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Virologic suppression and CD4 cell count recovery after initiation of raltegravir- or efavirenz- containing HIV treatment regimens

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Abstract

Objective—To explore the effectiveness of raltegravir-based antiretroviral therapy (ART) on treatment response among ART-naive patients seeking routine clinical care.

Design—Cohort study of adults enrolled in HIV care in the United States.

Methods—We compared virologic suppression and CD4 cell count recovery over a 2.5 year period after initiation of an ART regimen containing raltegravir or efavirenz using observational data from a US clinical cohort, generalized to the US population of people with diagnosed HIV. We accounted for nonrandom treatment assignment, informative censoring, and nonrandom selection from the US target population using inverse probability weights.

Results—Of the 2843 patients included in the study, 2476 initiated the efavirenz-containing regimen and 367 initiated the raltegravir-containing regimen. In the weighted intent-to-treat analysis, patients spent an average of 74 (95% CI: 41, 106) additional days alive with a suppressed

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viral load on the raltegravir regimen than on the efavirenz regimen over the 2.5-year study period. CD4 cell count recovery was also superior under the raltegravir regimen.

Conclusions—Patients receiving raltegravir spent more time alive and suppressed than patients receiving efavirenz, but the probability of viral suppression by 2.5 years after treatment was similar between groups. Optimizing the amount of time spent in a state of viral suppression is important to improve survival among people living with HIV and to reduce onward transmission.

Keywords

HIV; HIV integrase inhibitors; efavirenz; viral load; sustained virologic response

Introduction

Integrase inhibitors have expanded first-line treatment options for people living with HIV. Randomized trials have demonstrated that patients initiating regimens containing integrase inhibitors experience more rapid plasma HIV RNA suppression following treatment initiation and fewer adverse events than patients initiating other first-line regimens [1–9]. Furthermore, addition of an integrase inhibitor to an initial treatment regimen improves tolerability for patients with treatment-limiting toxicity with reverse transcriptase or protease inhibitors [10] and increases treatment efficacy for patients with prior treatment failure [7,11–14].

For these reasons, many patients new to antiretroviral therapy (ART) have initiated regimens containing integrase inhibitors since the first drug in this class, raltegravir, was approved on October 12, 2007. Here, we use observational data on ART-naïve patients from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) to compare virologic suppression [15,16] and CD4 cell count recovery over 30 months after initiation of an ART regimen containing raltegravir in combination with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) with a regimen containing efavirenz plus the same reverse transcriptase inhibitor backbone. We account for differences in patient characteristics between treatment groups (i.e., channeling bias) and between patients in CNICS and the population of people with diagnosed HIV in the US (lack of generalizability) using inverse probability weighting. Examining the immunologic trajectories of patients in an observational clinical setting reflects the performance of these regimens in clinical care, free from Hawthorne effects and selective enrollment into a trial population.

Methods

Study sample

Patients with a detectable viral load who initiated an antiretroviral therapy regimen containing TDF and FTC plus raltegravir or efavirenz at a CNICS site between 12 October 2007 and 31 December 2014 and had not previously initiated combination antiretroviral therapy, defined as treatment with 3 or more antiretroviral drugs, were eligible for inclusion in this analysis ($N = 3060$). Patients were excluded if they were missing information on transmission risk factor, race, sex, or baseline CD4 cell count ($n = 217$), leaving 2843 patients in the cohort.

Patients were followed from initiation of one of the regimens of interest until death, loss to follow-up, or administrative censoring at 2.5 years (30 months) after study entry or on December 31, 2014. Patients were considered to be lost to follow-up after 12 months without a documented clinic visit in which CD4 cell count or viral load was measured. Each CNICS site semiannually queries the United States Social Security Death Index and/or National Death Index to confirm reported deaths and record deaths not captured by the sites. Viral loads and CD4 cell counts were collected during the course of routine HIV care at each CNICS site.

We present results of both an intent-to-treat analysis, in which patients remained in their initial treatment group regardless of whether or not they later switched regimens, and a per protocol analysis, in which patients were censored at any change in treatment regimen, with 2 exceptions: 1) changes from the raltegravir regimen to another integrase inhibitor–based regimen (including fixed-dose combination of elvitegravir, cobicistat, TDF, and FTC or dolutegravir, TDF, and FTC; and 2) changes from the efavirenz regimen to the nonnucleoside reverse transcriptase inhibitor regimen of rilpivirine, TDF, and FTC.

Institutional review boards at each site approved CNICS study protocols, and patients provided written informed consent to be included in the CNICS cohort or contributed administrative and/or clinical data with a waiver of written informed consent where approved by local institutional review boards.

Target population

Results were generalized to a target population defined by all people with diagnosed HIV in the US between 2008 and 2014 to extrapolate study findings to the larger population of people living with HIV in the United States. Characteristics of this population, including race/ethnicity, sex, age group, and likely mode of transmission (i.e., male-to-male sexual contact, injection drug use) were provided by the Centers for Disease Control and Prevention from national HIV surveillance data [17,18].

Statistical methods

We compared the proportion of patients alive and virally suppressed and the mean CD4 cell count improvement over 30 months after ART initiation between patients initially prescribed the raltegravir and efavirenz regimens. We estimated the difference in CD4 cell count recovery between treatment groups by comparing the mean CD4 cell count at baseline to the mean CD4 cell count 30 months later in each treatment group. The proportion of patients alive and suppressed at each time point was estimated using the method formally described by Gouskova et al [15,19], adapted to account for nonrandom treatment assignment and the competing event of death, and the 30-month restricted mean time alive and suppressed was the sum of this proportion over the 30-month follow-up period.

We accounted for differences between patients in the study sample and the US population of people with diagnosed HIV, differences in baseline characteristics between patients prescribed each regimen, and informative censoring due to loss to follow-up or regimen switching using inverse probability weights. Technical details can be found in Appendix 1.

Results

Of the 2843 patients included in the study, 2476 initiated the efavirenz-containing regimen and 367 initiated the raltegravir-containing regimen (Table 1). In the intent-to-treat analysis weighted to account for sampling, nonrandom treatment assignment, and informative censoring, patients initiating efavirenz spent an average of 556 days of the 913-day study period alive and suppressed, while patients initiating raltegravir spent an average of 630 days in this state, for a difference of 74 (95% CI: 41, 106) days in favor of raltegravir. This difference in time suppressed is primarily driven by more rapid suppression under raltegravir than efavirenz. The probability of being alive and suppressed after 2 years was similar in the efavirenz group (70.3%) and in the raltegravir group (71.5%) (Figure 1). The advantage of raltegravir in terms of number of days virally suppressed was even greater in the “per protocol” analysis, in which patients were censored at a change in regimen (difference: 80 days; 95% CI: 50, 117).

CD4 cell count improved over time from treatment initiation for both groups. In the weighted intent-to-treat analysis, CD4 cell count improvement over the 30-month period was 215 cells/mm^3 for the efavirenz group and 247 cells/mm^3 for raltegravir group, for a difference of 32 (95% CI: 14, 49) cells/mm^3 in favor of raltegravir. Results were similar in the per protocol analysis (difference: 30 cells/$mm^{3;}$ 95% CI: 3, 57). Full tabular and graphical results are presented in Appendix 2.

Discussion

Patients receiving raltegravir had a modest advantage in terms of the mean time spent alive and virally suppressed over patients receiving efavirenz during the 30-month period following treatment initiation. As might be expected, this advantage was driven by initial viral suppression; patients initiating the raltegravir regimen experienced a shorter time to a measured viral load under 50 copies/mL than patients receiving efavirenz. The clinical impact of the difference in days suppressed for an individual patient is uncertain, but this difference may have an impact on onward transmission. In addition, reducing viral burden over time may play a role in reducing HIV-related inflammation [20,21] and other negative effects of chronic HIV infection [22–24].

Our result that patients initiating raltegravir experienced more rapid viral suppression than patients initiating efavirenz aligns with findings from randomized trials comparing efavirenz and raltegravir [1,25]. In the STARTMRK trial, long-term viral suppression over 5 years appeared to be superior in the raltegravir arm than the efavirenz arm, though much of this difference was due to treatment discontinuation in the efavirenz arm, which was treated as virologic failure [26]. The difference in CD4 cell count improvement was similar between this study (30 cells/mm^3 over approximately 130 weeks) and the STARTMRK trial (37 cells/mm^3 over 156 weeks) [27], though participants in STARTMRK who changed therapy, had virologic rebound, or experienced intolerance were discontinued from study, which may have influenced CD4 response results. The clinical benefits of relatively small but significant differences in CD4 cell response are unknown in the context of long-term (decades) antiretroviral therapy.

The current study complements the results from randomized trials. Here, we estimated that raltegravir was associated with superior viral suppression among patients in routine care settings under real-world adherence patterns, despite its higher pill burden. Even trials reporting results from intent-to-treat analyses, which typically do not account for nonadherence, are subject to Hawthorne effects in which participants may display different adherence patterns than they would under real world conditions. Accordingly, these trials may over- or underestimate the effectiveness of a given treatment regimen in routine clinical care [28]. In addition, results from this study in the CNICS cohort were generalized to the US population of people with diagnosed HIV to provide a population-level estimate of observed study effects [29]. Finally, because regimen switches for reasons other than virologic failure (e.g., tolerability, toxicity, or convenience) are increasingly common [30], we did not consider regimen switch to be virologic failure.

The potential for regimen switches in the context of routine care may explain why the estimated effect of raltegravir in the intent-to-treat analysis appeared to be attenuated compared with results from STARTMRK. For example, in the intent-to-treat analysis, positive results from patients who switched from efavirenz to an alternative therapy for reasons of toxicity or tolerability would be seen as beneficial outcomes for initial prescription of efavirenz. Therefore, these results may show efavirenz to perform better than it appeared to perform in trials that treated regimen switch as virologic failure. In addition, initiating therapy with a regimen that had sub-optimal outcomes in clinical trials may have improved outcomes in clinical practice, where switching therapy is frequently used to manage even mild or moderate adverse events. Such frequent switching may result in a smaller clinical impact of the initial therapy choice than seen in trials that treat regimen switching as failure. Switching therapy for intolerance has little clinical impact provided the switch is not accompanied by rebound in plasma HIV RNA, which carries a resistance risk that can be considered a life-long adverse event. Appendix 3 reports counts of patients in each arm who switched regimens. As expected, the estimated benefit of the raltegravir regimen in terms of number of days suppressed was greater when patients were censored at these changes in treatment regimen in the per-protocol analysis than in the intent-to-treat analysis.

In this study, patients receiving raltegravir spent more days alive and virally suppressed and had superior CD4 cell count recovery than patients receiving efavirenz over the 30 months following treatment initiation. Optimizing the amount of time spent in a state of viral suppression is important when considering antiretroviral treatment plans not only to improve survival among people living with HIV [31] but also to reduce onward transmission from people living with HIV to their HIV-uninfected partners [32–34].

Acknowledgments

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Appendix 1. Technical details

The date of initial viral suppression was the midpoint between the first viral load measurement under 50 copies/mL and the previous viral load measurement. The date of subsequent viral rebound was defined as the midpoint between the date of the first of 2 viral load measurements over 200 copies/mL and the previous viral load measurement [21].

The proportion suppressed in treatment group x at time t, $G_x(t)$, was the proportion of patients who had initially suppressed their viral loads following treatment by time t and had not yet experienced viral rebound or death following initial viral suppression, or $\hat{G}_x(t)=\hat{R}^s_x(t)-\{\hat{R}^r_x(t)+\hat{R}^d_x(t)\}$, where $\hat{R}^s_x(t)$ is the Aalen-Johansen estimate [23] of the risk of initial viral suppression following treatment initiation, $\hat{R}^r_x(t)$ is the estimate of the risk of viral rebound following initial suppression, and $\hat{R}^d_x(t)$ is the risk of death following initial viral suppression.

We also compared the 30-month restricted mean time alive and suppressed for each treatment group. The restricted mean time suppressed, $A_x(\tau)$, was the sum over follow-up time τ of the probability of being suppressed and alive at each time point, or $A_x(\tau)=\sum_0^\tau G_x(t)$, where t indexes days since treatment initiation.

To estimate the differences in CD4 cell count improvement and proportion with viral suppression under each treatment plan, we made several assumptions. First, we assumed that patients receiving raltegravir were exchangeable with patients receiving efavirenz, conditional on a set of measured baseline characteristics, including age, sex, black race vs. other, transmission risk factors (indicators for history of injection drug use and being a man who has sex with men), baseline CD4 cell count, prior AIDS diagnosis, history of depression and anxiety at baseline, and year of study entry. We accounted for differences in these patient characteristics between treatment groups using inverse probability of treatment weights. Treatment weights for each patient were the inverse probability of being assigned to raltegravir (rather than efavirenz) conditional on covariates L, or $W_X = f\{X\}/f\{X|L\}$, where $f\{X\}$ is the density of X evaluated at the observed value.

Because raltegravir was introduced in 2012 and its use increased over time, some of the apparent beneficial effect of raltegravir could have been due to improvements in clinical care that occurred concurrent with the increase in popularity of raltegravir. We accounted for this possible confounding by calendar period by including the year of CNICS enrollment in the treatment weights. However, confounding bias by date of study entry could remain after accounting for year of study entry if, within each year, later calendar dates were associated

with both an increase probability of raltegravir use and improved outcomes due to other improvements in clinical care.

Second, we assumed that patients in the study at time t were exchangeable with patients who were lost to follow-up at time t, conditional on the set of the measured time-fixed variables listed above and time-varying patient characteristics, including CD4 cell count, viral load, and history of AIDS diagnosis at the previous visit. We accounted for differences in these characteristics between patients remaining under observation and patients who had dropped out of the study using inverse probability of censoring weights [35]. Censoring weights for each person month were the inverse probability of having recorded data for CD4 cell count or viral load at time t, conditional on time-fixed and time-varying covariates $Z(t)$, or $W_C(t) = P\{\bar{C}(t) = 0\}/P\{\bar{C}(t) = 0|X = x, Z(t) = z(t)\}$, where $\bar{C}(t) = 0$ indicates that the patient remained in the study through time t.

Third, we accounted for differences between people initiating one of the two regimens of interest in CNICS and the target population of people with diagnosed HIV in the United States using inverse odds of sampling weights [36]. Sampling weights were estimated as $W_S = P(S = 0|V = v)/P(S = 1|V = v)$, where S is an indicator of being included in the study ($S_i = 1$) or the target population ($S_i = 0$), and V_i is a vector of covariates that differ between the sample and target population (here: sex, race, transmission risk factor, age, and year of study entry).

The numerator and denominator of the 3 sets of weights were estimated using logistic regression. The final weights for each person-month $W(t)$ were a product of the time-fixed sampling and exposure weights and the time-varying censoring weights.

When using the inverse probability weights, we assumed that patients had nonzero probability of sampling, being assigned to each treatment arm, and remaining in the study through time t, conditional on measured covariates. In addition, we assumed that parametric models for the weights were correctly specified; to improve the flexibility of the parametric models, we modeled all continuous covariates using restricted quadratic splines [37]. Finally, we assumed that all variables (treatment regimens, viral suppression, CD4 cell count, and covariates) were measured without error.

Appendix 2. Full tabular and graphical results

Table A1

Outcomes related to viral suppression and death among 2843 patients who initiated an antiretroviral therapy regimen containing efavirenz or raltegravir in combination with tenofovir DF/emtricitabine at a CNICS site between October 12, 2007 and December 31, 2014 at 8 US clinical sites, followed over 30 months after treatment initiation, generalized to the US population of people with HIV diagnosed between 2008 and 2014

Treatment	*n*	Number with viral suppression	Number with viral rebound	Deaths	Crude		Weighted [a]	
					Days alive & suppressed	Difference (95% CI)	Days alive & suppressed	Difference (95% CI)
Intent to treat analysis [b]								
Efavirenz	2476	1929	196	46	561	0	556	0
Raltegravir	367	315	35	12	660	99 (71, 127)	630	74 (41, 106)
Per protocol analysis [c]								
Efavirenz	2476	1669	134	31	555	0	543	0
Raltegravir	367	302	29	9	663	109 (80, 137)	626	83 (50, 117)

CNICS: Centers for AIDS Research Network of Integrated Clinical Systems

[a] Weights were the product of sampling weights (to account for differences in patient characteristics between the study population and the US population of people diagnosed with HIV), treatment weights (to account for differences in patient characteristics between treatment groups), and censoring weights (to account for differences in time-fixed and time-varying characteristics between those censored and those remaining in the study).

[b] The intent to treat analysis followed patients from treatment assignment until death, loss to follow-up, or administrative censoring.

[c] The per protocol analysis censored patients when they changed treatment regimens

Table A2

CD4 cell count at treatment initiation and 30 months later among 2843 patients who initiated an antiretroviral therapy regimen containing efavirenz or raltegravir in combination with tenofovir DF/emtricitabine at a CNICS site between October 12, 2007 and December 31, 2014 at 8 US clinical sites, generalized to the US population of people with HIV diagnosed between 2008 and 2014

Treatment	*n*	Mean CD4 cell count at treatment initiation	Mean CD4 cell count at 30 months after treatment initiation	Mean increase in CD4 cell count	Difference in CD4 cell count increase
Crude					
Efavirenz	2476	326	558	232	0
Raltegravir	367	358	618	260	28 (12, 43)
Weighted intent to treat [a,b]					
Efavirenz	2476	349	564	215	0
Raltegravir	367	330	577	247	32 (14, 49)
Weighted per protocol [a,c]					
Efavirenz	2476	349	568	218	0
Raltegravir	367	330	579	248	30 (3, 57)

CNICS: Centers for AIDS Research Network of Integrated Clinical Systems

[a]Weights were the product of sampling weights (to account for differences in patient characteristics between the study population and the US population of people diagnosed with HIV), treatment weights (to account for differences in patient characteristics between treatment groups), and censoring weights (to account for differences in time-fixed and time-varying characteristics between those censored and those remaining in the study).

[b]The intent to treat analysis followed patients from treatment assignment until death, loss to follow-up, or administrative censoring.

[c]The per protocol analysis censored patients when they changed treatment regimens

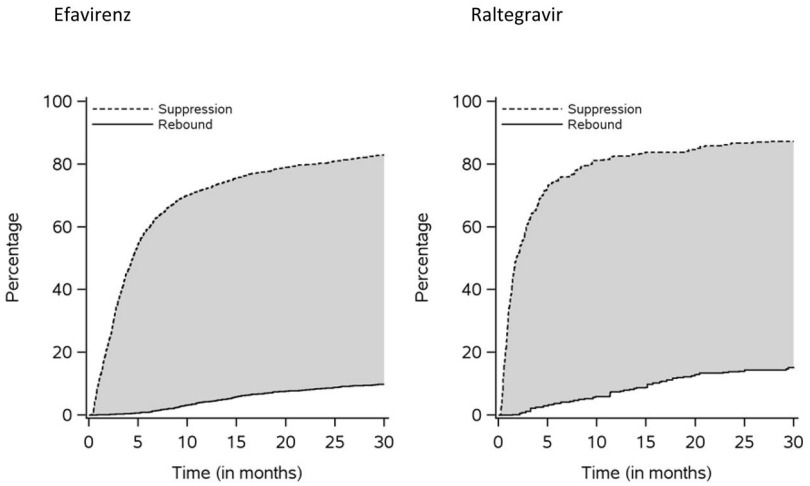

Figure A1.

Proportion achieving initial viral suppression (dotted lines) and viral rebound or death (solid lines) among 2486 patients who initiated efavirenz (left) and 368 patients who initiated raltegravir (right) in the CNICS between October 12, 2007 and December 31, 2014 (intent to treat analysis).

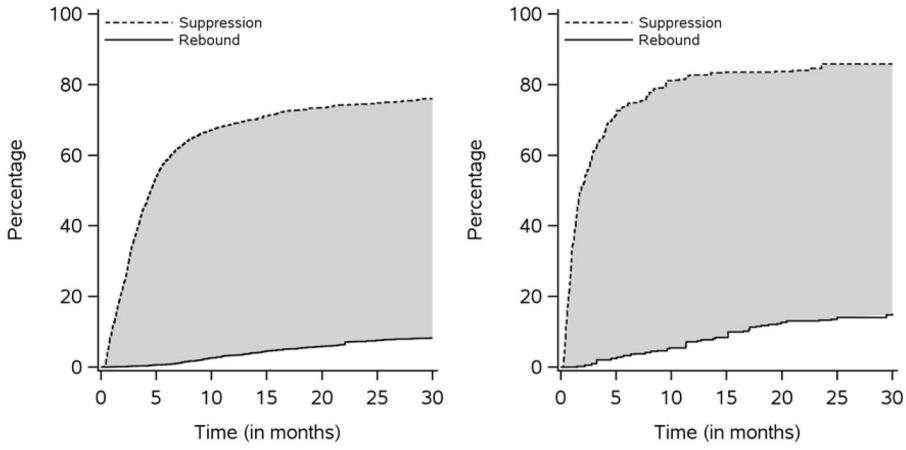

Figure A2.

Proportion achieving initial viral suppression (dotted lines) and viral rebound or death (solid lines) among 2486 patients who initiated efavirenz (left) and 368 patients who initiated raltegravir (right) in the CNICS between October 12, 2007 and December 31, 2014 (per protocol analysis).

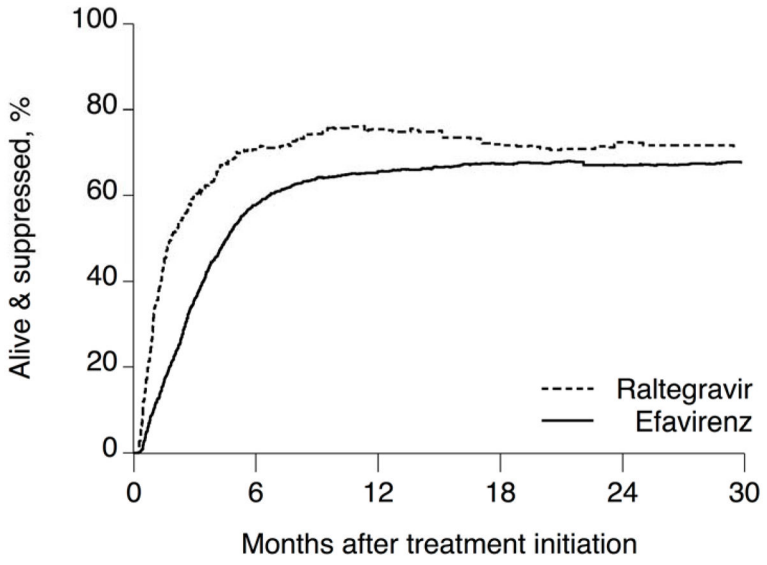

Figure A3.

Probability of being alive and in a state of suppression before viral rebound, $G_k(x)$, in the per protocol analysis for 2476 patients who initiated the efavirenz-containing regimen and 367 patients who initiated the raltegravir-containing regimen in the CNICS between October 12, 2007 and December 31, 2014 over 30 months of follow-up, weighted to generalize results to the US population of people with HIV diagnosed between 2008 and 2014 and to account for nonrandom treatment assignment and informative censoring.

Appendix 3. Regimen switching behavior among patients initiating an ART regimen containing tenofovir DF, emtricitabine, and raltegravir or efavirenz

Treatment group	*n*	Number switched prior to suppression	Number switched after suppression prior to rebound	Number switched after rebound
Efavirenz	2476	385	179	50
Raltegravir	367	24	30	8

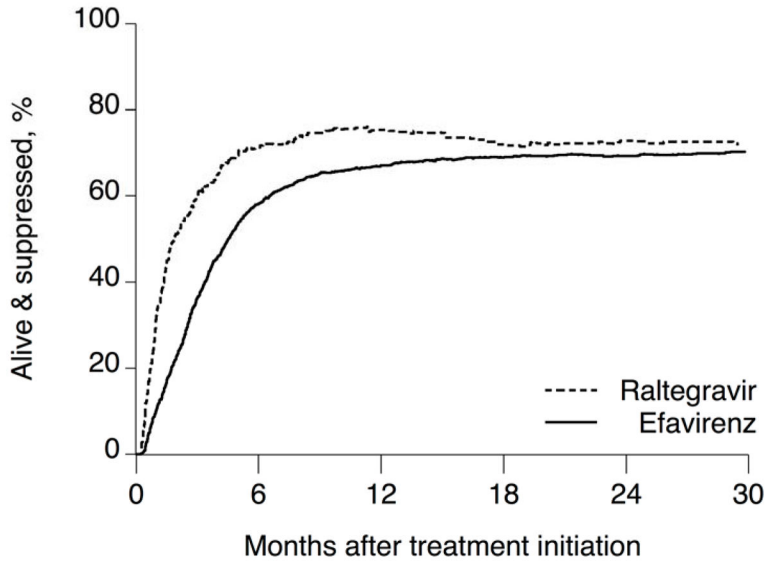

Figure 1.

Probability of being alive and in a state of suppression before viral rebound in the intent to treat analysis for 2476 patients who initiated the efavirenz-containing regimen and 367 patients who initiated the raltegravir-containing regimen in the CNICS between October 12, 2007 and December 31, 2014 over 30 months of follow-up, weighted to generalize results to the US population of people with HIV diagnosed between 2008 and 2014 and to account for nonrandom treatment assignment and informative censoring.

Table 1

Demographics and clinical characteristics at study entry of 2843 patients who initiated an antiretroviral therapy regimen containing efavirenz or raltegravir in combination with tenofovir DF/emtricitabine at a CNICS site between October 12, 2007 and December 31, 2014 at 8 US clinical sites

Characteristics	Efavirenz (*n* = 2476)		Raltegravir (*n* = 367)		Overall (*n*=2843)	US Target Population (*n* = 296,073)
	n	%	*n*	%	%	%
Male sex	2191	88	297	81	88	79
Black race	900	36	116	32	36	45
People who inject drugs	280	11	58	16	12	8
MSM	1787	72	237	65	71	65
Age at study entry						
18–24	287	12	25	7	11	20
25–34	789	32	105	29	31	29
35–44	727	29	109	30	29	23
45–54	528	21	92	25	22	19
55+	145	6	36	10	6	9
Year at study entry						
2008 – 2010	1462	59	151	41	57	45
2011 – 2013	868	35	202	55	38	41
2014 – 2015	40	2	14	4	2	13
History of depression or anxiety at baseline	526	21	94	26	22	NA
CD4 cell count at baseline						
<200	703	28	105	29	28	NA
200 – 350	747	30	85	23	29	NA
350 – 500	587	24	86	23	24	NA
500 – 750	343	14	68	19	14	NA
>750	96	4	23	6	4	NA
AIDS at baseline	296	12	51	14	12	NA

CNICS: Centers for AIDS Research Network of Integrated Clinical Systems; MSM: men who have sex with men; AIDS: autoimmune deficiency syndrome;