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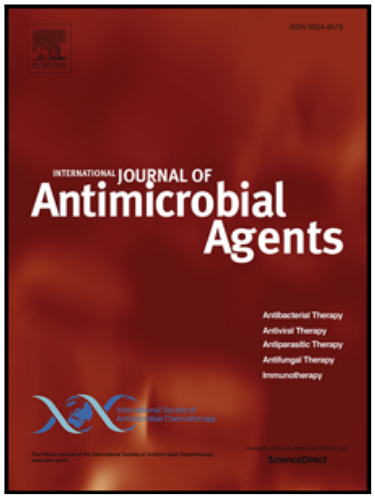

Characterization and outcomes of difficult-to-treat patients starting modern first-line ART regimens: data from the ICONA cohort

Roberta Gagliardini , Alessandro Tavelli , Stefano Rusconi , Sergio Lo Caputo , Vincenzo Spagnuolo , Maria Mercedes Santoro , Andrea Costantini , Alessandra Vergori , Franco Maggiolo , Andrea Giacomelli , Giulia Burastero , Giordano Madeddu , Eugenia Quiros Roldan , Antonella d'Arminio Monforte , Andrea Antinori , Alessandro Cozzi-Lepri , Icona Foundation Study Group

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Highlights

- In PLWH starting a modern ART regimen, estimated probability of becoming “difficult to treat" due to multiple failures is 6.5% by 6 year.
- Difficult to treat PLWH had a significantly higher prevalence of AIDS diagnosis, were older and had lower nadir of CD4 compared to the non- difficult to treat PLWH.
- At Cox regression analysis, difficult to treat PLWH showed a higher risk of experiencing virological failure (aHR 2.23, 95% CI: 1.33-3.73), treatment failure (aHR 1.70, 95% CI: 1.03-2.78), serious non-AIDS events/death (aHR 2.79, 95% CI: 1.18-6.61).

Characterization and outcomes of difficult-to-treat patients starting modern first-line ART regimens: data from the ICONA cohort

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Preliminary results of this study were presented as Poster at HIV DRUG THERAPY GLASGOW 2022 Conference, "*Characterization and outcomes of difficult to treat patients in an Italian cohort of PLWH starting modern ART regimens*" (P155) and the abstract was published in JIAS Volume25, IssueS6. Supplement: HIV Glasgow, 23–26 October 2022, Glasgow, UK / Virtual. October 2022 https://doi.org/10.1002/jia2.26009 and as oral presentation at Italian Conference on AIDS and Antiviral Research (ICAR) 2022 (OC 32 and OC36).

Abstract

Background: Treatment failures to modern ART raise concerns, as they could reduce future options. Evaluations of occurrence of multiple failures to modern ART are missing and their significance in the long run is unclear.

Material and Methods: People with HIV (PWH) in the ICONA cohort who started a modern first-line ART were defined as "difficult to treat" (DTT) if experienced ≥1 among: i) ≥2 VF (2 viral loads, VL>200 copies/mL or 1 VL>1000 copies/mL) with or without ART change; ii) ≥2 treatment discontinuations (TD) due to toxicity/intolerance/failure; iii) ≥1 VF followed by ART change plus ≥1 TD due to toxicity/intolerance/failure. A subgroup of the DTT participants were matched to PWH that, after the same time, were non-DTT. Treatment response, analyzing VF, TD, treatment failure, AIDS/death and SNAE (Serious non-AIDS event)/death were compared. Survival analysis by KM curves and Cox regression models were employed.

Results: Among 8,061 PWH, 320 (4%) became DTT. Estimates of becoming DTT was 6.5% (95% CI: 5.8-7.4%) by 6 years. DTT PWH were significantly older, with a higher prevalence of AIDS and lower CD4+ at nadir than the non-DTT. In the prospective analysis, DTT demonstrated a higher unadjusted risk for all the outcomes. Once controlled for confounders, significant associations were confirmed for VF (aHR 2.23, 1.33-3.73), treatment failure (aHR 1.70, 1.03-2.78), SNAE/death (aHR 2.79, 1.18-6.61).

Conclusions: A total of 6.5% of PWH satisfied our definition of DTT by 6 years from ART starting. This appears a more fragile group who may have higher risk of failure.

Keywords: Treatment failures, late presenters, ART, virological failure, treatment discontinuations.

1. Introduction

In the recent past, antiretroviral therapy (ART) has become easier to take, having fewer side effects and toxicities, showing less potential for drug–drug interactions and being generally less prone to confer drug resistance. As a result, an increase in adherence, potency, and durability of modern ART regimens is being seen, when compared to older treatment. In Italy, for example, the main reason to discontinue first-line ART is simplification [1,2]. Today, only 2-5% of regimens are discontinued because of intolerance or toxicity by one year [3,4] and 2-4% for virological failure (VF) by 2 years [4,5], with rates of VF showing a decline in more recent years [6]. The availability of potent and easy to take ART has resulted in life expectancy improvements for people with HIV (PWH). However, being this a long-life treatment, virological failures and toxicity events, albeit infrequent, should be nonetheless carefully managed. Indeed, multiple treatment failures to modern ART regimens are of concern, as they might limit future drug options and eventually lead to clinical failure. In fact, in some low- and middle-income countries (LMICs), second-line treatment failures still represent an issue, and PWH failing therapy are also frequently burdened by high mortality [7–10]. Even in recently published works [11–14], a history of prior virological failure has been shown to be associated with the risk of subsequent virological failure. However, real world estimates of rate of multiple failures to modern regimens are lacking and long-term consequences of repeated failures remain unclear.

The aim of this study was to characterize the proportion of subjects defined as “difficult-to-treat” because of having experienced at least two failures events in recent years despite receiving modern ART regimens. We focused only on failures that are likely to limit future treatment options, such as treatment failures for toxicities, intolerance or for virological reasons. Here we described the incidence of “difficult-to-treat” (DTT) status among individuals in the Icona Foundation Study cohort who initiated modern ART and we showed the virologic and clinical responses to the treatment that was started subsequently to the DTT classification.

2. Methods

2.1. *Study population and definitions*

A prospective cohort study including patients enrolled in Icona Foundation Study was conducted. ICONA Foundation Study is an Italian multi-centre prospective observational cohort of PWH. Demographic, epidemiological clinical and laboratory information are obtained for all the study participants and recorded in an electronic case report form [www.icona.org]. Dates of start and

stop of each antiretroviral and the main reason for discontinuation are collected as reported by the treating physician. All participating centres Institutional Review Boards approved the ICONA Foundation Study. To participate in the cohort each PWH signed a consent form, to comply with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amendment October 2013). PWH aged 18 or older enrolled in Icona Foundation Study, who started a modern ART and had at least one available follow-up visit constituted the study population. The dataset used for this analysis was locked in January 2022.

Modern ART was defined as: i) 2 nucleoside reverse transcriptase inhibitors (NRTI) among tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), abacavir (ABC), lamivudine (3TC) or emtricitabine (FTC) plus darunavir boosted (DRV/b) once daily or ii) 2 NRTI (among TAF, TDF, ABC, 3TC or FTC) plus any integrase strand transfer inhibitors (INSTI) among raltegravir (RAL), elvitegravir/cobicistat (EVG/c), dolutegravir (DTG), bictegravir (BIC) or iii) 2 NRTI (among TAF, TDF, ABC, 3TC or FTC) plus doravirine (DOR) or plus rilpivirine (RPV) or v) DTG+3TC.

PWH were classified as "difficult-to-treat" (DTT) if, after starting a modern regimen ART, they experienced at least one of the following events (whichever occurred first):

i) At least two VF (VF defined as two consecutive HIV-RNA > 200 copies/mL or a single HIV-RNA > 1000 copies/mL after at least 6 months from the initiation of ART) with or without subsequent ART change;

ii) At least two treatment discontinuations due to toxicity/intolerance/failure on two different regimens;

iii) At least one VF (VF defined as two consecutive HIV-RNA > 200 copies/mL or a single HIV-RNA > 1000 copies/mL after > 6 months from the initiation of ART) followed by ART change plus at least one treatment discontinuation due to toxicity/intolerance/failure.

The date of becoming DTT is defined as the index date. It has to be noticed that this definition is based exclusively upon expert opinion. Any change in any component of the ART regimen due to toxicity/intolerance/failure (as reported by the treating physician) was considered as discontinuation. Change of ART due to simplification or other reasons was not considered as discontinuation. Rebounds of HIV-RNA due to voluntary treatment interruptions (patients' decision) are not counted as events and not classified as failure of therapy.

Advanced HIV disease was defined as HIV infected subjects with CD4+ cells count less than 200 cell/mmc or with an AIDS- defining event at HIV diagnosis [15].

Baseline was defined as the time of first ART initiation.

AIDS events included any AIDS-defining conditions as reported by CDC [16].

Serious non–AIDS-defining events included cardiovascular disease (myocardial infarction, stroke, or invasive cardiovascular procedures), liver-related events (ascites, hepatic encephalopathy grade 3–4, hepatorenal syndrome, esophageal variceal bleeding, end-stage liver disease, hepatocellular carcinoma), chronic kidney disease (defined as a confirmed estimated glomerular filtration rate <60 mL/minute 1.73 m^2) or non–AIDS-defining malignancies (any malignancies other than Kaposi sarcoma, non-Hodgkin lymphoma or cervical cancer) [17].

A sensitivity analysis with an alternative definition of VF (two consecutive HIV-RNA > 50 copies/mL or a single HIV-RNA > 1000 copies/mL after at least 6 months from ART initiation) was performed.

2.2. Study objectives

The primary objective was to estimate the proportion of PWH fulfilling the definition of DTT and characterize subjects defined as DTT, focusing on the association between DTT and advanced HIV disease. Secondary objective was to compare the clinical and virological responses to a new regimen initiated after the DTT classification between DTT and a matched group of non-DTT PWH.

2.3. *Statistical analysis*

Baseline characteristics of participants according to whether they had advanced HIV disease at diagnosis and to whether they fulfilled the DTT definition in follow-up were compared by means of χ2 for categorical variables or Wilcoxon rank-sum (Mann-Whitney) test for continuous variables.

Time to first becoming DTT after ART start was estimated. Kaplan-Meier curves stratified by stage of HIV disease with log-rank test were employed to compare the cumulative probability of becoming DTT over time. Hazard ratio (HR) of becoming DTT according to stage of HIV disease was estimated by means of a standard Cox regression model after controlling for age, HIV-RNA at ART starting, calendar year of ART and nationality. According to our assumptions, this adjustment controlled for all sources of measured confounding, as described by the directed acyclic graph (DAG) in *Figure 1*. A subset of participants classified as DTT subsequently initiated a new regimen. We identified a sample of matched unexposed group of PWH in Icona cohort who, after approximately the same time (+/- 3 months) elapsed from baseline to the index date, were still free from DTT events and also initiated a new regimen. For each DTT participant we included two matched unexposed controls. We then compared the responses to this new treatment in DTT vs not DTT. The following endpoints were investigated: VF (defined as above); discontinuation of at

least one drug due to intolerance/toxicity/failure; treatment failure (composite of HIV-RNA > 200 copies/ml or discontinuation of at least one drug due to intolerance/toxicity/failure); new AIDS event/death, new serious non-AIDS event (SNAE)/death for any cause. A P value < 0.05 was considered as significant. Statistical analysis was conducted using SAS version 9.4.

3. Results

3.1. Study population

A total of 8,061 PWH were included in the main analysis: 18.3% were females, median age was 40 years (interquartile range, IQR, 31-49), 10.1% with an AIDS-defining event, their median CD4+ cells count at nadir was 346 cells/mmc (IQR 160-508), median log10 HIV-RNA was 4.73 (IQR 4.12-5.31) at baseline (*Table 1*). A modern ART regimen was started after a median time of 1 (IQR 1-6) month from HIV diagnosis. Initial ART regimens were INSTI-based (60%), DRV/b-based (21%) or NNRTI-based (19%).

Of the 8,061 PWH, 2,402 (30%) presented with advanced HIV disease at diagnosis, of whom 818 (34.1%) with an AIDS-defining event. PWH with advanced HIV were more frequently females (21.6% vs 16.9%), infected through heterosexual contacts (50% vs 32.4%), not Italians (61.9% vs 49.1%), older (44 years old vs 38), had more recent calendar year of baseline and had greater viral load than PWH without advanced HIV disease (*Table 2*).

A total of 320 participants (4%) experienced ≥1 of the DTT-defining events: 240 (75%) had 2 treatment discontinuations, 57 (18%) had one VF + one treatment discontinuation, 23 (7%) had 2 VF. In the sensitivity analysis with a different definition of VF, a total of 370 participants experienced ≥1 of the DTT-defining events.

3.2. Estimates of becoming difficult-to-treat

The cumulative estimated probability of becoming DTT was 2.2% (95% confidence interval, CI: 1.8-2.6) by two years and 6.5% (95% CI: 5.8-7.4) by six years from baseline (*Figure 2a*).

The cumulative estimated probability of becoming DTT according to the presence or not of advanced HIV disease at baseline was 1.7% (95% CI: 1.3-2.1) in PWH without advanced HIV disease versus 3.4% (95% CI: 2.5-4.2) in PWH with advanced HIV disease by two years and 5.3% (95% CI: 4.5-6.2) versus 9.6% (95% CI: 7.7-11.4) by six years (*Figure 2b,* log-rank p<0.0001).

PWH with advanced HIV disease had higher risk of becoming DTT in the unadjusted analysis (HR 1.84, 95% CI: 1.47-2.30, p<0.001) when compared to those without advanced HIV. However, after

controlling for age, HIV-RNA at ART starting, calendar year of ART and nationality, the association was attenuated and only marginally not significant (aHR 1.30, 95% CI: 0.98-1.74, p=0.07).

Results of the Cox regression model were similar in the sensitivity analysis, both in in the unadjusted (HR 2.07, 95% CI: 1.69-2.55, p<0.001) and in the adjusted analysis (HR 1.43, 95% CI: 1.10-1.87, p=0.009).

3.3. ART in difficult-to-treat PWH

The first failing ART regimens concurring to difficult-to-treat definition were NNRTI-based in 13.4% of cases, PI-based in 40.9% of cases, INSTI-based in 41.6% of cases, regimens with at least two anchor drugs in 2.8% of cases and others in 1.3%. The second failing ART regimens concurring to difficult-to-treat definition were NNRTI-based in 15.6% of cases, PI-based in 26.9% of cases, INSTI-based in 48.1% of cases, regimens with at least two anchor drugs in 6.6% and others in 2.8%.

3.4. Outcomes of difficult-to-treat PWH in matched analysis

Population characteristics at enrolment by difficult-to treat group in the matched analysis performed in the subset of 858 subjects (286 difficult-to-treat PWH and 572 not difficult-to-treat PWH) are shown in *Table 3*. When comparing baseline characteristics, DTT PWH had a significantly higher prevalence of AIDS diagnosis (24.1% vs 15.2%, p=0.001), were slightly older (median age 44 years vs 38, p<0.001), had lower nadir of CD4+ cells count (median value 260 cells/mmc vs 303, p=0.022), had higher prevalence of estimated glomerular filtration rate (EGFR) below 60 ml/min/1.73m^2 (8.7% vs 3.3%, p <0.001) and reported greater use of lipid- lowering agents (12.2% vs 6.8%, p=0.008) when compared to participants who were never classified as DTT in follow-up (*Table 3*).

Time from index date to initiation of the new regimen was 0 (same day) for DTT PWH and 54 days (IQR 28-78) for not difficult-to-treat PWH (p< 0.001).

The 286 DTT initiated a regimen including NNRTI + 2NRTI in 13.3% of cases, PI/b+ 1 or 2 NRTI in 16.1% of cases, INSTI+ 1 or 2 NRTI in 54.9% of cases, at least two anchor drugs in 11.2% of cases and other in 4.5%. Among the regimens composed by at least two anchor drugs, 25.0% included dolutegravir with boosted darunavir, 28.1% dolutegravir with rilpivirine, 12.5% rilpivirine with booster darunavir, 34.4% were different combinations (including maraviroc, etravirine, nevirapine, bictegravir and raltegravir). Only 18.7% of them (6/32) had a regimen composed by 4 or more

antiretroviral drugs. Changes from the different classes after becoming DTT are shown in *Figure 3*. The 572 not difficult-to-treat PWH initiated a regimen including NNRTI + 2NRTI in 21.7% of cases, PI/b+ 1 or 2 NRTI in 14.0% of cases, INSTI+ 1 or 2 NRTI in 55.6% of cases, at least two anchor drugs in 7% of cases and other in 1.8% (p-value 0.0017 for the comparison with DTT).

The cumulative estimated probability of virological failure by exposure groups was 17.8% (95% CI: 12.9-22.7) in DTT vs. 7.2% (95% CI: 5.1-10.1) in matched unexposed PWH by two years and 20.9% (95% CI: 15.3-26.5) vs. 8.9% (95% CI: 5.9-12.0) respectively by four years from starting the new regimen (the index date) (*Figure 4a,* log-rank p<0.0001).

The cumulative estimated probability of discontinuation of ≥1 drug due to intolerance/toxicity/failure was 17.0% (95% CI: 11.7-22.4) in DTT vs. 6.2% (95% CI: 4.1-9.2) in matched unexposed PWH by two years and 14.8% (95% CI: 8.9-20.7) versus 22.6% (95% CI: 15.7-29.5) by four years from the index date (*Figure 4b*).

The cumulative estimated probability of treatment failure was 19.1% (95% CI: 13.7-24.5) in DTT vs. 7.7% (95% CI: 5.1-10.4) in matched unexposed PWH by two years and 16.2% (95% CI: 10.3-22.2) versus 25.8% (95% CI: 18.6-32.9) respectively by four years from the index date (*Figure 4c*).

The cumulative estimated probability of AIDS event/death and of SNAE/death are shown in *Figures 4d* and *4e*.

In the Cox regression model, after controlling for HIV-RNA at ART starting, calendar year of ART, CD4 cells count at BL, CD4 cells count ad nadir and AIDS at baseline (the latter not included in the AIDS outcome), the association for the DTT group vs. unexposed with the risk of discontinuation due to intolerance/toxicity/failure was largely attenuated (aHR 1.54, 95% CI: 0.90-2.64). Conversely, for the risk of AIDS/death there appeared to be only modest confounding (aHR 2.22, 95% CI: 0.71-6.98) although results were no longer significant (*Figure 5*). In contrast, the other associations remained significant after the adjustment. Specifically, DTT group had higher risk of virological failure (aHR 2.23, 95% CI: 1.33-3.73), of treatment failure (aHR 1.70, 95% CI: 1.03-2.78) and of SNAE/death (aHR 2.79, 95% CI: 1.18-6.61) after controlling for confounding (*Figure 5*).

Results were similar in the sensitivity analysis and DTT group had higher risk of virological failure (aHR 4.46, 95% CI: 2.56-7.76) and of treatment failure (aHR 2.46, 95% CI: 1.53-3.95), while no association was found for AIDS/death or for SNAE/death after controlling for confounding.

4. Discussion

This study aimed to explore characteristics and outcomes of a target population of PWH with multiple failures to modern regimens, here defined as “difficult-to-treat”. This is an important group of patients who appear to be at higher risk of failing ART regimens, which are otherwise very potent and highly tolerated, and may need careful management.

Overall, it was found that a total of 6.5% of PWH who started a modern first-line ART satisfied our definition of DTT by 6 years from ART initiation. Not surprisingly, when some of the DTT population started a new regimen and were compared to a matched group of non-DTT, they experienced a higher risk of adverse outcomes in the long-term (virological failure, composite outcome of treatment failure and SNAE/death). A history of prior virological failure has been previously associated with a higher risk of following VF [11–13], although results have been conflicting [12,14]. In any case, to our knowledge, this is the first analysis that evaluates the association between multiple failures to modern ART regimens and the subsequent risk of both virological and clinical failure in non-LMIC countries.

DTT PWH showed characteristics that are commonly associated with poor clinical and virologic outcomes, such as a significantly higher prevalence of AIDS diagnosis, older age and lower CD4 cells count at nadir. Moreover, we found no evidence that DTT and non-DTT differ for characteristics related to social issues and comorbidities, such as being IDU, diabetes, smoking status, lipid levels, educational level, but only for eGFR levels and use of statins. The higher prevalence of low eGFR levels and of statins’ prescription in DTT PWH could be potentially attributable to the higher age, the more advanced HIV disease and/or the different antiretroviral drugs used, difficult to speculate without further investigating these issues in a multivariable analysis. The association between type of ART and DDT classification was not explored because a different study design would be required to understand whether this association might simply be due to confounding.

Our analysis also showed that PWH with advanced HIV disease at ART initiation were at significantly higher risk of becoming DTT, although attenuated after controlling for confounding factors. It is indeed well known how late and advanced HIV presentation are associated with poorer outcomes, including higher risk of disease progression and mortality, even in case of timely ART initiation [19–22], reduced rate of viral suppression [23], increased hospitalization risk and costs of health care [24,25] and suboptimal immune recovery [26–28]. Moreover, low CD4 cells count at time of ART starting has also been previously demonstrated to be associated with serious non-AIDS events [29].

One aspect that indirectly emerged from our analysis is that the prevalence of PWH with advanced HIV who initiate ART in our cohort is higher now than that registered in previous years. This finding is in line with Italian data by Istituto Superiore di Sanità (ISS, HIV/AIDS infection in Italy up to December 31, 2021) [30], European data by ECDC [31] and other recently published papers which focused on late HIV presentation [32,33]. Additionally, we documented a change in some of the characteristics historically associated with late presentation (very few intravenous drug users, IVDU, compared to a recent metanalysis [34], as elsewhere reported [33]) and confirmation of others (older age [22,32,33,35], heterosexual contacts as main risk factor for HIV transmission [33,36], and foreign nationality [22,32]).

Our estimate of the average rate of treatment discontinuation resulted in line with those of therapy discontinuations in similar studies [37].

Serious non-AIDS events have become a leading cause of morbidity and mortality in PWH, and early ART initiation was shown to greatly reduce the risk of SNAEs and mortality [38]. In our analysis, DTT was associated with higher risk of treatment failure and of developing SNAE/death, which was confirmed even after the adjustment for key confounders such as late HIV diagnosis and low CD4 cells count. The exact mechanisms leading from treatment failure to death have not been yet fully elucidated but could depend on low current CD4 count, older age, male sex, IVDU, AIDS diagnosis, HCV coinfection and a detectable HIV viral load which all have been associated with increased risk of mortality [39–42].

Most PWH who satisfied the DTT definition in our cohort, subsequently started a standardized regimen with 1 anchor drug + 1-2 NRTI, once daily, mainly INSTI-based, but more complex regimens (at least 2 anchor drugs) were prescribed in a higher proportion in comparison to non-DTT (11% of cases vs 7% of non-DTT), indicating potential lack of therapeutic options. Even if these regimens comprised a variety of ART combinations, the majority of patients had 2 or 3-drug regimens, mainly with drugs with high potency and high genetic barrier to resistance, as reported in other works involving highly treatment-experienced subjects [43–45].

Our analysis presents some limitations. First, our definition of DTT, although based on common clinical sense and expert opinion, is arbitrary and because genotypic testing results are not routinely collected in the cohort, our analysis did not account for participants' level of resistance. It would be interesting to apply this same definition to other settings and compare results. Of

note, it was a definition decided a priori before seeing any of the data and we did not consider alternative definitions. In particular, poor adherence leading to ART discontinuation is classified as patients' decisions, not therapy failure, and therefore does not concur to our definition of DTT. In addition, unfortunately no other more detailed adherence data are routinely collected in the cohort.

Moreover, we explored the association only with the condition of advanced HIV disease and not with the one of late presenters. Furthermore, generalizability of our results is limited, because PWH with longer history of ART, starting with older ART were excluded by definition in this analysis. Second, time from index date to initiation of the new regimen was slightly longer in not-exposed PWH versus DTT PWH, which may have led to a survivor selection of the not-exposed group. However, this may mean that our estimates of the difference in response to treatment between the exposure groups is underestimated. In addition, because of the way the data were collected it is possible that the rate of discontinuation for toxicity/intolerance has been under-estimated. Indeed, only severe toxicity leading to discontinuation are reported in the database and it is possible that the reason for drug changes which occurred for less severe events (e.g. small changes in metabolic, liver or renal parameters) is instead reported as simplification. In addition, because of the observational nature of the study, we cannot exclude unmeasured or residual confounding.

5. Conclusions

In conclusion, a non-negligible proportion of PWH in our cohort who received modern regimens ART appears to have failed or discontinued a number of these treatments. This group, which we defined as "difficult to treat", appears to be a potentially more vulnerable PWH population who continue to experience higher risk of treatment and clinical failures to subsequent regimens. Advanced presentation could be a determinant of becoming DTT; thus, every effort should be made to achieve early HIV diagnosis and treatment. Moreover, thorough management of failures and discontinuations, even in first line and with modern ART, is mandatory. It is therefore key to early identify DTT patients so that they can be carefully managed to prevent long-term morbidity and mortality.

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Declarations

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Competing Interests: RG reports payments to her institution from Gilead Sciences, speakers' honoraria/educational activities for ViiV Healthcare, Merck Sharp and Dohme and Gilead Sciences, advisor for Theratechnologies, Janssen-Cilag and Gilead Sciences. MMS has received funds for attending symposia, speaking and organizing educational activities from ViiV Healthcare, Janssen-Cilag and Theratechnologies. SR received grants from Gilead Sciences, Janssen and ViiV Healthcare; fees for advisory board meeting from MSD, Gilead Sciences, Janssen and ViiV Healthcare; conference and travel assistance from Gilead Sciences and Janssen. EQR received grants from Gilead Sciences and fees for advisory board meeting from MSD, Gilead Sciences, Janssen- Cilag. SLC has been advisor for Gilead Sciences, ViiV Healthcare, Janssen-Cilag, GSK and MSD, had received speakers' honoraria from Gilead Sciences, ViiV Healthcare, MSD and Janssen-Cilag and had received support for travel meetings from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare. VS received grants from Gilead Sciences, speakers' honoraria from Gilead Sciences, ViiV Healthcare. AV received an institutional grant from Gilead Sciences, speakers' honoraria/educational activities from Merck Sharp & Dohme and Janssen-Cilag, and served an advisor for Janssen-Cilag. AG received consultancy fees from Mylan and Jansen, speakers' fees from ViiV Healthcare and Gilead Sciences. GM received fees for advisory board from Gilead Sciences, ViiV Healthcare, Janssen-Cilag, Astra Zeneca and MSD, speakers' honoraria from Gilead Sciences and ViiV Healthcare and support for travel meetings from Gilead Sciences and ViiV Healthcare. FM was consultant on advisory boards for Bristol-Myers Squibb, Gilead, ViiV, Merck Sharp and Dome, Roche, Tibotec; he has received lecture fees from Abbott, Bristol-Myers Squibb,

Gilead, ViiV, Merck Sharp and Dome and has received research and educational grants from Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Jansen-Cilag.

ADM received grants for research for her institution by MSD; Gilead Sciences, ViiV Healtchcare and Jansen and received fees for advisory board meetings by ViiV Healthcare, Gilead Sciences, MSD, Pfizer. AA received grants for research for his institution by MSD; Gilead Sciences and ViiV Healtchcare, and fees for advisory board meeting and consultancy from Astrazeneca, ViiV Healthcare, Merck Sharp and Dohme, Gilead Sciences, GlaxoSmithKline, Janssen Cilag, Theratechnologies, Pfizer and Roche. The other authors have nothing to declare.

Ethical Approval: The ICONA Foundation study has been approved by Institutional Review Boards of all the participating centres. All PWH signed a consent form to participate in the cohort.

Sequence Information: Not applicable

Author contribution:

RG: Conceptualization, Writing - Original Draft.

AT: Data Curation and Methodology.

SR, SLC, VS, MMS, AC, AV, FM, AG, GB, GM, EQR: resources, Investigation and Writing - Review & Editing.

AAM, AA: Conceptualization and supervision.

ACL: Methodology, Validation, Formal analysis, Writing - Review & Editing and Supervision.

Figures

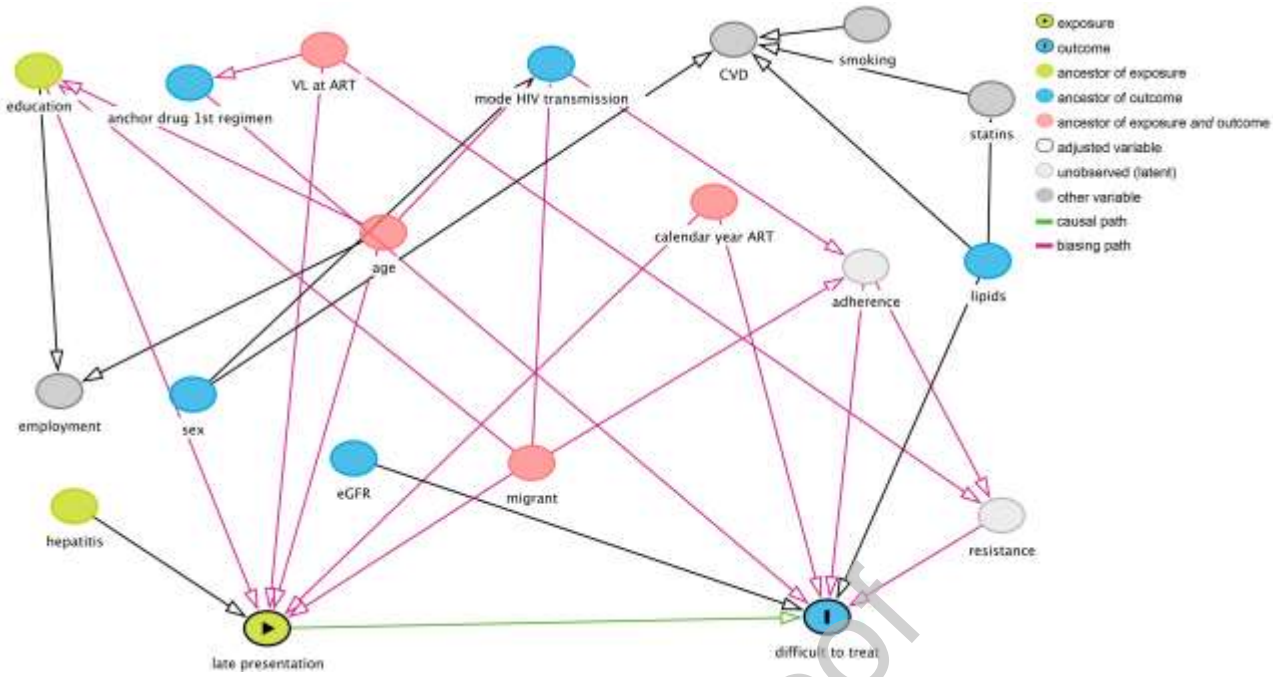
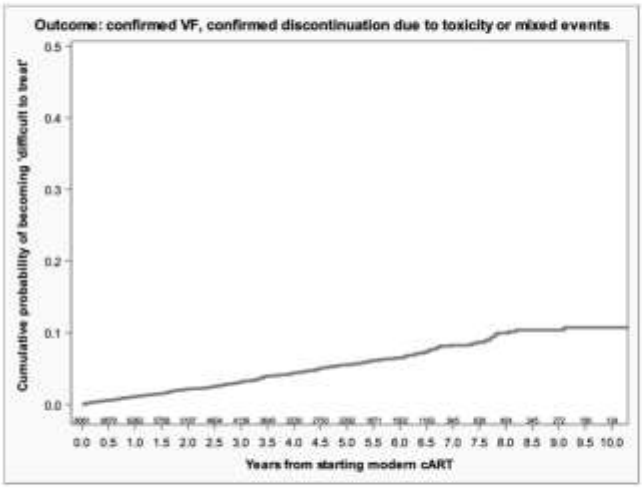
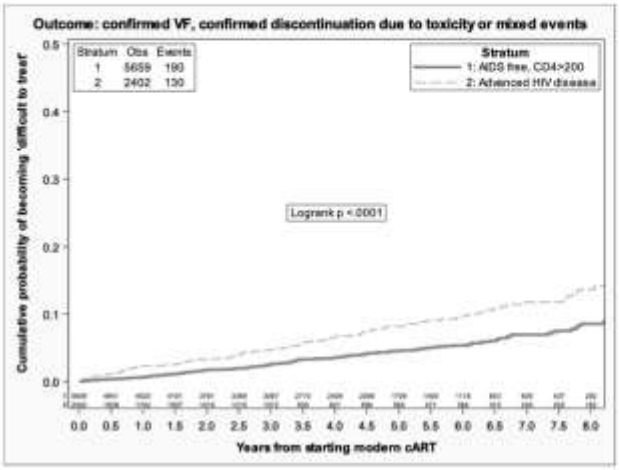


Figure 1: directed acyclic graph (DAG) of assumptions on causal structure of the data.



2-years estimates (95% CI)	6-years estimates (95% CI)	8-years estimates (95% CI)
2.2% (1.8-2.6%)	6.5% (5.8-7.4%)	9.95% (8.50-11.41)



	2-years estimates (95% CI)	6-years estimates (95% CI)	8-years estimates (95% CI)
Not advanced HIV disease	1.70% (1.29-2-05)	5.32% (4.47-6.17)	8.55% (6.89-10.21)
Advanced HIV disease	3.37% (2.54-4.19)	9.56% 7.71-11.39)	13.66% (10.72-16.60)

Figure 2: cumulative estimated probability of becoming DTT overall (a) and according to the presence or not of advanced HIV disease at baseline (b).

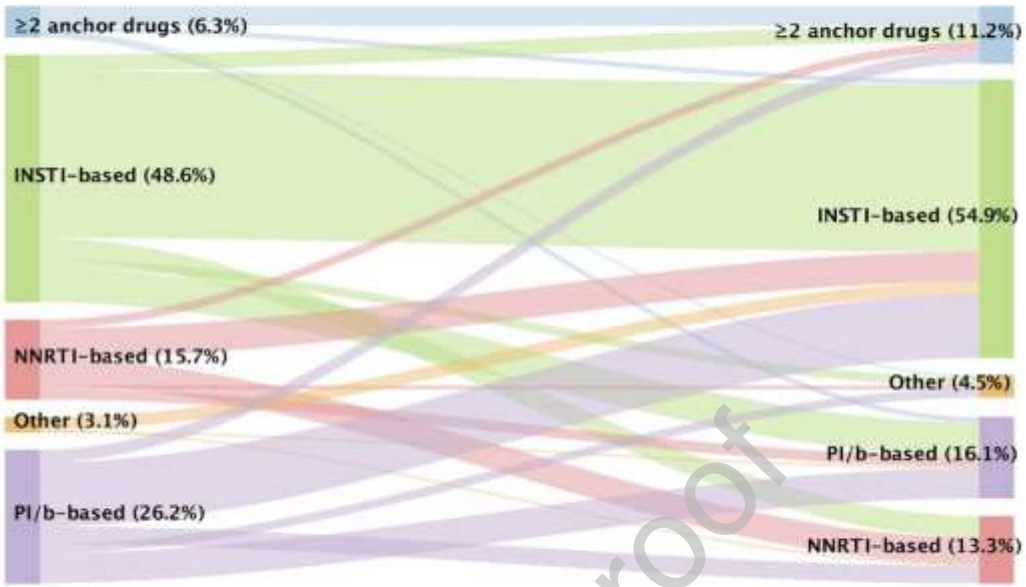
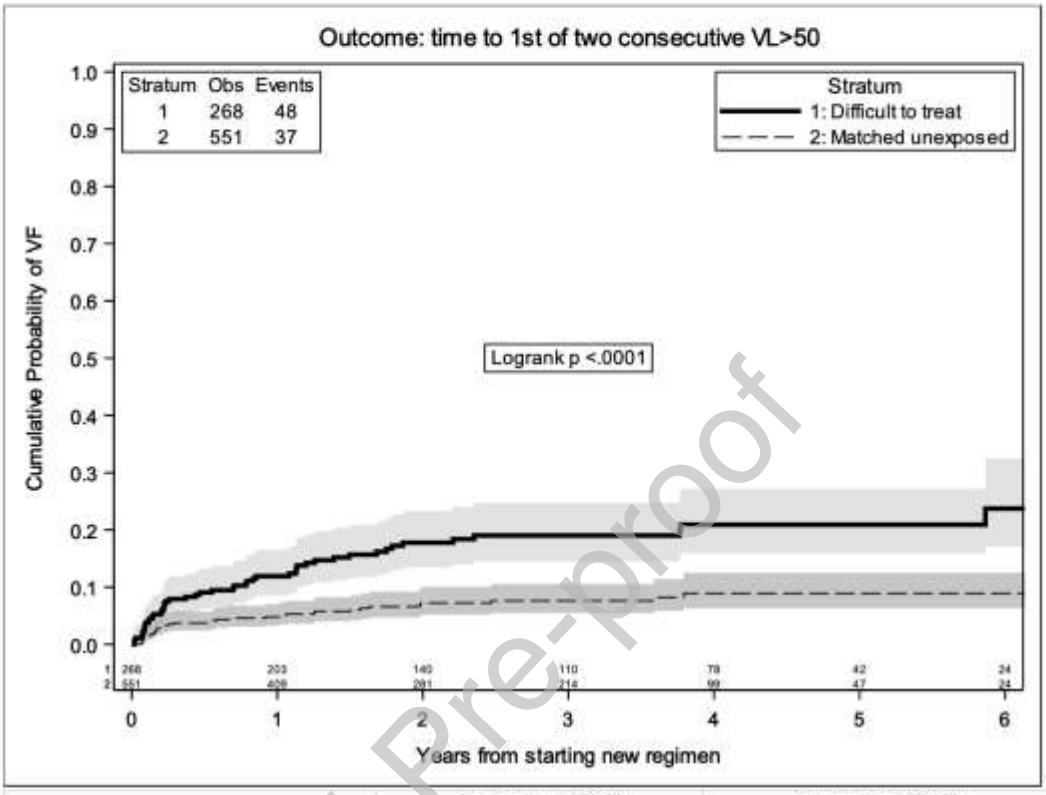
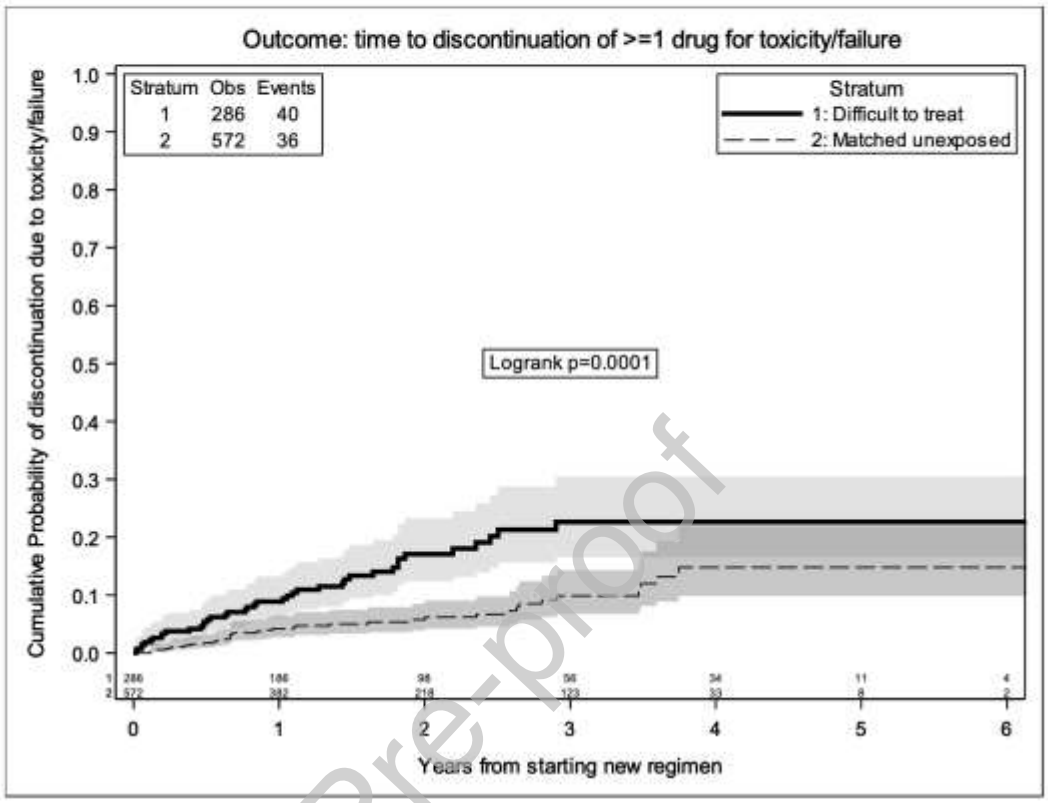


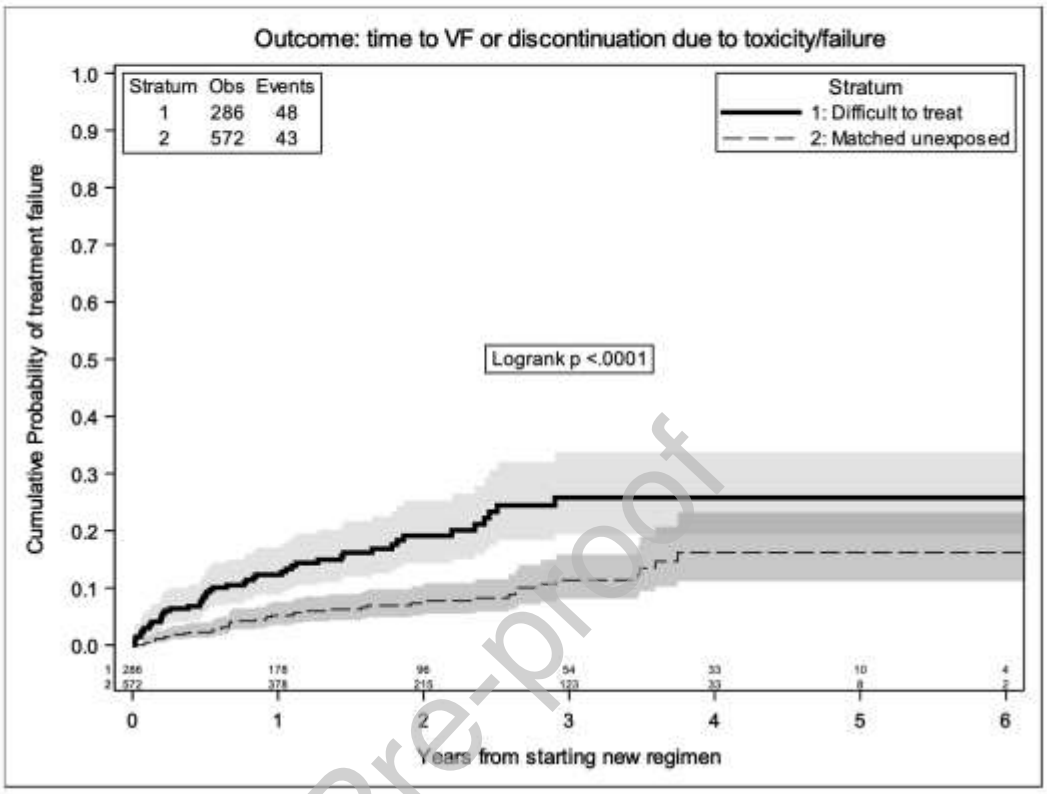
Figure 3: Sankey diagram showing changes of ART-classes after fulfilling the DTT definition in those changing regimen.



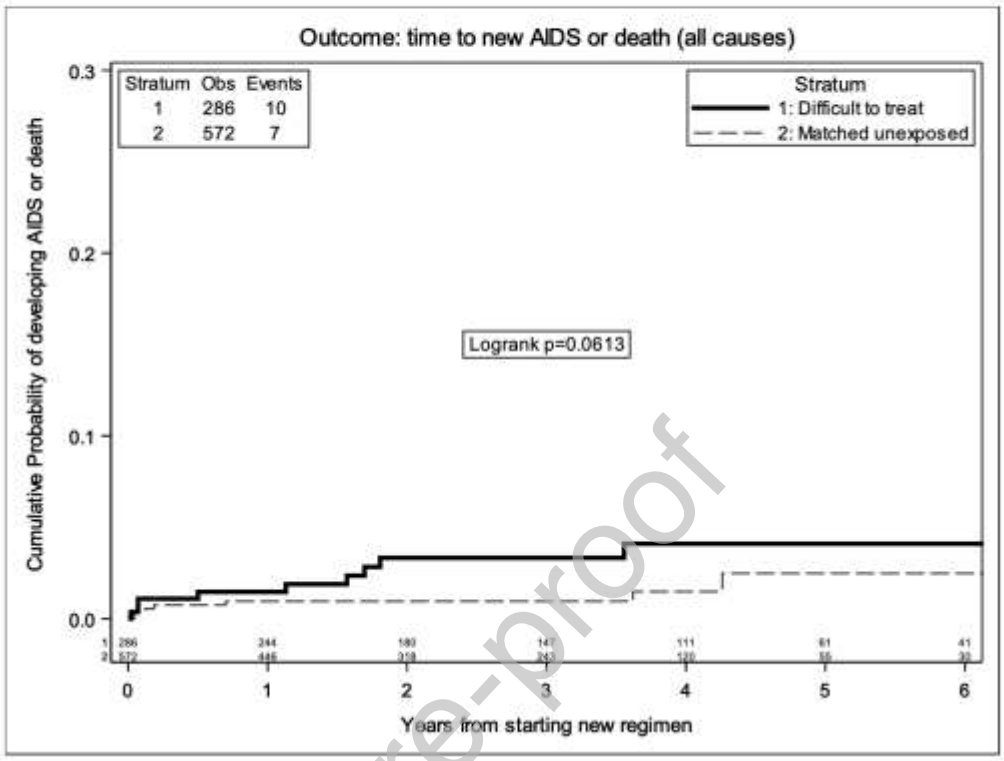
	2-years estimates (95% CI)	4-years estimates (95% CI)
Matched unexposed	7.2% (5.1-10.1)	8.9% (5.9-12.0)
DTT	17.8% (12.9-22.7)	20.9% (15.3-26.5)



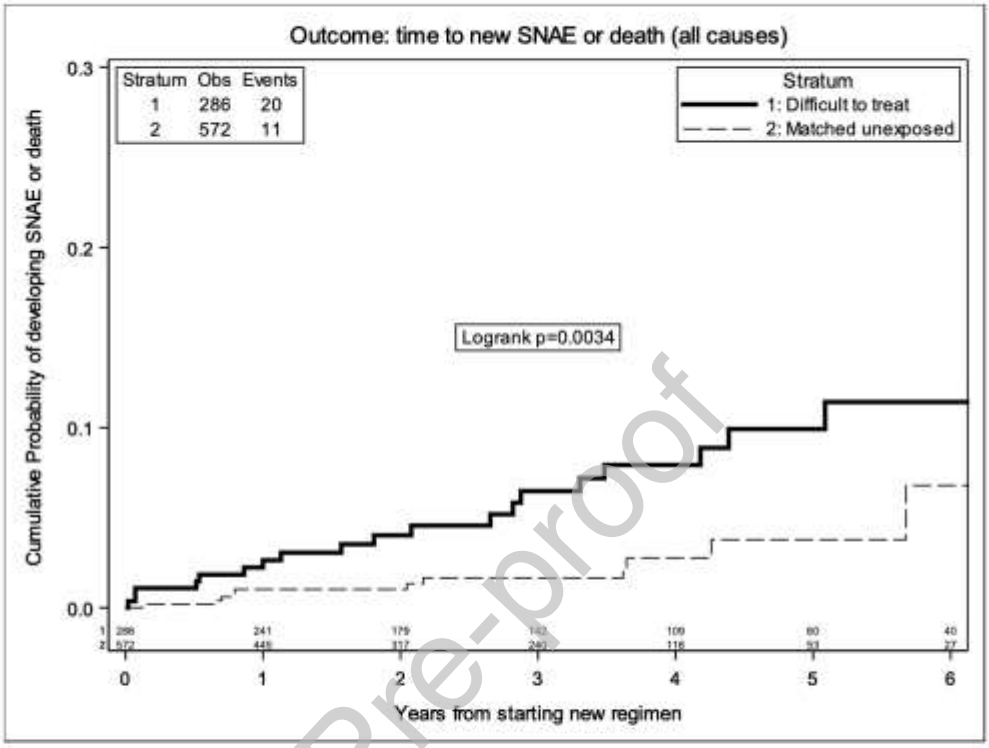
	2-years estimates (95% CI)	4-years estimates (95% CI)
Matched unexposed	6.2% (4.1-9.2)	14.8% (8.9-20.7)
DTT	17.0% (11.7-22.4)	22.6% (15.7-29.5)



	2-years estimates (95% CI)	4-years estimates (95% CI)
Matched unexposed	7.7% (5.1-10.4)	16.2% (10.3-22.2)
DTT	19.1% (13.7-24.5)	25.8% (18.6-32.9)

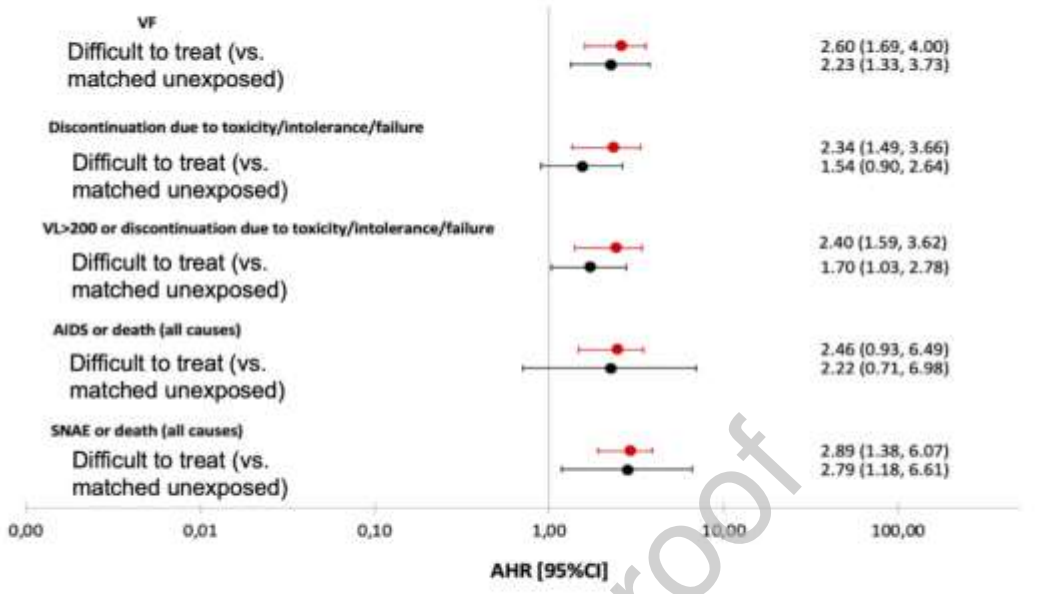


	2-years estimates (95% CI)	4-years estimates (95% CI)
Matched unexposed	0.9% (0.1-1.76)	1.5% (0.1-2.8)
DTT	3.3% (1.0-5.6)	4.1% (1.3-6.8)



	2-years estimates (95% CI)	4-years estimates (95% CI)
Matched unexposed	1.3% (0.3-2.4)	2.8% (0.8-4.7)
DTT	4.6% (1.9-7.2)	7.9% (4.0-11.8)

Figure 4: cumulative estimated probability of virological failure by exposure groups (a), cumulative estimated probability of discontinuation of at least one drug due to intolerance/toxicity/failure (b), cumulative estimated probability of treatment failure (c), cumulative estimated probability of AIDS event or death (d), cumulative estimated probability of SNAE or death (e).



Notes: unadjusted analysis in red, adjusted analysis in black.

Figure 5: Cox regression model for VF, discontinuation, treatment failure or clinical failure.

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Table 1: Descriptive characteristics of PLWH included in the analysis.

	Overall population (n=8061)
Female gender, n (%)	1473 (18.3%)
Age, median (IQR)	40 (31, 49)
Mode of HIV transmission, n(%)	
IVDU	486 (6.1%)
Homosexual contacts	3911 (49.2%)
Heterosexual contacts	3036 (37.7%)
Other/unknown	520 (6.5%)
AIDS diagnosis, n(%)	818 (10.1%)
HCV Ab, n(%)	
negative	6004 (74.5%)
positive	471 (5.8%)
missing	1586 (19.7%)
HBsAg, n(%)	
negative	6431 (79.8%)
positive	14 (0.2%)
missing	1616 (20.0%)
Nadir CD4+, cell/mmc, median (IQR)	346 (160, 508)
CD4+ at BL, cell/mmc, median (IQR)	353 (163, 532)
Viral load, log10 copies/mL, median (IQR)	4.73 (4.12, 5.31)
Time from HIV diagnosis to date of starting ART, months, median (IQR)	1 (1, 6)
Calendar year of BL, median (IQR)	2016 (2015, 2018)
Not Italian nationality, n (%)	4268 (52.9%)
Anchor drug started	
NNRTI	1506 (19%)
PI	1717 (21%)
INSTI	4838 (60%)

Notes: IQR, interquartile range; IVDU, intravenous drug users; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.

Table 2: Characteristics of PLWH with and without advanced HIV disease

	Advanced HIV disease (n=2402)	Not Advanced HIV disease (n=5659)	P-value
Female gender, n (%)	518 (21.6%)	955 (16.9%)	<.001
Age, median (IQR)	44 (36, 53)	38 (30, 47)	<.001
Mode of HIV transmission, n(%)			<.001
IVDU	137 (5.8%)	349 (6.3%)	
Homosexual contacts	836 (35.2%)	3075 (55.1%)	
Heterosexual contacts	1201 (50.0%)	1835 (32.4%)	
Other/unknown	198 (8.3%)	322 (5.8%)	
AIDS diagnosis, n(%)	818 (34.1%)	0 (0%)	<.001
HCV Ab, n(%)			0.244
negative	1759 (73.2%)	4245 (75.0%)	
positive	147 (6.1%)	324 (5.7%)	
missing	496 (20.6%)	1090 (19.3%)	
HBsAg, n(%)			0.091
negative	1938 (80.7%)	4493 (79.4%)	
positive	1 (0.0%)	13 (0.2%)	
missing	463 (19.3%)	1153 (20.4%)	
Nadir CD4+, cell/mmc, median (IQR)	76 (30, 142)	436 (325, 578)	<0.001
CD4+ at BL, cell/mmc, median (IQR)	77 (31, 143)	452 (336, 609)	<0.001
Viral load, log10 copies/mL, median (IQR)	5.34 (4.84, 5.81)	4.51 (3.90, 4.99)	<0.001
Time from HIV diagnosis to date of starting ART, months, median (IQR)	1 (0, 1)	2 (1, 14)	<0.001
Calendar year of BL, median (IQR)	2017 (2015, 2019)	2016 (2015, 2018)	<0.001
Not Italian nationality, n (%)	1487 (61.9%)	2781 (49.1%)	<.001
Anchor drug started			<.001
NNRTI	67 (2.8%)	1439 (25.4%)	
PI	751 (31.3%)	966 (17.1%)	
INSTI	1584 (65.9%)	3254 (57.5%)	

Notes: IQR, interquartile range; IVDU, intravenous drug users; ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.

Table 3: PLWH characteristics overall and according to difficult-to-treat definition in the matched set.

	Difficult-to-treat (n=286)	Not difficult-to-treat (n=572)	P-value	Overall population (n=858)
Female gender, n (%)	53 (18.5%)	93 (16.3%)	0.404	146 (17.0%)
Age, median (IQR)	44 (36, 53)	38 (30, 47)	<.001	40 (31, 49)
Mode of HIV transmission, n(%)				
IVDU	18 (6.4%)	35 (6.2%)	0.487	53 (6.2%)
Homosexual contacts	129 (45.6%)	289 (50.9%)		418 (49.1%)
Heterosexual contacts	120 (42.0%)	211 (36.9%)		331 (38.6%)
Other/unknown	16 (5.7%)	33 (5.8%)		49 (5.8%)
AIDS diagnosis, n(%)	69 (24.1%)	87 (15.2%)	0.001	156 (18.2%)
HCV Ab, n(%)				
negative	234 (81.8%)	475 (83.0%)	0.043	709 (82.6%)
positive	29 (10.1%)	34 (5.9%)		63 (7.3%)
missing	23 (8.0%)	63 (11.0%)		86 (10.0%)
HBsAg, n(%)				
negative	254 (88.8%)	489 (85.5%)	0.348	743 (86.6%)
positive	2 (0.7%)	8 (1.4%)		10 (1.2%)
missing	30 (10.5%)	75 (13.1%)		105 (12.2%)
Nadir CD4+, cell/mmc, median (IQR)	260 (81, 425)	303 (122, 458)	0.022	290 (109, 453)
CD4+ at index date, cell/mmc, median (IQR)	571 (302, 823)	606 (406, 841)	0.089	597 (379, 838)
Viral load at index date, log10 copies/mL, median (IQR)	1.38 (0.00, 1.81)	1.30 (0.00, 1.59)	<0.001	1.30 (0.00, 1.60)
Time from HIV diagnosis to index date, months, median (IQR)	41 (20, 71)	43 (21, 75)	0.585	42 (20, 75)
Calendar year of BL, median (IQR)	2017 (2016, 2019)	2018 (2017, 2019)	<0.001	2018 (2017, 2019)
Not Italian nationality, n (%)	78 (27.3%)	162 (28.3%)	0.747	240 (28.0%)
EGFR (CKD- Epi formula) < 60 ml/min/1.73m2	25 (8.7%)	19 (3.3%)	<.001	44 (5.1%)
Diabetes	15 (5.2%)	17 (3.0%)	0.098	32 (3.7%)
Smoking status, n (%)			0.614	
No	123 (43.0%)	262 (45.8%)		385 (44.9%)
Yes	107 (37.4%)	212 (37.1%)		319 (37.2%)
Unknown	56 (19.6%)	98 (17.1%)		154 (17.9%)
Total cholesterol, mg/dL Median (IQR)	182 (153, 219)	181 (155, 208)	0.412	181 (155, 213)
HDL cholesterol, mg/dL Median (IQR)	45 (37, 55)	46 (37, 54)	0.831	45 (37, 54)

Use of statins, n (%)	35 (12.2%)	39 (6.8%)	0.008	74 (8.6%)
Education, n (%)			0.108	
Primary school	10 (3.5%)	12 (2.1%)		22 (2.6%)
Secondary school	57 (19.9%)	83 (14.5%)		140 (16.3%)
College	90 (31.5%)	167 (29.2%)		257 (30.0%)
University	42 (14.7%)	84 (14.7%)		126 (14.7%)
Other/Unknown	87 (30.4%)	226 (39.5%)		313 (36.5%)
Anchor drug started				
NNRTI	45 (15.7%)	140 (24.5%)	0.049	185 (21.6%)
PI	61 (21.3%)	96 (16.8%)		157 (18.3%)
INSTI	187 (65.4%)	349 (61.0%)		536 (62.5%)

Notes: IQR, interquartile range; IVDU, intravenous drug users; Index date: date in which the subject fulfils DTT definition; EGFR, Estimated Glomerular Filtration Rate; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.