

Modelling cost-effectiveness of tenofovir for prevention of mother to child transmission of hepatitis B virus infection in South Africa

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33

34 **Abbreviations**

35 HBIG - hepatitis B immunoglobulin

36 HBV – hepatitis B Virus

37 HBeAg – hepatitis B e antigen

38 HBsAg – hepatitis B surface antigen

39 MTCT – mother to child transmission

40 PMTCT – prevention of mother to child transmission

41 POCT – point of care test

42 sSA – sub Saharan Africa

43 TDF - Tenofovir disoproxil fumarate

44 VL – viral load

45

46

47 **ABSTRACT**

48 In light of sustainable development goals for 2030, an important priority for Africa is to have
49 affordable, accessible and sustainable hepatitis B virus (HBV) prevention of mother to child
50 transmission (PMTCT) programmes, delivering screening and treatment for antenatal women and
51 implementing timely administration of HBV vaccine for their babies. We developed a decision-
52 analytic model simulating 10,000 singleton pregnancies to assess the cost-effectiveness of three
53 possible strategies for deployment of tenofovir in pregnancy, in combination with routine infant
54 vaccination: **S1**: no screening nor antiviral therapy; **S2**: screening and antiviral prophylaxis for all
55 women who test HBsAg-positive; **S3**: screening for HBsAg, followed by HBeAg testing and antiviral
56 prophylaxis for women who are HBsAg-positive and HBeAg-positive. Our outcome was cost per
57 infant HBV infection avoided and the analysis followed a healthcare perspective. S1 predicts 45
58 infants would be HBV-infected at six months of age, compared to 21 and 28 infants in S2 and S3,
59 respectively. Relative to S1, S2 had an incremental cost of \$3,940 per infection avoided. S3 led to
60 more infections and higher costs. Given the long-term health burden for individuals and economic
61 burden for society associated with chronic HBV infection, screening pregnant women and providing
62 tenofovir for all who test HBsAg+ may be a cost-effective strategy for South Africa.

63

64 **INTRODUCTION**

65

66 In order to meet targets set by International Sustainable Development Goals for the elimination of
67 Hepatitis B Virus (HBV) infection as a public health problem by the year 2030 (1) , enhanced efforts
68 are required to reduce the incidence of new cases. Strategies that set out to achieve this need to be
69 carefully evaluated, both on the grounds of effect on individual and population health, and also
70 based on value for money. HBV infection is highly endemic in many low/middle income settings (2),
71 where economic evaluations are particularly important for informing the appropriate deployment of
72 limited health care resources.

73

74 Prevention of mother to child transmission (PMTCT) is a cornerstone of HBV elimination strategies.
75 Reducing vertical transmission is crucial to population health, as up to 90% of neonates who are
76 exposed to HBV perinatally become chronic carriers, compared to only 5% of those exposed as
77 adults (3,4). Current recommended practice includes screening antenatal women for infection using
78 hepatitis B surface antigen (HBsAg), and risk-stratification based on further laboratory tests for
79 hepatitis B e-Antigen (HBeAg) and/or HBV DNA viral load (VL), which can be used to stratify the risk
80 of vertical transmission. PMTCT guidelines suggest administering a three dose HBV vaccine to all
81 infants with the first dose administered within 24 hours of birth and two other doses provided at 6
82 and 10 weeks respectively, as well as administering hepatitis B immunoglobulin (HBIG) to high risk
83 babies in the first day of life (5,6). Together, these strategies reduce the rate of vertical transmission
84 by 85%-95% (7), representing a crucial component of efforts towards HBV elimination (8–10).
85 However, breakthrough transmission can occur, especially among mothers with high HBV VL (11), in
86 settings where the first dose of vaccine is delayed, and where HBIG is not available. The use of
87 antivirals during pregnancy can therefore be included as an additional measure to decrease
88 transmission risk (12). Tenofovir disoproxil fumarate (TDF) has a track record of safety and efficacy in
89 this setting (13,14), and is included in some guidelines for HBV PMTCT (6,15).

90

91 HBV is endemic in Africa, with a prevalence of >8% in many populations (16,17). The risk of MTCT in
92 this continent is enhanced by lack of routine antenatal screening (18,19), deliveries taking place
93 outside healthcare facilities, delayed first dose of HBV vaccine until age six weeks by many vaccine
94 programmes, and limited access to TDF and HBIG (16,18). A meta-analysis of data from sub-Saharan
95 Africa (sSA) demonstrated a perinatal transmission rate of 38% among women who tested positive
96 for HBsAg and HBeAg, in the absence of any PMTCT interventions (20). An important priority for
97 Africa is to have affordable, accessible and sustainable PMTCT programmes that deliver screening

98 and treatment for antenatal mothers, and oversee timely administration of HBV birth vaccine for
99 their babies (8,21). Providing antiviral treatment for HBV PMTCT relies on HBV diagnosis, but
100 currently there is not widespread access to laboratory-based assays for HBsAg, HBeAg and HBV DNA
101 viral load, and many antenatal programmes do not provide routine HBV screening.

102

103 In order to identify the most cost-effective approach to HBV PMTCT we have evaluated antenatal
104 screening for HBV infection using standard laboratory assays for HBsAg and treating HBsAg-positive
105 women with TDF, based on South Africa as a model situation. In recognising the important role that
106 lateral flow assays can play in point of care testing (POCT) for HBsAg, we also assessed the cost
107 effectiveness of this approach to diagnostic screening (19,22). In South Africa, the majority of
108 pregnant women are not routinely screened for HBV infection, vaccination begins at six weeks of age
109 and HBIg is not available. Modelling the cost-effectiveness of HBV PMTCT interventions allows for a
110 combined analysis of clinical outcomes and potential budget impact, which is fundamental to inform
111 financial investment in HBV elimination programmes in sSA countries.

112

113 RESULTS

114 Cost-effectiveness of strategies for HBV PMTCT under base case assumptions

115 We modelled three different approaches to peri-partum TDF prophylaxis: **S1**: no screening or
116 antiviral therapy; **S2**: screening and antiviral prophylaxis for all women who test HBsAg-positive; **S3**:
117 screening for HBsAg, followed by HBeAg testing and antiviral prophylaxis for women who are HBsAg-
118 positive and HBeAg-positive (Fig.1). Based on the simulated scenario of 10,000 singleton pregnancies
119 in South Africa, with no antiviral therapy for HBV PMTCT (S1), and using a laboratory-based assay for
120 HBsAg detection, our model predicts 45 infants would be infected with HBV at age six months
121 (incidence 0.45%). If antiviral prophylaxis interventions are employed based on S2 and S3, this would
122 be reduced to 21 and 28 infants, (incidence 0.21% and 0.28%) respectively, at the cost of deploying
123 the intervention for the whole population. Compared to S1, cost per infection avoided was \$3,940
124 for S2, lower than for S3 which would be more costly and avoid a lower number of infections (Table
125 1; Fig.2).

126

127 **Table 1: Cost-effectiveness results under base case assumptions for screening for HBsAg using**
128 **laboratory-based assay on a simulated birth cohort of 10,000 live singleton infants.**

Strategy	Number of infant HBV infections ^a (95% CI)	Cost of deploying the intervention for the whole population ^b (n=10,000) in \$ (95% CI)	Incremental cost per infection avoided (\$)
S1	45 (29 - 121)	0	-
	21 (14 - 69)	94,571	3,940

S2		(94,487 - 95,509)	(compared to strategy S1)
S3	28 (19 - 76)	95,097 (94,980 - 97,244)	Dominated ^c (by strategy S2)

129

130 ^a World Health Organisation (WHO) criteria for HBV elimination states an aim of 90% reduction in new chronic
131 infection (1).

132 ^b Price of TDF estimated at \$2.48/month for strategies S2 and S3 (38).

133 ^c S3 is dominated due to both higher costs and higher infections compared to S2.

134 CI = confidence interval.

135

136

137 **Cost-effectiveness of strategies for HBV PMTCT under scenario analyses**

138 **(i) Antenatal screening for HBV infection using a rapid point of care test (POCT)**

139 POCT for HBsAg was cheaper in comparison to laboratory-based HBsAg assay (for S2: POCT \$23,401
140 vs lab test \$94,571 and for S3: POCT \$23,979 vs lab test \$95,097); (Table 1 & Table 2). Based on
141 reasonable assumptions about sensitivity of HBsAg detection via laboratory ELISA vs POCT (100%
142 and 97.6%, respectively(19)), from our simulated cohort, laboratory testing would detect all
143 maternal HBV infections (n=360 in our hypothetical cohort of 10,000), while the POCT approach
144 would detect 351 and miss nine cases of infection. This loss of sensitivity translates into a marginal
145 decrease in cost-effectiveness: the incremental cost per infection avoided is estimated at \$1,017
146 compared to \$978 if the test had 100% sensitivity.

147 **(ii) Recommended PMTCT guidelines: Universal birth dose vaccination and HBIG**

148 Incorporating universal birth dose vaccination and HBIG into our model, reduced the number of
149 infants infected at six months and cost per infection avoided (S2: 15 infants infected; S3: 24 infants
150 infected; and cost per infection avoided: \$3,152), (Table 2), compared to when PMTCT intervention
151 includes only TDF and HBV vaccination beginning at six weeks, (S2: 21 infants infected; S3: 28 infants
152 infected; and cost per infection avoided: \$3,940) (Table 1).

153 **(iii) HBV resistance to TDF**

154 When we accounted for potential HBV resistance to TDF, based on a prevalence of drug resistance
155 estimated at 0.8% (23), there was no change in incremental cost per infection avoided in S2.

156

157 **Table 2. Cost-effectiveness results of different PMTCT strategies under scenario analyses on a
158 simulated birth cohort of 10,000 live singleton infants.**

Strategy	Number of infant HBV infections ^a (95% CI)	Cost of deploying the intervention for the whole population (n=10,000) in \$ (95% CI)	Incremental cost per infection avoided (\$)
Scenario analysis (i): POCT testing			
S1	45 (28 – 119)	0	
	22 (14 – 73)	23,401	1,017

S2 ^b		(23,330 – 24,243)	(compared to strategy S1)
S3 ^b	28 (19 – 78)	23,979 (23,882 – 25,937)	Dominated ^c (by strategy S2)
Scenario analysis (ii): Universal birth dose vaccination			
S1	45 (28 - 123)	0	-
S2 ^d	15 (11 - 82)	94,571 (94,489 - 95,503)	3,152 (compared to strategy S1)
S3 ^d	24 (17 - 84)	95,097 (94,981 – 97,291)	Dominated ^c (by strategy S2)
Scenario analysis (iii): TDF resistance			
S1	45 (29 – 119)	0	-
S2 ^d	21 (14 – 71)	94,571 (94,496 – 95,515)	3,940 (compared to strategy S1)
S3 ^d	28 (18 – 79)	95,097 (94,980 – 97,252)	Dominated ^c (by strategy S2)

159

160 ^a World Health Organisation (WHO) criteria for HBV elimination states an aim of 90% reduction in new chronic
161 infection (1).

162 ^b Price of TDF estimated at \$2.42/month for strategies S2 and S3 when using POCT.

163 ^c S3 is dominated due to both higher costs and higher infections compared to S2.

164 ^d Price of TDF estimated at \$2.48/month for strategies S2 and S3 (38).

165 CI = confidence interval.

166

167 Data visualisation

168 We reproduced our decision model as an R Shiny application (source code available here:

169 <https://github.com/edward-burn/PMTCT-HBV-cost-effectiveness-analysis>. This can be used to
170 estimate cost-effectiveness of our three strategies using different input parameters. This will allow
171 the analysis to be re-run for the same comparison of strategies but in contexts where the
172 epidemiology of HBV infection, and costs of interventions, are different.

173

174 DISCUSSION

175 Antenatal screening and treating of pregnant women for HBV is not routinely performed in many
176 settings in sSA, despite the high population prevalence of HBV (19,24–27). In resource-limited
177 settings, screening and providing prophylactic TDF for all pregnant women who are HBsAg positive
178 may be the most efficient strategy, especially when using a POCT. These results are derived from a
179 theoretical model, and careful consideration is needed for application to different real world
180 settings.

182

183 Based on existing data for South Africa, screening and treating women with TDF from 28 weeks of
184 pregnancy to four weeks post-delivery reduces the number of infants with HBV at six months.

185 Previous studies have also reported on the safety and effectiveness of TDF for HBV PMTCT (13,28).

186 There is evidence for the cost-effectiveness of combining antiviral therapy during pregnancy with
187 HBV immunoprophylaxis, as highlighted by a systematic review and meta-analysis carried out in
188 China (29) and a study conducted in North America (30). Interestingly, a recent study in Thailand
189 conflicted with these findings by reporting no significant benefit of maternal TDF for PMTCT (31).
190 The lack of benefit from TDF in this case may be because all infants in the Thai study received birth
191 dose of both HBIG and HBV vaccine, followed by four additional doses of HBV vaccine; this enhanced
192 immunoprophylaxis probably accounts for the low rate of HBV transmission even among mothers
193 who did not receive TDF. However, it is difficult to apply any of these findings to sSA, which differs in
194 having limited (or no) access to HBIG, gaps in vaccine coverage, and delays in the first dose of HBV
195 vaccine (frequently until age six weeks) (16,18).
196
197 In this study, we provide a head-to-head economic analysis of simulated screening for HBsAg alone
198 vs. use of HBsAg in combination with risk stratification using HBeAg. Limited resources and
199 infrastructure have impeded antenatal diagnosis and treatment of HBV (27), and stratification of
200 HBsAg-positive antenatal women with HBV DNA level and/or HBeAg to determine eligibility for TDF
201 incurs further cost. Given that TDF is becoming more accessible for HBV treatment in Africa (10,32),
202 and has a well-established safety record as a result of antenatal use in HIV infection, treating all
203 HBsAg positive women should be safe and practical, as well as cost-effective. As this option is simple
204 to implement, it is therefore also most likely to be successful.
205
206 Given the high prevalence of HBV in Africa (27), POCT is an appealing route to increasing diagnosis
207 and therefore access to treatment. Although POCT proves advantageous on cost grounds, it is less
208 sensitive than laboratory assays. Furthermore, laboratory support remains key for monitoring
209 response to treatment, identifying and monitoring drug resistance, and evaluating prognosis.
210
211 There is a potential risk that increasing population exposure to TDF may increase selection of
212 resistance (32). However, the genetic barrier to TDF resistance is high, and more data are needed to
213 determine the prevalence and clinical significance of putative drug resistance mutations. When
214 accounting for an estimated background rate of HBV resistance to TDF, we show no change in the
215 cost per infection avoided. While we recognise that TDF resistance is not currently a significant
216 clinical concern, the modelling approach we have developed allows drug resistance to be factored
217 in.
218

219 Despite the potential for increased risk of HBV MTCT in HIV/HBV coinfection (33), there is evidence
220 to show that HIV has very little effect on HBV interventions (34). Since HIV guidelines now
221 recommend commencement of antiretroviral treatment as soon as HIV diagnosis is made (35), the
222 impact of HIV on HBV PMTCT is further reduced.

223

224 We used a simple model with only a single outcome measure, thus overlooking other possible
225 risks/benefits of antiviral therapy, including side-effects, drug interactions, and rebound hepatitis
226 after treatment cessation. However, extensive experience has led to the inclusion of TDF in first-line
227 regimens for HIV, including in pregnant women. Our base values were obtained from published
228 literature, but there are limited data for HBV epidemiology and transmission for most African
229 populations; we have acknowledged the lack of certainty around certain parameters by including
230 confidence intervals. HBV DNA testing is the gold standard approach to HBV diagnosis, but is often
231 not available in resource-limited settings; we therefore used HBeAg status as a surrogate marker to
232 represent infectivity and high VL and assumed 100% sensitivity for laboratory-based assays for
233 HBsAg and HBeAg. This does not account for occult infection and other false negatives and may lead
234 to an over-estimation of the cost-effectiveness of maternal TDF.

235

236 The assumption that the first dose of HBV vaccine is delayed until age six weeks is an over-
237 simplification: if birth dose vaccine is given more widely or targeted for infants born to HBsAg-
238 positive mothers, more new infections will be averted.

239

240 We used data for South Africa, but recognise that HBV prevalence is substantially higher in other SSA
241 settings (frequently reported at $\geq 8\%$, the WHO threshold for high endemicity (16,17)) and this may
242 influence the cost-effectiveness of proposed interventions. The low prevalence rate that we derived
243 from South Africa may be a reflection that many antenatal women themselves received HBV
244 vaccination as infants (if born after 1995). To facilitate cost-effectiveness simulations in other
245 settings where antenatal HBV prevalence might be higher, we have provided an on-line interactive
246 tool.

247

248 The findings of this study are applicable to settings where the cost of screening and treatment is
249 publicly funded; in situations where individuals meet the cost of their own screening and treatment,
250 our results cannot be applied to informing public health strategy. Our analysis did not consider the
251 need for healthcare and laboratory infrastructure to support our proposed interventions, costs of
252 monitoring pregnant women during TDF treatment, costs for clinical visits and counselling for

253 mothers testing HBsAg positive, leading to an underestimation of the total costs included in
254 providing robust PMTCT. However, this is offset by the potentially very substantial lifelong costs of
255 chronic HBV infection, both to individuals and to society, arising from morbidity and mortality
256 typically affecting young and middle-aged adults. This is difficult to quantify but leads to a
257 substantial burden of chronic disease with economic consequences for the health-care system, as
258 well as imposing financial consequences on families and society (21,36).

259
260 **Conclusion**

261 We have developed a simple, theoretical model that allows us to estimate the impact of providing
262 TDF to antenatal women in a lower/middle income country setting, either based on HBsAg status
263 alone, or incorporating risk-stratification with HBeAg. These strategies reflect safe, practical
264 interventions that could reasonably be deployed in many settings. There remains an urgent need for
265 more data to underpin the relevant epidemiology, risks of MTCT, and relative benefits of different
266 interventions in settings across sSA. In order to drive progress towards 2030 elimination targets,
267 sustained investment is required to drive improvements in clinical services, provide universal access
268 to antenatal screening, improve education of the public and health-care workers, and underpin
269 robust deployment of PMTCT interventions including vaccination and TDF therapy.

270
271 **METHODS**

272
273 **Target population and study perspective**

274 We used a hypothetical cohort of 10,000 pregnant South African women to evaluate the cost-
275 effectiveness of three different strategies for antiviral therapy with TDF:

276 **Strategy 1 (S1): No TDF prophylaxis.**

277 No pregnant woman is screened for HBsAg and therefore no HBV treatment is given
278 perinatally. To date, this is the situation in many resource-limited settings in sSA.

279 **Strategy 2 (S2): Screening and TDF prophylaxis for all women who test HBsAg positive.**

280 All pregnant women are screened for HBsAg; those who test positive are treated with TDF
281 from 28 weeks' gestation to four weeks post-partum.

282 **Strategy 3 (S3): Screening and TDF prophylaxis for women who are both HBsAg positive
283 and HBeAg positive.**

284 All pregnant women are screened for HBsAg; those who test positive are then screened for
285 HBeAg. Only those who are HBeAg positive are treated with TDF from 28 weeks' gestation to
286 four weeks post-partum.

288 We populated our model with data using a healthcare system perspective and therefore only
289 considered costs that would be directly incurred by the Department of Health (DOH). These costs
290 relate to screening and treatment of HBV infection during pregnancy. Individual patient information
291 was not included in this analysis. Ethics approval was not required for this study.

292

293 **Assumptions**

294 For the purposes of this analysis, we made a number of modelling assumptions:

- 295 • All pregnancies are singleton and result in the delivery of a live infant;
- 296 • All infants receive HBV vaccine at 6, 10 and 14 weeks, as per current standard practice in
297 South Africa (19). Even for babies born to mothers who are HBsAg+, birth dose vaccination is
298 not offered within 24 hours (due to lack of maternal screening);
- 299 • HBV screening uptake is 100% among antenatal women;
- 300 • HBsAg and HBeAg are tested using laboratory assays which are 100% sensitive and specific;
- 301 • Infants born to mothers who were HBsAg negative were assumed also to be HBsAg negative;
- 302 • We made assumptions around our point estimates due to lack of data.

303

304 **Theoretic modelling approach**

305 A decision tree providing a framework for comparison of the three strategies is shown in Fig. 1. The
306 decision tree considers the period covering weeks 28 through 40 of gestation up to six months post-
307 partum. Model structure was the same for all strategies. HBsAg-positive mothers had a defined
308 probability of being HBeAg positive or negative; these probabilities were the same for all strategies.
309 Children whose mothers were HBsAg positive had a probability of being HBsAg positive themselves
310 (i.e. a case of MTCT). This probability depended on whether the mother was also HBeAg positive and
311 whether antiviral prophylaxis was received by the mother during pregnancy, which varied between
312 strategies.

313

314 **Measurement of effectiveness**

315 Table 3 shows parameters used for input in our model. We searched the published literature, and
316 identified four studies from within the last six years that reported the prevalence of HBV infection
317 among pregnant women in South Africa (19,24–26). To calculate prevalence of HBV infection, we
318 combined the total number of women from each study who tested HBsAg-positive and divided these
319 by the total number of individuals included in these cohorts. From these pooled data, the overall
320 prevalence of HBsAg among pregnant women was 3.6% (129/3614). HBeAg status was reported for
321 126 of these 129; the prevalence of HBeAg among HBsAg+ women was 29/126 (23%).

322

323 We derived point estimates for perinatal transmission with and without antiviral therapy during
324 pregnancy from a published systematic review and a meta-analysis (13,20). In the absence of
325 intervention (HBV vaccination, HBIG and/or antiviral therapy), the perinatal transmission rate for
326 HBsAg+/HBeAg+ mothers in sSA was estimated at 38%, and for HBsAg+/HBeAg- mothers was 4.8%
327 (20). Due to lack of data, we used these estimates in our model, although we assumed that infants
328 were vaccinated starting at the age of six weeks.

329

330 There is only one randomised control trial that examines the efficacy of TDF on HBV PMTCT, in which
331 perinatal TDF reduced the risk of infant HBsAg seropositivity by 71% (12). However, data from a
332 systematic review and meta-analysis estimate this figure as 77% (13). We therefore reduced the
333 perinatal transmission rate for women receiving no TDF by 71% to obtain a point estimate for
334 perinatal transmission rate for those receiving TDF peripartum prophylaxis; these were estimated at
335 11.1% for HBeAg-positive women and 1.4% for HBeAg-negative women. We accounted for
336 uncertainty around point estimates, as the original study was conducted in China and with a
337 different protocol (combining TDF during pregnancy in combination with birth dose vaccine and
338 HBIG).

339

340 **Table 3: Parameters used for input into a model of cost-effectiveness of tenofovir for PMTCT in**
341 **South Africa, based on a simulated cohort of 10,000 antenatal women and their babies**
342

Parameter	Point estimate	Uncertainty (Lower bound - Upper bound)	Source (references)
p1: Probability of mother being HBsAg+	3.6%	3.1% - 7.4% ^b	(19,24–26)
p2: Probability of mother who is HBsAg+ being HBeAg+	23%	16.7% - 42.9% ^b	(19,24–26)
p3: Probability of mother who is HBsAg+ and HBeAg+ having child who is HBsAg+ (no PMTCT)	38.3%	7.0 – 74.4% ^b	(20)
p4: Probability of mother who is HBsAg+ and HBeAg- having child who is HBsAg+ (no PMTCT)	4.8%	0.1 – 13.3% ^b	(20)
Relative risk reduction (efficacy) of TDF	71%	26-89%	(13)
Antiviral adherence	73.5%	69.3% - 77.5%	(37)
S2: Cost of diagnostics: laboratory test for HBsAg	\$9.1 per mother		(42)
S3: Cost of diagnostics: laboratory test for HBsAg and HBeAg	\$9.1 per mother (HBsAg test) + \$9.1 for HBsAg+ mother (HBeAg test)		(42)

S2: Cost of diagnostics: POCT for HBsAg	\$2 * all mothers	(42)
S3: Cost of diagnostics: POCT for HBsAg+ and laboratory test for HBeAg+	\$2 * for all mothers (HBsAg test) + \$ 9.1 * for all HBsAg+ mothers (HBeAg test)	(42)
Treatment cost: monthly cost of TDF, applied to all HBsAg+ women (S2) or only to HBsAg+/HBeAg+ women (S3)	\$2.48 ^a /month	(38)
POCT sensitivity	97.6%	(19)
Estimated relative risk reduction (efficacy) of TDF when combined with birth dose vaccine and HBIG	90% 85% – 95%	(7)
Prevalence of TDF resistance	0.08%	(23)

343

344 ^aTo cover the cost of TDF treatment from 28 weeks' gestation to 4 weeks post-delivery, we multiplied the cost
345 for one month by four. A triangular distribution allows for uncertainty in all probabilities (except cost which we
346 assume is fixed).

347 ^bThe uncertainty values for p1 and p2 were derived from studies that had the lowest and highest HBsAg
348 prevalence rates, representing lower and higher bounds respectively; whereas uncertainty values for P3 and
349 P4 were from 95% confidence intervals around the mean value.

350

351

352 Due to lack of data on HBV antiviral adherence rates among pregnant women in sSA, we used HIV
353 antiretroviral adherence rate among women during and after pregnancy, obtained from a published
354 systematic literature review which included studies from low-income, middle-income, and high-
355 income countries (37); this is estimated at 73.5%. We incorporated an expected adherence of 73.5%
356 into the model, assuming that those mothers who didn't adhere would incur the full cost of
357 treatment but would have the same probability of transmission as un-treated women.

358

359 **Outcomes**

360 Our outcome was the cost per HBV infection avoided among infants at the age of six months. This
361 outcome was selected because it is quantifiable, clinically relevant and could be easily compared
362 between strategies.

364

365 **Estimating costs**

366 We derived costs for laboratory assays for HBsAg and HBeAg, and POCT, from a 2015 price list
367 produced by National Health Laboratory Services (NHLs) and DOH, South Africa. We used the cost of
368 TDF from International Medical products price guide for year 2015 (38). We converted the price of
369 HBsAg laboratory assay (R 108.86), HBsAg POCT (R18), HBeAg laboratory assay (R108.86) and HBV
370 DNA test (R1173.32) from South African Rand to USD; 1 Rand = 0.083 USD as at 1st May 2015. HBsAg

371 screening cost applied to all women in S2 and S3; HBeAg screening costs applied to women who
372 tested positive for HBsAg in S3. TDF costs applied to all women who tested positive for HBsAg in S2,
373 and women who tested positive for both HBsAg and HBeAg in S3.

374

375 **Scenario analysis**

376 We assessed the impact of three additional scenarios, estimating the number of MTCT cases, costs
377 and incremental cost per infection avoided in each case:

378

379 **(i) Antenatal screening for HBV infection using a rapid point of care test (POCT)**

380 We estimated the cost-effectiveness of using a POCT for HBsAg screening, based on a POCT
381 sensitivity of 97.6% and specificity of 100%, compared to laboratory ELISA HBsAg testing as the gold
382 standard (19). We incorporated this into the model by reassigning the proportion of women
383 expected to test falsely HBsAg- using a POCT into the untreated group and removing the cost of TDF
384 treatment for these individuals.

385

386 **(ii) Recommended PMTCT guidelines: Universal birth dose vaccination and HBIG**

387 To assess the cost-effectiveness of antenatal screening and treating of HBsAg-positive women with
388 TDF in combination with universal birth dose vaccine and HBIG, we estimated that perinatal
389 transmission rate will be reduced by 90% (7). To incorporate the impact of TDF in our cohort, we
390 therefore reduced the perinatal transmission rate by 90%; MTCT rates were thus estimated for
391 HBsAg+ women who are HBeAg+ and HBeAg- at 3.8% and 0.48% respectively.

392

393 **(iii) HBV resistance to TDF**

394 In order to consider the possible impact of drug resistance on the PMTCT strategies outlined here,
395 we estimated the prevalence of TDF resistance based on HBV sequences retrieved from the HBV
396 database (<https://hbvdb.ibcp.fr/HBVdb/>) (23) accessed on the 18th April 2018. The numerator was
397 the total number of sequences with mutations associated with reduced sensitivity/resistance to TDF
398 (rtA194T, rtN236T, rtS78T), (39,40) and the denominator was the total number of sequences
399 available in the database (49/6287, 0.8%). This prevalence was incorporated into the model by re-
400 assigning 0.8% of those receiving TDF into the untreated category (as although they receive the
401 drug, resistance would render this functionally equivalent to no treatment).

402

403 **Analytic methods and definitions**

404 We used the following definitions:

405 • A strategy was 'dominated' if it had a higher expected cost and more predicted cases of HBV
406 MTCT compared to an alternative strategy.

407 • The incremental cost per HBV infection avoided was determined by dividing the difference
408 in cost between two strategies over the difference in number of infections (41).

409 We compared the strategies by first applying decision rules to eliminate any strategies which were
410 dominated by others, and then estimated the incremental cost per infection avoided for the
411 remaining strategies.

412

413 The combined effect of uncertainty in probability estimates was assessed using probabilistic
414 sensitivity analysis, with 1000 Monte Carlo simulations run. We used triangular distributions to
415 approximate Beta distributions for probabilities. Triangular distributions required a lower and upper
416 bound, with the peak taken as the expected (mean) value. The impact of uncertainty is shown on a
417 cost-effectiveness plane, where sets of incremental costs and number of infections avoided are
418 plotted for S2 and S3, relative to S1.

419

420 **Standardised criteria**

421 Our analysis conforms to the standardised criteria for economic evaluations of health interventions
422 (our CHEERS checklist can be reviewed as Supplementary Table S1 on-line:
423 <https://doi.org/10.6084/m9.figshare.7265582.v1>

424

425 **CONFLICT OF INTEREST:**

426 We have no conflicts of interest to declare.

427

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434

435 **AUTHORS' CONTRIBUTIONS:**

- 436 • Conceived the study: JM, MA, PCM, CRT
- 437 • Literature review: JM
- 438 • Assimilated data to feed into the model : JM, DG, PCM
- 439 • Analysed the data : JM, EB, RPV, PCM
- 440 • Wrote the manuscript: JM, EB, PCM
- 441 • Edited and approved the final manuscript : all authors

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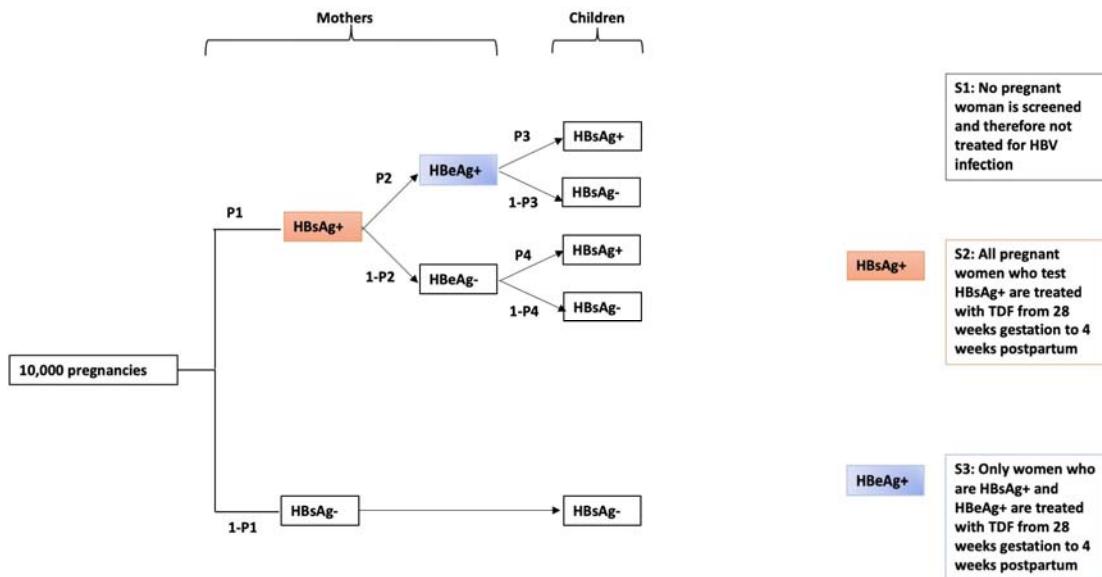
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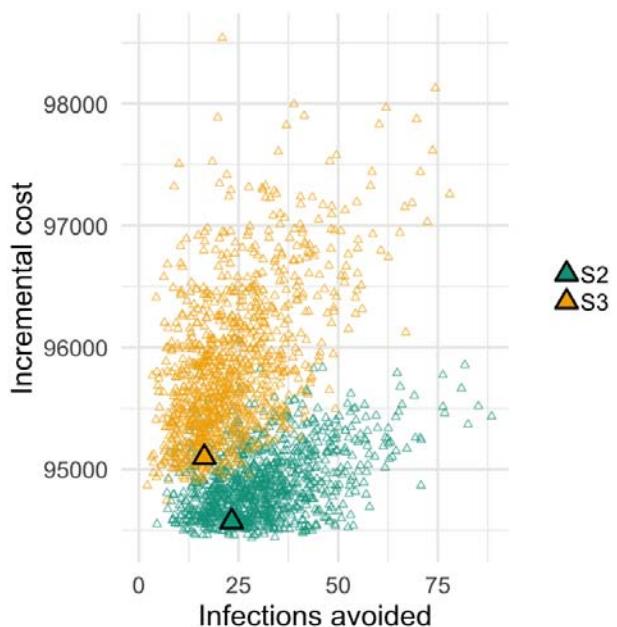
548 FIGURE LEGENDS



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Fig.1: Decision tree showing possible approaches to evaluation of HBV infection in a simulated cohort of 10,000 antenatal women, and in their infants at age six months. P1 is the probability of women testing positive for HBsAg; P2 is the probability of women who are positive for HBsAg also testing positive for HBeAg; P3 is the probability of infants born to HBsAg+/HBeAg+ mothers testing HBsAg+ at 6 months of age; P4 is the probability of infants born to HBsAg+/HBeAg- mothers testing HBsAg+ at 6 months of age. HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; TDF: Tenofovir disoproxil fumarate.

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560

561 **Fig.2: Cost-effectiveness (CE) plane for HBsAg using laboratory assay in a simulated cohort of**
562 **10,000 antenatal women.**

563 **S2:** All pregnant women are screened for HBsAg; those who test positive are treated with TDF from
564 28 weeks' gestation to 4 weeks post-partum.

565 **S3:** All pregnant women are screened for HBsAg, those who test positive are screened for HBeAg.
566 Only those who are HBeAg positive are treated with TDF from 28 weeks' gestation to 4 weeks post-
567 partum.

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