Predictors of virological failure and time to viral suppression of first line integrase inhibitor based antiretroviral treatment

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40-word summary: Integrase strand transfer inhibitor-based therapies are effective first-line treatments of HIV-infection. Among 1419 patients, we have identified a high baseline viral load, low CD4 cell counts and an AIDS defining event before treatment initiation as predictors for treatment failure.

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Abstract

Background

Integrase strand transfer inhibitors (InSTIs) are recommended for first-line treatment of HIV-infection. We identified risk factors, including baseline minor InSTI resistance mutations, for treatment failure of InSTI-based regimens.

Methods

We studied time to treatment failure and time to viral suppression among 1419 drug-naive patients in the Swiss HIV Cohort Study.

We performed Cox regression models adjusted for demographic factors, baseline HIV RNA/CD4 cell counts, AIDS defining events and the type of InSTI.

In 646 patients with a baseline genotypic resistance test of the integrase, we studied the impact of minor integrase resistance mutations.

Results

We observed 121 virological failures during 18'447 person-years of follow-up. A baseline viral load ≥100'000 cps/mL (multivariable Hazard Ratio (mHR): 2.2, 95% CI: 1.3-3.6) and an AIDS defining event (mHR: 1.8, 95% CI: 1.1-3.0) were associated with treatment failure. CD4 counts between 200-500 cells/µL (mHR: 0.5, 95% CI: 0.3-0.8) and >500 cells/µL (mHR: 0.4, 95% CI: 0.2-0.7) were protective. Median [IQR] time to viral suppression was 50 [29,107] days. Time to suppression was shorter in lower viral load strata (mHR: 0.7, 95% CI: 0.6-0.8) and in dolutegravir-based therapy (mHR: 1.2, 95% CI: 1.0-1.4). Minor resistance mutations were found at baseline in 104/646 (16%) patients with no effect on treatment outcome.

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Conclusion

Among drug-naïve HIV-infected individuals treated with InSTI-based regimens, factors associated with treatment failure, in particular high viral load and low CD4 counts remain similar to older treatments. Minor InSTI resistance mutations had no impact in this large observational cohort.

Keywords: HIV, integrase strand transfer inhibitors, drug resistance, minor drug resistance mutations, treatment outcome

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Introduction

Integrase strand transfer inhibitor (InSTI)-based antiretroviral therapies are recommended for first-line treatment of most individuals infected with HIV-1 [1]. These potent combinations achieve sustained virological suppression and treatment failures are rare. Nonetheless, it is important to identify patients with increased risk for therapy failure as it jeopardizes the long-term treatment success and facilitates the emergence of drug resistance.

Failure of potent antiretroviral therapy is associated with several factors [2, 3]. In phase III trials, InSTI-based regimens have proven to be at least equally potent as or superior to other antiretroviral regimens [4-7]. The second generation InSTIs dolutegravir (DTG) and bictegravir (BIC), have a high potency even among individuals with a high viral load or low CD4 count at baseline [5, 8-10]. Phase III trials showed that baseline plasma HIV-RNA did not affect DTG-based therapy, while for raltegravir the impact of baseline viral load is discussed controversially [8, 11]. Smaller clinical studies that encompassed drug naïve and treatment-experienced patients, suggested that older age [12, 13], lack of adherence [14], origin from a high prevalence country, injection drug use and a low CD4 count at baseline [13] increased the risk for failure of InSTI- based therapy.

Another possible reason for the failure of antiretroviral treatment is the presence of pretreatment drug resistance associated mutations (RAMs), mostly transmitted drug resistance mutations TDRs) [2, 15, 16]. Although large studies did not find a correlation between virological failure in drug naïve individuals on InSTIs and the presence of TDRs [17, 18], some case reports suggest otherwise [19-21]. In European studies, less than 1% of drug naïve or recently infected individuals had major InSTI-mutations [22-26]. However, 2% to 17.3% had minor RAMs that often occur as polymorphisms of the HIV-wild type [22-26].

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Although they are considered to have little effect on InSTI susceptibility, there is lack of research to which extent they affect InSTI-based treatments [27-29].

The objective of this study is to identify risk factors for treatment failure of InSTI-based combined antiretroviral treatment (cART) in drug naïve HIV-1 infected individuals from the Swiss HIV Cohort Study (SHCS) and to assess the impact of minor InSTI RAMs on treatment outcome.

Methods

Study population/study design

We used data from the Swiss HIV Cohorts Study (SHCS) and the SHCS drug resistance database. The SHCS is a nationwide, multicenter longitudinal study established in 1988. The SHCS population is highly representative as it encompasses 75% of all the patients receiving antiretroviral treatment and 69% of the people with AIDS living in Switzerland. The drug resistance database includes all genotypic resistance tests (GRT) conducted in Switzerland and is linked to the clinical database [30]. The SHCS continuously enrolls HIV infected individuals aged 18 years or older independent of the stage and severity of the disease. Data is collected using a structured form at registration and on the semi-annual visits. The ethical committees of all participating institutions have approved the SHCS and written informed consent is obtained from all participants [30, 31].

Patient selection

We included drug-naïve HIV infected individuals from the SHCS that started an InSTI based antiretroviral treatment between 1 January 2006 and 31 December 2018. If the HIV-RNA-load was not measured in a patient after treatment start, that patients was excluded.

To analyze pretreatment resistance patterns, we identified patients who received a baseline GRT including the integrase using the SHCS drug resistance database.

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Definition of drug resistance mutations

Minor and major RAMs were defined based on the IAS-USA recommendations [36] and the Stanford University HIV Drug Resistance Database Version 8.9-1 (https://hivdb.stanford.edu). The following mutations from the IAS-USA recommendations were included; *major mutations*: T66I, E92Q, G118R, F121Y, G140R, Y143CHR, S147G, Q148HKR, N155H, R263K; *minor mutations*: T66AK, L74M, E92G, T97A, E138AKT, G140ACS, S153FY.

The following RAMs from the HIV Drug Resistance Database with a HIVdb score ≥30 were also defined as major mutations: E92V, Y143AGK, Q146P, V151L, and N155S. Mutations with a penalty score ≥10 and <30 were in addition to the IAS-USA recommendations included as minor mutations: H51Y, L74FI, E95K, P142T, Q148N, V151I, N155D, E157Q, G163KR, S230R, D232N.

Outcome

Our primary endpoints were time to viral suppression and time to virological failure. The follow-up time was defined as the period from the start of the InSTI based regimen until the end of InSTI therapy. Data was censored at the last visit, the end of InSTI-based therapy or at the patient's death. Data was not censored when the patient changed from one InSTI to another or when NRTIs background ART was modified/adapted.

Time to viral suppression was defined as the time from treatment begin to the first viral load <50 HIV-RNA copies/mL. Virological failure was defined as follows:

(1) Two consecutive RNA values >50 copies/mL after at least 180 days of continuous treatment

(2) One value >50 copies/mL after 180 days of treatment, followed by treatment change to another drug class or

(3) No viral suppression < 50 copies/mL after more than 180 days of treatment.

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Statistical analysis

We used Stata/SE version 15.1 for the statistical analysis. We performed univariable and multivariable Cox regressions to identify the effect of baseline characteristics on time to viral suppression and time to virological failure. The following factors were considered: age at therapy start, ethnicity, transmission risk group, HIV-RNA load, CD4 cell count, history of an AIDS defining event at or before treatment start, the type of InSTI administered and the presence of InSTI RAMs. Another factor included was the financial independence of the individual: patients whose salary generated more than 50% of their income were considered more financially independent than those who predominantly relied on other sources for their income such as unemployment benefits. In the multivariable model, factors with a p-value <0.1 in the univariable model and previously described risk factors for treatment outcome (age at treatment start, ethnicity, transmission risk group, the type of InSTI) were included. Continuous variables were categorized if likelihood ratio tests showed significant departure from linearity. Levels of self-reported adherence between patients that experienced virological failure and those without treatment failure were compared using the Pearson chi2-test. Self-reported adherence is assessed every 6 months, the data closest to the treatment failure or censoring was chosen [32]. We tested the proportional hazard assumption by calculating Schönfeld residuals and by using graphical procedures. No violations of the proportionality hazard assumption were detected. The level of significance was considered at p-value <0.05. To assess whether our results differed by the administered InSTI, we performed additional analyses where we stratified by the type of InSTI. Additionally, we studied the subgroup of patients with a baseline viral load >100'000 copies/mL in detail.

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Results

Study population

We identified 1'472 HIV-1 infected drug naive individuals who started an InSTI based cART (**Figure 1**). We excluded 4 (0.3%) patients, as follow-up data was not available and 49 (3%) patients because of missing HIV-RNA values. Finally, 1'419 out of 1'472 (96%) patients were included to study the time to viral suppression and to virological failure. The InSTI most often administered was DTG (n=925, 65%), followed by EVG (n=281, 20%) and RTG (n=213, 15%). None of the participants received BIC, which was introduced in Switzerland only in 2018. **Table 1** shows the baseline characteristics of our study population. Of the 1,419 individuals in our study, 646 (45%) had a baseline GRT including the integrase performed and 378 (27%) had a baseline viral load ≥100'000 copies/mL.

Time to virological failure

During the 18'447-person-years of follow-up, we observed 121 virological failures. Twenty-three of 121 patients had a viral load >1000 HIV-RNA copies/mL at the time of virological failure. Nine of 121 patients did not reach viral suppression within 180 days and all others failed treatment after having achieved viral suppression. **Figure 2** and in the Supplementary Table 1 summarize the results of the multivariable analysis of time to virological failure. A hazard ratio (HR) >1 implies more virological failures in the analyzed group compared to the reference group.

Among patients with treatment failure a report of missing at least one dose of ART in the past month was more frequent (9 out of 121 (7.4%) vs 41 out of 1'298 (3.6%), p-exact=0.049) than among non-failing patients.

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A CD4 cell count at baseline above 200 cells/µL was associated with fewer failures (<200/ul: Reference, 200-500/µL: mHR 0.5, 95% CI 0.3-0.8; >500/µL: mHR: 0.4, 95% CI 0.2-0.7) (**Figure 3)**. An HIV-RNA load ≥100'000 copies/mL was associated with failures (mHR: 2.2, 95% CI 1.3-3.6) as compared to a viral load <10'000 copies/mL (**Figure 3**). In addition, patients that experienced an AIDS defining event had an increased chance for failure (mHR: 1.8, 95% CI 1.1-3.0). The two most common AIDS defining events were pneumocystis pneumonia and esophageal candidiasis, which occurred in 45 (3.2%) and 29 (2.0%) of 1419 patients, respectively.

A sub-analysis showed that the results were comparable when the data was censored at the change of any substance in the treatment regimen, not only at the end of InSTI-based therapy (Supplementary Table 2). The results were similar when the Cox regression analysis was restricted to patients on DTG (Supplementary Table 3), baseline HIV-RNA ≥100'000 copies/mL was associated with virological failure (mHR: 2.2, 95% CI: 1.1-4.4) while a CD4 count >200 was protective (200-500 cells/µL mHR: 0.4, 95% CI:0.2-0.8, >500 cells/µL mHR: 0.4, 95% CI: 0.2-0.8).

In the sub-analysis that included patients with a baseline viral load ≥100'000 copies/mL (Supplementary Table 4), only the CD4 count at baseline affected treatment outcome. Patients with at least 200 CD4 cells/µL had a lower chance for failure than those with < 200 cells/µL (200-500 cells/µL: mHR 0.3, 95% CI: 0.2-0.6, >500 cells/µL: 0.2, 95% CI: 0.05-0.6)

Time to viral suppression

Median [IQR] time to viral suppression was 50 [29,107] days and the median time between two HIV-RNA measurements in the first year was 10.4 [8.52, 12.96] weeks. **Figure 2** and Supplementary Table 1 show the results of the analysis for time to viral suppression . A

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hazard ratio (HR)>1 implies a shorter time to viral suppression in the analyzed group compared to the reference group.

A viral load ≥10'000 copies/mL at baseline was associated with longer time to suppression compared to a viral load <10'000 copies/mL (10'000-99'999 copies/mL: mHR: 0.7, 95% CI: 0.6-0.8, ≥100'000 copies/mL: mHR: 0.5, 95% CI: 0.4-0.6) (**Figure 3**). Patients on a first-line therapy with DTG (mHR: 1.2, 95% CI: 1.0-1.4) and financially independent patients had a shorter time to viral suppression (mHR: 1.6, 95% CI 1.1-2.4).

Among patients with an HIV-RNA load ≥100'000 copies/mL at baseline, time to viral suppression was shorter with a baseline CD4 count >500/µL (mHR: 1.5, 95% CI: 1.0-2.2). Time to suppression was also shorter under a first-line therapy with DTG (mHR: 1.7, 95% CI: 1.2-2.3) than under therapy with other InSTIs.

In the sub-analysis that included only patients on DTG time to viral suppression was increased in individuals with a viral load ≥10'000 copies/ml (10'000-99'999 copies/mL mHR: 0.8, 95% CI: 0.7-0.9, ≥100'000 copies/mL mHR: 0.6, 95% CI 0.5-0.7) and decreased in financially independent patients (mHR: 1.7, 95% CI:1.1-2.6) .

Across the analyses, other demographic factors and the mode of transmission were not significantly associated with the virologic outcome.

Impact of InSTI resistance associated minor mutations at baseline

Among 646 patients with a pretreatment GRT, no one had major mutations. We detected minor mutations in 104 (16%) patients. The most common mutations were L74I (n=65, 8.55%), V151I (n=14, 1.89%) and E157Q (n=14, 1.60%). All other RAMs were present in less than 1.6% of the cases (see Supplementary Table 5). The highest prevalence of L74I was found among subtype A (14 of 24 patients, 41.2%) and subtype G (5 of 12 patients, 41.7%)

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infections. L74I occurred among 30 of 364 (8.2%) of subtype B infections. We did not observe an effect of the presence of minor InSTI RAM on both therapeutic outcomes studied (Time to failure: mHR: 0.9 , 95% CI 0.4-1.9, Time to suppression: mHR: 1.0, 95% CI 0.8-1.2) (**Figure 4**). Most of the other risk factors found to correlate with the outcome in the primary analysis affected the therapeutic outcome in the subgroup (Supplementary Table 6).

Discussion

To our knowledge, this is the first observational study to analyze the risk factors for failing InSTI-based therapy in drug naïve HIV-1 infected individuals, including minor integrase RAMs.

In general, response to InSTI-based first-line treatment of drug naive patients was excellent. Nevertheless, a high viral load and/or a low CD4 count at baseline was associated with more treatment failures and lower time to suppression. Among patients presenting with a baseline viral load ≥10'000, DTG therapy showed a superior activity in decreasing the time to viral suppression than other InSTIs studied. The superiority of DTG over first generation InSTIs and other antiretroviral drugs in the treatment of drug naïve patients with a high viral load was shown by various randomized controlled studies [4-7]. However, contrary to the findings in those trials, high viral load / low CD4 count at baseline also jeopardized treatment success among participants on DTG in our study. These findings are in line with the NAMSAL and ADVANCE trials, which found evidence that treatment success on DTG is impaired among patients with a baseline viral >100'000 copies/mL [33, 34]. Transmitted and acquired NNRTI drug resistance are important drivers to change to DTG in resource limited settings [35]. DTG-based regimen are highly potent and cost-effective treatment options, although weight gain, in particular, in women of African origin under DTG even more aggravated with TAF based regimens was described [34, 36]. Nevertheless, altogether in resource limited settings

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where frequent RNA monitoring is difficult, a first-line therapy with DTG might be safer and more reliable in patients presenting with high baseline viral loads.

The presence of minor InSTI RAMs at baseline was not associated with worse outcome. Many of the minor RAMs we detected were present as polymorphisms even before InSTIs were introduced into the clinical routine in Europe [37]. L74I and V151I are polymorphic mutations. . L74I was most common among subtype A and G infections [38].E157Q is a common polymorphic mutation. Other large randomized controlled trials also found that InSTIs are effective among patients carrying E157Q mutant viruses [33]. All the other mutations we found, including T97A, are known to decrease InSTI susceptibility in combination with other mutations [39], which were not present in our patients. Hence, although pretreatment minor InSTI resistance associated mutations are common among drug naïve HIV-1 infected individuals in Switzerland, it is reassuring that their presence does not affect treatment outcome.

Across all analyses, time to viral suppression was shorter if patients were financially independent. There was a trend suggesting that older age at treatment start also decreased the risk for failure and the time to suppression. These findings might be explained by better adherence in patients with more favorable social conditions and in older patients [40]. In the absence of RAMs, non-adherence to therapy has been shown to be the most common reason for treatment failure [3]. The proportion of patients reporting decreased adherence in our study was also significantly higher in the group that experienced failure. These results show that disparities arising from demographic and economic factors in conjunction with presumably lower adherence remain relevant even in a cohort that is subject to regular follow-up, is based in a high-income country with universal health care access and participants being treated with the most potent drug classes.

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Limitations

Although the SHCS is highly representative and a considerable number of drug naïve participants had an integrase resistance test available, the number of treatment failures was small, which may impair the statistical power. We used a cut-off of 50 copies of RNA/mL to define a virological failure; the number of events was too small for multivariable analyses when we chose a cut-off of 200 or 500 RNA copies/mL. Furthermore, we had predominantly male Caucasian participants limiting the generalization of these findings to a more diverse group.

Conclusion

Many of the risk factors commonly associated with therapeutic failure such as the severity of immunodeficiency, stage of the disease and financial situation were still relevant despite the potency of InSTIs. The chance of virological failure was consistently associated with the baseline viral load and the CD4 count, even in patients on DTG.

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Author contributions. A.P., A. U. S., and H. F. G. conceived and designed the study. A.P. and A. U. S. performed the analysis. A. U. S., J. B., S. Y., T. K., M. P., M. S., H. F., A. C., P. S., M. C., E. B., and H. F. G. collected and contributed data. A.P., A. S., and H. F. G. wrote the manuscript. All authors read and approved the final manuscript.

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Members of the Swiss HIV Cohort Study

The members of the SHCS include the following: Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C, Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

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Tables

Table 1: Baseline characteristics

Baseline characteristics	All patients n=1'419	Patients with GRT n=646	No minor InSTI mutation n= 542	≥1 minor InSTI mutation n= 104
Median [IQR] age at start of cART	39 [31,49]	38 [30,49]	38 [30,49]	37 [31,47.5]
Sex (%)				
Male	1,176 (82.9)	539 (83.4)	457 (84.3)	82 (78.9)
Female	243 (17.1)	107 (16.6)	85 (15.7)	22 (21.2)
Ethnicity (%)				
White	1,096 (77.2)	508 (78.6)	425 (78.4)	83 (79.8)
Black	168 (11.8)	63 (9.8)	47 (8.7)	16 (15.4)
Other	155 (10.9)	75 (11.6)	70 (12.9)	5 (4.8)
Transmission category (%)				
MSM	842 (59.4)	402 (62.2)	335 (61.8)	67 (64.4)
Heterosexual males	241 (17.0)	99 (15.3)	89 (16.4)	10 (9.6)
Heterosexual females	195(13.7)	91 (14.1)	71 (13.1)	20 (19.2)
intravenous drug use	59 (4.2)	54 (8.4)	47 (8.7)	7 (6.73)
Other	81 (5.7)			
Subtype (%)				
B	364 (25.7)	364 (56.4)	312 (57.6)	52 (50.0)
non-B	253 (17.8)	253 (39.2)	204 (37.6)	49 (47.1)
n/a	802 (56.5)	29 (4.5)	26 (4.8)	3 (2.9)
HIV-RNA (%)				
< 10'000 copies/mL	437 (30.8)	194 (30.0)	161 (29.7)	33 (31.7)
10'000-99'999 copies/mL	604 (42.6)	260 (40.3)	218 (40.2)	42 (40.4)
≥100'000 copies/mL	378 (26.6)	192 (29.7)	163 (30.1)	29 (27.9)
Log median [IQR] HIV-RNA cps/mL	4.5 [3.5,5.1]	4.5 [3.7,5.2]		
CD4 cell count (%)				
<200 cells/µL	281 (19.8)	135 (20.9)	106 (19.6)	29 (27.9)
200-500 cells/µL	724 (51.0)	306 (47.4)	267 (49.3)	39 (37.5)
>500 cells/µL	414 (29.2)	205 (31.7)	169 (31.2)	36 (34.6)
Median [IQR] CD4 cells/µL	381 [226,549]	391[230,551]		
AIDS defining event at baseline (%)	125 (8.8)	43 (6.7)	35 (6.5)	8 (7.7)

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InSTI administered (%)					
	RGV	213 (15.0)	67 (10.4)	54 (10.0)	13 (12.5)
	EVG	281 (19.8)	124 (19.2)	108 (19.9)	16 (15.4)
	DTG	925 (65.2)	455 (70.4)	380 (70.1)	75 (72.1)
ART combinations (%)					
	3TC+ABC+DTG	460 (32.4)	227 (35.1)	198 (36.5)	29 (27.9)
	DTG+ETC+TDF	259 (18.3)	150 (23.2)	120 (22.1)	30 (28.9)
	DTG+ETC+TAF	143 (10.8)	42 (6.5)	34 (6.3)	8 (7.7)
	COB+ETC+EVG+TAF	130 (9.2)	53 (8.2)	47 (8.7)	6 (5.8)
	COB+ETC+EVG+TDF	123 (8.7)	59 (9.1)	50 (9.2)	9 (8.7)
	ETC+RGV+TDF	126 (8.9)	37 (5.7)	30 (5.5)	7 (6.7)
	Other drug combinations	178 (11.8)	78 (12.1)	63 (11.6)	15 (14.4)

Abbreviations: GRT=,genotypic resistance test, cART= combined antiretroviral treatment, MSM=Men who have sex with men, RGV=Raltegravir, EVG=Elvitegravir, DTG=Dolutegravir, 3TC=Lamivudine, ABC=Abacavir, ETC=Emtricitabin, TDF=Tenofovir, TAF=Tenofovir alafenamid, COB=cobicistat.

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Figure legends

Figure 1: Flow diagram of study inclusion.

Abbreviations: cART, combined antiretroviral therapy; GRT, genotypic resistance test

Figure 2: Multivariable Cox regression. Predictors of virological failure (**A**) and time to viral suppression (**B**) among drug-naïve HIV-infected individuals (n=1'419)

Abbreviations: RGV=Raltegravir, EVG=Elvitegravir, DTG=Dolutegravir, InSTI=Integrase strand transfer inhibitor, BL=baseline, MSM=men having sex with men, HR=multivariable hazard ratio

Figure 3: Kaplan –Meier curves with time to virological failure and time to suppression comparing patients by the CD4 cell count (A and B) and HIV-1 RNA copies/mL (C and D) at baseline.

Figure 4: Kaplan –Meier curves with time to virological failure and time to suppression comparing patients with and without InSTI resistance associated mutations.

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Figure 1

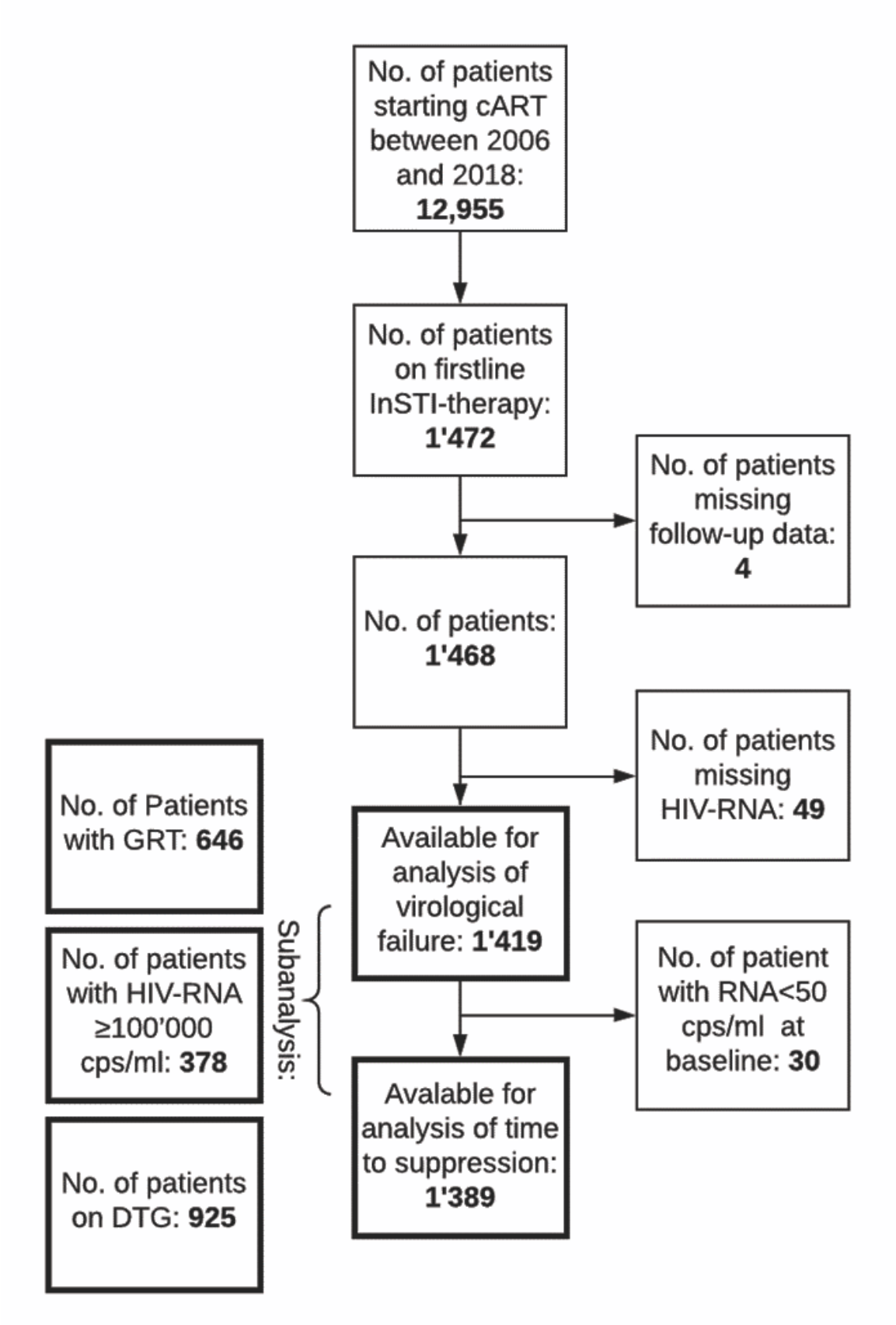

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Figure 2

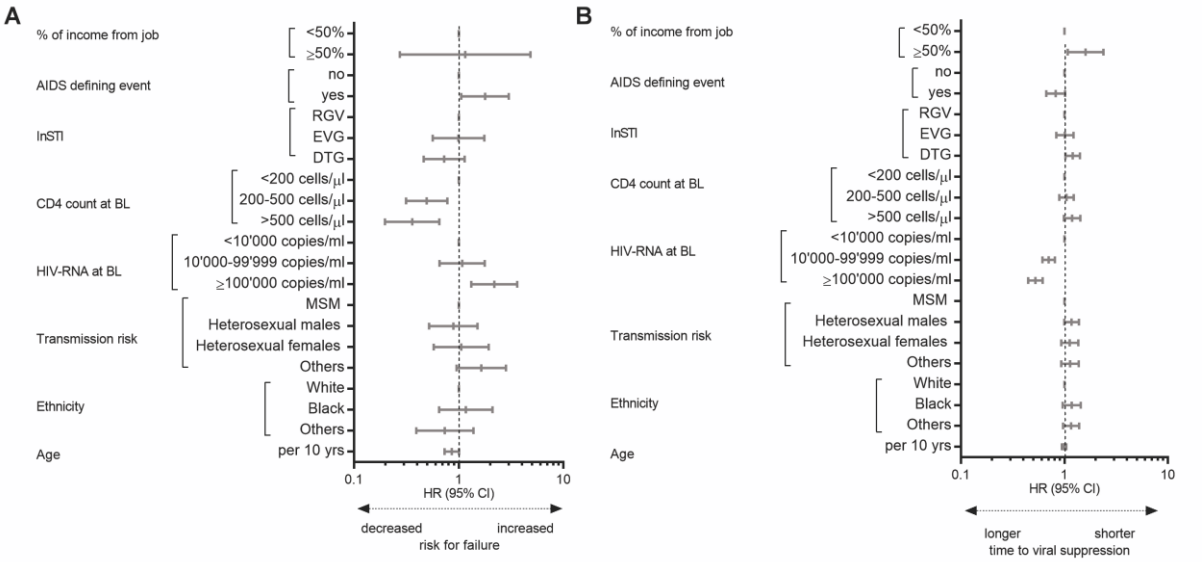

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Figure 3

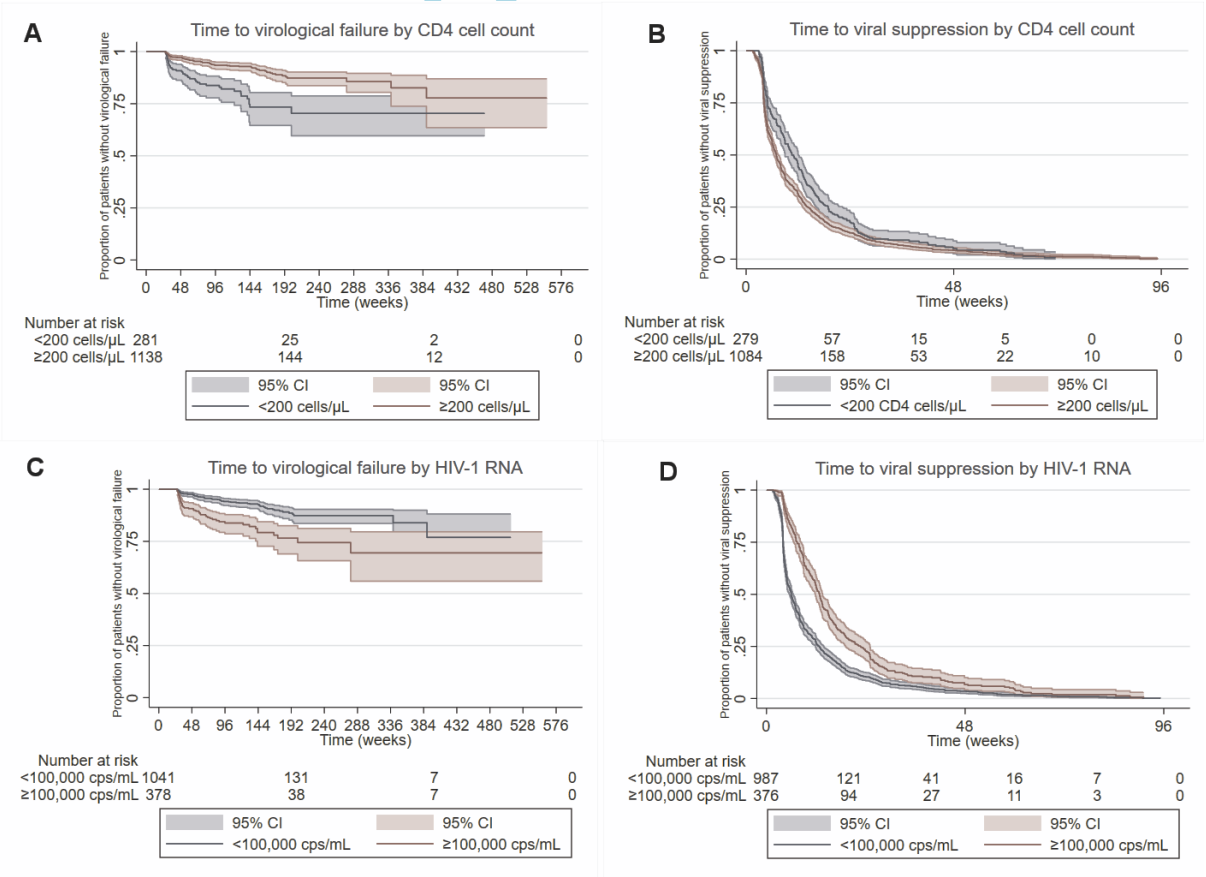

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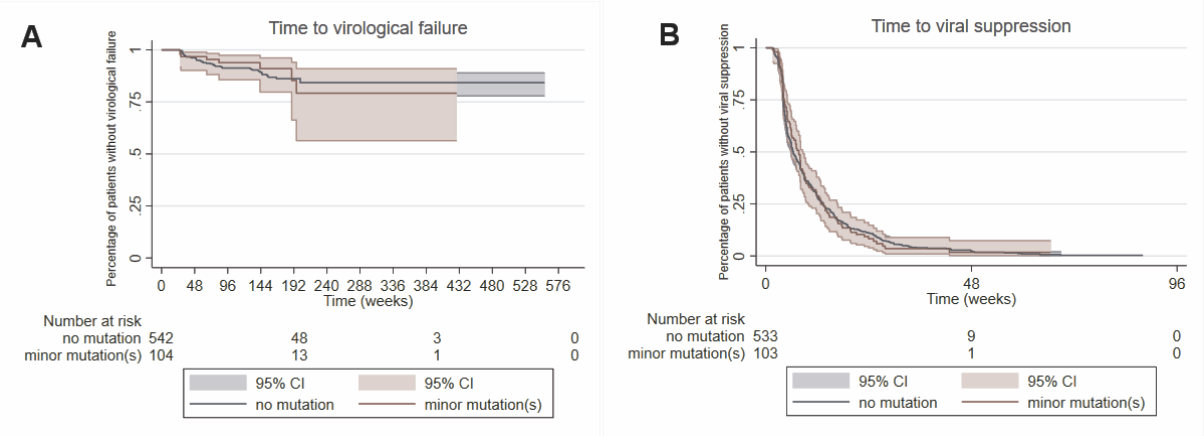
Figure 4



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