiretroviral therapy for
40 pregnant and breastfeeding women and short period of Pre-Exposure Prophylaxis (PrEP) to HIV
41 exposed uninfected (HEU) infants (option B+).

42 While progress has been made in the last few years toward expanding prevention of mother-to-child
43 transmission (PMTCT) programs and increased availability of antiretroviral therapy (ART), new HIV
44 infections among children are still unacceptably high. In 2020, about 150 000 children were infected
45 with HIV worldwide (2), a rate of infection 7.5 times higher than the target set by UNAIDS and
46 partners as part of the Super-Fast-Track Framework to end AIDS (3).

47 Most cases of MTCT result from a) new HIV infection during late pregnancy or breastfeeding period
48 (4) and b) non-attendance of antenatal care, or poor retention in care (5) including suboptimal
49 adherence to maternal ART (6–8) especially when ART is initiated during late pregnancy or
50 breastfeeding (9).

51 Improving maternal ART adherence is at the top of the research program agenda (10). However, even
52 if adherence is improved through dedicated interventions, significant residual transmission will remain
53 for several reasons. Many women do not have access to the program or do not comply with the
54 PMTCT cascade (attendance of the antenatal consultation, HIV-1 screening, referral for care, initiation
55 to ART). Furthermore, the 6 weeks' prophylaxis to exposed infants included in the B+ strategy do not
56 cover the whole period of breastfeeding exposure (11).

57 The “prevention of mother-to-child transmission of HIV-1: program evaluation and innovative
58 responsive intervention integrated in the expanded program of immunization” (PROMISE-EPI) study
59 aims to provide a second chance to mothers who have dropped out at any stage of the PMTCT cascade
60 to get back on track. These mothers are identified at a visit almost never missed for their infant: the
61 second extended program on immunization visit (EPI-2) performed when the infant is six to eight
62 weeks of age in sub-Saharan countries. During this visit, eligible mothers are invited to participate in
63 the clinical trial part of this study with the aim to evaluate the efficacy of an innovative response
64 intervention in order to protect their HEU infants against HIV-1 acquisition by breastfeeding.

65 The optimal PrEP intervention for HEU infants would result from a good risk-benefit balance between
66 efficacy, safety and risk of resistance among newly infected infants. Nevirapine and zidovudine are the
67 current WHO recommended drugs for HIV prophylaxis (12). Nevertheless, a high risk of resistance
68 associated with nevirapine prophylaxis has been reported by several studies (13–15) and serious
69 hematologic toxicity had been associated with zidovudine used as infant prophylaxis (16–18). The
70 choice of lamivudine as study prophylaxis drug was motivated by its good efficacy / safety profile
71 with no observed resistance demonstrated during the PROMISE-PEP study (19).

72 Herein, the study design, the challenges encountered and the lessons learnt during the implementation
73 of the PROMISE-EPI study are reviewed.

74

75 **2 Method**

76 2.1 Local settings

77 In 2019, 81% and 86% of pregnant women living with HIV, received ART for PMTCT in Burkina
78 Faso and Zambia respectively and the final HIV mother-to-child transmission rate including
79 breastfeeding period was 15.1% in Burkina Faso and 10.7% in Zambia (20, 21).

80 Both countries have adopted the WHO recommendations for PMTCT including: timing of HIV tests;
81 ART for pregnant and breastfeeding HIV infected mothers; early infant diagnosis for HIV and short
82 period of PrEP for HEU infants. In particular, national recommendations differ in the two countries
83 regarding infant sampling for early diagnosis. In Burkina Faso, a single blood sample is taken at the
84 “42th day well baby visit” for PCR test whereas 2 samples are taken in Zambia, at birth and at EPI-2
85 visit.

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2.2 Study objectives, associated design, eligibility criteria and endpoints

The study consists of 3 different components, each associated with distinct objectives.

Component 1 is proposed to all mothers attending the EPI-2 visit. Its description is presented in table 1.

Table 1: Description of Component 1

Objective	To monitor the ‘real life’ efficacy of the PMTCT cascade up to the second EPI visit
Design	Cross-sectional study
Inclusion/ Non-inclusion criteria	Inclusion criteria: -Mother aged 15 or older accompanying her infant to the EPI-2 visit -Infant between 5 and 16 weeks at the time of EPI-2
Procedures	Administration of a short questionnaire and HIV rapid test if not performed recently
Endpoints	-Proportion of mothers attending the 6-8 week EPI visit who: a) Attended PMTCT clinic at least once during their pregnancy, b) Have been tested for HIV-1 antenatally or during childbirth, c) Are HIV-1 infected -Proportion of HIV infected mothers : a) With suppressed viral load(<1000 HIV RNA copies/mL), b) Having initiated ART during pregnancy or following childbirth -Proportion of HIV exposed infant HIV tested with PCR at birth -Proportion of infants with a positive HIV-1 PCR who were initiated on ART at EPI-2

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Component 2/3 is proposed to all HIV positive mothers from Component 1 (newly and previously diagnosed) and their infant pair, who meet the couple eligibility criteria. At this point infants are tested for HIV-1 using a POC HIV-1 DNA PCR test (GeneXpert HIV-1 Qualitative) to determine the component affiliation and subsequent procedures (table 2):

- If HIV positive, the participant becomes part of Component 2 and is referred to the National HIV treatment Program.
- If HIV negative, the participant becomes part of Component 3, and is randomized to one of the two study arms (control or intervention).

Table 2: Description of Component 2 and 3

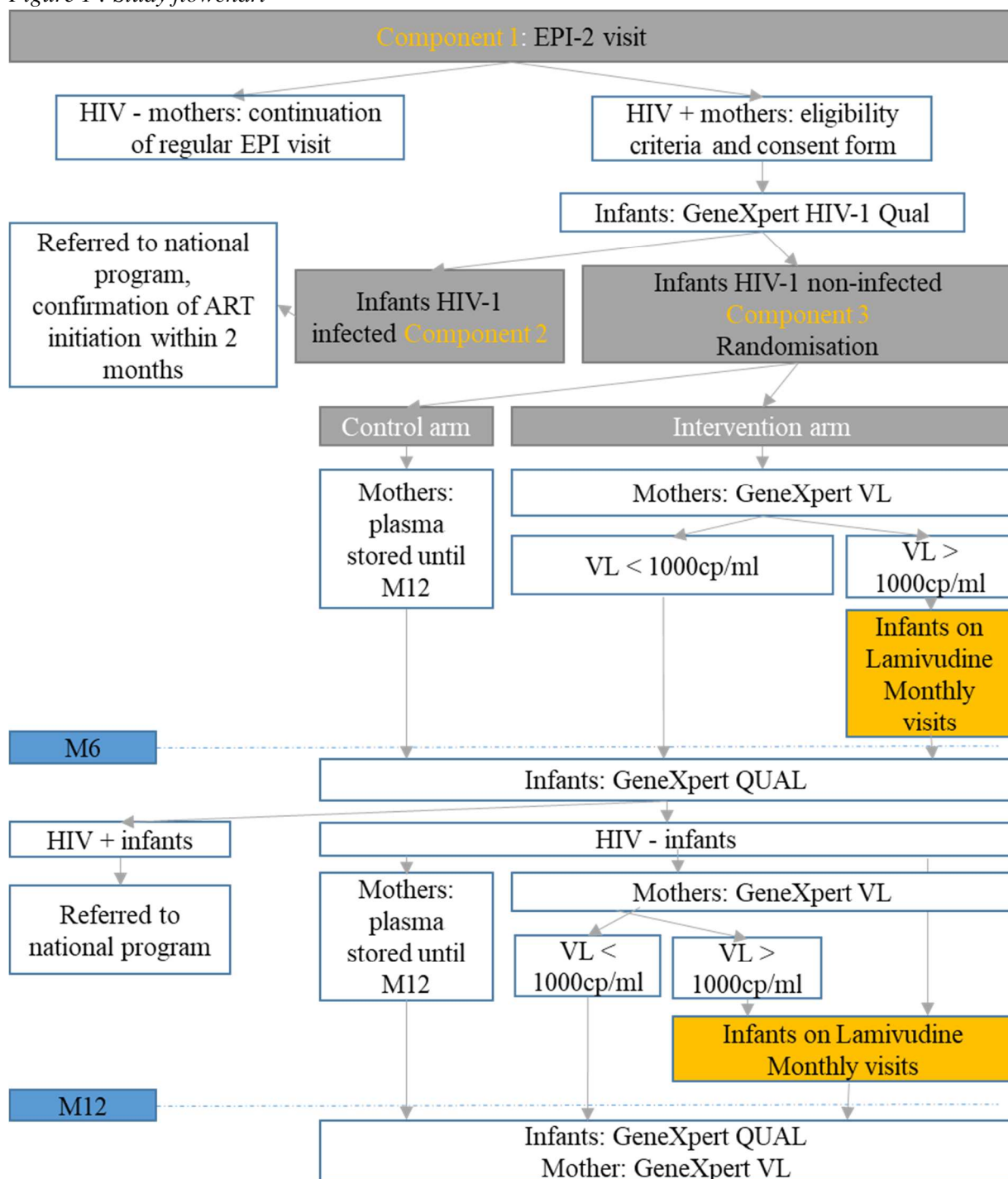
	<i>Component 2: HIV infected infants at EPI-2</i>	<i>Component 3 : HIV exposed uninfected infants at EPI-2</i>
Objectives	To evaluate a reinforced access to early paediatric ART among HIV-1 infected infants not engaged in care at EPI visit	Primary objective: To evaluate the efficacy of an innovative response intervention including point of care (POC) testing (maternal viral load and infant HIV diagnosis with immediate results) and infant single-drug PrEP (lamivudine) for high risk infants of HIV-1 acquisition by breastfeeding Secondary objectives: - To evaluate the safety of the intervention - To evaluate the diagnostic performance of plasma HIV viral load compared to breastmilk HIV viral load to identify infants at-risk of transmission via breastmilk

Inclusion/ Non- inclusion criteria	Inclusion criteria: - HIV-1 mother (with or without HIV-2) - Singleton infant - Infant breastfed at EPI-2 and the mother intends to continue breastfeeding at least until child is 6 months-old Non-inclusion criteria - Infant with: - Clinical symptoms or biological abnormalities of DAIDS classification 3 or 4 for adverse events on the day of inclusion - Severe congenital malformation - Known allergy to the study drug or its components - Already taking emtricitabine drug - Mother: - Living outside the study area or intending to move from the area within the next 12 months - Participating in another clinical trial		
	Inclusion criteria: - Infant with positive HIV-1 PCR POC test at EPI-2	Inclusion criteria: - Infant with negative HIV-1 PCR POC test at EPI-2	
Design	Cross-sectional study	Multi-centre and multi-country, parallel, controlled open-label trial	
Procedures	Information on HIV diagnosis confirmation and ART initiation are sought in the hospital registers at least 2 months after the diagnosis	Control group - EPI-2 and M6 visit: Mother's plasma stored for viral load testing at M12. (Outside the study, mothers can access the routine national program including HIV-1 plasma viral load testing).	Intervention group - EPI-2 and M6 visit: Maternal viral load testing by POC HIV-1 PCR (GeneXpert HIV-1 viral load) and lamivudine initiation for infants of virally unsuppressed mothers - Monthly visits for infants of virally unsuppressed mothers with lamivudine dispensation
		-M6 and M12: infant HIV-1 DNA PCR	
Endpoints	Proportion of HIV-infected breastfed infants identified during the second EPI visit and who were not engaged in HIV care at this time but who will be initiated on ART within 2 months after this visit	Primary endpoint: - Proportion of HEU infants who are PCR positive at 12 months, using POC HIV-1 DNA PCR test (GeneXpert® HIV-1 Qualitative) Secondary endpoints: - Adverse events rates at 12 months of age, including death and Grade 3 or 4 events based on Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events - Proportion of plasma HIV-1 viral load levels concordant with breastmilk HIV-1 viral load levels	

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104 At EPI-2 for Component 2 and 3 and at M6 and M12 for Component 3, the following procedures are
105 performed in addition to the ones described in table 2: infant physical examination; questionnaires
106 administration to the mother (socio-demographic data, medical history, attendance at counselling
107 sessions, PMTCT questions on breastfeeding, ART) and ART and adherence counselling are provided.
108 In the intervention group of Component 3, infants of virally unsuppressed mothers at EPI-2/ M6 visit
109 receive PrEP (lamivudine) with monthly visits, until 12 months of age or until breastfeeding cessation
110 (defined as 2 consecutive monthly visits where mother confirms the end of breastfeeding). In case of
111 lamivudine cessation, the participant continues to be followed in the study with M6 and M12 visits.
112 The intervention duration is 10 months (from 6-8 weeks to 12 months) (Figure 1).

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Figure 1 : Study flowchart



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2.3 Informed consent

An opt out consent was initially planned for Component 1 in both countries, but a signed consent was subsequently requested by the Zambian Ethic committees and Competent Authorities. A specific consent form is signed prior enrolment in Component 2/3.

Written informed consent is collected in the local language of the mother by investigators who underwent specific training. An independent third party assists mothers that are not able to read or write. Mothers between 15 and 18 years of age in Zambia and between 15 and 19 years of age in

125 Burkina Faso can be enrolled in the trial if they are accompanied by a referent adult of their choice
126 who will represent their interests and those of the infant.

127

128 2.4 Location and personnel

129 The choice of sites in West Africa (Burkina Faso) and Southern Africa (Zambia) was aimed at
130 ascertaining the generalizability of the proposed strategy in different cultural, epidemiological and
131 health system contexts.

132 The study is being conducted by the Centre Muraz in Burkina Faso and the University Teaching
133 Hospital in Zambia. Both institutions are experienced in MTCT prevention research programs through
134 their participations in several clinical trials.

135 In Burkina Faso, the study is on-going in two districts (Do and Dafra) of Bobo-Dioulasso and two
136 other districts (Baskuy and Boulmiougou) of Ouagadougou. Each district has one level/referral health
137 centre (CMA/CMU) and various Centres for Health and Social Promotion (CSPS). A total of 31
138 CSPSs were selected for Component 1 based on their willingness to participate, space and staff
139 capacity, and their accessibility/distance to the referral CMA/CMU. Eligible HIV positive mothers,
140 willing to participate in component 2/3 are referred to the CMA/CMU for follow-up activities after
141 obtaining informed consent.

142 In Zambia, 4 sites in the capital city, Lusaka, are involved (Chilenje, Bauleni, Matero Main and
143 Chaisa) where the study activities are collocated with the Maternal Child Health (MCH) department.
144 In contrast to Burkina Faso, site staff involved in the study in Zambia are solely dedicated to the study.
145 This study organization adjustment resulted from the different prevalence of HIV observed in each
146 country. In Burkina Faso, where prevalence is low, a high number of mothers must be screened at EPI-
147 2 in order to achieve the objective of Component 3, and therefore multiplying the number of recruiting
148 sites. In Zambia, each site deserves a dedicated team due to the high HIV prevalence. We do not
149 expect differences in the conduct of the study in the two countries but it may be easier to get answers
150 to queries in Zambia.

151 The PROMISE-EPI team received training on International Conference on Harmonisation Good
152 Clinical Practice (22) including ethical principles that have their origin in the Declaration of Helsinki
153 (23).

154 Community health workers are involved in the study at different levels depending on the country: In
155 Burkina Faso they have a key role in the transfer of participants between the CSPS and the
156 CMA/CMU and in both countries they are involved in providing support to mothers in order to avoid
157 loss to follow-up.

158

159 2.5 Laboratory assays

160 In Component 1, the Determine™ HIV-1/2 rapid test is used for initial diagnosis of the woman and
161 SD Bioline HIV-1/2 rapid test as confirmatory test. Due to the circulation of HIV-2 in Burkina-Faso,
162 the mothers already known to be HIV-positive at the time of Component 1 perform a SD Bioline HIV-
163 1/2 rapid test to avoid erroneously enrolment of mothers who are only HIV-2 infected.

164 The point of care HIV-1 PCR (GeneXpert HIV-1 Qualitative, Cepheid) is performed on the capillary
165 blood collected from infants. Mother blood samples (5ml) are collected by trained study nurses at EPI-
166 2, M6 and M12. Plasma is prepared for either HIV-1 viral load assay (GeneXpert HIV-1 viral load,
167 Cepheid) if the mother belongs to the intervention arm or for storage and later HIV-1 viral load assay
168 if the mother belongs to the control arm. Whenever blood is collected from mothers and infants dry
169 blood spot (DBS), aliquots are saved for quality control assessment and future investigations.

170 In Zambia only, 10 ml of manually-expressed milk from each breast is collected from mothers at 6-8
171 weeks, 6 months and 12 months post-partum for storage of acellular and cellular fractions.

172 Laboratory and quality control procedures are monitored to ensure Good Laboratory Practice (24).

173

174 2.6 PrEP

175 The lamivudine oral suspension is administered according to the baby's weight bands: 7.5 mg (0.75
 176 mL) twice daily if 2-4 kg, 25 mg (2.5 mL) twice daily if 4-8 kg and 50 mg (5 mL) twice daily if >8 kg.
 177 These dosages were calculated on the basis of previous pharmacokinetic study (25).
 178 Study drug compliance is assessed by the investigator at each visit based on a discussion with the
 179 participant and the quantity of lamivudine in the returned bottles.

180

181 2.7 Data collection and data management

182 The data collected are recorded in an electronic Case Report Form (CRF), using REDCap
 183 (<https://www.project-redcap.org/>, Vanderbilt University, Nashville, USA), a secure web application.
 184 Included in the data is information on PMTCT experience, clinical evaluation (with duplicate
 185 measurements for weight), medical history, laboratory samples taken and tests performed, study drug
 186 intake, concomitant treatment, adverse events. All data recorded are strictly confidential and coded,
 187 using a unique study subject identification code.

188 Verification of the completeness and consistency of the data is performed through a) a regular on site
 189 monitoring visits by the Centre Muraz in Burkina-Faso and the University Teaching Hospitals in
 190 Zambia and b) a central monitoring by the Pathogenesis and Control of Chronic and Emerging
 191 Infections, UMR 1058– INSERM unit following the monitoring procedures.

192

193 2.8 Randomisation

194 The participants of component 3 are allocated to one of two arms using a centralized randomization
 195 scheme incorporated in the eCRF (REDCap). The randomization list was elaborated using a 1:1 ratio,
 196 stratification by site (district for Burkina Faso) and permuted blocks of size 4 or 6.

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198 2.9 Statistical considerations

199 *Study size*

200 Sample size calculation was based on the primary outcome, i.e. the rate of infant HIV infection at 12
 201 months. This rate was hypothesized to range between 3% and 6%. These rates are conservative as the
 202 'official' PMTCT rate in Zambia was above 10% in 2019 (26). The responsive intervention is expected
 203 to lower this rate, to achieve around 2% transmission rate, based on the results of PROMISE-PEP
 204 study (1.5% (CI95%:0.8- 2.9) in the intention-to-treat population in the lamivudine arm) (19). A 50%
 205 reduction of the current PMTCT rate using the 'responsive' intervention would be deemed satisfactory
 206 enough to be worth implementing. The table 3 shows various hypotheses of sample size accounting for
 207 the various hypotheses of transmission rates in the two arms, with 80% power, 5% significance level
 208 and 15% lost-to-follow-up rate. The enrolment of 2000 infants in Component 3 (1750 in Zambia and
 209 250 in Burkina Faso) will allow covering the most reasonable hypotheses.

210

211 *Table 3: Hypotheses of sample size accounting for the various hypotheses of transmission rates in the*
 212 *two arms*

		Transmission rate in control group			
		3%	4%	5%	6%
Transmission rate in intervention group	1%	1992	1127	766	575
	1.5%	3827	1725	1058	741
	2%	9246	2852	1500	978
	2.5%	39537	3048	2254	1327

213

214 Component 1 sample size of 37 000 participants (25 000 in Burkina Faso and 12 000 in Zambia) was
215 based on HIV prevalence among women (1.1% and 14.9% in Burkina Faso and Zambia, respectively)
216 (27).

217 *Data analysis*

218 Analysis methods will follow the CONSORT guidelines (28) and recommendations of the GHENT
219 group related to the mother-to-child transmission studies (29,30) and breastfeeding patterns (31).

220 All tests will be two-sided. Descriptive results, efficacy and safety estimates and their corresponding
221 95% CIs will be presented. The statistical significance is set at $p < 0.05$. Potential confounders may be
222 considered for further adjustment if they are deemed imbalanced at baseline.

223 Analyses for the primary outcome, the acquisition of HIV-1 (i.e. a positive POC HIV-1 DNA PCR)
224 between EPI-2 visit and 12 months of age, will be undertaken on an intention-to-treat basis using chi-
225 squared test (χ^2 test) or Fisher's exact test depending on the number of observed events. Cumulative
226 event probabilities between 6-8 weeks and 12 months will be estimated with the Turnbull's extension
227 of the Kaplan-Meier procedure to interval-censored data, and will be compared between arms with a
228 log-rank test. Data of HIV-uninfected withdrawals and deaths will be censored at the last outcome
229 measurement. HEU withdrawals and deaths will be considered in these analyses following various
230 assumptions, corresponding to sensitivity analyses (such as: all unknown status considered positive, all
231 unknown status considered negative, weighting the probability of HIV infection according to baseline
232 maternal characteristics).

233 Concordance between plasma HIV-1 viral load levels and breast milk HIV-1 viral load levels will be
234 evaluated using Cohen's kappa statistic.

235

236 2.10 Authorizations and external boards

237 The study protocol has been submitted to and approved by the Ethic committee for Health Research
238 (CERS) and competent authority (Agence Nationale de Régulation Pharmaceutique: ANRP) in
239 Burkina Faso and by the Ethic committees (private Institutional Review Board: ERES converge and
240 Ministry of Health, National Health Research Authority: NHRA) and competent authority (Zambia
241 Medicines Regulatory Authority: ZAMRA) in Zambia.

242 The study is sponsored by France REcherche Nord and sud Sida-hiv Hépatites (ANRS).

243 A Scientific Advisory Board (SAB), including sponsor members, is established for the global
244 supervision of the trial. A Data Safety Monitoring Board (DSMB) monitors the overall conduct of the
245 study with the aim of protecting the safety and the interests of the study participants. An external
246 independent ethical advisor is also involved to assess the aims, objectives and methodology of the
247 study, the overview of the study operations and also provides guidance on ethical dilemmas.

248

249 2.11 Study schedule

250 The recruitment began in December 2019 in Zambia (19 months' inclusion period) and in December
251 2020 in Burkina Faso (10 months' inclusion period), with a 10 months' follow-up period.

252

253 2.12 Dissemination plan

254 A webpage was established to share information on the study (<https://promise.w.uib.no/>). Final results
255 are expected end of 2022. Relevant results will be shared with participants, study staff and key
256 relevant stakeholders, disseminated through peer-review international journals and presented at
257 conferences and scientific meetings.

258

259

260 **3 Challenges and adaptations**

261 Modification of the national guidelines in Zambia

262 The control arm of the PROMISE-EPI trial, being the standard of care for PMTCT in the country, is
263 subject to the distinct country policies and to amendment during the course of the trial.

264 When the study was implemented (2019), there was an important difference of standard of care for
265 infants at-high risk of HIV transmission between the two countries. Zidovudine/lamivudine/nevirapine
266 (AZT/3TC/NVP) was the PrEP recommended up to 12 weeks of age in Zambia (32), while in Burkina
267 Faso, the applied national recommendation was 6 weeks of nevirapine for all HEU infants. In the
268 Zambian guidelines, infants were considered at-high-risk of HIV acquisition if they were born to a
269 woman with established HIV infection a) who was not on ART; b) who had received less than 12
270 weeks of ART at the time of delivery, c) whose viral load was greater than 1000 copies/ml in the four
271 weeks before delivery. Because our intervention started at EPI-2, it was decided to postpone the
272 initiation of the study drug to M3 for these high-risk Zambian infants. Therefore, the standard of care,
273 and thus the control arm, were quite similar for both countries.

274 In January 2020, the Zambian government released new guidelines for treatment and prevention of
275 HIV infection (33) that modified the standard of care (control arm) in the following ways: a) triple
276 drug prophylaxis (AZT/3TC/NVP) prolonged until maternal viral suppression, and b) mothers viral
277 load measurements scheduled every 3 months.

278 As a consequence, and for ethical reasons, all mothers in the study are now encouraged to perform the
279 M9 viral load measurement as recommended by the 2020 guidelines (provided by the national
280 program, using central lab facility). EPI-2, M6 and M12 viral load measurements are already
281 performed within the study by a POC technique.

282 However, for the study, the main change brought by the 2020 Zambian guidelines was the infant PrEP:
283 triple-drug (control arm) versus single-drug (intervention arm). The equipoise of both prophylaxis
284 options needed to be re-evaluated in order to continue the study in Zambia. The Scientific Advisory
285 Board helped us to define the relevant questions. We hypothesized that the PROMISE-EPI
286 intervention arm is non inferior as compared to the standard of care in terms of efficacy (prevention of
287 breastfeeding transmission) while being safer (fewer serious adverse events (SAEs)), allowing for a
288 better adherence and not generating drug-resistant HIV mutants (either by transmission from mother to
289 infant or by selection in infected infants). The arguments were the following:

- 290
291 - *The efficacy of a single drug (lamivudine) used as prophylaxis in the HIV exposed uninfected*
292 *infants is not inferior to a triple-drug to prevent HIV acquisition.*

293 WHO recommendation for breastfed HIV-exposed uninfected infants is 6 weeks of infant single-drug
294 prophylaxis in the majority of the cases (12). Triple-drug prophylaxis has a very low level of scientific
295 evidence in this population, per current knowledge, and no clinical trial has assessed the efficacy and
296 safety of a triple-drug prophylaxis (zidovudine + lamivudine + nevirapine) in breastfed HIV-exposed
297 uninfected infants. No differences in efficacy between one- versus multiple-drug prophylaxis have
298 been demonstrated with short (6 weeks) prophylactic regimens in the French Paediatric Study (34) nor
299 with prophylactic regimens (nevirapine/zidovudine versus zidovudine) extended for 14 weeks in the
300 PEPI trial (17). Nevertheless, in the NICHD/HPTN 040 study, intrapartum HIV infection rates were
301 similar in the multidrug infant prophylaxis groups (zidovudine + nevirapine and zidovudine +
302 lamivudine + nelfinavir) and reduced when compared to the control group (zidovudine alone) (35). It
303 has to be highlighted that lamivudine taken as single PrEP had very low rates of HIV-1 postnatal
304 transmission for up to 50 weeks of breastfeeding in the PROMISE-PEP trial (19).

305 A new secondary objective was added to the protocol to answer this hypothesis: To assess the non-
306 inferiority of the efficacy of a single-drug versus triple-drug prophylactic regimen: a) to prevent HIV
307 transmission at one year of age; b) to assess the HIV-1 free survival at one year of age.

308 Roll out of the 2020 guidelines in Zambia started in March 2020, four months after the beginning of
309 the recruitment. A new sample size calculation showed that with an HIV transmission rate in
310 comparison arm of 1% and a lower limit for the difference “intervention-comparison triple drug arm”

311 of 2 %, 600 participants per arm will be needed (confidence level: 95% (one-sided); power 90%) to
312 allow a conclusion of non-inferiority.

313

314 - *A single drug (lamivudine) prophylaxis is safer than a triple drug prophylaxis*
315 *(zidovudine/lamivudine/nevirapine).*

316 Three studies have shown that the hematologic toxicity of zidovudine can lead to severe adverse
317 events and even death in HIV-exposed uninfected infants (16–18). In addition to safety concern,
318 adverse events can lead to prophylaxis cessation or suboptimal compliance to therapy which can in
319 turn lead to HIV acquisition.

320 Furthermore, rare and long term side effects following antiretroviral drugs exposure are suspected (in
321 particular with zidovudine) due to potential impact on the mitochondrial function (36,37). These
322 adverse events are currently under investigations but they will be difficult to identify during clinical
323 trials because of the long delay in clinical symptoms. It is reasonable to anticipate that the risk for rare
324 and long-term side effects increases with the number of antiretroviral drugs exposure.

325 A new secondary objective was added to the protocol to answer this hypothesis: To evaluate the safety
326 of a triple drug prophylaxis versus a single drug prophylaxis in infants up to one year of age.
327 According to the zidovudine safety profile, full blood count will be performed in infants at EPI-2 visit,
328 M6 and M12 in both arms to allow a better evaluation of the safety.

329

330 - *A single drug prophylaxis does not increase the risk of drug resistant HIV acquisition*
331 *compared to a triple drug prophylaxis*

332 In a WHO report with data from 2014 to 2016, the prevalence of HIV drug resistance for individuals
333 on ART in Zambia was 4.3% (95CI:1.9-9.5); all of them with Nucleoside Reverse Transcriptase
334 Inhibitors (NRTI) drug resistant mutations (DRM) (38). However, the frequency of NRTI DRM is
335 rather low in the infants and young children and overwhelmed by Non-Nucleoside Reverse
336 Transcriptase Inhibitors (NNRTI) DRM (39). Indeed, Poppe et al. showed that the frequency of
337 NNRTI DRM can be as high as 40% in HIV infected infants at 5 months of age (40). The high risk of
338 resistance associated with nevirapine prophylaxis was confirmed in several studies (13–15). As an
339 inference, this observation suggest that wild type virus represents the founder virus in most of the
340 cases of HIV acquisition postnatally. Other arguments supporting this assumption were found in
341 cohorts of breastfed infants whose mothers are treated with ART. In these infants, the HIV drug
342 resistance mutation subsequently identified likely emerged as a result of ingestion of sub-optimal
343 levels of antiretroviral drugs in breastmilk. Indeed, the children had wild-type infection or drug
344 resistance mutations profile that differed from that of the mother at the first time of PCR positivity in
345 three studies (14,39,41). In these observations (14,15,41), most of the infants acquired a wild type
346 virus and subsequently selected resistant mutants.

347 M184I/V variants, conferring resistance to lamivudine, which are among the most frequently
348 encountered mutations in patients treated with lamivudine or emtricitabine-containing regimens, also
349 displays reduced transmissibility as a result of impaired replication capacity (42).

350 Viral resistance genotyping was added to the protocol to follow this hypothesis. It will be performed
351 for the infants with a positive HIV-1 PCR at M6 and M12.

352

353 - *Better adherence to therapy can be better achieved with a single drug (lamivudine in syrup)*
354 *infant PrEP as compared to the triple drug regimen recommended by the 2020 Zambian*
355 *guidelines*

356 The triple-drug prophylaxis regimen as recommended by the 2020 Zambian guidelines is composed of
357 2 different formulations with different schedule of administration. Zidovudine/lamivudine is a
358 dispersible tablet to be taken twice daily and nevirapine is a syrup to be taken once daily. Many
359 variables influence adherence to a single-drug regimen or to a more complex regimen such as
360 formulation of drugs, number of tablet/syrup, schedule of administration, palatability (43). Suboptimal
361 observance may increase the risk of HIV acquisition, including acquisition of a resistant virus.

362
363 The DSMB agreed with the revised rationale, adapted objectives and study design in response to the
364 modification of the Zambian guidelines. The DSMB proposed to act as clinical event adjudication
365 committee with quarterly review of the HIV transmission and serious adverse events in the two arms.
366 The initial objectives remain applicable for participants included prior to the implementation of the
367 2020 guidelines in Zambia as well as for participants from Burkina Faso. The amended protocol was
368 submitted to and approved by the ethic committees and competent authorities.
369

370 Impact of COVID-19:

371 Some challenges were experienced in Zambia due to the COVID-19 outbreak. Recruitment was
372 suspended for one month due to the lockdown in April 2020 but the follow-up visits were performed
373 as initially planned.

374 The main challenge faced was the difficulty in maintaining the supply of the study drug. In July 2020,
375 the available stock of lamivudine expired. The study team was able to obtain a certificate of approval
376 for extended use of the expired drug from the national medicines and regulatory authorities. The
377 approval was granted following drug assay test results that confirmed non-degradation of the drug and
378 safety of use for an extended period of 1 month. However, a few days after approval, a public uproar
379 forced the Zambian team together with the Zambian authority (ZAMRA) to withdrawal the drug. In
380 this emergency context, four options were considered by the Zambian PROMISE-EPI team: a) to
381 withdraw lamivudine and give nothing to the HIV exposed infants of the intervention group; b) to give
382 the triple drug offered in the national program (AZT/3TC/NVP) as for the control group; c) to give
383 zidovudine/lamivudine; d) to give abacavir/lamivudine (abacavir/lamivudine). The first option was
384 excluded because it was considered unethical and second and third options were ruled out due to the
385 safety concern regarding zidovudine. Abacavir/lamivudine was considered as the best available
386 alternative based on its good safety profile and drug availability. The main safety concern with
387 abacavir is hypersensitivity, which is extremely rare in Zambia, given the very low prevalence of the
388 HLA-B*57:01 allele in the African population compared with the European population (44).
389 Abacavir/lamivudine is indeed recommended as first line treatment in Zambia, combined with
390 lopinavir, for the HIV-infected children above two weeks of age (33). The abacavir/lamivudine dosage
391 was calculated to correspond to the dosage of lamivudine as described in the protocol without having
392 abacavir overdose.

393 All bodies of the trial were informed of this situation (Ethic Committees, Scientific Advisory Board,
394 sponsor and DSMB). The DSMB recommendations were as follows: a) to closely monitor the adverse
395 events; b) to switch back the infants to lamivudine, as soon as it becomes available, after having
396 verified they were not HIV infected; c) to check resistance among the infants who seroconvert. A
397 specific written informed consent form was provided to and signed by the participants. Monthly and
398 M6 visits were maintained but inclusions were interrupted during the month-long absence of the study
399 drug (lamivudine). Infants in the intervention group whose mothers were virally unsuppressed were on
400 abacavir/lamivudine for about 1 month. None of them experienced serious adverse events while taking
401 abacavir/lamivudine and all of them remained HIV negative at the time of lamivudine prophylaxis
402 reintroduction. Eventually, a new drug supplier was identified to mitigate the risk of supply chain
403 disruption.

404
405

406 **5 Discussion**

407 By focusing on identifying mothers at-risk of HIV transmission during an almost never-missed visit
408 for their infant, the PROMISE-EPI implementation study addresses the suboptimal PMTCT program
409 implementation and monitoring in low and middle-income countries, which is critical to the control of
410 paediatric HIV. Furthermore, this study aims to demonstrate the usefulness of an infant single PrEP
411 administered to high-risk infants, not only during the first 6 weeks of life, as internationally

412 recommended (1), but until the end of the recommended breastfeeding period, for the infants of virally
413 unsuppressed mothers, thanks to point of care tests. According to the WHO guidelines, HIV positive
414 mothers should exclusively breastfeed their infants for the first 6 months of life, introducing
415 appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life
416 (12). The risk of late HIV postnatal transmission is not negligible. This has been shown in
417 observational studies, including prospective cohorts, where mixed feeding has been associated with an
418 increased risk of HIV-1 transmission as compared to exclusive breastfeeding (45–48). Potential
419 mechanisms include greater gut damage with mixed breastfeeding than with exclusive breastfeeding
420 (49).

421 The study design has some limitations. First, the primary objective evaluates the intervention at 12-
422 month of age. It does not consider a possible prolonged period of breastfeeding and thus exposure to
423 HIV beyond 1 year. Nevertheless, virally unsuppressed mothers at M12 are referred to national
424 program for adherence counselling and ART optimization. Second, the rescue intervention proposed in
425 PROMISE-EPI study is based on the EPI-2 visit and therefore does not identify breastfeeding mothers
426 who seroconvert after 2 months' post-partum.

427 Unexpected difficulties were faced during the study implementation due to the COVID-19 outbreak
428 and the change in HIV standard of care in Zambia. Setting up a study with 'standard of care' as the
429 control arm is always challenging because of the possible modification of the recommendations during
430 the study. In this case, modifications in HIV guidelines in Zambia in 2020, led the team to deeply
431 review the equipoise of single- versus multiple-drug regimens for prophylaxis in HIV exposed
432 uninfected infants. It has to be kept in mind that the targeted benefit/risk ratio of an antiretroviral drug
433 regimen used as HIV prophylaxis in infants is much higher than the one expected for therapy in those
434 infected. In the HIV context, the success of a prophylaxis combines good efficacy, safety and
435 adherence. In proposing to administer triple-drug prophylaxis to HEU infants, the 2020 Zambian
436 guidelines are driven by practicalities and the availability of drug formulations, but not on scientific
437 evidence for a better tolerance and efficacy profile. Furthermore, the current trends are toward
438 antiretroviral therapy simplification for HIV infected patients in order to make treatment more
439 convenient avoiding toxicity and reducing costs (50). A similar approach seems relevant in the context
440 of prophylaxis for infants.

441 The unexpected challenges raised by the modification of the Zambian guidelines and the intermittent
442 non-availability of the study drug were promptly identified and ethical, cultural and scientifically
443 relevant solutions were found. We took advantage of the PROMISE-EPI study to assess the relevance
444 of these new HIV prevention recommendations, explore alternative options of drug supply and learn
445 how to navigate the ethical dilemma with the regulatory authorities.

446

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450 Competing interests/conflict of interests

451 The authors declare that they have no competing interest and no conflict of interests.

452

453 Author's contribution

454 PVdP, CK and PF: coordinating investigators. PVdP, NN JPM, CK, NM and TT: study conception,
455 planning and design. PVdP, NN, JPM, TT, BM, AM, SED, CK, CC, MM and PF: preparation of the
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