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SHORT COMMUNICATION

Long-term quantitative hepatitis B surface antigen (HBsAg) trajectories in persons with and without HBsAg loss on tenofovir-containing antiretroviral therapy

Lorin Begré[1,2] | **Anders Boyd**[3,4] | **Luisa Salazar-Vizcaya**[1] | **Franziska Suter-Riniker**[5] | **Charles Béguelin**[1] | **Jürgen K. Rockstroh**[6] | **Huldrych F. Günthard**[7,8] | **Alexandra Calmy**[9] | **Matthias Cavassini**[10] | **Marcel Stöckle**[11] | **Patrick Schmid**[12] | **Enos Bernasconi**[13] | **Massimo Levrero**[14,15] | **Fabien Zoulim**[14,15] | **Gilles Wandeler**[1] | **Andri Rauch**[1] | **the Swiss HIV Cohort Study (SHCS)**

[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, Amsterdam, The Netherlands

[4]Stichting HIV Monitoring Amsterdam, Amsterdam, The Netherlands

[5]Institute for Infectious Diseases, University of Bern, Bern, Switzerland

[6]HIV-Clinic, Department of Medicine I, University Hospital Bonn, Bonn, Germany

[7]Department of Infectious Diseases, University Hospital Zurich, Zurich, Switzerland

[8]Institute of Medical Virology, University of Zurich, Zurich, Switzerland

[9]Division of Infectious Diseases, University Hospital Geneva, University of Geneva, Geneva, Switzerland

[10]Division of Infectious Diseases, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland

[11]Division of Infectious Diseases & Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland

[12]Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

[13]Division of Infectious Diseases, Regional Hospital Lugano EOC, University of Geneva and University of Southern Switzerland, Lugano, Switzerland

[14]Hepatology Department, Hospices Civils de Lyon and University of Claude Bernard Lyon 1 (UCLB1), Lyon, France

[15]UMR Inserm U1052–CNRS 5286, Cancer Research Center of Lyon (CRCL), Lyon, France

Correspondence
Lorin Begré, Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse, 3010 Bern, Switzerland.
Email: lorinaaron.begre@insel.ch

Abstract

Objectives: Improving the understanding of the patterns of quantitative hepatitis B surface antigen (qHBsAg) trajectories associated with HBsAg loss is important in light of novel anti-hepatitis B virus agents being developed. We

Gilles Wandeler and Andri Rauch contributed equally.

The members of the Swiss HIV Cohort Study (SHCS) are listed in Appendix A.

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evaluated long-term qHBsAg trajectories in persons with HIV and HBV during tenofovir-containing antiretroviral therapy in the Swiss HIV Cohort Study.

Methods: We included 29 participants with and 29 without HBsAg loss, defined as qHBsAg <0.05 IU/mL. We assessed qHBsAg decline during therapy in both groups and used agglomerative hierarchical clustering to identify different qHBsAg trajectory profiles in persons with HBsAg loss.

Results: The median follow-up time was 11.9 years (IQR 8.4–14.1), and the median time to HBsAg loss was 48 months (IQR 12–96). Among participants with HBsAg loss, 79% had a qHBsAg decline ≥1 $\log_{10}$ IU/mL 2 years after starting tenofovir. The trajectories in qHBsAg levels during tenofovir therapy were heterogeneous, characterized by five distinct profiles. Among participants without HBsAg loss, only 7% had a qHBsAg decline ≥1 $\log_{10}$ IU/ml after 2 years.

Conclusions: Most persons with HIV who experienced HBsAg loss had an early decline in qHBsAg levels, with diverse trajectories during long-term tenofovir therapy. In persons without HBsAg loss, qHBsAg levels remained remarkably stable over time.

KEYWORDS
HBsAg, hepatitis B, HIV, tenofovir, trajectories

INTRODUCTION

In the era of widely available antiretroviral therapy (ART), hepatitis B virus (HBV) coinfection remains an important cause of morbidity and mortality among persons with HIV (PWH) [1]. The majority of persons with HIV and HBV are treated with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) as part of their ART, as recommended by international guidelines [2, 3]. This treatment usually suppresses HBV viral load (VL), but a sterilizing cure of HBV infection cannot be achieved [4]. Hepatitis B surface antigen (HBsAg) loss is associated with improvements in clinical outcomes, including a reduction in hepatocellular carcinoma incidence [5]. PWH may have higher rates of HBsAg clearance compared to persons without HIV, but persistence of this outcome remains unclear [6, 7]. In the Swiss HIV Cohort Study (SHCS), 16% of 262 persons with HIV/HBV starting tenofovir-containing ART experienced HBsAg clearance [8]. Therefore, current guidelines recommend lifelong HBV therapy in persons with HIV/HBV [2, 3].

Low quantitative hepatitis B surface antigen (qHBsAg) levels before starting HBV therapy have been associated with higher odds of achieving HBsAg loss among persons with and without HIV [9, 10]. However, there are limited data on the long-term trajectories of qHBsAg levels in persons experiencing HBsAg loss during tenofovir-containing ART. Understanding patterns of qHBsAg trajectories which are associated with HBsAg loss is important to inform clinical trials evaluating novel anti-HBV agents [11].

We aimed to evaluate long-term trajectories of qHBsAg and HBV DNA levels in persons with HIV/HBV with and without HBsAg loss during tenofovir-containing ART in the SHCS [12]. Furthermore, we used a clustering method to identify distinct qHBsAg trajectory profiles among participants with HBsAg loss.

METHODS

We included persons with HIV and chronic hepatitis B, defined as two consecutive positive HBsAg tests at least 6 months apart, who started TDF or TAF and experienced HBsAg loss during follow-up in the SHCS. For comparison, we selected participants remaining HBsAg-positive with similar baseline characteristics using 1:1 matching based on age (±10 years), sex at birth, lamivudine treatment prior to initiating tenofovir, and CD4+ T-cell count category at start of tenofovir therapy (<200, 200–349, ≥350 cells/μL). Main outcomes were the proportion of participants with ≥1 $\log_{10}$ IU/ml decline after 1 and 2 years of follow-up, the median decline in qHBsAg levels after 1 and 2 years of follow-up, the time to HBsAg loss and the proportion of participants with HBV viral suppression and hepatitis B surface antibody (anti-HBs) seroconversion.

The SHCS (www.shcs.ch) is an ongoing, nationally-representative cohort study, which includes over 70% of

all PWH on ART in Switzerland [12]. Sociodemographic and clinical data, and laboratory data are prospectively recorded at registration and every 6 months thereafter using standardized protocols (http://shcs.ch/292-instructions). All centres' local ethical committees approved the cohort study, and all patients provided written informed consent.

We defined baseline as the start date of the first tenofovir-containing ART and measured qHBsAg and HBV DNA using stored plasma samples at baseline, after 6, 12, 18 and 24 months, and yearly thereafter until the last available sample before death, loss to follow-up, 6 months after cessation of the last tenofovir-containing regimen, or database closure on 31 December 2020, whichever happened first. Participants could switch between TDF and TAF during follow-up, and follow-up continued after the interruption of tenofovir if participants resumed tenofovir therapy any time later on. However, follow-up was censored if participants did not resume tenofovir therapy. We defined the time point of HBsAg loss as the first occurrence of a qHBsAg measurement <0.05 IU/mL. Anti-HBs seroconversion was defined as an anti-HBs measurement ≥10 IU/L after HBsAg loss, and HBV viral suppression as a HBV DNA < 20 IU/mL. Liver cirrhosis was assessed by liver biopsy, transient elastography >11 kPA or aspartate aminotransferase to platelet ratio index (APRI) >2 as described previously [13].

qHBsAg measurements were performed using a commercial chemiluminescent microparticle immunoassay (ARCHITECT HBsAg, Abbott, Sligo, Ireland) with a sensitivity of ≤0.05 IU/mL. When summarizing qHBsAg decline, missing qHBsAg measurements after start of tenofovir treatment were linearly interpolated with the closest neighbouring values. HBV DNA was assessed with quantifications performed during routine clinical care using accredited assays with a lower limit of detection ≤20 IU/mL or with the commercial quantitative nucleic acid test COBAS HBV on the COBAS 4800 system (Roche Diagnostics, Rotkreuz, Switzerland). In participants with HBsAg loss, we quantified anti-HBs at the time of HBsAg loss and in the latest available stored plasma sample using a commercial chemiluminescent microparticle immunoassay (Alinity i Anti-HBs, Abbott, Sligo, Ireland).

We modelled qHBsAg levels and HBV VL over time using generalized linear models with maximum likelihood estimation, while incorporating follow-up time as restricted cubic splines with five knots located at the 5th, 27.5th, 50th, 72.5th and 95th percentile. We identified distinct profiles of individual qHBsAg trajectories among participants with HBsAg loss using an agglomerative hierarchical clustering algorithm on the individual's qHBsAg trajectory between baseline and the first qHBsAg < 0.05 IU/mL. In order to cluster participants, we first calculated the Jaccard's distance between each possible pair of participants and used these distances to infer clusters of participants by means of the Ward method as agglomeration criterion using the 'hclust' package in R [14, 15]. We then iteratively assessed cluster-specific qHBsAg trajectories until the fourth level of the hierarchy. All analyses were performed using Stata/MP 16.1 (StataCorp, College Station, TX, USA) and R Statistical Software (v4.1.2; R Core Team 2021, Vienna, Austria).

RESULTS

We included 29 participants experiencing HBsAg loss and 29 remaining HBsAg-positive after starting tenofovir-containing ART. Median follow-up duration was 12.3 years (interquartile range [IQR] 10.4–14.1) for participants with HBsAg loss and 11.1 years (IQR 7.9–14.1) for participants without loss. Median age of all participants was 41 years (IQR 37–46), 12/58 (21%) were assigned female sex at birth, 8/58 (14%) had a CD4+ T-cell count <200 cells/μL and 48/58 (83%) received lamivudine prior to tenofovir therapy for a median duration of 6.3 years (IQR 4.3–7.7) (Table S1). Among participants with available hepatitis B e antigen (HBeAg) status at baseline, 13/27 (48%) with HBsAg loss and 10/24 (42%) without loss were HBeAg-positive. At baseline, the median qHBsAg level was 2293 IU/mL (IQR 113–28 574) among participants with HBsAg loss and 9731 (IQR 2994–16 368) among those without loss. During follow-up, qHBsAg levels were assessed at a median of 12 time points per person (IQR 9–15). Liver cirrhosis was present in 2/29 (7%) participants with and in 4/28 (14%) without HBsAg loss. Treatment interruptions were reported in 12/29 (41%) participants with HBsAg loss (cumulative time without tenofovir: median 374 days, IQR 72–1738) and in 12/29 (41%) without loss (median 469 days, IQR 93–1507). During follow-up, 76% of participants with HBsAg loss and 62% of those without loss reported never missing a dose. Of the participants with HBsAg loss, 4/29 (14%) died and two (7%) left the cohort for HIV care outside of the SHCS. Of those without HBsAg loss, 3/29 (10%) died and four (14%) left the cohort for HIV care outside of the SHCS.

At baseline, HBV VL was suppressed in 8/29 (28%) participants with HBsAg loss and in 7/29 (24%) without loss. In participants with unsuppressed HBV VL at baseline, a first suppressed HBV viral load was observed after a median of 12 months (IQR 6–18 months for participants with HBsAg loss and 6–24 months for those without loss).

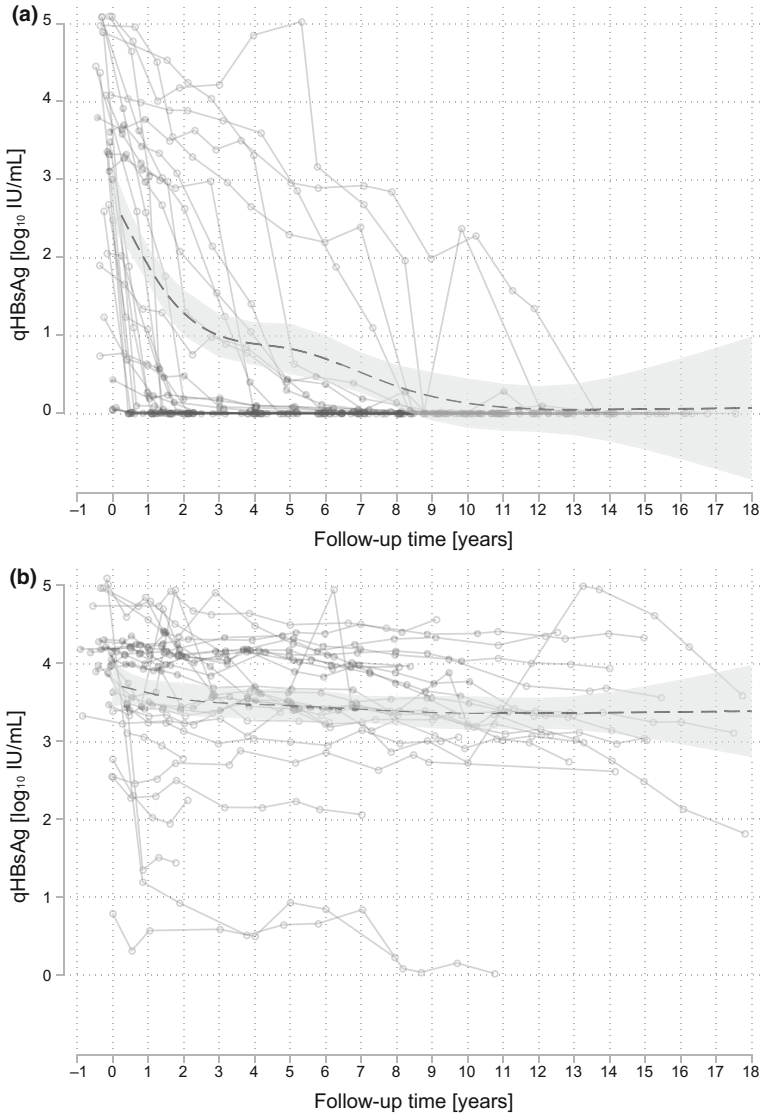

FIGURE 1 Trajectories of quantitative hepatitis B surface antigen (qHBsAg) levels in participants with (a) and without (b) hepatitis B surface antigen (HBsAg) loss during treatment with tenofovir-containing antiretroviral therapy. qHBsAg levels over time modelled using generalized linear model with maximum likelihood estimation, while incorporating follow-up time as restricted cubic splines with five knots located at the 5th, 27.5th, 50th, 72.5th and 95th percentiles (dashed line) with 95% confidence intervals (shaded area) and individual trajectories of qHBsAg (circles with connecting solid lines). Follow-up time refers to time since start of tenofovir therapy.

HBV DNA ≥ 20 IU/mL after initial suppression was observed in 3/29 (10%) participants with HBsAg loss and in 11/27 (41%) without loss. Figure S1a,b shows individual HBV DNA levels over time among participants with and without HBsAg loss.

HBsAg loss occurred after a median of 48 months (IQR 12–96). Among the participants with HBsAg loss, 8/29 (28%) experienced HBsAg loss during the first year of tenofovir therapy, and an additional 5/29 (17%) experienced loss during the second year. 4/29 (14%) participants experienced HBsAg loss during years three to five and 11/29 (38%) 6–10 years after starting tenofovir therapy. Among participants with a qHBsAg ≥1 $\log_{10}$ IU/mL at tenofovir start, 19/24 (79%) participants with HBsAg loss and 2/28 (7%) participants without loss experienced a ≥ 1 $\log_{10}$ IU/mL decline in qHBsAg levels during the first 2 years of tenofovir therapy. Median change in qHBsAg levels was −0.56 IU/mL (IQR −2.16 to −0.18) after 1 year and −1.69 IU/mL (IQR −3.00 to −0.65) after 2 years of tenofovir therapy among participants with HBsAg loss (Figure 1a) and −0.12 IU/mL (IQR −0.34 to −0.03) after 1 year and −0.12 IU/mL (IQR −0.53 to −0.04) after 2 years among participants without loss (Figure 1b). Of the participants with HBsAg loss, 15/28 (54%) had anti-HBs antibodies ≥10 IU/L at some point during follow-up.

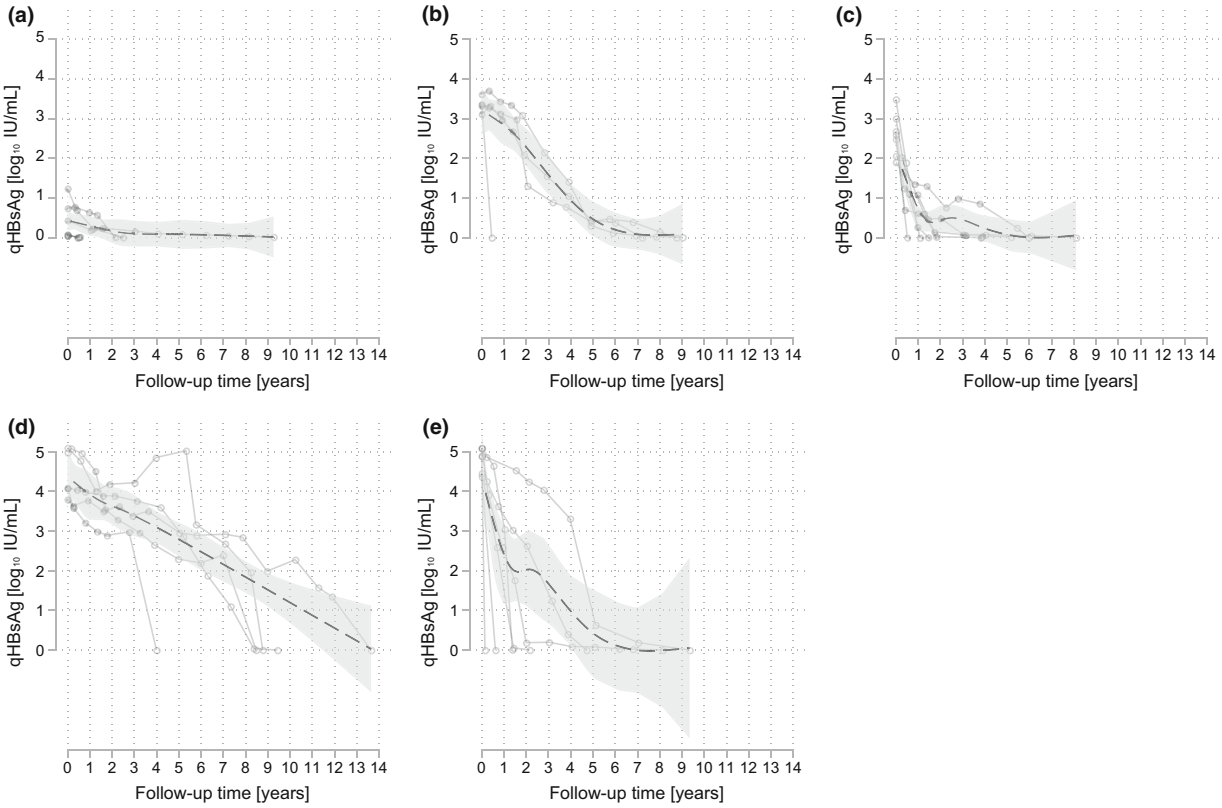

FIGURE 2 Profiles of quantitative hepatitis B surface antigen (qHBsAg) trajectories by means of agglomerative hierarchical clustering among participants with hepatitis B surface antigen (HBsAg) loss during tenofovir-containing antiretroviral therapy: (a) low baseline qHBsAg levels, early HBsAg clearance; (b) intermediate baseline qHBsAg levels, steady decline; (c) intermediate baseline qHBsAg levels, fast decline; (d) high baseline qHBsAg levels, steady decline and (e) high baseline qHBsAg levels, fast decline. qHBsAg levels over time from tenofovir start to first qHBsAg < 0.05 IU/mL for every profile were modelled using generalized linear models (dashed line) with 95% confidence intervals (shaded area). Individual trajectories of qHBsAg levels are represented by circles with connecting solid lines. Follow-up time was incorporated as restricted cubic splines with five knots located at the 5th, 27.5th, 50th, 72.5th and 95th percentiles.

Using agglomerative hierarchical clustering, we inferred five distinct profiles of qHBsAg trajectories among the participants with HBsAg loss (Figure 2, Table S2, Figures S2 and S3).

DISCUSSION

Approximately 80% of participants who experienced HBsAg loss had a $\geq 1-\log_{10}$ decline in qHBsAg levels within the first 2 years of tenofovir-containing ART. In participants without HBsAg loss, qHBsAg levels remained remarkably stable during long-term follow-up. Our data suggest that early qHBsAg level changes precede HBsAg loss during tenofovir-containing ART.

Most participants with HBsAg loss had a rapid decline in qHBsAg levels after starting tenofovir therapy, similar to findings from a Dutch multicentre study [9]. However, a significant proportion of participants experienced a slow decline in qHBsAg levels and achieved HBsAg loss more than 5 years after starting tenofovir therapy, which supports the current recommendations of repeating HBsAg assessments in persons with HIV/HBV beyond the first years of therapy [2, 3]. Spontaneous or treatment-induced HBsAg loss is durable in most persons, although HBsAg seroreversions have been observed in ∼5% of persons with chronic HBV infection [16]. In our study, all participants who experienced HBsAg loss had qHBsAg levels below the limit of detection at the last study visit. Identifying PWH with HBsAg loss has implications for clinical monitoring due to the reduction of the risk for liver-related complications, and may also offer the possibility of receiving tenofovir-free dual antiretroviral therapy in persons without liver cirrhosis [2, 3, 17]. Furthermore, such information could identify persons who would benefit most from novel immunomodulatory therapies.

Using agglomerative hierarchical clustering, we identified five distinct profiles of qHBsAg trajectories among persons with HBsAg loss. One cluster consisted of

individuals with low baseline qHBsAg and HBV DNA levels, whereas the other four clusters had higher baseline levels and differed with regard to the slope of the qHBsAg decline during tenofovir therapy. As HBsAg is produced from cccDNA and integrated DNA, a deeper understanding of the source of HBsAg production patterns in the different phases of infection is needed to predict and monitor HBV treatment responses [18, 19]. Moreover, differences in the restoration of functional immune responses may additionally contribute to the observation of different clusters of qHBsAg trajectories [20]. Considering such clusters when evaluating the effect of novel HBV drugs on qHBsAg levels is important as, for example, individuals reaching HBsAg loss without a fast qHBsAg decline after treatment initiation may be missed in phase II clinical trials with limited follow-up time.

Our study provides detailed information on qHBsAg trajectories in persons with HIV/HBV during long-term tenofovir therapy. Using rigorous inclusion and matching criteria, we were able to compare qHBsAg trajectories in individuals with and without HBsAg loss independent of previous therapy and potential individual demographic and clinical factors. As the main aim of our study was to improve our understanding of the kinetics of qHBsAg trajectories in a small, well-characterized sample of participants, our study was not designed to evaluate specific demographic, clinical and virological predictors of HBsAg loss. For instance, despite similar rates of treatment interruptions in both groups, more frequent HBV replication episodes in participants without HBsAg loss may have reduced the likelihood of achieving undetectable HBsAg levels. In addition, linear interpolation of qHBsAg measurements at years without available plasma sample could have underestimated short-lasting qHBsAg changes, but was unlikely to have substantially affected long-term trajectories. Finally, we could not assess whether HBsAg loss would have persisted after stopping tenofovir therapy as this treatment was continued during follow-up.

In conclusion, our findings show that the majority of persons with HIV/HBV experiencing HBsAg loss have a qHBsAg decline of at least 1 $\log_{10}$ IU/mL within 2 years of tenofovir therapy. However, long-term qHBsAg trajectories among persons who experience HBsAg loss during tenofovir-containing ART were diverse, and HBsAg clearance also occurred more than 5 years after starting tenofovir therapy.

AUTHOR CONTRIBUTIONS

Lorin Begré, Anders Boyd, Massimo Levrero, Fabien Zoulim, Gilles Wandeler and Andri Rauch conceived the study. Lorin Begré and Luisa Salazar-Vizcaya analysed the data. Lorin Begré, Anders Boyd, Gilles Wandeler and Andri Rauch wrote the first draft of the manuscript. Lorin Begré, Franziska Suter-Riniker, Charles Béguelin, Huldrych F. Günthard, Alexandra Calmy, Matthias Cavassini, Marcel Stöckle, Patrick Schmid, Enos Bernasconi, Gilles Wandeler and Andri Rauch collected and provided data for the study. All authors interpreted the data, reviewed and commented on the draft, and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Lorin Begré, Anders Boyd, Luisa Salazar-Vizcaya, Franziska Suter-Riniker, Charles Béguelin, Alexandra Calmy, Marcel Stöckle, Patrick Schmid, Massimo Levrero and Fabien Zoulim declared no conflicts of interest.

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ORCID

Lorin Begré https://orcid.org/0000-0003-1015-8947

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

The Swiss HIV Cohort Study (SHCS)

Members of the Swiss HIV Cohort Study. Abela I, Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Hachfeld A, Haerry D (Deputy of 'Positive Council'), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Jackson-Perry D (Patient Representatives), Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Kusejko K (Head of Data Centre), Labhardt N, Leuzinger K, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nemeth J, Nicca D, Notter J, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Salazar-Vizcaya L, Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Wandeler G, Weisser M, Yerly S.