

## **Incidence and predictors of single drug discontinuation according to the presence of HCV coinfection in HIV patients from the ICONA Foundation Cohort Study.**

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### **Running title**

Discontinuation of cART in HIV mono-infected and HIV/HCV co-infected patients.

## **Abstract**

To evaluate incidence rates of and predictors for any antiretroviral (ART) drug discontinuation by HCV infection status in a large Italian cohort of HIV infected patients. All patients enrolled in ICONA who started combination antiretroviral therapy (cART) containing abacavir or tenofovir or emtricitabine or lamivudine plus efavirenz or rilpivirine or atazanavir/r or darunavir/r (DRV/r) or lopinavir/r or dolutegravir or elvitegravir or raltegravir were included. Multivariate Poisson regression models were used to determine factors independently associated with single ART drug discontinuation. Inverse Probability Weighting method to control for potential informative censoring was applied. Data from 10,637 patients were analyzed: 1,030 (9.7%) were HCV-Ab positive. Overall, there were 15,464 ART discontinuations due to any reason in 82,415.9 person-years of follow-up (PYFU) for an incidence rate (IR) of 18.8 (95% confidence interval [95%CI] 18.5-19.1) per 100 PYFU. No difference in IR of ART discontinuation due to any reason between HCV-infected and -uninfected patients was found. In a multivariable Poisson regression model, HCV-infected participants were at higher risk of darunavir/r discontinuation due to any reason (adjusted incidence rate ratio = 1.5, 95%CI 1.01-2.22, *p value* = 0.045) independently of demographics, HIV-related, ART and life-style factors. Among DRV/r treated patients, we found that HCV-viremic patients had twice the risk of ART discontinuation due to any reason than HCV-aviremic patients. In conclusion, HIV/HCV coinfecting patients had a marginal risk increase of DRV/r discontinuation due to any reason compared with those without coinfection.

## **Key Words**

HIV/HCV coinfection, cART, drug discontinuation, toxicity.

## **Introduction**

The widespread use of combination antiretroviral therapy (cART) has substantially improved the prognosis of patients infected with HIV [1]. As a consequence of the reduction of AIDS-related events, non-HIV-related diseases now account for about half of all deaths [1, 2]. Chronic hepatitis C (CHC) is a leading cause of non-HIV-related mortality and morbidity among HIV-infected patients [3]. HIV coinfection with Hepatitis C virus (HCV) has been associated with an increased risk of drug-related hepatotoxicity in the first cART era [4]. Moreover, the extent of liver fibrosis in HIV-infected patients with CHC seems to be an important determinant of the risk of hepatotoxic events due to altered hepatic drug metabolism [5]. Additional data on the durability of different antiretroviral (ART) drugs according to the presence of HCV coinfection, in terms of overall ART discontinuation and long-term toxicities, and on the effect of HCV-treatment on the rate of ART discontinuation in HIV/HCV coinfecting patients are needed [6, 7]. The aim of the study is to evaluate the incidence rates of and risk factors for discontinuation of different ART drugs due to any reasons and due to toxicity by HCV status in a large Italian cohort of HIV-infected patients.

## **Patients and Methods**

### **Study participants**

The study population was selected from the Italian Cohort of Antiretroviral-Naïve patients (ICONA) Foundation Cohort Study. The ICONA study is an Italian multicenter prospective observational study of HIV-infected patients that was set up in April 1997. Study participants enrolled up to June 2016 were included. Clinical and laboratory data and data regarding any drug taken by the patient are collected for all participants and recorded using an electronic data collection form ([www.iconafoundation.it](http://www.iconafoundation.it)). Patients are monitored for HCV status and tested regularly at least once a year when found to be HCV-Ab negative and results of the tests updated. All date of start and stop of each ART drugs are recorded together with the main reason for stopping as reported by the treating physician. All data are updated at the occurrence of any clinical event and in the absence of such an event, at least every 6 months. Details of the cohort and data collection have been previously reported [8].

### **Inclusion criteria**

All patients enrolled in ICONA who started cART defined as at least three ART drugs, including abacavir (ABC) or tenofovir (TDF) and emtricitabine (FTC) or lamivudine (3TC) plus efavirenz (EFV) or rilpivirine (RPV) or ritonavir-boosted-atazanavir (ATV/r) or -darunavir (DRV/r) or -lopinavir (LPV/r) or dolutegravir (DTG) or elvitegravir/cobicistat (EVG/COBI) or raltegravir (RAL) were included, regardless of whether this was their first cART regimen or not. Patients with Hepatitis B infection at baseline were excluded from the analysis due to possible confounding factor for the analyses. In a sensitivity analysis we included only patients who started 3TC-based regimens after the year 2002.

### **Study endpoints**

Although, the main hypothesis is that HIV/HCV co-infected have an increased risk of stopping because of toxicity, because some of the stops due to toxicity are often classified as 'unknown' in cohort studies, we focused on two primary endpoints: ART drug discontinuation due to any reasons, and ART drug discontinuation due to any reasons except stopping for

simplification or viral/immunological failure. As a secondary endpoint we restricted to ART drug discontinuation due to toxicity/intolerability. We both analysed discontinuation of  $\geq 1$  drug in the regimen and the risk of stopping single drugs.

## Definitions

ART drug discontinuation are recorded in the ICONA database according to a specified possible reasons for stopping which include the following: toxicity/intolerability, simplification, viral/immunological failure, non-adherence, and other reasons. These categories of discontinuation was defined follows: toxicity/intolerability including stop due to ART adverse events or patient's intolerance; simplification including strategies to reduce pill burden or ART drugs in the regimen; viral/immunological failure including absence or partial viral/immunological effectiveness of current ART drugs; non-adherence including ART drug intake  $< 95\%$  in the past 6 months. ART drug discontinuation due to toxicity/intolerability was categorised into the following groups: liver, kidney, gastrointestinal (GI) tract, cardiovascular, central nervous system/peripheral nervous system (CNS/PNS), metabolism, hematology, other/unspecified. Dosage adjustments and structured treatment interruptions were not counted as discontinuations in this analysis. Discontinuations of fixed dose combination regimens were defined as events only if there was not a recorded re-starting date within a month of the date of stopping (e.g. no event was ascribed to FTC or TDF if Truvada was stopped and subsequently Atripla started within 30 days). AIDS diagnosis was defined using the 1993 Centers for Disease Control and Prevention criteria [9]. Liver fibrosis was defined using the FIB-4 score, and was calculated by Sterling's formula:  $\text{age (years)} \times \text{AST (U/l)} / (\text{platelets (10}^9/\text{l)} \times (\text{ALT (U/l)})^{1/2})$ . Advanced liver fibrosis was defined by a FIB-4 score  $> 3.25$  [10]. Body Mass Index (BMI) was calculated according to a standardized definition as weight in kilograms divided by height in meters squared. Alcohol consumption was derived from three separate questions administered by treating physicians to the participants, regarding whether they use alcohol, what type of drinks and with which frequency/week, and was categorized as hazardous, moderate, abstaining and unknown. Hazardous drinking defined as  $> 2$ - $3$  units/day for women and  $> 3$  units/day for men.

## Statistical analysis

Characteristics of the study population at the time of starting one of the regimens including the specific aforementioned drugs (baseline) were described after stratification for HCV-Ab status into three groups as follows: a) HCV-Ab negative (comparator), b) HCV-Ab positive, c) HCV-Ab not tested. Secondly and only for the primary endpoint analysis, we considered the HCV viremic infection (at baseline) stratifying by: a) HCV-Ab negative (same comparator as above), b) HCV-Ab positive and HCV-RNA positive, c) HCV-Ab positive and HCV-RNA negative, d) HCV-Ab positive and HCV-RNA unknown. Descriptive statistics were expressed as median (IQR) for continuous variables or as proportions for categorical variables stratified by HCV infection categories. Incidence of each ART discontinuation was expressed per 100 person-years of follow-up (PYFU). Exposure time period was defined as time from the date of starting the ART drug to the date of stopping the drug due to any reasons or to date the person was last seen if he/she did not discontinue. For each ART drug we fitted separate univariable and multivariable Poisson regression models to assess risk of drug discontinuation. A person could contribute person-years and events to more than one drug model. For example someone who started on 3TC/ABC/EFV contributed to all three separate drug models for 3TC, ABC and EFV. Multivariable models were fitted only for drugs showing  $> 100$  events. Two separate approaches to analysis were used. In these analysis for specific reason of stopping, an Inverse Probability Weighting (IPW) method to control for potential informative censoring was applied. To

construct multivariable models we used the following sequence of adjustment for potential confounding factors: a) Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status), b) Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load), c) Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Numerical variables were fitted either as continuous or categorical using pre-specified groups as described in Table 1 of Results. For the endpoint of stopping due to any reason, all factors considered, including HCV infection exposure, were fitted as time-fixed using the values measured at baseline. In the analysis in which specific reasons for stopping have been considered, by means of the IPW approach and a Poisson matched for these weights to control for confounding, some time-varying factors (e.g. BMI, CD4 count, HIV-RNA) were fitted as time-dependent covariates. All analyses were performed using SAS (version 9.4, SAS Institute, Cary North Carolina USA).

## Results

### Study population

We included 10,637 patients, and among these, 1,030 (9.7%) were HCV-Ab positive. Among patients with available information on HCV-RNA, 43% (217 out of 506) was positive and 14% (72 out of 506) was negative, respectively. Table 1 shows the main characteristics of the study population. In brief, the median age was 38 (IQR 32-46) years; 2,593 (24%) patients were female; 1,837 (17%) patients became HIV-infected through injection drug use (IDU), 4,263 (40%) patients were infected through heterosexual contact, and 3,773 (36%) through homosexual contact. HCV infected patients were more likely to be infected with HIV by IDU than those HCV uninfected individuals (69% versus 2%, respectively). Median (IQR) CD4+ cell count at cART initiation was 315 (170-459) cells/ $\mu$ l and median (IQR) HIV-RNA was 4.64 (3.87-5.19)  $\log_{10}$  copies/ml. Median (IQR) calendar year of starting cART in HCV-infected and -uninfected patients was 2001 (1998-2011) and 2012 (2007-2014), respectively (Table 1).

### Overall ART discontinuation

Overall, there were 15,464 ART discontinuations due to any reasons in 82,415.9 PYFU for an incidence rate (IR) of 18.8 (95% confidence interval [95%CI] 18.5-19.1) per 100 PYFU. Overall, among HCV-infected and -uninfected patients there were 1,046 and 5,574 ART discontinuations in 4,816.4 and 25,982.1 PYFU, corresponding to 21.7 (95%CI 20.4-23.1) and 21.5 (95%CI 20.9-22.0) cases per 100 PYFU, respectively ( $p$  value = 0.71). The overall observed number of ART discontinuations due to any reason in viremic- and aviremic-HCV patients were 297 over 1,292.9 PYFU and 84 over 479.3 PYFU, corresponding to an IR of 23.0 (95%CI 20.4-25.7) and 17.5 (95%CI 14.0-21.7) per 100 PYFU, respectively ( $p$  value = 0.03). The most frequent causes of ART discontinuation due to any reason were: simplification (3,401; 22%), toxicity/intolerability (2,979; 19%), non-adherence (1,720; 11%), viral/immunological failure (853; 6%), suspension (431; 3%), others (3,344; 22%), and unknown (2,736; 18%) (Table 2).

### Nucleoside reverse transcriptase inhibitors (NRTIs)

There were 10,056 ART discontinuations due to any reason in 52,145 PYFU (IR 19.3, 95%CI 18.9-19.7 per 100 PYFU). Among HCV-infected and -uninfected patients there were 775 and 3,642 ART discontinuations in 3,480 and 16,839 PYFU (IR 22.3, 95%CI 20.7-23.9, and IR 21.6, 95%CI 20.9-22.3, per 100 PYFU, respectively;  $p$  value = 0.46). The overall

observed number of ART discontinuations due to any reason in viremic- and aviremic-HCV patients were 188 over 859.1 PYFU and 55 over 292.8 PYFU, corresponding to an IR of 21.9 (95%CI 18.9-25.2) and 18.8 (95%CI 14.2-24.5) per 100 PYFU, respectively ( $p$  value = 0.32) (Table S1). When investigating NRTI as a class, HCV infection was not associated with higher risk of NRTI discontinuations due to any reason after controlling for a number of potentially confounding factors (Table 3). Similarly, viremic-HCV patients did not show an increased risk of ART discontinuation due to any reason compared to HCV-Ab positive but aviremic participants (Table S2). Table S3 and S4 show multivariable Poisson regression models for the other endpoints. In brief, among HCV-infected patients, only 3TC showed an increased risk of ART discontinuation due to any reason except stopping for simplification or viral/immunological failure in model #1 but not in other models (adjusted incidence rate ratio [aIRR] 1.19, 95%CI 1.02-1.38,  $p$  value = 0.03). Results for the association with HCV in people taking 3TC were similar after restricting to those who initiated 3TC-based regimen after 2002 (data not shown). No difference between HCV-infected and -uninfected patients was found in the analysis with endpoint discontinuation due to toxicity/intolerability as reported by the treating clinicians. The most frequent causes of toxicity (1,924 out of 10,056; 19%) were: metabolism (20%), GI tract (18%), kidney (14%), CNS/PNS (11%), liver (9%), hematology (6%), cardiovascular (0.2%), and other/unspecified toxicities (22%). In an unadjusted analysis, when only discontinuation due to liver causes were analyzed, we found that HCV infection was associated with an increased risk of discontinuation of 3TC (RR 3.50, 95%CI 1.28-10.03) but not of ABC (RR 2.11, 95%CI 0.04-26.3), TDF (RR 2.03, 95%CI 0.49-6.45), or FTC (RR 1.17, 95%CI 0.13-5.17).

### **Non-Nucleoside reverse transcriptase inhibitors (NNRTIs)**

There were 2,092 ART discontinuations due to any reasons in 11,009.6 PYFU (IR 19.0, 95%CI 18.2-19.8). Among HCV-infected and -uninfected patients there were 108 and 673 ART discontinuations in 553.2 and 2,710.4 PYFU (IR 19.5, 95%CI 16.0-23.6, and IR 24.8, 95%CI 23.2-26.5, per 100 PYFU, respectively;  $p$  value = 0.02). The overall observed number of ART discontinuations due to any reason in viremic- and aviremic-HCV patients were 36 over 152.8 PYFU and 6 over 38.3 PYFU, corresponding to an IR of 23.6 (95%CI 16.5-32.6) and 15.7 (95%CI 5.8-34.1) per 100 PYFU, respectively ( $p$  value = 0.36) (Table S1). HCV infection was not associated with higher risk of NNRTI discontinuations when considered as the whole class due to any reason after controlling for a number of potentially confounding factors (Table 3). Furthermore, no association between HCV-viremic infection and ART discontinuation was found (Table S2). No difference between HCV-infected and -uninfected patients in ART discontinuation due to any reason except stopping for failure/simplification and due to toxicity/intolerability was found (Table S3 and S4). The most frequent causes of toxicity (360 out of 2,092; 17%) were: CNS/PNS (26%), metabolism (21%), GI tract (14%), liver (7%), kidney (6%), hematology (3%), and other/unspecified toxicities (23%). No cardiovascular events leading to drug discontinuations were observed. In the unadjusted analysis, when only discontinuations due to liver causes were analyzed, HCV infection was not associated with an increased risk of EFV discontinuation (RR 1.04, 95%CI 0.02-10.51). Only one RPV liver-related discontinuation was observed.

### **Protease inhibitors (PIs)**

There were 2,768 ART discontinuations due to any reason in 15,930.5 PYFU (IR 17.4, 95%CI 16.7-18.0). Among HCV-infected and -uninfected patients there were 139 and 1024 ART discontinuations in 684.5 and 5420 PYFU (IR 20.3, 95%CI

17.1-24.0, and IR 19.5, 95%CI 18.4-20.8, per 100 PYFU, respectively;  $p$  value = 0.42). The overall observed number of ART discontinuations due to any reason in viremic- and aviremic-HCV patients were 62 over 229.2 PYFU and 19 over 120.8 PYFU, corresponding to an IR of 17.2 (95%CI 20.7-34.7) and 16.1 (95%CI 9.5-24.6) per 100 PYFU, respectively ( $p$  value = 0.03) (Table S1). HCV infection was associated with higher risk of DRV/r discontinuation due to any reason in model #2 (adjusted for demographics and HIV related factors) (aIRR 1.50, 95%CI 1.01-2.22,  $p$  value = 0.045) and was only marginally attenuated when controlling only for demographics (Model #1; aIRR 1.47, 95% 1.00-2.17,  $p$  value = 0.053) (Table 4). Of note, when, we grouped participants according to the results of HCV-RNA test, the magnitude of the effect was bigger and DRV/r was associated with a 2-fold increased risk of ART discontinuation due to any reason in all models (aIRR 2.2 [95%CI 1.2-4.0] in Model #1, aIRR 2.1 [95%CI 1.1-4.0] in Model #2, and aIRR 2.0 [95%CI 1.1-3.8] in Model #3, respectively). HCV viremic infection was associated with higher risk of LPV/r discontinuation due to any reason in model #3 but not in other models (aIRR 1.67, 95%CI 1.01-2.76,  $p$  value 0.045) (Table S5). No difference between HCV-infected and -uninfected patients in ART discontinuation due to any reason except stopping for failure/simplification and due to toxicity/intolerability was found (Table S6 and S7). Among PI-treated patients, the following toxicities (582 out of 2,768; 21%) were found: GI tract (26%), metabolism (18%), liver (11%), kidney (11%), CNS/PNS (6%), hematology (3%), cardiovascular (0.3%), and other/unspecified toxicities (24%). In an unadjusted analysis, when only discontinuations due to liver causes were analyzed, we found that HCV infection was associated with an increased risk of discontinuation of LPV/r (RR 7.19, 95%CI 1.55-36.23) but not of ATV/r (RR 1.42 95%CI 0.15-6.64). No DRV/r liver-related discontinuations were observed.

### Integrase inhibitor (INIs)

The overall observed number of ART discontinuations due to any reason was 548 over 3,149.9 PYFU, corresponding to an IR of 17.4 (95%CI 16.0-18.9) per 100 PYFU. Among HCV-infected and -uninfected patients there were 24 and 235 ART discontinuations in 98.7 and 1,012.7 PYFU (IR 24.3, 95%CI 15.6-36.2, and IR 23.2, 95%CI 20.3-26.4, per 100 PYFU, respectively;  $p$  value = 0.81). The overall observed number of ART discontinuations due to any reason in viremic- and aviremic-HCV patients were 11 over 51.8 PYFU and 4 over 27.5 PYFU, corresponding to an IR of 15.3 (95%CI 10.6-38.0) and 27.1 (95%CI 4.0-37.2) per 100 PYFU, respectively ( $p$  value = 0.54) (Table S1). HCV infection was not independently associated with higher risk of INI discontinuations due to any reason (Table 4). With respect to single drugs, no association between HCV-viremic infection and the risk of RAL discontinuation was found. Risk of ELV- and DLG-discontinuation was not estimable due to low number of events (Table S5). Table S6 and S7 shows multivariable Poisson regression models for the other endpoints. Among INI-treated patients, the following toxicities (93 out of 548; 17%) were found: GI tract (27%), metabolism (17%), liver (13%), kidney (11%), CNS/PNS (11%), hematology (1%), cardiovascular (1%), and other/unspecified toxicities (19%). In an unadjusted analysis, when only discontinuations due to liver causes were analyzed, we found that HCV infection was not associated with an increased risk of discontinuation of RAL (RR 2.88, 95%CI 0.05-35.89). No DTG or EVG liver-related discontinuations were observed.

### Discussion

In this analysis from the ICONA cohort, we evaluated the incidence and risk factors for ART discontinuation in HIV/HCV coinfecting patients compared to HIV monoinfected patients. Overall, we observed a total of 15,464 ART discontinuations

due to any reason with the following frequency breakdown: simplification (22%), toxicity/intolerability (19%), non-adherence (11%), viral/immunological failure (6%), other/unknown (42%).

When single ART drug was analyzed, DRV/r was the only drug which showed evidence of an increased risk of ART discontinuation due to any reason among HCV-infected patients compared to those without HCV-infection. Specifically, HIV/HCV coinfecting patients were found to have a 50% increased risk of ART discontinuation when adjusted for demographics plus HIV related factors. The magnitude of the effect was only marginally attenuated after controlling for other confounding factors, including life-style and previous and current history of cART.

Among DRV/r treated patients, we found that HCV-viremic patients had twice the risk of ART discontinuation due to any reason than HCV-aviremic patients. These findings are consistent to those by Grint in EuroSIDA cohort who found that viremic HCV-positive patients had an increased risk of ART discontinuation due to toxicity or patient/physician choice compared to aviremic patients [11].

Overall, we observed a low rate of ART discontinuation due to toxicity/intolerability. These results are in contrast with those of other studies published in early cART era where ART discontinuation accounted for about half of patients who started their first-line cART regimen [8]. These differences can be mainly explained by ART drugs that we investigated in this study. Indeed, in this analysis, we included only newer ART drugs while early studies included older ART regimens such as D-drug- or first-generation PI-containing regimens [12, 13]. Overall, our findings are consistent with those from recent observational studies, including ICONA cohort study, where in recent years ART discontinuation is more likely due to ART simplification than due to toxicity [14, 15].

In our cohort, we found a low rate of ART discontinuation due to hepatotoxicity that accounted for no more of 15% across all ART classes. These findings confirm the hepatic safety profile of most recently approved ART drugs and are consistent with those observed by others [16].

In particular, HCV infection was not associated with an increased risk of DRV/r discontinuation due to toxicity compared to uninfected patients. In a previous ICONA analysis including 703 patients with or without HCV coinfection who started a DRV/r-containing regimen, viremic HCV patients did not show any severe (grade 3 and 4) liver enzyme elevations (LEEs) but experienced low grade LEEs more frequently than HCV-uninfected patients [17].

Finally, we observed that advanced liver fibrosis, defined by a FIB-4 score >3.25, was not associated with an increased risk of ART discontinuation due to toxicity/intolerability across all ART drugs evaluated. Advanced liver fibrosis is associated to an increased of hepatotoxicity in HIV/HCV coinfecting patients in some studies, but not in others [18, 19]. However, most of these studies have evaluated the rate of LEE but not rate of ART discontinuation in subjects with HCV coinfection [20].

The major strengths of our study are that it is based on a large cohort of HIV-infected patients with a long follow-up and that we evaluated only newer ART drugs. Furthermore, we utilized a robust endpoint definition less likely to be prone to misclassification bias due to subjective reporting of the reason for stopping. However, when we used endpoint relying on the specific reason for stopping we have used IPW to account for potential informative of censoring (e.g. stopping due to failure is unlikely to be independent of stopping because of toxicity).

However, our study has also some limitations that need to be taken into account. For some of the drugs (EVG and DTG) we had a small number and/or a short time of follow-up. As a result there was a lack in power to detect differences in incidence rates of ART discontinuation. Another limitation is that although some biases could have been



accounted for in the adjusted analyses in the different models, unmeasured confounding that we did not account for may still exist. In particular, we cannot exclude that clinicians have chosen potentially less hepatotoxic ART drugs for HCV infected patients, supposed to be at higher risk of toxicity introducing bias for indication. Finally, a general under-reporting of toxicity, as with all observational studies, is possible.

In conclusion, in our cohort, HIV/HCV coinfecting patients had a marginal risk increase of DRV/r discontinuation due to any reason. Although this is likely to be due to toxicity of the drug when we used alternative endpoints trying to distinguish according to the reasons reported we found less evidence for a difference. These results warrant further investigations to better characterize the role of HCV infection as an independent prognostic factor for cART discontinuation and to determine how HIV/HCV-coinfecting patients should be prioritized for HCV treatment.

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The ICONA study was approved by the institutional review boards or ethics committees of each clinical site.

## Informed consent

All patients signed an informed consent form before be enrolled at each local clinical site.

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**Table 1: Baseline characteristics when starting cART by HCV-Ab status.**

	HCV-Ab negative N= 4633	HCV-Ab positive N= 1030	HCV-Ab unknown N= 4974	Total N= 10637
<b>Gender, n (%)</b>				
Female,	1091 (23.5%)	258 (25.0%)	1244 (25.0%)	2593 (24.4%)
<b>Age (years), n (%)</b>				
median (IQR)	38 (31, 47)	38 (34, 44)	39 (33, 45)	38 (32, 46)
<b>Region, n (%)</b>				
North	2343 (50.6%)	543 (52.7%)	2841 (57.1%)	5727 (53.8%)
South	557 (12.0%)	191 (18.5%)	613 (12.3%)	1361 (12.8%)
Center	1733 (37.4%)	296 (28.7%)	1520 (30.6%)	3549 (33.4%)
<b>Nationality, n (%)</b>				
Italian	3659 (79.0%)	944 (91.7%)	4352 (87.5%)	8955 (84.2%)
<b>Mode of HIV transmission, n (%)</b>				
Heterosexual	2211 (47.7%)	173 (16.8%)	1879 (37.8%)	4263 (40.1%)
Homosexual	1933 (41.7%)	107 (10.4%)	1733 (34.8%)	3773 (35.5%)
Injection drug use	112 (2.4%)	714 (69.3%)	1011 (20.3%)	1837 (17.3%)
Other	377 (8.1%)	36 (3.5%)	351 (7.1%)	764 (7.2%)
<b>Year starting cART, n (%)</b>				
median (IQR)	2012 (2007, 2014)	2001 (1998, 2011)	2010 (2002, 2013)	2011 (2002, 2013)
<b>Education, n (%)</b>				
Primary school	1350 (29.1%)	345 (33.5%)	1601 (32.2%)	3296 (31.0%)
Middle school	366 (7.9%)	104 (10.1%)	318 (6.4%)	788 (7.4%)
Secondary school	978 (21.1%)	373 (36.2%)	1215 (24.4%)	2566 (24.1%)
University	1459 (31.5%)	181 (17.6%)	1384 (27.8%)	3024 (28.4%)
Other/Unknown	480 (10.4%)	27 (2.6%)	456 (9.2%)	963 (9.1%)
<b>Employment, n (%)</b>				
Employed	2826 (61.0%)	563 (54.7%)	3143 (63.2%)	6532 (61.4%)
Unemployed	562 (12.1%)	313 (30.4%)	728 (14.6%)	1603 (15.1%)
Other	482 (10.4%)	72 (7.0%)	436 (8.8%)	990 (9.3%)
Unknown	763 (16.5%)	82 (8.0%)	667 (13.4%)	1512 (14.2%)
<b>Previous AIDS diagnosis, n (%)</b>				
Yes	891 (19.2%)	244 (23.7%)	617 (12.4%)	1752 (16.5%)
<b>CD4 cell count, cells/<math>\mu</math>l</b>				
Median (IQR)	269 (110, 423)	243 (110, 382)	361 (250, 504)	315 (170, 459)
$\leq$ 200	1657 (35.8%)	427 (41.5%)	782 (15.7%)	2866 (26.9%)
201-350	1063 (22.9%)	265 (25.7%)	1367 (27.5%)	2695 (25.3%)
>350	1466 (31.6%)	295 (28.6%)	2403 (48.3%)	4164 (39.1%)
Unknown	447 (9.6%)	43 (4.2%)	422 (8.5%)	912 (8.6%)
<b>HIV-RNA (<math>\log_{10}</math> copies/ml)</b>				
Median (IQR)	4.84 (4.15, 5.40)	4.79 (4.08, 5.30)	4.42 (3.58, 5.00)	4.64 (3.87, 5.19)
$\leq$ 1000	346 (7.5%)	94 (9.1%)	740 (14.9%)	1180 (11.1%)
1001-10000	528 (11.4%)	128 (12.4%)	840 (16.9%)	1496 (14.1%)
>10000	3227 (69.7%)	748 (72.6%)	2927 (58.8%)	6902 (64.9%)
Unknown	532 (11.5%)	60 (5.8%)	467 (9.4%)	1059 (10.0%)
<b>Alcohol consumption, n (%)</b>				
Abstain	1682 (36.3%)	257 (25.0%)	1465 (29.5%)	3404 (32.0%)
Moderate	1027 (22.2%)	114 (11.1%)	1129 (22.7%)	2270 (21.3%)
Hazardous	273 (5.9%)	79 (7.7%)	344 (6.9%)	696 (6.5%)
Unknown	1651 (35.6%)	580 (56.3%)	2036 (40.9%)	4267 (40.1%)

**Table 2: Number of patients on cART for each drug and frequency of drug discontinuations.**

Drug	N	Total discontinuations 15464	Viral/immunological failure 853	Toxicity/intolerability 2979	Simplification 3401	Non-adherence 1720	Other 3775	Unknown 2736
<b><i>NRTIs</i></b>								
Abacavir	2363	821	71 (8.6)	170 (20.7)	124 (15.1)	142 (17.3)	162 (19.7)	152 (18.5)
Lamivudine	5207	2930	266 (9.1)	585 (20.0)	390 (13.3)	575 (19.6)	783 (26.7)	331 (11.3)
Tenofovir	7717	3339	127 (3.8)	632 (18.9)	856 (25.6)	277 (8.3)	879 (26.3)	568 (17.0)
Emtricitabine	7302	2966	90 (3.0)	557 (18.8)	810 (27.3)	223 (7.5)	765 (25.8)	521 (17.6)
<b><i>NNRTIs</i></b>								
Efavirenz	3142	1928	91 (4.7)	331 (17.2)	446 (23.1)	174 (9.0)	577 (29.9)	309 (16.0)
Rilpivirine	1803	164	2 (1.2)	29 (17.7)	20 (12.2)	8 (4.9)	23 (14.0)	82 (50.0)
<b><i>PIs</i></b>								
Lopinavir/r	1612	1104	87 (7.9)	208 (18.8)	167 (15.1)	130 (11.8)	208 (18.8)	304 (27.5)
Darunavir/r	2120	665	34 (5.1)	111 (16.7)	229 (34.4)	46 (6.9)	117 (17.6)	128 (19.2)
Atazanavir/r	2206	999	50 (5.0)	263 (26.3)	190 (19.0)	108 (10.8)	168 (16.8)	220 (22.0)
<b><i>INIs</i></b>								
Raltegravir	1134	436	28 (6.4)	72 (16.5)	141 (32.3)	30 (6.9)	68 (15.6)	97 (22.2)
Dolutegravir	652	70	7 (10.0)	10 (14.3)	25 (35.7)	4 (5.7)	14 (20.0)	10 (14.3)
Elvitegravir	774	42	-	11 (26.2)	3 (7.1)	3 (7.1)	11 (26.2)	14 (33.3)

**Table 3: NRTI's and NNRTI's incidence rates of discontinuation and multivariate models.**

	No. events	PYFU	Rate/100PYFU[95%CI]	Unadjusted Rate ratio[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Abacavir</b>							
Overall	821	6302	13.03 (10.79, 12.28)				
HCV-Ab negative	161	1351	11.91 (10.21, 13.90)	1.00	1.00	1.00	1.00
HCV-Ab positive	40	213.3	18.75 (13.75, 25.56)	1.53 (1.07, 2.18) 0.018	0.95 (0.66, 1.37) 0.774	1.01 (0.69, 1.48) 0.948	0.98 (0.67, 1.43) 0.905
HCV-Ab unknown	620	4738	13.09 (12.10, 14.16)	1.13 (0.94, 1.35) 0.194	0.91 (0.75, 1.10) 0.313	0.97 (0.78, 1.20) 0.765	0.95 (0.77, 1.18) 0.652
<b>Lamivudine</b>							
Overall	2930	13770	21.28 (16.97, 18.13)				
HCV-Ab negative	930	4504	20.65 (19.36, 22.02)	1.00	1.00	1.00	1.00
HCV-Ab positive	424	1769	23.97 (21.79, 26.36)	1.17 (1.04, 1.31) 0.009	0.93 (0.81, 1.07) 0.292	0.94 (0.82, 1.09) 0.410	0.94 (0.82, 1.08) 0.396
HCV-Ab unknown	1576	7497	21.02 (20.01, 22.09)	1.03 (0.95, 1.11) 0.521	0.93 (0.81, 1.07) 0.292	1.03 (0.93, 1.13) 0.551	1.03 (0.93, 1.13) 0.566
<b>Tenofovir</b>							
Overall	3339	16259	20.54 (16.51, 17.57)				
HCV-Ab negative	1308	5591	23.40 (22.16, 24.70)	1.00	1.00	1.00	1.00
HCV-Ab positive	164	788.3	20.80 (17.85, 24.24)	0.91 (0.77, 1.07) 0.242	0.93 (0.78, 1.11) 0.416	0.92 (0.77, 1.10) 0.388	0.92 (0.77, 1.09) 0.330
HCV-Ab unknown	1867	9880	18.90 (18.06, 19.77)	0.82 (0.77, 0.88) <.001	0.79 (0.73, 0.85) <.001	0.85 (0.78, 0.92) <.001	0.86 (0.79, 0.93) <.001
<b>Emtricitabine</b>							
Overall	2966	15814	18.76 (15.28, 16.32)				
HCV-Ab negative	1243	5393	23.05 (21.80, 24.37)	1.00	1.00	1.00	1.00
HCV-Ab positive	147	709.3	20.72 (17.63, 24.36)	0.91 (0.76, 1.08) 0.264	1.00 (0.84, 1.20) 0.968	1.00 (0.83, 1.20) 0.988	0.99 (0.82, 1.19) 0.911
HCV-Ab unknown	1576	9712	16.23 (15.45, 17.05)	0.72 (0.67, 0.78) <.001	0.74 (0.68, 0.80) <.001	0.84 (0.77, 0.92) <.001	0.86 (0.78, 0.93) <.001
<b>Efavirenz</b>							
Overall	1928	8707	22.14 (17.40, 18.87)				
HCV-Ab negative	623	2107	29.57 (27.33, 31.98)	1.00	1.00	1.00	1.00
HCV-Ab positive	104	506.5	20.53 (16.94, 24.88)	0.78 (0.63, 0.97) 0.026	0.87 (0.68, 1.10) 0.243	0.86 (0.68, 1.10) 0.233	0.86 (0.68, 1.10) 0.237
HCV-Ab unknown	1201	6094	19.71 (18.63, 20.86)	0.70 (0.64, 0.78) <.001	0.73 (0.65, 0.81) <.001	0.78 (0.70, 0.88) <.001	0.81 (0.72, 0.90) <.001
<b>Rilpivirine</b>							
Overall	164	2302	7.12 (5.70, 7.67)				
HCV-Ab negative	50	603.4	8.29 (6.28, 10.93)	1.00	1.00	1.00	1.00
HCV-Ab positive	4	46.67	8.57 (3.22, 22.84)	1.03 (0.36, 3.00) 0.953	0.77 (0.26, 2.30) 0.644	0.80 (0.26, 2.47) 0.692	0.80 (0.26, 2.51) 0.708
HCV-Ab unknown	110	1652	6.66 (5.52, 8.03)	0.80 (0.58, 1.12) 0.198	0.67 (0.48, 0.95) 0.022	0.59 (0.42, 0.84) 0.003	0.57 (0.40, 0.81) 0.002

Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for ABC (3TC, DRV/r, ATV/r, EFV); 3TC (zidovudine [ZDV], nevirapine, EFV); TDF (FTC, DRV/r, ATV/r, EFV); FTC (TDF, EFV, LPV/r, DRV/r, ATV/r); EFV (TDF/FTC, ZDV/3TC); RPV (TDF/FTC).

**Table 4: PI's and INI's incidence rates of discontinuation and multivariate models.**

	No. events	PYFU	Rate/100PYFU[95%CI]	Unadjusted Rate ratio[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Lopinavir/r</b>							
Overall	1104	4217	26.18 (19.67, 21.85)				
HCV-Ab negative	408	1496	27.27 (24.75, 30.05)	1.00	1.00	1.00	1.00
HCV-Ab positive	64	260.1	24.61 (19.26, 31.44)	0.89 (0.68, 1.16) 0.400	1.10 (0.83, 1.45) 0.512	1.06 (0.81, 1.40) 0.666	1.07 (0.81, 1.42) 0.620
HCV-Ab unknown	632	2460	25.69 (23.76, 27.77)	0.96 (0.85, 1.09) 0.518	1.06 (0.93, 1.20) 0.404	1.07 (0.93, 1.23) 0.333	1.10 (0.95, 1.26) 0.204
<b>Darunavir/r</b>							
Overall	665	4666	14.25 (11.60, 13.37)				
HCV-Ab negative	297	1876	15.83 (14.13, 17.74)	1.00	1.00	1.00	1.00
HCV-Ab positive	35	160.7	21.78 (15.64, 30.34)	1.39 (0.95, 2.03) 0.089	1.47 (1.00, 2.17) 0.053	1.50 (1.01, 2.22) 0.045	1.42 (0.96, 2.12) 0.083
HCV-Ab unknown	333	2629	12.67 (11.38, 14.10)	0.81 (0.69, 0.94) 0.008	0.89 (0.76, 1.03) 0.125	0.93 (0.78, 1.11) 0.438	0.94 (0.79, 1.12) 0.481
<b>Atazanavir/r</b>							
Overall	999	7049	14.17 (11.70, 13.14)				
HCV-Ab negative	319	1868	17.07 (15.30, 19.06)	1.00	1.00	1.00	
HCV-Ab positive	40	263.7	15.17 (11.13, 20.68)	0.89 (0.63, 1.25) 0.506	0.84 (0.58, 1.20) 0.330	0.86 (0.60, 1.23) 0.395	0.85 (0.59, 1.21) 0.362
HCV-Ab unknown	640	4917	13.02 (12.05, 14.06)	0.77 (0.67, 0.89) <.001	0.83 (0.72, 0.97) 0.017	0.93 (0.79, 1.10) 0.386	0.92 (0.78, 1.08) 0.325
<b>Raltegravir</b>							
Overall	436	2192	19.90 (15.20, 18.04)				
HCV-Ab negative	194	657.8	29.49 (25.62, 33.95)	1.00	1.00	1.00	1.00
HCV-Ab positive	20	76.08	26.29 (16.96, 40.75)	0.90 (0.55, 1.47) 0.670	0.94 (0.57, 1.55) 0.816	0.94 (0.57, 1.55) 0.808	0.93 (0.56, 1.54) 0.785
HCV-Ab unknown	222	1458	15.23 (13.35, 17.37)	0.53 (0.43, 0.64) <.001	0.65 (0.53, 0.80) <.001	0.75 (0.60, 0.94) 0.013	0.74 (0.60, 0.93) 0.010
<b>*Dolutegravir</b>							
Overall	70	411.3	17.02 (11.54, 17.82)				
HCV-Ab negative	25	152.1	16.44 (11.11, 24.33)	1.00	1.00	1.00	1.00
HCV-Ab positive	2	6.08	32.88 (8.22, 131.5)	2.00 (0.46, 8.67) 0.355	2.10 (0.50, 8.82) 0.311	2.30 (0.57, 9.20) 0.240	2.58 (0.75, 8.83) 0.132
HCV-Ab unknown	43	253.2	16.98 (12.60, 22.90)	1.03 (0.63, 1.69) 0.897	0.93 (0.54, 1.61) 0.798	0.99 (0.52, 1.89) 0.985	1.10 (0.57, 2.12) 0.786
<b>*Elvitegravir</b>							
Overall	42	546.6	7.68 (5.20, 9.35)				
HCV-Ab negative	16	202.8	7.89 (4.83, 12.88)	1.00	1.00	1.00	1.00
HCV-Ab positive	2	16.58	12.06 (3.02, 48.22)	1.52 (0.34, 6.86) 0.586	1.76 (0.35, 8.77) 0.490	1.45 (0.29, 7.34) 0.654	1.16 (0.27, 4.97) 0.844
HCV-Ab unknown	24	327.2	7.34 (4.92, 10.94)	0.93 (0.50, 1.74) 0.825	1.01 (0.52, 1.96) 0.985	1.20 (0.60, 2.42) 0.610	1.00 (0.46, 2.17) 0.997

\*Events <100; Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for LPV/r (TDF/FTC, ZDV/3TC); DRV/r (TDF/FTC, ABC/3TC); ATV/r (TDF/FTC, ABC/3TC); RAL (TDF/FTC, ABC/3TC, TDF/FTC/DRV/r); DTG (TDF/FTC, ABC/3TC); EVG (TDF/FTC).

## **Supplementary materials**



**Table S1: Summary of number of events and incidence rate of discontinuation by HCV-RNA status.**

	No. Events (PYFU)	Rate/ 100PYFU [95%CI]
<b>ALL drugs</b>		
Overall	6620 (30639)	21.60 (21.42, 22.48)
HCVAB-	5574 (25802.1)	21.60 (21.04, 22.18)
HCVAB+ and HCV-RNA+	297 (1292.9)	22.97 (20.43, 25.74)
HCVAB+ and HCV-RNA-	84 (479.3)	17.52 (13.98, 21.69)
HCVAB+ and HCV-RNA unknown	665 (3064.7)	21.70 (20.08, 23.41)
<b>NRTIs</b>		
Overall	4417 (20319)	21.74 (21.10, 22.39)
HCVAB-	3642 (16839)	21.62 (20.93, 22.34)
HCVAB+ and HCV-RNA+	188 (859.07)	21.88 (18.87, 25.24)
HCVAB+ and HCV-RNA-	55 (292.75)	18.78 (14.15, 24.45)
HCVAB+ and HCV-RNA unknown	532 (2328.7)	22.84 (20.94, 24.87)
<b>NNRTIs</b>		
Overall	781 (3264.4)	23.92 (22.27, 25.67)
HCVAB-	673 (2710.4)	24.83 (22.98, 26.78)
HCVAB+ and HCV-RNA+	36 (152.8)	23.56 (16.50, 32.62)
HCVAB+ and HCV-RNA-	6 (38.28)	15.67 (5.75, 34.11)
HCVAB+ and HCV-RNA unknown	66 (362.2)	18.22 (14.09, 23.18)
<b>PIs</b>		
Overall	1163 (5924.4)	19.63 (18.51, 20.79)
HCVAB-	1024 (5240)	19.6 (18.36, 20.77)
HCVAB+ and HCV-RNA+	62 (229.2)	17.2 (20.74, 34.68)
HCVAB+ and HCV-RNA-	19 (120.8)	16.1 (9.46, 24.55)
HCVAB+ and HCV-RNA unknown	58 (334.4)	19.7 (13.16, 24.42)
<b>INIs</b>		
Overall	259 (1111.4)	23.30 (20.55, 26.32)
HCVAB-	235 (1012.7)	17.4 (20.33, 26.37)
HCVAB+ and HCV-RNA+	11 (51.8)	15.3 (10.60, 37.98)
HCVAB+ and HCV-RNA-	4 (27.5)	27.1 (3.96, 37.21)
HCVAB+ and HCV-RNA unknown	9 (39.4)	22.5 (10.43, 43.31)

**Table S2: NRTI's and NNRTI's incidence rates of discontinuation due to any reason and multivariate models stratified by HCV-RNA status.**

	No.events	PYFU	Rate/ 100PYFU[95%CI]	Unadjusted RR[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Abacavir</b>							
Overall	201	1565	12.85 (9.94, 12.91)				
HCV-Ab negative	161	1351	11.91 (10.21, 13.90)	1.00	1.00	1.00	1.00
HCV-RNA positive	16	68.67	23.30 (14.27, 38.03)	1.81 (1.14, 2.88) 0.013	1.14 (0.57, 2.29) 0.712	1.31 (0.66, 2.61) 0.442	1.32 (0.65, 2.65) 0.442
HCV-RNA negative	2	29.17	6.86 (1.71, 27.42)	0.47 (0.17, 1.26) 0.133	0.38 (0.18, 0.78) 0.008	0.39 (0.17, 0.87) 0.022	0.39 (0.17, 0.91) 0.029
HCV-RNA unknown	22	115.5	19.05 (12.54, 28.93)	1.65 (1.00, 2.72) 0.050	1.04 (0.58, 1.86) 0.904	1.06 (0.58, 1.93) 0.850	1.03 (0.56, 1.88) 0.925
<b>Lamivudine</b>							
Overall	1354	6273	21.59 (16.90, 18.62)				
HCV-Ab negative	930	4504	20.65 (19.36, 22.02)	1.00	1.00	1.00	1.00
HCV-RNA positive	36	150.9	23.85 (17.21, 33.07)	1.20 (0.84, 1.70) 0.319	1.18 (0.80, 1.75) 0.396	1.21 (0.82, 1.79) 0.336	1.20 (0.80, 1.78) 0.377
HCV-RNA negative	12	49.58	24.20 (13.74, 42.62)	1.17 (0.64, 2.12) 0.611	1.24 (0.70, 2.17) 0.462	1.24 (0.71, 2.17) 0.455	1.17 (0.66, 2.07) 0.581
HCV-RNA unknown	376	1569	23.97 (21.67, 26.52)	1.16 (1.03, 1.31) 0.013	1.02 (0.83, 1.24) 0.874	1.02 (0.83, 1.24) 0.868	1.00 (0.82, 1.22) 0.978
<b>Tenofovir</b>							
Overall	1472	6379	23.08 (17.89, 19.62)				
HCV-Ab negative	1308	5591	23.40 (22.16, 24.70)	1.00	1.00	1.00	1.00
HCV-RNA positive	71	317.4	22.37 (17.73, 28.23)	0.97 (0.75, 1.24) 0.782	0.95 (0.72, 1.25) 0.715	0.96 (0.73, 1.26) 0.762	0.95 (0.72, 1.26) 0.728
HCV-RNA negative	20	109.7	18.24 (11.77, 28.27)	0.80 (0.51, 1.24) 0.318	0.77 (0.49, 1.22) 0.268	0.81 (0.52, 1.25) 0.338	0.80 (0.52, 1.24) 0.316
HCV-RNA unknown	73	361.3	20.21 (16.07, 25.42)	0.89 (0.70, 1.13) 0.343	0.87 (0.65, 1.16) 0.341	0.92 (0.69, 1.23) 0.562	0.91 (0.68, 1.23) 0.549
<b>Emtricitabine</b>							
Overall	1390	6102	22.78 (17.68, 19.44)				
HCV-Ab negative	1243	5393	23.05 (21.80, 24.37)	1.00	1.00	1.00	1.00
HCV-RNA positive	65	322.1	20.18 (15.83, 25.73)	0.89 (0.68, 1.14) 0.352	0.92 (0.69, 1.23) 0.562	0.97 (0.73, 1.29) 0.831	0.96 (0.72, 1.28) 0.761
HCV-RNA negative	21	104.3	20.13 (13.12, 30.87)	0.86 (0.57, 1.30) 0.472	0.90 (0.59, 1.35) 0.602	0.97 (0.64, 1.45) 0.876	0.96 (0.64, 1.44) 0.832
HCV-RNA unknown	61	282.9	21.56 (16.78, 27.71)	0.95 (0.73, 1.23) 0.704	0.97 (0.71, 1.31) 0.833	1.05 (0.78, 1.43) 0.740	1.05 (0.77, 1.42) 0.768
<b>Efavirenz</b>							
Overall	727	2614	27.82 (20.38, 23.18)				
HCV-Ab negative	623	2107	29.57 (27.33, 31.98)	1.00	1.00	1.00	1.00
HCV-RNA positive	34	134.3	25.33 (18.10, 35.44)	1.12 (0.80, 1.55) 0.517	1.03 (0.66, 1.60) 0.902	1.06 (0.67, 1.66) 0.811	1.05 (0.66, 1.66) 0.847
HCV-RNA negative	6	29.08	20.63 (9.27, 45.92)	0.67 (0.30, 1.52) 0.336	0.62 (0.28, 1.42) 0.260	0.62 (0.28, 1.37) 0.234	0.61 (0.27, 1.36) 0.225
HCV-RNA unknown	64	343.2	18.65 (14.60, 23.83)	0.65 (0.50, 0.85) 0.002	0.95 (0.66, 1.35) 0.768	1.00 (0.70, 1.43) 0.994	0.99 (0.69, 1.42) 0.960
<b>Rilpivirine</b>							
Overall	54	650.1	8.31 (5.82, 9.74)				
HCV-Ab negative	50	603.4	8.28 (6.28, 10.93)				
HCV-RNA positive	2	18.5	10.81 (2.71, 43.22)				
HCV-RNA negative	0	9.2	0.00 (0.00, -)		Not estimable		
HCV-RNA unknown	2	19.0	10.53 (2.63, 42.09)				

Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for ABC (3TC, DRV/r, ATV/r, EFV); 3TC (zidovudine [ZDV], nevirapine, EFV); TDF (FTC, DRV/r, ATV/r, EFV); FTC (TDF, EFV, LPV/r, DRV/r, ATV/r); EFV (TDF/FTC, ZDV/3TC); RPV (TDF/FTC).

**Table S3: NRTI's and NNRTI's incidence rates of discontinuation and Poisson regression models using IPW stratified by HCV-Ab status (time-dependent) - Stopping for all reasons except stopping for failure/simplification.**

	All reasons			All reasons except failure/simplification			Failure/simplification			Estimates from weighted Poisson models, i.e. stopping for failure/simplification treated as a competing risk			
	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	Unadjusted RR[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Abacavir</b>													
Overall	821	6302	13.03 (10.79, 12.28)	626	6302	9.93 (8.37, 9.72)	195	6302	3.09 (2.60, 3.43)				
HCV-Ab negative	547	4588	11.92 (10.96, 12.96)	399	4588	8.70 (7.88, 9.59)	148	4588	3.22 (2.74, 3.78)	1.00	1.00	1.00	1.00
HCV-Ab positive	225	1346	16.72 (14.67, 19.05)	191	1346	14.19 (12.32, 16.35)	34	1346	2.52 (1.81, 3.54)	1.28 (1.07, 1.54) 0.008	1.07 (0.81, 1.42) 0.638	1.08 (0.81, 1.44) 0.605	1.05 (0.78, 1.39) 0.763
HCV-Ab unknown	49	368.5	13.30 (10.05, 17.59)	36	368.5	9.77 (7.05, 13.54)	13	368.5	3.52 (2.05, 6.07)	1.16 (0.81, 1.67) 0.419	1.04 (0.72, 1.49) 0.851	0.97 (0.67, 1.41) 0.869	0.97 (0.67, 1.41) 0.881
<b>Lamivudine</b>													
Overall	2930	13770	21.28 (16.97, 18.13)	2274	13770	16.51 (13.64, 14.72)	656	13770	4.76 (4.21, 4.89)				
HCV-Ab negative	1765	8809	20.04 (19.12, 20.99)	1312	8809	14.89 (14.11, 15.72)	453	8809	5.14 (4.69, 5.63)	1.00	1.00	1.00	1.00
HCV-Ab positive	954	3981	23.96 (22.49, 25.53)	795	3981	19.97 (18.63, 21.41)	159	3981	3.99 (3.41, 4.66)	1.26 (1.15, 1.38) <.001	1.19 (1.02, 1.38) 0.025	1.16 (0.99, 1.34) 0.060	1.15 (0.99, 1.35) 0.061
HCV-Ab unknown	211	979.5	21.54 (18.82, 24.65)	167	979.5	17.05 (14.65, 19.84)	44	979.5	4.49 (3.34, 6.04)	1.07 (0.91, 1.26) 0.412	1.07 (0.90, 1.28) 0.460	1.03 (0.86, 1.22) 0.753	1.03 (0.87, 1.23) 0.717
<b>Tenofovir</b>													
Overall	3339	16259	20.54 (16.51, 17.57)	2356	16259	14.49 (12.18, 13.14)	983	16259	6.04 (5.36, 6.05)				
HCV-Ab negative	2410	11547	20.87 (20.05, 21.72)	1671	11547	14.47 (13.79, 15.18)	739	11547	6.40 (5.95, 6.87)	1.00	1.00	1.00	1.00
HCV-Ab positive	600	3058	19.62 (18.11, 21.26)	473	3058	15.47 (14.14, 16.93)	127	3058	4.15 (3.49, 4.94)	1.01 (0.90, 1.12) 0.924	1.10 (0.96, 1.28) 0.176	1.13 (0.98, 1.30) 0.097	1.11 (0.96, 1.28) 0.148
HCV-Ab unknown	329	1654	19.89 (17.86, 22.16)	212	1654	12.82 (11.20, 14.67)	117	1654	7.07 (5.90, 8.48)	0.89 (0.77, 1.03) 0.108	0.87 (0.75, 1.01) 0.063	0.84 (0.73, 0.98) 0.022	0.85 (0.73, 0.98) 0.030
<b>Emtricitabine</b>													
Overall	2966	15814	18.76 (15.28, 16.32)	2066	15814	13.06 (11.09, 12.03)	900	15814	5.69 (5.04, 5.73)				
HCV-Ab negative	2194	11253	19.50 (18.70, 20.33)	1510	11253	13.42 (12.76, 14.11)	684	11253	6.07 (5.64, 6.55)	1.00	1.00	1.00	1.00
HCV-Ab positive	461	2933	15.72 (14.35, 17.22)	358	2933	12.21 (11.01, 13.54)	103	2933	3.51 (2.89, 4.26)	0.89 (0.79, 1.01) 0.067	1.02 (0.87, 1.20) 0.828	1.09 (0.93, 1.27) 0.312	1.06 (0.91, 1.25) 0.452
HCV-Ab unknown	311	1628	19.10 (17.09, 21.35)	198	1628	12.16 (10.58, 13.98)	113	1628	6.94 (5.77, 8.34)	0.89 (0.77, 1.04) 0.133	0.86 (0.74, 1.00) 0.053	0.83 (0.72, 0.97) 0.019	0.84 (0.72, 0.98) 0.029
<b>Efavirenz</b>													
Overall	1928	8707	22.14 (17.40, 18.87)	1391	8707	15.98 (13.11, 14.45)	537	8707	6.17 (5.34, 6.29)				
HCV-Ab negative	1362	6058	22.48 (21.32, 23.71)	973	6058	16.06 (15.08, 17.10)	389	6058	6.42 (5.81, 7.09)	1.00	1.00	1.00	1.00
HCV-Ab positive	387	2052	18.86 (17.07, 20.84)	302	2052	14.72 (13.15, 16.47)	85	2052	4.14 (3.34, 5.12)	0.97 (0.85, 1.11) 0.685	1.00 (0.82, 1.21) 0.972	0.99 (0.82, 1.21) 0.944	0.97 (0.80, 1.18) 0.770
HCV-Ab unknown	179	597.1	29.98 (25.89, 34.71)	116	597.1	19.43 (16.20, 23.31)	63	597.1	10.55 (8.24, 13.50)	0.90 (0.74, 1.10) 0.300	0.88 (0.71, 1.08) 0.213	0.85 (0.69, 1.05) 0.122	0.88 (0.71, 1.08) 0.216
<b>Rilpivirine</b>													
Overall	164	2302	7.12 (5.70, 7.67)	142	2302	6.17 (4.92, 6.77)	22	2302	0.96 (0.59, 1.38)				
HCV-Ab negative	128	1793	7.14 (6.00, 8.49)	112	1793	6.25 (5.19, 7.52)	16	1793	0.89 (0.55, 1.46)	1.00	1.00	1.00	1.00
HCV-Ab positive	23	210.9	10.90 (7.25, 16.41)	20	210.9	9.48 (6.12, 14.70)	3	210.9	1.42 (0.46, 4.41)	1.54 (0.95, 2.50) 0.078	1.09 (0.61, 1.95) 0.774	1.02 (0.56, 1.86) 0.955	0.99 (0.54, 1.83) 0.980
HCV-Ab unknown	13	298.0	4.36 (2.53, 7.51)	10	298.0	3.36 (1.81, 6.24)	3	298.0	1.01 (0.32, 3.12)	0.54 (0.28, 1.03) 0.061	0.54 (0.28, 1.05) 0.070	0.56 (0.27, 1.17) 0.121	0.55 (0.27, 1.13) 0.104

Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for ABC (3TC, DRV/r, ATV/r, EFV); 3TC (zidovudine [ZDV], nevirapine, EFV); TDF (FTC, DRV/r, ATV/r, EFV); FTC (TDF, EFV, LPV/r, DRV/r, ATV/r); EFV (TDF/FTC, ZDV/3TC); RPV (TDF/FTC).

**Table S4: NRTI's and NNRTI's incidence rates of discontinuation and Poisson regression models using IPW stratified by HCV-Ab status (time-dependent) - Stopping for toxicity/intolerance.**

	All reasons			Stopping for toxicity/intolerance			All reasons for stopping except toxicity/intolerance			Estimates from weighted Poisson models, i.e. stopping for all other reasons treated as a competing risk			
	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	Unadjusted RR[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Abacavir</b>													
Overall	821	6302	13.03 (10.79, 12.28)	170	6302	2.70 (2.25, 3.03)	651	6302	10.33 (8.69, 10.06)				
HCV-Ab negative	547	4588	11.92 (10.96, 12.96)	110	4588	2.40 (1.99, 2.89)	437	4588	9.53 (8.67, 10.46)	1.00	1.00	1.00	1.00
HCV-Ab positive	225	1346	16.72 (14.67, 19.05)	46	1346	3.42 (2.56, 4.56)	179	1346	13.30 (11.49, 15.40)	1.08 (0.76, 1.54) 0.664	1.25 (0.77, 2.01) 0.370	1.29 (0.80, 2.09) 0.292	1.21 (0.75, 1.96) 0.434
HCV-Ab unknown	49	368.5	13.30 (10.05, 17.59)	14	368.5	3.80 (2.25, 6.41)	35	368.5	9.50 (6.82, 13.23)	1.75 (0.98, 3.12) 0.060	1.52 (0.86, 2.68) 0.154	1.31 (0.68, 2.51) 0.422	1.30 (0.70, 2.44) 0.406
<b>Lamivudine</b>													
Overall	2930	13770	21.28 (16.97, 18.13)	585	13770	4.25 (3.76, 4.40)	2345	13770	17.03 (14.01, 15.10)				
HCV-Ab negative	1765	8809	20.04 (19.12, 20.99)	351	8809	3.98 (3.59, 4.42)	1414	8809	16.05 (15.24, 16.91)	1.00	1.00	1.00	1.00
HCV-Ab positive	954	3981	23.96 (22.49, 25.53)	185	3981	4.65 (4.02, 5.37)	769	3981	19.32 (18.00, 20.73)	1.11 (0.92, 1.33) 0.273	1.25 (0.92, 1.69) 0.156	1.23 (0.91, 1.66) 0.182	1.22 (0.90, 1.65) 0.197
HCV-Ab unknown	211	979.5	21.54 (18.82, 24.65)	49	979.5	5.00 (3.78, 6.62)	162	979.5	16.54 (14.18, 19.29)	1.31 (0.96, 1.78) 0.092	1.27 (0.92, 1.74) 0.150	1.21 (0.87, 1.67) 0.259	1.23 (0.89, 1.69) 0.202
<b>Tenofovir</b>													
Overall	3339	16259	20.54 (16.51, 17.57)	632	16259	3.89 (3.46, 4.03)	2707	16259	16.65 (13.78, 14.77)				
HCV-Ab negative	2410	11547	20.87 (20.05, 21.72)	471	11547	4.08 (3.73, 4.46)	1939	11547	16.79 (16.06, 17.56)	1.00	1.00	1.00	1.00
HCV-Ab positive	600	3058	19.62 (18.11, 21.26)	108	3058	3.53 (2.93, 4.27)	492	3058	16.09 (14.73, 17.58)	0.86 (0.69, 1.06) 0.149	0.99 (0.75, 1.32) 0.963	0.98 (0.74, 1.31) 0.910	0.95 (0.71, 1.26) 0.723
HCV-Ab unknown	329	1654	19.89 (17.86, 22.16)	53	1654	3.20 (2.45, 4.19)	276	1654	16.69 (14.83, 18.78)	0.79 (0.59, 1.05) 0.105	0.84 (0.63, 1.13) 0.260	0.84 (0.63, 1.14) 0.261	0.87 (0.65, 1.18) 0.379
<b>Emtricitabine</b>													
Overall	2966	15814	18.76 (15.28, 16.32)	557	15814	3.52 (3.13, 3.69)	2409	15814	15.23 (12.73, 13.72)				
HCV-Ab negative	2194	11253	19.50 (18.70, 20.33)	424	11253	3.77 (3.43, 4.14)	1770	11253	15.73 (15.01, 16.48)	1.00	1.00	1.00	1.00
HCV-Ab positive	461	2933	15.72 (14.35, 17.22)	85	2933	2.90 (2.34, 3.59)	376	2933	12.82 (11.59, 14.19)	0.82 (0.65, 1.04) 0.105	0.85 (0.61, 1.17) 0.306	0.87 (0.63, 1.19) 0.386	0.83 (0.61, 1.14) 0.249
HCV-Ab unknown	311	1628	19.10 (17.09, 21.35)	48	1628	2.95 (2.22, 3.91)	263	1628	16.15 (14.32, 18.23)	0.77 (0.57, 1.03) 0.083	0.79 (0.58, 1.08) 0.133	0.78 (0.57, 1.07) 0.122	0.80 (0.59, 1.10) 0.172
<b>Efavirenz</b>													
Overall	1928	8707	22.14 (17.40, 18.87)	331	8707	3.80 (3.28, 4.06)	1597	8707	18.34 (14.81, 16.20)				
HCV-Ab negative	1362	6058	22.48 (21.32, 23.71)	229	6058	3.78 (3.32, 4.30)	1133	6058	18.70 (17.64, 19.82)	1.00	1.00	1.00	1.00
HCV-Ab positive	387	2052	18.86 (17.07, 20.84)	65	2052	3.17 (2.48, 4.04)	322	2052	15.69 (14.07, 17.50)	0.73 (0.54, 0.99) 0.040	0.98 (0.65, 1.47) 0.904	0.98 (0.64, 1.48) 0.913	0.96 (0.63, 1.46) 0.840
HCV-Ab unknown	179	597.1	29.98 (25.89, 34.71)	37	597.1	6.20 (4.49, 8.55)	142	597.1	23.78 (20.18, 28.03)	1.63 (1.05, 2.53) 0.029	1.33 (0.84, 2.10) 0.228	1.33 (0.84, 2.09) 0.223	1.36 (0.86, 2.13) 0.187
<b>*Rilpivirine</b>													
Overall	164	2302	7.12 (5.70, 7.67)	29	2302	1.26 (0.84, 1.73)	135	2302	5.86 (4.67, 6.48)				
HCV-Ab negative	128	1793	7.14 (6.00, 8.49)	22	1793	1.23 (0.81, 1.86)	106	1793	5.91 (4.89, 7.15)	1.00			
HCV-Ab positive	23	210.9	10.90 (7.25, 16.41)	6	210.9	2.84 (1.28, 6.33)	17	210.9	8.06 (5.01, 12.97)	2.35 (0.96, 5.76) 0.063		Not estimable	
HCV-Ab unknown	13	298.0	4.36 (2.53, 7.51)	1	298.0	0.34 (0.05, 2.38)	12	298.0	4.03 (2.29, 7.09)	0.28 (0.04, 2.06) 0.210			

\*Events <100; Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for ABC (3TC, DRV/r, ATV/r, EFV); 3TC (zidovudine [ZDV], nevirapine, EFV); TDF (FTC, DRV/r, ATV/r, EFV); FTC (TDF, EFV, LPV/r, DRV/r, ATV/r); EFV (TDF/FTC, ZDV/3TC); RPV (TDF/FTC).

**Table S5: PI's and INI's incidence rates of discontinuation due to any reason and multivariate models stratified by HCV-RNA status.**

	No.events	PYFU	Rate/ 100PYFU[95%CI]	Unadjusted RR[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Lopinavir/r</b>							
Overall	472	1756	26.87 (19.51, 22.90)				
HCV-Ab negative	408	1496	27.27 (24.75, 30.05)	1.00	1.00	1.00	1.00
HCV-RNA positive	23	65.08	35.34 (23.48, 53.18)	1.22 (0.80, 1.86) 0.345	1.54 (0.96, 2.46) 0.074	1.53 (0.95, 2.45) 0.077	1.67 (1.01, 2.76) 0.045
HCV-RNA negative	7	41.67	16.80 (8.01, 35.24)	0.67 (0.29, 1.53) 0.340	0.87 (0.38, 1.96) 0.733	0.89 (0.39, 2.01) 0.771	1.01 (0.44, 2.31) 0.990
HCV-RNA unknown	34	153.3	22.17 (15.84, 31.03)	0.79 (0.56, 1.11) 0.174	1.22 (0.81, 1.83) 0.337	1.11 (0.72, 1.72) 0.638	1.19 (0.77, 1.84) 0.425
<b>Darunavir/r</b>							
Overall	332	2037	16.30 (12.65, 15.44)				
HCV-Ab negative	297	1876	15.83 (14.13, 17.74)	1.00	1.00	1.00	1.00
HCV-RNA positive	17	57.50	29.57 (18.38, 47.56)	1.86 (1.12, 3.09) 0.016	2.20 (1.20, 4.04) 0.011	2.11 (1.12, 3.95) 0.020	2.04 (1.09, 3.79) 0.025
HCV-RNA negative	7	32.33	21.65 (10.32, 45.41)	1.38 (0.59, 3.19) 0.455	1.46 (0.65, 3.27) 0.360	1.53 (0.67, 3.48) 0.313	1.54 (0.67, 3.52) 0.311
HCV-RNA unknown	11	70.83	15.53 (8.60, 28.04)	1.00 (0.52, 1.92) 0.988	1.15 (0.59, 2.24) 0.679	1.03 (0.51, 2.06) 0.942	0.99 (0.48, 2.04) 0.973
<b>Atazanavir/r</b>							
Overall	359	2132	16.84 (13.06, 15.82)				
HCV-Ab negative	319	1868	17.07 (15.30, 19.06)	1.00	1.00	1.00	1.00
HCV-RNA positive	22	106.6	20.64 (13.59, 31.35)	1.21 (0.77, 1.89) 0.413	1.32 (0.78, 2.26) 0.303	1.39 (0.81, 2.38) 0.237	1.41 (0.82, 2.40) 0.211
HCV-RNA negative	5	46.83	10.68 (4.44, 25.65)	0.61 (0.26, 1.40) 0.241	0.65 (0.28, 1.49) 0.306	0.70 (0.30, 1.62) 0.404	0.69 (0.31, 1.53) 0.362
HCV-RNA unknown	13	110.3	11.79 (6.85, 20.31)	0.70 (0.39, 1.25) 0.225	0.81 (0.39, 1.65) 0.556	0.81 (0.40, 1.65) 0.570	0.81 (0.40, 1.65) 0.570
<b>Raltegravir</b>							
Overall	214	733.8	29.16 (19.97, 25.29)				
HCV-Ab negative	194	657.8	29.49 (25.62, 33.95)	1.00	1.00	1.00	1.00
HCV-RNA positive	10	20.92	47.81 (25.72, 88.85)	1.52 (0.85, 2.72) 0.154	1.47 (0.76, 2.85) 0.256	1.42 (0.73, 2.77) 0.302	1.45 (0.73, 2.89) 0.286
HCV-RNA negative	2	21.42	9.34 (2.34, 37.34)	0.32 (0.08, 1.33) 0.117	0.33 (0.08, 1.32) 0.117	0.37 (0.10, 1.35) 0.132	0.36 (0.10, 1.24) 0.104
HCV-RNA unknown	8	33.75	23.70 (11.85, 47.40)	0.84 (0.39, 1.80) 0.645	1.12 (0.46, 2.70) 0.809	1.12 (0.45, 2.77) 0.806	1.11 (0.43, 2.88) 0.823
<b>*Dolutegravir</b>							
Overall	27	158.17	17.07 (9.88, 20.00)				
HCV-Ab negative	25	152.1	16.43 (11.1, 24.3)				
HCV-RNA positive	0	2.4	0.00 (0.00, -)				
HCV-RNA negative	1	2.6	38.71 (5.45, 274.80)		Not estimable		
HCV-RNA unknown	1	1.1	92.31 (13.0, 655.30)				
<b>*Elvitegravir</b>							
Overall	18	219.4	8.21 (4.57, 11.26)				
HCV-Ab negative	16	202.8	7.89 (4.83, 12.88)				
HCV-RNA positive	1	28.5	11.76 (1.66, 83.51)				
HCV-RNA negative	1	3.5	28.57 (4.02, 202.83)		Not estimable		
HCV-RNA unknown	0	4.6	0.00 (0.00, -)				

\*Events <100; Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for LPV/r (TDF/FTC, ZDV/3TC); DRV/r (TDF/FTC, ABC/3TC); ATV/r (TDF/FTC, ABC/3TC); RAL (TDF/FTC, ABC/3TC, TDF/FTC/DRV/r); DTG (TDF/FTC, ABC/3TC); EVG (TDF/FTC).

**Table S6: PI's and INI's incidence rates of discontinuation and Poisson regression models using IPW stratified by HCV-Ab status (time-dependent) - Stopping for all reasons except stopping for failure/simplification.**

	All reasons			All reasons except stopping for failure/simplification			Stopping for failure/simplification			Estimates from weighted Poisson models, i.e. stopping for failure/simplification treated as a competing risk			
	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	Unadjusted RR[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Lopinavir</b>													
Overall	1104	4217	26.18 (19.67, 21.85)	850	4217	20.16 (15.76, 17.82)	254	4217	6.03 (5.02, 6.38)				
HCV-Ab negative	775	2762	28.06 (26.16, 30.11)	590	2762	21.37 (19.71, 23.16)	185	2762	6.70 (5.80, 7.73)	1.00	1.00	1.00	1.00
HCV-Ab positive	252	1213	20.77 (18.36, 23.50)	199	1213	16.40 (14.27, 18.85)	53	1213	4.37 (3.34, 5.72)	0.86 (0.73, 1.02) 0.079	0.94 (0.74, 1.20) 0.634	0.96 (0.76, 1.23) 0.760	0.97 (0.76, 1.23) 0.795
HCV-Ab unknown	77	241.8	31.85 (25.48, 39.82)	61	241.8	25.23 (19.63, 32.43)	16	241.8	6.61 (4.05, 10.81)	0.97 (0.75, 1.25) 0.816	1.03 (0.79, 1.34) 0.838	1.01 (0.78, 1.32) 0.935	1.01 (0.77, 1.31) 0.966
<b>Darunavir</b>													
Overall	665	4666	14.25 (11.60, 13.37)	402	4666	8.62 (7.20, 8.69)	263	4666	5.64 (4.73, 5.98)				
HCV-Ab negative	487	3487	13.97 (12.78, 15.26)	294	3487	8.43 (7.52, 9.45)	193	3487	5.53 (4.81, 6.37)	1.00	1.00	1.00	1.00
HCV-Ab positive	84	642.7	13.07 (10.55, 16.19)	57	642.7	8.87 (6.84, 11.50)	27	642.7	4.20 (2.88, 6.13)	1.07 (0.80, 1.43) 0.660	1.27 (0.90, 1.79) 0.172	1.28 (0.90, 1.82) 0.162	1.26 (0.89, 1.79) 0.189
HCV-Ab unknown	94	536.1	17.53 (14.33, 21.46)	51	536.1	9.51 (7.23, 12.52)	43	536.1	8.02 (5.94, 10.81)	1.13 (0.83, 1.52) 0.437	0.90 (0.67, 1.23) 0.521	0.84 (0.62, 1.15) 0.283	0.83 (0.61, 1.14) 0.259
<b>Atazanavir</b>													
Overall	999	7049	14.17 (11.70, 13.14)	759	7049	10.77 (9.07, 10.39)	240	7049	3.40 (2.89, 3.71)				
HCV-Ab negative	714	4933	14.47 (13.45, 15.57)	530	4933	10.74 (9.87, 11.70)	184	4933	3.73 (3.22, 4.31)	1.00	1.00	1.00	1.00
HCV-Ab positive	218	1667	13.08 (11.45, 14.94)	177	1667	10.62 (9.17, 12.31)	41	1667	2.46(1.81, 3.34)	1.03 (0.86, 1.23) 0.763	0.93 (0.70, 1.22) 0.597	0.92 (0.70, 1.21) 0.549	0.91 (0.69, 1.20) 0.484
HCV-Ab unknown	67	449.2	14.92 (11.74, 18.95)	52	449.2	11.58 (8.82, 15.19)	15	449.2	3.34 (2.01, 5.54)	1.05 (0.79, 1.39) 0.745	0.98 (0.73, 1.30) 0.863	0.89 (0.67, 1.18) 0.407	0.93 (0.70, 1.24) 0.612
<b>Raltegravir</b>													
Overall	436	2192	19.90 (15.20, 18.04)	267	2192	12.18 (9.66, 12.12)	169	2192	7.71 (6.15, 8.23)				
HCV-Ab negative	321	1609	19.95 (17.88, 22.26)	196	1609	12.18 (10.59, 14.01)	125	1609	12.96 (8.46, 19.90)	1.00	1.00	1.00	1.00
HCV-Ab positive	68	420.8	16.16 (12.74, 20.49)	45	420.8	10.69 (7.98, 14.32)	23	420.8	5.47 (3.63, 8.22)	0.89 (0.64, 1.23) 0.478	0.96 (0.61, 1.52) 0.870	0.97 (0.61, 1.54) 0.904	0.97 (0.61, 1.54) 0.895
HCV-Ab unknown	47	161.8	29.04 (21.82, 38.65)	26	161.8	16.07 (10.94, 23.60)	21	161.8	7.77 (6.52, 9.26)	1.26 (0.83, 1.91) 0.271	1.04 (0.67, 1.60) 0.865	1.03 (0.66, 1.60) 0.909	0.98 (0.62, 1.55) 0.945
<b>*Dolutegravir</b>													
Overall	70	411.3	17.02 (11.54, 17.82)	38	411.3	9.24 (6.07, 11.20)	32	411.3	7.78 (5.00, 9.80)				
HCV-Ab negative	46	308.8	14.89 (11.16, 19.89)	25	308.8	8.09 (5.47, 11.98)	21	308.8	6.80 (4.43, 10.43)				
HCV-Ab positive	8	31.33	25.53 (12.77, 51.05)	6	31.33	19.15 (8.60, 42.62)	2	31.33	6.38 (1.60, 25.52)			Not estimable	
HCV-Ab unknown	16	71.17	22.48 (13.77, 36.70)	7	71.17	9.84 (4.69, 20.63)	9	71.17	12.64 (6.58, 24.30)				
<b>*Elvitegravir</b>													
Overall	42	546.6	7.68 (5.20, 9.35)	39	546.6	7.14 (4.79, 8.81)	3	546.6	0.54 (0.11, 1.38)				
HCV-Ab negative	29	409.3	7.08 (4.92, 10.19)	26	409.3	6.35 (4.32, 9.33)	3	409.3	0.73 (0.24, 2.27)				
HCV-Ab positive	6	39.67	15.13 (6.80, 33.67)	6	39.67	15.13 (6.80, 33.67)	0	39.67	0.00 (0.00, .)			Not estimable	
HCV-Ab unknown	7	97.58	7.17 (3.42, 15.05)	7	97.58	7.17 (3.42, 15.05)	0	97.58	0.00 (0.00, .)				

\*Events <100; Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cART) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for LPV/r (TDF/FTC, ZDV/3TC); DRV/r (TDF/FTC, ABC/3TC); ATV/r (TDF/FTC, ABC/3TC); RAL (TDF/FTC, ABC/3TC, TDF/FTC/DRV/r); DTG (TDF/FTC, ABC/3TC); EVG (TDF/FTC).

**Table S7: PI's and INI's incidence rates of discontinuation and Poisson regression models using IPW stratified by HCV-Ab status (time-dependent) - Stopping for toxicity/intolerance.**

	All reasons			Stopping for toxicity/intolerance			All reasons for stopping except toxicity/intolerance			Estimates from weighted Poisson models, i.e. stopping for failure/simplification treated as a competing risk			
	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	No. events	PYFU	Rate/100PYFU[95%CI]	Unadjusted RR[95%CI] p-value	Model 1 IRR[95%CI] p-value	Model 2 IRR[95%CI] p-value	Model 3 IRR[95%CI] p-value
<b>Lopinavir/r</b>													
Overall	1104	4217	26.18 (19.67, 21.85)	208	4217	4.93 (4.10, 5.34)	896	4217	21.25 (16.50, 18.58)				
HCV-Ab negative	775	2762	28.06 (26.16, 30.11)	133	2762	4.82 (4.06, 5.71)	642	2762	23.25 (21.52, 25.12)	1.00	1.00	1.00	1.00
HCV-Ab positive	252	1213	20.77 (18.36, 23.50)	51	1213	4.20 (3.19, 5.53)	201	1213	16.57 (14.43, 19.02)	0.86 (0.62, 1.20) 0.371	1.20 (0.70, 2.05) 0.505	1.13 (0.66, 1.94) 0.654	1.09 (0.64, 1.85) 0.746
HCV-Ab unknown	77	241.8	31.85 (25.48, 39.82)	24	241.8	9.93 (6.65, 14.81)	53	241.8	21.92 (16.75, 28.70)	2.05 (1.32, 3.17) 0.001	2.07 (1.34, 3.17) <.001	2.20 (1.43, 3.38) <.001	2.14 (1.40, 3.27) <.001
<b>Darunavir/r</b>													
Overall	665	4666	14.25 (11.60, 13.37)	111	4666	2.38 (1.92, 2.77)	554	4666	11.87 (9.79, 11.46)				
HCV-Ab negative	487	3487	13.97 (12.78, 15.26)	87	3487	2.49 (2.02, 3.08)	400	3487	11.47 (10.40, 12.65)	1.00	1.00	1.00	1.00
HCV-Ab positive	84	642.7	13.07 (10.55, 16.19)	16	642.7	2.49 (1.53, 4.06)	68	642.7	10.58 (8.34, 13.42)	1.05 (0.61, 1.81) 0.847	1.35 (0.65, 2.78) 0.419	1.27 (0.60, 2.68) 0.533	1.21 (0.59, 2.49) 0.607
HCV-Ab unknown	94	536.1	17.53 (14.33, 21.46)	8	536.1	1.49 (0.75, 2.98)	86	536.1	16.04 (12.99, 19.82)	0.62 (0.30, 1.28) 0.195	0.41 (0.19, 0.87) 0.020	0.40 (0.18, 0.87) 0.021	0.40 (0.18, 0.88) 0.023
<b>Atazanavir/r</b>													
Overall	999	7049	14.17 (11.70, 13.14)	263	7049	3.73 (3.18, 4.04)	736	7049	10.44 (8.81, 10.11)				
HCV-Ab negative	714	4933	14.47 (13.45, 15.57)	195	4933	3.95 (3.44, 4.55)	519	4933	10.52 (9.65, 11.47)	1.00	1.00	1.00	1.00
HCV-Ab positive	218	1667	13.08 (11.45, 14.94)	51	1667	3.06 (2.33, 4.03)	167	1667	10.02 (8.61, 11.66)	0.79 (0.57, 1.07) 0.130	0.74 (0.45, 1.22) 0.239	0.69 (0.42, 1.15) 0.155	0.67 (0.41, 1.11) 0.122
HCV-Ab unknown	67	449.2	14.92 (11.74, 18.95)	17	449.2	3.78 (2.35, 6.09)	50	449.2	11.13 (8.44, 14.69)	0.97 (0.59, 1.58) 0.893	0.95 (0.58, 1.57) 0.845	0.88 (0.53, 1.47) 0.623	0.95 (0.57, 1.60) 0.853
<b>*Raltegravir</b>													
Overall	436	2192	19.90 (15.20, 18.04)	72	2192	3.29 (2.50, 3.94)	364	2192	16.61 (12.92, 15.62)	1.00			
HCV-Ab negative	321	1609	19.95 (17.88, 22.26)	49	1609	3.05 (2.30, 4.03)	272	1609	16.91 (15.01, 19.04)	1.32 (0.76, 2.29)			
HCV-Ab positive	68	420.8	16.16 (12.74, 20.49)	17	420.8	4.04 (2.51, 6.50)	51	420.8	12.12 (9.21, 15.95)	0.327		Not estimable	
HCV-Ab unknown	47	161.8	29.04 (21.82, 38.65)	6	161.8	3.71 (1.67, 8.25)	41	161.8	25.33 (18.65, 34.41)	1.17 (0.50, 2.75) 0.718			
<b>*Dolutegravir</b>													
Overall	70	411.3	17.02 (11.54, 17.82)	10	411.3	2.43 (1.15, 4.03)	60	411.3	14.59 (9.88, 15.88)				
HCV-Ab negative	46	308.8	14.89 (11.16, 19.89)	9	308.8	2.91 (1.52, 5.60)	37	308.8	11.98 (8.68, 16.54)				
HCV-Ab positive	8	31.33	25.53 (12.77, 51.05)	0	31.33	0.00 (0.00, .)	8	31.33	25.53 (12.77, 51.05)			Not estimable	
HCV-Ab unknown	16	71.17	22.48 (13.77, 36.70)	1	71.17	1.41 (0.20, 9.98)	15	71.17	21.08 (12.71, 34.96)				
<b>*Elvitegravir</b>													
Overall	42	546.6	7.68 (5.20, 9.35)	11	546.6	2.01 (0.99, 3.28)	31	546.6	5.67 (3.68, 7.34)				
HCV-Ab negative	29	409.3	7.08 (4.92, 10.19)	11	409.3	2.69 (1.49, 4.85)	18	409.3	4.40 (2.77, 6.98)				
HCV-Ab positive	6	39.67	15.13 (6.80, 33.67)	0	39.67	0.00 (0.00, .)	6	39.67	15.13 (6.80, 33.67)			Not estimable	
HCV-Ab unknown	7	97.58	7.17 (3.42, 15.05)	0	97.58	0.00 (0.00, .)	7	97.58	7.17 (3.42, 15.05)				

\*Events <100; Model #1: demographics (age, gender, ethnicity, region, mode of HIV transmission, calendar year of starting cAR) plus metabolic factors (BMI and diabetes status); Model #2: Model #1 plus HIV related factors (previous ART use, concomitant ART use, previous AIDS diagnosis, CD4 cell count, HIV-RNA viral load); Model #3: Model 2 plus liver factors (FIB4 and alcohol use). Concomitant ART drugs adjusted for LPV/r (TDF/FTC, ZDV/3TC); DRV/r (TDF/FTC, ABC/3TC); ATV/r (TDF/FTC, ABC/3TC); RAL (TDF/FTC, ABC/3TC, TDF/FTC/DRV/r); DTG (TDF/FTC, ABC/3TC); EVG (TDF/FTC).