

BRIEF REPORT

Hepatitis B reactivation following switch away from tenofovir-containing anti-retroviral therapy in people living with HIV: A case series and lessons for practice

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The potential for hepatitis B reactivation must be considered when switching people with HIV and prior hepatitis B exposure away from tenofovir-containing combined anti-retroviral therapy. Four

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cases of hepatitis B reactivation from the United Kingdom are presented. Hepatitis B mutations, risk factors and pre- and post-switch recommendations are explored.

INTRODUCTION

Since the advent of combined anti-retroviral therapy (cART), HIV treatment has been based on a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs), typically tenofovir (TFV) plus lamivudine (3TC) or emtricitabine (FTC). More recently, standard-of-care cART regimens can consist of just one NRTI, typically 3TC. Consequently, at least one agent with low-barrier (3TC) or high-barrier (TFV) to resistance activity against hepatitis B virus (HBV) [1] has been part of first-line ART over the last three decades.

However, the cART landscape is evolving, with introduction of regimens with no HBV activity. These include fixed-dose combination dolutegravir/rilpivirine (DTG/RPV) and long-acting cabotegravir/rilpivirine (LA-CAB/RPV), both recommended as suppressed switch options in consensus treatment guidelines [2–4].

When switching to HBV-inactive cART or regimens with low-barrier to HBV resistance, the risk of HBV reactivation in people with prior HBV exposure needs consideration. People at risk have serological evidence of exposure including positive HBV core antibody (anti-HBc), with or without detectable surface antibody (anti-HBs), and undetectable HBV DNA.

HBV reactivates due to the persistence of covalently closed circular DNA (cccDNA) archived in host hepatocyte nuclei [5]. HBV reactivation carries a small but significant risk of fulminant liver failure or death. If it persists undetected then risks include liver cirrhosis and hepatocellular carcinoma, as well as onward transmission. HBV also demonstrates significant genetic variability with high mutation rates. Several HBV genomic variants have important clinical significance given implication in immune and diagnostic escape [6].

We describe four cases of HBV reactivation in people with HIV and prior HBV exposure after switching from TFV-containing cART (Figure 1). We illustrate risk factors and lessons learnt. This includes, to our knowledge, the first reported case of HBV reactivation in a patient on 3TC-containing ART, DTG/3TC.

HBV targeted and whole genome sequencing (WGS) by next-generation sequencing (NGS) was performed (Appendix 1 for methodologies; Appendix 1 Table 1 and 2 for results) and important mutations are briefly explored.

All four cases were HBV genotype A with no drug-related mutations.

HBV reactivations on switch from TFV-containing to HBV-inactive cART

Case 1:

A male (early 40s, born in England) developed HBV reactivation after switching from efavirenz (EFV) + tenofovir disoproxil/emtricitabine (TDF/FTC) to DTG/RPV. He had a history of diet-controlled type 2 diabetes mellitus.

Diagnosed with HIV-1 in 2006 with markers of prior HBV exposure (HBsAg -, anti-HBc +, anti-HBs 20 IU/L), he developed HBV reactivation in 2009 (HBeAg +, HBV DNA 730,000 IU/ml). He initiated HBV active (TDF/FTC) cART (duration 15 years) and HBsAg was lost after 8 years. Anti-HBe and anti-HBs remained negative.

In 2024, four months after switching to HBV-inactive cART (DTG/RPV) he developed asymptomatic HBV reactivation (HBsAg+, HBeAg +, HBV DNA 616,594,900 IU/ml, peak alanine transaminase (ALT) 1,592 IU/ml).

HBV sequencing:

- Escape mutation 122R associated with altered HBsAg expression, immune and diagnostic escape.

Case 2:

A male (early 70s, born in England) with no significant other medical history developed HBV reactivation after switching from raltegravir (RAL) + TDF/FTC to doravirine (DOR) + DTG as part of a clinical trial.

He was informed of a positive anti-HBc result whilst donating blood in the 1970s. Diagnosed with HIV-1 in 2000 with a nadir CD4+ T cell count of 140 cells/mm³, he commenced cART the same year.

He was on HBV-active cART, 3TC (7 years) followed by TDF/FTC (16 years). Prior to trial enrolment, he consistently had anti-HBs >100 IU/L. Despite this, he developed HBV reactivation (HBsAg+, HBeAg +, HBV DNA 616,594,900 IU/ml) 12 months after switching to DOR + DTG. Although monitoring for HBV reactivation was not part of trial protocol, a rise in ALT (59 IU/ml) prompted HBsAg and HBV DNA testing. He remained asymptomatic with peak ALT of 66 IU/ml.

HBV sequencing:

- Escape mutations 142S (detected at 5%) and 144A associated with immune escape.

Case 3:

A male (mid-40s, born in Brazil) developed HBV reactivation after switching from DOR/3TC/TDF to LA-CAB/RPV.

Diagnosed with HIV-1 in 2000, serology in 2003 indicated prior HBV exposure (HBsAg -, anti-HBc +, anti-HBs 80 IU/l). From 2000 he was on HBV active cART including 3TC (8 years) then

TDF/ FTC or 3TC (16 years). He consistently had low-level anti-HBs (29 IU/L at switch) and no other significant medical history.

He switched to LA-CAB/RPV in 2024. HBV reactivation was detected 11 months later (HBsAg +, HBeAg+, HBV DNA 83,176 IU/ml). He developed jaundice and significant transaminitis (peak ALT 3,665 IU/ml) requiring a short hospital admission. Fortunately, ALT improved on starting TFV.

HBV sequencing:

- Escape mutations 133T and 145R associated with immune and diagnostic escape.

HBV reactivation on 3TC-containing ART

Case 4:

A male (late 30s, born in Brazil) developed HBV reactivation after switching from darunavir/ritonavir (DRV/r) + TDF/FTC to DTG/3TC. He had a history of traumatic splenectomy.

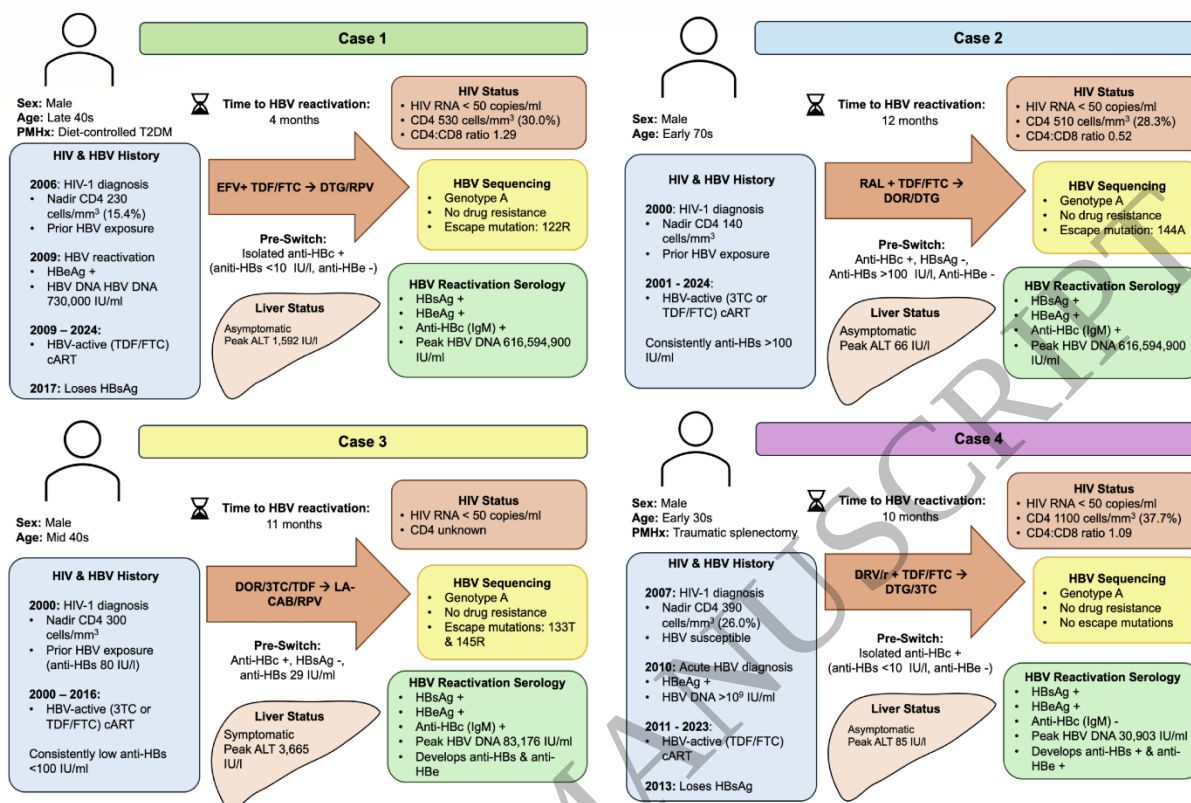
Diagnosed with HIV-1 in 2007 with susceptibility to HBV (HBsAg -, anti-HBc -, anti-HBs <10 IU/L), he did not receive HBV vaccination. He developed acute HBV infection in 2010 with HBV DNA >10⁹ IU/ml. He was untreated until starting HBV active (TDF/FTC containing) cART in 2011, losing HBsAg in 2013, but never mounted anti-HBs or anti-HBe response, thus developing isolated anti-HBc positivity.

He remained on TFV-containing cART (12 years) and switched from DRV/r + TDF/FTC to DTG/3TC in 2024. 10 months after switch, HBsAg was checked as part of routine care and HBV reactivation was confirmed (HBsAg+, HBeAg +, HBV DNA 30,903 IU/ml) with no clinical sequelae and peak ALT 85 IU/l.

HBV sequencing:

- No escape mutations.

Figure 1: Summary of Hepatitis B Reactivation Cases



Legend: ALT: alanine transaminase; Anti-HBc: hepatitis B core antibody; Anti-HBe: hepatitis B e-antibody; Anti-HBs: hepatitis B surface antibody; cART: combined antiretroviral therapy; DOR: doravirine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; LA-CAB: long-acting cabotegravir; PMHx: past medical history; RAL: raltegravir; RPV: rilpivirine; SHB: small hepatitis B surface protein; TDF: tenofovir disoproxil fumarate; T2DM: type 2 diabetes mellitus; 3TC: lamivudine

Lessons from Case Series:

Potential risk factors for HBV reactivation:

- Lack or low anti-HBs titres increases risk of HBV reactivation [7–10]
- Presence of robust anti-HBs does not confer full protection [10].
- Recorded history of HBsAg positivity [11].
- Incomplete immune reconstitution with cART [12], despite normal CD4+ T-cell count and percentage [12].
- Low nadir CD4 count [7,8].
- Ageing-associated immunosenescence [13–15].
- Prior exposure to 3TC or known HBV-associated 3TC resistance if switching to TFV-sparing 3TC-containing regimens.

Pre- & post-switch recommendations:

- People at risk of HBV reactivation should receive appropriate counselling.

Monitoring:

- Test HBsAg, anti-HBs and HBV DNA prior to switching from TFV-containing cART.
- After switch, ideally check HBsAg, HBV DNA and transaminases regularly [3].
- At a minimum monitor ALT regularly, any increase should prompt HBsAg and HBV DNA testing.
- Avoid switch to TFV-free regimens if monitoring is unavailable.
- Clinical trials should include HBV reactivation monitoring if assessing TFV-sparing cART in at-risk participants.
- Certain mutations are associated with HBsAg assay escape [16]; HBV DNA is a more robust marker of reactivation in this circumstance.

Vaccination:

- Offer HBV screening and vaccination to all people with HIV.
- Offer HBV screening and vaccination to partners and household members of people who develop or are at risk of HBV reactivation.
- Currently there is a lack of data to support the role of vaccination in preventing HBV reactivation in people with isolated anti-HBc.

These four cases of HBV reactivation contribute to growing evidence that HBV reactivation is an important consideration when switching away from TFV-containing cART, including 3TC-containing regimens. Analysis of clinical trials data of individuals with isolated anti-HBc positivity treated with DTG/3TC showed no cases of HBV reactivation but testing was only undertaken when HBV reactivation was clinically suspected [17].

Anti-HBc IgM was positive in three cases, an acute marker of primary infection and reactivation. The clinical histories and serology in these cases indicate reactivation. Fortunately, none of these individuals developed fulminant hepatitis, although one did require hospitalisation. All recommenced TFV-containing cART and their HBV markers and liver function normalised over a matter of weeks or short months, in keeping with other studies and case reports [8]. Significant health anxiety and psychological distress related to potential onward transmission was reported in all cases.

NGS confirmed clinically important mutations in three cases at 5% and 20%. 122R is associated with altered expression of HBsAg, immune and diagnostic escape [18]. 145R and 144A are well-described escape mutations that occur in the HBsAg “a” determinant region causing evasion of the host immune response [19]. Mutation-driven structural changes render antibodies less able to bind to HBsAg. 133T is associated with additional N-linked glycosylation sites and has been shown to be associated with immune escape and HBV reactivation [20].

A recent scoping review [8] demonstrated an overall 1.6% HBV reactivation rate in people with anti-HBc positivity (HBsAg negative) treated with HBV-inactive ART. There was significant heterogeneity in risk estimates, which were higher in individuals who lacked detectable anti-HBs. Similar findings were demonstrated in the Veterans Aging Cohort study, with a higher risk (20.2%) in people with a documented history of HBsAg positivity [11]. Caution may be needed in these individuals, although only two of our cases had documented prior HBsAg positivity.

We described several potential risk factors for HBV reactivation, however further research is needed. There is a critical need for evidence-based guidance and risk assessment tools, including safe, pragmatic and cost-effective monitoring strategies across diverse settings. Safe implementation of novel HBV-inactive cART for people living with HIV and prior HBV exposure is of paramount importance and better clinical trial and real-world data is essential to inform best practice.

Ethical statement:

We thank all the patients for consenting to this publication.

Acknowledgements:

The authors have no reported conflicts of interest that are related to the content of this manuscript.

Funding source: None

Author contributions:

FO: conception and design of the manuscript; acquisition, analysis, or interpretation of data for the manuscript; participation in drafting and revision of the manuscript.

PDO: acquisition, analysis, or interpretation of data for the manuscript; participation in drafting and revision of the manuscript.

MJB: acquisition, analysis, or interpretation of data for the manuscript; participation in drafting and revision of the manuscript.

EN: acquisition, analysis, or interpretation of data for the manuscript; participation in drafting and revision of the manuscript.

LW: participation in drafting and revision of the manuscript

PCM: participation in drafting and revision of the manuscript

SF: participation in drafting and revision of the manuscript

AM: acquisition, analysis, or interpretation of data for the manuscript.

IG: conception and design of the manuscript; acquisition, analysis, or interpretation of data for the manuscript; participation in drafting and revision of the manuscript

CB, PG, JB: HBV WGS protocol development and wet lab

MB: Bioinformatic analysis of HBV WGS data

ALT TEXT FOR FIGURE 1:

Cases of hepatitis B reactivation labelled case 1 to 4. Presented in graphical format with demographics, relevant HIV and hepatitis B history, and information pertaining to hepatitis B reactivation including serology, HBV escape mutations and liver outcome.

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ART, antiretroviral therapy; **ARV**, antiretroviral; **CD4**, cluster of differentiation 4; **DDI**, drug–drug interaction; **HIV-1**, human immunodeficiency virus type 1; **MDR**, multidrug-resistant.

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