Single- Versus Multiple-Tablet HIV Regimens: Adherence and Hospitalization Risk

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ABSTRACT

Objectives: To evaluate the impact of antiretroviral therapy as a single-tablet regimen (STR) and multiple-tablet regimen (MTR) on outcomes in human immunodeficiency virus (HIV)/AIDS patients using electronic health records from the Veterans Healthcare Administration (VHA).

Study Design: Retrospective cohort.

Methods: This study evaluated VHA patients to whom HIV medications were dispensed as STRs or MTRs during the study period (January 1, 2006, to July 30, 2012). Patients were followed from the index date (ie, start of regimen) until treatment discontinuation, end of study period, last date of healthcare-related activity, or death. Differences in outcomes of hospitalization, adherence defined as a medication possession ratio of ≥95%, and undetectable viral load were evaluated using a Cox-proportional hazard and logistic model controlling for covariates measured during a 6-month baseline period.

Results: A total of 15,602 patients (6191 STR and 9411 MTR) met all study criteria. The study sample was, on average, aged 52 years with similar CD4 counts (mean ± SD: 432.2 ± 282.8 vs 419.3 ± 280.9; $P = .287$), but a significantly lower proportion of STR versus MTR patients had an undetectable viral load at baseline (42% vs 46%; $P < .001$). After controlling for baseline covariates, the STR cohort had twice the odds of being adherent (odds ratio [OR], 1.98; $P < .001$), 31% had a significantly lower hazard of having a hospitalization (hazard ratio, 0.69; $P < .001$), and 21% had higher odds of having an undetectable viral load during follow-up (OR, 1.21; $P < .001$).

Conclusions: STR is associated with higher adherence rates, decreased hospitalizations, and more patients with an undetectable viral load in VHA patients with HIV/AIDS.

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More than 1 million individuals in the United States are living with human immunodeficiency virus (HIV) infection, representing an increase over the past 10 years, with an average incidence of approximately 50,000 new diagnoses per year.[1,2] For patients living with HIV, antiretroviral therapy (ART) has transformed the disease and directly resulted in reduced morbidity and mortality from HIV-associated illness. Therefore, current HHS guidelines recommend the initiation of ART in HIV patients to reduce the risk of disease progression and for the prevention of transmission of HIV.[3]

Despite the importance of ART in managing HIV, barriers to adherence still exist; adherence rates are less than optimal and range from 60% to 80%.[4-7] The clinical consequences of poor adherence to ART are well documented and include incomplete viral suppression, disease progression, and death,[3,4,8-11] whereas HIV viral suppression, reduced rates of resistance, increased survival, and improved quality of life are associated with ART adherence.[3] Drug resistance, with a prevalence of 6% to 16%, is an important consequence of nonadherence.[3]

HIV guidelines recommend preferred ARTs that include single-tablet regimens (STRs) and multiple-tablet regimens (MTRs). Among other factors—including, but not limited to, presence of adverse events, depression, alcohol and drug use, work schedules, changes in daily routines, and decrease in cognitive function—the high daily pill burden of MTR ART regimens is associated with a decrease in adherence to ART,[12-14] and is a strong predictor of discontinuation of combination ART.[15] The number of pills in a regimen and number of daily doses correlate with adherence rates.[12-17] When MTR options are available, discordant adherence to individual components of an ART regimen can occur.[13,15,16]

Current treatment guidelines recommend 4 or fewer pills per day with once- or twice-daily dosing.[3,18,19] Studies of STRs have shown significant improvements in patient adherence and virologic outcomes[20-22]; therefore, the role of regimen

factors, such as pill burden, is critical to improving adherence. The purpose of the current study is to evaluate the impact of STRs versus MTRs on adherence to highly active antiretroviral therapy (HAART) and the associated risk of hospitalization in patients with HIV receiving care within the Department of Veterans Affairs (VA) Veterans Health Administration (VHA) system. In addition, the impact of STRs and MTRs on viral load was explored.

Take-Away Points

This study:

- Advances knowledge of managed care decision makers regarding advantages of single-tablet regimens; and
- Informs formulary decision processes regarding antiretroviral therapy to help improve outcomes in patients with HIV/AIDS.

METHODS

This retrospective cohort study was conducted using data from the VHA electronic health record (EHR) system. The VHA EHR includes clinical and utilization information from 14 million unique individuals receiving care from 140 VA medical centers and 600 outpatient clinics across the United States. The VHA facilities provide a broad spectrum of medical, surgical, and rehabilitative care. National VHA EHR data were searched to obtain individual-level information on demographics, administrative claims, vital signs, mortality, laboratory results, and pharmacy dispensation. (The completeness, utility, accuracy, validity, and access methods of the available data are described on the VA website.)

Study Design and Sample Selection

The date of the first HAART regimen identified during the enrollment period (July 1, 2006, to September 30, 2011) was designated as the index date. Patients were required to remain on their HAART regimen for a minimum of 60 days after the index date and to have continuous enrollment in the VHA for at least 6 months before and 60 days after the index date (**eAppendix Figure 1** [eAppendices available at **www.ajmc.com**]). The follow-up period varied for each patient; however, a 60-day minimum follow-up period was required to ensure that the treatment was being received and that outcomes could be attributed to treatment.

Patients who had a dispensation for any of the drugs of interest were identified as the initial study population. Drugs of interest encompassed 5 classes of drugs included in a complete HAART regimen: a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), a nonnucleoside/nucleotide reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), a chemokine receptor 5 (CCR5) antagonist, and an integrase inhibitor. From this study population, patients were included if they had a diagnosis or past medical history of HIV/AIDS during the study period and receipt of a complete HAART regimen during the enrollment period. A complete HAART regimen was defined as a regimen containing 2 NRTIs plus a third agent (ie, another NRTI, an NNRTI, a PI, a CCR5 antagonist, or an integrase inhibitor). Additionally, patients had to have at least 1 clinical encounter, 1 pharmacy encounter, and 1 laboratory encounter at a VHA facility within 6 months after the index date.

After initial identification, patients were categorized based on the daily pill count of their complete HAART regimen into either an STR or MTR cohort. Patients were assigned to the STR cohort if they received a complete HAART regimen consisting of a single tablet at any point during the enrollment period, regardless of prior or subsequent use of other regimens. Patients were assigned to the MTR cohort if they received a complete HAART regimen consisting of 2 or more tablets per day at any point during the enrollment period and if they did not receive a regimen consisting of a single tablet per day at any point during the enrollment period.

Study Outcomes

The follow-up periods were variable for each patient; patients were followed from the index date (ie, start of HAART regimen) until the earliest of treatment discontinuation, end of study period, last date of healthcare-related activity noted in the database, or death. Outcomes were assessed for a minimum of 60 days and included adherence—defined as having a medication possession ratio (MPR) ≥95%—and clinical outcomes, assessed by hospitalizations and viral load. Adherence was also alternately defined using the common threshold of ≥80%.

Briefly, MPR is a composite measure that evaluates both medication skipping and discontinuation. MPR was calculated over the duration of the patient's HAART regimen using the number of days for all HAART regimen components (from pharmacy claims data) divided by the number of days between the first and last fill date of HAART, multiplied by 100. The hazard and number of hospitalizations during the follow-up period were both evaluated. Any hospitalization was considered, regardless of diagnosis.

Data on viral load during follow-up was obtained for each patient, where available, at the visit closest to the date of end of treatment. Undetectable viral load was defined as having a viral load value <50 copies/mL or a re-

sult report interpretation of being negative/undetectable in the blood depending on the assay used. Additionally, mean viral load values were also reported.

Statistical Analyses

A descriptive analysis of the final sample was performed using standard summary statistics, such as means and proportions. Baseline characteristics captured during the pre-index period included the following: age, gender, race, geographic region, index year, pre-index medications, Charlson comorbidity index (CCI) score,[23] presence of mental health disorders or drug/alcohol abuse, and CD4 count. Inter-cohort differences were quantified using *t* tests for continuous variables and χ^2 tests for categorical variables.

Cohort differences in mean MPR values and the proportion of patients defined as being adherent based on MPR threshold values (≥80% and ≥95%) were evaluated. Adjusted differences in mean MPR values between cohorts were assessed using multivariate ordinary least squares regression. Cox proportional survival analysis models were used to evaluate differences in the hazards of experiencing hospitalization and having a detectable viral load during follow-up. Additionally, Poisson models were used to evaluate differences in the number of hospitalizations, and they incorporated the differing lengths of follow-up of the patients.

All multivariate statistical analyses were adjusted for potential confounders (ie, age, race, geographic region, CCI score, mental health disorders, drug/alcohol abuse disorders, index year, treatment-naïve status, and number of pills per day). For patients with viral load information in the pre-index period, pre-index viral load was included as an additional covariate. Pre-index viral load was obtained from the EHR at the visit closest to the index date. All statistical tests that were performed tested a 2-sided hypothesis of no difference between treatment groups at a significance level of .05.

RESULTS

A total of 24,852 patients with HIV/AIDS were identified in the VHA EHR data set. Of these, 15,602 patients met all the study criteria and comprised the study population (**eAppendix Figure 2**), 9411 patients (60.3%) received an MTR of HAART, and 6191 (39.7%) received an STR. Patients were excluded mainly due to the following: lack of a HAART regimen for a minimum of 60 days after the index date (22.9%), noncontinuous eligibility during the pre-index period (17.2%), and noncontinuous eligibility during the first 60 days of the follow-up period (8%).

As expected, the majority of patients were male (97.4%) with a mean age of 52 years (**Table 1**). Overall, the comorbidity burden among the study sample was moderate; patients receiving an MTR had a slightly higher comorbidity burden, as shown by higher CCI scores (1.7 vs 1.5; *P* <.001) and prevalence of mental health disorders (67% vs 64%; *P* <.001). Two-thirds of the sample had diagnoses for mental health disorders, with about 40% having drug and substance abuse disorders; no difference was noted in the cohorts in the prevalence of drug and substance abuse disorders. A significantly higher proportion of STR patients were treatment-naïve compared with MTR patients (28% vs 13%; *P* <.001). All STR and MTR patients received an NRTI; however, the majority of STR patients received an NNRTI (92.8%) and the majority of MTR patients received a PI (69.3%). At study entry, a significantly lower proportion of STR patients had an undetectable viral load compared with MTR patients (42% vs 46%; *P* <.001); however, the cohorts were similar in terms of CD4-positive counts at baseline.

Adherence Outcomes

As shown in **Figure 1**, at a threshold of 95%, a significantly higher proportion of STR versus MTR patients were adherent (75% vs 55.7%; *P* <.001). Similar results were noted using the ≥80% threshold (STR vs MTR: 90% vs 77.5%; *P* <.001). After adjusting for baseline covariates, patients in the STR cohort had almost 2 times the odds of being adherent (MPR ≥95%), as shown in **Table 2** (odds ratio [OR], 1.98; 95% CI, 1.81-2.17; *P* <.0001). All other covariates included in the model significantly predicted adherence except for the CCI score. Of note, viral load at baseline was a significant predictor of adherence, and its exclusion did not affect the magnitude or direction of the main predictor (regimen type); hence, final results of the model include viral load at baseline. Adherence defined as MPR ≥80% demonstrated similar results (data not shown); the odds of adherence were slightly more than 2 times higher with the STR versus MTR group (OR, 2.16; 95% CI, 1.92-2.43; *P* <.001).

Clinical Outcomes

Less than one-third (29.5%) of the study sample had a hospitalization after the index date. Compared with patients receiving an MTR, a lower proportion of patients receiving an STR had hospitalizations (26.8% vs 31.3%; *P* <.001). In addition, the average number of hospitalizations per patient was lower (2.2 vs 2.7; *P* <.001) and the number of days from index date to hospital admission was longer (376 vs 345 days; *P* <.001). After adjusting for covariates, STR patients had 31% lower odds of experiencing a hospitalization during follow-up (hazard ratio [HR], 0.69; 95% CI, 0.64-0.74; *P* <.001) (**Figure 2**). The number of hospitalizations was also significantly lower for the

Table 1. Study Sample Description at Study Entry

Characteristics	Total (N = 15,602)	STR (n = 6191)	MTR (n = 9411)	*P*
Age, years: mean ± SD	52.1 ± 9.5	51.6 ± 9.9	52.4 ± 9.3	**<.001**
Male, n (%)	15,201 (97.4%)	6006 (97%)	9195 (97.7%)	**.007**
Race, n (%)				
White	6609 (42.4%)	2500 (40.4%)	4109 (43.7%)	<.001
African American	7330 (47%)	3054 (49.3%)	4276 (45.4%)	**<.001**
Other	1663 (10.7%)	637 (10.3%)	1026 (10.9%)	**<.001**
Geographic region, n (%)				
Midwest	1877 (12%)	697 (11.3%)	1180 (12.5%)	**<.001**
Northeast	2514 (16.1%)	927 (15%)	1587 (16.9%)	**<.001**
South	8099 (51.9%)	3458 (55.9%)	4641 (49.3%)	**<.001**
West	2897 (18.6%)	1071 (17.3%)	1826 (19.4%)	**<.001**
Other/unknown	215 (1.4%)	38 (0.6%)	177 (1.9%)	**<.001**
CCI score, mean ± SD				
Without AIDS	1.61 ± 1.88	1.5 ± 1.83	1.68 ± 1.92	**<.0001**
With AIDS	7.52 ± 2.04	7.37 ± 2.04	7.62 ± 2.03	**<.0001**
Mental health disorders, n (%)	10,225 (65.5%)	3962 (64%)	6263 (66.5%)	**.001**
Drug/alcohol abuse disorders, n (%)	6122 (39.2%)	2388 (38.6%)	3734 (39.7%)	.167
HAART therapy, n (%)				
NRTI	15,601 (100%)	6191 (100%)	9410 (100%)	.417
NNRTI	8661 (55.5%)	5747 (92.8%)	2914 (31%)	**<.001**
PI	6519 (41.8%)	0 (0%)	6519 (69.3%)	
CCR5	3 (0%)	NA	3 (0%)	
FI	105 (0.7%)	NA	105 (1.1%)	
II	0 (0%)	NA	0 (0%)	
Treatment-naïve, n (%)	2897 (18.6%)	1701 (27.5%)	1196 (12.7%)	**<.001**
Viral load				
Have viral load data at baseline, n (%)	15,356 (98.4%)	6086 (98.3%)	9270 (98.5%)	
Undetectable viral load, n (%)	6963 (44.6%)	2604 (42.1%)	4359 (46.3%)	**<.001**
CD4 count at baseline				
Have CD4 count at baseline, n (%)	11,382 (73.0%)	4595 (74.2%)	6787 (72.1%)	
CD4 count (mean ± SD)	424.5 ± 281.7	432.2 ± 282.8	419.3 ± 280.9	.2873

CCI indicates Charlson comorbidity index; CCR5, chemokine receptor 5 antagonist; FI, fusion inhibitor; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; II, integrase inhibitor; MTR, multiple-tablet regimen; NA, not applicable, because no STR contains these drug classes; NNRTI, nonnucleoside/nucleotide reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; STR, single-tablet regimen. Figures in bold indicate statistical significance at α = .05.

STR compared with the MTR cohort, with STR patients having 44% fewer hospitalizations compared with MTR patients (incidence rate ratio, 0.56; 95% CI, 0.53-0.58; *P* <.001). Similar to the adherence model, viral load was a significant predictor of future hospitalization risk, and its exclusion did not affect the impact of type of regimen (HR, 0.67; 95% CI, 0.62-0.72; *P* <.001). Therefore, the final model included viral load at baseline.

Overall, during follow-up, the proportion of patients with undetectable viral load increased to 61.3% from a baseline level of 44.6%. The improvement was noted in both cohorts, with a significantly higher number of STR patients having an undetectable viral load compared with MTR patients during follow-up (63.9% vs 59.6%; *P* <.001) (**Figure 3**). After accounting for baseline viral load detectability and other covariates, the STR cohort had 21% higher odds of having an undetectable viral load during follow-up (OR, 1.21; 95% CI, 1.11-1.32; *P* <.001). STR patients also had significantly lower viral load values compared with MTR patients (7376.2 vs 8673.6; *P* <.001).

DISCUSSION

This retrospective database analysis of US veterans compared 2 types of HAART, STR and MTR. The goal of the study was to assess the impact of pill burden on adherence, hospitalization, and viral load. This study found that patients receiving an STR had significantly better adherence than patients receiving an MTR. At MPRs of 95% and 80%, a significantly higher portion of STR patients was adherent compared with MTR patients. Furthermore, STR patients were 2 times more likely to be adherent compared with MTR patients. Patients receiving an STR also had a 31% lower risk of hospitalizations, 46% fewer hospitalizations, and 21% greater odds of undetectable viral load compared with MTR patients.

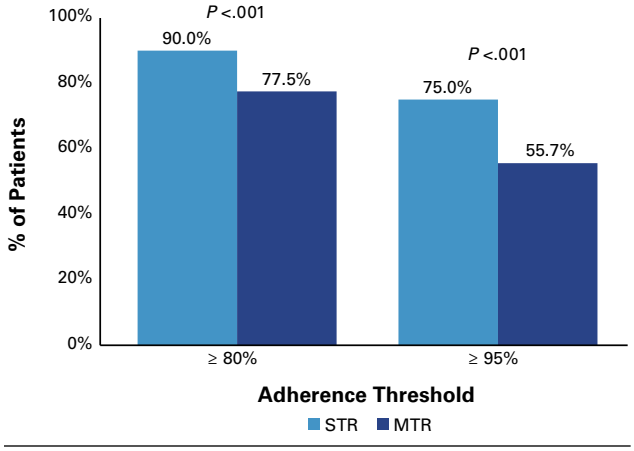
The outcomes in our study are consistent with meta-analyses conducted by Parienti et al,[24] van Galen et

Table 2. Effect of Type of Regimen (STR vs MTR) on Adherence Defined as MPR >95%

Predictors	Odds Ratio	95% CI	*P*
STR (ref = MTR)	1.980	1.810-2.165	**<.001**
Estimate from model excluding viral load at baseline	2.037	1.865-2.225	**<.001**
Age	1.011	1.007-1.015	<.001
Race (ref = white)			<.001
African American	0.551	0.510-0.595	**<.001**
Other	0.683	0.606-0.768	.137
Region (ref = Northeast)			
Midwest	1.284	1.128-1.462	.399
South	1.274	1.157-1.403	.364
West	1.775	1.572-2.003	**<.001**
Unknown	0.968	0.720-1.302	**.042**
CCI score (without AIDS)	0.986	0.967-1.005	.154
Has mental health disorder (ref = no)	1.117	1.035-1.205	**.004**
Has drug or alcohol abuse (ref = no)	0.819	0.760-0.882	**<.001**
Calendar year (ref = 2011)			<.001
2006	0.318	0.244-0.415	**<.001**
2007	0.402	0.309-0.523	**<.001**
2008	0.382	0.292-0.501	**<.001**
2009	0.476	0.361-0.628	.627
2010	0.594	0.447-0.788	**.003**
Treatment-naïve (ref = no)	1.244	1.111-1.392	**.001**
HIV detectable at baseline (ref = no)	1.264	1.174-1.362	**<.001**

CCI indicates Charlson comorbidity index; HIV, human immunodeficiency virus; MPR, medication possession ratio; MTR, multiple-tablet regimen; ref, reference; STR, single-tablet regimen. Figures in bold indicate statistical significance at α = .05.

Figure 1. Unadjusted Adherence Based on MPR Threshold Values[a]



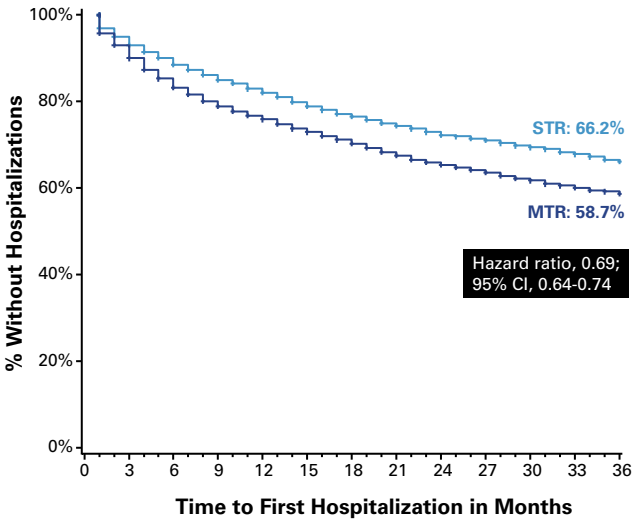
MPR indicates medication possession ratio; MTR, multiple-tablet regimen; STR, single-tablet regimen.
[a]Odds ratio adjusted for covariates at study entry: age, race, geographic region, Charlson comorbidity index score, mental health disorders, drug/alcohol abuse disorders, index year, treatment-naïve status, and undetectable viral load.

al,[25] and Nachega et al,[26] and with other similar studies using claims data in other populations.[15,16] Parienti and colleagues' meta-analysis reported an improvement in adherence with a once-daily regimen compared with a twice-daily regimen.[24] Van Galen and colleagues reported a meta-analysis demonstrating that administering medications as a fixed-dose combination improved adherence compared with the same active drugs administered as separate pills; however, they also noted that there is a limited number of randomized controlled trials regarding the subject.[25] Nachega and colleagues reported a meta-analysis of randomized controlled trials demonstrating that a lower pill burden was associated with better adherence and virological suppression.[26] Sax and colleagues demonstrated that patients who received treatment as a single pill per day had significantly better adherence than patients who received 3 or more pills per day, and they were less likely to have a hospitalization.[16]

Additional studies have also demonstrated that patients who were adherent were less likely to have a hospital stay.[8,15] Given our large national sample size, we feel our data are robust in evaluating the effects of pill burden on adherence and hospitalization. Additionally, this study demonstrated that the pill burden has an impact on viral load. After accounting for baseline viral load detectability and other covariates, the STR cohort had 20% higher odds of having an undetectable viral load during follow-up.

Among patients receiving complex, multi-pill regimens, adherence estimates range from 60% to 70%.[4-6] Our cohort of patients receiving an MTR demonstrated that pill burden might be related to HIV clinical outcomes. Achieving optimal outcomes in HIV treatment requires a sustained level of adherence. Studies conducted on patients receiving older HAART regimens identified a necessary adherence rate of at least 95% to achieve a lower risk of virologic failure, fewer hospital days, and reduced morbidity and mortality.[4,6,25] Simpler regimens with longer half-lives and pharmacokinetic enhancers are now utilized in HAART regimens; however, in our study, having an STR and ultimately, a smaller pill burden, improved adherence, decreased hospitalizations, and improved viral load in spite of longer half-lives and pharmacokinetic enhancers for MTR.

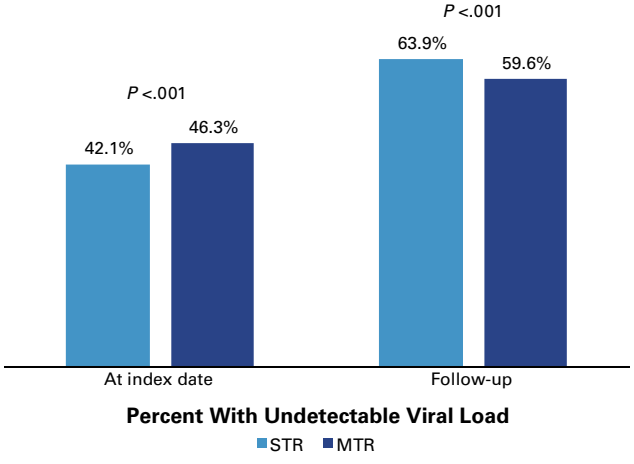
Figure 2. Adjusted Risk of Hospitalization for STR Compared With MTR Cohort



MTR indicates multiple-tablet regimen; STR, single-tablet regimen.

This study attempted to control for various differences in the study population and the effects these differences might have on adherence and hospitalization. Specifically, multivariate logistic regression was undertaken to control for age, race, geographic location, CCI score, mental health disorders, drug and alcohol abuse, index year, treatment-naïve status, number of pills per day, and undetectable viral load. After adjusting for the baseline covariates, patients in the STR cohort had almost 2 times the odds of being adherent and a 31% lower hazard of experiencing a hospitalization during follow-up. All other covariates included in the model significantly predicted adherence except for the CCI score.

Figure 3. Unadjusted Percentage of Patients With Undetectable Viral Load



MTR indicates multiple-tablet regimen; STR, single-tablet regimen.

Limitations

Our study has several limitations common to observational claims database analyses. Adherence was measured from filled prescriptions; however, studies have suggested that pharmacy refill rates and MPRs are good depictions for actual medication adherence.[27] Because patients were not randomized to the different treatments, we cannot exclude unmeasured confounding factors that may have influenced our outcomes. Among the most important, is that clinical trials have demonstrated that resistance or virologic failure is significantly less common in the boosted PI treatments than in NNRTI-based treatments.[28,29] As such, providers may have preferentially prescribed a boosted PI to their less-adherent patients. Additionally, individualized HIV therapy can be difficult to control when evaluating antivirals. Patients may have been on an MTR because of genotypic results or salvage therapy with CCR5 antagonists. Although we attempted to control for select variables through use of multivariable models that include some of these factors, residual confounding may remain.

CONCLUSIONS

Adherence to ART in patients with HIV is critical for disease management, reducing morbidity and mortality, and preventing disease transmission, since poorer outcomes have been associated with nonadherence to ART. Results of our database study demonstrate that ART with an STR is associated with improved clinical outcomes, as shown by a reduced risk of hospitalizations, fewer hospitalizations, and longer time to hospitalization than ART with an MTR. Healthcare providers and payers may see a benefit in improved adherence with HAART using an STR versus an MTR based on decreased hospitalization rates and other improvements in clinical outcomes. These clinical outcomes could potentially decrease total healthcare costs in HIV patients. Future research to improve adherence, whether through drug therapy advancements through development of more STRs or other interventions, is needed.

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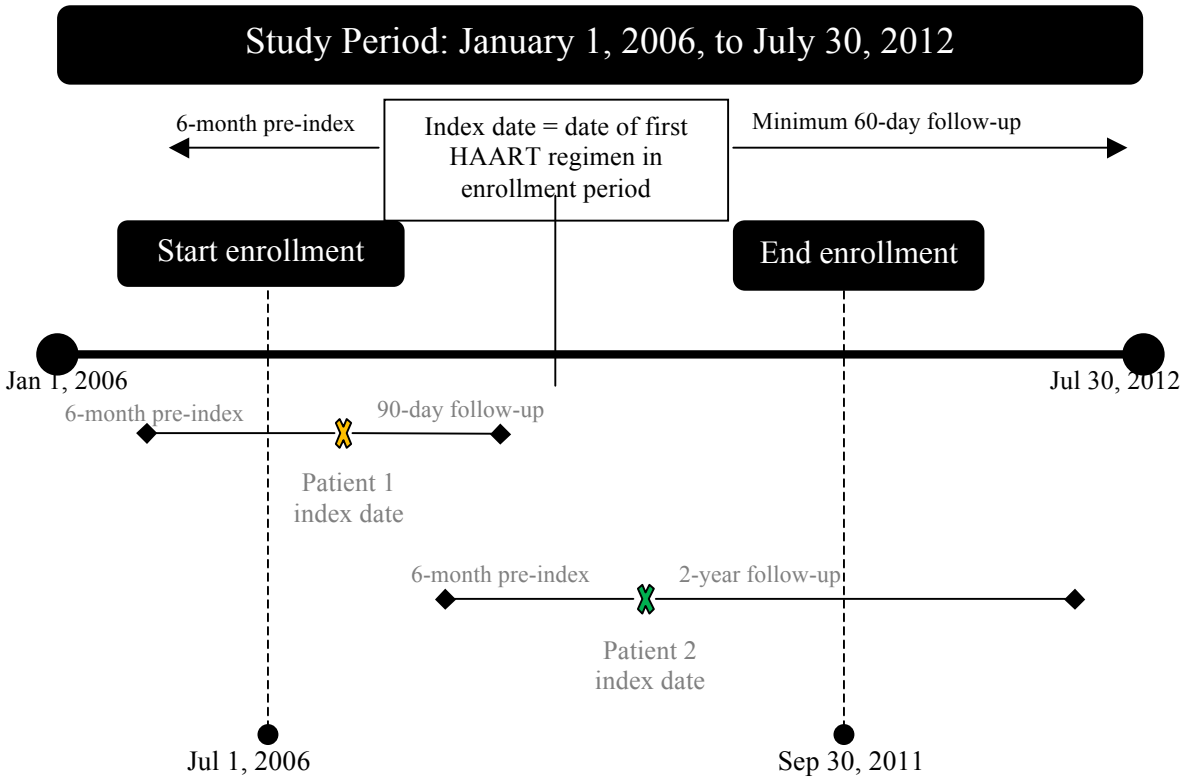
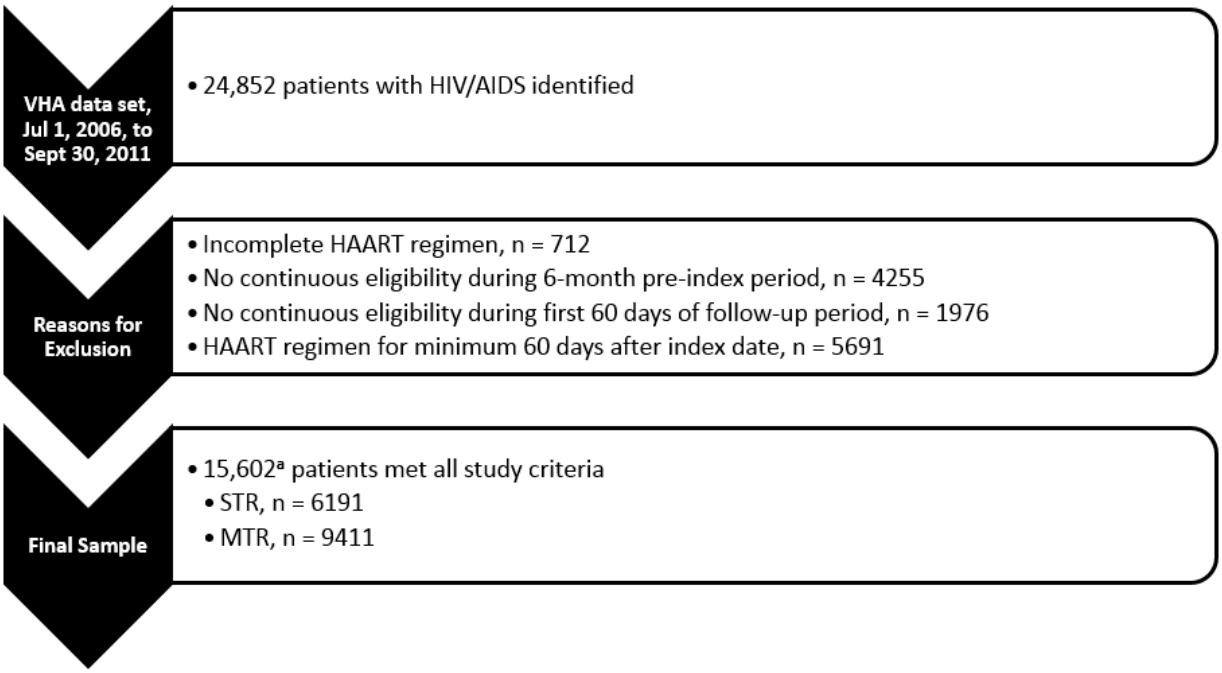
eAppendix Figure 1. Study Design



HAART indicates highly active antiretroviral therapy.

eAppendix Figure 2. Study Attrition[a]



HAART indicates highly active antiretroviral therapy; HIV, human immunodeficiency virus; MTR, multiple-tablet regimen; STR, single-tablet regimen; VHA, Veterans Health Administration.

[a]Numbers of patients for each exclusion criteria are not mutually exclusive.