# HBV REPLICATION DURING TENOFOVIR THERAPY IS FREQUENT IN HIV/HBV-COINFECTION

**Eveline Hofmann[1], Bernard Surial[1], Noémie Boillat-Blanco[2], Huldrych F Günthard[3,4], Marcel Stöckle[5], Enos Bernasconi[6], Patrick Schmid[7], Alexandra Calmy[8], Franziska Suter-Riniker[9], Andri Rauch[1], Gilles Wandeler[1,10], Charles Béguelin[1] and the SHCS**

**Author Affiliations:** [1]Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Service of Infectious Diseases, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [3]Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; [4]Institute of Medical Virology; University of Zurich, Zurich Switzerland; [5]Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland; [6]Division of Infectious Diseases, Regional Hospital of Lugano, Lugano, Switzerland; [7]Division of Infectious Diseases, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland; [8]Division of Infectious Diseases, Geneva University Hospital, University of Geneva, Geneva, Switzerland; [9]Institute for Infectious Diseases, University of Bern, Switzerland; [10]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

**Corresponding author:**

Eveline Hofmann

Department of Infectious Diseases

Bern University Hospital

University of Bern

CH-3010 Bern – Switzerland

E-Mail: eveline.hofmann@insel.ch

**Running Title:** Tenofovir in HIV/HBV-coinfection

## ABSTRACT

In the Swiss HIV Cohort Study, 61/222 (27%) HIV-suppressed persons with chronic hepatitis B virus (HBV) infection had HBV replication after two years on tenofovir, of whom 77% were suppressed thereafter. Self-reported adherence to therapy and HBV viral load at tenofovir initiation were predictors of persistent replication.



**Key Words:** Coinfection; hepatitis B virus; human immunodeficiency virus; tenofovir; viral replication

## INTRODUCTION

Worldwide, approximately 8% of persons living with HIV (PLWH) have chronic hepatitis B virus (HBV) coinfection [1]. Despite optimal treatment with tenofovir-containing antiretroviral therapy (ART), some individuals experience incomplete HBV suppression: in a systematic review including 550 individuals with HIV/HBV coinfection on tenofovir, only 79% achieved HBV suppression at two years [2]. Ongoing viral replication during antiviral therapy contributes to the progression of liver disease and is associated with a higher risk of developing hepatocellular carcinoma [3-5].

Previous studies have generally included small numbers of individuals from heterogeneous populations over short follow-up periods [4, 6, 7]. We aimed to describe the determinants of persistent HBV replication despite HIV suppression on tenofovir-containing ART in the Swiss HIV Cohort Study (SHCS).

## MATERIAL AND METHODS

We considered all SHCS (www.shcs.ch) participants with chronic HBV infection, defined as the presence of two reactive hepatitis B surface antigen (HBsAg) test results >6 months apart, and at least four years of tenofovir-containing ART before October 2019. Participants with an HIV RNA ≥200 cp/ml at the time-point of HBV virological outcome assessment were considered to have suboptimal ART adherence and excluded from these analyses. Further exclusion criteria were: No HBV DNA or HBsAg available at tenofovir start; and missing HBV DNA measurements on tenofovir. The SHCS is a longitudinal, observational cohort study initiated in 1988 including >80% of PLWH on ART in Switzerland [8]. Clinical and laboratory data were collected prospectively every six months. Self-reported treatment adherence was assessed using standardized questionnaires, with good adherence being defined as having missed zero or one dose of ART during the preceding four weeks [9]. Our main outcomes were HBV suppression at 2 years and at the latest follow-up visit. HBV suppression was defined as HBV DNA <20 IU/mL,

low-level viremia as HBV DNA 20-2000 IU/mL, and high-level viremia as HBV DNA >2000 IU/mL [4]. “Persistent viremia” was defined as an HBV viral load ≥20 IU/mL both after 2 years and at the latest follow-up. The SHCS was approved by the local ethical committees of the participating centers, and written informed consent was obtained from all participants.

Demographic and clinical characteristics at tenofovir start were described using either absolute numbers and proportions, or medians and interquartile ranges (IQR). We determined the proportion of participants with HBV replication (HBV-DNA >20 IU/mL) after two years and persistent replication at the time of the latest available follow-up, and explored related risk factors using multivariable logistic regression adjusted for sex, age, ethnicity, CDC Stage 3, prior HBV-active ART (lamivudine or emtricitabine), hepatitis D virus (HDV)-coinfection, CD4 cell count, as well as HBV DNA levels (per log10 IU/ML) at tenofovir start and treatment self-reported adherence at two years [6]. Statistical analyses were performed using Stata version 16.0.

## RESULTS

### *Study Population*

Of 272 PLWH with chronic hepatitis B, we excluded 21 with replicating HIV and 29 with missing HBV DNA measurements at two years (Supplementary Figure). Among the remaining 222 individuals, median age was 41 years (IQR, 36-47), 43 (19%) were women, 47 (21%) of sub-Saharan African origin, and 162 (73%) had a previous AIDS defining condition (Supplementary Table). At tenofovir start, 130/222 participants (59%) had been previously treated with a lamivudine or emtricitabine containing ART, 3/222 (1%) with a non-HBV active ART, and 89/222 (40%) were ART-naïve. From the 133 ART-experienced individuals at the time of tenofovir initiation, 95 (71%) had an HIV viral load ≤200 cp/ml. Of 221 participants with available measurements, 103 (47%) had a CD4 count >350 cells/µL at tenofovir start. At tenofovir start, 34/221 (15%) had a suppressed HBV viral load, 58/221 (26%) had low-level, and 129/221 (59%)

had high-level hepatitis B viremia. HDV coinfection was documented in 30/218 (14%), of whom 67% were replicating at tenofovir start.

***HBV replication at 2 years***

Hepatitis B viremia was present in 61/222 (27%) participants at two years, including 6/61 (10%) with high-level viremia (Figure 1A). The proportion of individuals reporting good adherence was higher in individuals with a suppressed HBV viral load (144/147, 98%) than in those with ongoing HBV replication (56/61, 92%, *P*=0.03). In multivariable analyses, persistent hepatitis B viremia at two years was associated with high HBV DNA levels at tenofovir start (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.20-1.57), whereas it was less likely in individuals with a CD4 count >350/µl at tenofovir start (OR 0.41, 95% CI 0.19 – 0.90), in those with hepatitis D coinfection (OR 0.07, 95% CI 0.01-0.59), or in individuals with good self-reported adherence at two years (OR 0.04, 95% CI 0.01 – 0.33, Figure 1B).

***Long-term HBV replication***

Participants were followed for a median of 8.4 years (IQR, 5.2-10.9) on tenofovir-containing ART. At the latest follow-up visit, 32 of 205 (16%) participants had HBV replication (Figure 1A). Among 61 individuals with HBV replication at 2 years, 14 (23%) had persistent viremia: 11 (79%) were men, 3 (21%) of sub-Saharan African origin, 8 (57%) had a previous AIDS-defining condition, 7 (50%) had been previously treated with a lamivudine or emtricitabine-containing ART regimen, and 12 (86%) had high-level hepatitis B viremia at tenofovir start. We identified 18/161 (11%) individuals with HBV suppression at two years who experienced incident HBV replication at the latest follow-up visit.

## DISCUSSION

In this nationwide cohort of HIV-suppressed PLWH with HBV coinfection, 27% participants had hepatitis B virus replication after two years of tenofovir-containing ART. After prolonged therapy, only 23% of those with replication at two years had persistent viremia. Self-reported adherence to ART and a high HBV viral load at tenofovir initiation were important predictors of replication at two years.

Although some cohorts of PLWH/HBV with long-term follow-up and comparable proportions of pretreated individuals showed similar HBV suppression rates, our results contrast with recent studies: HBV suppression rates after five years of tenofovir were 96% in an observational study in Taiwan, and 99% in Australia [10, 11]. Differences in the natural history of HBV infection and HBV genotypes across settings, as well as the variations in the definition of HBV suppression could be potential explanations for the different observations [12]. In addition, in the study by Audsley et al, individuals who had previously been treated with tenofovir were also included in the analysis, which may be a reason for the high rates of undetectable hepatitis B viremia at baseline (90% compared to 15% in our cohort) [10].

In our study, participants with sub-optimal self-reported treatment adherence were 25 times more likely to have ongoing HBV replication at two years, despite HIV suppression. These results support the assumption that the adherence level in PLWH and HBV coinfection may have to be higher in order to reach HBV than HIV suppression [4, 6, 13]. As shown in other studies, individuals with HDV coinfection were significantly less likely to have ongoing hepatitis B replication after two years, whereas individuals with high HBV-DNA levels at tenofovir start were more likely to have persistent HBV replication [14]. Even in the presence of HIV, HDV appears to be dominant over HBV and to exert an inhibitory effect on HBV replication [14].

Three-quarters of participants with replicating HBV after two years of tenofovir therapy achieved HBV suppression after prolonged therapy. Thus, replication after two years of tenofovir does not necessarily imply treatment failure; the duration to achieve HBV suppression may be longer, as

it has been shown in previous studies [2, 4]. However, the majority of individuals who achieved HBV suppression in our study had reached this outcome after 3 years of tenofovir therapy [4, 11].

We identified a few participants with suppressed hepatitis B viral load at two years but with replication at a later time point on tenofovir therapy, underlining the importance of long-term follow-up of individuals with HIV/HBV coinfection. First, because ongoing viral replication during antiviral therapy has a negative impact on serological and clinical outcomes [3-5]. Second, because the mechanisms for the reemergence of HBV replication are still unclear and, as shown in our study, HIV suppression does not seem to be a good proxy for HBV suppression.

Our study is one of the largest to have examined long-term data on HBV replication during continuous tenofovir therapy among persons with suppressed HIV RNA. However, during the observation period, most participants received tenofovir disoproxil fumarate (TDF) and not tenofovir alafenamide (TAF). Although previous studies showed a comparable efficacy of TDF and TAF in viral suppression in HBV monoinfection, it remains to be determined if results from TDF treatment outcomes are fully applicable to TAF [15]. As we did not systematically measure tenofovir diphosphate levels from dried blood spots, we had to rely on self-reports of treatment adherence with a risk of over-estimating it.

## CONCLUSIONS

Although HBV replication is frequent after two years of tenofovir in HIV/HBV-coinfection, most individuals eventually achieve viral suppression. Clinical and virological long-term monitoring of these individuals is important as virological rebound rarely occurs. In order to minimize the negative impact of persistent HBV replication on clinical outcomes, it will be crucial to understand why a minority of individuals do not reach suppression, including by conducting genome-wide HBV sequencing analyses and immunological studies.

## NOTES

**Acknowledgments:** We thank the participants, physicians, and study nurses for excellent patient care and the data and coordination center for continuous support.

**Members of the SHCS**: 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, Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Kusejko K (Head of Data Centre), Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nemeth J, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Wandeler G, Yerly S.

**Funding:** This study has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (SNF grant number 177499) (to HFG and EB). GW was supported by a Professorship from the Swiss National Science Foundation [PP00P3_176944]. CB was supported by the NEAT-ID Foundation. The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers). AR reports support as Advisory Boards for MSD and Gilead Sciences, travel grants from Gilead Sciences and Pfizer, and research support as investigator-initiated trial grant from Gilead Sciences (all renumeration went to institution).

**Conflict of interest statement:** EH reports support for attending meetings and/or travel from Gilead Sciences and ViiV Healthcare (paid to institution). BS reports grant from Institutional Grant Inselspital Bern; support for attending meetings and/or travel from Gilead Sciecnes and ViiV Healthcare (paid to institution), participation on a Data Safety Monitoring Board or Advisory Board for Gilead Sciences (paid to institution). HFG reports grants from NIH, Yvonne Jacob Foundation, unrestricted research grant by Gilead Sciences (paid to institution), participation on a Data Safety Monitoring Board or Advisory Board for Merck, Gilead Sciences, Janssen, ViiV, GSK, and Novartis (paid to author). MS reports participation on a Data Safety Monitoring Board or Advisory Board for Gilead Sciences, ViiV Health Care, Moderna, MSD, and Pfizer. EB reports grants or contracts from Merck Sharp and Dohme (paid to institution), support for attending meetings and/or travel from Abbvie, Gilead Sciences, Merck Sharp and Dohme, Pfizer AG, and ViiV Healthcare (paid to institution), and participation on a Data Safety Monitoring Board or Advisory Board for Gilead Sciences, Merck Sharp and Dohme, Pfizer AG, ViiV Healthcare, Ely Lilly, and Astra Zeneca (Paid to institution). PS has received consulting/advisory board membership fees from Gilead Sciences. AC reports grants from Gilead, ViiV, Healthcare, MSD (Unrestricted educational grant (Groupe LIPO et métabolisme) – grant to the institution), and MSD (research grant). AR reports advisory Boards for MSD (paid to institution). GW reports grants or contracts from Gilead Sciences and Roche Diagnostics (paid to institution), payment or honoraria for lectures, presentations, speakers, and bureaus, manuscript writing or educational events from Gilead Sciences and MSD (paid to institution). The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. They declared further conflicts of interest outside the submitted work using the ICMJE Form for Disclosure of Potential Conflicts of Interest.

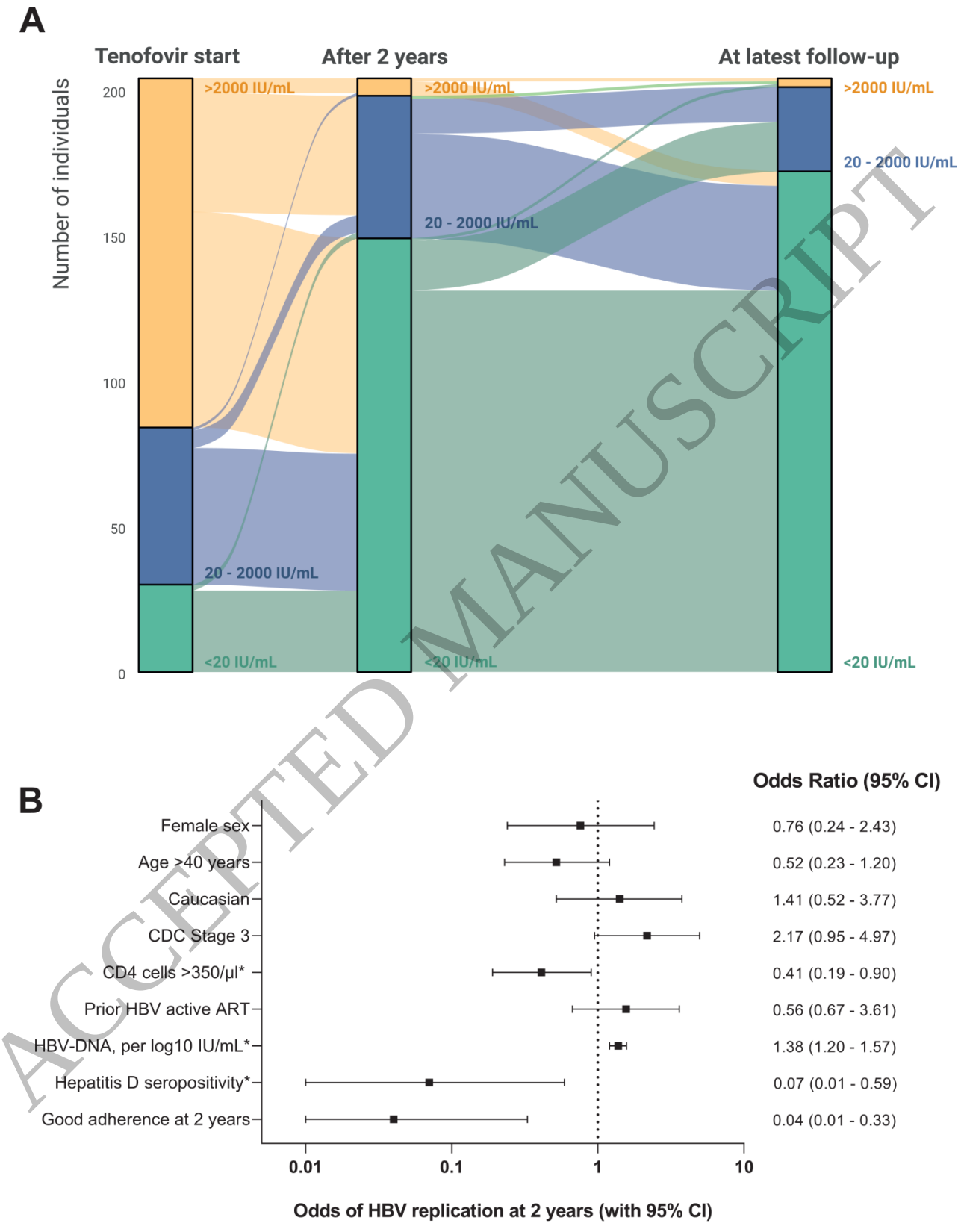
## REFERENCES


1. Leumi S, Bigna JJ, Amougou MA, Ngouo A, Nyaga UF, Noubiap JJ. Global Burden of Hepatitis B Infection in People Living With Human Immunodeficiency Virus: A Systematic Review and Meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2020**; 71(11): 2799-806.
2. Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PloS one **2013**; 8(7): e68152.
3. Sun Y, Wu X, Zhou J, et al. Persistent Low Level of Hepatitis B Virus Promotes Fibrosis Progression During Therapy. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association **2020**; 18(11): 2582-91.e6.
4. Boyd A, Gozlan J, Maylin S, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfected patients undergoing long-term tenofovir: virological and clinical implications. Hepatology (Baltimore, Md) **2014**; 60(2): 497-507.
5. Yip TC, Wong GL, Chan HL, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. Journal of hepatology **2019**; 70(3): 361-70.
6. Matthews GV, Seaberg EC, Avihingsanon A, et al. Patterns and causes of suboptimal response to tenofovir-based therapy in individuals coinfected with HIV and hepatitis B virus. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2013**; 56(9): e87-94.
7. Weissmann L, Picone CM, Gouvêa MSG, et al. Hepatitis B viremia in HIV-coinfected individuals under antiretroviral therapy. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases **2019**; 23(6): 441-50.
8. Scherrer AU, Traytel A, Braun DL, et al. Cohort Profile Update: The Swiss HIV Cohort Study (SHCS). International journal of epidemiology **2022**; 51(1): 33-4j.

9. Glass TR, Sterne JA, Schneider MP, et al. Self-reported nonadherence to antiretroviral therapy as a predictor of viral failure and mortality. Aids **2015**; 29(16): 2195-200.
10. Audsley J, Avihingsanon A, Littlejohn M, et al. Long-Term TDF-Inclusive ART and Progressive Rates of HBsAg Loss in HIV-HBV Coinfection-Lessons for Functional HBV Cure? Journal of acquired immune deficiency syndromes (1999) **2020**; 84(5): 527-33.
11. Huang YS, Sun HY, Chang SY, et al. Long-term virological and serologic responses of chronic hepatitis B virus infection to tenofovir disoproxil fumarate-containing regimens in patients with HIV and hepatitis B coinfection. Hepatology international **2019**; 13(4): 431-9.
12. Liaw YF, Brunetto MR, Hadziyannis S. The natural history of chronic HBV infection and geographical differences. Antiviral therapy **2010**; 15 Suppl 3: 25-33.
13. Chotiyaputta W, Hongthanakorn C, Oberhelman K, Fontana RJ, Licari T, Lok AS. Adherence to nucleos(t)ide analogues for chronic hepatitis B in clinical practice and correlation with virological breakthroughs. Journal of viral hepatitis **2012**; 19(3): 205-12.
14. Boyd A, Lacombe K, Miailhes P, et al. Longitudinal evaluation of viral interactions in treated HIV-hepatitis B co-infected patients with additional hepatitis C and D virus. Journal of viral hepatitis **2010**; 17(1): 65-76.
15. Abdul Basit S, Dawood A, Ryan J, Gish R. Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection. Expert Rev Clin Pharmacol **2017**; 10(7): 707-16.

## FIGURE LEGENDS

**Figure 1** *A*, Distribution and course of HBV DNA levels at tenofovir start, after two years of therapy and at latest follow-up. *B*, Forest plot of possible risk factors for HBV replication (HBV-DNA >20 IU/mL) at two years (multivariable analysis). Good adherence was defined as having missed zero or one, and poor adherence as having missed two or more doses of ART during the preceding four weeks. Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; CDC stage, center for disease control and prevention stage; DNA, deoxyribonucleic acid.




*At tenofovir start

**Figure 1**
**195x260 mm ( x DPI)**