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Adherence and HIV RNA Suppression in the Current Era of Highly Active Antiretroviral Therapy (HAART)

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Abstract

Background—We examined trends in adherence to highly active antiretroviral therapy (HAART) and HIV RNA suppression, and estimated the minimum cutoff of adherence to newer HAART formulations needed for HIV RNA suppression by regimen type.

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Methods—We used VA pharmacy dispensing data from the Veterans Aging Cohort Study Virtual Cohort between October 2000 and September 2010, and defined adherence as the duration of time the patient had the medications available, relative to the total number of days between refills for all antiretrovirals in a year. Temporal trends in adherence and viral load suppression were examined by the patient's most frequently used HAART regimen in the year. The minimum needed adherence was defined as the level at which the odds of suppression was not significantly different than that observed with 95% adherence using repeated measures logistic regression.

Results—21,865 HAART users contributed 82,217 person-years of follow-up. There was a significant increase ($p_{\text{trend}} < 0.001$) in the proportion virally suppressed even among those with <95% adherence (2001: 38% to 2010: 84%) and the trend was similar when restricting to their first HAART regimen. For NNRTI multi-pill users, the odds of suppression did not differ for 85-89% adherence compared to those with 95% adherence, odds ratios: 0.82 (0.64, 1.04), but for PI users, the odds of suppression significantly differed if adherence levels were <95% compared to 95% adherence.

Conclusions—Although all HIV-infected persons should be instructed to achieve perfect adherence, concerns of slightly lower adherence should not hinder prescribing new HAART regimens early in HIV infection.

Keywords

Adherence; current HAART; HIV RNA suppression; Veterans Health Administration Center

Introduction

Over the past decade, the proportion of individuals on highly active antiretroviral therapy (HAART) who achieve HIV RNA suppression has increased dramatically.¹ This success has been attributed to improved medication adherence due to decreased HAART toxicity, fixed-dose combination pills, and simplified dosing strategies.^{2,3}

With improved second-generation formulations of non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., rilpivirine, etravirine), protease inhibitors (PIs) (e.g., darunavir, atazanavir), and newer classes like integrase strand transfer inhibitors (INSTIs) (e.g., raltegravir), levels of adherence as those required with early HAART regimens (i.e., 95%),^{4,5} may not be needed for maximal treatment effectiveness. A better understanding of the levels of adherence needed for effective treatment in the current era of HAART could further inform clinical care, and also alleviate provider concerns about prescribing HAART to patients with barriers to adherence at early stages of HIV infection, e.g., high-risk behaviors, sociodemographics, and comorbidities.⁶

We sought to determine whether adherence to HAART and HIV RNA suppression have changed over time, and estimate the minimum optimal adherence level for HIV RNA suppression by HAART regimen type using data from a large, population-based cohort study.

Methods

Source population

The analysis used longitudinal pharmacy refill data collected prospectively from HIV-positive persons on HAART and followed in the Veterans Aging Cohort Study Virtual Cohort (VACS VC) from October 1, 2000 to September 30, 2010. Details of the VACS VC have been previously described.⁷ Laboratory and clinical data, and outpatient prescriptions for each subject were obtained by linking Immunology Case Registry, and Pharmacy Benefits Management Registry records, respectively.⁸ HAART was defined using DHHS guidelines.⁹ Only person-years in which HAART was used for at least 180 days in the year were included.

For each person-year, we used the regimen most frequently refilled to classify HAART as NNRTI-based, PI-based (including users of PIs, and both NNRTIs and PIs), INSTI-based, or 3 nucleoside reverse transcriptase inhibitors (NRTI) containing abacavir or tenofovir. We classified regimens as being single versus multi-pill, and whether administered once-daily versus twice-daily.

Outcomes and Exposures

Since HIV RNA levels were determined using assays with varying detection limits,⁸ we used values of <400 copies/mL as non-detectable viral load, and used the last HIV RNA test of the year for analyses. Sustained suppression was examined among those with multiple viral load measurements in a year and was defined as having undetectable levels following their first measurement if suppressed.

We calculated adherence to HAART using the medication possession ratio defined by Steiner and colleagues¹⁰ which measures the duration of time the patient had the medications available, relative to the total number of days between refills. This was calculated for each person-year that contained at least one refill as follows:

$$\frac{\sum_{ARVs} \text{Number of days supplied with drug in a year}}{\sum_{ARVs} \text{Total number of days between first and last refill}} * 100$$

We excluded stockpilers (20.2% of study population), defined as person-years with a refill frequency exceeding the scheduled dosing interval by more than 5% since the Steiner algorithm was not validated in this subgroup.^{8,11}

Potential confounders of viral load suppression and adherence included sociodemographic, behavioral, disease and treatment characteristics. Fixed characteristics included race, smoking, and geographical location obtained at the first time seen after October 1, 2000 (baseline). Time-varying factors for each year included alcohol abuse, drug abuse, and major depression obtained using ICD-9 diagnosis codes recorded at one inpatient and two outpatient visits, the number of antiretrovirals used, number of days in possession of HAART regimens, regimen type, time since first HAART initiation, and mean CD4 cell count.

Statistical methods

We graphically depicted temporal trends of adherence, suppression, regimen type and dosing frequency from 2001-2010. The change in adherence over time was determined using linear mixed effects models with adherence percent as outcome, accounting for repeated measures over time, and adjusting for confounders. In sensitivity analysis, we restricted the entire population to: a). those who were in follow-up after Jan 1, 2009 (i.e., including those starting before or after 2009, but in follow-up between 2009 and 2010) to avoid a biased temporal trend due to earlier attrition of those with worse outcomes from low adherence, and b). person-years on the first HAART regimen, since switching regimens may not be random, and may result from lower adherence and drug resistance.

We defined the minimum optimal adherence as the level of adherence at which the odds of suppression were not statistically different from that observed among those with 95% adherence. To focus on newer HAART regimens, we restricted this analysis to data from 2006 onwards and used logistic regression with viral load suppression as the outcome, and adherence percent as the primary exposure controlling for repeated measures over time and adjusting for confounders. Since characteristics informing prescribing patterns may affect adherence and HIV RNA suppression, we adjusted for this possible confounding by indication using propensity scores to weight the repeated measures logistic regression model. The propensity score for using an NNRTI-based regimen was determined by logistic regression which included age, race, geographical location, time since first HAART initiation, and CD4 count, HIV RNA suppression, drug abuse, alcohol abuse, and major depression diagnosis lagged to the previous year. Using the propensity score, weights were generated as the average treatment effect for the treated (ATT), and included in the repeated measures logistic regression model as a covariate.

$$ATT, T = E[Y_i(1) - Y_i(0) | T_i = 1; Y = \text{NNRTI use (yes=1 and no=0)}]$$

In sensitivity analyses, we varied the restriction on the number of days on HAART in the year to 270 days and 330 days.

All analyses were performed using SAS 9.2 (Cary, North Carolina, USA) and STATA 12.1 (College Station, Texas, USA); p-value <0.05 was used to define statistical significance.

Results

Study population characteristics

A total of 21,865 HAART users contributed 82,217 person-years between October 1, 2000 and September 30, 2010. At baseline, the mean age was 45.7 (standard deviation (SD): 9.9) years, 98% were male, and 46.5%, 41.6%, and 7.6% were black, white and Hispanic, respectively (Table 1). Almost 60% were current smokers, 47% used VA facilities in the South, 23.3% in the Northeast, and less than 20% in the Midwest and West, respectively. Unadjusted, those with 95% adherence were older, less likely to have abused alcohol or

drugs, and had higher CD4 cell counts compared to those with lower adherence during follow-up.

The use of PI-based and NNRTI-based multi-pill regimens declined between 2001 and 2010 from 65% to 43%, and 33% to 16%, respectively (Supplemental Figure 1). Single pill regimen use and INSTI-based regimen use increased steeply since 2006 from 1% to 29%, and 0% to 11% respectively, in 2010. All the participants on single pill regimens were using efavirenz(EFV)/tenofovir disoproxil fumarate(TDF)/emtricitabine(FTC).

Adherence

The proportion of HAART users with ≥95% adherence increased marginally from 37% in 2001 to 42% in 2010 (Figure 1). More users of NNRTI-based regimens were ≥95% adherent than users of PI-based regimens. Up to 2006, multi-pill regimens were associated with significantly better adherence if taken once-daily versus twice-daily (Supplemental Figure 2). From 2006 onwards, users of single pill regimens had better adherence than those using regimens comprised of multiple pills and doses. After accounting for within-person correlation, there was a 13% increase in the adherence every two years on average (Supplemental Table 1).

HIV RNA suppression

Among those with <95% adherence, the proportion suppressed increased over time from 38% in 2001 to 84% in 2010 ($p_{\text{trend}} < 0.001$) (Figure 2A), and did not appreciably differ when restricted to persons who were in follow-up after 2009 or on their first HAART regimen. This increase in viral suppression was observed even among those with 75-79% adherence (Figure 2B). Across all years, HAART users had an average of 3 HIV RNA tests per year, and the proportion with sustained viral load increased over time from 77.5% in 2001 to 92.0% in 2010. This trend occurred across regimen types but at different levels (Supplemental Figure 3).

Minimum optimal adherence

Overall, HIV RNA suppression for persons with 90-94% adherence did not differ from those with ≥95% adherence (odds ratios (OR): 1.05 (0.91, 1.21)) (Supplemental Table 2). However, the proportion suppressed among users of an NNRTI-based regimen was higher at all adherence levels compared to that among users of PI-based and INSTI-based regimens (Figure 3). The significant ($p < 0.05$) difference in the minimum optimal adherence by regimen type persisted even after adjusting for the propensity for using NNRTIs and therefore we used stratified analyses to identify treatment-specific cutoffs. Users of PI-based regimens were less likely to suppress virus if <95% adherent compared to ≥95% adherent (e.g., 90-94% adherence, OR: 0.88 (0.77, 0.99)) (Figure 4). Conversely, among NNRTI users, the odds of HIV RNA suppression at adherence levels as low as 85% did not significantly differ compared to that with ≥95% adherence (OR: multi-pill users: 0.82 (0.64, 1.04), single pill users: 0.88 (0.69, 1.11)). There were no differences in the proportions virally suppressed in NNRTI users with 90-94% adherence compared to ≥95% adherence (OR: 1.10 (0.89, 1.36)).

Sensitivity analyses by varying the number of days on HAART inclusion criterion, and restricting to the first HAART regimen did not alter our results appreciably (Supplemental Figure 4, Supplemental Table 3).

Discussion

In this population of HIV-infected treated persons seeking care at a Veterans Health Administration Center, adherence and viral load suppression improved between 2001 and 2010, concomitant with use of newer HAART regimens. The proportion suppressed increased over time even among those with less than perfect adherence. More of those using NNRTI-based regimens had adherence 95%, and also a higher proportion suppressed at lower levels of adherence compared to those using other regimens.

The utilization of newer HAART regimens in this study population is similar to that in other HIV-infected populations.¹² Single-pill use began in 2006, and rose to almost 30% in 2010. The higher adherence observed with the use of single pill regimens conforms with studies contrasting the ease of use of single pill regimens and once-daily formulations with multi-dose regimens^{12,13,14,15,16,17} and also with studies of medication use in the general population.¹⁸ Lower toxicity profiles may also have contributed to improved adherence to newer drugs. Our estimation was restricted to those who were on HAART for at least 180 days in the year. Given that the complement is comprised of persons who just started HAART as well as the poorest adherers, i.e., those who discontinued treatment, their inclusion would serve to dampen the estimate of high adherence. However since the proportion of HAART users with less than 180 days on HAART decreased over time (data not shown), our finding of improved adherence over time is conservative.

In addition to being easier to administer, newer HAART formulations do not necessitate consistently high levels of adherence for viral load suppression as required by older HAART formulations.^{2,16} Second-generation drugs have enhanced pharmacokinetic profiles, lower toxicities and lower resistance rates, and lead to sustained viral load suppression.^{2,19,20} Our finding of a higher proportion sustaining viral load suppression in the latter era compared to the earlier era is consonant with the improved effectiveness of the newer drugs. Although a relatively new formulation, INSTI-based regimens had a lower proportion suppressed over time compared to other regimens. This may be attributed to the fact that this was the first-line regimen for less than 1% of the study population; their initial use was therefore predominantly as a salvage regimen for patients with failed prior regimens, who were as a consequence, more prone to virologic failure.

Our data suggest that adherence levels lower than 95% may be sufficient for viral load suppression in populations using newer NNRTI formulations. Although based on relatively imprecise estimates (i.e., wide confidence intervals), 85-89% adherence on NNRTI-based regimens may be sufficient for viral load suppression; 82.2% of this group suppressed virus compared to 84.6% of those with 95% adherence. The inference of effective treatment with less than perfect adherence concurs with the literature suggesting that on the basis of pharmacy refill data, chronically ill patients using 80% of their medications are generally categorized as being adherent to their treatment.²¹ While being 85% adherent to HAART

may be sufficient for optimal virologic outcomes in a population, we would like for this message to be interpreted with caution at the individual level. Several non-HAART related barriers such as treatment access, behavioral factors, and comorbidities, may lead to sub-optimal adherence, resistance and treatment failure.³ Providers must continue to encourage patients to achieve perfect adherence, but comprehensive adherence improvement strategies may be administered on a case-by-case basis.²²

There were limitations in our study. We calculated adherence using pharmacy refill records, making the assumption that the medications were used as dispensed. While pharmacy refill records have the disadvantage that they may misrepresent adherence,³ they are not associated with recall error and social-desirability bias as with other adherence measures like self-report and pill count.³ Although our findings are generalizable due to the large sample size with a widespread geographical distribution in the US, extrapolating our findings to women is limited since our population was predominantly male. The population had a higher CD4 count on average, and a higher proportion suppressed while on HAART than some other studies,²³ and this may indicate different medication choices in this population. The generalizability of our findings is also limited due to the population being insured through the VA, indicating good access to care. The internal validity of our study is however boosted by this very fact since 98% of the participants do not refill their prescriptions outside of the VA.²⁴ Resistance data were not available, and hence we do not know if PI-based regimens were used preferentially among patients with known resistance or known poor adherence.

Despite the limitations, our study had several strengths. Over 20,000 HAART users were followed >10 years allowing us to reliably examine trends in adherence and viral load suppression, and determine the minimum adherence cutoff by HAART regimen type after controlling for potential confounding by indication. Our findings regarding NNRTI-based regimens having relatively better adherence and virologic outcomes will enrich research on adherence in the current era by focusing attention to very low adherers. These data also serve as a guide for providers treating HIV-infected persons.

An integral component of the treatment of HIV like other chronic illnesses is adherence. With newer HAART regimens, adherence is easier, and high adherence levels are not required for viral load suppression. Providers should not let concerns regarding barriers to adherence hinder the prescription of newer HAART regimens at early stages of the disease.²⁵ A recent report by the Institute of Medicine on HIV treatment and quality of care states that “improving access to, and consistent use of medicines by HIV-infected individuals would decrease their risk of transmitting the virus to others.”²⁶ Efforts must be made to maximize the prescription and use of single pill regimens. Future work should focus on the use of other approved single pill regimens and newer drugs now included as recommended regimens in more recent guidelines, and their use in populations with poor access to and retention in care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Distribution of ≥95% adherence over time (2001-2010)

The proportion of person-years with ≥95% adherence. The HAART regimens can be identified as: ■■■■■ blue line for NNRTI-based regimens, ■■■■■ red line for PI-based regimen, and ■■■■■ green line for INSTI-based regimen. The HAART regimen is the most frequently refilled regimen for each person-year. INSTI-based regimen use is 2008-2010. NNRTI-based regimen includes single pill and multi-pill regimens. 82,217 person-years were used for this analysis.

Figure 2. A. Proportion suppressed among those with <95% adherence (2001-2010)

The proportion of person-years suppressing HIV RNA among those with <95% adherence: — blue line for all persons, — red line for persons who were in follow-up after 2009, and — green line for persons on their first HAART regimen.

B. Proportion suppressed among those with <95% adherence (2001-2010). The proportion of person-years suppressing HIV RNA among those with <95% adherence by levels of adherence between 75% and 95% divided into four groups: — blue line for 75-79%, — red line for 80-84%, — green line for 85-89%, and — purple line for 90-94%.

Figure 3. Proportion suppressed by adherence category (2006-2010)

The proportion suppressing HIV RNA by levels of adherence in the current HAART era. The HAART regimens can be identified as: ■■■■■ green line for NNRTI-based single pill, ■■■■ light blue line for NNRTI-based multi-pill, ■■■■ red line for PI-based regimen, ■■■■ purple line for INSTI-based regimen, and — black line for all persons. The HAART regimen is the most frequently refilled regimen for each person-year. INSTI-based regimen use is 2008-2010.

Figure 4. Odds ratios (OR) and 95% CI of HIV RNA suppression by adherence category (2006-2010)

The dots in the forest plot represent the OR estimates, and the bars represent the 95% CI. The ORs come from a repeated measures logistic regression model with viral load suppression as outcome and adherence levels as exposure, adjusted for age, race, alcohol abuse, major depression, drug abuse, geographical location, and time since first HAART initiation. The size of the dots represents the sample size of the exposure category. The HAART regimens can be identified as: green triangle for PI-based regimen, red square for NNRTI-based single-pill regimen, blue diamond for NNRTI-based multi-pill regimen. The HAART regimen is the most frequently refilled regimen for each person-year. INSTI-based regimen use is 2008-2010. 48,308 person-years were used for this analysis.

Table 1
Characteristics of study population (2001-2010)

Characteristics	Baseline N persons=21,865	Adherence <95% (N person-years= 48,662)	Adherence ≥95% (N person-years= 33,555)
Age, mean (SD)	45.7 (9.9)	51.9 (9.4)	53.6 (9.7)
Black (%)	46.6	49.3	38.0
Male (%)	98.0	97.9	98.3
Smoking at baseline (%)	57.2	58.6	48.4
Alcohol abuse (%) ^δ	10.5	9.8	6.3
Drug abuse (%) ^δ	13.4	13.1	8.1
Depression status (%) ^δ	7.7	7.5	6.9
CD4 count (cells/mm ³), mean (SD)	422.1 (265.5)	480.6 (281.6)	521.0 (277.8)
Geographical location (%) [*]			
Northeast	23.4	25.8	23.2
Midwest	13.8	12.7	14.1
South	46.5	46.6	44.6
West	16.3	14.9	18.0
Year 2006 onwards	35.9	57.5	60.5
Adherence at baseline, mean (SD)	87.6 (13.7)	N/A	N/A

^{*} Northeast: CT, ME, MA, NH, NJ, NY, PA, MD, DC, DE, RI, VT; Midwest: IL, IN, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI; South: AL, AR, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV; West: AK, AZ, CA, CO, HI, ID, MT, NV, NM, OR, UT, WA, WY;

^δ Based on ICD-9 diagnosis codes