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Risk of Viral Failure Declines with Duration of Suppression on HAART, Irrespective of Adherence Level

Viviane D. Lima^{1,2}, David R. Bangsberg³, P. Richard Harrigan^{1,2}, Steven G. Deeks⁴, Benita Yip¹, Robert S. Hogg^{1,5}, and Julio S.G. Montaner^{1,2}

¹British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, British Columbia, Canada

²Division of AIDS, Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

³Massachusetts General Hospital, Harvard Medical School, Harvard Initiative for Global Health, Boston, Massachusetts, USA

⁴University of California, San Francisco, California, USA

⁵Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada

Abstract

Objective—To model the effect of adherence and duration of viral suppression on the risk of viral rebound.

Methods—Viral rebound was defined as the first of at least 2 consecutive viral loads >400 copies/mL following initial viral suppression. The main exposures were adherence, presence of ARV class resistance before rebound or censoring date, and the percentage of follow-up time with viral suppression.

Results—A total of 274 (N=1305; 21%) individuals experienced viral rebound. Median time of suppression before rebound was 2 years. Viral rebound was less likely to occur among those with longer duration of continuous viral suppression (odds ratio 0.37; 95% confidence interval [CI] 0.32-0.42). Among individuals with moderate levels of adherence (80%–<95%), the probability of virologic failure was 0.85 after being suppressed for 12 months and it was 0.08 after 72 months being suppressed (*p*-value <0.01). Individuals with drug resistance were at a higher risk of viral rebound.

Conclusions—The risk of viral rebound decreased with longer duration of viral suppression within each of adherence strata studied. While perfect adherence remains an important goal of therapy to prevent disease progression, individuals with long-term viral suppression may be able to miss more doses without experiencing viral rebound.

Send correspondence to: Viviane Dias Lima, PhD; St. Paul's Hospital/BC Centre for Excellence in HIV/AIDS; Room 608, 1081 Burrard Street; Vancouver, British Columbia; V6Z 1Y6; CANADA; vlima@cfenet.ubc.ca; Phone: 604-806-8796; Fax: 604-806-9044.

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Keywords

Adherence; HAART; virologic failure; viral rebound; resistance; long-term suppression

INTRODUCTION

Modern highly active antiretroviral therapy (HAART) suppresses HIV-1 RNA plasma viral load (hereafter referred to as pVL) below detectable limits for long periods, enabling immune reconstitution, reducing HIV drug resistance and preventing clinical disease progression [1-5]. However, the success of HAART has been accompanied by important challenges, with long-term high adherence to HAART being the major determinant of therapy success [1-5].

It is well recognized that high levels of adherence are necessary for achieving viral suppression (i.e. <50 copies/mL). The adherence level may vary among the various antiretroviral drug classes, but most studies have concluded that adherence levels in excess of 95% are necessary for achieving an optimal virologic response during the first year of therapy and avert disease progression [2,3,6,7]. Maintaining such high levels of adherence over, potentially, decades of treatment may represent a burden for some individuals.

Untreated HIV infection is associated with very high rates of viral replication and viral evolution. Theoretical models and subsequent empiric data demonstrated that complete (or near complete) suppression of HIV replication is generally achieved with regimens containing three potent antiretroviral drugs and near perfect adherence [8-10]. Once effective therapy is initiated, the total body burden of replication of competent virus declines, at least during the first few years of therapy [11,12]. This latter observation suggests that the level of drug exposure necessary to maintain viral suppression may be lower than the level necessary to achieve an initial virologic response, which has been shown to be true in a recent small cohort study and in previous induction maintenance studies [13-16]. Based in part on these theoretical considerations, the objective of this study is to model the effect of adherence and duration of viral suppression on the risk of viral rebound in a large cohort of treatment naïve individuals starting HAART in British Columbia (BC), Canada. We hypothesize that the level of adherence required to prevent viral rebound declines with the duration of continuous viral suppression.

METHODS

Study Population

This study was conducted using retrospective data from the BC Centre for Excellence in HIV/AIDS registry database, which is the only distribution source of antiretroviral agents, at no cost, to all clinically eligible HIV-infected individuals in BC [2,3]. Through its HIV/AIDS Drug Treatment program (DTP) established in 1992, antiretrovirals are distributed based on guidelines generated by the Centre's therapeutic committee and in accordance with the latest guidelines of use of antiretrovirals for adults and adolescents published by the International AIDS Society-USA [1]. Typically, patients are monitored by physicians at intervals no longer than three months, and their prescriptions are renewed or modified and their addresses are updated. In order to maintain the profile of DTP patients up-to-date, the consent form signed by these individuals at the time of enrolment allows us to conduct regular linkages with a number of provincial administrative databases to obtain their current information regarding mortality and morbidity. Deaths are identified on a continuous basis from physician reports and through record linkages carried out with the BC Division of Vital Statistics. Morbidity information is obtained from linkages with administrative databases containing hospital discharge data, emergency admissions, medical visits and laboratory testing.

Eligible study participants were ≥ 18 years old, naïve to antiretroviral therapy when they started a regimen consisting of two nucleoside/nucleotide analogues plus either (1) a non-nucleoside reverse transcriptase inhibitor [NNRTI], or (2) a protease inhibitor boosted with ≤ 400 mg/day ritonavir [boosted PI], or (3) a single protease inhibitor [non-boosted PI]. In this study, we decided to use an intention to treat approach, and to not update changes in treatment over time. These individuals have started HAART between January 01, 2000 and June 30, 2006, and were followed until June 30, 2007, and they were included if they had at least one baseline CD4 cell count and a pVL measurement available within six months prior to the first antiretroviral starting date. The data were adjusted for 1) scheduled treatment interruptions, given that information on the return date of the individual to the program is unclear; 2) individuals moving out of the province; 3) deaths from non AIDS or AIDS-related causes; 4) lost to follow-up; and 5) individuals enrolled in a blinded trial involving receiving placebo medication. In these situations, we opted to censor an individual at the last contact date before each of these events. This analysis has received ethical approval from the University of British Columbia Ethics Review Committee at the St Paul's Hospital site.

Laboratory Data

The Centre's guidelines recommend that pVL and CD4 cell count be monitored at baseline, at four weeks after starting antiretroviral therapy and every three months thereafter. The Roche Amplicor Monitor ultrasensitive assay version 1.5TM (Roche Diagnostics, Laval, Quebec, Canada) was used to measure pVL centrally at the St Paul's Hospital virology laboratory in BC, with the lower and upper limits of quantification ranging from 50 to 100,000 copies/mL. CD4 cell counts were measured by flow cytometry, followed by fluorescent monoclonal antibody analysis (Beckman Coulter, Inc., Mississauga, Ontario, Canada). HIV drug resistance genotyping was performed centrally at the Centre's laboratory on samples with pVL ≥ 250 copies/mL collected at baseline and following HAART initiation. Samples were assigned to one of four resistance categories based on a modification of the IAS-USA table [17]. Samples were considered resistant if they displayed one or more major resistance mutations in any of the four categories: 1) lamivudine/emtricitabine (184I/V); 2) any other nucleoside reverse transcriptase inhibitors (41L, 62V, 65R, 67N, 69D or insertion, 70R, 74V, 75I, 151M, 210W, 215F/Y or 219E/Q); 3) any non-nucleoside reverse transcriptase inhibitors (100I, 103N, 106A/M, 108I, 181C/I, 188C/H/L, 190A/S, P225H, M230L or 236L); and 4) any protease-inhibitors (30N, 46I/L, 48V, 50L/V, 54V/L/M, 82A/F/S/T, 84V, or 90M). Lamivudine/emtricitabine resistance was considered as a separate resistance category due to its high frequency and the lack of cross-resistance conferred to other nucleoside reverse transcriptase inhibitors.

Outcome Measure

The main outcome was viral rebound defined as the first of at least two consecutive pVLs >400 copies/mL following initial viral suppression (*i.e.* first of at least 2 consecutive pVL <50 copies/mL) (coded as yes vs no).

Covariates

The main exposures in this analysis were longitudinal adherence level, percentage of follow-up time with pVL <50 copies/mL and presence of drug resistance in any of the four resistance categories before rebound or censoring date. To calculate the percentage of follow-up time with pVL <50 copies/mL, we were required to also obtain pVL measurements longitudinally, *i.e.* every three months, from the date of first suppression (time zero) until the viral rebound or censoring date of the study. Longitudinal adherence levels were synchronized with the dates of the pVL measurements. Adherence level, for each period, was defined as the number of days of antiretroviral drugs dispensed divided by the number of days of follow-up (expressed as percent). Estimates of adherence to antiretroviral therapy were based on the different

regimen exposures for each patient. Although patients with undetectable pVL less commonly have medications changed, the regimens can change due to adverse effects or other medical and non-medical reasons, and we also accounted for those changes. Measuring adherence to any specific antiretroviral drug as index medication when it can be changed at any point in time makes it difficult for accurate monitoring. For this reason, the measure of adherence that we chose to adopt does not use any specific index medication, and it only measures the overall exposure to any antiretroviral regimen. For descriptive purposes, we also presented information on adherence during the first year of therapy; however, this measure of adherence was not included in any of the statistical analysis. For the longitudinal analysis, we categorized adherence into four groups: 0%–<40%, 40%–<80%, 80%–<95% and ≥95%. These bounds have been previously shown to be important in explaining antiretroviral drug resistance, immunologic and virologic outcomes [2,18]. The other explanatory variables investigated were measured at the time of HAART initiation, and they included: age, gender, pVL ($\log_{10}$ transformed), AIDS diagnosis, history of injection drug use (IDU), and year of first therapy. Nadir CD4 cell count was also considered in the model and defined as the lowest CD4 for a person before receiving therapy and until the time of first suppression. Note that nadir CD4 cell count was based on CD4 cell count data available in our database, which captures 90% of all CD4 tests done in the province. HAART regimens were classified at the time of first suppression (NNRTI, boosted or multiple PIs and other ARV combinations). In sensitivity analyses, we investigated whether therapy switches influenced the odds of viral rebound among those who rebounded and those who were suppressed until the end of follow-up. The allowable switches were NNRTI ↔ unboosted PI, NNRTI ↔ boosted PI, NNRTI ↔ multiple PI, unboosted PI ↔ boosted PI, unboosted PI ↔ multiple PI, and boosted PI ↔ multiple PI.

Statistical Analyses

To analyse the longitudinal effect of the main exposures and the previous explanatory variables on the odds of viral rebound, we built explanatory models using Generalized Estimating Equations assuming a binomial distribution, a logit link function and an autoregressive correlation structure of order 1 [19]. A backward stepwise technique was used in the selection of covariates for an explanatory model [18]. The selection of variables was based on two criteria: Akaike Information Criterion (AIC) and Type III p-values. These two criteria balance the model choice on finding the best explanatory model (Type III p-values – lower p-values indicate more significance) and at the same time a model with the best goodness-of-fit statistic (AIC – lower values indicate better fit). At each step of this process, the AIC value and the Type III p-values of each variable are recorded, and the variable with the highest Type III p-value is dropped, until there are no more variables left. The final model has the lowest AIC. Categorical variables were compared using the Chi-Square or Fisher's exact test, and continuous variables were compared using the Wilcoxon rank-sum test. All analyses were performed using SAS software version 9.1.3 Service Pack 3 (SAS, Cary, NC).

RESULTS

Overall Cohort Characteristics

A total of 1305 antiretroviral naïve adults (84% males) were eligible to participate in this study. At baseline, the median age was 42 years (interquartile range [IQR] 36–49 years), the median CD4 cell count nadir was 130 cells/mm³ (IQR 50–200 cells/mm³), the median pVL was 5.0 $\log_{10}$ copies/mL (IQR 4.7–5.0 $\log_{10}$ copies/mL) and 22% of individuals had a history of IDU. At the time of suppression, 543 (41%) individuals have not been tested for resistance, mainly due to the fact that their viral loads were <250 copies/mL and, therefore, genotypic testing could not be performed.

As of June 30, 2007, 8.4% of individuals died of non AIDS or AIDS-related causes (rate 17.0 per 1000 person-years), 3.8% were lost to follow-up (rate 9.9 per 1000 person-years), 1.8% moved out of BC (rate 4.6 per 1000 person-years), 0.1% censored because they've enrolled in a blinded trial involving receiving placebo medication (rate 0.2 per 1000 person-years), and 88.0% were followed until the study ending date (rate 232.0 per 1000 person-years).

Risk of Viral Rebound

Of the 1305 individuals who achieved an initial virologic response, 274 (21%) subsequently experienced viral rebound. The median time of suppression before rebound in these 274 individuals was 2.0 years (IQR 1.1-3.5 years). Viral rebound after suppression was independently associated with being female, having a history of IDU, starting HAART in 2000-2001 (as compared to after 2001), receiving treatment regimen that did not include an NNRTI or a boosted PI, being younger and having resistance to any class of antiretrovirals (p-values <0.01) (Table 1). In total, 239 (23%) of individuals who did not experience a viral rebound changed therapy during the time they were suppressed, and 67 (24%) individuals changed therapy in the group that rebounded. These percentages were not statistically different (p-value 0.51).

The duration of prior viral suppression was also predictive of subsequent rebound risk. Viral rebound was less likely to occur among those with long duration of suppression (in years) (odds ratio (OR): 0.37; 95% confidence interval (CI) 0.32-0.42). This translates into an odds of viral rebound decrease of 8% per month of continuous viral suppression across all adherence levels. For individuals with high levels of adherence ($\geq 95\%$), the probability of rebound was 0.10 (IQR: 0.07-0.40) after being suppressed for 12 months and 0.04 (IQR 0.02-0.06) after being suppressed for 72 months. Amongst individuals with moderate levels of adherence (80%-<95%), the probability of rebound was 0.85 (IQR 0.16-0.94) after being suppressed for 12 months and 0.08 (IQR 0.03-0.21) after being suppressed for 72 months. Among individuals with low adherence (<40%) the probability of rebound was 0.68 (IQR 0.29-0.85) after being suppressed for 12 months and 0.05 (IQR 0.03-0.10) after 72 months (Figure 1). In this analysis, therapy switches between the time of first suppression and the end of follow-up did not play a role in the individual's probability of viral rebound.

The level of adherence was also a consistent factor explaining the outcome once viral suppression was achieved. After adjusting for duration of suppression, individuals with adherence <95% were 11% more likely to rebound (<40% - OR: 1.16, 95% CI 1.12-1.21; 40%-<80% - OR: 1.07, 95% CI 1.05-1.10; and 80%-<95% - OR: 1.09, 95% CI 1.03-1.14) than those $\geq 95\%$ adherent. Individuals with drug resistance prior to achieving viral rebound were 2.78 (95% CI 1.68-4.59) times more likely to experience viral rebound than those with no resistance; in addition, individuals not tested, mostly often because their viral loads were <250 copies/mL, were at lower risk to rebound (OR: 0.61; 95% CI 0.39-0.94) (Table 1).

DISCUSSION

It is well-known that high levels of adherence are necessary to achieve an initial viral response. The degree to which high levels of adherence are needed to maintain viral suppression, once achieved, has not been previously well defined. In our cohort of over 1000 well characterized individuals receiving their initial HAART regimen, we found that once viral suppression was initially achieved, high levels of adherence ($\geq 95\%$) were still needed for at least the first year. Over time, however, the risk of viral rebound strongly decreased with maintained viral suppression, irrespective of the level of adherence.

Our data are consistent with recent findings by Rosenblum et al. who also found that the risk of viral rebound declined over time in a smaller, far more heterogeneous group of marginally

housed highly treatment experienced individuals followed in San Francisco [13]. In that cohort, the risk of virologic failure for adherence between 75%–<90% was 0.34 after one month of suppression and 0.06 after 12 months of suppression. Our findings are also consistent with induction maintenance studies and lopinavir-ritonavir monotherapy studies that suggest lower levels of antiretroviral drug exposure are required to sustain viral suppression once viral suppression is achieved than when initiating therapy with high level viraemia [14–16]. These data suggest that individuals are most vulnerable to missed doses shortly after achieving viral suppression, and may be able to better tolerate missed doses with long-term viral suppression.

One possible explanation for our finding is that lower levels of drug exposure are required to prevent viral rebound because the overall viral burden declines over time. This was perhaps most clearly shown by Palmer and colleagues [12], who used a novel real-time reverse transcriptase-initiated PCR assay with single-copy sensitivity to quantify the level of viremia in long-term protease inhibitor treated individuals. The level of residual viraemia, which the authors assumed was coming from a long lived cellular reservoir rather than active replication, declined during the first 9–15 months of therapy, and then reached a stable level. These data are generally consistent with a number of other observations using different assays [11, 20–23].

Another possible explanation for our findings is survivor bias. This bias may be entirely responsible for the observed decreases in probability of viral rebound with longer suppression. Specifically, the subpopulation of individuals who remain virally suppressed for longer periods may differ in many important ways from the rest of the enrolled cohort. We, therefore, cannot infer any cause-effect relationship between duration of suppression and lower probability of viral rebound. To address this issue, we conducted several sub-analyses to determine if this effect holds after stratifying for pre-HAART factors, such as CD4 cell count, history of injection drug use and sex, and for post-HAART factors such as regimen type, adherence and duration of viral suppression. Note that the list of possible covariates used in these sub-analyses is not exhaustive, and we acknowledge that there are several other possible factors, not available in our data, that we could have stratified the data by. Overall, we observed that in our multivariate analyses, adjusting for both baseline and time-dependent factors, duration of viral suppression was still highly associated to subsequent rebound risk, with those individuals with longer duration of suppression having a lower risk of subsequent viral rebound. There were subtle differences depending on how we stratified the data, but the message in all sub-analyses was that the “cost” of missed doses declines the longer an individual is suppressed. Although this phenomenon is observed throughout many clinical practices, it is still not clear what mechanism (e.g. reservoir size, genetic factors, selection bias) explains our findings. Because of these limitations, it is important to reinforce the message to individuals that sustained and near perfect adherence increases the probability of long-term viral suppression.

There are several novel aspects to this study. Our cohort had a median duration of follow-up after achieving suppression of four years (minimum 0.2 years, maximum 7.2 years), included individuals initiating therapy receiving the three most common classes of antiretrovirals, and offered comprehensive adherence information. Additionally, our study was carried out within a province-wide treatment program providing free access to medical attention, combination antiretroviral therapy, and laboratory monitoring. We are confident, therefore, that our results were not highly influenced by access to therapy, a factor that has often compromised the interpretation of other cohort studies.

There are several potential limitations in our study. First, we used time updated pharmacy-refill compliance to therapy as a surrogate for adherence. This is a conservative measure of adherence that likely overestimates the true level of adherence. It is important to mention that there is no gold standard to measure adherence, and given that our data were obtained from a

registry of all HIV patients who have ever received therapy in British Columbia, this measure of adherence was chosen as the most appropriate and effective method to assess adherence in our setting. Second, although we showed that having resistance to any class prior to suppression did not affect the risk of rebound, we cannot discard the possibility of measurement bias, given that 40% of our study participants lacked prior resistance data. Third, we used an intention to treat approach and did not update changes in treatment over time in the main analyses. However, our sensitivity analyses indicated that therapy switches did not affect the risk of viral rebound.

In summary, our results demonstrate that duration of continuous viral suppression under HAART had a strong effect in preventing viral rebound regardless of the adherence level. Our results reinforce the message to individuals that sustained and near perfect adherence increases the probability of long-term viral suppression, particularly critical at the earliest stages of treatment, however, as the resilience of HAART increases over time, it is possible that individuals remain fully suppressed even after missing some doses of medication. Therefore, we call for a multidisciplinary long-term comparative study of early failures versus sustained suppressors as one of the ways to better understand the factors associated with the phenomenon observed in this study.

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Figure 1.

Estimated probabilities of viral rebound according to the percentage of follow-up time with suppressed (< 50 copies/mL) HIV-1 plasma viral load by adherence level ($0\% - < 40\%$, $40\% - < 80\%$, $80\% - < 95\%$, $\geq 95\%$). Data are median values; bars show interquartile range. N*: Number of study participants that have contributed to a particular stratum at a point in time.

Table 1

Baseline characteristics associated with viral rebound and multivariate analysis result of baseline and time-dependent factors associated with viral rebound.

Variable	Rebound		p-value	Odds Ratio of Rebound (95% confidence interval)
	No (N=1031)	Yes (N=274)		
Gender				
Male	893 (86.6%)	197 (71.9%)	<0.01	1.00 (–)
Female	138 (13.4%)	77 (28.1%)		1.68 (1.05 - 2.69)
Age (years)*	43 (36 - 50)	39 (33 - 46)	<0.01	0.98 (0.96 - 1.00)
Injection drug use history				
No	843 (81.8%)	168 (61.3%)	<0.01	1.00 (–)
Yes	188 (18.2%)	106 (38.7%)		1.77 (1.17 - 2.69)
Year of first ARV				
2000 - 2001	212 (20.6%)	140 (51.1%)	<0.01	1.00 (–)
2002 - 2004	289 (28.0%)	89 (32.5%)		0.26 (0.16 - 0.42)
2005 - 2006	530 (51.4%)	45 (16.4%)		0.03 (0.01 - 0.05)
Regimen at time of first supression				
NNRTI	394 (38.2%)	116 (42.3%)	<0.01	1.00 (–)
Boosted PI or Multiple PIs	564 (54.7%)	111 (40.5%)		0.63 (0.42 - 0.94)
Other	73 (7.1%)	47 (17.2%)		1.17 (0.63 - 2.20)
Longitudinal adherence				
≥95%	NA	NA		1.00 (–)
80% - <95%	NA	NA		1.09 (1.03 - 1.14)
40% - <80%	NA	NA		1.07 (1.05 - 1.10)
<40%	NA	NA		1.16 (1.12 - 1.21)
Adherence (1 year)				
≥95%	827 (80.2%)	136 (49.6%)	<0.01	NA
80% - <95%	108 (10.5)	47 (17.2%)		NA
40% - <80%	64 (6.2%)	66 (24.1%)		NA
<40%	32 (3.1%)	25 (9.1%)		NA
Resistance to any class [†]				
No	229 (22.2%)	88 (32.1%)	<0.01	1.00 (–)
Yes	120 (11.6%)	106 (38.7%)		2.78 (1.68 - 4.59)
Not tested	682 (66.2%)	80 (29.2%)		0.61 (0.39 - 0.94)
Nadir CD4 cell count (cells/mm ³) (per 100 cells)*	1.3 (0.5 - 2.0)	1.4 (0.4 - 2.3)	0.17	1.26 (1.07 - 1.47)
Baseline Plasma HIV-1 RNA level (log ₁₀ copies/mL)*	5.0 (4.7 - 5.0)	5.0 (4.5 - 5.0)	0.05	NS
Time suppressed (years)*	2.3 (1.2 - 3.8)	1.3 (0.7 - 2.2)	<0.01	0.37 (0.32 - 0.42)

* These variables were summarized by the median and interquartile range in parenthesis.

[†] Samples are considered resistant if they displayed one or more major resistance mutations in any of the four categories: lamivudine/emtricitabine (184I/V); any other nucleoside reverse transcriptase inhibitors (41L, 62V, 65R, 67N, 69D or insertion, 70R, 74V, 75I, 151M, 210W, 215F/Y or 219E/Q); any non-nucleoside reverse transcriptase inhibitors (100I, 103N, 106A/M, 108I, 181C/I, 188C/H/L, 190A/S, P225H, M230L or 236L); and any

protease-inhibitors (30N, 46I/L, 48V, 50L/V, 54V/L/M, 82A/F/S/T, 84V, or 90M). NS standing alone denotes that the variable was not selected in the final statistical model.

NA denotes not applicable.