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Do contemporary antiretrovirals increase the risk of end-stage liver disease? Signals from patients starting therapy in the NA-ACCORD

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Abstract

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Conflicts of Interest

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Purpose: Despite effective antiretroviral therapy, rates of end-stage liver disease (ESLD) remain high. It is not clear whether contemporary antiretrovirals contribute to the risk of ESLD.

Methods: We included patients from cohorts with validated ESLD data in the North American AIDS Cohort Collaboration on Research and Design. Patients had to initiate ART after 1 Jan 2004 with a nucleos(t)ide backbone of either abacavir/lamivudine or tenofovir/emtricitabine and a contemporary third (anchor) drug. Patients were followed until a first ESLD event, death, end of a cohort's ESLD validation period, loss to follow-up or 31 Dec 2015. We estimated associations between cumulative exposure to each drug and ESLD using a hierarchical Bayesian survival model with weakly informative prior distributions.

Results: Among 10,564 patients included from 12 cohorts, 62 had an ESLD event. Of the nine anchor drugs, boosted protease inhibitors atazanavir and darunavir had the strongest signals for ESLD, with increasing hazard ratios (HR) and narrowing credible intervals (CrI), from a prior HR of 1.5 (95% CrI 0.32–7.1) per five year's exposure to posterior HRs respectively of 1.8 (95% CrI 0.82–3.9) and 2.0 (95% CrI 0.86–4.7). Both backbones and efavirenz showed no signal. Hepatitis C coinfection was the most important covariate risk factor (HR 4.4, 95 % CrI 2.6–7.0).

Conclusions: While contemporary antiretrovirals pose less risk for ESLD than hepatitis coinfection, atazanavir and darunavir had a toxicity signal. We show how hierarchical Bayesian modelling can be used to detect toxicity signals in cohort event monitoring data even with complex treatments and few events.

Keywords

adverse events; Bayesian statistical methods; end-stage liver disease; hepatocellular carcinoma; HIV; pharmacovigilance

Introduction

The success of antiretroviral therapy has meant that patients with HIV now live long enough that end-stage liver disease (ESLD) has become an important cause of morbidity and mortality.¹ Early antiretroviral drugs, particularly didanosine and stavudine, are known to increase the risk of ESLD.^{2,3} The effects of these drugs can persist for years after exposure ends.^{2,4} However it is not clear whether cumulating exposure to contemporary antiretroviral drugs increases the risk of ESLD. Protease inhibitors promote dyslipidemia and insulin resistance leading to hepatic steatosis;⁵ exposure to efavirenz may also lead to hepatic steatosis⁶ and nevirapine may be hepatotoxic beyond an early hypersensitivity reaction.⁷ Tenofovir is widely used and has an important role in HIV hepatitis B coinfection⁸ so studies that suggest it is also hepatotoxic are a concern.^{2,9}

Life-long antiretroviral therapy (ART) and the potential for toxicities such as ESLD to emerge only after years of exposure create a challenge for pharmacovigilance.¹⁰ Immediate toxicities can be detected in clinical trials but trials seldom have follow-up beyond a year and patients with comorbidities are often excluded, such as those with hepatitis B virus (HBV) or hepatitis C virus (HCV) who have the highest risk of liver injury.^{10,11} When cumulating exposure is an important element of an adverse event, cohort studies can play a role in signal detection.¹² They provide the covariate data needed to take confounding into

account; whereas spontaneous reporting systems cannot provide the treatment and clinical history needed for adjustment.

Cohort studies can include patients already on treatment when observation begins ('prevalent users') or only include newly treated patients ('new users'). New user designs play an important role in drug safety studies.¹³ Prevalent user designs suffer from the 'depletion of susceptibles':¹⁴ the early loss of those at risk of the adverse event prior to the study, leaving only those who are able to tolerate the drug. The harm caused by a drug may be underestimated in prevalent users who provide the majority of person-time in the analysis.^{13,15,16} A new user design is also preferable when drugs have carry-over or cumulative effects; otherwise it is difficult to establish both treatment duration and pre-treatment values of confounding variables.^{13,15} The disadvantage of new user designs is their effective sample size:¹⁶ fewer new users will be available for study and the length of follow-up for them will be shorter, reducing the number of events available for an analysis, especially for rare events with long latencies.

Pharmacovigilance requires extracting a signal from background noise. Multiple tests lead to false positives and "spuriously impressive associations" are to be expected when there are few events.¹¹ The US Food and Drug Administration (FDA) has been using Bayesian methods for some time to detect signals in spontaneous reporting data.¹⁷ Bayesian methods for detecting signals from observational case control or cohort data were developed in the 1990's;¹⁸ they have been applied to HIV cohort research¹⁹ but have not been widely adopted. Yet simulation shows that the expected advantages of these methods apply to the detection of adverse events associated with ART.²⁰

We sought to detect those components of contemporary ART most likely to increase the risk of ESLD with a new user design, Bayesian methods for signal detection and data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Patients and methods

Patient selection

The NA-ACCORD is a collaboration of clinical and interval HIV cohorts from Canada and the United States.²¹ Data collected at more than 200 clinical sites are transferred to a data management centre at the University of Washington for quality control; data are then harmonised for analysis by an epidemiology and biostatistics group at the Johns Hopkins University. The research activities of each participating cohort and of the NA-ACCORD have been approved by the institutional review boards of each cohort and by the Johns Hopkins School of Medicine.

We selected treatment naive patients from clinical cohorts contributing validated ESLD data to the NA-ACCORD. We excluded patients with no evidence of ART, those with evidence of an undetectable viral load before their first recorded ART and those starting ART more than a year before enrolling in their cohort. We included patients starting ART after 1 January 2004, the year in which the FDA approved fixed dose combinations of both abacavir and lamivudine, and tenofovir and emtricitabine. Patients had to be starting one of these two

backbones plus one of nine contemporary anchor drugs. We also excluded patients not yet 18 years old when starting ART or with either ESLD or end-stage renal disease (estimated glomerular filtration rate < 30 ml/min/1.73m²) before the start of follow-up.

Outcome, exposure and covariates

Patients were screened for ESLD using an algorithm developed by the NA-ACCORD.²² ESLD events were then confirmed by medical record review or taken from a validated cancer registry and the event classified as either ascites, spontaneous bacterial peritonitis, variceal haemorrhage, hepatic encephalopathy or hepatocellular carcinoma (HCC). Our outcome of interest was a first validated ESLD event during follow-up. For each patient, follow-up began when first starting ART or when the ESLD validation period began at their site, whichever came last. Follow-up ended with the earliest of: a first ESLD event, death, the end of the ESLD validation period at their site, loss to follow-up (one year after a last recorded CD4 cell count or HIV RNA), or 31 December 2015.

Data were analysed as a set of yearly intervals for each patient using the counting process format for survival data (Supplementary Material; Appendix A).²³ Each interval had cumulative drug exposures and covariate values at the beginning of a year and an indicator for whether an event had occurred or not by the end of that year. Drug exposures were cumulated by each month of use and then scaled per five years; the interval length was set to one for a full year or to an appropriate fraction of a year in the first and last years of follow-up.

Covariates were selected prior to analysis using causal diagrams.²⁴ Given few events, we included only potential confounding variables strongly associated with ESLD in previous studies. The covariates were: an age-adjusted measure of fibrosis when starting ART (FIB-4²⁵), chronic HBV (surface antigen, e antigen or DNA positive), HCV exposure (antibody or RNA positive), any report of alcohol dependence or abuse – all as fixed covariates; and time-dependent CD4 cell count and detectable HIV RNA. Covariates were as defined in an earlier NA-ACCORD study (see Table 1 footnotes).²⁶ Hepatitis covariates were treated as fixed because these infections most likely occurred around the time of HIV infection regardless of when testing took place.²⁷ The alcohol covariate was also treated as fixed, regardless of when reported, because the method and frequency of reporting varied between sites.

Statistical analysis

Associations between drug exposures and ESLD events were estimated using a piecewise exponential Cox model.²⁸ The baseline hazard function was partitioned into three segments, each with its own hazard rate, such that there was approximately the same number of events in each segment. Baseline hazard rates were allowed to vary between cohorts. Individual anchor drugs were modelling hierarchically, their associations with outcome allowed to vary around an estimated association for the drug class mean.^{19,20} Each nucleos(t)ide backbone was modelled as a fixed dose combination.

Given few events and model complexity, we took a fully Bayesian approach fitting this model using Markov Chain Monte Carlo. This allowed us to first, employ hierarchies for the

baseline hazard function, cohort effects and anchor drug exposures so that estimates ‘borrow strength’ across related subgroups;²⁹ and second, add weakly informative prior information to avoid false positives so that any unstable estimates ‘shrink’ towards contextually sensible values.³⁰ We provide code for fitting this model using PROC MCMC in SAS (Supplementary Material; Appendix A). The model was then used in sensitivity analyses to assess the reliability of signals from the main analysis (Supplementary Material; Appendix B). We explored decisions made when selecting patients, choosing covariates and asserting prior distributions.

Prior information

Prior to analysis, we asserted weakly informative prior distributions for all model parameters.³⁰ Baseline hazard rates were distributed gamma, with parameters reflecting historical NA-ACCORD data in mono-infected patients with approximately 50 ESLD events reported over 50,000 patient years of follow-up (PYFU) from 1996 to 2005;²⁷ we then discounted these data by a factor of 0.1.³¹ We assumed baseline hazard rates would vary among cohorts, with a rate in each cohort between 80% to 125% of the average with 95% confidence.

Anchor drug exposures (per five year’s cumulative use) were represented in the model by a drug class mean plus a residual effect for each individual drug.¹⁹ We assumed that hazard ratios for residual drug effects were between 0.5 and 2.0 with 95% confidence. We asserted normal priors for log hazard ratios associated with each of the three drug classes and two backbones:³² we assumed uncertain direction priors for cumulative exposure to each backbone^{33,34} and to the integrase inhibitor drug class;^{35,36} but we assumed that cumulative exposure to both boosted protease inhibitors^{8,37} and to non-nucleoside reverse-transcriptase inhibitor was possibly harmful.³⁸

Likewise we asserted a normal prior for the log hazard ratio associated with each covariate.³² For the fixed covariates, we assumed higher FIB-4 at baseline, alcohol abuse or dependency, HBV and HCV were all probably harmful; for the time-dependent covariates, we assumed increasing CD4 cell count (per 100 cells/mm³) was possibly beneficial and detectable HIV RNA was possibly harmful.^{27,33,34,39}

Results

Patient selection and characteristics

We identified 27,464 new users with reliable drug records from among 56,419 patients screened for ESLD (Figure 1). Of these, we included 10,563 adults starting contemporary ART after 1 January 2004 with follow-up during a period of ESLD validation and without evidence of end-stage renal disease or an earlier ESLD event.

Among patients selected for analysis, 62 had a validated ESLD event during follow-up. On average, those with an event were older than those without, with a lower CD4 cell count and higher fibrosis score when starting ART (Table 1). They were more likely to have HBV or HCV and to have evidence of alcohol dependence or abuse.

Outcomes and ART

The 62 first ESLD events were classified as: ascites, 42; hepatic encephalopathy, 12; spontaneous bacterial peritonitis, 7; and hepatocellular carcinoma, 3. The median length of follow-up was 3.3 years. Rates of ESLD were (per 1000 PYFU): 1.5 in all patients; 0.4 in those infected with HIV only; 2.8 in those coinfecting with HBV; 7.2 in those coinfecting with HCV; and 13.1 in those coinfecting with both.

Most patients started ART with a backbone of tenofovir and emtricitabine (Table 2). The most common anchor drugs were atazanavir and darunavir (both boosted by ritonavir) and efavirenz. There were 10 events among patients starting boosted darunavir; relatively few patients started this drug and they had a relatively short median follow-up. In contrast, there were 26 events in patients starting efavirenz but many more patients started this drug with a relatively lengthy period of follow-up. Relatively few patients started integrase inhibitors; most were followed for only a short period and few experienced an event. Elvitegravir was the most common integrase inhibitor but those starting raltegravir were followed for longer.

Among the 10,563 patients, 511 (5%) had HBV. Of those with HBV, 501 (98%) had at least some exposure to tenofovir, with a median exposure of 31 months during a median follow-up of 35 months since starting ART.

Model results

Of the three anchor drug classes, boosted protease inhibitors had the strongest signal for ESLD (Table 3). For both darunavir and atazanavir, there was an appreciable shift in median hazard ratio (HR) – from prior to posterior – and a narrowing of credible intervals (CrI). There was also an appreciable shift for efavirenz, but towards a weaker signal than anticipated. In contrast, prior and posterior HRs and CrIs were similar for all integrase inhibitors and for the drug class itself, indicating there was little information in these data about the risk of ESLD associated with exposure to integrase inhibitors. There was no ESLD signal for either nucleos(t)ide backbone.

Covariate associations were largely in line with expectations, in that posterior intervals were contained entirely within prior intervals (Table 3). The association with alcohol dependence or abuse was perhaps weaker than expected – our covariate was a crude measure of excessive alcohol consumption. The association with HCV was perhaps stronger than expected: HCV was clearly the most harmful risk factor; more harmful than HBV.

Estimates of the baseline hazard rate suggest a slight increase in the risk of ESLD with time on ART (Table 3). Essentially these are estimates of the rate of ESLD in treated patients with an absence of risk factors as they age. Note that these rates were lower than expected; none of the three posterior intervals were contained entirely within the prior interval.

Discussion

In this study of new users of contemporary ART using validated ESLD data, boosted protease inhibitors atazanavir and darunavir had the strongest signal for ESLD. This did not seem to be a class effect, as there was no signal with lopinavir. There was also no

signal with efavirenz. With other anchor drugs – both non-nucleoside reverse-transcriptase inhibitors and integrase inhibitors – there was not enough information in these data to draw even tentative conclusions. There was no toxicity signal for either of the two nucleos(t)ide backbones despite their pivotal role in ART.

A study from the D:A:D using prevalent users and conventional frequentist methods led to unexpected results.² Exposure to tenofovir was harmful, exposure to emtricitabine was protective but exposure to lamivudine was not. However 68% of those on tenofovir were also on emtricitabine. Even if it were possible to untangle separate signals for two drugs usually taken in combination, clinical interest will be in the net effect of fixed dose combinations. We modelled nucleos(t)ide backbones as combinations; tenofovir and emtricitabine had no toxicity signal in our data. Emtricitabine and lamivudine are also considered interchangeable.^{40,41} It is not clear how many antiretrovirals were assessed but possibly as many as 14 different drugs.⁹ When many drugs are included in a conventional model, the probability of at least one false positive is high (~25% to 35%²⁰).

There are links between the approach taken here and the Bayesian method used by the FDA to detect toxicity signals in MedWatch data.¹⁷ The FDA's method shrinks unstable Poisson rates towards gamma prior distributions that represent no association.^{42,43} The piecewise exponential Cox model can be viewed as a Poisson rate in each segment of time under follow-up²⁸ and we use a gamma prior distribution for the baseline rate in each segment. However we also shrink unstable estimates for individual drugs towards a drug class mean; that mean represents no association for some drugs but not for others, where background information suggests a possible drug class effect. Shrinkage towards the null is appropriate in the FDA's automated system. However even in that system, including contextually relevant prior information would allow signals to be detected earlier, from fewer events.⁴⁴ Using prior information based on the drug class is consistent with accepted practice in adverse event reporting – a single adverse event drug exposure combination should not be viewed in isolation but in the context of other similar adverse events and other similar drugs.⁴³ An evaluation of the FDA's method has shown it works well in practice;⁴⁵ simulation suggests the approach taken here will work better than conventional frequentist methods.²⁰

A key issue is the baseline rate of events. Our original prior reflected the historical rate of events in NA-ACCORD data, roughly 1 per 1000 PYFU in HIV mono-infected patients.²⁷ In D:A:D data,² the rate in mono-infection was much lower (0.12 per 1000 PYFU) and similar to posterior estimates for our data when less emphasis was placed on historical events in the NA-ACCORD (Supplementary Material; Appendix B – Sensitivity Analysis 8). Our estimates then suggest that the rate of events declines slightly as patients age; while counter-intuitive, this could reflect a depletion of susceptibles. With a lower baseline rate, signals for the two protease inhibitors will be stronger. However the composition of ESLD events in the D:A:D data was very different: they excluded ascites as an event, the most common event in our data, but then reported a high rate of hepatic encephalopathy. These differences probably explain the lower rate of ESLD in D:A:D data.

Note too that although liver cirrhosis is the most common cause of ascites, other causes include various intra-abdominal cancers, end-stage renal disease, pancreatitis, and heart failure with reduced ejection fraction. However all ascites events in our study were confirmed by medical record review to be hepatic in origin. With ascites excluded as an event, a higher rate of hepatic encephalopathy is to be expected in the D:A:D study, as a subsequent first ESLD event. Hepatic encephalopathy is a difficult clinical diagnosis to make, as no one test confirms or excludes it. These different definitions of ESLD could promote or downplay the influence of a particular drug so that the results from the two studies then differ.

The signals in these data are by no means certain. This is shown in a sensitivity analysis where the loss of a single event in a patient exposed to darunavir weakened the signal for that drug (Supplementary Material; Appendix B – Sensitivity Analysis 2). Many of the sensitivity analyses caused shifts in signals and our estimates have wide credible intervals. This is to be expected with relatively few events and a complex model. Nevertheless the shifts were predictable in direction and often informative in themselves. And the lack of a signal does not mean a drug is safe. Pharmacovigilance is an ongoing process and as data accrue, “the negative signals of today may appear as positive in the future”.¹⁷

Our results have two implications. First, treating HCV has the greatest potential to reduce the risk of ESLD. HCV coinfection was roughly twice as harmful as five year’s exposure to darunavir. That HCV was more harmful than HBV is consistent with the near universal use of tenofovir in patients with HBV to control HBV viral replication, and this is likely to attenuate the risk associated with this coinfection. HCV was seldom treated during the period of our study. Second, our view is that boosted darunavir should be investigated first. Darunavir had a slightly stronger signal than atazanavir but crucially its signal strengthened when, in a sensitivity analysis, we reduced the influence of the drug class mean (Supplementary Material; Appendix B – Sensitivity Analysis 6). Darunavir has been linked to liver injury in an FDA review of adverse event reports.⁴⁶

Pharmacovigilance generates hypotheses for pharmacoepidemiologic study.¹¹ Cohorts are important for the study of ‘Type C’ adverse events,¹² where an exposure contributes to the risk of the event but that contribution takes time to become apparent, there are multiple causal factors and complicated treatment histories with the risk of confounding. When signals are not apparent in data from clinical trials,⁴⁷ then it is more likely the adverse event has a latency period. Yet it is also often plausible that risk will not increase indefinitely with increasing exposure, but will plateau. When patients must be followed for long periods before events occur and patients and clinicians are free to vary treatment, investigators will need to address both time-dependent confounding and uncertain relationships between cumulating exposure and the adverse event.⁴⁸

We show how a Bayesian approach can be used to detect toxicity signals in contemporary ART using a cohort of new users with relatively few adverse events and exposure to a variety of antiretroviral drugs. Our results suggest that untreated HCV confers a greater risk of ESLD but that signals associated with cumulating exposure to boosted darunavir and atazanavir warrant further study with data and designs able to establish causality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- We describe a fully Bayesian hierarchical model suitable for detecting toxicity signals in longitudinal cohort data with complex treatments and few adverse events. We give SAS code for fitting this model using Markov Chain Monte Carlo.
- Results from this model show no association between end-stage liver disease and either of the two nucleos(t)ide combinations that are the backbone of contemporary antiretroviral therapy (abacavir/lamivudine and tenofovir/emtricitabine).
- Protease inhibitors atazanavir and darunavir have the strongest signals for end-stage liver disease. This does not seem to be a drug class effect, as lopinavir has no signal.

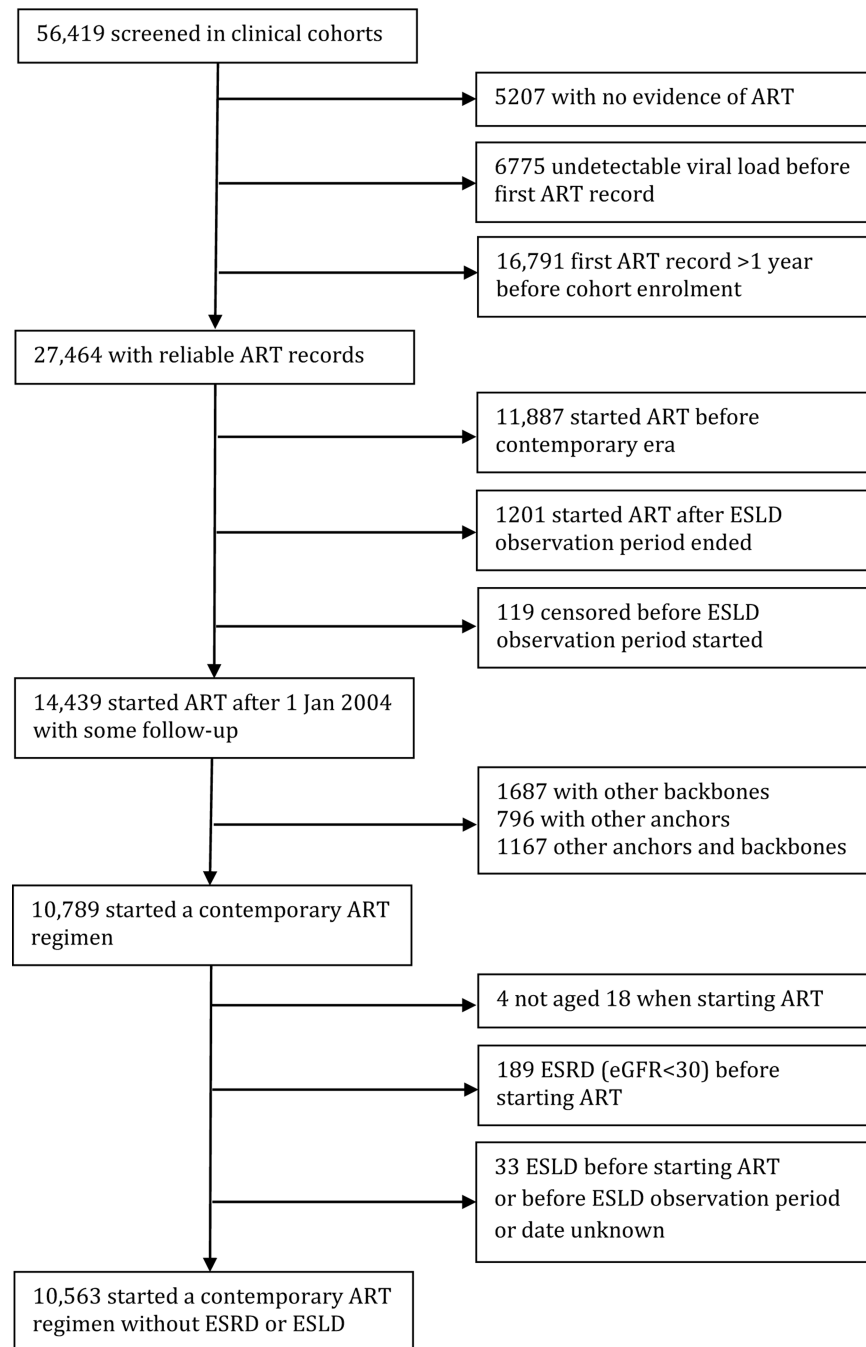


Fig 1. Patient selection

Patients selected for our analysis from among those screened for end-stage liver disease or hepatocellular carcinoma in clinical cohorts of the North American AIDS Cohort Collaboration on Research and Design. ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; ESLD, end-stage liver disease; ESRD, end-stage renal disease.

Table 1.

NA-ACCORD patient characteristics when starting a contemporary antiretroviral therapy, for all patients included in our analysis and for those patients with validated end-stage liver disease (ESLD) event during follow-up.

Characteristic	All patients		Patients with ESLD	
	Percent (%) or median	n=10,563 (% missing)	n=62 (% missing)	
Demographic				
Female, %		16	19	
Black or African American, non-Hispanic, %		37	39	
White, non-Hispanic, %		44	39	
Hispanic, %		12	18	
Other race or ethnicity, %		5	5	
Unknown race and ethnicity, %		2	0	
Age, median (years)		38	47	
Clinical				
CD4 cell count, median (cells/mm ³) ^a		280 (2)	200	
CD4 percent, median ^a		18 (4)	15	
APRI > 2, % ^{a,b}		3 (6)	35	
FIB-4 > 3.25, % ^{a,c}		5 (7)	48	
BMI, median (kg/m ²) ^{a,d}		25 (17)	24 (10)	
Comorbidities				
Hepatitis B, % ^e		5	16	
Hepatitis C, % ^f		12	68	
Diabetes, % ^g		4	5	
Alcohol dependence or abuse, % ^h		28 (3)	61	

^aBased on the last measurement in the two years prior to starting antiretroviral therapy or if none available, the first measurement in the six months after starting.

^bAspartate aminotransferase to platelet ratio index⁴⁹ – a measure of liver fibrosis.

^cFIB-4 index²⁵ – a measure of liver fibrosis.

^dBody mass index.

^eHepatitis B virus (HBV) defined as any recorded: (1) positive HBV surface antigen (HBsAg), (2) positive HBV e antigen (HBeAg), or (3) detectable HBV DNA.

^fHepatitis C virus (HCV) defined as any recorded: (1) positive HCV antibody test; (2) detectable HCV RNA, or (3) an available HCV genotype.

^gDiabetes mellitus defined as (before starting antiretroviral therapy): (1) a haemoglobin A1c >6.5%, (2) a prescription of anti-diabetic medication, or (3) a diabetes diagnosis plus prescription of a diabetes-related medication.

^hDefined as ever having had: (1) a diagnosis of alcohol dependence or abuse; (2) a patient self report of at risk alcohol use or binge drinking; or (3) documented at risk alcohol use found in medical records when reviewing data for an ESLD sub-study

Table 2.

The number of patients starting each combination of a contemporary antiretroviral therapy and for these patients, the median length of follow-up (years) and number of events (end-stage liver disease or hepatocellular carcinoma).

NRTI Backbone		Abacavir with lamivudine ^a		Tenofovir with emtricitabine ^{a,b}		
Anchor	Number of patients	Median follow-up	Number of events	Number of patients	Median follow-up	Number of events
Boosted PIs						
Atazanavir ^c	192	6.7	4	1746	4.3	12
Darunavir ^c	85	2.7	1	1036	2.8	10
Lopinavir ^c	106	5.4	0	473	5.4	6
NNRTIs						
Efavirenz	202	6.9	0	4505	4.2	26
Nevirapine	22	3.7	0	111	2.8	0
Rilpivirine	0	0	0	483	2.3	0
INSTIs						
Elvitegravir ^c	0	0	0	884	1.3	1
Dolutegravir	145	0.7	0	135	1.0	0
Raltegravir	35	2.2	1	403	3.5	1

INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside (or nucleotide) reverse-transcriptase inhibitor; PI, protease inhibitor.

^a Lamivudine and emtricitabine were treated as interchangeable. A few patients started on abacavir and emtricitabine; likewise a few patients started on tenofovir and lamivudine.

^b Either tenofovir or TAF – with some cohorts, the two were not coded separately. However the first TAF based regimen was approved by the FDA in November 2015 so most use would be of tenofovir.

^c Boosted with ritonavir; for elvitegravir, boosted with cobicistat (occasionally with ritonavir).

Table 3.

Prior and posterior credible intervals (CrI) for model parameters in the main analysis.

Parameter	Prior		Posterior	
	Hazard ratio (or hazard rate)	Median 95% CrI	Median 95% CrI	
Anchor drug class or individual drug ^a				
Boosted PIs	1.5	0.37 to 6.0	1.7	0.75 to 3.6
Atazanavir ^b	1.5	0.32 to 7.1	1.8	0.82 to 3.9
Darunavir ^b	1.5	0.32 to 7.1	2.0	0.86 to 4.7
Lopinavir ^b	1.5	0.32 to 7.1	1.5	0.56 to 3.7
NNRTIs	1.5	0.37 to 6.0	1.3	0.57 to 3.1
Efavirenz	1.5	0.32 to 7.1	1.1	0.49 to 2.5
Nevirapine	1.5	0.32 to 7.1	1.5	0.51 to 4.2
Rilpivirine	1.5	0.32 to 7.1	1.5	0.50 to 4.1
INSTIs	1.0	0.25 to 4.0	1.2	0.37 to 3.3
Elvitegravir ^b	1.0	0.21 to 4.7	1.3	0.34 to 4.3
Dolutegravir	1.0	0.21 to 4.7	1.2	0.32 to 4.1
Raltegravir	1.0	0.21 to 4.7	1.3	0.34 to 3.8
NRTI backbones				
Abacavir	1.0	0.25 to 4.0	0.95	0.39 to 2.3
Tenofovir ^c	1.0	0.25 to 4.0	0.78	0.36 to 1.8
Covariates				
Alcohol dependence or abuse	2.0	0.50 to 8.0	1.5	0.93 to 2.3
CD4 cell count (per 100 cells/mm ³) ^d	0.67	0.17 to 2.7	0.91	0.81 to 0.99
Detectable HIV RNA ^d	1.5	0.37 to 6.0	1.6	0.97 to 2.6
Hepatitis B virus	2.0	0.50 to 8.0	2.1	1.1 to 3.8
Hepatitis C virus	2.0	0.50 to 8.0	4.4	2.6 to 7.0
Log FIB-4 (per 0.3 log units) ^e	2.0	0.50 to 8.0	2.1	1.8 to 2.4
Baseline hazard rate (per 1000 PYFU) ^f				
First two years	0.93	0.32 to 2.0	0.39	0.22 to 0.69
Three to five years	0.93	0.32 to 2.0	0.41	0.21 to 0.70
Six years or more	0.93	0.32 to 2.0	0.53	0.23 to 1.11

INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside (or nucleotide) reverse-transcriptase inhibitor; PI, protease inhibitor; PYFU, patient years of follow-up.

^aThe prior for each individual drug was the sum of two normal distribution priors – the prior for the drug class plus the prior for the residual effect of individual drugs beyond the drug class.

^bBoosted with ritonavir; for elvitegravir, boosted with cobicistat (or occasionally with ritonavir).

^cEither tenofovir or TAF – because with some cohorts, the two were not coded separately. However the first TAF based regimen was approved by the FDA in November 2015 so most cumulative exposure would have been to tenofovir.

^dTime updated. All other covariates (except FIB-4) were if ever reported because the methods and frequency of recording hepatitis status and alcohol use varied widely across cohorts.

^eFIB-4 index ²⁵ when starting antiretroviral therapy. This was highly skewed; log FIB-4 was closer to symmetric with an interquartile range of 0.33; hence 0.3 log units represents an appreciable shift in this marker of fibrosis.

^fUnlike other parameters, these are hazard rates (per 1000 years PYFU); not hazard ratios. The prior for the baseline hazard rate in each segment was gamma (shape=5, rate=5000) with a mean rate of 1 event per 1000 PYFU.

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