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Adherence Required On Dolutegravir

Allison Catalano
aac81@georgetown.edu

The impact of self-reported adherence measures on viral suppression of individuals with HIV-1 on dolutegravir-containing first-line antiretroviral therapy

Allison Catalano

Yale School of Public Health

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Department: Epidemiology of Microbial Disease
Yale School of Public Health
Primary Advisor: Jeremy Schwartz, MD
Secondary Advisors: Suzanne McCluskey, MD,
Mark Siedner, MD, MPH

Abstract

Background Historically, there has been an emphasis placed on maintaining and ART adherence level of >95% to achieve and maintain viral suppression and to minimize the development of drug resistance which is a significant threat to ART efficacy globally. Recently, the WHO recommended a switch tenofovir, lamivudine, dolutegravir (TLD) as preferred first-line ART, due to its high barrier to drug resistance. We hypothesize that dolutegravir is more forgiving and that individuals with imperfect adherence will still be able to achieve viral suppression.

Methods We analyzed data from a cohort of 500 ART-experienced adults with HIV in Uganda who were switched from NNRTI-containing first-line ART to (TLD) as part of routine care. We compared the proportion with viral suppression to < 50 copies/mL across different levels of self-reported adherence. We performed chi-square or fisher's exact tests to determine significance of these associations. We also fit unadjusted and adjusted generalized estimating equations with viral suppression as the outcome of interest and self-reported adherence as the predictor of interest.

Results There was a significant difference between adherence ability categories (p=0.001). There was a significant difference between adherence percentage categories at 48 weeks, but not 24 weeks (p=0.038). In the unadjusted GEE models of covariates, female gender (OR 4.04 95% CI 1.36-12.00, p=0.012), duration on ART prior to enrollment (OR 1.16 95% CI 1.07, 1.26, p= <0.001), and having taken 3TC/AZT/NVP as compared to 3TC/TDF/EFV (OR 2.52 95% CI 1.08, 5.86, p= 0.032) were significant predictors of viral suppression. Adherence ability of "good" or less versus "excellent" was a significant predictor of viremia (aOR 0.28 95% CI 0.10, 0.80, p = 0.018). Reporting an adherence percentage of 80% versus 100% was a significant predictor of viremia (aOR 0.32 95% CI 0.10, 0.99, p = 0.048). There was no significant difference between the optimal adherence group and the next lowest reported adherence level for all measures of adherence. There was no significant difference between any of the groups for measures of adherence frequency.

Conclusions Dolutegravir does seem to be more forgiving and suboptimal adherence of less than 95% may be acceptable for viral suppression. However, individuals reporting poor adherence still have a significantly higher risk for viremia and this effect is more pronounced with time suggesting poor durability even with early suppression. This highlights the importance of adherence counseling and monitoring of individuals reporting low adherence.

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Secondary Mentors:

Mark Siedner, MD, MPH | Medical Practice Evaluation Center, Massachusetts General Hospital, Associate Professor, Harvard Medical School

Jeremy Schwartz, MD | Associate Professor of Medicine and Epidemiology Yale School of Medicine

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Introduction

Increasing rates of pre-treatment and acquired drug resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART) have been observed over time, especially in sub-Saharan Africa ADDIN EN.CITE [1, 2]. In part due to these increasing rate of HIV drug-resistance to NNRTIs, the World Health Organization recommended the use of dolutegravir as the preferred first-line therapy for both treatment-naïve and treatment-experienced individuals who had previously been on NNRTI-based therapy. Dolutegravir is a second-generation integrase strand transfer inhibitor administered in a once daily fixed-dose combination with tenofovir disoproxil fumarate and lamivudine, known as TLD, and has been shown to have a high barrier to drug-resistance, as compared to NNRTIs ADDIN EN.CITE [3, 4]. It is also highly potent and has demonstrated high tolerability ADDIN EN.CITE [5, 6].

ART must be taken daily over one's lifetime to maintain viral suppression in individuals living with human immunodeficiency virus (HIV). In current clinical practice, emphasis has been placed on maintaining an ART adherence threshold of 95% or greater to maintain virologic suppression and to prevent the development of drug resistance. However, the 95% threshold is based on findings from a study of un-boosted protease-inhibitors ADDIN EN.CITE [7] and has been extrapolated to all ART regimens. Given the higher barrier to resistance for dolutegravir, the adherence threshold required to achieve and maintain viral suppression on dolutegravir-based treatment may be more forgiving.

The goal of this study is to determine if the impact of self-reported adherence to TLD on viral suppression. We hypothesize that, given the higher barrier to drug resistance of dolutegravir, the adherence threshold required to achieve viral suppression will be lower than the 95% adherence threshold used in current clinical practice.

Methods

Study Population and Design

We analyzed data collected from a prospective observational cohort study of 500 ART-experienced adults (age 18 years and above) living with HIV in Uganda who were programmatically transitioned from NNRTI-based first-line ART to TLD in 2019, intended to remain in care at the Mbarara Regional Referral Hospital Immune Suppression Syndrome Clinic for at least one year, and lived within 50 kilometers of the clinic (NCT04066036)[8]. Participants were included if they had been on NNRTI-containing ART for at least six-months prior to switch to TLD. Study participants were enrolled on the day of switch to TLD and were followed-up at 24- and 48-weeks post-enrollment. The cohort study collected baseline demographic and health history information and data on self-reported adherence ADDIN EN.CITE [9] at each visit, including percentage of ART taken, adherence frequency, and adherence ability over the past one month. HIV-1 RNA viral load was measured retrospectively from plasma specimens obtained at each study visit. For this secondary analysis, we only included data from participant visits for which both self-reported adherence data and viral load results were available.

Primary Outcome of Interest

The primary outcome of interest for this analysis is viral suppression, as defined by a HIV-1 RNA viral load of less than 50 copies/mL ADDIN EN.CITE [10].

Predictors of Interest

The primary predictors of interest for this analysis are self-reported measures of adherence including adherence percentage, adherence ability, and adherence frequency ADDIN EN.CITE [9]. Adherence percentage was based on a question asking participants what percent of the time they were able to take their pills in the past month and was measured in deciles between 0% and 100%. For analysis, adherence percentage was grouped into individuals with 80% adherence or less, 90% adherence, and 100% adherence. Adherence frequency was measured on a six-level Likert scale[11] and participants were asked to rate how often they took all of their tablets in the past month from "none of the time" to "all of the time." For analysis, adherence frequency was divided into those who rated their frequency at "a good bit of the time" or less, "most of the time," and "all of the time." Adherence ability was also measured on a six-level Likert scale, and participants were asked to rate their ability to take all their tablets as directed in the past month from "very poor" to "excellent". For analysis, adherence ability was grouped into those who rated their ability "good" or less, "very good," and "excellent."

We also defined a global binary metric that incorporated responses from all three adherence assessments. We considered individuals as having either perfect adherence with 100% adherence, all of the time frequency, and excellent ability or imperfect adherence with any individual reporting suboptimal adherence in any of the categories. We also conducted a sensitivity analysis for individuals with missing data for 24- or 48- weeks and based their total adherence based on their 24- or 48-week adherence measures.

Statistical Analysis

We determined and compared the proportion virally suppressed in each adherence level category for each predictor of interest including global adherence and ran chi-squared or fisher's exact tests (for categories with $N<10$) to determine statistical significance at an alpha level of 0.05.

To account for longitudinal data with repeated measures at each follow-up visit, we fit generalized estimating equations (GEE) with viral suppression as the outcome of interest and self-reported adherence as the primary predictor of interest. We assumed an exchangeable correlation structure for repeated measured within each participant. We fit separate models for each adherence predictor. We modeled each qualitative self-reported adherence measure, frequency and ability, as categorical as we do not feel that the difference in affect between groups is proportional. We modeled the quantitatively reported adherence percentage as both categorical and numeric. We fit both adjusted and unadjusted GEE models. In the adjusted models, we included age, gender, duration on ART, and ART regimen prior to enrollment as covariates. Statistical analysis was conducted in R.

Results

Table 1 summarizes the baseline characteristics of the participants included in this study. Forty-one percent of participants were women. The median age was forty-seven years at the time of enrollment (IQR 40, 53). The most common ART regimen prior to enrollment was lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and efavirenz (EFV). The second most common regimen was lamivudine (3TC), zidovudine (AZT), and nevirapine (NVP). The median time on ART at enrollment was 8.83 years

(IQR 5.71, 12.16).

Table 1. Participant characteristics at the time of study enrollment

Characteristic	N=500
Female, n (%)	205 (41.00)
Age (years), median (IQR)	47 (40, 53)
Previous ART regimen, n (%)	
3TC/TDF/EFV	222 (44.44)
3TC/AZT/NVP	193 (38.60)
Other	85(16.96)
Duration on ART (years), median (IQR)	8.83 (5.71, 12.16)

Percentage virally suppressed

For both visits at 24 weeks and 48 weeks post-enrollment, there was no significant difference between groups when assessing viral suppression for those in different adherence frequency categories (Figure 1A). There was a statistically significant difference in the proportion virally suppressed for both 24 and 48 -weeks between adherence ability categories (Figure 1B). Regarding adherence ability, at 24 weeks, 80%, 97%, and 97% of those who reported an ability of "good" or less, "very good" or "excellent," respectively, were virally suppressed (p=0.002). At 48 weeks, 73%, 96%, and 94% of those who reported an ability of "good" or less, "very good" or "excellent," respectively, were virally suppressed (p=0.001). There was a statistically significant difference in the proportion suppressed at 48 weeks, but not 24 weeks when using adherence percentage as the predictor of interest (Figure 1C). At 48 weeks, 86%, 95%, and 97% of those who reported an adherence percentage of 80% or less, 90%, and 100% respectively, were virally suppressed (p=0.038). There was not a significant difference in global self-reported adherence between those were perfectly adherent as compared to those who were sub-optimally adherent (Figure 1D). This stayed true after sensitivity analysis to include individuals with missing adherence measures from 24- or 48-weeks.

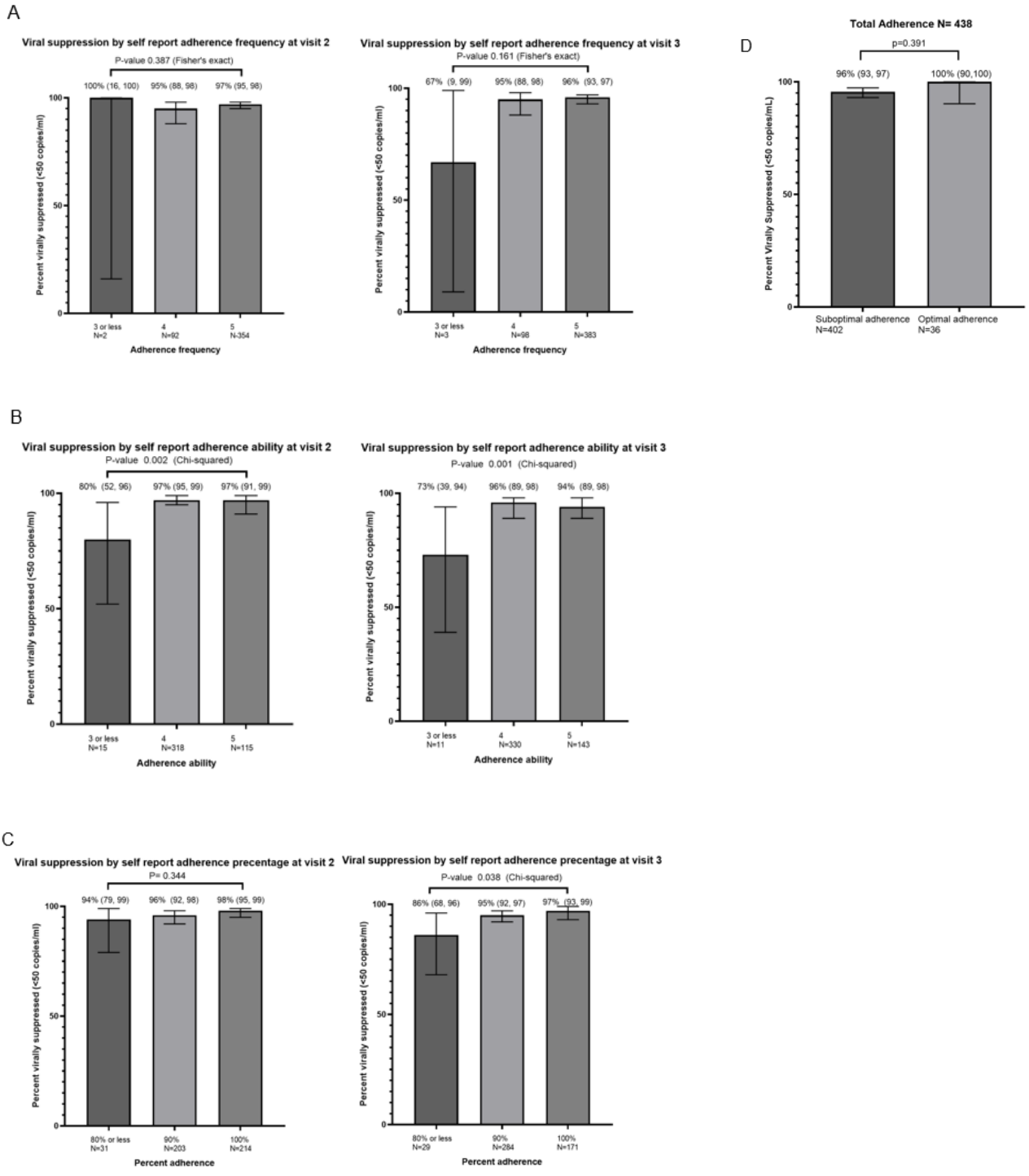

Figure 1. Proportion virally suppressed by predictors of interest. (A) Proportion virally suppressed by adherence frequency. (B) Proportion virally suppressed by adherence ability. (C) Proportion virally suppressed by adherence percentage. (D) Proportion virally suppressed by total adherence.

Significant predictors of viral suppression

In the unadjusted GEE models of covariates, female gender (OR 4.04 95% CI 1.36-12.00, p=0.012), duration on ART prior to enrollment (OR 1.16 95% CI 1.07, 1.26, p= <0.001), and having taken 3TC/AZT/NVP as compared to 3TC/TDF/EFV (OR 2.52 95% CI 1.08, 5.86, p= 0.032) were significant predictors of viral suppression (Table 2A). When using adherence ability as the predictor of interest (Table 2A), reporting an ability of "good" or less as compared to reporting an ability of "excellent" was a significant predictor of viremia (aOR 0.28 95% CI 0.10, 0.80, p = 0.018). Female gender remained a significant predictor of interest in the multivariable model, but all other covariates were not significant (Table 2A). Reporting lower adherence frequency was not a significant predictor of viremia, and female gender remained a significant predictor for viral suppression in the adjusted model (Table 2B). When assessing adherence percentage grouped into three categories, reporting an adherence percentage of 80% or less as compared to reporting an adherence percentage of 100% was a significant predictor of viremia (aOR 0.32 95% CI 0.10, 0.99, p = 0.048) and female gender remained a significant predictor of viral suppression in the multivariate model (Table 2C). When using adherence percentage as a numeric variable as the predictor of interest, increased adherence percentage was a significant predictor of viral suppression (aOR 1.70 95% CI 1.31, 2.21, p = <0.001), and female gender remained a significant predictor of viral suppression in the multivariable model (Table 2D).

A. Adherence Ability

	Unadjusted Model		**Adjusted Model**	
Variable	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Female	4.04 (1.36, 12.00)	0.012	3.27 (1.07, 9.98)	0.037
Age	1.03 (0.988, 1.07)	0.176	0.99 (0.96, 1.03)	0.585
Duration on ART (years)	1.16 (1.07, 1.26)	<0.001	1.09 (0.97, 1.23)	0.147
Previous ART regimen				
3TC/TDF/EFV	Reference			
3TC/AZT/NVP	2.52 (1.08, 5.86)	0.032	1.48 (0.49, 4.47)	0.489
Other	3.69 (0.802, 17.00)	0.094	2.31 (0.49, 11.00)	0.293
Adherence Ability				
Excellent	Reference			
Very good	1.58 (0.75, 3.29)	0.226	1.96 (0.92, 4.18)	0.080
Good or less	0.18 (0.06, 0.52)	0.001	0.28 (0.10, 0.80)	0.018

B. Adherence Frequency

	Unadjusted Model		Adjusted Model	
Variable	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Female	4.04 (1.36, 12.00)	0.012	3.25 (1.07, 9.85)	0.037
Age	1.03 (0.988, 1.07)	0.176	0.99 (0.95, 1.02)	0.431
Duration on ART	1.16 (1.07, 1.26)	<0.001	1.10 (0.96, 1.26)	0.177
Previous ART regimen				
(3TC/TDF/EFV)	Reference			
(3TC/AZT/NVP)	2.52 (1.08, 5.86)	0.032	1.28 (0.36, 4.52)	0.699
Other	3.69 (0.802, 17.00)	0.094	2.40 (0.50, 11.40)	0.271
Adherence Frequency				
All of the time	Reference			
Most of the time	0.70 (0.32, 1.53)	0.374	0.84 (3.29, 53.50)	0.660
A good bit of the time or less	0.14 (0.01, 1.35)	0.088	0.17 (0.38, 1.85)	0.166

C. Adherence Percent

	Unadjusted Model		Adjusted Model	
Variable	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Female	4.04 (1.36, 12.00)	0.012	3.48 (1.14, 10.60)	0.028
Age	1.03 (0.988, 1.07)	0.176	0.99 (0.95, 1.03)	0.628
Duration on ART	1.16 (1.07, 1.26)	<0.001	1.07 (0.93, 1.22)	0.346
Previous ART regimen				
(3TC/TDF/EFV)	Reference			
(3TC/AZT/NVP)	2.52 (1.08, 5.86)	0.032	1.43 (0.42, 4.88)	0.568
Other	3.69 (0.802, 17.00)	0.094	2.90 (0.60, 14.00)	0.184
Adherence Percentage				
100%	Reference			
90%	0.53 (0.26, 1.09)	0.082	0.56 (0.26, 1.21)	0.140
80% or less	0.24 (0.08, 0.73)	0.012	0.32 (0.10, 0.99)	0.048

D. Adherence Percentage Numeric

	Unadjusted Model		Adjusted Model	
Variable	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Female	4.04 (1.36, 12.00)	0.012	3.47 (1.11, 10.80)	0.032
Age	1.03 (0.988, 1.07)	0.176	0.99 (0.95, 1.03)	0.508
Duration on ART	1.16 (1.07, 1.26)	<0.001	1.07 (0.94, 1.22)	0.307
Previous ART regimen				
(3TC/TDF/EFV)	Reference			
(3TC/AZT/NVP)	2.52 (1.08, 5.86)	0.032	1.52 (0.45, 5.17)	0.505
Other	3.69 (0.802, 17.00)	0.094	3.08 (0.60, 15.80)	0.176
Adherence Percentage	1.73 (1.32, 2.27)	<0.001	1.70 (1.31, 2.21)	<0.001

Table 2. Adjusted and unadjusted generalized estimating equation models for (A) adherence ability, (B) adherence frequency, (C) adherence percentage categorically, and (D) adherence percentage numerically.

Discussion

Concerns about adherence can be a limiting factor in initiation of ART due to fear of treatment failure and development of drug resistance ADDIN EN.CITE [12, 13], despite the clear benefits of ART in viral control, prevention of opportunistic infection, and transmission of HIV [16-18]. In this longitudinal cohort study of 500 ART-experienced individuals in Uganda, viral suppression was achieved by >95% of participants with self-reported adherence of 90% or greater (Figure 1). Rates of viral suppression were still >85% in those reporting 80% adherence or less at 48 weeks (Figure 1). Still, lower self-reported adherence was significantly associated with viral non-suppression (Figure 1, Table 2).

Our study used multiple measures of self-reported adherence, both numeric as percentage and categorical on a Likert scale, to assess adherence. Self-report adherence measures are easier to obtain than objective measures of adherence, which often require financial resources for reagents and tests, specialized laboratory capacity, electronic record systems, and more extensive training for staff [14]. While there are limitations to using self-report adherence such as subjectivity and inaccuracy, these measures still have a critical role in assessing adherence and can be easily implemented across diverse settings[15].

There is general consensus that self-reported adherence is often an over-estimate of true adherence level due to social desirability bias ADDIN EN.CITE [16-19], and virologic failure occurs at higher than expected rates among even those reporting optimal adherence [20]. Considering this, our findings suggest that dolutegravir is likely more forgiving, as there were high rates of viral suppression in those groups reporting optimal adherence, as well as in those reporting less than optimal adherence. In fact, these individuals may be overestimating their adherence yet still have high rates of viral suppression.

A significant observation from our findings is that the effect size is more pronounced at 48 weeks versus 24 weeks (Figure 1). This highlights that it is vital to continue monitoring of individuals reporting poor adherence, even with early viral suppression as suppression may not be durable. The cause of viremia in these individuals is beyond the scope of this study but may be due to poor drug levels required for viral suppression or may reflect the time required for drug resistance mutations to develop in the setting of poor adherence. Additional studies to better characterize the longitudinal dynamics of viral suppression in the setting of adherence to Dolutegravir would be informative.

Further studies are planned to understand if HIV-1 viremia in those reporting lower adherence on dolutegravir (80% or less and adherence ability of "good" or less) is due to insufficient medication levels for viral control versus due to development of drug resistance mutations. This is important as TLD could remain a viable option for viral control despite temporary periods of viremia due to low drug levels if drug resistance is not present and if adherence can be optimized.

There are limitations to our study including the measure of adherence by self-report data. In addition, most individuals in our cohort reported optimal adherence levels, leading to a challenge in assessment of TLD efficacy at lower adherence levels. Analyses using objective measures of adherence are planned. Our study is also limited to ART-experienced individuals and is limited to a cohort in a set geographic region in Uganda.

In conclusion, our findings suggest that dolutegravir may be more forgiving, allowing for viral suppression even in the absence of perfect adherence. However, counseling on adherence to decrease risk for viremia and emergency of drug resistance remains of critical importance. Our findings also suggest that early viral suppression may not be durable in individuals reporting low adherence and continued monitoring is vital.

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