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Mortality in relation to hepatitis B virus (HBV) infection status among HIV-HBV coinfecting patients in sub-Saharan Africa after immediate initiation of antiretroviral therapy Running head: HBV profiles and mortality in HIV

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► **To cite this version:**

Gérard Menan Kouamé, Amir M Mohareb, Audrey Gabassi, Delphine Gabillard, Raoul Moh, et al.. Mortality in relation to hepatitis B virus (HBV) infection status among HIV-HBV coinfecting patients in sub-Saharan Africa after immediate initiation of antiretroviral therapy Running head: HBV profiles and mortality in HIV. *Journal of Viral Hepatitis*, 2020, 10.1111/jvh.13461 . hal-03146766

HAL Id: hal-03146766

<https://hal.sorbonne-universite.fr/hal-03146766v1>

Submitted on 19 Feb 2021

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1 **Mortality in relation to hepatitis B virus (HBV) infection status among HIV-HBV co-**
2 **infected patients in sub-Saharan Africa after immediate initiation of antiretroviral**
3 **therapy**

4

5 **Running head:** HBV profiles and mortality in HIV

6

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56 **Key Words:** HIV, hepatitis B virus, CD4+ cell count, mortality, sub-Saharan Africa

57

58 **Word count:** Abstract – 250/250, Text – 3425/3500

59

60 **Funding:** This work was supported by the Agence Nationale de Recherches sur le
61 SIDA et les hépatites virales (ANRS), Paris, France. GMK also received doctoral
62 funding from the ANRS. AMM received funding from National Institutes of Health NIAID
63 T32AI007433 and NIAID R37AI058736. EPH received funding from National Institutes
64 of Health NHLBI K01HL123349. Its contents are solely the responsibility of the authors
65 and do not necessarily represent the official views of the NIH.

66 **ABSTRACT**

67

68 **Background**

69 It is unknown how past and active hepatitis B virus (HBV) infection affect
70 immunorecovery and mortality in people with HIV who initiate tenofovir-based anti-
71 retroviral therapy (ART).

72

73 **Methods**

74 Using data collected between 2008- 2015, we studied people with HIV in sub-Saharan
75 Africa initiating immediate ART in the Temprano randomized control trial. We classified
76 participants into HBV groups at ART-initiation: hepatitis B surface antigen (HBsAg)-
77 positive with HBV DNA ≥ 2000 IU/mL; HBsAg-positive with HBV DNA < 2000 IU/ml;
78 isolated HBcAb-positive; resolved infection (HBsAb-positive/HBcAb-positive); and HBV
79 non-immune/vaccinated (HBcAb-). We compared square-root CD4-cell count increases
80 using a mixed-effect, non-linear regression adjusted for age, sex, baseline CD4 cell
81 count, and HIV RNA. We compared all-cause mortality using Bayesian parametric
82 survival regression.

83

84 **Results**

85 Among 879 participants, 24 (2.7%) had HBsAg with high HBV DNA, 76 (8.6%) HBsAg
86 with low HBV DNA, 325 (37.0%) isolated anti-HBcAb, 226 (25.7%) resolved HBV
87 infection, and 228 (25.9%) HBV non-immune/vaccinated. We found no significant
88 difference in CD4 cell increases between the four HBV-infection groups after adjustment

89 ($p=0.16$). Participants with HBsAg and high HBV DNA had the highest incidence of all-
90 cause mortality [1.9/100 person-years, 95% Credible Interval (CrI)=1.0-3.4]. By
91 comparison, incidence rates of mortality were reduced by 57% (95%CrI=-79%,-13%),
92 60% (95%CrI=-82%,-12%), and 66% (95%CrI=-84%,-23%) in those who had isolated
93 anti-HBcAb-positive, resolved HBV infection, and HBV non-immune/vaccinated,
94 respectively.

95

96 **Conclusion**

97 Individuals with HIV and past HBV infection or isolated anti-HBcAb-positive serology,
98 much like HBV non-immune/vaccinated, experience lower mortality than those with
99 HBsAg and high HBV DNA. Additional HBV-related management would not be
100 necessary for these individuals.

101 INTRODUCTION

102

103 The burden of hepatitis B virus (HBV) co-infection among people with HIV remains high
104 in sub-Saharan Africa, despite effective strategies to prevent and treat both infections.

105 The prevalence of HBV, as determined by hepatitis B surface antigen (HBsAg), among
106 people with HIV is approximately 10% worldwide¹ and is even higher in many parts of
107 sub-Saharan Africa.^{1,2} Antiretroviral therapy (ART), particularly with regimens containing
108 HBV-active drugs such as tenofovir disoproxil fumarate (TDF), are able to suppress
109 both HIV and HBV replication.³ The differential mortality benefit of TDF-containing ART
110 in HIV-HBV co-infected versus HIV mono-infected patients has been uncertain in
111 epidemiological studies to date.⁵

112

113 Many observational studies have shown no difference in the HIV virologic response to
114 ART among people with HIV-HBV co-infection compared to HIV mono-infection.⁶⁻⁸ In
115 Nigeria, people with HIV-HBV co-infection, including those with positive Hepatitis B e-
116 antigen (HBeAg), had comparable rates of HIV virologic suppression after 48 weeks of
117 ART compared to those with HIV mono-infection.⁹ These data support no difference in
118 HIV suppression between people with HIV-HBV co-infection and HIV mono-infection,
119 even at varying degrees of HBV activity. However, conflicting data are available
120 regarding the differences in immunologic recovery following ART initiation between
121 people with HIV-HBV co-infection and HIV mono-infection. Some studies have shown
122 impaired CD4 count recovery among people with HIV-HBV co-infection initiating ART,⁸

123 others have shown no difference,^{7,10} and some have even suggested accelerated
124 immunorecovery when compared to people with HIV mono-infection.^{6,11}

125

126 Furthermore, individuals with HIV-HBV co-infection are at strongly increased risk of all-
127 cause mortality compared to those who are HIV mono-infected in the absence of

128 effective ART.¹² Since higher levels of both HIV and HBV replication are individually

129 associated with higher mortality rates^{13–15}, the antiviral activity of TDF-containing ART

130 would be assumed to reduce mortality rates in people with HIV-HBV co-infection.

131 However, some studies in treated co-infected individuals have demonstrated higher

132 mortality compared to those with HIV mono-infection, even after adjustment for HIV-

133 related factors^{10,16–20}, and thus reduced viral replication might not fully translate to lower

134 rates of mortality.

135

136 A number of factors may explain these heterogeneous findings. One of the more

137 important reasons could be that some of these studies defined the presence or absence

138 of HBV infection solely on the basis of HBsAg. Data are indeed emerging on the

139 prevalence of other HBV profiles in HIV co-infection: namely, isolated Hepatitis B core

140 antibody (HBcAb) positivity; occult HBV infection (presence of HBV DNA without

141 HBsAg); and resolved infection (presence of HBcAb and HBV surface antibody

142 [HBsAb]).^{6,17,21–23} To build further on these data, our objective was to determine the

143 trajectory of immunologic recovery as measured by CD4+ cell count and the rate of all-

144 cause mortality among people with HIV initiating ART in Côte d'Ivoire according to the

145 following different HBV serologic profiles: active HBV infection (including with high and

- 146 low HBV DNA); resolved HBV infection; isolated anti-HBcAb antibody; non-infected/
147 non-immune to HBV; and vaccinated against HBV.

148 **METHODS**

149

150 **Participants and study design**

151 We conducted a secondary analysis of participants in the Temprano ANRS 12136
152 study, a randomized controlled, 2x2 factorial, superiority trial, conducted in nine clinics
153 in Côte d'Ivoire. The trial design and results have been previously reported²⁴. In brief,
154 from March 18, 2008 and July 16, 2012, patients were included based on the following
155 criteria: newly diagnosed HIV infection, 18 years of age or older, CD4+ count below 800
156 cells/mm³, and not yet eligible for ART-initiation according to concomitant guidelines
157 from World Health Organization (WHO) guidelines²⁵⁻²⁷ Patients were excluded if they
158 had active tuberculosis (TB) or severe liver disease, defined by plasma aspartate
159 aminotransferase (AST) or alanine aminotransferase (ALT) levels more than 4 times the
160 upper limit of normal (ULN) or any other severe liver diseases determined by the treating
161 physician.

162

163 **Trial arms and treatment**

164 Participants were randomly assigned to one of four arms: two “deferred ART” arms
165 (arms 1 and 2), in which ART initiation was deferred until patients met concurrent WHO
166 starting criteria; and two “immediate ART” arms (arms 3 and 4), in which ART was
167 initiated immediately on inclusion. In arms 2 and 4, participants received 6-month
168 isoniazid prophylaxis for tuberculosis. First-line ART regimen in all arms contained
169 TDF/emtricitabine. The third agent was preferably efavirenz. In the case of

170 contraindication to efavirenz, the third drug was either zidovudine or lopinavir/ritonavir.
171 In this analysis, we only included individuals randomized to the “immediate ART” arms.

172

173 **Follow-up**

174 We analysed data collected between March 18, 2008 and Jan 5, 2015. The baseline
175 time point was the time of randomization. All participants were followed for 30 months.
176 The first Temprano study participant completed 30 months of follow-up in September
177 2010. From this date, all patients who reached the 30-month visit were asked to
178 continue follow-up in a post-trial phase (PTP) until the last patient completed their 30-
179 month trial visit (closing date: 5 January 2015). Both the Temprano study and PTP had
180 similar procedures: patients had quarterly visits at their healthcare center and were
181 requested to present for additional visits any time they encountered a medical event;
182 CD4+ count and plasma HIV-1 RNA were measured every 6 months; consultations,
183 CD4+ count, viral load, and antiretroviral drugs were free of charge; and patients who
184 did not present at a trial visit were traced by experienced social workers. In the
185 Temprano trial, transportation for unscheduled visits, consultations, hospitalization, and
186 nonantiretroviral drugs were free of charge when morbidity events occurred during the
187 trial. In PTP, patients were required to pay out-of-pocket, similar to other patients
188 followed in routine care at the same center.

189

190 **Study parameters**

191 Blood tests including CD4+ count, plasma HIV-1 RNA, and serum transaminases were
192 performed at baseline and every six months. HBsAg serology was performed at

193 baseline using an enzyme-linked immune-assay (ELISA) test (Monolisa® AgHBS Ultra,
194 Bio-Rad, Marnes la Coquette, France). From frozen samples stored at -80°C, anti-
195 HBcAb and anti-HBsAb serology were also performed using an ELISA test (Monolisa®
196 anti-HBs plus, anti-hepatitis B core antibody-anti-HBc-plus, Bio-Rad). HBV infection
197 status was based on AASLD HBV guidance and was defined as follows: HBsAg-
198 positive; isolated anti-HBcAb+; resolved HBV infection (HBcAb and HBsAb positive);
199 non-immunized (HBcAb negative and HBsAb negative); vaccinated (HBcAb negative
200 and HBsAb positive) (Box 1).

201
202 Baseline HBV DNA viral loads were quantified for HBsAg-positive (to assess HBV
203 activity) and non-immunized individuals (to assess seronegative occult HBV infection),²⁸
204 using an in-house polymerase chain reaction (PCR)-based assay (QuantiFast SYBR®
205 Green PCR kit, detection limit: 12 copies/mL; Qiagen, Courtaboeuf, France; Light Cycler
206 480; Roche, Boulogne-Billancourt, France) or a commercially-available PCR assay
207 (COBAS®Amplicor HBV Monitor, detection limit: 60 IU/mL; Roche Diagnostics, Meylan,
208 France). To ensure comparability between assays, viral loads were reported in IU/mL
209 [conversion factor: 1 IU/mL=2.8 copies/mL].²⁹

210

211 **Statistical analysis**

212 Patient characteristics at baseline were compared across HBV-infection groups using
213 Pearson's χ^2 or Fisher's Exact tests for categorical variables and Kruskal-Wallis for
214 continuous variables. Follow-up time began at baseline and ended at death, loss to
215 follow-up (LTFU), or 5 January 2015, whichever occurred first.

216

217 To examine the effect of HBV status on immunologic recovery, we used mixed-effect,
218 non-linear regression and modeled increase in CD4+ cell count as a square-root
219 function over time. We obtained stratum-specific estimates by including an interaction
220 term between HBV-infection group and follow-up time. We used random-intercept and
221 random-coefficient for time to account for variation between individuals with respect to
222 CD4+ T-cell count at ART-initiation and during follow-up, with unstructured covariance
223 between random-intercept and random-coefficient. Models were both unadjusted and
224 adjusted for CD4+ cell count at ART-initiation, HIV RNA level at inclusion (>5.0 versus
225 $\leq 5.0 \log_{10}$ copies/mL), age (>35 versus ≤ 35 years), and sex.

226

227 To examine the effect of HBV status on all-cause mortality, we used parametric survival
228 regression with exponentially distributed survival functions and modeled the proportional
229 hazards of mortality during follow-up. As a reference group, we used HBsAg-positive
230 individuals in a first model and HBsAg-positive individuals with HBV DNA ≥ 2000 IU/mL
231 in a second model. The threshold of 2000 IU/mL was pre-specified in our analysis
232 based on levels corresponding to active infection and treatment indication among HBV
233 mono-infected individuals.³⁰

234

235 Because few deaths were expected, we supposed that parameter estimates from
236 standard regression techniques could be exaggerated and uncertain.³¹ To minimize this
237 bias, we used a penalized regression approach whereby uncertain estimates from the
238 data are pulled towards more realistic ones assumed from prior knowledge.³² Briefly,

239 survival models were fit using a Bayesian approach. For each HBV infection group, a
240 prior distribution of hazards ratios (HRs) was first specified based on the anticipated
241 strength of association (Supplementary Table 1).³³ These distributions were assigned
242 from a previous analysis of the Temprano study.¹⁷ Since the intercept of this model
243 estimates the incidence rates (IR) of the reference group, the prior distribution of this
244 parameter was based on IR from previous studies of HIV-HBV co-infected individuals,
245 overall and with high HBV-DNA viral loads,^{17,34} estimated at 1.0 per 100 person-years
246 [95% credible interval (CrI) 0.3-4.0] and 2.0 per 100 person-years (95%CrI=0.5-8.0),
247 respectively. Using these priors together with the data, a posterior distribution of HRs
248 was estimated with Markov Chain Monte Carlo methods from the “bayes” prefix
249 commands in STATA. The median of this distribution defined the parameter estimate
250 (termed “posterior-HR”) and their 2.5% and 97.5% quantiles defined the 95%CrI. Since
251 posterior-HR need to be interpreted with the priori distributions, both prior-HR and
252 posterior-HR are provided.

253

254 All reported *p*-values were two-sided and no adjustments for multiple comparisons were
255 applied. Statistical analyses were performed using STATA (v15.0, College Station,
256 Texas).

257

258 **Sensitivity analyses**

259 Since specification of the prior distribution can influence posterior HRs,³⁵ we repeated
260 the analysis using (1) non-informative priors and (2) a different prior HR distribution
261 whose effect size was weaker.

262

263 **Funder, registration, and ethics**

264 The Temprano trial protocol was approved by the Côte d'Ivoire National Ethics

265 Committee for Health Research. It was registered at Clinical Trials.gov (NCT00495651).

266 Signed informed consent was provided prior to participating in the trial. The sponsor had

267 no role in the conduct of the study and interpretation of the data.

268 **RESULTS**

269

270 **Description of the study population**

271 In the Temprano trial, 1032 individuals were randomized to receive immediate ART. Of
272 them, 153 (14.8%) did not have available serum samples to determine HBV-infection
273 group and were excluded. In total, 879 participants were included in this secondary
274 analysis. Clinical characteristics were similar between those who were included versus
275 those who were not, except that included individuals had lower CD4+ cell counts and
276 more advanced WHO clinical stage (Supplementary Table 2).

277

278 One hundred (11.4%) participants were HBsAg-positive (24 and 76 with HBV DNA
279 ≥ 2000 IU/mL and HBV DNA < 2000 IU/mL, respectively). Of the other HBV-infection
280 groups, 325 (37.0%) had isolated anti-HBcAb positive serology, 226 (25.7%) had
281 resolved infection, 203 (23.1%) were non-immunized/ non-infected, and 25 (2.8%) were
282 vaccinated. All non-immunized individuals were tested for HBV DNA viral loads, and
283 none had detectable HBV DNA. Due to the few numbers of vaccinated individuals,
284 these individuals were grouped with non-immunized individuals in further analysis.

285

286 Baseline characteristics are compared across HBV infection groups in Table 1. HBsAg-
287 positive individuals were more frequently male, had higher ALT levels, including a
288 higher proportion with ALT greater than the upper limit of normal (ULN), yet this was
289 mostly observed in those with HBV-DNA ≥ 2000 IU/mL [versus < 2000 IU/mL,
290 respectively: median ALT: 32 versus 19 IU/mL ($p=0.002$); proportion with ALT $> ULN$:

291 37.5% versus 18.4% ($p=0.05$]). HBsAg-positive and isolated anti-HBc antibody-positive
292 individuals were more likely to be treated with LPV/r as a third agent compared to the
293 other HBV subgroups. Non-immunized/ vaccinated individuals were younger than
294 participants from all other groups.

295

296 **Immunologic Recovery during antiretroviral therapy**

297 Participants were followed for a median of 61 months (IQR=46-71). Median follow-up
298 was no different between HBV-infection groups ($p=0.26$). At baseline, mean CD4+
299 count was lowest in the isolated anti-HBc antibody-positive group ($460/\text{mm}^3$,
300 $95\%CI=445-476$) and highest in the non-immunized/ vaccinated group ($483/\text{mm}^3$,
301 $95\%CI=464-502$). At the end of follow-up, mean CD4+ count was lowest in the HBsAg-
302 positive group ($691/\text{mm}^3$, $95\%CI=639-744$) and remained highest in the non-immunized/
303 vaccinated group (757 mm^3 , $95\%CI=717-797$). Based on the mixed-effect non-linear
304 regression model, there was no significant difference in CD4+ cell increase during
305 treatment between HBV-infection groups, both unadjusted ($p=0.18$) and adjusted for
306 baseline CD4+ count, HIV RNA, age, and sex ($p=0.16$) (Figure 1A). No significant
307 difference was observed when further stratifying on baseline HBV-DNA level ≥ 2000 and
308 $< 2000 \text{ IU/mL}$: unadjusted, $p=0.15$; adjusted, $p=0.13$ (Figure 1B).

309

310 **Incidence of all-cause mortality with respect to HBV-infection status**

311 During follow-up, there were 37 deaths. IRs and $95\%CrI$ across HBV infection groups
312 (obtained from the Bayesian exponential model) are provided in Figure 2. When
313 compared to HBsAg-positive individuals (modeled $IR=1.3/100PY$, $95\%CrI=0.7-2.1/100$

314 PY) (Table 2), mortality IRs were reduced by 32% (95%CrI=-67%, +28%) in those with
315 isolated anti-HBcAb-positive serology, 35% (95%CrI=-72%,+22%) in those with
316 resolved infection, and 43% (95%CrI=-75%, +11%) in those who were non-immunized
317 or vaccinated (modeled IR=0.7/100PY, 95%CrI=0.3-1.5/100PY). When compared to
318 HBsAg-positive individuals with HBV-DNA ≥ 2000 IU/mL (modeled IR=2.0/100PY,
319 95%CrI=1.0-3.4/100PY) (Table 2), mortality IRs were reduced by 56% (95%CrI=-83%,
320 +3%) in those with HBsAg-positive serology and HBV-DNA <2000 IU/mL, 57%
321 (95%CrI=-79%, -13%) in those with isolated anti-HBcAb-positive serology, 60%
322 (95%CrI=-82%,-12%) in those with resolved infection, and 66% (95%CrI=-84%, -23%)
323 in those who were non-immunized/ vaccinated (modeled IR=0.7/100PY, 95%CrI=0.3-
324 1.5/100PY).

325

326 **Sensitivity analysis**

327 In the model with HBsAg-positive individuals without stratification on HBV DNA levels,
328 the posterior-HRs were slightly closer to one (i.e., reductions in mortality were slightly
329 attenuated) when using non-informative priors (Supplementary Table 3). In the model
330 with HBsAg-positive individuals stratified on HBV DNA levels, the posterior-HRs were
331 also closer to one when using a prior with a weaker effect (Supplementary Table 4),
332 with only non-immunized/ vaccinated individuals having a 95%CrI falling below 1. The
333 posterior-HRs were similar when using non-informative priors on this model, yet 95%CrI
334 were much wider (Supplementary Table 3).

335 **DISCUSSION**

336

337 In this analysis of people with HIV initiating ART in Côte d'Ivoire, participants in different
338 HBV subgroups exhibited no difference in immunologic recovery over the first five years
339 of ART when compared to participants with HIV mono-infection. However, adults with
340 high baseline HBV DNA levels had higher rates of all-cause mortality than other HBV
341 subgroups, including HBV non-immunized/vaccinated, by the end of the follow-up
342 period. These findings provide important information on the clinical evolution of people
343 with HIV with respect to their HBV infection status.

344

345 The first notable finding in this analysis is the distribution of HBV serologic profiles
346 among people with HIV. Among individuals with sufficient stored blood for testing, more
347 than 75% had evidence of past or present infection. The largest HBV subgroup in this
348 cohort was comprised of people with isolated anti-HBcAb (37.0%), followed by resolved
349 HBV infection (25.7%) and HBV non-immune/vaccinated (23.1%). This distribution is
350 comparable to a prior cross-sectional study sampling patients from HIV clinics in Côte
351 d'Ivoire[21]. In cohort studies of people with HIV in the U.S., where HBV is not endemic,
352 the most common HBV subgroup noted was non-immune/vaccinated (66-74%) followed
353 by resolved HBV infection (20-23%) and isolated anti-HBcAb (3.5-6%)[6,17]. Possible
354 explanations for these observed subgroup differences among people with past or
355 present HBV infection include: (1) timing of HBV infection, with co-infected individuals in
356 sub-Saharan Africa being mostly infected with HBV long before HIV infection and co-
357 infected individuals in the U.S. more likely to be in the "window phase" of acute HBV

358 infection; (2) immunologic differences, which may produce a different proportion of
359 individuals due to the timing of waning anti-HBsAb levels following resolved HBV
360 infection; and to a lesser extent (3) genetic differences in HBV, which may result in
361 HBsAg that escapes detection due to mutations on the surface gene.³⁶

362

363 We found that no participant in this cohort had seronegative occult HBV infection on
364 study enrolment, defined as a detectable HBV DNA without HBsAg, anti-HBcAb, and
365 anti-HBs antibodies. The estimated prevalence of seronegative occult HBV among
366 people living with HIV ranges from 0% to 18%, depending on the study.³⁷⁻⁴⁰ Compared
367 to other studies, our cohort had a relatively high median CD4+ count and 90% were in
368 WHO Stage I or II disease on enrolment, indicating a less immunosuppressed
369 population able to control intrahepatic HBV replication more effectively.²⁷ Testing
370 constraints limited our ability to determine the prevalence of seropositive occult HBV
371 (detectable HBV DNA without HBsAg but with anti-HBcAb). However, even people with
372 seropositive occult HBV infrequently have elevated HBV DNA so we would not expect
373 them to incur a higher mortality rate than those who are HBsAg positive with low HBV
374 DNA levels.

375

376 Participants with HBsAg positivity, with and without high HBV DNA, exhibited
377 comparable rates of CD4+ count recovery in the first five years of ART as other HBV
378 serologic profiles. These findings are in contrast to an analysis of 4,773 participants
379 initiating ART in the Swiss HIV cohort, which showed impaired CD4 count recovery at
380 36 weeks in participants who had isolated HBcAb and HBsAg positivity.⁷ That study,

381 mostly comprised of men, noted several baseline differences between those with and
382 without HBsAg, including lower baseline CD4+ counts (median, 218 cells/mm³) and a
383 higher prevalence of HCV antibody (20.9%), which were not apparent in our study. In a
384 prior analysis in Côte d'Ivoire, participants with HBsAg positivity and a high HBV DNA
385 demonstrated an accelerated rate of CD4+ count recovery compared to other HBV
386 serologic profiles.¹⁰ That study also excluded participants with advanced liver disease,
387 but baseline CD4+ counts were overall lower than the current analysis. Interestingly, a
388 study of people with HIV-HBV co-infection in Nigeria found no difference in rates of
389 immunologic recovery to those with HIV mono-infection despite having lower baseline
390 CD4+ count (median, 107 cells/mm³) and higher HIV viral load (median, 4.96 log
391 copies/mL).⁸ Taken together, the reasons for differences in observed immunorecovery
392 remain unclear.

393
394 Despite showing comparable rates of CD4+ count recovery, people with HIV-HBV co-
395 still incurred a higher mortality rate compared to those with HIV mono-infection. This
396 finding was evident for those with positive HBsAg and high HBV DNA levels at baseline
397 and has been noted in other HIV-HBV cohorts in sub-Saharan Africa,^{3,34,41} all of which
398 included participants who initiated ART at lower CD4 thresholds. It is noteworthy that we
399 were able to establish this finding in an analysis restricted to participants who were
400 randomized to receive ART immediately after HIV diagnosis, with extensive use of TDF-
401 based regimens, and a low overall mortality rate. It could be speculated that our
402 estimates were inflated due to sparse data issues (Supplementary table 5); however,
403 we applied a regression technique aimed at mitigating this bias.

404

405 Prior studies have noted that people with HIV-HBV co-infection are more likely to
406 experience hepatitis flares compared to those with HIV mono-infection, but it is not clear
407 if liver disease is itself the driver of excess mortality among people with HIV-HBV co-
408 infection.¹⁵ Participants with HBsAg in our cohort, particularly those with high HBV DNA
409 viral loads, were more likely to have elevated baseline ALT levels, but this frequency
410 was still relatively low (<25%), and no participant had an ALT level >4 x ULN at study
411 entry because of the Temprano inclusion criteria. However, it is unclear whether
412 baseline levels of fibrosis may have contributed to the differences in mortality observed
413 between those with and without HBV co-infection.

414

415 Our study has limitations. First, there was a considerable proportion of participants with
416 missing data at baseline, for whom immunosuppression was less severe and with
417 missing data on causes of death, which made us unable to further analyze the
418 underlying reasons for increased mortality. In addition, individuals with ALT levels >4x
419 ULN were excluded from the Temprano trial, thus, participants were less likely to have
420 severe liver disease. Further, individuals in this cohort were not treated with integrase
421 strand transfer inhibitors, which have now become the standard of care of first-line ART.
422 The included population might not represent the entire HIV-HBV disease spectrum
423 observed currently in sub-Saharan Africa. Second, virologic and biochemical markers of
424 HBV replication fluctuate in the absence of ART,⁴² and individuals could have had their
425 HBV infection status misclassified prior to ART initiation. Finally, despite the large

426 number of individuals with complete HBV serology and regular follow-up, few deaths
427 occurred during follow-up.

428 **CONCLUSION**

429

430 In a cohort of people with HIV in Côte d'Ivoire who initiated ART immediately after
431 diagnosis, 74.0% of participants had prior HBV exposure with 11.4% being HBsAg
432 positive and 2.7% having HBsAg with a high HBV DNA. All HBV subgroups exhibited
433 similar trajectories of CD4+ count recovery. However, participants with HBsAg and high
434 HBV DNA levels incurred a higher rate of all-cause mortality. We observed no
435 difference in all-cause mortality between HBsAg-negative HBV subgroups, suggesting
436 that HBsAg and HBV DNA (among those HBsAg-positive) are the most important HBV
437 markers to assess in people with HIV initiating ART. Non-immunologic factors, such as
438 the presence of baseline liver disease, should be investigated as possible causes of
439 differences in mortality.

440

441 **Competing Interests**

442 The authors declare no competing interests.

443

444 **Funding**

445 This work was supported by the Agence Nationale de Recherches sur le SIDA et les
446 hépatites virales (ANRS), Paris, France. GMK also received doctoral funding from the

447 ANRS. AMM received funding from National Institutes of Health NIAID T32AI007433

448 and NIAID R37AI058736. EPH received funding from National Institutes of Health

449 NHLBI K01HL123349. Its contents are solely the responsibility of the authors and do not
450 necessarily represent the official views of the NIH.

451

452 **Author Contributions**

453 **AMM, GMK, and ABo** were responsible for the statistical analysis, interpretation of the
454 data and drafting the manuscript. **DG, ABa,** and **AE** coordinated data collection and

455 management and provided critical revision of the manuscript. **AG, SM, HM,** and **CDe**

456 gave technical support, were responsible for HBV virologic measurements and provided

457 critical revision of the manuscript. **EPH** provided methodological assistance and

458 provided critical revision of the manuscript. **RM, CDa, XA, KL, SPE** and provided

459 important advice regarding the TEMPRANO, assisted in data collection and

460 management and provided critical revision of the manuscript.

461

462 **Acknowledgements**

463 We thank all patients who participated in this trial; members of SMIT, CeDReS,
464 CEPREF, USAC, CIRBA, CNTS, La Pierre Angulaire, Hopital General Abobo,
465 Formation Sanitaire Anonkoua Koute, Centre de sante El Rapha, the Programme
466 PACCI team, and INSERM U1219 IDLIC teams for their valuable contributions; Gilead
467 Sciences, for the donation of Truvada; and Merck Sharp & Dohme, for the donation of
468 Stocrin.

469

470

471 **DATA AVAILABILITY STATEMENT**

472

473 The data from the Temprano Study are owned by the ANRS. Original data can be
474 requested by submitting a study proposal to the principal investigators of the study. The
475 proposal format can be obtained from the corresponding author
476 (a.c.boyd@amsterdamumc.nl or anders.boyd@iplesp.upmc.fr). The principal
477 investigators of the study will check each proposal for compatibility with the general
478 objectives, ethical approvals, and informed consent forms of the Temprano study, and
479 potential overlap with ongoing work. This study contains original data. **AB, GMK, DG,**
480 **CD, RM, XA** and **SE** had full access to all the data in the study and take responsibility
481 for the integrity of the data and the accuracy of the data analysis.

482

483

484 **STATEMENT OF SIGNIFICANCE**

485

486 Individuals who have been infected with hepatitis B virus (HBV) can either resolve their
487 infection or become chronically infected. For HIV-positive individuals, this could have an
488 impact on their risk of dying during treatment. In this study, we observed that HIV-
489 positive individuals in Côte d'Ivoire who started their treatment early and had highly
490 active, chronic HBV infection had a higher risk of death. This was in comparison to HIV-
491 positive individuals who were never infected or had resolved HBV infection. These
492 findings suggest that presence of chronic HBV infection, and not resolved HBV
493 infection, warrants closer monitoring in HIV-positive individuals.

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- 615

616 **TABLES**

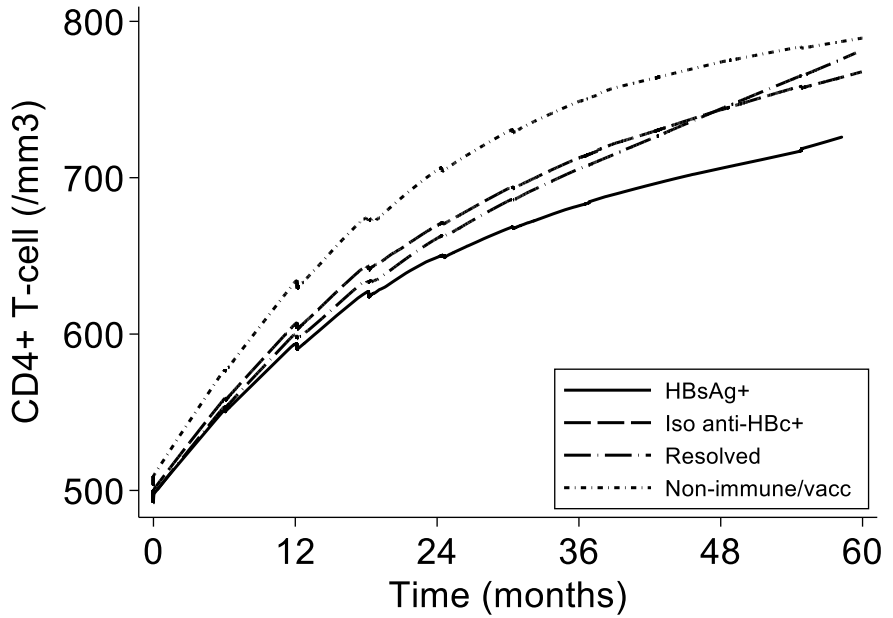
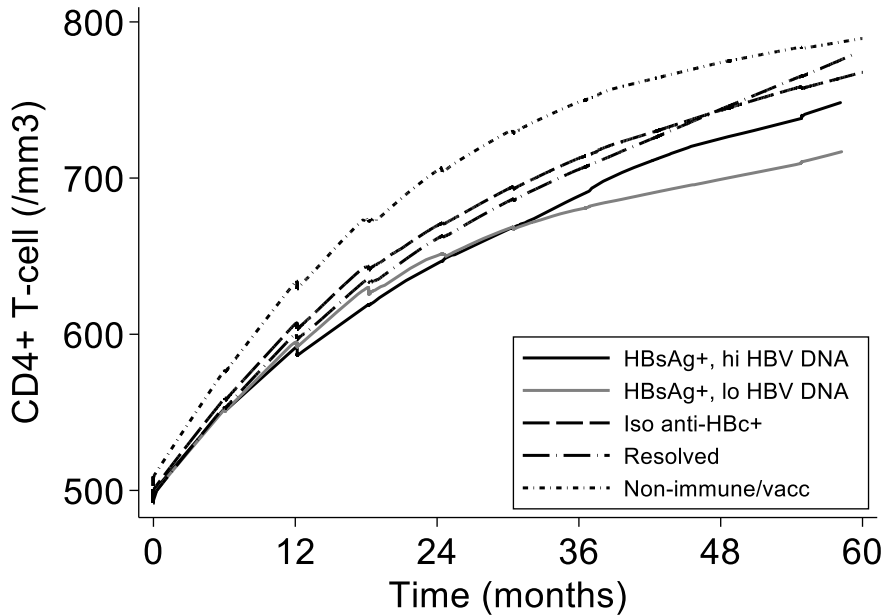
617 **Box 1. Definition of HBV infection status**

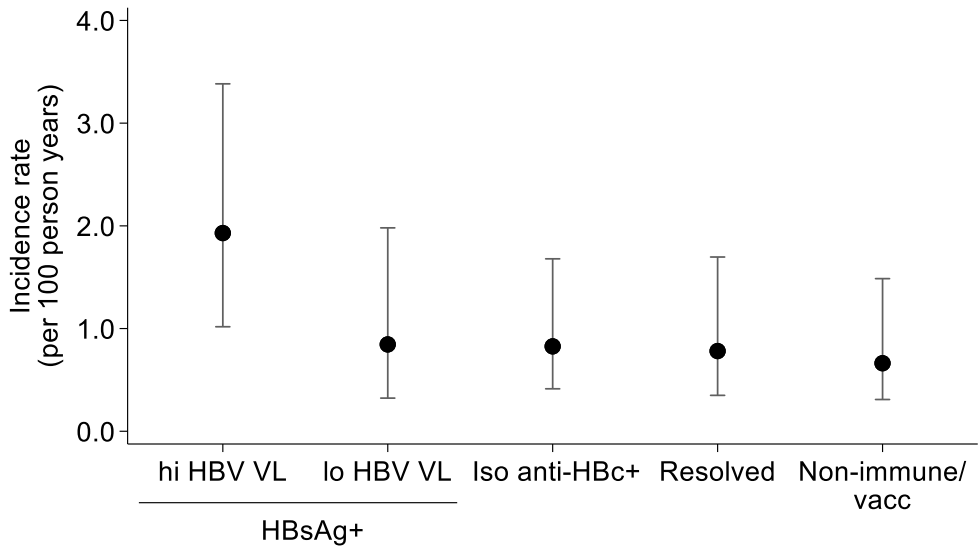
HBV infection group	HBV serology [†]		
	HBsAg	anti-HBcAb	anti-HBsAb
HBsAg-positive	+	N/A	N/A
Isolated anti-HBcAb+	-	+	-
Resolved infection	-	+	+
Non-immunized	-	-	-
Vaccinated	-	-	+

618 Note: Anti-HBcAb and anti-HBsAb were not measured for HBsAg-positive individuals.

619 [†]Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBcAb,
620 anti-hepatitis B core antibodies; anti-HBsAb, anti-hepatitis B surface antibodies.

621

A**B**



Supplement to: Mohareb AM, Kouamé GM, Gabassi A, et al. Mortality in relation to HBV-infection status among HIV-HBV co-infected patients in sub-Saharan Africa after immediate initiation of antiretroviral therapy.

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Supplementary Table 1. Prior distributions used in analysis

Assumed direction of association	HR (95% CrI)
Probably protective	0.50 (0.13-2.00)
Possibly protective	0.69 (0.17-2.70)
Unknown direction	1.00 (0.25-4.00)

Abbreviations: CrI, credible interval; HR, hazards ratio.

All priors based on log-normal distribution with mean $\ln(\text{HR})$ and variance 1/2 [1].

Reference:

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Supplementary Table 2. Comparison of individuals included and not included in analysis

	Included <i>n</i> =879	Not included <i>n</i> =153	<i>p</i> -value*
Median age, years (IQR)	35 (30-42)	35 (30-40)	0.88
Female	701 (80)	118 (79)	0.76
Median BMI, kg/m ² (IQR)	22 (20-25)	22 (20-26)	0.76
WHO clinical stage			0.04
1	560 (64)	92 (61)	
2	225 (26)	51 (34)	
3	89 (10)	7 (5)	
4	5 (<1)	0 (0)	
Median CD4 cell count/mm ³ (IQR)	459 (365-561)	543 (445-668)	<0.001
Median HIV-1 RNA, log ₁₀ copies/ml (IQR)	4.7 (4.0-5.3)	4.6 (4.0-5.2)	0.16
Plasma ALT, median (IQR)	18 (14-26)	18 (13-23)	0.18
Plasma ALT >1×ULN, <i>n</i> (%)	109 (12)	12 (8)	0.15
First-line ART regimen			0.14
TDF–FTC plus EFV	602 (68)	112 (75)	
TDF–FTC plus LPV/r	72 (8)	6 (4)	
TDF–FTC plus ZDV	205 (23)	32 (21)	
Randomized to IPT, <i>n</i> (%)	441 (50)	75 (50)	0.97

All statistics are *n* (%) unless otherwise indicated. The table only includes participants randomized to the two 'immediate ART' arms (arms 3 and 4) of the ANRS Temprano trial.

n, number in groups; IQR, interquartile range; BMI, body mass index; IPT, Isoniazid Preventive Therapy; WHO, World Health Organization; ART, Antiretroviral Therapy; TDF, tenofovir; FTC, emtricitabine; ZDV, zidovudine; LPV/r, lopinavir/ritonavir; ALT, alanine transaminase; ULN, upper limit of normal. BMI, body mass index; Ag, antigen; Ab, antibodies; HBsAg, hepatitis B surface antigen; anti-HBc, anti-hepatitis B core.

**p*-value for comparison between groups using Pearson's χ^2 or Fisher's Exact test for categorical variables and Kruskal-Wallis test for continuous variables.

Supplementary Table 3. Incidence of all-cause death according to hepatitis B virus infection group (using non-informative priors[†])

Infection group [‡]	Posterior HR (95% CrI)
Model 1	
HBsAg-positive	Ref
Isolated anti-HBc Ab-positive	0.66 (0.25-1.93)
Resolved infection	0.60 (0.20-1.82)
Non-immunized/Vaccinated	0.51 (0.16-1.58)
Model 2 [§]	
HBsAg-positive, HBV DNA \geq 2000 IU/mL	Ref
HBsAg-positive, HBV DNA <2000 IU/mL	0.31 (0.06-1.72)
Isolated anti-HBc Ab-positive	0.33 (0.10-1.46)
Resolved infection	0.29 (0.08-1.33)
Non-immunized/Vaccinated	0.26 (0.07-1.20)

Abbreviations: anti-HBc Ab, anti-hepatitis B core antibodies; CrI, credible interval; HBsAg, Hepatitis B surface antigen; HBV DNA, Hepatitis B virus deoxyribonucleic acid; HR, hazard ratio.

HRs and 95% CrI were obtained from univariable Bayesian exponential survival models.

[†]Non-informative priors (i.e. those that bear minimal influence when estimated the posterior distribution) were log normal distributions with mean $\ln(1)$ and variance 100.

[‡]Determined from serological results at inclusion, defined in Box 1.

[§]Parameter estimates should be interpreted with caution as a high level of autocorrelation between iterations was observed for all parameter estimates in this model.

Supplementary Table 4. Incidence of all-cause death according to hepatitis B virus infection group (using priors with weaker effects)

Infection group[†]	Prior HR (95% CrI)	Posterior HR (95% CrI)
Model 2		
HBsAg-positive, HBV DNA \geq 2000 IU/mL	Ref	Ref
HBsAg-positive, HBV DNA <2000 IU/mL	0.69 (0.17-2.77)	0.58 (0.21-1.38)
Isolated anti-HBc Ab-positive	0.69 (0.17-2.77)	0.54 (0.25-1.10)
Resolved infection	0.69 (0.17-2.77)	0.50 (0.23-1.06)
Non-immunized/Vaccinated	0.69 (0.17-2.77)	0.44 (0.20-0.93)

Abbreviations: anti-HBc Ab, anti-hepatitis B core antibodies; CrI, credible interval; HBsAg, Hepatitis B surface antigen; HBV DNA, Hepatitis B virus deoxyribonucleic acid; HR, hazard ratio.

HRs and 95% CrI were obtained from univariable Bayesian exponential survival models.

[†]Determined from serological results at inclusion, defined in Box 1.

Supplementary Table 5. Incidence of all-cause death according to hepatitis B virus infection group (without using Bayesian approach)

Infection group[†]	HR (95% CI)
Model 1	
HBsAg-positive	Ref
Isolated anti-HBc Ab-positive	0.63 (0.24-1.66)
Resolved infection	0.58 (0.20-1.67)
Non-immunized/Vaccinated	0.50 (0.17-1.49)
Model 2	
HBsAg-positive, HBV DNA \geq 2000 IU/mL	Ref
HBsAg-positive, HBV DNA <2000 IU/mL	0.31 (0.06-1.56)
Isolated anti-HBc Ab-positive	0.30 (0.09-1.06)
Resolved infection	0.28 (0.07-1.04)
Non-immunized/Vaccinated	0.24 (0.06-0.93)

Abbreviations: anti-HBc Ab, anti-hepatitis B core antibodies; CI, confidence interval; HBsAg, Hepatitis B surface antigen; HBV DNA, Hepatitis B virus deoxyribonucleic acid; HR, hazard ratio.

HRs and 95% CI were obtained from univariable exponential survival models.

[†]Determined from serological results at inclusion, defined in Box 1.