Dettaglio abstract

N. pgm: OC 64

Title: Reactivation of hepatitis B virus is a frequent event in anti-HBc-positive/HBsAg-negative HIV-infected patients switching to Tenofovir sparing therapy as revealed by highly sensitive HBV assays

Presentation type: Oral Communication

Session/Topic
Insights on epidemiological and clinical management of hepatitis viruses

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Abstract
Background: Tenofovir-sparing antiretroviral therapy (ART) is increasingly used in the setting of HIV-infection, raising the issue to properly identify those anti-HBc-positive/HBsAg-negative patients who can safely suspend this drug. Here, we aim to unravel HBV replication kinetics after tenofovir withdrawal in anti-HBc-positive/HBsAg-negative HIV-infected patients.
Methods: This study includes 101 HIV-infected patients from ICoNA cohort, all anti-HBc-positive/HBsAg-negative and mostly Anti-HBs-positive (71%; median (IQR): 69 (10-932)mIU/ml]. All patients were treated with TDF/TAF-containing ART for >12 months and switched to TDF/TAF-sparing ART, including LAM in 73 patients and no-active HBV drugs in 28 patients. At switching (T0), 98% of patients has undetectable HIV-RNA.
For each patient, a plasma sample is analyzed at T0 and during the first 12 months of TDF/TAF-sparing ART (T1). HBV-reactivation (HBV-R) during TDF/TAF-sparing ART is defined as HBV-DNA>1IU/ml in patients with negative HBV-DNA at T0 or >2-fold increase in HBV-DNA from T0 to T1. HBV-DNA and -RNA are quantified by highly sensitive droplet digital PCR (LLOD:1IU/ml) and anti-HBc by Fujirebio (anti-HBc>15COI indicating active HBV reservoir based on Salpini,2020). Factors associated with HBV-R are assessed by multivariate analysis.
Results: At T0, despite TDF/TAF therapy, 34 (33.7%) patients have detectable HBV-DNA (median[IQR]: 2[1-5]IU/ml). Among the remaining 67 patients, 9% has detectable HBV-RNA (median[IQR]:6[5-7]IU/ml) and anti-HBc>15COI, indicating a transcriptionally active cccDNA. Notably, an active HBV replication at T0 is found more frequently in patients with low-level anti-HBs (42% of patients with vs 22.7% without Anti-HBs<100 IU/ml has detectable HBV-DNA, p=0.04).
At T1, after TDF/TAF withdrawal, HBV-R occurs in 40 (39.6%) patients (median[IQR] HBV-DNA: 4[2-13]IU/ml) with no difference between LAM- vs no LAM-group (42.5% vs 32.1%, P=0.3). Among HBV-R cases, 32.5% has HBV-DNA>10IU/ml (median[IQR]: 31[15-73]IU/ml) and 25% has ALT>40U/L.
Notably, HBV-R is confirmed in 77% of patients with an additional sample available during TDF/TAF-sparing ART (median [IQR] HBV-DNA:24[13-31]IU/ml), supporting persistent HBV replication.
Finally, nadir CD4+T cell count<100cells/ul is the only factor significantly associated with a higher risk to develop HBV-R (OR: 5.3 [1.6-17.4], p=0.007), after correcting for patients' demographics, viro-immunological parameters and ART duration.
Conclusion: A conspicuous fraction of HIV-infected anti-HBc-positive/HBsAg-negative patients has an

active intrahepatic reservoir that can predispose to HBV-reactivation under suboptimal/absent pharmacological pressure. The status of HIV-driven immunecompromission can exacerbate this phenomenon. Highly sensitive and accurate assays to measure HBV replicative activity are crucial for a proper management of HIV-infected anti-HBc-positive/HBsAg-negative patients that are candidate to TDF/TAF-sparing regimen.