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Hepatitis B reactivation is rare after switching from tenofovir, two European studies show

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Two large studies of people switching to tenofovir-sparing regimens presented at the 20th European AIDS Conference (EACS 2025) in Paris show that hepatitis B reactivation is a rare event after the hepatitis B-suppressive drug is removed.

Hepatitis B virus (HBV) can be successfully suppressed by antiretroviral regimens containing tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). Switching to a tenofovir-sparing, two-drug HIV treatment regimen poses a risk of hepatitis B reactivation in people with past hepatitis B exposure. As such regimens – including dolutegravir/lamivudine and cabotegravir/rilpivirine – are more widely used, there have been concerns that hepatitis B reactivation may be seen more frequently in people with HIV.

Hepatitis B cccDNA persists in the nucleus of liver cells and cannot be cleared by current hepatitis B antiviral drugs, which stop replication. The withdrawal of antiviral treatment active against hepatitis B can lead to a reactivation of HBV replication. Reactivation can also be triggered by immunosuppression due to ageing or cancers, by immunosuppressive treatment or by loss of vaccine-induced immunity.

The consequences of reactivation can include severe liver inflammation leading to rapid progression of liver disease and onward transmission of hepatitis B. If HBV activity goes undetected for a long time, reactivation could lead to liver cirrhosis or hepatocellular carcinoma (HCC, liver cancer).

Past exposure is signalled by antibodies to hepatitis B core protein (anti-HBc). Around 30% of people with HIV have anti-HBc. People who have been vaccinated against hepatitis B and who have never experienced infection have antibodies to hepatitis B surface protein (anti-HBs) but not to core protein.

Reactivation may be signalled by increases in liver enzymes and the presence of antibodies to hepatitis B core antigen (anti-HBc). An isolated liver enzyme increase in a person who is positive for anti-HBc should be an indicator for further tests for hepatitis B surface antigen (a sign of active viral replication) and hepatitis B DNA to check if reactivation has occurred. In people without prior anti-HBc, a liver enzyme increase accompanied by anti-HBc detection suggests acute hepatitis B infection.

The two studies presented at EACS 2025 investigated the incidence and outcomes of hepatitis B reactivation in people who switched to tenofovir-sparing regimens.

The Swiss HIV Cohort looked at hepatitis B reactivation in people who switched to tenofovir-sparing regimens and who had stored plasma samples from prior to switching and one year

after switching. The study matched 197 people who switched to regimens containing emtricitabine or lamivudine (HBV-suppressive drugs) to 197 people who switched to regimens that did not contain these drugs.

The two groups were broadly comparable in demographic and HIV-related characteristics, with the exception of viral suppression. People not taking emtricitabine or lamivudine after switching were more likely to have detectable viral load (21% vs 11% > 50 copies/ml, p<0.01), but less likely to have elevated ALT liver enzymes (>40 IU/L) (p=0.03). Just under a third of participants had detectable anti-HBc but only 1.4% had detectable HBV DNA.

During a median post-switch follow-up of 1.3 years, there was no difference in the proportions who experienced ALT flares >80 IU/L between the two groups. 5.6% of those taking a regimen with no drugs active against hepatitis B experienced reactivation compared to 1.1% of those taking a regimen containing emtricitabine or lamivudine. However, in all cases, HBV DNA was below the limit of quantification and none of those who tested positive for HBV on a qualitative assay were positive for hepatitis B surface antigen.

“We believe that our findings are reassuring for persons with HIV and positive anti-HBc and their physicians that switching to a non-tenofovir-based ART [regimen] is possible,” Dr Lorin Begré of Bern University Hospital concluded.

The Hospital Clinic in Barcelona carried out a prospective observational study of hepatitis B reactivation in people who switched to injectable cabotegravir/rilpivirine between 2023 and February 2025, a total of 741 patients. After switching, participants underwent monitoring for liver enzyme elevations and symptoms at weeks 12, 28 and every six months. If liver enzymes were elevated or clinical symptoms raised suspicion of hepatitis B reactivation or seroconversion, participants underwent testing for HBV markers including HBV DNA.

The study population was 92% male, had a median age of 45 years and 55% were born outside Spain. Participants had been taking antiretroviral treatment for a median of eight years prior to switching and the median follow-up time was 54 weeks.

Participants were divided into five groups according to their baseline hepatitis B serology: chronic hepatitis B infection (hepatitis B surface antigen positive) (0.5%); resolved chronic infection (hepatitis B surface antigen negative, HBsAb-positive) (22%); isolated antibody to HBV core protein (anti-HBc-positive) (3%); HBV-vaccinated (61%); or without HBV immunity or exposure (no serological reactivity) (12%).

A total of 17% of participants experienced liver enzyme elevations during follow-up and there was no significant difference between the groups in the proportions who experienced liver enzyme elevations. Importantly, no one experienced hepatitis B reactivation apart from two participants who had undetected chronic hepatitis B at the time of switching; both reverted to treatment with tenofovir alafenamide, emtricitabine and bictegravir and experienced resuppression of HBV. Two other participants with undetected chronic hepatitis B switched in error did not experience HBV reactivation before resuming tenofovir-containing treatment.

“I really think it is time to put this story to bed, because there is so much concern about hepatitis B reactivation,” commented Professor Sanjay Bhagani, a hepatitis consultant at London’s Royal Free Hospital.

But even if the risk of reactivation is extremely low, people with HIV need to be counselled that the risk exists, warned Dr Flora Olcott of the Mortimer Market Centre clinic in London. She has seen four patients experience HBV reactivation. “It's a very scary time for them,” she said. “They've lost faith in the healthcare system: they feel like they've been neglected and not counselled properly.”

Speakers at the European AIDS Conference agreed that for people with anti-HBc and those without immunity, hepatitis B vaccination is essential to protect against acute hepatitis B infection, as anti-HBc does not protect against infection. Two people in the Swiss HIV Cohort acquired acute hepatitis B infection after switching to tenofovir-sparing treatment.

References

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