16° CONGRESSO NAZIONALE ICAR Italian Conference on AIDS and Antiviral Research 19-21 GIUGNO ROMA UNIVERSITA' CATTOLICA DEL SACRO CUORE CENTRO CONGRESSI EUROPA

SHORT COMMUNICATION

Novel insights in the management of chronic viral hepatitis

SC 2 Safety and effectiveness of switching PWH with occult HBV infection to tenofovir-sparing regimens

Authors

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ABSTRACT

Background: There is increasing concern about the occurrence of breakthrough/relapse of hepatitis B (HBV) and transaminase flare among anti-HBV core-positive (HBcAb) people living with HIV (PWH) who discontinue anti-HBV-containing antiretroviral drugs.

Materials and Methods: PWH antigen S of HBV (HBsAg) negative and HBcAb-positive, irrespectively of HBsAb serostatus, on a stable (>18 months) TXF-containing regimen with HIV-RNA ≤50 copies/mL by January 2017 and free from liver events and transaminases elevation at screening were included. A per-protocol emulation trial approach by 'cloning and weighting' was used to compare PWH continuing 3 drugs, TXF- containing regimens (3DR, control arm) with PWH who switched to TXF-sparing but XTC-containing regimens (trial 1) or switched to NRTI-sparing dual regimens (trial 2), intervention arms. Primary endpoint was the 1-year risk of ALT≥2 ULN (42 M; 30F); secondary endpoint was the 5 risk of occurrence of FIB-4 increase >3.25. Unadjusted and weighted Kaplan-Meier (KM) estimates were calculated. The following factors were used in the model for the censoring weights: age, sex, body mass index (BMI), alcohol use, diabetes, dyslipidemia and HCVAb/HBsAb serostatus.

Results: In trial 1 (natural course), 217 PWH were included in the switch arm, 816 maintained TXF-containing regimens. The intervention arm was enriched with MSM, participants of Italian nationality, higher frequency of alcohol use and lower prevalence of diabetes. In the unadjusted natural course analysis, the 1-year risk of ALT≥2ULN was higher in PWH switching to the TXF-sparing regimen (11 pts [5.5%] vs. in those remaining on a TXF-containing arm 14 [1.9%], p=0.005) but weighted KM estimates were reversed with 0.60% in intervention vs. 2.51% in control (difference -1.91 [CI95% -3.01, -1.11], Table). In the weighted model, there was no evidence for a difference in the 5-year risk of FIB-4 increase >3.25 (2.6% higher in intervention 95% CI:-6.5;+8.6%). Trial 2 included 79 PWH who were switched to NRTI-sparing regimens vs. 756 remaining on a 3DR TXF-containing therapies.. Participants in the intervention arm were slightly older, MSM, more likely of Italian nationality and with higher CD4 count. In the unadjusted analysis, there was no evidence for a difference in the 1-year risk of ALT elevation ≥2 ULN (2 participants [2.5%] in the NRTI-sparing switched arm vs. 14 participants [1.9%] in the 3DR-based arm, p=0.91). In the weighted model, the risk of occurrence of ALT elevation >=2ULN was 0.68% in the switch arm and 2.14% in 3DR (difference -1.46 [CI 95%: -2.43, -0.70]), Table.

Conclusions: Under our model assumptions, PWH/HBcAb-positive who maintained a 3DR containing TXF, showed a higher risk of short-term ALT elevation possibly correlated with the greater drug burden. In contrast, for the 5-year risk of liver fibrosis results were inconclusive; we found a higher risk in those who were switched to TXF-sparing regimens vs. those who were kept on active anti-HBV drugs, although with large uncertainty around the estimate.

Table 1: Emulation results trial 1 and 2 – KM estimates of 1-year risk of ALT elevation ≥2 ULN (primary endpoint).

	Trial 1 **Intervention:** Switch to a TXF-sparing but 3TC-based		**Trial 2** **Intervention:** Switch to a TXF- and XTC-sparing	
Strategy	**1-year risk of ALT>=2(%)**	**95% CI**	**1-year risk of ALT>=2(%)**	**95% CI**
	Original cohort		***Original cohort***	
KM estimates				
Intervention	5.47	2.58, 8.40	2.58	0.00, 6.39
Stay on 3DR	1.98	1.25, 3.17	1.98	1.01, 3.46
Difference[1]	3.50	0.34, 6.82	0.60	-2.75, 4.25
	Emulated cohort (clones only)		***Emulated cohort (clones only)***	
KM estimates				
Intervention	0.63	0.11, 1.16	0.49	0.12, 0.97
Stay on 3DR	2.58	1.88, 3.75	2.05	1.03, 3.22
Difference[2]	-1.95	-2.97, -1.15	-1.56	-2.39, -0.78
	Emulated cohort (cloned and weighted)		***Emulated cohort (cloned and weighted)***	
Weighted[&] KM estimates				
Intervention	**0.60**	**0.15, 1.31**	**0.68**	**0.16, 1.32**
Stay on 3DR	**2.51**	**1.68, 3.77**	**2.14**	**0.87, 3.43**
Difference[3]	**-1.91**	**-3.01, -1.11**	**-1.46**	**-2.43, -0.70**

[*]The 95% CI were calculated using 100 bootstrap replicates
[1]These differences are prone to both confounding and immortal-time biases
[2]These differences are prone to informative censoring
[3]These differences account for all types of biases, under the assumptions detailed in methods
[&]Weighted for age, BMI, alcohol use, dyslipidaemia, HCVAb/HBsAb serostatus and mode of HIV transmission