



HAL
open science

CD4+ T Cell Recovery and Hepatitis B Virus Coinfection in HIV-Infected Patients from Cote d'Ivoire Initiating Antiretroviral Therapy

Laura Houghtaling, Raoul Moh, Mariama Abdou Chekaraou, Delphine Gabillard, Xavier Anglaret, Serge Paul Eholié, Fabien Zoulim, Christine Danel, Karine Lacombe, Anders Boyd

► **To cite this version:**

Laura Houghtaling, Raoul Moh, Mariama Abdou Chekaraou, Delphine Gabillard, Xavier Anglaret, et al.. CD4+ T Cell Recovery and Hepatitis B Virus Coinfection in HIV-Infected Patients from Cote d'Ivoire Initiating Antiretroviral Therapy. *AIDS Research and Human Retroviruses*, 2018, 34 (5), pp.439-445. 10.1089/aid.2017.0272 . hal-03194156

HAL Id: hal-03194156

<https://hal.science/hal-03194156>

Submitted on 28 May 2024

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

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

CD4+ T Cell Recovery and Hepatitis B Virus Coinfection in HIV-Infected Patients from Côte d'Ivoire Initiating Antiretroviral Therapy

Laura Houghtaling,¹ Raoul Moh,²⁻⁴ Mariama Abdou Chekaraou,⁵ Delphine Gabillard,^{6,7} Xavier Anglaret,^{2,6,7} Serge Paul Eholie,²⁻⁴ Fabien Zoulim,⁵ Christine Danel,^{2,6,7} Karine Lacombe,^{8,9} Anders Boyd¹⁰,
for the ANRS 1269 Trivacan and ANRS 12240 VarBVA Studies

Immunorecovery could be attenuated in HIV-hepatitis B virus (HBV) coinfection versus HIV monoinfection during antiretroviral therapy (ART), yet, whether it also occurs in individuals from sub-Saharan Africa without severe comorbidities is unknown. In this study, 808 HIV-infected patients in Côte d'Ivoire initiating continuous ART were included. Six-month CD4+ count trajectories and the proportion reaching CD4+ T cell counts $>350/\text{mm}^3$, HIV-RNA <300 copies/mL, still alive and not lost to follow-up within 18 months (“optimal immunorecovery”) were compared between coinfecting groups. At inclusion, 80 (9.9%) patients were HIV-HBV coinfecting, 40 (50.0%) of whom had high HBV-DNA viral load (VL) ($>10^4$ copies/mL). Coinfecting patients with high HBV-DNA replication initiated ART with significantly lower median CD4+ T cell counts [$216/\text{mm}^3$, interquartile range (IQR) = 150–286] compared to coinfection with low HBV-DNA replication ($268/\text{mm}^3$, IQR = 178–375) or HIV monoinfection ($257/\text{mm}^3$, IQR = 194–329) ($p = .003$). These patients had significantly faster rates of CD4+ cell count increase from baseline after adjusting for baseline age, World Health Organization stage III/IV, and CD4+ cell counts ($p = .04$), yet, were not more likely to exhibit optimal immunorecovery (82.5% vs. 80.0% and 77.9%, respectively) ($p = .8$). In conclusion, change in CD4+ cell counts after ART-initiation was accelerated in coinfecting patients with high HBV DNA VLs, but this did not lead to increased rates of optimal immunorecovery.

Keywords: antiretroviral therapy, immune restoration, sub-Saharan Africa, treatment response, viral replication

Introduction

WITHIN THE FIRST MONTHS after initiating antiretroviral therapy (ART), patients infected with the HIV exhibit large increases in CD4+ cell count.¹ Higher increases during this period have been associated with long-term CD4+ cell reconstitution,^{2,3} decreased risk of opportunistic diseases,⁴ and reduction of short-term mortality^{5,6}; underscoring the clinical importance of strong CD4+ cell recovery. Epide-

miological studies have identified a variety of risk-factors involved in reduced CD4+ cell recovery, such as older age, lower body mass index (BMI), longer duration of HIV infection, and increased CD8+ T cell activation,^{1,7,8} while no differences in recovery have been observed between specific antiretroviral agents and HIV subtypes.⁹

One determinant of immune recovery that has received particular attention over the past decade has been coinfection with hepatitis B virus (HBV). Although much of the literature

¹Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, Minnesota.

²Programme PAC-CI, ANRS Research Site, Treichville University Hospital, Abidjan, Côte d'Ivoire.

³Department of Infectious and Tropical Diseases, Treichville University Teaching Hospital, Abidjan, Côte d'Ivoire.

⁴Medical School, University Felix Houphouët Boigny, Abidjan, Côte d'Ivoire.

⁵Cancer Research Center of Lyon, INSERM, Unité 1052, CNRS, UMR 5286, Lyon, France.

⁶INSERM, U1219, Epidémiologie-Biostatistique, Bordeaux, France.

⁷University of Bordeaux, ISPED, Bordeaux, France.

⁸Department of Infectious and Tropical Diseases, Saint-Antoine Hospital, AP-HP, Paris, France.

⁹INSERM, Sorbonne Universités, Institut Pierre Louis d'épidémiologie et de Santé Publique, F75012, Paris, France.

¹⁰INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique, F75012, Paris, France.

has observed no difference between HIV monoinfected and HIV-HBV coinfecting patients in achieving undetectable HIV-RNA after ART-initiation,^{10,11} there is some evidence that immunorecovery may be different.^{12,13} For example, the Swiss HIV Cohort study recently observed significantly slower increases in CD4+ cell count among patients on-treatment with hepatitis B surface antigen (HBsAg)-positive or isolated hepatitis B core antigen positive serology than HBsAg-negative patients or those with resolved HBV infection.¹⁴

In sub-Saharan Africa (SSA), some reports suggest differences in CD4+ cell count increase after ART-initiation between patients with or without HBV coinfection,¹⁵ while others do not.^{16–18} Studies in these settings are generally confined to patients with severe immunocompromised status where average baseline CD4+ cell counts are <100 cells/mL, thereby altering the course of CD4 recovery.¹ Furthermore, most of these studies lacked information on HBV-DNA, making it difficult to establish the direct link between more active forms of HBV-infection and immunorecovery.

We used existing data from the Trivacan study, a large randomized control trial among treatment-naïve HIV-infected patients from SSA without severe comorbidities, to evaluate the effect of HIV-HBV coinfection, including HBV-replication, on CD4 cell recovery during continuous ART. We also examined whether HIV-HBV coinfection was related to reaching specific levels of CD4+ cell count during therapy.

Materials and Methods

Study population

Patients participated in the ANRS 1269 Trivacan study, which was a prospective, randomized, open-label, multicenter trial in Abidjan, Côte d'Ivoire (ClinicalTrials.gov No. NCT00158405).^{19,20} In brief, study inclusion criteria were as follows: age ≥ 18 years, HIV-1 or mixed HIV-1/2 infection, ART-naïve, and CD4+ cell count between 150 and 350/mm³ or CD4 percentage between 12.5% and 20.0%. Patients with any one of the following were not included: residence outside of Abidjan, unwillingness to participate, pregnancy, severe renal or hepatic disease, severe psychiatric disorder, any ongoing severe clinical features of undiagnosed origin, severe hematological disorder, or Karnofsky score <50.

A total of 840 patients started ART at inclusion, receiving zidovudine and lamivudine (LAM) with either efavirenz or lopinavir/ritonavir. Patients underwent a 6- to 18-month phase of continuous ART during a prerandomization period, and those achieving CD4 > 350/mm³ and plasma HIV-1 RNA <300 copies/mL were randomized to a treatment strategy arm, as detailed elsewhere.^{19,20} The analysis presented herein only includes the prerandomization period.

All participants gave written informed consent, and the study protocol was approved by the Ministry of Health of Côte d'Ivoire and the French National Agency for Research on AIDS and Viral Hepatitis (ANRS, Paris, France).

Assessing biological parameters

All patients were tested for HBsAg at study inclusion (Mini Vidas[®] assay; Biomérieux, Marcy l'Etoile, France), which was then confirmed using the Architect i2000 assay

(Abbott Laboratories, Rungis, France). From samples stored at -80°C , hepatitis B “e” antigen (HBeAg) and anti-HBe antibodies were detected at study inclusion using the Elecsys assay (Roche Diagnostics, Meylan, France). HBV-DNA viral loads (VLs) were quantified at study inclusion using an in-house polymerase chain reaction (PCR)-based assay (detection threshold: 12 copies/mL).²¹

Plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were collected at study inclusion, while only AST levels were available every 6 months during follow-up. Elevated transaminase levels were defined as an AST or ALT >40 IU/L.

CD4+ cell counts (True Count technique on FACScan, Becton Dickinson, Aalst-Enembogem, Belgium) were obtained at study inclusion and every 3 months. Plasma HIV-1 RNA was quantified using real-time PCR and was measured at study inclusion every 6 months.

Statistical analyses

Patients were grouped as HIV monoinfected or HIV-HBV coinfecting, the latter of which was further stratified on HBV-VL >10⁴ copies/mL (“high HBV-DNA replication”) and HBV-VL $\leq 10^4$ copies/mL (“low HBV-DNA replication”) at ART-initiation. The choice of threshold was determined from a previous study in SSA, demonstrating higher mortality rates when HBV DNA VLs were at or above these levels.²² The clinical relevance of this threshold was confirmed in a previous study from the Trivacan study group.²³ Characteristics between groups were compared at study inclusion using Kruskal–Wallis test for continuous variables and Pearson’s chi-squared or Fisher’s exact test for categorical variables.

We modeled mean change in CD4+ T cell with mixed-effect linear regression models suppressing the fixed-effect intercept and including a random-intercept to account for patient variability at ART-initiation. To avoid bias due to differential loss to follow-up in patients achieving randomization criteria early, follow-up started at treatment initiation (defined as “baseline”) and included the first 6 months when all patients were not yet randomized. Fractional polynomial (FP) functions up to the second-order were compared by maximum likelihood ratio tests with the highest fitting model achieved as a second-order FP with continuous time and time transformed to the power of 2: FP[2, (1, 2)]. Multivariable adjustment was performed using independent covariables affecting CD4+ cell levels over time (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/aid) and included the following: age at study inclusion, World Health Organization (WHO) clinical stage III/IV, and CD4 cell count at study inclusion. Interaction between HBV-groups was tested using a method developed by Royston and Sauerbrei.²⁴

We then used randomization as an end-point to indicate “optimal” immunorecovery during ART. Patients who were randomized (achieved CD4 > 350/mm³, plasma HIV-1 RNA <300 copies/mL within 18 months, still alive, not lost to follow-up, and absence of ≥ 1 criteria for nonrandomization) were compared with those who were nonrandomized. Univariable odds ratios (OR) and 95% confidence intervals (CIs) were estimated for baseline determinants using logistic regression models. A multivariable model was constructed by

including all covariables with a p value $<.1$ from univariable analysis in a full model and removing variables above this threshold in backwards-stepwise manner. Coinfection group was forced in the model regardless of p value.

All analyses were conducted using STATA statistical package (v14.2, College Station, TX) and significance was determined using a p value $<.05$.

Results

Description of the study population

Of the 840 individuals enrolled in the Trivacan study between December 2002 and April 2004, 32 (3.8%) were not included in analysis due to the following reasons: did not have available HBsAg-status at inclusion ($n=1$), did not have confirmed HBsAg-status ($n=25$), or did not have available HBV-DNA at inclusion ($n=6$). In total, 808 patients were included, of whom 728 were HIV monoinfected and 80 were HIV-HBV coinfecting (40 with low and 40 with high HBV-DNA VL).

Table 1 provides a description of the study population at inclusion and compares infection groups. HIV-HBV coinfecting versus HIV monoinfected patients were significantly more likely to be male and have elevated transaminase levels. Coinfecting patients with high HBV-DNA VL, compared to all others, had significantly lower nadir CD4+ cell count (median = 198 vs. 240/mm³, respectively, $p=.009$), lower current CD4+ cell count (median = 215 vs. 257/mm³, respectively, $p=.003$), elevated transaminase levels (65.0% vs. 27.1%, respectively, $p<.001$), and higher ALT (median = 37 vs. 21 IU/L, respectively, $p<.001$) and AST levels (median = 46 vs.

30 IU/L, respectively, $p<.001$). Among coinfecting patients, there were significantly higher proportions of HBeAg-positive serology ($p<.001$) and HBV-DNA levels ($p<.001$) in those with high versus low HBV-DNA VL.

Change in CD4 cell count from ART-initiation and coinfection status

In this analysis, we included 795 patients with CD4+ cell counts at study inclusion and at least once during follow-up. Median change in CD4+ cell count from baseline increased at month 3 (+118/mm³; IQR = +53, +197) and at month 6 (+140/mm³; IQR = +54, +229). Median changes in CD4+ cell count stratified on HBV-infection group are depicted in Figure 1A, demonstrating rather large variability in individual trajectories. When applying the FP model to change in CD4+ cell count, there was no significant difference in rate of CD4 cell count increase between HBsAg-positive and HBsAg-negative patients ($p=.3$) after adjusting on baseline age, WHO stage III/IV, and baseline CD4+ cell count. However, as shown in Figure 1B, a significantly faster adjusted increase in CD4+ cell counts was observed among coinfecting patients with high baseline HBV-DNA levels compared with HIV monoinfected patients ($p=.04$), but not compared to coinfecting patients with low baseline HBV-DNA ($p=.11$).

Achieving randomization criteria and coinfection status

At the end of the 18-month prerandomization phase, 176 (21.8%) patients were not randomized and 632 (78.2%) were randomized. Reasons for nonrandomization include the

TABLE 1. DESCRIPTION OF THE STUDY POPULATION AT INCLUSION PER INFECTION GROUP

	HIV-HBV coinfecting			HIV mono-infected (n = 728)	p ^c
	HBV-DNA $\leq 10^4$ copies/mL (n = 40)	HBV-DNA $> 10^4$ copies/mL (n = 40)	Total (n = 80)		
Gender, M/F (% males)	14/26 (35.0)	13/27 (32.5)	27/53 (33.8)	165/563 (22.7)	0.04
Age, years ^a	33 (28–37)	36 (32–42)	35 (30–39)	34 (29–40)	NS
Current smoker ^b	3 (7.5)	4 (10.3)	7 (8.9)	28 (3.9)	NS
BMI, kg/m ^{2a}	21 (20–24)	21 (19–23)	21 (19–23)	21 (19–24)	NS
WHO clinical stage ^b					NS
Stage I	8 (20.0)	6 (15.0)	14 (17.5)	163 (22.4)	
Stage II	20 (50.0)	13 (32.5)	33 (41.3)	295 (40.5)	
Stage III	12 (30.0)	18 (45.0)	30 (37.5)	210 (28.7)	
Stage IV	0 (0.00)	3 (7.5)	3 (3.8)	60 (8.2)	
HIV-RNA > 300 copies/mL ^b	37 (94.9)	39 (100.0)	76 (97.4)	691 (96.8)	NS
Current CD4+ counts/mm ^{3a}	268 (178–375)	215 (150–286)	223 (163–302)	257 (194–329)	NS
Nadir CD4+ counts/mm ^{3a}	239 (178–313)	198 (150–286)	220 (163–292)	240 (181–314)	NS
HBeAg-positive ^b	1 (2.5)	23 (57.5)	24 (30.0)	—	NTP
HBV-DNA, copies/mL ^a	3.08 (2.58–3.39)	7.43 (6.04–8.22)	4.08(3.08–7.43)	—	NTP
ALT, IU/L ^a	21 (15–27)	37 (22–61)	27 (18–45)	21 (15–31)	0.002
AST, IU/L ^a	31 (25–38)	46 (34–84)	36 (28–52)	30 (24–40)	$<.001$
Elevated liver enzymes ^{b,d}	7 (17.5)	26 (65.0)	33 (41.3)	197 (27.1)	0.009

^aMedian (IQR).

^bn (%).

^cSignificance between HIV-HBV coinfecting and HIV monoinfected groups determined using Kruskal–Wallis test for continuous variables and Pearson’s chi-squared test or Fisher’s exact test for categorical variables.

^dDefined as ALT or AST > 40 IU/L.

ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; F, female; HBeAg, hepatitis B “e” antigen; HBV, hepatitis B virus; IQR, interquartile range; M, male; NS, not significant; NTP, no test performed; WHO, World Health Organization.

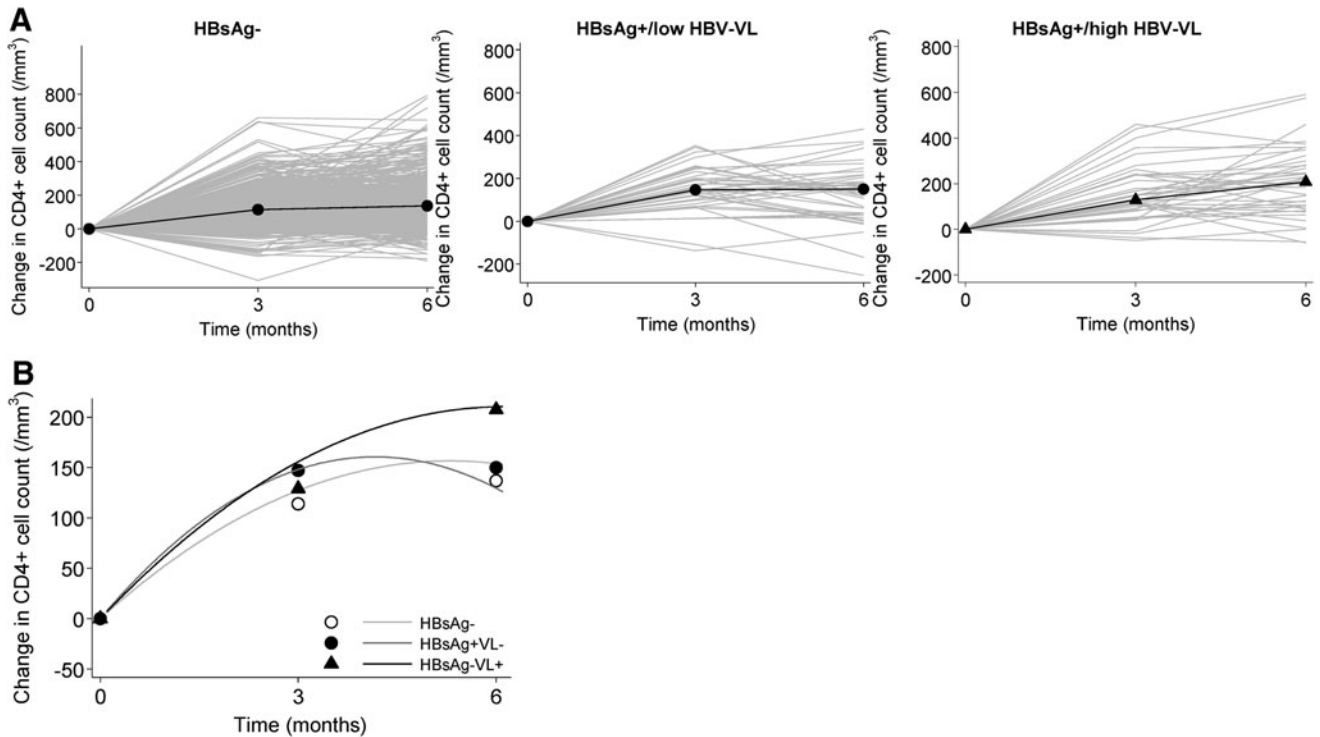


FIG. 1. Immunological recovery after initiation of ART by HBV infection status. Individual changes in CD4+ T cell count (gray lines) and their unadjusted medians are given at ART-initiation, 3 and 6 months (A). Predicted trajectories of change in CD4+ T cell count adjusted for baseline age, WHO stage III/IV and CD4+ cell counts are also provided along with unadjusted median levels (B). Patients were regrouped as follows: HIV monoinfected, HIV-HBV coinfecting with HBV-DNA VL $\leq 10^4$ copies/mL at study inclusion (VL-), and HIV-HBV coinfecting with HBV-DNA VL $>10^4$ copies/mL at study inclusion (VL+). ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; WHO, World Health Organization; VL, viral load.

following: death before 18 months ($n=20$), lost to follow-up before 18 months ($n=22$), CD4+ T cell count $<350/\text{mm}^3$ ($n=95$) and/or detectable HIV-1 RNA at last measurement ($n=28$), and other ($n=29$). No significant differences were observed between coinfection groups with respect to the CD4+ T cell count ($p=.8$) or HIV-1 RNA VL ($p=.3$) randomization criterion. As shown in the multivariable analysis presented in Table 2, the only factor significantly associated with randomization was higher baseline CD4+ T cell count. Of note, there were no significant differences in the odds of randomization between HIV monoinfected versus coinfecting patients ($p=.19$), even when considering high or low baseline HBV-DNA at inclusion ($p=.8$ and $p=.12$, respectively). Similar observations were found when comparing HIV monoinfected versus coinfecting patients with HBeAg-negative (adjusted OR=1.26, 95% CI=0.61–2.59) or HBeAg-positive serology (adjusted OR=2.25, 95% CI=0.73–6.91).

Discussion

Using data from a large patient population in SSA, we demonstrate that HBV coinfecting patients with high HBV DNA VLs initiated ART with significantly lower CD4+ T cell counts when compared with HIV monoinfection. During treatment, these patients had significantly faster increases of CD4+ cell change from baseline even after adjusting on well-known factors influencing CD4 levels.²⁵ Nevertheless,

this significant increase did not affect the ability to achieve adequate reconstitution within 18 months of therapy, as largely deemed by having CD4+ cell counts $>350/\text{mm}^3$ and HIV-1 RNA <300 copies/mL. We provide particular insight on the immunorecovery of ART-treated coinfecting patients from Côte d'Ivoire, exhibiting a markedly improved initial immunological status compared to other studies from SSA.^{16–18}

The significantly faster increase in CD4+ cell count among coinfecting patients with high HBV DNA VLs was fairly surprising. Most research in this setting has indicated either comparable or decreased rates of CD4+ cell increases after initiating ART between co- and monoinfection.^{14–18} A variety of factors could explain the discrepancies between studies, such as age, gender, BMI, and tuberculosis infection.^{3,7,26,27} Importantly, CD4+ T cell count at ART-initiation has been established as one of the more critical determinants of T cell recovery.¹ The fact that coinfecting patients with high HBV DNA VL already started ART with much lower CD4 cell levels likely augmented their probability for accelerated immunorecovery compared with other infection groups; nevertheless, we did adjust for baseline CD4+ cell counts. Interestingly, individual trajectories of CD4+ cell counts revealed that stable or slightly decreasing levels during treatment rarely occurred in coinfecting patients with high VL. This observation likely influenced the mean change from baseline in this group, leading to a significant association.

TABLE 2. DETERMINANTS FOR RANDOMIZATION DURING THE PRERANDOMIZATION PHASE

Baseline characteristics	n	Univariable		Multivariable ^a	
		OR (95% CI)	p	OR (95% CI)	p
Gender					
Male	192	1.00			
Female	616	1.18 (0.80–1.73)	NS		
Age (per 10 years)	808	1.06 (0.86–1.30)	NS		
BMI (per kg/m ²)	808	1.05 (1.00–1.10)	.04		
WHO clinical stage					
Stage I	177	1.00			
Stage II	328	0.66 (0.41–1.06)	NS		
Stage III	240	0.59 (0.36–0.97)	.04		
Stage IV	63	0.51 (0.26–1.01)	NS		
CD4+ cell count (per 100/mm ³)	808	2.45 (1.96–3.05)	<.001	2.49 (1.99–3.12)	<.001
Nadir CD4+ cell count during follow-up (per 100/mm ³)	808	3.75 (2.87–4.89)	<.001		
ALT					
<19 IU/L in F, <30 IU/L in M	280	1.00			
≥19 IU/L in F, ≥30 IU/L in M	318	0.91 (0.61–1.36)	NS		
AST					
<19 IU/L in F, <30 IU/L in M	122	1.00			
≥19 IU/L in F, ≥30 IU/L in M	686	1.27 (0.81–1.99)	NS		
HBV coinfection group ^b					
HIV+/HBV–	728	1.00		1.00	
HIV+/HBV+ low VL	40	1.14 (0.51–2.51)	NS	1.12 (0.48–2.61)	NS
HIV+/HBV+ high VL	40	1.34 (0.58–3.08)	NS	1.98 (0.84–4.71)	NS

Randomization was defined as CD4 > 350/mm³ and plasma HIV-1 RNA < 300 copies/mL by the end of 18 months of continuous antiretroviral therapy. Patients switching or permanently discontinuing treatment, lost to follow-up, or dead were considered as nonrandomized.

^aIn the multivariable model, HBV coinfection group was forced. BMI and WHO clinical stage were removed because they no longer had an associated *p* value below the predefined threshold (*p* = .284 and *p* = .561, respectively).

^b“Low” and “high” VL defined as at or below 10⁴ copies/mL and above 10⁴ copies/mL, respectively.

CI, confidence interval; OR, odds ratio; VL, viral load.

Considering that compensated and decompensated liver fibrosis has been linked to severe immunosuppression in HIV-HBV coinfecting patients,²⁸ it is conceivable that liver fibrosis could impact CD4+ T cell trajectories during treatment. Accordingly, some evidence has pointed to reduced CD4+ T cell recovery with higher measures of transient elastography,²⁹ yet, the implications of HBV-infection from their analysis were unclear. Part of the reason for differences between the studies described above could then stem from the degree of liver fibrosis in coinfecting populations. As patients with physician-assessed liver disease were excluded from our study, the prevalence of cirrhosis would be likely low, and hence, immunorecovery would be similar to noncirrhotic patients. Future studies with more specific data on liver fibrosis would help clarify the role of HBV-induced liver fibrosis on immunorecovery.

Suboptimal immunorecovery during ART has been recently exposed as a major problem in SSA, with 38% of HIV-infected patients unable to achieve CD4+ T cell counts > 350/mm³ within 5 years after ART-initiation.³⁰ In our study, randomized patients were mostly reflective of those with “optimal” immunorecovery, whereas nonrandomized individuals constituted a group at-risk of incomplete immunorecovery. HBV-infection status, either at high or low levels of HBV-DNA replication, was not associated with being unable to reach randomization criteria (i.e., CD4 > 350/mm³, plasma HIV-1 RNA < 300 copies/mL within 18 months, etc.). This finding would contend that other factors, namely age, gender,

AIDS-defining illness at ART-initiation, and most relevant to our data, CD4+ T cell count,^{27,30,31} are more predictive of continuously low CD4+ T cell count levels during follow-up.

There are certain limitations of our study that need to be addressed. First, follow-up was shorter compared to other studies in SSA. This forced us to use a different FP approach compared to previous models, possibly masking a plateau-effect of CD4+ T cell counts during later years of ART.¹⁴ Coupled with the lack of follow-up HBV VL measurements, we were also unable to explore the interaction between HIV and HBV VLs. Second, we did not have data on other infections, such as hepatitis C virus, making it difficult to understand their role in immunorecovery. Third, this analysis concerned only antiretroviral agents that were available at the time of the Trivacan study. We cannot conclude whether treatment with newer agents evokes different rates of CD4+ T cell count. Fourth, the definition of suboptimal immunorecovery was not limited to only CD4+ cell count < 350/mm³ but other randomization criteria (including death, loss to follow-up, ongoing severe HIV disease, ART regimen modification during the prerandomization phase, pregnancy, and ART regimen, including abacavir or nevirapine). As this represented roughly 40% of nonrandomized individuals,²⁰ their inclusion could have biased the direct effect of various determinants on immunorecovery. Nevertheless, many of these other criteria could be linked with insufficient immunorecovery,¹ thus reducing the effect of this bias. Finally,

there were small groups of coinfecting patients in this study, which may have reduced the power necessary to establish significant differences.

In summary, we found an accelerated increase in CD4 T cell recovery among HIV-HBV coinfecting patients with high HBV DNA VLs at ART initiation, but this did not influence the probability of insufficient immune recovery. Our findings were likely related to the differences in degree of immunosuppression at ART-initiation between infection groups, the extent of HBV control during treatment, the shorter length of follow-up, or a combination thereof. Although these results are encouraging for coinfecting patients, their long-term implications need to be evaluated. As more patients are expected to commence ART at higher CD4+ T cell counts with more effective agents, future research should explore if the lack in differences between HBV-infection groups is maintained in treated patients from SSA with mild immunosuppression.

Acknowledgments

We thank all patients who participated in the Trivacan trial. We also gratefully acknowledge the valuable contributions of the SMIT, CeDReS, CEPREF, USAC, CIRBA, CNTS, the Programme PACCI team, as well as INSERM exU593 and U897 teams. This work was supported by funds from the Agence Nationale de Recherche sur le Sida et les Hépatites (ANRS 1269/ANRS 12104 and ANRS 12240). A postdoctoral fellowship from the ANRS and SIDACTION was awarded to A.B. for some of the work presented in this article.

ANRS 1269 Trivacan study group: *Investigators*: Clinical care in Abidjan, Côte d'Ivoire—Service des Maladies Infectieuses et Tropicales (SMIT): Emmanuel Bissagnene (principal investigator), Serge Eholie, Auguste Kadio, Gustave Nzunetu, Cyprien Rabe, Aristophane Tanon. Centre Intégré de Recherches Biocliniques d'Abidjan (CIRBA): Olivier Ba-Gomis, Henri Chenal, Charles Diby, Denise Hawerlander. Centre National de Transfusion Sanguine (CNTS): Lambert Dohoun, Charlotte Huet, Seidou Konate, Albert Minga, Abo Yao. Unité de Soins Ambulatoires et de Conseil (USAC): Constance Kanga, Jonas Séri, Calixte Guéhi. Centre de Prise en Charge et de Formation (CePREF): Amani Anzian, Mamadou Diarrassouba, Nicole Dakoury-Dogbo, Joachim Gnokoro, Eugène Messou, Catherine Seyler, Siaka Toure.

Biology—Centre de Diagnostic et de Recherches sur le SIDA (CeDReS), CHU de Treichville, Abidjan, Côte d'Ivoire: Dominique Bonard (mycobacteriologist), Arlette Emieme (trial monitor), André Inwolé (immunologist), Hervé Menan (parasitologist), Timothée Ouassa (bacteriologist), François Rouet (virologist), Thomas-d'Aquin Toni (virologist), Ramatou Toure (trial monitor). Service de Virologie, CHU Necker, Paris, France: Marie-Laure Chaix (virologist), Christine Rouzioux (virologist). Service de Pharmacologie Clinique, CHU Bichat Claude-Bernard, Paris, France: Gilles Peytavin (pharmacologist).

Trial coordination team: Abidjan, Côte d'Ivoire—Programme PACCI: Christine Danel (coordinator), Romuald Konan (trial pharmacist), Raoul Moh (trial monitor), Delphine Sauvageot (trial monitor), Souleymane Sorho (data manager). Bordeaux, France—INSERM U593: Xavier Anglaret (coordinator), Delphine Gabillard (trial statistician), Yves-Antoine Flori (economist), Roger Salamon (principal investigator).

Steering Committee: Françoise Barré-Sinoussi, François Boué, Geneviève Chêne, François Dabis, Pierre Marie Girard, Catherine Leport, Yves Souteyrand.

Independent Data Safety Monitoring Board: Dominique Costagliola (independent statistician), Jean-François Del-fraissy, Nicolas Meda, Thérèse N'Dri-Yoman, Philippe van de Perre.

Representatives of the French Agence Nationale de Recherches sur le SIDA (ANRS, Paris, France): Brigitte Bazin, Séverine Blesson, Chantal Canon, Michel Kazatchkine.

ANRS 12240 VarBVA study group: Karine Lacombe, Raoul Moh (principal investigators), Mariama Abdou Chekaraou, Fabien Zoulim (study virologists), Anders Boyd, Delphine Gabillard (study statisticians), Christine Danel, Xavier Anglaret, Serge Paul Eholie, Sarah Maylin, Constance Delaugerre, Pierre-Marie Girard (coinvestigators).

Author Disclosure Statement

No competing financial interests exist.

References

1. Battegay M, Nüesch R, Hirschel B, Kaufmann GR: Immunological recovery and antiretroviral therapy in HIV-1 infection. *Lancet Infect Dis* 2006;6:280–287.
2. Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, Vernazza P, *et al.*: Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clin Infect Dis* 2005;41:361–372.
3. Kanters S, Nachega J, Funk A, Mukasa B, Montaner JSG, Ford N, *et al.*: CD4(+) T-cell recovery after initiation of antiretroviral therapy in a resource-limited setting: A prospective cohort analysis. *Antivir Ther* 2014;19:31–39.
4. Takuva S, Maskew M, Brennan AT, Long L, Sanne I, Fox MP: Poor CD4 recovery and risk of subsequent progression to AIDS or death despite viral suppression in a South African cohort. *J Int AIDS Soc* 2014;17:18651.
5. Lawn SD, Myer L, Orrell C, Bekker L-G, Wood R: Early mortality among adults accessing a community-based antiretroviral service in South Africa: Implications for programme design. *AIDS* 2005;19:2141–2148.
6. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell M-L: Association of age with mortality and virological and immunological response to antiretroviral therapy in rural South African adults. *PLoS One* 2011;6:e21795.
7. Koethe JR, Limbada MI, Giganti MJ, Nyirenda CK, Mullen L, Wester CW, *et al.*: Early immunologic response and subsequent survival among malnourished adults receiving antiretroviral therapy in Urban Zambia. *AIDS* 2010;24:2117–2121.
8. Hunt PW, Cao HL, Muzoora C, Ssewanyana I, Bennett J, Emenyonu N, *et al.*: Impact of CD8+ T-cell activation on CD4+ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy. *AIDS* 2011;25:2123–2131.
9. Geretti AM, Harrison L, Green H, Sabin C, Hill T, Fearnhill E, *et al.*: Effect of HIV-1 subtype on virologic and immunologic response to starting highly active antiretroviral therapy. *Clin Infect Dis* 2009;48:1296–1305.
10. Lincoln D, Petoumenos K, Dore GJ; Australian HIV observational database: HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. *HIV Med* 2003;4:241–249.

11. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, *et al.*: Hepatitis B and HIV: Prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005;19:593–601.
12. Idoko J, Meloni S, Muazu M, Nimzing L, Badung B, Hawkins C, *et al.*: Impact of hepatitis B virus infection on human immunodeficiency virus response to antiretroviral therapy in Nigeria. *Clin Infect Dis* 2009;49:1268–1273.
13. Chun HM, Mesner O, Thio CL, Bebu I, Macalino G, Agan BK, *et al.*: HIV outcomes in hepatitis B virus coinfecting individuals on HAART. *J Acquir Immune Defic Syndr* 2014;66:197–205.
14. Wandeler G, Gsponer T, Bihl F, Bernasconi E, Cavassini M, Kovari H, *et al.*: Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. *J Infect Dis* 2013;208:1454–1458.
15. Hawkins C, Christian B, Ye J, Nagu T, Aris E, Chalamilla G, *et al.*: Prevalence of hepatitis B co-infection and response to antiretroviral therapy among HIV-infected patients in Tanzania. *AIDS* 2013;27:919–927.
16. Matthews GV, Manzini P, Hu Z, Khabo P, Maja P, Matchaba G, *et al.*: Impact of lamivudine on HIV and hepatitis B virus-related outcomes in HIV/hepatitis B virus individuals in a randomized clinical trial of antiretroviral therapy in southern Africa. *AIDS* 2011;25:1727–1735.
17. Hoffmann CJ, Charalambous S, Martin DJ, Innes C, Churchyard GJ, Chaisson RE, *et al.*: Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program. *Clin Infect Dis* 2008;47:1479–1485.
18. Sarfo FS, Kasim A, Phillips R, Geretti AM, Chadwick DR: Long-term responses to first-line antiretroviral therapy in HIV and hepatitis B co-infection in Ghana. *J Infect* 2014;69:481–489.
19. Danel C, Moh R, Minga A, Anzian A, Ba-Gomis O, Kanga C, *et al.*: CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): A randomised trial. *Lancet* 2006;367:1981–1989.
20. Danel C, Moh R, Chaix M-L, Gabillard D, Gnokoro J, Diby C-J, *et al.*: Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: A randomized trial involving West African adults. *J Infect Dis* 2009;199:66–76.
21. Boyd A, Moh R, Gabillard D, le Carrou J, Danel C, Anglaret X, *et al.*: Low risk of lamivudine-resistant HBV and hepatic flares in treated HIV-HBV-coinfecting patients from Côte d’Ivoire. *Antivir Ther* 2015;20:643–654.
22. Velen K, Charalambous S, Innes C, Churchyard GJ, Hoffmann CJ: Chronic hepatitis B increases mortality and complexity among HIV-coinfecting patients in South Africa: A cohort study. *HIV Med* 2016;17:702–707.
23. Boyd A, Houghtaling L, Moh R, Abdou Chekaraou M, Gabillard D, Eholié SP, *et al.*: Clinical outcomes during treatment interruptions in HIV-hepatitis B virus co-infected patients from Sub-Saharan Africa. *Am J Trop Med Hyg* 2017;97:1936–1942.
24. Royston P, Sauerbrei W: A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med* 2004;23:2509–2525.
25. Nash D, Katyal M, Brinkhof MWG, Keiser O, May M, Hughes R, *et al.*: Long-term immunologic response to antiretroviral therapy in low-income countries: A collaborative analysis of prospective studies. *AIDS* 2008;22:2291–2302.
26. Lawn SD, Myer L, Edwards D, Bekker L-G, Wood R: Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS* 2009;23:1717–1725.
27. de Monteynard L-A, Matheron S, Gilquin J, Pavie J, de Truchis P, Grabar S, *et al.*: Influence of geographic origin, sex, and HIV transmission group on the outcome of first-line combined antiretroviral therapy in France. *AIDS* 2016;30:2235–2246.
28. Ioannou GN, Bryson CL, Weiss NS, Miller R, Scott JD, Boyko EJ: The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. *Hepatology* 2013;57:249–257.
29. Collazos J, Valle-Garay E, Carton JA, Montes AH, Suarez-Zarracina T, De la Fuente B, *et al.*: Factors associated with long-term CD4 cell recovery in HIV-infected patients on successful antiretroviral therapy. *HIV Med* 2016;17:532–541.
30. Nakanjako D, Kiragga AN, Musick BS, Yiannoutsos CT, Wools-Kaloustian K, Diero L, *et al.*: Frequency and impact of suboptimal immune recovery on first-line antiretroviral therapy within the International Epidemiologic Databases to Evaluate AIDS in East Africa. *AIDS* 2016;30:1913–1922.
31. Lawn SD, Myer L, Bekker L-G, Wood R: CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. *BMC Infect Dis* 2006;6:59.