HBcAb positivity increases the risk of severe hepatic fibrosis development in HIV-HCV-positive subjects from the ICONA Italian cohort of HIV-infected patients

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Abstract

The aim of this study was to investigate the impact of HBcAb positivity on the progression of liver fibrosis (Fibrosis-4 score > 3.25) in the Italian cohort of HIV-infected individuals naïve to antiretroviral treatment (ICONA). All patients with FIB-4 < 3.25 at baseline were evaluated prospectively: 6966 PLWH (People Living with HIV) patients were screened and classified based on HBV and HCV serology. Patients who were HBcAb+/HCV-/HBsAg- and HCV+/HBcAb+/HBsAg-, or HBsAg+/HBcAb+/HCV- had CD4+ cell counts below the nadir and significantly higher prevalence of AIDS diagnosis at baseline than the other groups (p < 0.0001). Cox regression model adjusted for age, HIV transmission mode, country of birth and alcohol consumption, showed a higher relative risk (HR) of progression to FIB-4 > 3.25 in HCV+/HBcAb+/HBsAg- patients (HR 7.2, 95% CI 3.8 -13.64).

HBcAb+ contribute to liver damage in HIV+/HCV+/HBcAb+/HBsAg- subjects. A careful monitoring for signs of previous HBV infection is needed in this kind of patients.

Keywords: Anti-HBc, HIV-HBV coinfection, HBV, Liver fibrosis, OBI
Introduction

Although recent data show a reduction in liver-related and AIDS-related mortality among antiretroviral (High Active Antiretroviral Therapy HAART) treated patients diagnosed with HIV infection in the 2000s [1], however, coinfection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) remains a challenge for clinicians. In HBV endemic areas of the world (Asian and African countries), but also in European cohorts of co-infected people, HIV-HBV co-infection is characterized by accelerated progression to cirrhosis and hepatocellular carcinoma [2, 3]. Published data show that the recovery of CD4 count is slowed down in HIV/HBV coinfected people with chronic hepatitis B (CHB), who also show reduced HBs antigen (HBsAg) and HBe antigen (HBeAg) seroclearance compared to monoinfected HBV patients [4]. Furthermore, data on the clinical impact of resolved HBV infection, specifically the presence of anti-HBc (HBcAb) with or without anti-HBs (HBsAb) antibodies, in HIV positive patients are lacking. The presence of HBV-DNA in serum or in liver tissue, in the absence of signs of active infection, has been demonstrated in anti-HBc-positive patients and has been defined as occult hepatitis B (OBI) [5]. OBI is observed most frequently in bone marrow/organ recipients and in people undergoing immunosuppressive treatments and chemotherapy, probably linked to compromised host defences and, consequently, deregulation of HBV replication control. The role of OBI in HBV mono-infected patients is recognized as a risk factor for the progression of liver disease, fibrosis, end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) [6,7,8]. In HBV endemic countries, OBI is quite common in HIV-infected patients [9], and some studies have reported a trend towards increased ALT and AST in OBI individuals with HIV [10, 11]. Data on the efficacy of HAART regimens containing HBV-active drugs in suppressing HBV-DNA levels in PLWH with OBI are limited and not always consistent. On the other hand,
detectable levels of HBV-DNA as well as the emergence of mutated HBV strains are reported in HIV patients with OBI on HAART [9,12].

With the ultimate aim of understanding the influence of HBcAb positivity on the outcome of liver damage, the evolution of severe liver fibrosis was evaluated in coinfection patients from the Italian cohort of antiretroviral naïve HIV patients (ICONA) foundation.

Materials and Methods

Study population

This analysis includes prospectively collected data of HIV-infected individuals enrolled in the ICONA cohort. The ICONA Foundation is an observational cohort of HIV-infected individuals who were antiretroviral naïve at the time of enrolment. This cohort was set up in January 1997 and currently consists of more than 14,000 patients from 50 Italian infectious disease units. The ICONA Foundation study has been approved by the Institutional Review Board (IRB) of all participating centres; sensitive data from patients are seen only in aggregate form. All patients signed a consent form to participate in ICONA, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (1983 revision). Demographic and socio-behavioural data, initiation and discontinuation dates of each antiretroviral drug, HIV viral load and CD4 cell count every 3±6 months, AIDS defining diseases according to Centers for Disease Control and Prevention (CDC) criteria as well as non-HIV related diseases and death were recorded for all enrolled patients. In particular, alcohol consumption information was collected by physician interviews at study enrolment and at subsequent clinical visits during follow-up (a unit of alcohol in Italy is defined as containing 14 g of pure alcohol, which corresponds to 125 ml of wine, 330 ml of a can of beer and 40 ml of liquor). Haematochemical data, including liver function parameters, were also available at 3±6 month intervals. Further details are available at http://www.fondazioneicona.org/.
Endpoint and inclusion criteria

Patients belonging to the ICONA Foundation Study Cohort with a mild or moderate fibrosis level at baseline (defined as Fibrosis-4 score [FIB-4] <3.25, corresponding to F0-F2 METAVIR) were prospectively evaluated to investigate the influence of isolated HBcAb positivity on the risk of occurrence of advanced liver fibrosis (defined at the time of the first of two consecutive values of FIB-4 >3.25, corresponding to F3-F4 METAVIR) after the date of their first available HBV serologic test (baseline and time zero for the analysis). Patients who were never tested for HBV or already showed an FIB-4 >3.25 at baseline were excluded. Five groups of PLWH patients were defined according to the results of their HBV and HCV serology tests at baseline: A) HCV-/HBsAg-/HBcAb-; B) HCV+/HBsAg-/HBcAb-; C) HBcAb+/HCV-/HBsAg-; D) HCV+/HBcAb+/HBsAg-; E) HBsAg+/HBcAb+/HCV-. There were additional 62 patients with the HBsAg+/HBcAb+/HCV+ profile who were excluded from this analysis.

Statistical analysis

The characteristics of the study population were described and compared across the five exposure groups with the Kruskal-Wallis or Pearson’s chi-square test as appropriate. Standard survival analysis of the time to advanced liver fibrosis by means of Kaplan-Meier curves and Cox regression models with time-fixed covariates measured at baseline was performed. The following factors were included as covariates in the model and were identified as possible confounders of the association between the exposure of interest and the risk of advanced liver fibrosis: age, mode of HIV transmission and nation of birth. In a separate model, we further adjusted for alcohol consumption, which was determined by physician interviews at study enrolment and at subsequent clinical visits (at least every 6 months) during follow-up [14]. The model assumptions have been described by means of a direct acyclic graph (DAG), which was built using DAGitty vers. 2.3 released 2015-08-19, available at...
With this DAG, controlling for age, mode of HIV transmission and nation of birth was sufficient to block all the backdoor pathways from exposure to outcome. We have performed a sensitivity analysis with an alternative endpoint, using the threshold of 1.45 instead of 3.25 for Fib4 elevation (Results are shown as Supplemental table and Supplemental figure).

To evaluate whether the risk of liver fibrosis in group HBcAb+/HCV-/HBsAg- (C) varied according to the type of treatment used at the time of the serology test, we performed an additional survival analysis using a weighted marginal structural Cox regression model. The simulated intervention was treatment with TDF/TAF or LMV-based vs TDF/TAF or LMV-sparing regimens. To increase statistical power, we evaluated the endpoints of Fib4 elevation >3.25 (using a single value above the threshold) and >1.45 (two consecutive values above this lower threshold). The set of variables included to construct the weights were the time-fixed factors described above (age, mode of HIV transmission and nation of birth) as well as most recent HIV viraemia and CD4 cell count values. Indeed, in this analysis of the association between anti-HBV treatment and outcome, HIV viraemia and CD4 cell count are time-varying confounders affected by prior treatment that could not be correctly controlled for in a standard unweighted Cox regression model.

**Patients Consent Statement**

The ICONA study has been approved by institutional review boards of all the participating centres. Data are collected prospectively from the date of entry in the cohort until the last available follow-up for all patients who agree to participate and sign consent forms, in accordance with the ethical standards of the Committee on Human Experimentation and the Helsinki Declaration. Demographic, clinical and laboratory data and information on therapies retrospectively collected and recorded in anonymous form.
Results

Overall description of the study population

Among the 6966 patients with more than one serologic HBV test result included in the study (table 1), 1242 (23.6) were female. Patients acquired HIV predominantly through sexual contacts (42% homosexual and 41.9% heterosexual). Patients with a history of injecting drug use accounted for 9.6%. The median age of the study population was 38 years (IQR 31-45). Interestingly, almost 19% of patients were of foreign nationality. Regarding participants’ viroimmunological status at baseline, patients had a median viral load of HIV of 4.32 log_{10} cp/mL (IQR 2.88-5.00) and a median CD4 cell count of 429/mm3 (IQR 258-618). The CD4 cell count nadir at baseline was 355 cell/mm3 (IQR 190-531). Six hundred and eighty-one patients (9.8%) had an AIDS-defining diagnosis before baseline, while 1169 (18.9%) showed a baseline CD4 cell count ≤ 200 cells/mm3.

Study population stratified by exposure groups

Table 1 shows the number and characteristics of the study population stratified by baseline exposure groups: 5264 patients (61%) were HIV monoinfected, (Group A); 490 (5.7%) were HIV+ HCV+/HBsAg-/HbcAb- coinfectcd (group B); 533 (7.6%) were HIV+ HbcAb+/HCV-/HBsAg- (group C); 312 (4.4%) were HIV+ HCV+/HbcAb+/HBsAg- (group D); and 367 (4%) were HIV+ HBsAg+/HbcAb+/HCV- (group E) patients. Overall, HbcAb+/HCV-/HBsAg- (group C), HCV+/HBsAg-/HbcAb- (group B), HCV+/HbcAb+/HBsAg- (group D) and HBsAg+/HbcAb+/HCV- coinfectcd patients (group E) had a significantly higher prevalence of AIDS diagnosis at baseline than HIV monoinfected patients (group C 72 [13.5%], group B 55[11%], group D 45 [14.4%] and group E 54 [15%] vs group A 455 [9%], p<0.001). Patients with previous HBV infection, with or without HCVAb positivity (groups D and C, respectively), were older than those of the other groups (group C median age 42
years [IQR 35-50], group D median age 41 years [IQR 36-46] vs group A age 37 years [IQR 30-44], group B 39 years [IQR 33-45] and group E 39 years [IQR 33-46], p<0.0001). Among HCV-positive patients, those that were HBcAb negative or positive (groups B and D, respectively), were more frequently injecting drug users (group B 281 [57.5%] and group D 244 [78.7%] vs group A 109 [2.1%], group C 18 [3.4%] and group E 13 [3.6%] p<0.001) and had a longer follow-up time than other populations (group B 48 months [IQR 16-100], and group D 49 months [IQR 14-121] vs group A 40 months [IQR 13-75], group C 35 months [IQR 13-75] and group E 36 [9-75], p<0.001). HBsAg+/HBcAb+/HCV- or HBcAb+/HCV-/HBsAg- patients (groups E and C) were more frequently of foreign origin (p<0.001). Interestingly, HBsAg+/HBcAb+/HCV- patients (group E) and HBcAb+/HCV-/HBsAg-patients (group C) had lower median CD4 counts (group C 385 [IQR 200-563], group E 423 [IQR 223-642] vs group A 432 cells/mm3 [IQR 263-618], group B 446 [IQR 295-636] and group D 435 [IQR 272-640], p<0.0001) and a more frequent CD4 cell baseline value < 200 cells/mm3 than the other groups (group C 120 [25.2%] and group E 75 [23.6%] patients versus group An 861 [18.6%], group B 69 [15.3%] and group D 44 [14.8%] patients, p<0.001).

Liver fibrosis evolution during follow-up

Overall, 180 patients developed an FIB-4 > 3.25 during the 10 years follow-up period, and the risks calculated according to the exposure group were as follows: group A 42/5264 (0.8%), group B 27/490 (5.5%), group C 9/533 (1.6%), group D 41/312 (13.1%), and group E 8/367 (2.1%). The unweighted Kaplan-Meier estimates of the probability of experiencing an FIB-4 >3.25 at 3, 7 and 10 years from baseline are reported in Fig.1. When compared to HIV-monoinfected patients, the probability of developing an FIB-4 > 3.25 at 3, 7 and 10 years was higher in groups of HCV+/HBsAg-/HBcAb- or HCV+/HBcAb+/HBsAg- patients (group B
and D) (3, 7 and 10-year percent of FIB-4 >3.5: group B 4.2 [CI 95% 2.1-6.4], 8.5 [CI 95% 5.0-11.9] and 11.1% [CI 95% 6.6-15.5]; group D 7.6 [CI 95% 4.3-10.9]; 15.5 [CI 95% 10.3-20.6]; 20.7 [CI95% 14.4-27.0]), with higher values in group D.

From fitting a Cox regression model after controlling for age, risk factor for HIV transmission, country of origin at baseline and alcohol consumption (Table 2), still using HIV mono-infection as the comparator group, evidence for a significantly higher risk of progression to FIB-4>3.25 was found in group B (HCV+) (adjusted RH [CI 95%] 3.88 [2.13-7.08], p <0.001), in group D (HCV+/HBcAb+) [adjusted RH [CI 95%] 7.20 [3.80-13.64], p <0.001) and in group E (HBsAg+) (adjusted RH [CI 95%] 2.48 [1.16-5.32], p 0.008, respectively). In the unadjusted analysis, a higher risk of progression to FIB-4>3.25 was also shown for group C (HBcAb+) (RH 2.13, CI 95% 1.04-4.37), p=0.040); however, the association was largely attenuated after controlling for age, risk of HIV transmission and nationality and alcohol consumption (adjusted RH [CI 95%] 1.68 [0.81-3.49], p=0.162).

**Risk of liver fibrosis according to the presence or absence of anti-HBV drugs in the HAART composition at baseline**

Given the potential effect of anti-HBV drugs (lamivudine [LMV], tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) in preventing liver fibrosis we simulated a trial comparing LMV, TDF or TAF-based with LMV, TDF or TAF-sparing regimens in the subset of participants belonging to group C (HBcAb+/HCV-/HBsAg-) (Table 3a and 3b). As expected, because of confounding by indication, participants treated with TDF/TAF or LMV-based regimens were found to be at higher risk of developing liver fibrosis. This bias was however attenuated, especially for the endpoint of elevation>1.45 in the weighted analysis, suggesting a 15% reduction in risk of moderate elevation in people treated with the anti-HBV drugs (weighted RH=0.85, 95% CI:0.32-2.30, p=0.76). Overall, although the analysis is
likely to be underpowered, there was little evidence to support that treating patients with HAART containing anti-HBV drugs had a large impact on risk of fibrosis in this group.

**Discussion**

In the ICONA cohort, a high risk of FIB-4>3.25 liver fibrosis progression was demonstrated in all groups of HIV/HBV and HCV-coinfected patients; however, higher values were detected in the group of HCV+/HBcAb+/HBsAg- subjects (HR 7.20, CI 95% 3.80-13.64), followed by the HCV+/HBsAg-/HBcAb- group (HR 3.88, CI 95% 2.13-7.08), than in the other groups. The use of anti-HBV active drugs (LMV, TDF or TAF) in HAART compositions did not seem to significantly influence liver fibrosis evolution in the subset of HBcAb-positive participants.

ESLD, as the result of severe liver fibrosis, is the leading non-AIDS cause of death among PLWH [13]. Several clinical studies [14, 15, 16] reported that HIV alone increases the evolution of hepatic fibrosis in mono-infected patients, and the persistence of HIV viremia, even at low levels, has been associated with an increase in inflammation and the consequent induction of hepatocyte apoptosis [17, 18, 19]. In the course of HIV infection, a series of contributing factors have been associated with hepatic injury (such as drugs and alcohol) [20, 21]; however, HCV and HBV chronic hepatitis have a central role. In particular, PLWH with active HBV and HCV infections are at a 3.73 and 6.66 times higher risk, respectively, of liver-related death [22]

Little is known about the influence of HBcAb positivity on hepatic liver damage in the course of HIV infection. Commonly, HBcAb is the sign of a past/resolved infection; however, it could be the only marker of OBI, a condition characterized by the persistence of intrahepatic cccHBV-DNA and the occasional reappearance of HBV-DNA viremia [22]. Liver-related
outcomes among HIV/HCV-infected patients with CHB have been reported by a number of studies [23, 24, 25], and it is known that liver-related deaths occur more frequently among patients with triple HIV/HBV/HCV chronic infections; however, very little is known about HIV/HCV-infected patients with signs of a previous HBV infection.

Bhattacharya D. and colleagues, in a large cross-sectional study on a cohort of 44,180 HIV-infected American veterans (Veterans Ageing Cohort Study-Virtual Cohort -VACS-VC), found that the isolated anti-HBc pattern was associated with advanced hepatic fibrosis in HIV/HCV-coinfected patients but not in HIV infection without concomitant HCV infection [26]. This result is consistent with our findings, and occasional HBV viremia could contribute to the increase in liver damage in HCV coinfected subjects. As early as 2009, Morsica and co-authors, analysing the data of coinfected patients of the ICONA cohort, found that 15% of HIV/HbcAb positive subjects had detectable HBV-DNA in their plasma, and 22% of these had no active drugs against HBV in their HAART composition [27]. The study concluded that it was advisable to monitor HBV-DNA blood levels in this category of subjects to avoid, over the years, the occurrence of liver damage as a result of active HBV replication. Poor control of the progression of liver damage despite the use of anti-HBV active drugs was also reported by several French studies on HIV patients with active chronic HBV infection [28, 29,30]. Moreover, we did not find any significant protective effect on fibrosis evolution in the group of HCV+/HbcAb+/HBsAg- patients receiving HAART containing anti-HBV drugs compared to those receiving HAART without anti-HBV drugs.

In our analysis, a lower risk of severe hepatic fibrosis was demonstrated in the population of HIV-HbcAb positive patients, which also seems to indicate a limited benefit of the inclusion of LMV, TDF or TAF treatment in HAART.

Before drawing final conclusions, a number of limitations need to be mentioned: first, the lack of HBV-DNA viremia levels, that limited the possibility of assessing the impact of true
OBI rather than potential OBI; second, the characterization of HCV co-infection took place only via the serological detection of antibodies against HCV rather than HCV-viremia data. Moreover, information on anti-HCV treatments (IFN- or direct-acting antivirals-based) during follow-up was lacking; third, although the alcohol abuse data were collected in the ICONA database via physician interviews at study enrolment and subsequent clinical visits, patient under-reporting use (due to social desirability and fear of the impact on antiretroviral therapy initiation) is possible, so residual confounding bias due to misclassification of alcohol consumption is possible. Also, participants have been compared on the basis of their serology status and antiretroviral treatment received at the time of their first HBV serology test, ignoring the fact that participants’ status and treatment might have changed over follow-up. In conclusion, in our cohort of HIV-infected patients seen for care in Italy, coinfection with hepatitis viruses was associated with an increased risk of severe liver fibrosis development compared to HIV-mono infection. The association was particularly strong in the HIV/HCV co-infected group with signs of resolved HBV infection (HBcAb positive). Our data suggest that anti-HBc positivity contribute to liver damage in HCV+/HBcAb+/HBsAg- HIV-positive subjects. These findings reinforce the need for careful monitoring for signs of previous HBV infection in HIV/HCV positive patients and suggest that underlying active HBV replication (OBI) may contribute to liver damage in these patients.
Table 1 Main characteristics of HIV infected patients by baseline HBV and HCV serology group - Fib4 analysis

| Characteristics                                | HCV/HBsAg-/HBeAb | HCV+/HBsAg-/HBeAb | HCV-/HBsAg-/HBeAb+ | HCV+/HBsAg+/HBeAb+ | p-value | Total |
|------------------------------------------------|------------------|-------------------|-------------------|-------------------|---------|-------|
| N                                              | 5264             | 490               | 533               | 312               | 367     | 6966  |
| Gender, n (%)                                   |                  |                   |                   |                   | <.001   |       |
| Female                                         | 1242 (23.6%)     | 188 (38.4%)       | 121 (22.7%)       | 60 (19.2%)        | 76 (20.7%) | 1687 (24.2%)  |
| Mode of HIV Transmission, n (%)                 |                  |                   |                   |                   | <.001   |       |
| Injecting drug use                              | 109 (2.1%)       | 281 (57.5%)       | 18 (3.4%)         | 244 (78.7%)       | 13 (3.6%) | 665 (9.6%)  |
| Homosexual contacts                             | 2434 (46.5%)     | 80 (16.4%)        | 219 (41.5%)       | 27 (8.7%)         | 156     | 2916 (42.1%) |
| Heterosexual contacts                           | 2340 (44.5%)     | 110 (22.4%)       | 258 (48.4%)       | 34 (10.9%)        | 174     | 2916 (41.9%) |
| Other/Unknown                                   | 354 (6.8%)       | 18 (3.7%)         | 33 (6.3%)         | 5 (1.6%)          | 20 (5.5%) | 430 (6.2%)  |
| Nationality, n (%)                              |                  |                   |                   |                   | <.001   |       |
| Not Italian                                     | 955 (18.1%)      | 40 (8.2%)         | 184 (34.5%)       | 24 (7.7%)         | 112     | 1315 (18.9%) |
| AIDS diagnosis, n (%)                           |                  |                   |                   |                   | <.001   |       |
| Yes                                            | 455 (8.6%)       | 55 (11.2%)        | 72 (13.5%)        | 45 (14.4%)        | 54 (14.7%) | 681 (9.8%)  |
| Calendar year of baseline*, Median (IQR)        |                  |                   |                   |                   | <.001   |       |
| 2012 (2009-2015)                                | 2009 (2003-2013) | 2012 (2008-2015) | 2005 (2003-2011) | 2012 (2008-2016) | 2012     |
| 2012 (2008-2015)                                | 2012 (2008-2015) | 2012 (2008-2015) | 2012 (2008-2015) | 2012 (2008-2015) | 2012     |
| Age, years                                      |                  |                   |                   |                   | <.001   |       |
| Median (IQR)                                    | 37 (30-44)       | 39 (33-45)        | 42 (35-50)        | 41 (36-46)        | 39 (33-46) | 38 (31-45)  |
| CD4 count, cells/mm3                            |                  |                   |                   |                   | <.001   |       |
| Median (IQR)                                    | 432 (263-618)    | 446 (295-636)     | 385 (200-563)     | 435 (272-640)     | 423 (223-642) | 429 (258-618) |
| CD4 count nadir, cells/mm3                      |                  |                   |                   |                   | <.001   |       |
| Median (IQR)                                    | 368 (207-544)    | 347 (170-500)     | 293 (131-460)     | 291 (172-501)     | 323 (144-510) | 355 (190-531) |
| CD8 count, cells/mm3                            |                  |                   |                   |                   | 0.205   |       |
| Median (IQR)                                    | 877 (618-1230)   | 825 (641-1206)    | 870 (599-1251)    | 952 (685-1357)    | 830 (626-1188) | 874 (624-1229) |
| HIV-RNA, log10 copies/mL                        |                  |                   |                   |                   | <.001   |       |
| Median (range)                                  | 4.38 (0.00-8.00) | 3.90 (0.00-7.04)  | 4.30 (0.00-6.36)  | 4.34 (0.00-7.00)  | 4.32 (0.00-8.00) |
| CD4 count, n(%) | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) |
|----------------|--------------|--------------|--------------|--------------|
| <=200 cells/mm3 | 4.38 (3.18-5.03) | 4.00 (2.61-5.06) | 3.66 (1.95-4.69) | 4.36 (1.90-4.96) |
|                | <.001        | <.001        | <.001        | <.001        |
|                | 861 (18.6%) | 69 (15.3%) | 120 (25.2%) | 44 (14.8%) |
|                | 3.90 (1.91-4.82) | 75 (23.6%) | 1169 (18.9%) | 72 (28.2%) |
| Time from HIV diagnosis to date of HBV serology, months |
| Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) |
| Antivirals started, n (%) |
| Zidovudine | 321 (6.1%) | 71 (14.5%) | 47 (8.8%) | 58 (18.6%) |
| Lamivudine | 679 (12.9%) | 116 (23.7%) | 90 (16.9%) | 78 (25.0%) |
| Abacavir | 291 (5.5%) | 30 (6.1%) | 31 (5.8%) | 13 (4.2%) |
| Tenofovir | 1481 (28.1%) | 100 (20.4%) | 179 (33.6%) | 15 (4.1%) |
| Lamivudine | 1515 (28.8%) | 85 (17.3%) | 178 (33.4%) | 12 (3.3%) |
| TAF | 92 (1.7%) | 3 (0.6%) | 7 (1.3%) | 2 (0.6%) |
| Rilpivirine | 177 (3.4%) | 7 (1.4%) | 15 (2.8%) | 3 (1.0%) |
| Stavudine | 138 (2.6%) | 4 (0.8%) | 25 (4.7%) | 5 (1.6%) |
| Triumeq | 94 (1.8%) | 4 (0.8%) | 8 (1.5%) | 1 (0.3%) |
| Genvoya | 49 (0.9%) | 2 (0.4%) | 4 (0.8%) | 1 (0.3%) |
| Dolutegravir | 269 (5.1%) | 12 (2.4%) | 24 (4.5%) | 4 (1.3%) |
| Elvitegravir | 187 (3.6%) | 6 (1.2%) | 29 (5.4%) | 6 (1.9%) |
|Raltegravir | 227 (4.3%) | 13 (2.7%) | 19 (3.6%) | 5 (1.6%) |
| Follow-up time, months |
| Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) |
| Alcohol use, n (%) | 0.003 |
| None | 1927 (36.6%) | 160 (32.7%) | 203 (38.1%) | 106 (34.0%) |
| Moderate | 1265 (24.0%) | 112 (22.9%) | 108 (20.3%) | 67 (21.5%) |
| Hazardous | 336 (6.4%) | 35 (7.1%) | 36 (6.8%) | 35 (11.2%) |
| Unknown | 1736 (33.0%) | 183 (37.3%) | 186 (34.9%) | 104 (33.3%) |
Table 2. Hazard ratios of Fib4 elevation >3.25 from fitting a Cox regression model

| Exposure group                  | Unadjusted RH (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|--------------------------------|-------------------------|---------|----------------------|---------|
| Group A (HCVAb-/HBsAg-/HBcAb-) | 1                       |         | 1                    |         |
| Group B (HCVAb+/HBsAg-/HBcAb-) | 5.82 (3.59-9.46)        | <.0001  | 3.88 (2.13-7.08)     | <0.001  |
| Group C (HCVAb-/HBsAg+/HBcAb+) | 2.13 (1.04-4.37)        | 0.040   | 1.68 (0.81-3.49)     | 0.162   |
| Group D (HCVAb+/HBsAg-/HBcAb+) | 13.12 (8.51-20.24)      | <0.001  | 7.20 (3.80-13.64)    | <0.001  |
| Group E (HCVAb-/HBsAg+/HBcAb+) | 2.79 (1.31-5.94)        | 0.008   | 2.48 (1.16-5.32)     | 0.019   |

*adjusted for age, mode of HIV transmission, nation of birth and level of alcohol consumption
Table 3

A. Relative hazards of developing a Fib4>3.25 from fitting a weighted Cox regression model

| HAART at baseline       | Relative hazards (95% CI) of Fib4>3.25 |         |         |
|-------------------------|----------------------------------------|---------|---------|
|                         | Undjusted                              | Adjusted|         |
|                         | 95% CI | p-value | 95% CI | p-value |
| TDF/TAF or LMV-sparing  | 1.00  | 1.00    |        |         |
| TDF/TAF or LMV-based    | 1.26 (0.65, 2.44)                      | 0.501   | 1.13 (0.48, 2.64) | 0.775 |

B. Relative hazards of developing a Fib4>1.45 from fitting a weighted Cox regression model

| HAART at baseline       | Relative hazards (95% CI) of Fib4>1.45 |         |         |
|-------------------------|----------------------------------------|---------|---------|
|                         | Undjusted                              | Adjusted|         |
|                         | 95% CI | p-value | 95% CI | p-value |
| TDF/TAF or LMV-sparing  | 1.00  | 1.00    |        |         |
| TDF/TAF or LMV-based    | 1.38 (0.77, 2.47)                      | 0.279   | 0.85 (0.32, 2.30) | 0.756 |

*adjusted for age, gender, mode of HIV transmission, nation of birth current CD4 count and HIV-RNA using inverse probability of weighting
Figure Legends

Figure 1: KM plot of time to a Fib4>3.45 (confirmed value) stratified by HBV serology status
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