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Risk of Liver Decompensation with Cumulative Use of Mitochondrial Toxic Nucleoside Analogues in HIV/Hepatitis C Virus Coinfection

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Abstract

Purpose—Among patients dually infected with human immunodeficiency virus (HIV) and chronic hepatitis C virus (HCV), use of antiretroviral therapy (ART) containing mitochondrial toxic nucleoside reverse transcriptase inhibitors (mtNRTIs) might induce chronic hepatic injury, which could accelerate HCV-associated liver fibrosis and increase the risk of hepatic decompensation and death.

Methods—We conducted a cohort study among 1,747 HIV/HCV patients initiating NRTI-containing ART within the Veterans Aging Cohort Study (2002–2009) to determine if cumulative

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mtNRTI use increased the risk of hepatic decompensation and death among HIV/HCV-coinfected patients. Separate marginal structural models were used to estimate hazard ratios (HRs) of each outcome associated with cumulative exposure to ART regimens that contain mtNRTIs versus regimens that contain other NRTIs.

Results—Over 7,033 person-years, we observed 97 (5.6%) decompensation events (incidence rate, 13.8/1,000 person-years) and 125 (7.2%) deaths (incidence rate, 17.8 events/1,000 person-years). The risk of hepatic decompensation increased with cumulative mtNRTI use (1–11 months: HR, 1.79 [95% confidence interval [CI], 0.74–4.31]; 12–35 months: HR, 1.39 [95% CI, 0.68–2.87]; 36–71 months: HR, 2.27 [95% CI, 0.92–5.60]; >71 months: HR, 4.66 [95% CI, 1.04–20.83]; $p=0.045$) versus non-use. Cumulative mtNRTI use also increased risk of death (1–11 months: HR, 2.24 [95% CI, 1.04–4.81]; 12–35 months: HR, 2.05 [95% CI, 0.68–6.20]; 36–71 months: HR, 3.04 [95% CI, 1.12–8.26]; >71 months: HR, 3.93 [95% CI, 0.75–20.50]; $p=0.030$).

Conclusions—These findings suggest that cumulative mtNRTI use may increase the risk of hepatic decompensation and death in HIV/HCV coinfection. These drugs should be avoided when alternatives exist for HIV/HCV patients.

Keywords

drug-induced liver injury; hepatotoxicity; hepatic decompensation; hepatitis C; HIV; mitochondrial toxicity

INTRODUCTION

Because of shared risk factors, coinfection with chronic hepatitis C virus (HCV) occurs in 10–30% of patients with human immunodeficiency virus (HIV) infection.^{1–3} Prior studies suggest that antiretroviral therapy (ART) slows progression of HCV-associated liver fibrosis, possibly by reducing HIV-related inflammation and immune dysfunction.^{4–7} As a result, guidelines recommend administration of ART to all HIV/HCV-coinfected patients, regardless of CD4 cell count.⁸

Despite the benefits of ART, 16–69% of HIV/HCV-coinfected patients develop liver enzyme elevations after ART initiation,^{9–16} and such antiretroviral-induced liver injury may arise from different mechanisms. One important mechanism of liver injury is mitochondrial toxicity, which is caused by drug-induced depletion of mitochondrial DNA.¹⁷ Liver injury due to mitochondrial toxicity may develop after initiation of certain antiretrovirals within the nucleoside reverse transcriptase inhibitor (NRTI) class, specifically didanosine, stavudine, zidovudine, or zalcitabine.¹⁷ These mitochondrial toxic NRTIs (mtNRTIs) are no longer recommended as part of first-line HIV treatment regimens, but some are still used within ART regimens in resource-constrained settings due to their low cost, or may be selected for patients with pre-existing drug resistance.⁸

Presently, it remains unclear if cumulative use of mtNRTIs among HIV/HCV-coinfected patients hastens progression to hepatic decompensation, the main endpoint of chronic viral hepatitis defined by development of any clinical complication of cirrhosis, including ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy.¹⁸ Prolonged exposure to mtNRTIs could lead to chronic hepatic injury, which might accelerate

HCV-associated liver fibrosis progression and increase risk of hepatic decompensation. Further, hepatic injury induced by these agents may persist even after they have been discontinued and affect subsequent liver function.¹⁹ Studies that evaluate the risk of hepatic decompensation associated with cumulative use of antiretrovirals among HIV/HCV-coinfected patients are needed to examine the hepatic safety of these drugs in this population.

Our aim was to determine if cumulative use of mtNRTIs (didanosine, stavudine, zidovudine, or zalcitabine) increased risk of hepatic decompensation among HIV/HCV-coinfected patients compared with use of other NRTIs. We hypothesized that longer duration of use of these antiretrovirals was associated with a higher risk of decompensation in coinfecting individuals.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study among ART-treated HIV/HCV-coinfected patients in the Veterans Aging Cohort Study (VACS) between January 1, 2002 and December 31, 2009.²⁰ We restricted our analyses to 2002–2009 because this was the period of greatest variability in mtNRTI initiation (Appendix 1). The VACS consists of electronic medical record data from HIV-infected patients receiving care at Veterans Affairs (VA) medical facilities across the United States (US). Data included inpatient and outpatient diagnoses (recorded using International Classification of Diseases, Ninth Revision [ICD-9] codes), procedures, laboratory results, and pharmacy data. Date of death was ascertained from the VA Vital Status file.²¹ This study was approved by the institutional review boards of the University of Pennsylvania and Corporal Michael J. Crescenz VA Medical Center.

Study Patients

Coinfected patients were included if they had: 1) a diagnosis of HIV, 2) detectable HCV RNA, 3) initiated ART (use of at least three antiretrovirals from two different classes⁸) that included an NRTI between 2002 and 2009, 4) at least one measurement showing HIV RNA >500 copies/mL within 6 months prior to starting ART (to identify new ART initiators²²), and 5) at least 6 months of observation before initiating ART. Patients were excluded if prior to follow-up they had hepatic decompensation (defined below) or received interferon-based HCV therapy (since treatment reduces the risk of hepatic decompensation^{23,24}).

The 6 months prior to the start of follow-up represented the baseline period. Follow-up began on the date of ART initiation and continued until hepatic decompensation, death, initiation of HCV therapy, switching to a non-NRTI-containing ART regimen (since this analysis focused on NRTI users), discontinuation of ART (no further antiretroviral fills within 30 days after the last prescription's days' supply), or last visit before December 31, 2011.

Ascertainment of mtNRTI Use

Our primary exposure was use of any mtNRTI (didanosine, stavudine, zalcitabine, and zidovudine), which was determined on a monthly basis via prescription fills. Patients were classified as exposed for any month (30-day period) covered by the fill. Exposure was captured using two variables: current and cumulative mtNRTI use. Over each month of follow-up, current mtNRTI use was represented by an indicator variable, taking a value of 1 if the patient was exposed in that month or 0 if not. Cumulative use was defined as the total number of months of past use, excluding the current month. Patients receiving two mtNRTIs were not classified as having double the time on the drugs, since it is unclear if the effect of dual exposure is additive.

Main Study Outcome

The primary outcome was incident hepatic decompensation, which was defined by one hospital discharge ICD-9 diagnosis or two or more outpatient ICD-9 diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage (Appendix 2). A prior study validated this definition, with 91% of events confirmed by medical records.²⁵ Two outpatient diagnoses were required to exclude events that might be suspected but not confirmed at follow-up visits. Based on the results of the prior validation study,²⁵ we did not include ICD-9 diagnoses for hepatic encephalopathy, which could indicate decompensation, because these diagnoses were often linked to unrelated conditions (e.g., narcotic overuse, stroke). The decompensation date was defined as the hospital discharge date (for persons identified by hospital diagnosis) or initial outpatient diagnosis date (for those identified by outpatient diagnoses). As a secondary outcome, we evaluated all-cause mortality.

Data Collection

Baseline demographic and clinical data included: age, sex, race/ethnicity, body mass index, diabetes mellitus, alcohol dependence/abuse, injection/non-injection drug use, year of ART initiation, ART regimen, exposure to other antiretrovirals associated with hepatotoxicity (abacavir, nevirapine, saquinavir, or tipranavir¹⁷), and potentially hepatotoxic non-antiretroviral drugs (defined below). Diabetes was defined by serum glucose ≥ 200 mg/dL, ICD-9 diagnosis, or anti-diabetic medication use.^{26,27} Alcohol dependence/abuse²⁸ and injection/non-injection drug use^{28,29} were defined by validated ICD-9 diagnoses. Use of potentially hepatotoxic non-antiretroviral medications was determined by a fill for acetaminophen (alone or in combination with an opioid), statins (pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, or rosuvastatin), duloxetine, isoniazid, metformin, thiazolidinediones (pioglitazone, rosiglitazone), or valproic acid. These drugs were selected because of their known potential for acute liver injury³⁰ and frequency of prescription among HIV/HCV patients.^{31,32}

Baseline laboratory data collected from dates closest to but prior to start of follow-up included: pre-ART HIV RNA, pre-ART CD4 count, HCV RNA, HCV genotype, hepatitis B surface antigen, serum creatinine, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count. Baseline FIB-4, a noninvasive measure of advanced hepatic fibrosis, was determined by: $(\text{age [years]} \times \text{AST [U/L]}) / ((\text{platelet count [10}^9/\text{L]}) \times (\text{ALT [U/L]})^{1/2})$.³³ Because liver fibrosis can progress by one stage within 4 years

among ART-treated HIV/HCV-coinfected persons,³⁴ we determined baseline FIB-4 scores using the component tests within a 2-year period around the start of follow-up. FIB-4 scores <1.45 were considered no/minimal fibrosis, and scores >3.25 as advanced hepatic fibrosis/cirrhosis.³³

Time-varying variables included those that may influence the choice of antiretrovirals selected among coinfecting patients and affect the risk of hepatic decompensation: diabetes status, ART regimen, exposure to a potentially hepatotoxic antiretroviral, exposure to any hepatotoxic non-antiretrovirals, hepatitis B surface antigen status, HIV RNA, CD4 count, creatinine, hemoglobin, ALT, AST, platelet count, and FIB-4. When multiple results of the same test were measured within a month, we used the lowest value for CD4 count, hemoglobin, and platelet count and highest value for HIV RNA, AST, ALT, and creatinine. When a laboratory test was not updated in a given month, we carried forward the value from the previous month.

Statistical Analysis

Overview—The goal of this analysis was to determine if cumulative mtNRTI use increased the risk of hepatic decompensation among HIV/HCV patients. In clinical settings, laboratory results might be affected by prior ART use and influence selection of future ART regimens. We therefore used marginal structural models to account for time-dependent confounding.^{35–37}

Derivation of patient-specific weights—We first modeled the probability of receiving an mtNRTI and the probability that a patient remained uncensored to develop patient-specific weights at baseline and over each month of follow-up.³⁸ Although the traditional method of modeling these probabilities is logistic regression, the validity of this method depends on this model being correctly specified.³⁷ To overcome this limitation, we used an alternative method, SuperLearner, which is an ensemble machine-learning method that incorporates a variety of prediction algorithms and uses cross-validation to choose an optimal prediction based on a set of different algorithms.^{39,40} SuperLearner has been shown to be more robust to deviations from parametric assumptions in observational studies.⁴¹ The prediction algorithms incorporated included logistic regression, generalized additive models, naïve Bayes classifiers, and multivariate adaptive regression splines.⁴² We used 2-fold cross-validation in SuperLearner to select the best algorithm or combination for prediction.

For each patient, the probability of mtNRTI treatment at each month and the probability of remaining uncensored at each month were multiplied, and the inverse of these probabilities yielded the patient-specific weights.³⁸ To prevent outlying data from exerting undue influence over the sample, we truncated weights at the 0.5th and 99.5th percentiles.

Causal effect of mtNRTI use on hepatic decompensation and death—The weights were used to estimate parameters within marginal structural models. To estimate the risk of decompensation associated with cumulative mtNRTI use, a marginal structural Cox model was specified, where the covariates were: year of ART initiation, month on ART, current mtNRTI use (current versus not), and total months of mtNRTI use (excluding the current month), which was categorized by duration of exposure (0 months [reference]; 1–11

months; 12–35 months; 36–71 months; >71 months). The categories of cumulative mtNRTI use were chosen to align closely with quartiles of exposure, while representing meaningful divisions of months exposed. Hazard ratios (HRs) with 95% confidence intervals (CIs) were determined. A separate marginal structural Cox model was used to estimate the risk of death associated with cumulative mtNRTI use. To test if increasing mtNRTI exposure was associated with a higher risk of decompensation or death, we repeated analyses by substituting the categorized cumulative treatment covariates in models with a continuous variable.

Since liver disease progression might have led to cessation of ART, censoring patients at ART discontinuation might underestimate the risk of decompensation with cumulative mtNRTI use. We therefore repeated this analysis without treating ART discontinuation as a censoring event. In this analysis, all time-varying variables were updated until a censoring event.

Descriptive analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). Marginal structural models were fitted in R 3.1.0 using SuperLearner and geepack packages.⁴³ We used multiple imputation, by means of 10 imputations using all variables in Table 1 and outcomes, to assign values for missing data.⁴⁴ Results across the 10 datasets were combined to arrive at CIs that accounted for within- and across-dataset variances.⁴⁵

Sensitivity analyses—We conducted three sensitivity analyses to assess the robustness of our findings. First, we compared the impact of 2-fold cross-validation (used in primary analyses) versus 10-fold cross-validation to reduce the likelihood for overfitting by SuperLearner.

Second, we assessed how sensitive our results were to the use of SuperLearner models to estimate patient-derived weights by substituting traditional logistic regression. We evaluated three methods to derive weights: 1) SuperLearner for all weights (treatment and censoring), 2) logistic regression for all weights, and 3) SuperLearner for treatment weights and logistic regression for censoring weights.

Finally, since there is no standard mechanism for choosing a truncation point for weights, we examined HRs of decompensation with cumulative mtNRTI use after truncating weights at alternative locations (99.9th, 99.5th, 99th, and 98th percentiles) and leaving them untruncated.

RESULTS

Patient Characteristics

Between 2002 and 2009, 1,747 HIV/HCV patients met inclusion criteria (Figure 1). Absence of HCV RNA assessment was a common reason for exclusion, but there were no clinically relevant differences in the characteristics between included patients and those excluded due to lack of HCV RNA (data not shown).

The cohort was predominantly male and black, and 6.2% had a documented history of alcohol dependence/abuse (Table 1). The majority had infection with HCV genotype 1 and a

high baseline HCV RNA level. Patients dispensed an mtNRTI at ART initiation were younger, more commonly had a history of alcohol dependence/abuse, and had a lower prevalence of advanced hepatic fibrosis/cirrhosis by FIB-4.

The median duration of follow-up was 3.7 (interquartile range, 1.7–6.0) years. A total of 181 (10.4%) patients initiated HCV therapy during follow-up and were censored.

Hepatic Decompensation Events and Mortality

Ninety-seven (5.6%) decompensation events occurred over 7,033 person-years (incidence rate, 13.8/1,000 person-years). At the time of initial decompensation, 70/97 (72.2%) patients presented with ascites, 6/97 (6.2%) with spontaneous bacterial peritonitis, and 28/97 (28.9%) with variceal hemorrhage. Patients dispensed an mtNRTI at ART initiation more commonly developed decompensation than those who were not (59 [7.1%] versus 38 [4.2%]; $p=0.009$). A total of 125 (7.2%) patients died during follow-up (incidence rate, 17.8 events/1,000 person-years).

Risk of Hepatic Decompensation and Death with Cumulative mtNRTI Use

Appendix 3 shows the relative hazards of hepatic decompensation associated with cumulative mtNRTI use within an unadjusted and unweighted model, a baseline-adjusted but unweighted model, and the marginal structural model. HRs of cumulative mtNRTI use were higher when compared to those from unweighted models.

Based on the marginal structural model, HRs of decompensation increased with greater cumulative mtNRTI use whether modeled as continuous ($p=0.045$) or categorical, particularly with ≥ 71 months of use (Figure 2). HRs for decompensation increased with both current cumulative mtNRTI exposure and past cumulative mtNRTI exposure (Figure 3). Results were similar when analyses were repeated without censoring at ART discontinuation (Appendix 4).

Cumulative mtNRTI use was also associated with a higher risk of death. HRs of death increased with higher cumulative mtNRTI use when considered as a continuous covariate ($p=0.030$) or categorical (Figure 2). HRs of death also increased with both current and past cumulative mtNRTI exposure (Figure 3).

Sensitivity Analyses

HRs of hepatic decompensation associated with cumulative mtNRTI exposure were almost identical when using 2-fold and 10-fold cross-validation for derivation of patient-specific weights (Appendix 5). However, the use of logistic regression to derive both treatment and censoring weights resulted in HRs that differed in magnitude from those obtained using SuperLearner to develop both treatment and censoring weights (with either 2-fold or 10-fold cross-validation) and from those using SuperLearner with 2-fold cross-validation to develop treatment weights and logistic regression to derive censoring weights (Appendix 5). Similar HRs and 95% CIs were observed across different truncation points (99.9th, 99.5th, 99th, and 98th percentiles) or when not truncated (Appendix 6). The empirical distribution of the weights varies slightly from imputation to imputation. For the untruncated weights, the

maximum ranged from 6.95 to 13.99 between the 10 imputations. The maximum of the 99.5th truncated weights ranged from 2.76 and 3.05.

DISCUSSION

In this study of HIV/HCV-coinfected patients who newly initiated ART in the VA healthcare system, we found that increasing mtNRTI exposure was associated with higher HRs of hepatic decompensation and death. HRs for both endpoints increased with current and past cumulative mtNRTI exposure, suggesting that the risk of these adverse outcomes persists even after discontinuation of the drugs. This finding suggests that greater exposure to mtNRTIs might hasten progression to end-stage liver disease and death among HIV/HCV patients and that this risk may persist well after their discontinuation. Coinfected patients with prolonged mtNRTI exposure might benefit from closer monitoring for development of hepatic decompensation, even after these drugs' discontinuation. Further, clinicians prescribing mtNRTIs in resource-constrained settings should avoid their use in HIV/HCV patients if other agents are available.

Few other studies have evaluated the effects of cumulative antiretroviral use on liver complications. Our findings are consistent with those of a recent analysis of 45,544 HIV-infected patients who initiated ART in Europe, the US, and Australia in the Data Collection on Adverse Events of Anti-HIV Drugs study⁴⁶ In that study, higher rates of end-stage liver disease were observed with greater cumulative (per 5 years) exposure to stavudine (relative rate, 1.46 [95% CI, 1.20–1.77]) and didanosine (relative rate, 1.32 [95% CI, 1.07–1.63]). Sensitivity analyses among viral hepatitis-coinfected patients demonstrated similar findings. Notably, that study did not control for time-dependent confounding. A cohort study of 205 HIV/HCV patients who received interferon/ribavirin therapy and underwent pre-treatment and post-treatment liver biopsies in France found that didanosine use was associated with threefold higher odds of worsening of hepatic fibrosis.⁴⁷ Similarly, a cross-sectional analysis of 671 HIV/HCV patients in France found that a median use of didanosine of >5 months increased the odds of advanced hepatic fibrosis via transient elastography by 70%.⁴⁸

The increased risk of hepatic decompensation and death associated with increasing mtNRTI use is biologically plausible. These agents can inhibit human mitochondrial DNA polymerase gamma, which can result in depletion of mitochondrial DNA and impairment of mitochondrial functionality.^{49,50} Continued mitochondrial dysfunction can persist even after discontinuation of the offending agent and lead to oxidative damage, hepatic steatosis, hepatocellular injury, and development of hepatic fibrosis that can progress to cirrhosis.^{48,51}

This study provides methodological contributions for future pharmacoepidemiological analyses evaluating the effects of cumulative exposure to antiretrovirals on health outcomes. In our primary analyses, we used SuperLearner with 2-fold cross-validation to model the probability of mtNRTI treatment and probability of censoring at each month of follow-up to obtain patient-specific weights. Sensitivity analyses demonstrated that we could accurately derive these weights and save computational time by using SuperLearner with 2-fold cross-validation to model the monthly probability of mtNRTI treatment but use logistic regression to model the monthly probability of censoring. Sensitivity analyses showed that our results

are robust to the choice of truncation point. We did not have unduly large weights, so truncation did not alter the results.

Our study has several potential limitations. First, we might have underestimated the number of decompensation events since our definition did not include hepatic encephalopathy. However, outcomes were identified using a validated definition that had a negative predictive value of >99%.²⁵ Further, the incidence rate of decompensation among coinfecting patients in this study (13.8/1,000 person-years) was similar to that reported in another cohort of coinfecting patients (11.6/1,000 person-years).⁶ Second, confounding by indication is a concern since ART regimen selection was by clinician choice.⁵² We modeled the probability of mtNRTI treatment over each month of follow-up, but bias due to channeling may remain.⁵³ Given mtNRTIs' known potential for adverse effects, clinicians might have more likely prescribed these drugs to coinfecting patients with less liver fibrosis. However, channeling mtNRTIs away from sicker patients would result in a lower likelihood of developing hepatic decompensation, biasing results toward the null hypothesis. Finally, our sample included mostly male US patients, and results may not be generalizable to coinfecting women, patients outside the US, or those treated according to more recent management guidelines. Our study also excluded patients who received antiviral treatment for chronic HCV prior to the start of follow-up and censored observation time at initiation of HCV therapy. Thus, this study cannot inform the impact that successful HCV therapy might have on the risk of decompensation associated with mtNRTI use.

In conclusion, cumulative mtNRTI use was associated with an increased risk of hepatic decompensation and death among HIV/HCV-coinfecting patients. These agents should be avoided in HIV/HCV patients when other options are available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Cumulative mitochondrial toxic nucleoside reverse transcriptase inhibitor (NRTI) use increases the risk of both hepatic decompensation and death in the setting of human immunodeficiency virus (HIV)/chronic hepatitis C virus (HCV) coinfection.
- The risk for decompensation and death increased with current and past cumulative mtNRTI exposure, suggesting that the risk of these adverse outcomes persists even after discontinuation of the drugs.
- Coinfected patients with prolonged mtNRTI exposure might benefit from closer monitoring for development of hepatic decompensation, even after these drugs' discontinuation.
- Clinicians prescribing mtNRTIs in resource-limited settings should avoid their use in HIV/HCV patients if other agents are available.

Figure 1.

Selection of HIV/hepatitis C virus (HCV)-coinfected patients for inclusion in the study.

Abbreviations: ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid; NRTI, nucleoside reverse transcriptase inhibitor; VACS, Veterans Aging Cohort Study

*HIV infection determined by the presence of one hospital or two outpatient International Classification of Diseases, Ninth Revision HIV diagnosis codes.

†ART defined as the use of at least three antiretrovirals from two different classes or 3 nucleoside analogues

‡Follow-up began on the date of ART initiation

Figure 2.

Forest plots of hazard ratios of hepatic decompensation and death associated with current and cumulative* mitochondrial toxic nucleoside reverse transcriptase inhibitor use.

Abbreviations: CI, confidence interval; mtNRTI, mitochondrial toxic nucleoside reverse transcriptase inhibitor

*Cumulative use is the total number of months treated with an mtNRTI (as determined by prescription fills), not including the current month.

Figure 3a. Hepatic decompensation. **Figure 3b.** Death. **Figure 3.**

Forest plots of hazard ratios of hepatic decompensation (Figure 3a) and death (Figure 3b) associated with current and past cumulative mitochondrial toxic nucleoside reverse transcriptase inhibitor (mtNRTI) use compared to no (current or past) mtNRTI use. Current mtNRTI use refers to treatment regimens where, once mtNRTI use began, it did not stop. Past mtNRTI use refers to treatment regimens that involve past, but not current, mtNRTI use. Abbreviations: CI, confidence interval; mtNRTI, mitochondrial toxic nucleoside reverse transcriptase inhibitor

Table 1

Baseline characteristics of patients at initiation of antiretroviral therapy, overall and by use of a mitochondrial toxic nucleoside reverse transcriptase inhibitor.

Characteristic*	Overall (n=1,747)	Dispensed mtNRTI (n=836)	Not Dispensed mtNRTI (n=911)	P
Median age (years, IQR)	51 (47–55)	50 (46–53)	52 (48–56)	<0.001
Male sex	1,717 (98.3)	823 (98.4)	894 (98.1)	0.62
Race/ethnicity				0.31
Black	1,149 (65.8)	547 (65.4)	602 (66.1)	
Caucasian	409 (23.4)	188 (22.5)	221 (24.3)	
Hispanic	134 (7.7)	74 (8.9)	60 (6.6)	
Other/Unknown	55 (3.1)	27 (3.2)	28 (3.1)	
Body mass index				0.08
<18.5 kg/m ²	100 (5.7)	48 (5.7)	52 (5.7)	
18.5–24.9 kg/m ²	967 (55.4)	490 (58.6)	477 (52.4)	
25–29.9 kg/m ²	485 (27.8)	215 (25.7)	270 (29.6)	
30 kg/m ²	186 (10.6)	78 (9.3)	108 (11.9)	
Missing weight and/or height	9 (0.5)	5 (0.6)	4 (0.4)	
Diabetes mellitus	122 (7.0)	59 (7.1)	63 (6.9)	0.91
History of alcohol dependence/abuse	108 (6.2)	66 (7.9)	42 (4.6)	0.004
HCV genotype				<0.001
1 or 4	1,198 (68.6)	542 (64.8)	656 (72.0)	
2 or 3	147 (8.4)	67 (8.0)	80 (8.8)	
Other	2 (0.1)	0 (0.0)	2 (0.2)	
Not tested	400 (22.9)	227 (27.2)	173 (19.0)	
HCV RNA[†]				0.06
400,000 IU/mL and/or 1,000,000 copies/mL	1,415 (81.0)	671 (80.3)	744 (81.7)	
<400,000 IU/mL and/or <1,000,000 copies/mL	241 (13.8)	109 (13.0)	132 (14.5)	
Quantitative, value undeterminable	19 (1.1)	13 (1.3)	6 (0.7)	
Qualitative HCV RNA result only	63 (3.6)	39 (4.7)	24 (2.6)	
HCV genotype only	9 (0.5)	4 (0.5)	5 (0.5)	
Hepatitis B surface antigen				<0.001
Positive	66 (3.8)	29 (3.5)	37 (4.1)	
Negative	1,503 (86.0)	691 (82.7)	812 (89.1)	
No result available at baseline	178 (10.2)	116 (13.9)	62 (6.8)	
Median Pre-ART HIV RNA (log₁₀ copies/mL, IQR)	54,300 (12,766–141,000)	58,734 (14,251–161,574)	49,500 (12,019–120,000)	0.10
Median Pre-ART CD4 cell count (cells/mm³, IQR)	211 (96–312)	208 (88–310)	215 (106–313)	0.66
CD4 cell count				0.23
500 cells/mm ³	110 (6.3)	60 (7.2)	50 (5.5)	
350–499 cells/mm ³	217 (12.4)	100 (12.0)	117 (12.8)	

Characteristic *	Overall (n=1,747)	Dispensed mtNRTI (n=836)	Not Dispensed mtNRTI (n=911)	P
200–349 cells/mm ³	586 (33.5)	268 (32.1)	318 (34.9)	
<200 cells/mm ³	803 (46.0)	389 (46.5)	414 (45.4)	
Not tested at baseline	31 (1.8)	19 (2.3)	12 (1.3)	
Hemoglobin				0.95
<10 g/dL	129 (7.4)	60 (7.2)	69 (7.6)	
10 g/dL	1,616 (92.5)	775 (92.7)	841 (92.3)	
No result available at baseline	2 (0.1)	1 (0.1)	1 (0.1)	
Median serum creatinine (g/dL, IQR)	1.0 (0.8–1.1)	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.71
FIB-4				<0.001
<1.45	473 (27.1)	245 (29.3)	228 (25.0)	
1.45–3.25	824 (47.2)	389 (46.5)	435 (47.7)	
>3.25	395 (22.6)	170 (20.3)	225 (24.7)	
No result available at baseline	55 (3.1)	32 (3.8)	23 (2.5)	
Non-antiretroviral drugs associated with hepatotoxicity				
Acetaminophen	558 (31.9)	238 (28.5)	320 (35.1)	0.003
Isoniazid	27 (1.5)	14 (1.7)	13 (1.4)	0.68
Metformin	55 (3.1)	18 (2.2)	37 (4.1)	0.023
Statins	72 (4.1)	29 (3.5)	43 (4.7)	0.19
Thiazolidinediones	5 (0.3)	0 (0.0)	5 (0.5)	0.032
Valproic acid	9 (0.5)	5 (0.6)	4 (0.4)	0.64
Antiretroviral use				
Nucleos(t)ide reverse transcriptase inhibitors				
Abacavir	313 (17.9)	176 (21.1)	137 (15.0)	0.001
Didanosine	78 (4.5)	78 (9.3)	0 (0.0)	<0.001
Emtricitabine	704 (40.3)	16 (1.9)	688 (75.5)	<0.001
Lamivudine	940 (53.8)	729 (87.2)	211 (23.2)	<0.001
Stavudine	124 (7.1)	124 (14.8)	0 (0.0)	<0.001
Tenofovir	889 (50.9)	97 (11.6)	792 (86.9)	<0.001
Zalcitabine	1 (0.1)	1 (0.1)	0 (0.0)	0.30
Zidovudine	664 (38.0)	664 (79.4)	0 (0.0)	<0.001
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz	875 (50.1)	359 (42.9)	516 (56.6)	<0.001
Nevirapine	93 (5.3)	68 (8.1)	25 (2.7)	<0.001
Protease inhibitors				
Amprenavir	3 (0.2)	3 (0.4)	0 (0.0)	0.07
Fosamprenavir	28 (1.6)	6 (0.7)	22 (2.4)	0.005
Atazanavir	263 (15.1)	41 (4.9)	222 (24.4)	<0.001
Darunavir	12 (0.7)	4 (0.5)	8 (0.9)	0.31
Indinavir	29 (1.7)	27 (3.2)	2 (0.2)	<0.001
Lopinavir	280 (16.0)	146 (17.5)	134 (14.7)	0.12
Nelfinavir	110 (6.3)	100 (12.0)	10 (1.1)	<0.001

Characteristic [*]	Overall (n=1,747)	Dispensed mtNRTI (n=836)	Not Dispensed mtNRTI (n=911)	P
Saquinavir	9 (0.5)	9 (1.1)	0 (0.0)	0.002
Tipranavir	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Integrase inhibitor				
Raltegravir	14 (0.8)	0 (0.0)	14 (1.5)	<0.001
Entry inhibitor				
Maraviroc	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Fusion inhibitor				
Enfuvirtide	3 (0.2)	2 (0.2)	1 (0.1)	0.51

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; mtNRTI, mitochondrial toxic nucleoside reverse transcriptase inhibitor; RNA, ribonucleic acid

^{*} Results reported as n (%) unless otherwise specified.

[†] Based on highest baseline HCV RNA result.