HIGHER RATES OF HBsAG CLEARANCE WITH TDF-CONTAINING THERAPY IN HBV/HIV COINFECTION

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Background

HIV-infected individuals are at high risk of developing chronic hepatitis B (HBV) after acute infection, while functional cure of this chronic infection (Hepatitis B surface antigen [HBsAg] clearance, eventually followed by acquisition of anti-hepatitis B surface antigen [Anti-HBs]) is a rare event.
Related factors to HBV cure in this setting are not fully characterized, and there are no data on quantitative HBsAg follow-up.
Primary objective: HBsAg loss and Anti-HBs seroconversion incidence calculation.

Methods

HIV-infected individuals with chronic HBV infection starting combined antiretroviral-anti-HBV treatment were retrospectively included from the French National Dat'AIDS cohort (NCT02898987).
Inclusion criteria:
- Positive HBsAg for at least 6 months
- HBV/HIV therapy initiation (e.g. 3 groups of treatment)

HCV co-infected subjects and individuals receiving Entecavir or Interferon were **excluded.**
Primary outcome measures were HBsAg clearance confirmed by HBsAg loss and Anti-HBs seroconversion on two consecutive measurements.

Study flowchart

A total of **1419 Individuals** were allocated to three groups according to HBV therapy schedule (Figure 1).

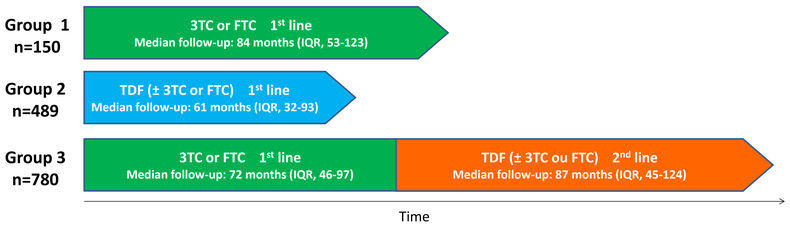

Figure 1. Study design and median follow-up according to HBV therapy schedule.

Statistical analysis

We used a Bayesian approach to compare HBsAg clearance at month 72 of HBV/HIV active therapy (half of the participants still on follow-up at that date) in a multivariate logistic regression model.
Using lowly informative *priors, posterior* distribution parameters were estimated using program JAGS within the rjags package in R version 3.1.1 in a mixt logistic model.
Predictors of HBsAg clearance are expressed as relative risks.
Predictors of HBsAg clearance were considered as clinically relevant when the **probability (Pr) of the Odds ratio (OR) being above 1 or under 1 was of at least 95%.**

Results

Patients' characteristics

Participant's baseline characteristics were similar between groups (*Table 1*).

Table 1. Baseline demographics and biological parameters on antiretroviral-anti-HBV therapy

Group*	n	HIV-1 /HIV-2	Time since HIV Infection (months)	C CDC stage	CD4 nadir (/mm³)	Male	HTS /MSM	Age (years)	French /African	HDV	Time since HBV Infection (months)	Baseline		
												HIV-RNA (log_{10} copies/mL)	CD4 T cells (/mm³)	HBV-DNA (log_{10} copies/10^6 PBMCs)
Group 1	150	149 /1	10 (6-14)	49 (33%)	164 (26-317)	127 (84%)	53 /79	36 (31-43)	54 /30	4 (3%)	7 (7-8)	4.7 (3.8-5.0)	301 (200-420)	3.6 (3.4-4.2)
Group 2	489	479 /10	6 (6-11)	138 (28%)	148 (10-264)	325 (66%)	318 /133	38 (32-45)	116 /253	37 (8%)	6 (6-7)	4.7 (4.1-5.3)	250 (129-380)	3.7 (3.4-4.2)
Group 3	780	776 /8	9 (6-13)	296 (38%)	111 (11-238)	625 (80%)	285 /414	34 (29-41)	270 /204	44 (6%)	7 (6-7)	4.8 (4.1-5.3)	253 (120-378)	3.8 (3.3-4.1)
Total	1419	1404 /19	10 (6-13)	483 (34%)	133 (13-251)	1077 (76%)	656 /626	37 (30-43)	440 /487	85 (6%)	7 (6-7)	4.8 (4.0-5.2)	257 (131-382)	3.7 (3.4-4.1)

Results are expressed as n (%) or median(IQR).
HTS, heterosexual; MSM, Men who have sex with men, HDV, hepatitis Delta virus.

HBsAg clearance and Anti-HBs seroconversion

Patients were followed-up for a median of 89 months (IQR, 56-118).
In asubset of individuals with available HBsAg quantitative data, the median HBsAg level at baseline was of 1287 (IQR, 262-5094).

HBsAg clearance and Anti-HBs seroconversion incidence:
- 97 individuals cleared HBsAg (6.8%) → **0.7/100 patient-years**
- of whom, 67 seroconverted for Anti-HBs (4.7%) → **0.5/100 patient-years**

HBsAg clearance occurred in 25, 19 and 53 individuals in group 1, 2 and 3 at a median time of 73, 45 and 137 months, respectively.
Figure 2 depicts Kaplan-Meier analysis of both HBsAg clearance and Anti-HBs seroconversion according to HBV therapy regimen.

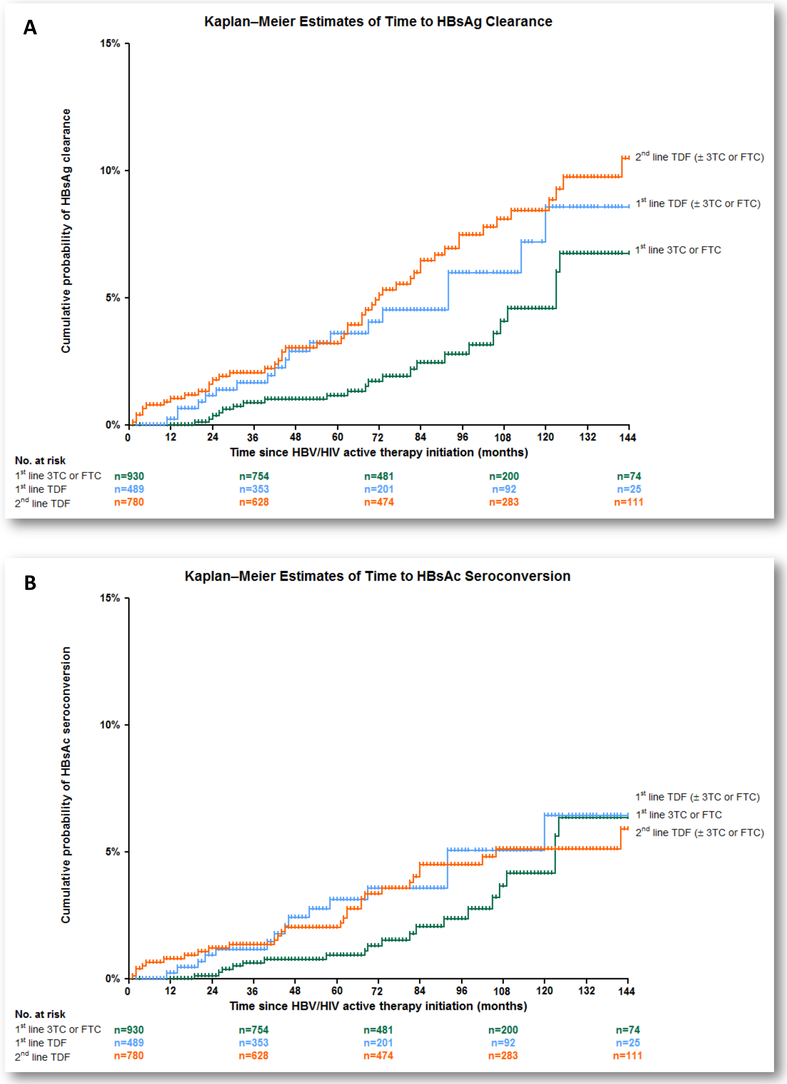

Figure 2. Kaplan-Meier estimates of time to (A) HBsAg clearance and (B) Anti-HBs seroconversion according to anti-HBV therapy.

HBsAg clearance proportion (Figure 2A) is relevantly higher on TDF-containing regimen during all the follow-up.
Anti-HBs seroconversion proportion (Figure 2B) is relevantly higher on TDF-containing regimen before month 96, but is less accurate after month 96 because of the limited number of subjects.

Multivariate predictors of HBsAg clearance

Multivariate Bayesian analysis (Table 2) showed a high CD4 nadir, a short delay between HBV diagnosis and treatment, a longer time on HBV therapy, an African origin and TDF-based therapy as independent predictors of HBsAg clearance (Probability of odds ratio [OR]>1, >95%).

Table 2. Multivariate analysis

Variable	OR	95% (Credibility interval)	Pr [OR > 1)
Delay between HBV diagnosis and treatment (per 1-month increment)	0.95	0.91-1.00	3%
Time on HBV therapy (per 1-month increment)	1.08	1.04-1.13	100%
African origin	2.32	1.28-3.97	99%
TDF 1st line	3.03	1.41-5.02	100%
TDF 2nd line	2.95	1.37-5.53	96%
CD4 Nadir (per 100-/mm³ increment)	1.08	0.96-1.20	95%

Of note, Bayesian analysis suggested that TDF-based regimen as first line (OR, 3.03) or second line (OR, 2.95) increased rates of HBsAg clearance at 72 months when compared to 3TC/FTC alone as first line (Figure 3).

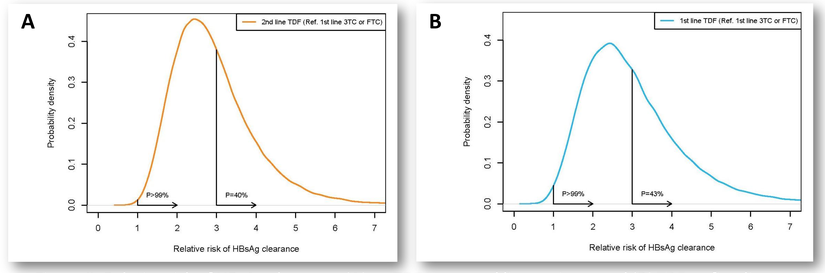

Figure 3. Relative risk of HBsAg clearance (A) on TDF as second line regimen and (B) TDF as first line regimen, compared to FTC or 3TC as first line.

Quantitative HBsAg & HBV-DNA follow-up

Longitudinal follow-up of quantitative HBsAg (Figure 4) on treatment showed a slow decrease in HBsAg serum levels (-1 IU/mL per year).

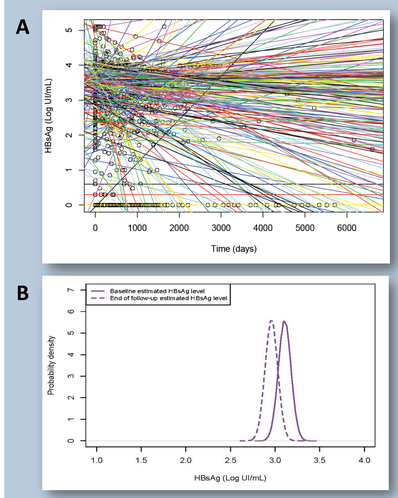

Figure 4. HBsAg dynamics on HBV therapy (A) and Bayesian modelling of HBsAg evolution at baseline and at the end of follow-up (B) [n=259].

Median HBV-DNA decreased from 3.65 to 2.06 log IU/mL, from baseline to the end of follow-up, respectively (Figure 5), with 89% being undetectable (<15 IU/mL) at the end of follow-up.

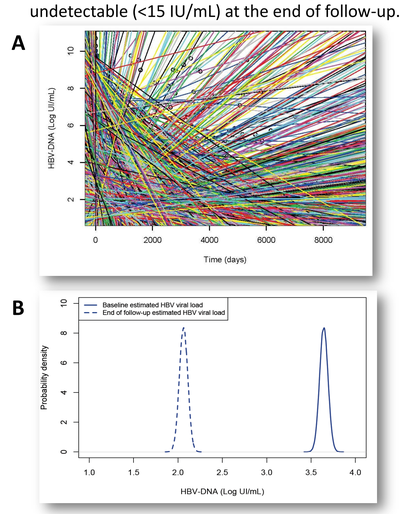

Figure 5. HBV-DNA dynamics on HBV therapy (A) and Bayesian modelling of HBV-DNA evolution at baseline and at the end of follow-up (B) [n=896].

Conclusions

HBsAg clearance and Anti-HBs seroconversion rates were low while on HBV therapy at 0.7 and 0.5 per 100 patients-years, respectively. Higher CD4 nadir, prompt initiation of HBV therapy, mainly with TDF-based regimen, improved HBsAg clearance. Quantitative HBsAg significantly decreased, therefore could be a prognostic factor of HBV clearance.