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**Addition of etravirine does not enhance the initial decline of HIV-1 RNA in
treatment-experienced patients receiving raltegravir**

Running head: initial decline of viral load

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Abstract

Objective : The importance of an early reduction of HIV-1 RNA as a marker for positive longer term outcome is still under debate. We investigate whether antiretroviral-experienced patients receiving raltegravir plus etravirine have a higher early reduction of HIV-1 RNA compared with patients receiving raltegravir.

Design: An observational study of treatment-experienced patients.

Methods: The objective is investigated in 349 patients included in a raltegravir resistance study. The early outcome is defined as a reduction of HIV-1 RNA at week 8. The crude method that consists to define all measurements below the limit of quantification to be equal to the limit of quantification provides biased estimates. Such a reduction is censored by the limit of quantification and is subject to selection bias in observational studies.

Results: Crude method showed a significant higher reduction in HIV-1 RNA reduction in patients receiving raltegravir plus etravirine compared with patients receiving raltegravir (mean reduction of 2.1 versus 1.8 \log_{10} copies/ml). However, survival methods adjusted for both censoring, due to the limit of quantification, and confounding factors lead to a non-significant difference between the two treatment groups (mean reduction of 2.8 versus 2.7 \log_{10} copies/ml)..

Conclusion: Taking into account censoring and confounding factors, our study did not demonstrate a higher early reduction of HIV-1 RNA in patients receiving raltegravir with versus without etravirine.

Keywords: Antiretroviral therapy, Propensity score, Kaplan-Meier estimates, HIV-1 RNA reduction, limits of quantification

1. Introduction

Highly active antiretroviral therapy is the standard of care for patients with HIV infection and is usually the combination of three antiretroviral agents¹. Raltegravir was the first integrase strand-transfer inhibitor (INSTI) that prevents proviral DNA-strand transfer^{2,3}. In randomized trials, raltegravir showed good tolerability and proved remarkably efficient in combination therapy at reducing viral loads both in treatment-naïve and antiretroviral-experienced patients^{2,4,5}. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are frequently used components of combination antiretroviral therapy¹. Etravirine is an expanded-spectrum NNRTI with a potent and broad in vitro activity against HIV-1, including virus with NNRTI resistance associated mutations⁶. Its efficacy and safety in treatment-experienced patients have been demonstrated in phase III trials^{7,8}.

Current outcomes in HIV-1 infected study are percentages of patients with plasma HIV-1 RNA level <50 copies over time and the percentage at week 48 is widely used as primary endpoint in randomized clinical trials. Raltegravir-based regimen had rapid antiretroviral activity in treatment-naïve and treatment-experienced patients with a much higher percent of patients with HIV-1 RNA <50 copies/ml for weeks 2-16 compared with other regimen^{2,5}. The clinical significance of a more rapid HIV-1 RNA decline has not been clearly established but some authors suggested that early virological response to therapy increase the likelihood of maintaining or obtaining a latter response^{4,9,10}. There is also legitimate concern that minority drug-resistant mutants may be selected during the initial HIV-1 RNA decay phase following antiretroviral therapy initiation, thus undermining efficacy of treatment¹¹. Continuous outcome such as endpoint based on the magnitude of reduction in viral load provides usually more information than a binary outcome (below or above 50 copies/ml). Reduction in plasma HIV-1 RNA is also used in trials as a complement to endpoints based on percentage of patients achieving virological suppression¹². Interpretations of magnitude of reduction, however, can be biased by limits of detection of virologic assays, particularly lower limits

of quantification. Survival methods, including Kaplan-Meier curves, have been proposed to take into account censoring of HIV-1 RNA reduction ¹².

Observational resistance studies in HIV infected patients involve participants with treatment failure on their current regimen, who were thus given a new regimen including the drug under study for resistance. Furthermore, other drugs may be introduced in the regimen leading to a combination of more than three drugs with most of the new drugs introduced for the first time. The choice of the drugs and the number of drugs in the new regimen is based on some patient's characteristics at failure including levels of viral load and prior antiretroviral exposure. Then for a specific drug, treated and non-treated participants differ in their distribution of confounding variables. Methods using propensity scores have expanded the analytic tools available to researchers to make unbiased comparisons between treatment groups in observational studies ¹³. Inverse probability of treatment weighting (IPTW) using propensity score and propensity score matching have been suggested as promising methods with time-to-event outcomes ^{14,15}. Adjusted Kaplan-Meier estimator and corresponding log-rank test have been introduced to reduce confounding effects using IPTW with time-invariant treatment ¹⁶.

In the present work we investigate in treatment-experienced patients receiving a raltegravir-containing regimen for the first time whether the additional introduction of etravirine for the first time increases the effectiveness of such a combination. Specifically, we explore whether etravirine enhance the early and rapid decline of viral load observed previously in patients receiving a raltegravir-based regimen ^{2,4}. Data from an observational resistance study are used with HIV-1 RNA reduction at week 8 as outcome. Crude and adjusted methods for confounding are applied to the data for comparisons.

2. Material and methods

2.1. Study population

In 2012, the Agence Nationale de Recherche sur le SIDA (ANRS) conducted a resistance study in patients receiving a raltegravir (RAL)-containing regimen for the first time¹⁷. All patients included in the study experienced virologic failure and were treatment-experienced but had not previously received raltegravir or another INSTI. In each center, sociodemographic, clinical and virologic data were collected for all patients treated with the studied drug and an optimised background regimen. The study investigated the potential impact of natural polymorphisms in the integrase gene on the virologic response. The main analysis, however, did not suggest that these baseline integrase polymorphic mutations were associated with the virologic response¹⁷. In addition to raltegravir, etravirine and darunavir, a protease inhibitor (PI), were two other 'recent' drugs that were introduced for the first-time in many patients. Patients receiving a PI, including darunavir, and a NNRTI, except etravirine, for the first time were excluded of the present analysis. Then, in the present study, we analysed the 349 patients receiving then either raltegravir for the first time or raltegravir and etravirine for the first time.

2.2. Statistical methods

The outcome was the HIV-1 RNA reduction from baseline to week 8 (-/+ 2 weeks). The crude method is simply to define all HIV-1 RNA levels at week 8 below the limit of quantification to be equal to the limit of quantification. The two limits of quantification used by the virology laboratories at this time were 40 and 50 copies/ml. Usually HIV-1 RNA levels are transformed using the \log_{10} scale. For example, a patient having HIV-1 RNA measurements of 2000 copies/ml at baseline and 200 copies/ml at week 8 has an observed reduction of 1 \log_{10} . In the crude method a magnitude of reduction can be calculated for all patients and standard statistical procedures can be used to compare treatment groups. For instance, a standard analysis with a linear model and a Wilcoxon non-parametric test were carried out to compare treatment groups.

Assuming that the baseline HIV-1 RNA measurement is within the range of quantification, a censored reduction is observed when the measurement at week 8 is below the limit of quantification. An

equivalent structure of data exists between a censored reduction in HIV-1 RNA and censored time-to-event¹². Thus, Kaplan-Meier method is used to estimate the cumulative frequency distribution of the magnitude of HIV-1 RNA reduction. Such method has already been used with reduction of viral load and other biomarkers^{18,19}. Further analyses based on Kaplan-Meier estimates can also be made such as log-rank test to compare treatment groups with respect to viral load reduction. It was demonstrated that the crude method provides a biased estimate of the median reduction and that censored method greatly improves such estimates¹². An apparent difficulty is that a reduction in HIV-1 RNA level may be negative (ie, when HIV-1 RNA levels rise from baseline to week 8), although time-to-event data remain positive. This can be easily circumvented by adding any single number (+2 in our data) to each HIV-1 RNA reduction so that all observations are positive and then subtracting this number from all observations subsequent to the analysis.

Considering that HIV-1 RNA levels are at least approximately normally distributed after transformation on the \log_{10} scale, parametric analyses may be used¹². Such parametric analyses assumed that the cumulative frequency distribution follow the form of a normal distribution. Comparison of residuals obtained with the Kaplan-Meier method to those obtained with a parametric model provides a check of the normality assumption. Such parametric analyses provide estimated mean adjusted for censoring.

An implicit assumption of the Kaplan-Meier and other survival analysis is the so-called noninformative censoring assumption. In our setting, noninformative censoring corresponds to the assumption that the magnitude of reduction is not related to the baseline HIV-1 RNA level¹². If this is not satisfied, further analyses on treatment comparisons should be adjusted by baseline HIV-1 RNA levels. We investigated the dependence of censoring and baseline HIV-1 RNA level by an analysis of covariance introduced for censored data¹². Both parametric and nonparametric approaches have been used to investigate the noninformative censoring assumption. Baseline HIV-1 RNA levels,

however, is one of the main confounding variables considered in the propensity score approach described below.

Propensity score methods are increasingly being applied to reduce or minimize the effects of confounding when estimating the effects of treatments when using non-randomized studies^{13,15}. The propensity score is the probability of receiving a given treatment, conditional on observed baseline variables. It is a balancing score: conditional on the propensity score, the distribution of measured observed baseline covariates is expected to be balanced in the two treatment groups. Among the different propensity score methods, inverse probability of treatment weighting (IPTW) and propensity score matching are recommended for survival outcomes¹⁴. Propensity scores are unknown and usually estimated via a parametric model. Stabilized weights were used as IPTW using logistic regression models. For the i^{th} subject the stabilized weight is $sw_i = \Pr[Z_i = 1] / \Pr[Z_i = 1 | X_i]$ where $\Pr[Z_i = 1]$ is the marginal probability of receiving raltegravir and etravirine and $\Pr[Z_i = 1 | X_i]$ is the probability of receiving raltegravir and etravirine conditional on the baseline covariates X . Covariates X were selected among the following variables: baseline viral load, baseline CD4 cell count, age, sex, subtype (B or non-B subtype), number of previous drugs used, and the ANRS global resistance score for drugs in the optimised background regimen (drugs other than raltegravir and etravirine). The global score is calculated as follows. For each antiretroviral drug we determined a resistance score of 0 or 1 depending on whether the virus was classified as susceptible/intermediate resistant or resistant according to the ANRS algorithm, respectively. The global resistance score is the sum of all these scores. The score represents, in addition to the number of drugs previously received, the treatment-failure-resistance history of the patient.

Stabilized weights were estimated in following recent recommendations²⁰. In particular, we investigated different specifications for continuous covariates including linear terms (continuous), four-knot restricted cubic splines and categories using the median value of the corresponding variable. Criteria to retain the best subset of variables with best specifications were based on mean,

standard deviation and extreme values of estimated weights and balance diagnostics including computation of standardized difference in the weighted sample ^{20,21}. Adjusted Kaplan-Meier estimates using IPTW provide confounder-adjusted 'survival' curves and log-rank statistics ¹⁶. All statistical analyses were done with SAS version 9.4. In particular the Proc Lifetest with the weight option was used to compute adjusted Kaplan-Meier curves.

3. RESULTS

Of the 349 patients included, 191 (55%) patients started raltegravir and etravirine (raltegravir/etravirine group) for the first time and 158 patients started only raltegravir (raltegravir group) for the first time. Baseline characteristics are summarized in Table 1. Patients in the raltegravir/etravirine group had higher levels of baseline HIV-1 RNA (median: 4.6 vs. 3.9 log₁₀ copies/mm³) and a lower number of CD4 cell count (123 vs. 242 cells/mm³) than patients in the raltegravir group. Furthermore, patients in the raltegravir/etravirine group had previously received more antiretroviral drugs than patients in the raltegravir group (median, 13 vs 11) leading also to a higher number of resistant drugs according to the ANRS algorithm (median, 13 vs. 9). There was no difference in the number of NRTIs and PIs in the optimised background regimen between the two treatment groups. Resistance associated mutations to etravirine are displayed in Table 2 (IAS-USA list) ²² and prevalence of integrase polymorphic mutations shown in appendix Figure 1. Overall, 178 (51%) patients had a plasma HIV-1 RNA level below the limit of quantification (50 or 40 copies/ml) at week 8. There were a lower percentage of patients below the limit of quantification in the raltegravir/etravirine group than in the raltegravir group (48% versus 55%) which may be partially explained by the lower level of baseline HIV-1 RNA in the latter group.

Using the crude method (in which all values below the limit of quantification were replaced by the value of 40 or 50 copies/ml), estimated mean and median reductions were 2.08 and 2.35 in the raltegravir/etravirine group and 1.82 and 1.75 in the raltegravir group, respectively (Table 3). The means difference was statistically significant, p=0.025, and a Wilcoxon rank test between the two

groups was also significant ($p=0.018$). The use of censored methods provided not only larger estimated means and medians but also much smaller differences between treatment groups. Estimated median reductions were 2.77 and 2.93 in the raltegravir/etravirine and raltegravir groups, respectively. The Kaplan-Meier estimates of the distribution of HIV-1 RNA reduction lead to a not significant difference between the two groups (Figure 1, $p=0.92$). Using parametric analysis adjusted for censoring, estimated mean reduction were 2.78 and 2.67 in the raltegravir/etravirine and raltegravir groups, respectively (Table 3, $p=0.58$).

To assess the extent and effect of informative censoring, treatment comparisons were repeated adjusting for the effect of baseline HIV-1 RNA using an analysis of covariance. The baseline HIV-1 RNA effect was significant using both non-parametric ($p=0.02$) and parametric analyses ($p=0.04$), patients with higher baseline levels tend to have larger reductions. Such results implied that treatment comparisons are affected by informative censoring resulting from a dependence on baseline HIV-1 RNA level. Although differences between treatment groups were slightly altered after adjustment for baseline level, conclusions based on p value remain unchanged ($p=0.96$ and $p=0.43$, table 3).

The logistic model was used to estimate stabilized weights (IPTW). The final stabilized weights involved the following four variables: baseline HIV-1 RNA, baseline CD4, the number of previous drugs received, and the ANRS global resistance score for drugs other than raltegravir and etravirine. The 'best' weights were obtained with the four variables included in the model as categories using median values of each variable. The mean of estimated stabilized weights was 0.997 (standard deviation, 0.45) the 1/minimum and maximum estimated weights were 1.72 and 2.49, respectively. Absolute standardized difference in the weighted sample were 2.2, 1.2, 1.8 and 0.9% for baseline HIV-1 RNA, baseline CD4, the number of previous drugs received, and the ANRS global resistance score, respectively. Other diagnostics including the comparison of interactions and higher-order moments in the two treatment groups could not be computed because none of the four variables included in the propensity score model was used as continuous variables. Adjusted Kaplan-Meier

survival curves (Kaplan-Meier curves in the weighted sample) for the two treatment groups are reported in Figure 2. The two curves are somewhat similar to those displayed in Figure 1 and provided a not significant difference between the two treatment groups ($p=0.59$). Then, after adjusting for both censoring due to the limit of quantification and imbalanced baseline characteristics in patients between the two treatment groups, there was no statistical difference in the HIV-1 RNA reduction at week 8 between the raltegravir/etravirine and raltegravir groups.

4. Discussion

The crude method defining all HIV-1 RNA levels below the limit of quantification to be equal to the limit of quantification is straightforward but is known as providing biased estimates¹². Such a bias concerned not only estimates of the magnitude of HIV-1 RNA reduction but also difference estimates between treatment groups. The method, however, is still widely used in the publication and communication of randomized and non-randomized studies. In our data, applying the crude method showed an apparent larger mean and median HIV-1 RNA reductions in patients receiving raltegravir and etravirine compared with patients receiving raltegravir ($p<0.05$). A first analysis with the Kaplan-Meier method, that takes into account the censoring of HIV-1 RNA measurements by the limit of quantification, showed a not significant difference in HIV-1 RNA reduction between these two treatment groups ($p=0.92$). Although, a covariance analysis demonstrated that the assumption of noninformative censoring was violated, implying that further analyses should be adjusted by the baseline HIV-1 RNA levels, such analyses lead also to not significant differences between treatment groups. Such findings based on survival methods, however, may be suspected to bias due to the lack of randomization in our study. Survival analyses based on propensity score approach, taking into account confounding factors, confirmed that there was not significant difference in HIV-1 RNA reduction between patients receiving raltegravir plus etravirine and patients receiving raltegravir.

There is a clinical and virological interest of a more rapid HIV-1 RNA decline although this question is still debating^{4,9,10}. Percentages of patients below a limit of quantification in weeks 2-16 provide only a partial picture of a rapid decline in viral load. For example, in patients with viral suppression (HIV-1 RNA <50 copies/ml) it has been shown that a higher percentage of patients receiving a nevirapine-containing regimen had a residual viremia below 1 copy/ml compared with patients receiving an efavirenz-containing regimen²³. Some authors argued that patients achieving an early virological response to therapy and who continued therapy had a strong likelihood of maintaining or improving those responses for up to 96 weeks¹⁰. Not only is initial suppression of plasma viremia critical for achieving desired treatment responses, but durability of that response is essential because it indicates tolerability and the lack of emergence of drug-resistant virus⁴. It has been shown that drug-resistant viruses can be selected and be replicated even in the first weeks of suppressive ART, thus, potency of antiretroviral therapy during the initial treatment period is of particular interest²⁴. In particular selection of preexisting minority variants of drug-resistant HIV-1 can lead to virological failure in patients who receive antiretroviral therapy with low genetic resistance barriers²⁵. Therefore, we think that there is still an interest in this topic although in our study antiretroviral-experienced patients receiving etravirine plus raltegravir did not exhibit a significantly higher reduction in HIV-1 RNA at week 8 than patients receiving raltegravir.

Several assumptions were required in the analyses of the present work. A covariance analysis showed that the noninformative censoring assumption required for the Kaplan-Meier method was violated. In our context this implied that the value at which a patient's HIV-1 RNA reduction becomes censored was determined by the patient's baseline HIV-1 RNA level¹². However, taking into account baseline HIV-1 RNA levels in both parametric and non-parametric survival analyses provided similar conclusions that without such an adjustment. In addition, the baseline HIV-1 RNA variable is included in the propensity score model and then both methods based on it are adjusted for baseline HIV-1 RNA levels. The use of a parametric version of the Kaplan-Meier method to estimate mean of HIV-1 RNA reduction assume that the HIV-1 RNA level on the log₁₀ scale are at least approximately normally

distributed. Comparing both residuals obtained from the Kaplan-Meier method and from a parametric model confirmed that assumption (data not shown).

Causal inference using the propensity score requires four assumptions: consistency, unmeasured confounders, positivity, and no misspecification of the propensity score model²⁰. Consistency means that a subject's potential outcome under the treatment actually received is equal to the subject's observed outcome. Our work implicitly assumes that consistency holds, which is reasonable assumption when estimating the effect of medical treatments. No unmeasured confounding is a critical assumption in propensity score analyses. For the assumption of no unmeasured confounding to hold, we have to measure enough joint predictors of exposure and outcome such that, within the levels of these predictors, associations between exposure and outcome that are due to their common causes will disappear²⁰. It is known that variables that are unrelated or weakly related to the treatment exposure but related to the outcome should be included in the propensity score model²⁶. We believed that the four variables (baseline HIV-1 RNA and CD4, antiretroviral treatment history and the ANRS global resistance score) retained in the final propensity score model are the most important predictive factors of our week-8 outcome. Positivity is the condition that all subjects have a non-zero probability of receiving each treatment. Cole and Hernan recommend that the assumption is accepted when the mean of stabilized weight is close to one and when there are no extreme values²⁰. Such conditions are satisfied in our study with a mean of 0.997 and a 1/minimum and maximum estimated of 1.72 and 2.49. It was also noted that estimated weights with the mean far from one or very extreme values are indicative of misspecification of the propensity score model²⁰. We investigated different specifications of our model to choose the 'best' specification according to Cole and Hernan²⁰ although we did not use other regression models or machine learning.

The present study has several limitations. First, because this was an observational cohort study, selection bias may have been an issue. However, this was partly addressed by adjusting for potential baseline confounders. Second, optimized background regimens were heterogeneous and no

information of compliance on regimens was recorded. Third, sample sizes in the two treatment groups were relatively small.

In conclusion, we did not demonstrate that antiretroviral-experienced patients receiving raltegravir and etravirine for the first time had a higher HIV-1 RNA reduction at week 8 compared with patients receiving raltegravir for the first time. We aimed at comparing crude method, censored methods and adjusted censored methods both to estimate and compare HIV-1 RNA reduction between treatment groups. Our findings confirmed that crude methods provided biased estimate of viral load reduction. The different steps of our analyses may be used for many other biological variables censored with some limits of quantification.

Table 1. Characteristics of the 349 patients participating in the present study.

Characteristics	Raltegravir + etravirine n=191	Raltegravir n=158
Median age (years)	47 (43, 51)	45 (41, 52)
Median log ₁₀ HIV RNA level (copies/ml)	4.6 (3.6, 5.1)	3.9 (3.1, 4.8)
Median CD4 cell count (cells/mm ³)	123 (28, 285)	242 (102, 390)
Median number of ARV agents associated with the current regimen		
NRTIs	2 (1, 2)	2 (1, 2)
PIs	1 (0, 1)	1 (0, 1)
Median number of previous ARV agents received		
All agents	13 (11, 15)	11 (7, 14)
NRTIs	6 (5, 7)	6 (4, 6)
NNRTIs	1 (1, 2)	1 (1, 2)
Pis	5 (4, 6)	4 (2, 5)
Median ANRS global resistance score	13 (10, 14)	9 (2, 13)
Median ANRS NRTIs resistance score	5 (4, 6)	4 (0, 5)
Median ANRS NNRTIs resistance score	2 (1, 2)	1 (0, 2)
Median ANRS PIs resistance score	6 (5, 7)	4 (1, 6)
Male gender	153 (80%)	108 (68%)
Subtype B	164 (96%)	109 (69%)
Main NRTIs in the background regimen		
Lamivudine/Emtricitabine	137 (72%)	118 (75%)
Abacavir	53 (28%)	47 (30%)
Tenofovir	89 (47%)	90 (57%)
Other drug in the background regimen		
Enfuvirtide	48 (25%)	30 (19%)

Abbreviations: NRTI, Nucleoside Reverse Transcriptase Inhibitors; NNRTI, Nonnucleoside Reverse Transcriptase Inhibitors; PI, Protease Inhibitor; ANRS, Agence Nationale de Recherche sur le SIDA ;

Table 2. Prevalence of resistance associated mutations to Etravirine (IAS-USA drug mutations list January 2017).

Mutations	Raltegravir + etravirine n=191	Raltegravir n=158
V90I	13 (7%)	11 (7%)
A98G	30 (16%)	8 (5%)
L100I	20 (11%)	8 (5%)
K101EHP	27 (14%)	11 (7%)
V106I	8 (4%)	5 (3%)
E138AGKQ	12 (6%)	11 (7%)
V179DFT	5 (3%)	10 (6%)
Y181CIV	59 (31%)	32 (21%)
G190AS	54 (28%)	19 (12%)
M230L	3 (2%)	4 (3%)

Table 3. HIV-1 RNA reductions in log₁₀ copies/ml differences and significance of differences between treatment groups.

	Raltegravir + etravirine	Raltegravir	Differences	p value
Crude mean	2.08	1.82	0.26	0.025
Crude median	2.35	1.75	0.60	0.018*
Censored mean	2.78	2.67	0.11	0.58
Censored median	2.77	2.93	-0.16	0.92
Adjusted censored mean	2.67	2.66	0.01	0.96
Adjusted censored median	2.59	2.73	-0.14	0.53

*Wilcoxon rank test.

Figure 1. Kaplan-Meier estimates and corresponding log-rank test of the distribution of HIV-1 RNA reductions between baseline and week 8.

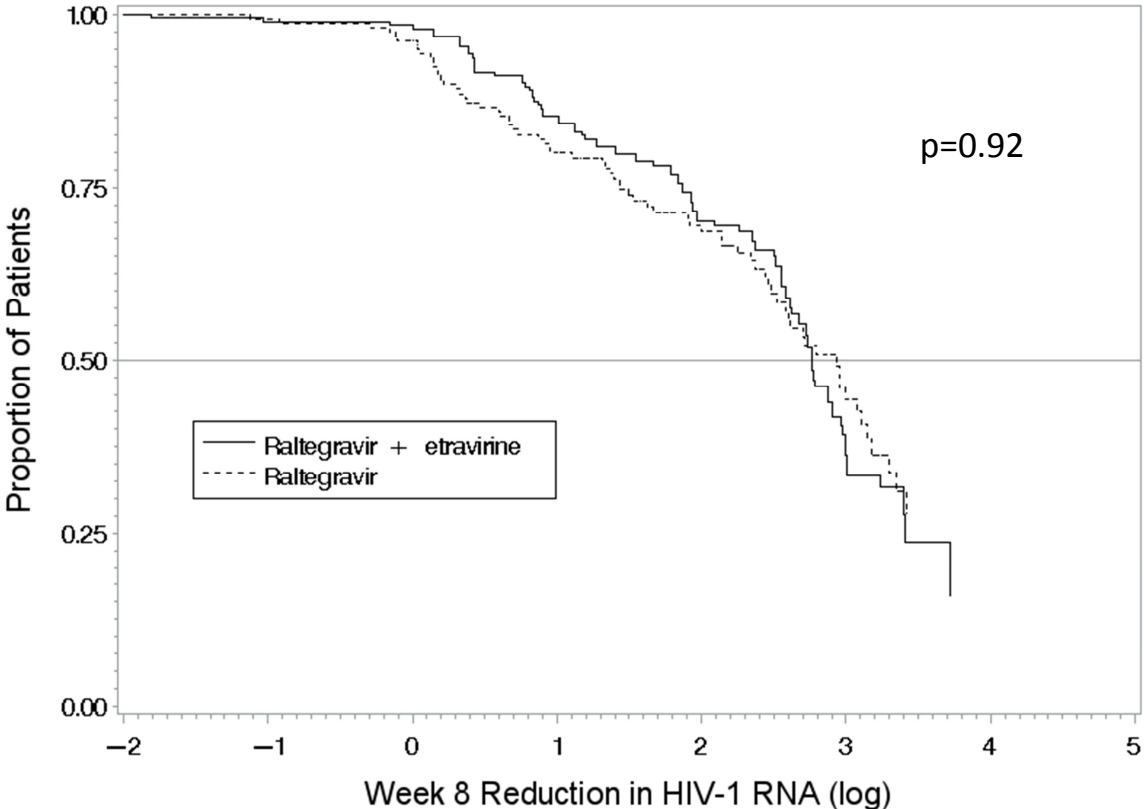
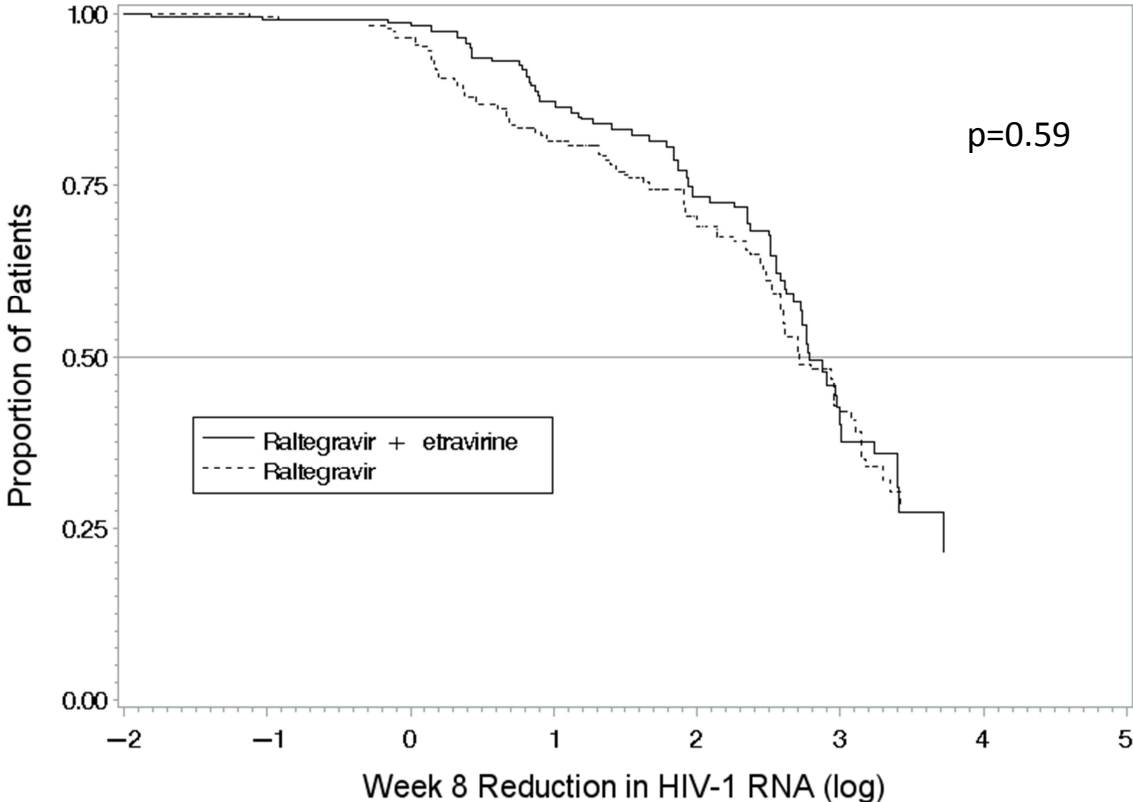


Figure 2. Adjusted Kaplan-Meier estimates using invers probability of treatment weighting and corresponding log-rank test of the distribution of HIV-1 RNA reductions between baseline and week 8.



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