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Illustration of a measure to combine viral suppression and viral rebound in studies of HIV therapy

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Abstract

Viral load is an important tool for assessing antiretroviral treatment efficacy. However, the most common viral load endpoint, virologic failure, may be flawed. We illustrate an alternative endpoint that estimates the average time patients spent suppressed prior to rebound in the AIDS Clinical Trials Group A5095 trial. Patients averaged 644 days suppressed in the 3-drug arm and 686 days suppressed in the 4-drug arm, for a difference of 42 days in favor of the 4-drug regimen (95% CI: –11, 96). These results agree with results using virologic failure as the endpoint but better emphasize the separate suppression and rebound processes.

Introduction

Plasma HIV-1 RNA (henceforth, viral load) is an important biomarker to monitor infection and to assess the prognosis of patients with HIV. Clinicians use measurements of viral load together with CD4 cell count, symptoms, and AIDS-defining illnesses to inform treatment decisions and assess the efficacy of a given antiretroviral treatment (ART) regimen ¹.

Viral load is also an important measure for researchers wishing to describe effects of a treatment over time or to compare effects of treatment regimens ². Perhaps the most commonly used endpoint to compare the efficacy of treatment plans is the time to “virologic failure” ^{3–7}. The time to virologic failure for patients whose viral load is not suppressed by a predetermined time during the study period is often set to that predetermined time ^{5,6} or time zero ⁸. In addition, studies using virologic failure as an endpoint often ignore viremia prior to suppression by measuring the time to virologic failure as the time from study onset to viral rebound ⁷.

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Conflicts of Interest:

The authors declare no conflicts of interest.

Gouskova et al ⁹ formalized an alternative endpoint based on multistate methods ¹⁰ that uses information on time to both viral load suppression and rebound to estimate the probability of being suppressed as a function of time from study onset. Here, we provide an illustrative example in which we estimate this measure to compare the efficacy of two treatment regimens in a randomized trial.

Methods

We compare this alternative endpoint between treatment arms in publicly-available de-identified data from the AIDS Clinical Trials Group A5095 trial ⁶ conducted between March 2001 and March 2005. Briefly, 1125 therapy-naïve patients infected with HIV-1 were randomized to one of 3 arms: a triple-nucleoside regimen (zidovudine, lamivudine, and abacavir), a 3-drug standard of care regimen with efavirenz (zidovudine, lamivudine, and efavirenz), or a 4-drug regimen with efavirenz (zidovudine, lamivudine, abacavir, and efavirenz). We limit the analysis to patients randomized to the 3- and 4-drug efavirenz-containing regimens (as did Gulick et al ⁶) because the triple-nucleoside group was discontinued. Data for 761 of the 765 patients in the 3- and 4-drug arms were available in the public-use dataset. Treatment was initiated at randomization. Study visits were conducted at weeks 2, 4, 8, 12, 16, 20, 24, and then every 8 weeks, and viral load was measured at each study visit. Here we perform an intent-to-treat analysis in which we estimate the effect of being randomized to a specific treatment regimen, rather than the effect of the actual treatment received.

Patients were followed from randomization until viral rebound or censoring at time of death, loss to follow-up, or 1012 days. A patient is considered lost to follow-up if his last visit was before day 1012 and he had not yet experienced viral rebound or death.. Following Gulick ⁶, a patient's viral load was "suppressed" if it was below 200 copies/mL, and a patient was considered to have experienced viral rebound if his viral load rose above 200 copies/mL after dropping below this threshold. Alternative thresholds for suppression and rebound could be chosen. We assume that viral load was unsuppressed until the first viral load measurement in which viral load was suppressed (and likewise for viral rebound).

To summarize treatment effects, we compare the mean time patients spend in a state of viral suppression in each trial arm ⁹. We define a patient to be in a "state of viral suppression" after initial viral suppression and prior to first viral rebound. To estimate this outcome measure for one treatment arm, we begin by estimating the probability of being in a state of suppression at each time point. Specifically, being suppressed at time t requires that a patient has already experienced viral suppression by time t , but not yet experienced viral rebound. Accordingly, the probability of being in a state of suppression can be denoted by $G(t)$ and estimated for each treatment arm x as $\hat{G}_x(t) = \hat{S}_x^R(t) - \hat{S}_x^S(t)$, where $\hat{S}_x^R(t)$ is the product limit estimator of the Kaplan-Meier survivor function for rebound for treatment arm $X = x$ and $\hat{S}_x^S(t)$ is the survivor function for initial viral suppression for that treatment arm. Note that $\hat{S}_x^R(t)$ will always be greater than $\hat{S}_x^S(t)$ because, by definition, a patient's viral load cannot rebound before it is suppressed below the threshold value. The quantity $\hat{G}_x(t)$ has the intuitive interpretation as the proportion of patients in treatment arm x who have not yet

rebounded, excluding those who have not yet initially suppressed. This measure can be summarized as the τ -restricted mean time spent in a state of suppression (prior to rebound) by integrating $\hat{G}_x(t)$ over the study period τ . Because the survivor functions can change at most once per day, the mean time suppressed over the 1012-day follow-up period for

treatment arm x can be calculated as the Riemann sum $A(x) = \sum_{k=1}^{1012} G_x(t_k)$. The components of this measure for each arm can be seen in figure 1.

The difference in mean time spent in a state of suppression can be compared between treatment regimens, with inference based on the closed-form equation for the variance presented in Supplemental Digital Content: Appendix 1 or a nonparametric bootstrap. Additional technical details and SAS computer code are provided in Appendices 1 and 2.

Results

The 761 participants were 81% male, had a mean age of 37, and were predominantly white (41%) or black (35%). The prevalence of hepatitis C virus was 10% and the prevalence of hepatitis B virus was 3%. Demographic characteristics were similar between the 380 patients in the 3-drug arm and the 381 patients in the 4-drug arm.

Over the 1012 days of follow-up, 12 patients died (8 in the 3-drug arm and 4 in the 4-drug arm) and 236 patients became lost to follow-up (111 in the 3-drug arm and 125 in the 4-drug arm). Over the course of follow-up, 356 patients in the 3-drug arm (93.7%) and 354 patients in the 4-drug arm (92.9%) responded to treatment by suppressing their HIV-1 RNA viral load below 200 copies/mL at one or more time points. The median time from randomization to initial viral load suppression was 56 days in both groups. During the course of follow-up, 121 patients in the 3-drug arm and 112 patients in the 4-drug arm experienced viral rebound after initial viral suppression. The probability of being in a state of suppression prior to rebound at each time during follow-up, $G_x(t)$, can be seen for both arms in Figure 2. Over the 1012-day follow-up period, the average number of days suppressed prior to rebound was 644 in the 3-drug arm and 686 in the 4-drug arm, for a difference of 42 days in favor of the 4-drug regimen (95% CI: -11, 96).

Discussion

Using the proposed endpoint, we have demonstrated that the 4-drug regimen conferred a slight benefit over the 3-drug regimen in terms of number of days spent in a state of viral suppression without viral rebound. These results agree with an existing study using virologic failure as the endpoint ⁶, which noted that the time to virologic failure, defined as the first of two successive viral load measurements above 200 copies/mL after 16 weeks, was not significantly longer in the 4-drug arm. However, the particular advantages of the 4-drug regimen regarding time to initial suppression and rebound are seen more readily using the proposed approach.

In addition to providing an endpoint that is readily interpretable and simple to communicate, the proposed approach avoids several pitfalls associated with using virologic failure as an

endpoint. For example, virologic failure is sometimes defined as the time to the first viral load measurement over 200 copies/mL at or after 16 weeks from randomization^{5,6}. Under this definition, the time to virologic failure is set to the ad hoc time point of 16 weeks if the patient fails to respond to treatment by achieving a suppressed viral load by that time. When the event of interest is virologic failure, the event pool is a mixture of 2 distinct types of events: patients who have experienced virologic suppression and then rebound, and patients who did not achieve virologic suppression on or before the cut point. Such a composite endpoint fails to keep inferences distinct between these event types. For example, use of virologic failure as a composite endpoint hides differences in early suppression dynamics between treatment arms. Similarly, differences in the time to suppression are hidden if the time to virologic failure is estimated as the time from suppression to rebound only among patients who suppress.

The approach to measuring viral suppression illustrated here is based on the probability of being suppressed over time using ideas from multistate models developed for multiple time-to-event endpoints¹⁰. As formalized by Gouskova et al.⁹, this approach can be extended to incorporate a time-varying weight to place greater importance on the probability of suppression at any time window during follow-up. For example, the weights can be used to improve precision by down weighting time points when the probability difference is highly variable (e.g., by applying a weight of 1/standard-error of the probability difference at each time point). Alternatively, weights can be used to tailor the analysis to research questions emphasizing outcomes at certain time windows. For example, if replication ceases at treatment initiation for both treatment arms, and the time to suppression is merely a function of the size and composition of a patient's viral reservoir^{11–13}, early differences in time spent in a state of suppression may be clinically less important than differences at later times. In this scenario, the investigator could down-weight the differences in the probability of suppression at these early time points to focus the analysis on differences in the probability of suppression after some clinically relevant time-point. When weights are set to 1 for all time points, as in the example presented here, the integral of the difference in the probability of suppression over time has the intuitive interpretation of the difference in the restricted mean number of days suppressed prior to rebound between treatment arms.

We have used this approach to compare the mean number of days spent in a state of suppression between arms of a randomized trial. This approach could also be used to compare suppression between exposure groups in observational studies using inverse probability weights^{14,15} or the parametric g-formula^{16,17} to account for confounding by measured variables. Extensions of this approach to observational studies would allow this endpoint to be used when examining the effects of exposures that are unlikely to be randomized. In addition, while we define a patient to be in a state of viral suppression after initial viral suppression and prior to first viral rebound, this approach can be extended to allow for multiple cycles of suppression and rebound.

HIV-1 RNA viral load remains an important outcome measure in HIV randomized trials and observational studies. We have illustrated an endpoint that uses information on the time to viral suppression and time to subsequent viral rebound to provide a single summary measure of the mean time spent in a state of viral suppression before viral rebound in each treatment

arm. This endpoint is well defined, has an appealing graphical representation, and facilitates straightforward comparisons of treatment effects between studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Illustration of the survival curve for suppression ^a (solid line), the survival curve for rebound (dashed line), and the restricted mean time spent in a state of suppression ^b for 380 patients in the 3-drug arm (panel A) and 381 patients in the 4-drug arm (panel B) of the ACTG A5095 trial over 1012 days of follow-up

^aThe survival curves for initial viral suppression, $\hat{S}_0^S(t)$, and viral rebound, $\hat{S}_0^R(t)$ were estimated using the Kaplan-Meier product limit estimator of the survivor function. Details are provided in the Supplemental Digital Content: Appendix

^bThe restricted mean number of days spent in a state of suppression (i.e., time after initial suppression and prior to viral rebound) over the 1012-day follow-up period for each arm

was estimated as $A(x) = \sum_{k=0}^{1012} G_x(t_k)$ where $\hat{G}_x(t) = \hat{S}_x^R(t) - \hat{S}_x^S(t)$

Figure 2.

Probability of being in a state of suppression prior to viral rebound, $G_x(t)$, for 380 patients in the 3-drug arm and 381 patients in the 4-drug arm of the ACTG A5095 trial over 1012 days of follow-up