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 [1].

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 $\hat{G}_x(t) = \hat{R}_x^s(t) - \{\hat{R}_x^r(t) + \hat{R}_x^d(t)\}$, where $\hat{R}_x^s(t)$ is the Aalen-Johansen estimate [2] of the risk of initial viral suppression following treatment initiation, $\hat{R}_x^r(t)$ is the estimate of the risk of viral rebound following initial suppression, and $\hat{R}_x^d(t)$ 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 [3]. 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 [4]. 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 [5]. 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).

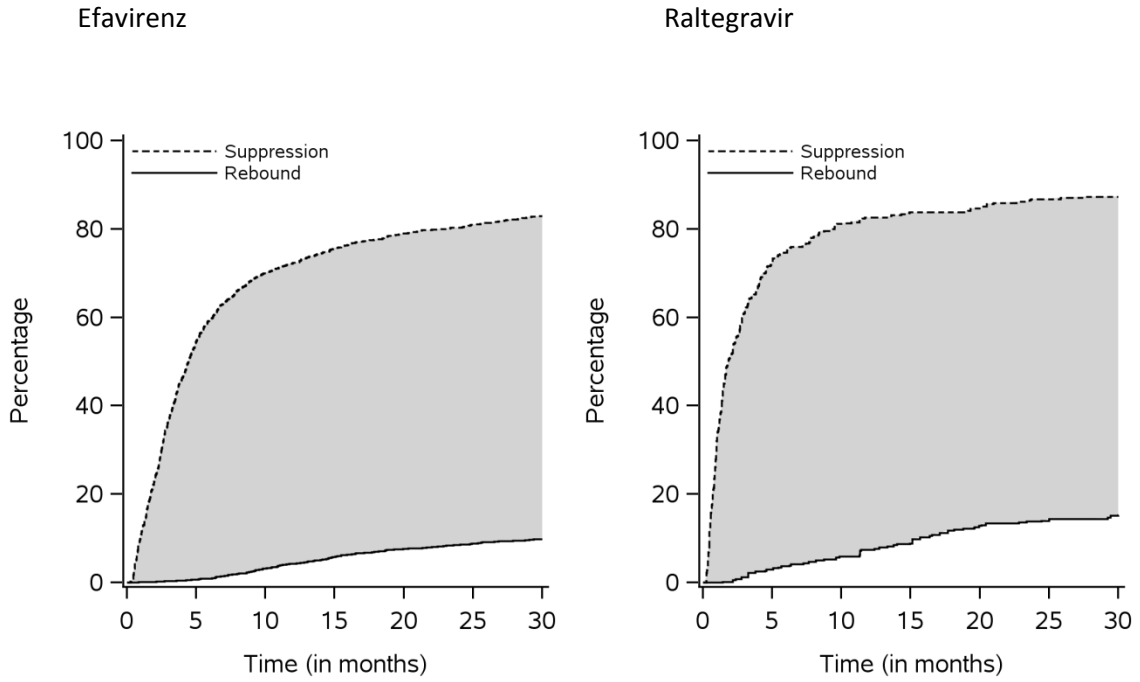


Figure A2. Proportion achieving initial viral suppression (dotted lines) and viral rebound or death (solid lines) among 2486 patients who initiated efavirenz (left) and 368 patients who initiated raltegravir (right) in the CNICS between October 12, 2007 and December 31, 2014 (per protocol analysis).

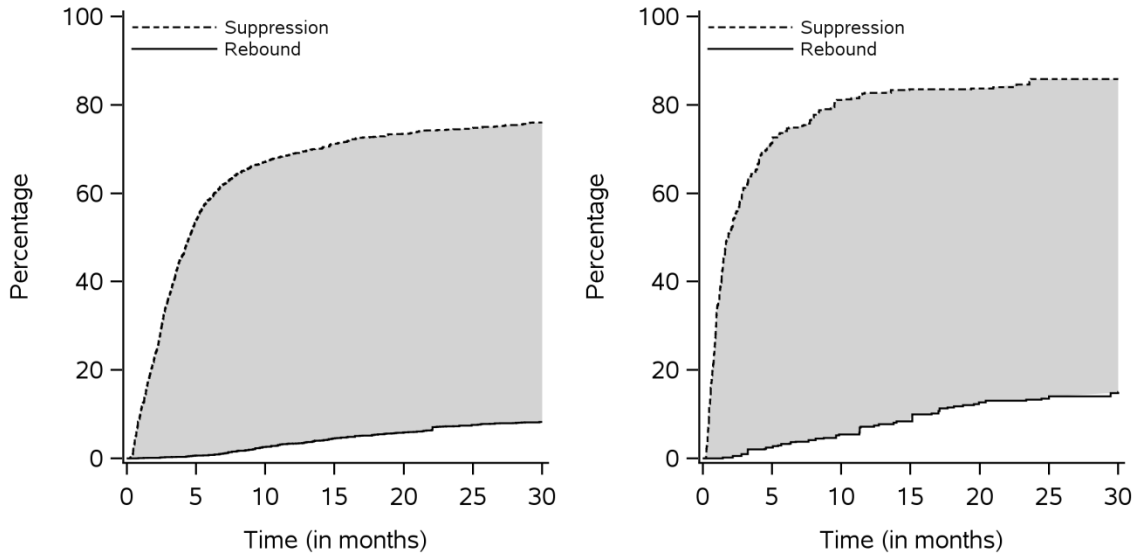
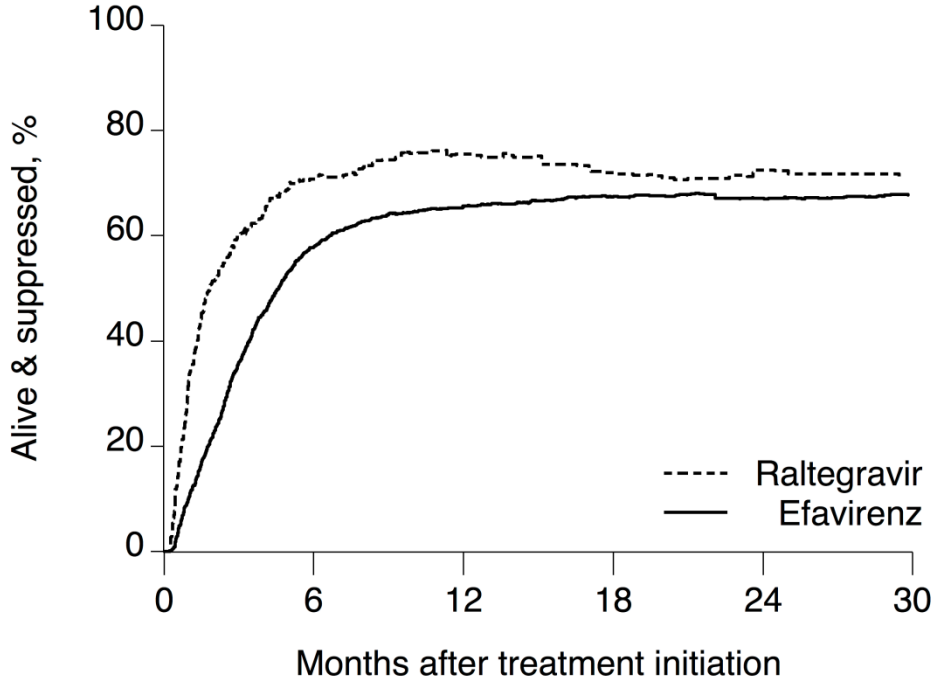


Figure A3. Probability of being alive and in a state of suppression before viral rebound, $G_k(x)$, in the per protocol analysis for 2476 patients who initiated the efavirenz-containing regimen and 367 patients who initiated the raltegravir-containing regimen in the CNICS between October 12, 2007 and 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

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4 Westreich D, Edwards JK, Stuart EA, Lesko CR, Cole SR. Transportability of trial results using inverse odds of sampling weights. *Am J Epidemiol* 2017; :In press.

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