Long-term trends in qHBsAg levels in persons with and without functional HBV cure in the Swiss HIV Cohort Study

SWISS HIV COHORT STUDY

Lorin Begré[1,2], Anders Boyd[3], Franziska Suter-Riniker[4], Charles Béguelin[1], Jürgen Rockstroh[5], Huldrych F. Günthard[6], Alexandra Calmy[7], Matthias Cavassini[8], Marcel Stöckle[9], Patrick Schmid[10], Enos Bernasconi[11], Massimo Levrero[12], Fabien Zoulim[12], Gilles Wandeler[1]*, Andri Rauch[1]* and the Swiss HIV Cohort Study
* equal contribution

[1]Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Graduate School for Health Sciences, University of Bern, Bern, Switzerland; [3]Department of Infectious Diseases, Research and Prevention, Public Health Service of Amsterdam, and stichting hiv monitoring Amsterdam, The Netherlands; [4]Institute for Infectious Diseases, University of Bern, Bern, Switzerland; [5]HIV Clinic, Department of Medicine, University Hospital Bonn, Bonn, Germany; [6]University Hospital Zurich and Institute of Medical Virology, University of Zurich, Zurich, Switzerland; [7]Division of Infectious Diseases, University Hospital Geneva, University of Geneva, Geneva, Switzerland; [8]Division of Infectious Diseases, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland; [9]Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland; [10]Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [11]Division of Infectious Diseases, Regional Hospital Lugano, University of Geneva and University of Southern Switzerland, Lugano, Switzerland; [12]Hepatology Department, INSERM U1052, Hospices Civils de Lyon, Cancer Research Center of Lyon, University of Lyon, Lyon, France

Background:
- Functional cure of hepatitis B virus (HBV) infection occurs infrequently in persons living with HIV and hepatitis B
- Individual trends in quantitative hepatitis B surface antigen (qHBsAg) levels could predict functional HBV cure

Objective:
To compare long-term trends in qHBsAg levels among persons living with HIV and hepatitis B with and without functional HBV cure during treatment with tenofovir in the Swiss HIV Cohort Study

Table 1: Baseline characteristics of participants with and without functional HBV cure.

	Participants with functional HBV cure N = 29	Participants without functional HBV cure N = 29	p-value
Female sex	6/29 (21%)	6/29 (21%)	1.00
Median age [years]	42.0 (38.0-46.0)	39.0 (36.0-46.0)	0.28
European origin	22/29 (76%)	14/29 (48%)	0.06
Median BMI [kg/m^2]	22.9 (21.0-25.5)	22.7 (19.2-26.9)	0.93
Lamivudine pre-treatment	24/29 (83%)	24/29 (83%)	1.00
CD4$^+$ T-cell count <200 cells/µl	4/29 (14%)	4/29 (14%)	1.00
CDC stage C	8/29 (28%)	10/29 (34%)	0.78
Median HBV DNA [log$_{10}$ IU/ml]	3.0 (1.2-7.5)	4.0 (1.5-7.9)	0.98
Median qHBsAg [log$_{10}$ IU/ml]	3.4 (2.1-4.5)	4.0 (3.5-4.2)	0.15
qHBsAg <1 log$_{10}$ IU/ml	5/29 (17%)	1/29 (3%)	0.19
HBeAg positive	13/27 (48%)	10/24 (42%)	0.78
ALT elevation	16/29 (55%)	15/29 (52%)	1.00

ALT: alanine aminotransferase, BMI: body mass index, CDC: centers for disease control and prevention, DNA: deoxyribonucleic acid, HBeAg: hepatitis B e antigen, HBV: hepatitis B virus, qHBsAg: quantitative hepatitis B surface antigen

Time to functional HBV cure
- Median time to qHBsAg <0.05 IU/ml: 48 months (IQR 12-96)
- 8/29 (28%) participants experienced functional HBV cure during the first year of tenofovir therapy
- 5/29 (17%) participants experienced functional HBV cure during the second year of tenofovir therapy
- 4/29 (14%) participants experienced functional HBV cure 2 to 5 years after tenofovir start
- 11/29 (38%) participants experienced functional HBV cure 5 to 10 years after tenofovir start

Table 2: Proportion of participants with >1 log$_{10}$ IU/ml decline during treatment with tenofovir.

qHBsAg decline	Participants with functional HBV cure* N = 24	Participants without functional HBV cure* N = 28	p-value
>1 log$_{10}$ IU/ml after 1 year	13/24 (54%)	2/28 (7%)	<0.001
>1 log$_{10}$ IU/ml after 2 years	19/24 (79%)	2/28 (7%)	<0.001
>1 log$_{10}$ IU/ml after 5 years	22/24 (92%)	3/25 (12%)	<0.001
>1 log$_{10}$ IU/ml after 10 years	19/19 (100%)	5/18 (28%)	<0.001

* only participants with qHBsAg >1 log10 IU/ml at start of tenofovir therapy included.
HBV: hepatitis B virus, qHBsAg: quantitative hepatitis B surface antigen

Material and methods:
- 29 participants who experienced functional HBV cure and 29 participants without functional HBV cure on tenofovir-containing antiretroviral therapy
- Median of 12 qHBsAg measurements per participant (interquartile range [IQR] 9-15)
- 1:1 matching based on age (10-year calliper), sex, pre-treatment with lamivudine and CD4$^+$ T-cell count category
- Functional HBV cure defined as first qHBsAg <0.05 IU/ml.
- Assessment of time from start of tenofovir treatment to functional HBV cure. qHBsAg measured 6-monthly during the first 2 years of tenofovir treatment and 12-monthly thereafter.
- Modelling of qHBsAg levels over time using linear regression with time as function of fractional polynomials

Figure: Trends in quantitative HBsAg levels in participants with (A) and without (B) functional HBV cure during treatment with tenofovir.

qHBsAg levels modelled as fractional polynomials of time (dashed line) with 95% confidence intervals (shaded area) and individual trajectories of qHBsAg (circles with connecting solid lines).
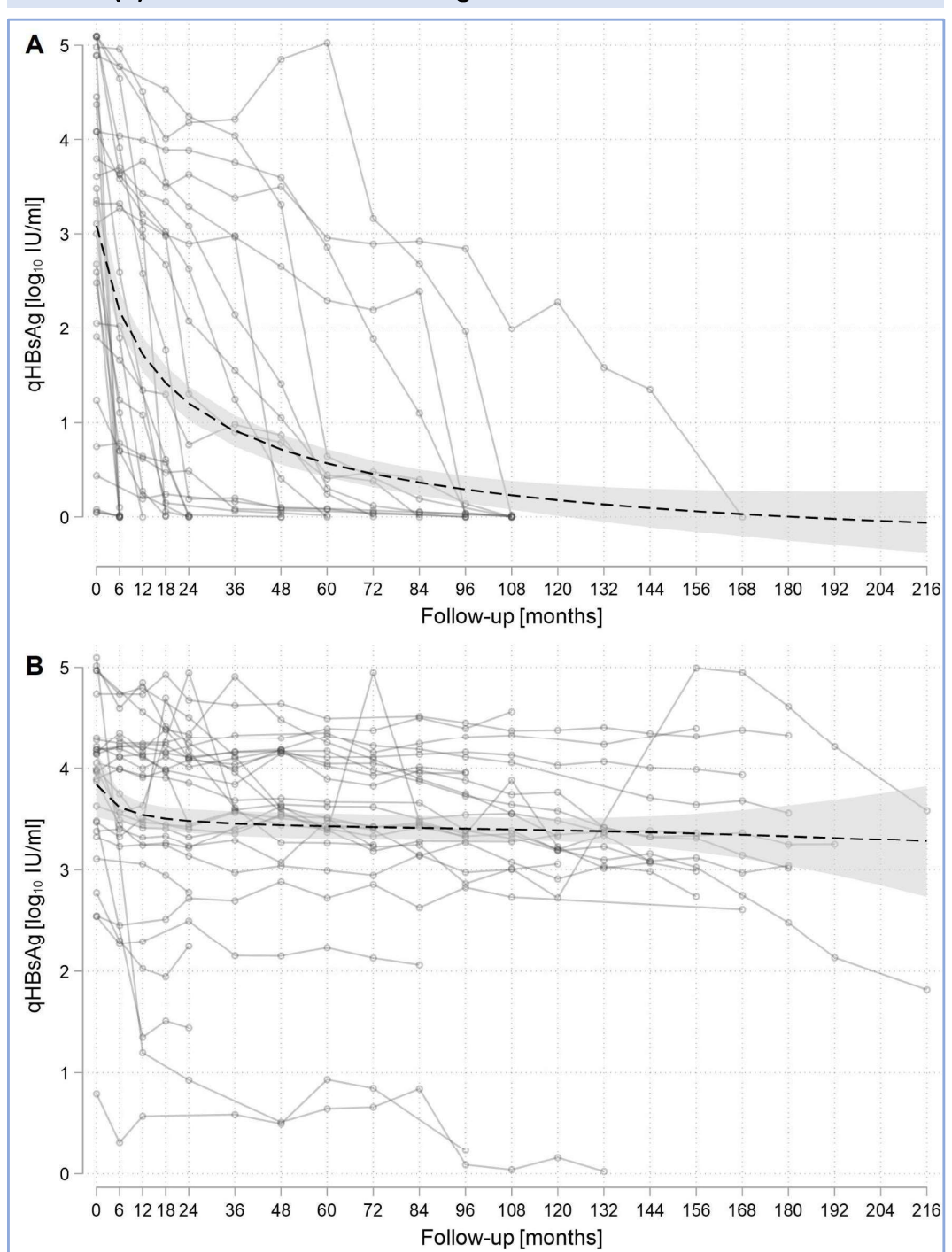
Conclusion:
Most persons living with HIV/HBV exhibiting functional HBV cure experienced a more than 1-log10 decline in qHBsAg levels within the first two years on tenofovir. However, some persons with functional HBV cure did not have an immediate qHBsAg decline. In most patients without functional HBV cure, qHBsAg levels remained remarkably stable during long-term follow-up.