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Virologic outcomes among adults with HIV using integrase inhibitor-based antiretroviral therapy

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Conflicts of interest

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Abstract

Background: Integrase strand transfer inhibitor (InSTI)-based regimens have been recommended as first-line antiretroviral therapy (ART) for adults with HIV. But data on long-term effects of InSTI-based regimens on virologic outcomes remain limited. Here we examined whether InSTI improved long-term virologic outcomes compared with efavirenz (EFV).

Methods: We included adults from the North American AIDS Cohort Collaboration on Research and Design who initiated their first ART regimen containing either InSTI or EFV between 2009 and 2016. We estimated differences in the proportion virologically suppressed up to 7 years of follow-up in observational intention-to-treat and per-protocol analyses.

Results: Of 15 318 participants, 5519 (36%) initiated an InSTI-based regimen and 9799 (64%) initiated the EFV-based regimen. In observational intention-to-treat analysis, 81.3% of patients in the InSTI group and 67.3% in the EFV group experienced virologic suppression at 3 months after ART initiation, corresponding to a difference of 14.0% (95% CI 12.4-15.6). At 1 year after ART initiation, the proportion virologically suppressed was 89.5% in the InSTI group and 90.2% in the EFV group, corresponding to a difference of −0.7% (95% CI −2.1 to 0.8). At 7 years, the proportion virologically suppressed was 94.5% in the InSTI group and 92.5% in the EFV group, corresponding to a difference of 2.0% (95% CI −7.3 to 11.3). The observational per-protocol results were similar to intention-to-treat analyses.

Conclusions: Although InSTI-based initial ART regimens had more rapid virologic response than EFV-based regimens, the long-term virologic effect was similar. Our findings may inform guidelines regarding preferred initial regimens for HIV treatment.

Keywords

antiretroviral therapy; efavirenz; integrase strand transfer inhibitors; treatment-naive adults with HIV; trial emulation; virologic suppression

Introduction

Modern antiretroviral therapy (ART) is highly effective in suppressing plasma viremia (i.e. HIV RNA viral load), which is a well recognized biomarker for HIV prognosis and a key component of the U=U (Undetectable = Untransmittable) concept for ending the HIV epidemic [1]. Integrase strand transfer inhibitors (InSTI)-based regimens have

been recommended as first-line ART for adults since 2015 [2,3]. Randomized trials have demonstrated that patients initiating InSTI-based regimens experienced more rapid control of plasma viremia, as well as better tolerability, compared with those initiating other regimens [4-11]. However, these trials had limited follow-up periods (48–96 weeks). Randomized evidence of long-term effectiveness of InSTI-based regimens on virologic outcomes remains unavailable, which is particularly relevant as life expectancy continues to increase, although not equitably by race, ethnicity, sex, and HIV acquisition risk factor [12].

Using observational data from a large collaboration of cohort studies in the United States and Canada, we aimed to replicate and extend the randomized evidence, and examine whether those initiating a regimen of InSTI with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), and emtricitabine (FTC) improved long-term plasma HIV viremia when compared with those initiating a regimen of efavirenz (EFV an active comparator agent that was considered the gold standard for HIV treatment for several years) with the same nucleoside reverse transcriptase inhibitor backbone, across up to a 7-year follow-up period after ART initiation.

Methods

Study design

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is the largest multisite collaboration of clinical and interval HIV cohorts in the United States and Canada. Details on this collaboration have been published previously [13]. Briefly, the NA-ACCORD consists of more than 25 cohorts and 200 clinical care sites that prospectively collect data on more than 180 000 adults with HIV. Cohort demographic, medication, laboratory, diagnostic, and vital status data are securely transferred annually to the central Data Management Core (University of Washington, Seattle, Washington, USA), where the data undergo quality control and are harmonized across cohorts for analyses by the Epidemiology/Biostatistics Core (Johns Hopkins University, Baltimore, Maryland, USA). The human subjects research activities of the NA-ACCORD and each participating cohort have been approved by their respective local Institutional review boards, and the University of North Carolina School of Medicine.

Study population and eligibility criteria

In this study, we included people with HIV who were ART-naive adults (≥ 18 years old) and initiated an ART regimen consisting of two nucleoside reverse transcriptase inhibitors (i.e. TDF or TAF, and FTC) and either InSTI [i.e. raltegravir (RAL), dolutegravir (DTG), elvitegravir/cobicstat (EVG/COBI)] or EFV while in follow-up between July 2009 and December 2016 from clinical cohorts in the NA-ACCORD. The follow-up began in 2009, rather than 2007 when RAL was first approved by the US Food and Drug Administration as RAL was recommended only for those with drug resistance from 2007 to 2009. Patients excluded were: those having prior ART experience; those with baseline HIV virologic suppression (HIV RNA viral load <200 copies/ml) that was measured within 90 days before to 7 days after ART initiation (potentially indicative of an undocumented ART exposure); those without any measurements of HIV RNA viral load after ART initiation. Study

population was restricted to ART-naive patients to avoid possible selection bias because of the inclusion of prevalent users, and to mimic a randomized trial where treatment-naive patients were randomly assigned to either the InSTI-based regimen or the active comparator EFV-based regimen via adjusting for baseline confounders measured in the NA-ACCORD.

Outcome measurements

The primary outcome was virologic suppression (HIV RNA viral load <200 copies/ml) as documented by repeated measurements during the follow-up period after ART initiation. The timing and frequency of observed laboratory measurements for HIV RNA viral load since ART initiation, a function of healthcare seeking behavior and completed clinical visits with a provider, varied across cohorts and study participants. To harmonize data, we categorized time-updated HIV RNA viral load into 3-month intervals. If there were multiple HIV RNA measurements within a 3-month interval, an average of these measurements was calculated and used. If there were no HIV RNA measurements within a 3-month interval, this interval would have missing outcomes on virologic suppression.

Covariates

Baseline covariates were selected that were potential confounders for the effect of ART initiation on the virologic outcome. Age, sex, race, ethnicity, and HIV acquisition risk groups (individuals reporting previous injection drug use, MSM, heterosexual behavior, or other) were self-reported at enrolment into the NA-ACCORD. History of any clinical AIDS diagnosis, hepatitis C infection (having a positive antibody test, or a detectable RNA, or the presence of hepatitis C genotype test), hepatitis B infection (defined as positive surface antigen test, a positive e-antigen test, or a positive DNA test result), diagnosis of depression, diagnosis of anxiety, diabetes mellitus (a glycosylated hemoglobin ≥6.5%, diabetes-specific medication, or a diagnosis with a diabetes-related medication), treated hypertension (clinical diagnosis and prescription of antihypertensive medication), elevated total cholesterol (≥240mg/dl), and statin prescription were recorded at ART initiation [14,15]. BMI, which was captured at the closest date to ART initiation, was calculated as weight (kilograms) divided by height (meters) squared. Baseline $CD4^+$ cell count (cells/μl) was recorded at the closest date to ART initiation within the window from 90 days before to 7 days after ART initiation. Calendar year at ART initiation and cohort identities were captured as indicator variables.

Time-varying covariates, which were used when accounting for ART treatment changes, included time-updated $CD4^+$ cell count, new occurrences of clinical diseases or conditions (i.e. diabetes mellitus, depression, anxiety, treated hypertension, and elevated total cholesterol) after ART initiation.

Statistical analyses

Each participant was followed from date of ART initiation (study entry for individuals and time origin for our study design) until the date of the last HIV RNA measurement, or administrative end of follow-up (at 7 years, or 31 December 2016).

Missing baseline covariates and missing measurements of HIV RNA viral load (after harmonizing into 3-month intervals) were imputed 20 times using multiple imputation by chained equations (see eSupplement Section 1, http://links.lww.com/QAD/C296) [16,17]. The imputation model included all baseline covariates, treatment regimen variable, and the repeatedly measured outcomes for HIV RNA viral load [18]. Baseline $CD4^+$ cell count and repeatedly measured HIV viral load were log-transformed to avoid negative imputed values. Restricted quadratic splines with four knots at 5th, 35th, 65th, and 95th percentiles were then used to model continuous baseline covariates including age, BMI, and baseline $CD4^+$ cell count [19].

For primary analyses, we estimated the observational analog of the intention-to-treat effect of initiating an InSTI-based regimen compared with initiating the EFV-based regimen on virologic outcome (being virologically suppressed or not) regardless of ART treatment changes. For the intention-to-treat analysis, in each imputed dataset, inverse probability of treatment weights were constructed to account for potential baseline confounding. These weights were assigned to each participant to create the intention-to-treat population, and then applied to repeated observed measures of being HIV virologically suppressed or not within each participant. Using the weighted observed measures of being HIV virologically suppressed or not, we then calculated the proportion virologically suppressed over follow-up by treatment groups in the intention-to-treat population. For the intention-to-treat effect, we estimated the difference in the proportion virologically suppressed in the InSTI-based regimen group, versus the EFV-based regimen group, at 3 months, 6 months, 9 months, 1 year, 3 years, 5 years, and 7 years since ART initiation. The standard error for these differences was estimated from a nonparametric bootstrap with 200 random samples of participants with replacement for each imputed dataset [20]. Rubin's rules were applied to pool the results across imputed datasets to obtain the pooled differences with 95% confidence intervals (CIs).

We also estimated the observational analog of the per-protocol effect of initiating and remaining on an InSTI-based regimen compared with initiating and remaining on the EFV-based regimen on the virologic outcomes [21,22]. For the per-protocol analysis, participants were censored when they deviated from their initial treatment strategy (i.e. ART treatment change). ART treatment changes were those with ART treatment discontinuations and switches. Treatment changes that were considered allowable exceptions and hence were not censored included: a change from one InSTI-based regimen to another InSTI-based regimen (for instance, from a RAL-based regimen to a DTG-based regimen); a change from the EFV-based regimen to a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen of rilpivirine, TDF and FTC; and switch between TDF and TAF. Stabilized inverse probability of censoring weights were constructed by conditioning on time-varying covariates to account for treatment changes over follow-up [23,24]. The censoring weights were combined with inverse probability of treatment weights, and each participant was then weighted to create the per-protocol population. Using the weighted observed measures of being HIV virologically suppressed or not, we then calculated the proportion virologically suppressed over follow-up by treatment groups in the per-protocol population. For the per-protocol effect, we also estimated the difference in proportions virologically suppressed for initiating and remaining on an InSTI-based regimen versus initiating and remaining on

the EFV-based regimen at 3 months, 6 months, 9 months, 1 year, 3 years, 5 years, and 7 years since ART initiation.

In secondary analyses, we included imputed measures of being HIV virologically suppressed in the statistical analyses mentioned above, and estimated the difference in proportions virologically suppressed for intention-to-treat and per-protocol effects, in order to examine whether any selection bias occurred because of missing outcomes of being HIV virologically suppressed at some time intervals.

SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Results

A total of 15 318 participants in the NA-ACCORD were eligible and included in the study population. Among these participants, 5519 (36.0%) initiated an InSTI-based regimen, and 9799 (64%) initiated the EFV-based regimen between 2009 and 2016. Of 5519 patients initiating an InSTI-based regimen, 1783 (32.3%) initiated RAL, 3137 (56.8%) initiated EVG/COB, and 599 (10.9%) initiated DTG. In the intention-to-treat population, the median follow-up duration was 28 months (interquartile range 15–45) for the InSTI group and 57 months (interquartile range 41–71) for the EFV group. In the per-protocol population, after censoring patients at treatment changes, the median duration on the initial ART regimens was 16 months (interquartile range 7–31) for the InSTI group and 30 months (interquartile range 11–50) for the EFV group. Secular trends of ART initiation in Fig. 1 show an increased proportion of participants initiating InSTI-based regimens from 2009 to 2016. Baseline characteristics at ART initiation are described in Table 1. There were more female individuals, nonblacks, male individuals who reported male-to-male sexual contact as a risk factor for HIV infection, persons who had a diagnosis of depression or anxiety prior to ART initiation in the InSTI group, compared with the EFV group.

During the 7-year follow-up period, there were a total of 124 822 HIV viral load measurements recorded (34 781 in the InSTI group and 90 041 in the EFV group) after harmonizing into 3-month intervals. The InSTI group had a median of five viral load measurements (interquartile range, 3–8), and the EFV group had a median of nine viral load measurements (interquartile range, 5–13). A total of 479 deaths occurred during the follow-up, with 116 in the InSTI group and 363 in the EFV group. The crude proportion virologically suppressed from the raw data (i.e. without imputation and modeling, and keeping persons assigned as initial ART group) is depicted in Fig. 2a. The proportion virologically suppressed was 81.9% in the InSTI group, and 65.8% in the EFV group at 3 months after ART initiation, and then increased to 91.9% in the InSTI group and 92.3% in the EFV group at 7 years (shown in Fig. 3a).

In the intention-to-treat analyses, after accounting for baseline confounding, the proportion virologically suppressed is shown in Fig. 2b. The intention-to-treat differences in the proportion virologically suppressed in the InSTI-based regimen versus the EFV-based regimen, at 3 months, 6 months, 9 months, 1 year, 3 years, 5 years, and 7 years since

ART initiation are described in Fig. 3b. For example, at 3 months after ART initiation, the proportion virologically suppressed was 81.3% in the InSTI group, and 67.3% in the EFV group, corresponding with a difference of 14.0% (95% CI 12.4–15.6). At 9 months, the proportion difference was −3.9% (95% CI −5.3 to −2.4). The proportion virologically suppressed was similar after 1 year since ART initiation. At 1 year after ART initiation, the proportion virologically suppressed was 89.5% in the InSTI group and 90.2% in the EFV group, corresponding with a difference of −0.7% (95% CI −2.1 to 0.8). At 7 years after ART initiation, the proportion virologically suppressed was 94.5% in the InSTI group, and 92.5% in the EFV group, corresponding with a difference of 2.0% (95% CI: −7.3 to 11.3).

Sixty-eight percent of the participants initiating an InSTI-based regimen (3750/5519) and 71% of the participants initiating the EFV-based regimen (6975/9799) had a treatment change before the last measurement of HIV viral load or completing the study. In the per-protocol analyses after accounting for baseline confounding and these treatment changes, the model-fitted proportion virologically suppressed is shown in Fig. 2c. The per-protocol differences in the proportion virologically suppressed in the InSTI-based regimen versus the EFV-based regimen, at 3 months, 6 months, 9 months, 1 year, 3 years, 5 years, and 7 years since ART initiation are described in Fig. 3c. At 3 months after ART initiation, the proportion virologically suppressed was 81.3% in the InSTI group, and 67.3% in the EFV group, corresponding with a difference of 14.0% (95% CI 8.7–19.3). At 9 months, the proportion difference was −4.7% (95% CI −8.3 to −1.0). At 1year after ART initiation, the proportion virologically suppressed was 91.1% in the InSTI group, and 93.0% in the EFV group, corresponding with a difference of −1.8% (95% CI −4.9 to 1.3). At 7 years after ART initiation, the proportion virologically suppressed was 100% in the InSTI group, and 92.5% in the EFV group, corresponding with a difference of 7.5% (95% CI −0.3 to 15.4).

The results of secondary analyses by including both the observed and imputed measures of being HIV virologically suppressed were similar to the main analyses (see eSupplement Section 2, http://links.lww.com/QAD/C296).

Discussion

Using observational data from this large collaboration of HIV cohorts in the United States and Canada with up to 7 years of follow-up after ART initiation, we found that InSTI-based regimens had more rapid virologic response compared with EFV-based regimens among treatment-naive adults living with HIV especially during the first 3 months since ART initiation. Rapid virologic suppression among InSTI group may have implications for help reducing HIV transmission. However, both the intention-to-treat and per-protocol analyses showed that, 1 year after ART initiation, InSTI-based and EFV-based regimens showed similar effects on longer term virologic outcomes. Although the per-protocol analyses showed a potential virologic benefit of InSTI at 7 years from ART initiation, this estimate was imprecise because of the smaller per-protocol sample that remained on the initial ART regimens at the end of the study. Our study adds to the medical literature by demonstrating a lack of significant long-term difference between InSTI-based as compared with EFV-based regimens.

Our results that patients initiating an InSTI-based regimen experienced more rapid virologic suppression than those initiating EFV-based regimens, align with the findings from prior randomized trials: STARTMRK (RAL versus EFV) [4], SINGLE (DTG versus EFV) [7], Study 102 (EVG versus EFV) [9], and NAMSAL (DTG versus low-dose EFV) [25]. The STARTMRK trial showed a shorter time to achieve virologic suppression for patients on raltegravir than on efavirenz within 48 weeks after randomization. At 48 and 96 weeks (about 1 and years), RAL-based regimen was found to be noninferior to EFV-based regimen on virologic suppression [4,5]. At week 240 (about 5 years), the study showed RAL induced significantly better virologic suppression, though most of this difference could be explained by more treatment discontinuations among patients on efavirenz [26]. In the SINGLE study that compared DTG-based regimens with the EFV-based regimens, at week 48 (about 1 year), the proportion virologically suppressed was higher in the DTG group than in the EFV group [7]. The DTG group also had a shorter median time to virologic suppression and lower rate of treatment discontinuations than the EFV group. The Study 102 trial, which compared co-formulated EVG/COBI/FTC/TDF versus co-formulated EFV/FTC/TDF, showed noninferiority of the EVG-based regimen to the EFV-based regimen on virologic suppression, and comparable number of treatment discontinuations [9]. The NAMSAL trial compared the dolutegravir with low-dose efavirenz (a 400 mg dose), and showed that a dolutegravir-based regimen was noninferior to an EFV-based regimen with regard to virologic suppression at weeks 48 and 96 (about 1 and 2 years) [25,27].

Furthermore, our findings on virologic outcomes within 1 year after ART initiation were also consistent with the results from several observational studies [28,29]. Edwards *et al.* [28] used data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) and found that patients initiating raltegravir spent more time alive and virologically suppressed than those initiating efavirenz, which was primarily driven by more rapid virologic response to raltegravir. The probability of being alive and virologically suppressed at 2.5 years in the raltegravir group was similar to that in the efavirenz group. In a retrospective single-center study of 155 treatment-naive patients, Jacobson and Ogbuagu [29] found patents on InSTI-based regimens experienced higher rates of virologic suppression within the 1 year after initiation, and shorter median time to virologic suppression compared with patients on other ART regimens (including efavirenz).

Our study is subject to limitations. First, being observational data, treatment regimens were not randomly assigned. In order for the approach employed to mimic a randomized trial, all predictors of treatment regimen and censoring that are associated with the outcomes would need to be measured and included, which might not be the case. Second, while most published randomized trials used the definition of virologic suppression as HIV RNA viral load less than 50 copies/ml, we chose to use the threshold of HIV RNA less than 200 copies/ml as there was a portion of cohorts during this study period that had HIV viral load measurement with lower limit of detect greater than 50 copies/ml during 2009–2016. Future research could also focus on durable viral suppression (defined as consistent viral suppression for at least 12 months prior) if viral loads are measured more frequently [30]. Third, potential selection bias may exist as we did not account for death that occurred after the last measurement of viral load. Patients might die as a consequence of unsuppressed viral load, leading to differences in viral load between those who remained in the study and

those who died during follow-up, which were not captured in our analyses. Fourth, there were still 5–10% of our study population who remained virologically unsuppressed during the follow-up, even at 7 years after ART initiation under the per-protocol analyses. It may be because of relatively poor ART adherence among a portion of the study participants. However, as the NA-ACCORD did not record information on ART adherence (and the NA-ACCORD only recorded ART prescription), we did not examine this issue. Fifth, although restriction to TDF (or TAF)/FTC backbone allows us to avoid the potential influence of different backbones, it limits the sample size as well as impacts the composition of the InSTI group. For example, DTG was often formulated with ABC/3TC backbones. However, participants who initiated DTG/ABC/3TC were not included in our analysis, leading to relatively smaller proportion of DTG initiators in the InSTI group. Last, in our study, there was about one quarter of participants with missing baseline HIV viral load. Although these missing values were imputed, there is still some remaining uncertainty as virologic suppression is the main outcome. However, after examining the data, 80% of these participants with missing baseline HIV viral load had virologic suppression at 3 months after ART initiation. The results were similar to our main findings, alleviating the related concern.

We used a large observational cohort collaboration to replicate findings from randomized trials and extend the evidence base to a longer follow-up of 7 years, among a larger and widely representative sample of treatment-naive adults living with HIV in a real-world routine-care setting, which complements the findings from prior randomized trials and observational studies [31]. We adopted a new-user study design and modern statistical and causal inference approaches to perform intention-to-treat and per-protocol analyses to mitigate concerns about baseline confounding and treatment discontinuations or switches, and provided comprehensive evidence about the longer term effect of InSTIs on virologic outcomes. We found that although InSTI-based regimens had more rapid response compared with efavirenz-based regimens, the longer term effect on virologic outcomes was similar.

Our study also showed that the proportion of ART treatment changes including treatment switches and treatment discontinuations was high and comparable among patients initiating InSTI-based regimens and patients initiating efavirenz-based regimens; this finding differs from the results from randomized trials that InSTI-based regimens had fewer treatment discontinuations [4,7]. Although the reasons for treatment changes were not captured in the NA-ACCORD, this discrepancy between clinical trials and our study might indicate the potential shortcomings of (shorter duration) randomized trials in terms of accurately reflecting the real-world settings.

Combined with studies showing the potential adverse effects associated with InSTI including neuropsychiatric toxicity [32-34] and weight gain [35-38], with literature indicating potential increase in neural tube defects associated with DTG [39], and with our previous studies that suggest there was no benefit of InSTI over efavirenz on clinical outcomes [40,41], our results on a relatively similar long-term virologic effect of InSTI bring into question whether InSTI-based regimens should be prioritized for ART-naive patients, although there could be some benefit to short-term virologic suppression for InSTI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Brooks. **University of Alabama at Birmingham 1917 Clinic Cohort:** Michael S. Saag, Michael J. Mugavero and James Willig. **University of California at San Diego:** William C. Mathews. **University of North Carolina at Chapel Hill HIV Clinic Cohort:** Joseph J.Eron and Sonia Napravnik. **University of Washington HIV Cohort:** Mari M. Kitahata and Heidi M. Crane. **Vanderbilt Comprehensive Care Clinic HIV Cohort:** Timothy R. Sterling, David Haas, Peter Rebeiro and Megan Turner. **Veterans Aging Cohort Study:** Janet Tate, Robert Dubrow, and David Fiellin.

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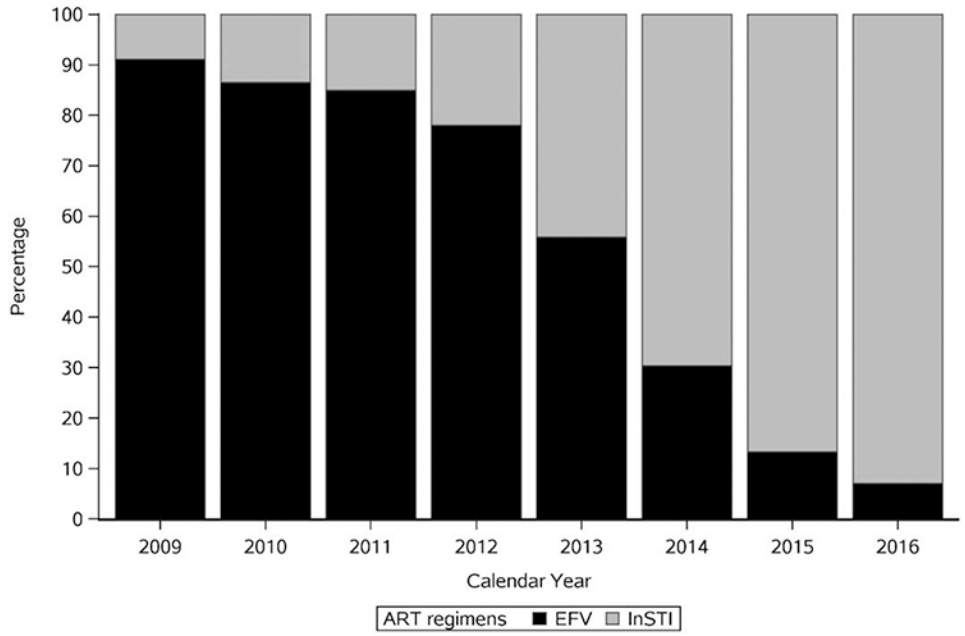

Fig. 1. Secular trend in proportion initiating integrase strand transfer inhibitor-based versus efavirenz-based regimens between July 2009 and December 2016 among 15 318 adults with HIV in the North American AIDS Cohort Collaboration on Research and Design, the United States and Canada.

ART, antiretroviral therapy; EFV,efavirenz; InSTI, integrase strand transfer inhibitor;NA-ACCORD, the North American AIDS Cohort Collaboration on Research and Design.

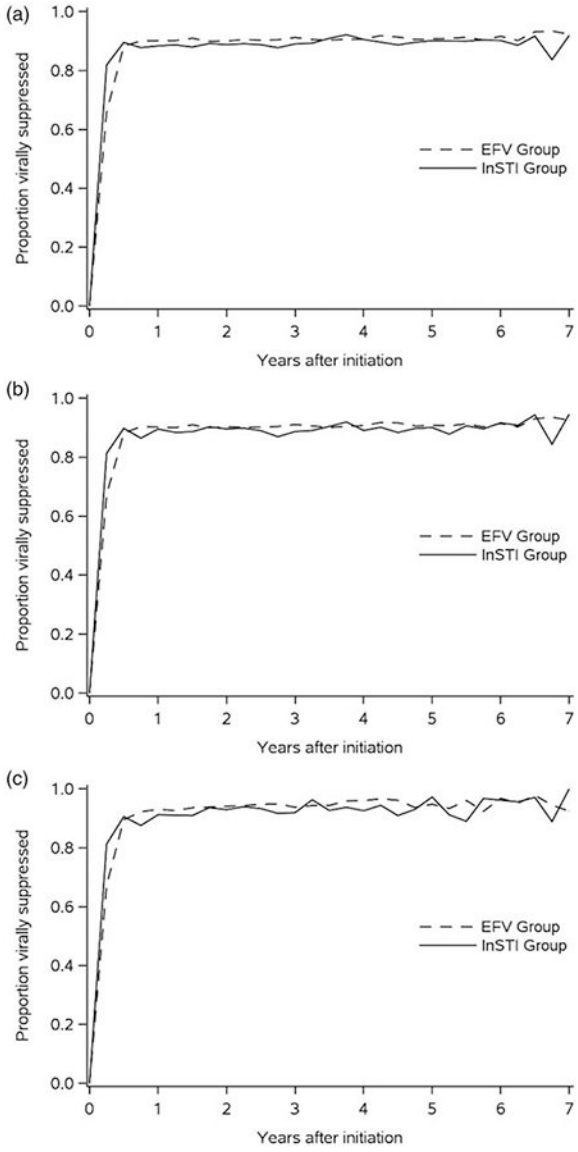

Fig. 2. Proportion virologically suppressed (<200 copies/ml) by antiretroviral therapy group (integrase strand transfer inhibitor-based versus efavirenz-based regimens) across 7-year follow-up among 15 318 adults with HIV in the the North American AIDS Cohort Collaboration on Research and Design, the United States and Canada.

The upper panel (a) represents crude analyses, the middle panel (b) represents intention-to-treat analyses that accounted for baseline confounding (see text for methodology), and the lower panel (c) represent per-protocol analyses that accounted for baseline confounding and ART treatment changes (ART treatment discontinuations and switches). ART, antiretroviral therapy.

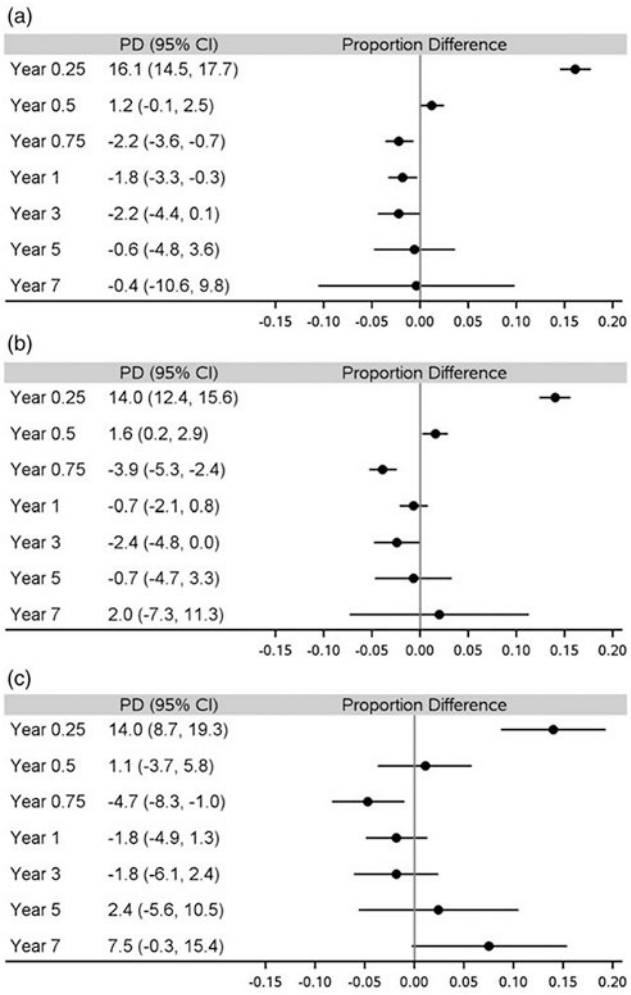

Fig. 3. Proportion difference virologically suppressed (<200 copies/ml) comparing InSTI-based regimen with efavirenz-based regimen across 7-year follow-up among 15 318 adults with HIV in the North American AIDS Cohort Collaboration on Research and Design, the United States and Canada.

The upper panel (a) represents crude analyses, the middle panel (b) represents intention-to-treat analyses that accounted for baseline confounding (see text for methodology), and the lower panel (c) represent per-protocol analyses that accounted for baseline confounding and ART treatment changes (ART treatment discontinuations and switches). ART, antiretroviral therapy.

Table 1.

Characteristics at antiretroviral therapy initiation of 15 318 adults with HIV initiating an integrase strand transfer inhibitor-based regimen or an efavirenz-based regimen between July 2009 and December 2016 in the North American AIDS Cohort Collaboration on Research and Design, overall and by treatment regimens, the United States and Canada.

Characteristic	Number (%) of participants	
	InSTI-based regimen[a] (*n* = 5519)	EFV-based regimen[a] (*n* = 9799)
Age, median (IQR) (years)	38.0 (28.0–49.0)	41.0 (31.0–51.0)
Female	836 (15.2)	1055 (10.8)
Black race	2193 (39.7)	4414 (45.0)
Hispanic ethnicity	667 (12.1)	1261 (12.9)
BMI, median (IQR)	25.1 (22.3–28.7)	25.1 (22.4–28.6)
Injection drug use	533 (9.7)	1036 (10.6)
Male-to-male sexual contact	3036 (55.0)	4343 (44.3)
Heterosexual behavior	1273 (23.1)	1931 (19.7)
Previous AIDS diagnosis	459 (8.3)	705 (7.2)
Hepatitis B co-infection	206 (3.7)	404 (4.1)
Hepatitis C co-infection	559 (10.1)	1120 (11.4)
Previous depression diagnosis	831 (15.1)	1024 (10.5)
Previous anxiety diagnosis	667 (12.1)	722 (7.4)
Diabetes mellitus	276 (5.0)	555 (5.7)
Hypertension	814 (14.8)	1843 (18.8)
Elevated total cholesterol	218 (4.0)	483 (4.9)
Statin prescription	344 (6.2)	840 (8.6)
Baseline $CD4^+$ cell count[b], median (IQR) (cells/μl)	346.0 (169.0–514.0)	316.0 (174.0–451.0)
Baseline viral load, median (IQR) (copies/ml)	44591.0.0 (12 712.5–151 552.5)	41 772.5 (10 700.0–132 824.0)
Calendar year at ART initiation, median (IQR)	2014 (2013–2015)	2011 (2010–2012)

ART, antiretroviral therapy;EFV, efavirenz;InSTI, integrase strand transfer inhibitor; IQR, interquartile range;NA-ACCORD, the North American AIDS Cohort Collaboration on Research and Design.

[a]Both regimens included the same backbone of tenofovir disoproxil fumarate [or tenofovir alafenamide], and emtricitabine.

[b]Baseline was defined as the date of ART initiation.