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Single tablet HIV regimens facilitate virologic suppression and retention in care among treatment naïve patients

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Abstract

Newer HIV regimens are typically taken once daily but vary in the number of pills required. Whether the number of pills in a once-daily HIV regimen affects clinical outcomes is unknown. We retrospectively compared adherence, retention in care, and virologic outcomes between patients starting a once daily single-tablet regimen (STR) to patients starting a once-daily multi-tablet regimen (MTR) in a publicly funded clinic in the United States. Outcomes were measured in the year after starting ART and included retention in care, virologic suppression, and medication possession ratio of at least 80%. Data from patients initiating therapy from January 1, 2008 to December 31, 2011 were analyzed with both unadjusted and propensity-score adjusted regression. Overall, 622 patients started with an STR (100% efavirenz-based) and 406 with an MTR (65% atazanavir-based and 35% darunavir-based) regimen. Retention in care was achieved in 80.7% of STR patients vs. 72.7% of MTR patients (unadjusted OR 1.57, 95% CI 1.17-2.11; adjusted OR 1.49, 95% CI 1.10-2.02). Virologic suppression occurred among 84.4% of STR patients vs. 77.6% of MTR patients (unadjusted OR 1.56; 95% CI 1.14-2.15; adjusted OR 1.41; 95% CI 1.02-1.96). There was no difference in the proportion of patients achieving at least 80% adherence, as measured by medication possession ratio (33.0% of STR patients and 30.1% of MTR patients; unadjusted OR 1.14; 95% CI 0.87-1.50; adjusted OR 1.04, CI 0.79-1.38). While it is difficult to eliminate confounding in this observational study, retention in care and virologic outcomes were better in patients prescribed STRs.

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Author Contributions:

TZ conceived of the study. TZ and JC collected data. CAF, VH, and TPG developed the data analysis plan. VH performed the statistical analysis. CAF, VH, and TZ wrote the first draft of the manuscript. TPG and TZ contributed to revision of the manuscript. All authors approved the final manuscript prior to submission.

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Keywords

Adherence; pill burden; retention in care

Introduction

The advent of highly active antiretroviral therapy (HAART) in the mid-1990s led to marked reductions in mortality due to HIV infection (Acri, Grossberg, & Gross, 2010). However, benefitting from early HAART regimens required high levels of adherence to complex regimens involving up to dozens of pills per day (Kitahata et al., 2004; Maggiolo et al., 2007). Newer regimens are typically only taken once daily, and many newer regimens only require taking a single tablet daily (Astuti and Maggiolo, 2014). In the era of single tablet regimens (STRs), once-daily antiretroviral therapy (ART) is now standard with many providers believing that decreased pill burden improves patient's quality of life, increases the likelihood of virologic suppression, improves tolerability, and increases medication adherence (Thompson et al., 2012). Although patients prefer STRs to multiple tablet regimens (MTRs) (Airoldi et al., 2010) and report higher adherence rates when taking STRs in many (Sterrantino, Santoro, Bartolozzi, Trotta, & Zaccarelli, 2012) though not all studies (Buscher, Hartman, Kallen, & Giordano, 2012), there is limited evidence documenting the impact of once-daily dosing of STR on virologic outcomes compared to once-daily MTRs (Cotte et al., 2017; Nachega et al., 2014; Scott Sutton, Magagnoli, & Hardin, 2016). The effect of the pill burden of a once-daily ART regimen on retention in care, a key challenge in managing patients with HIV infection (Giordano et al., 2007) and a critical component of the HIV cascade (Gardner, McLees, Steiner, del Rio, & Burman, 2011), also remains unknown. As older MTR regimens become available in generic formulations (Walensky et al., 2013), payers may come to insist that MTRs be preferred to STRs for economic reasons (Engsig et al., 2014). This may disproportionately impact patients who already face increased barriers to adherence (Falagas, Zarkadoulia, Pliatsika, & Panos, 2008). Accordingly, we set out to study adherence to ART, retention in care, and virologic outcomes in patients receiving once daily STRs and MTRs in a publicly funded HIV clinic in the United States.

Methods

This was a retrospective study of patients initiating antiretroviral therapy at Thomas Street Health Center (TSHC), a free-standing HIV clinic that is part of the county-run Harris Health System in Harris County, Texas. Harris County is a primarily urban county which includes Houston, the fourth-largest city in the United States and one of its most diverse. Subjects were included if they filled prescriptions at the in-house TSHC pharmacy and were initiating one of five standard first-line tenofovir-based once-daily regimens between January 1, 2008 and December 31, 2011. Dates when medications were dispensed were obtained from TSHC's electronic pharmacy database. We assumed that all fills were for 30 pills. Basic demographics and laboratory data were assessed by querying the electronic medical record.

We assessed adherence by calculating the proportion of days covered, and considered 80% or greater for the year as adherent (Sattler, Lee, & Perri, 2013). We also assessed retention in care during the first year as measured by laboratory data, using the definition provided by the Health Resources and Services Administration (2 viral load measurements obtained after start of ART separated by at least 3 months within the first year) (Gardner, et al., 2011). We also assessed time to switch from original regimen, and the proportion of patients who achieved virologic suppression (viral load <400 copies/mL) at least once during the first year, both using an intention to treat analysis as well as assessing the proportion who achieved virologic suppression while on their initial regimen. We chose <400 copies/mL as the cutoff because the assay used during 2008, the first year of the data period used, had this as the assay's threshold of detection. We also performed analyses stratifying by year where a cutoff of 50 copies/mL was used in years 2009 through 2011.

Statistical methods

In comparing demographics, we compared continuous variables using t-tests or the Wilcoxon rank sum test, as appropriate, and categorical variables were compared by the use of χ^2 testing or Fisher's exact test, as appropriate.

Regression models for categorical outcomes utilized logistic regression (Hosmer, Lemeshow, & Sturdivant, 2013). We performed unadjusted analysis as well as adjusted analyses where we accounted for baseline differences between STR and MTR subjects by the use of propensity scores (Rosenbaum and Rubin, 1983). The propensity score was derived using treatment type (STR or MTR) as the outcome in a logistic regression model and age, sex, African-American race, Hispanic ethnicity, intravenous drug use, HIV sexual transmission risk (men who have sex with men [MSM] versus others), initial viral load, initial CD4 count, insurance status (dichotomized as insured vs uninsured), and hepatitis C status as predictors. We then utilized inverse probability treatment weights in analyses of outcomes. Weighting each subject by $1/P$, where P is the probability derived from the propensity score model that the subject would receive the treatment which he or she in fact actually did receive, may reduce imbalance in the confounders which were incorporated into the propensity score between the treatment and control arm (Austin, 2011).

All analysis was performed using STATA 12 (College Station, TX). This study was approved by the institutional review boards of Baylor College of Medicine and Harris Health System. As a retrospective analysis of previously collected data, the requirement for individual informed consent was waived.

Results

A total of 2095 patients entered care during the period in question, of whom 1028 met the inclusion criteria for this study (Figure 1). Baseline demographics are presented in the left half of Table 1. Subjects were more likely to receive an STR if they were male, if they were younger, if they had a lower baseline viral load or higher baseline CD4 count, and if they were not an injection drug user. The demographics of the population after using the weighting procedure are presented in the right half of Table 1; the STR and MTR

populations are much more similar in terms of demographics in this table, suggesting that the propensity score method was able to balance the covariates of interest for this analysis.

The regimens prescribed are seen in Table 2. Among the 622 (60.5%) STR subjects, 100% were prescribed coformulated tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/efavirenz. Among the 410 (39.5%) MTR subjects, 65.2% were prescribed TDF/FTC/atazanavir/ritonavir and 34.8% TDF/FTC/darunavir/ritonavir.

Outcomes of interest are shown in Table 3. Retention in care one year after starting ART was achieved in 80.7% of STR patients vs. 72.7% of MTR patients (unadjusted OR 1.57; 95% CI 1.17-2.11; $p=0.003$). This difference remained significant in the propensity-adjusted analysis (aOR 1.49; 95% CI 1.10-2.02; $p=0.011$). Virologic suppression at any point in year one, regardless of regimen change, occurred among 84.4% of STR patients vs. 77.6% of MTR patients (unadjusted 1.56; 95% CI 1.14-2.15; $p=0.006$). This result remained significant in the propensity-adjusted analysis (aOR 1.41; 95% CI 1.02-1.96; $p=0.04$). Differences were somewhat attenuated when examining virologic suppression while on the original regimen, with 79.4% of STR recipients versus 72.9% of MTR recipients achieving that outcome (unadjusted 1.43; 95% CI 1.07-1.92; $p=0.016$; aOR 1.28, 95% CI 0.95-1.73, $p=0.11$).

We examined pharmacy fill data as well, although our analysis was unable to account for patients who opted to switch pharmacies during the first year. We observed that 33.0% of STR recipients and 30.1% of MTR recipients achieved at least 80% proportion of days covered (PDC) for the year (unadjusted 1.14; 95% CI 0.87-1.50; $p=0.328$). This finding was replicated in the propensity-score model (aOR 1.04, CI 0.79-1.38, $p=0.77$). Similarly, 29.6% of STR recipients and 25.9% of MTR recipients achieved at least 80% PDC with the initial regimen (unadjusted OR 1.20, CI 0.91-1.60, $p=0.195$; aOR 1.08, CI 0.81-1.45, $p=0.586$). We attempted to estimate the extent to which change in pharmacy might be occurring. Overall, 13.3% of MTR recipients and 15.8% of STR recipients were observed to have an undetectable viral load despite not filling medication in the 90 days prior to the viral load measurement, suggesting that they were obtaining their medications elsewhere. This difference was not statistically significant ($p=0.28$). As a sensitivity analysis, we reran the analyses for virologic and retention-in-care excluding these patients who suppressed despite not obtaining a refill at this pharmacy, and obtained similar results to those presented above (data not shown).

We performed several additional sensitivity analyses. Although we lack reliable data on depression in our data set, we did have data on visits to the psychiatry clinic by patients. Fewer patients with psychiatry visits received an STR (22.5% vs 28.3%, $p=0.035$), consistent with prescribers avoiding efavirenz-based regimens in patients with psychiatric disease due to the neuropsychiatric effects of the drug. However, repeating the propensity score analysis while including this variable did not lead to meaningful changes in the odds ratios calculated (data not shown). As psychiatry visit data is a very imperfect marker of depression or psychiatric disease, we chose to use the propensity score analysis without this variable as our definitive analysis. As a second sensitivity analysis, we repeated the viral load analyses above separately for each year of the study using the date of ART initiation to determine the year. We used a viral load cutoff of 400 copies/mL to determine undetectable

for 2008, and a lower viral load cutoff of 50 copies/mL for subsequent years. Although the proportion of patients who were virologically suppressed was, as expected, lower with the lower cutoff, the conclusion that superior virologic outcomes were obtained with STR regimens was unchanged (data not shown).

Within the first year, 53 MTR patients (13.1%) and 97 STR patients (15.6%) switched regimens ($p=0.26$). There was no statistically significant difference among those who switched in the proportion of patients who were virologically suppressed, as 22 of 53 MTR patients (41.5%) and 34 of 97 STR patients (35.1%) were virologically suppressed ($VL<400$ copies/mL) at the time of switch ($p=0.43$). STR recipients who switched regimens switched after a median of 162 days (IQR 90-244), while MTR recipients switched after a median of 140 days (IQR 42-214). This difference was not statistically significant ($p=0.17$). Of the STR patients who switched regimens, 3 (3.1%) switched to another STR regimen (3 to tenofovir/emtricitabine/rilpivirine). Of the patients initially on an MTR regimen, 9 (17.0%) switched to an STR regimen (1 to tenofovir/emtricitabine/rilpivirine, 8 to tenofovir/emtricitabine/efavirenz).

Discussion

In an observational cohort of patients starting once-daily antiretroviral regimens, we found that STRs, compared with once-daily MTRs, are associated with higher rates of virologic suppression and retention in care in the first year, even after the use of the propensity score method to adjust for observed confounders of choice of initial antiretroviral regimen. We did not, however, demonstrate a difference in fill rates using pharmacy data.

Our paper stands out as one of the few published studies to directly compare STR and once-daily MTR regimens in a clinical rather than research setting. Cotte *et al* observed superior virologic outcomes with STRs compared with once daily MTRs in a large prospective cohort from France (Cotte, et al., 2017). However, their study was performed in a setting with overall low rates of virologic failure ($<5\%$ of all patients) and in a setting with universal access to healthcare, whereas our study was conducted in a county health system among a racially and ethnically diverse mostly uninsured population with significant barriers to adherence and retention in care. Nachega *et al* performed a meta-analysis of randomized control trials and found that, within the strata of once-daily regimens, decreased pill burden was associated with enhanced regimen adherence and greater likelihood of viral suppression. However, no trials comparing STRs directly to once-daily MTRs were included in this meta-analysis (Nachega, et al., 2014). Furthermore, the subjects were observed in a clinical trial setting, and the extent to which clinical trial data in HIV research can be extrapolated to real-world outcomes remains unclear. (Routman et al., 2010)

All the patients in our study were initially treated with a regimen that included either efavirenz or ritonavir-boosted atazanavir or darunavir. To eliminate potential confounding, we restricted our population of study to persons being prescribed tenofovir-containing regimen. When atazanavir with ritonavir was compared with efavirenz in ACTG 5202, similar virologic, tolerability, and safety outcomes were seen in the patients given a tenofovir-based NRTI backbone; patients were given efavirenz separately from the NRTI

backbone in this study (Daar et al., 2011). In a randomized study comparing darunavir to atazanavir, virologic outcomes were similar between darunavir and atazanavir, but the rate of adverse effects leading to discontinuation was higher in the atazanavir arm (Lennox et al., 2014). While it is difficult to extrapolate clinical trial results into routine care, these results suggest that clinical efficacy of the regimens we compared is similar, further suggesting that effectiveness in routine care may be impacted by pill burden.

Our work has a number of limitations. Once daily MTRs regimens in our cohort were protease inhibitor-based regimens, which may have been preferentially prescribed to patients seen as potentially non-adherent by their providers due to the high barrier to antiretroviral resistance exhibited by the protease inhibitor class of drug (Wensing, van Maarseveen, & Nijhuis, 2010). We used a propensity score model to reduce the risk of confounding bias, and our calculations showed that our approach balanced the covariates of interest between the MTR and STR cohorts. The covariates which factored into our propensity model are similar to those of other published work in this area using a similar approach (Cotte, et al., 2017), lending credence to our findings. However, this methodology cannot account for confounding by unmeasured factors (Austin, 2011), and we cannot rule out the possibility that patients who received MTRs in our study had higher barriers to adherence, even after adjusting for the covariates included in our model. As a sensitivity analysis, we re-ran our analysis separately for men and women (since efavirenz is teratogenic and less likely to be prescribed to women), with little change in the results. Recently, newer integrase inhibitors such as dolutegravir (Comi and Maggiolo, 2016) have been developed which offer once daily dosing and higher barriers to resistance. Similarly, newer formulations of protease inhibitors such as darunavir and atazanavir which are co-formulated with a boosting agent with fewer side effects and facilitating decreased pill burden have reached the market (Kakuda et al., 2015), and a darunavir-containing STR is in clinical trials (Mills et al., 2015). Future observational research in this area will benefit from the weakening of the correlation between drug class and pill burden, allowing for research designs which more effectively separate the effect of drug class from that of pill burden. Previous work comparing outcomes between classes of antiretrovirals has used the instrumental variable technique, using physician preference for one class of medication over another as an instrument (Nelson et al., 2013). Instrumental variable analysis, if patients are assigned to providers at random, can account for confounding even by unobserved variables (Brookhart, Rassen, & Schneeweiss, 2010). To our knowledge, such an analysis has yet to be performed to compare the effectiveness of STRs to MTRs for the treatment of HIV. Unfortunately, we do not have accurate physician data with which to conduct an instrumental variable analysis with our dataset.

We used pharmacy fill data, an imperfect measure of adherence (Sattler, et al., 2013). We do not have data on why patients stopped filling medications, and we do not know who switched pharmacies versus who was lost to follow-up. A significant proportion of patients may have switched to an offsite pharmacy, resulting in missing data that would appear as non-adherence. Since the proportion of patients who maintained virologic suppression despite lack of recent refills was similar between arms, the rate of transfer to outside pharmacies appears to have been similar between the two cohorts. In addition, such missing data do not affect the retention in care and virologic outcomes we observed. We lack data on

the reason for loss to follow up in our clinic; patients who moved elsewhere, switched providers, or were incarcerated would be counted as not being retained in care according to our methodology, and all are common occurrences in this population (Giordano, et al., 2007). However, these challenges are inherent in the study of underserved populations.

Conclusion

In a non-clinical trial setting, patients taking STRs demonstrate similar adherence and better retention in HIV care and better virologic suppression than do patients on MTRs. These observational data suggest STRs may facilitate improved clinical outcomes. The development of newer protease inhibitor and integrase inhibitor regimens with co-formulated components will allow for more robust estimates of the potential benefits of STR regimens as compared to once-daily MTRs in real world settings.

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Figure 1.
Flowchart of patients into study

Table 1

Demographics of the study cohort (n=1028)

Unweighted		Propensity-score weighted								
	Multi-tablet Regimen (n=406)		Single Tablet Regimen (n=622)			p-value	Multi-tablet Regimen (n=406)		Single Tablet Regimen (n=622)	
Mean Age (SD)	42.2 (10.4)		41.2 (11.9)			0.16	41.6 (11.0)		41.7 (11.5)	
Age	#	%	#	#	#	0.001	#	%	#	#
<25	11	2.7	44	7.1			26.4	5.2	27.5	5.3
25-34	92	22.7	173	27.8			127.9	25.0	130.7	25.4
35-44	138	34.0	151	24.3			145.6	28.5	145.8	28.4
45-54	114	28.1	170	27.3			146.7	28.7	143.8	28.0
55-64	42	10.3	73	11.7			54.7	10.7	56.2	10.9
65+	9	2.2	11	1.8			10.6	2.1	10.3	2.0
Median initial viral load	88500		74600			0.26	82900		79500	
Initial viral load	#	%	#	#	#	0.35	#	%	#	#
<400	35	8.7	65	10.5			48.5	9.5	49.6	9.6
400-999	10	2.5	27	4.3			19.1	3.7	18.7	3.6
1000-9999	54	13.4	77	12.4			67.0	13.1	65.4	12.7
10000-99999	119	29.5	186	29.9			147.3	28.8	150.6	29.3
100000-999999	155	38.4	234	37.6			199.1	38.9	198.0	38.5
100000+	31	7.7	33	5.3			30.8	6.0	32.0	6.2
Median initial CD4 count	169.5		203.5			0.07	186		181	
Initial CD4 count	#	%	#	#	#	0.02	#	%	#	#
0-49	116	28.7	166	27.0			142.9	27.9	142.4	27.7
50-99	38	9.4	57	9.2			48.7	9.5	47.4	9.2
100-199	79	19.6	83	13.3			82.8	16.2	83.3	16.2
200-499	140	34.7	272	43.7			202.3	39.5	205.0	39.9
500+	31	7.7	44	7.1			34.9	6.8	36.1	7.0
Race/Ethnicity						0.873				
Asian non-Hispanic	2	0.5	3	0.5			2.7	0.5	2.5	0.5
Black non-Hispanic	242	59.6	373	60.0			300.6	58.7	303.6	59.0

	Unweighted			p-value	Propensity-score weighted		
	Multi-tablet Regimen (n=406)	Single Tablet Regimen (n=622)			Multi-tablet Regimen (n=406)	Single Tablet Regimen (n=622)	
Hispanic	128	31.5	192		165.0	32.2	163.8
White non-Hispanic	33	8.1	54		41.6	8.1	44.4
Other	1	0.3	0		1.8	0.4	0
Gender				0.004			
Female	133	32.8	152		143.0	27.9	142.2
Male	273	67.2	470		368.8	72.1	372.0
Risk Factor				0.01			
Heterosexual	228	56.2	325		281.1	54.9	277.0
Intravenous drug use	31	7.6	21		27.8	5.4	24.7
MSM	125	30.8	234		176.0	34.4	176.5
MSM&IDU	5	1.2	8		5.7	1.1	9.5
Other	11	2.7	21		15.1	2.9	16.5
Hepatitis C Status				0.31			
HCV positive	57	14.0	74		67.4	13.2	66.7
HCV negative	349	86.0	548		444.4	86.8	447.6
Insurance status*				0.04			
Uninsured	319	78.6	526		424.0	82.9	426.1
Medicare	9	2.2	10		8.7	1.7	9.9
Medicaid	71	17.5	83		70.1	13.7	75.7
Private	7	1.7	3		9.0	1.8	2.6

* Due to low numbers of patients with private insurance or Medicare, insurance was dichotomized as “Insured vs uninsured” for the purpose of the propensity score weighting.

Table 2

Regimen

	#	%
Single tablet regimens	622	60.5%
Efavirenz/TDF/FTC	622	60.5%
Multiple tablet regimens	406	39.5%
Atazanavir/Ritonavir/TDF/FTC	263	25.6%
Darunavir/Ritonavir/TDF/FTC	143	13.9%

Table 3

Outcomes of Interest in the first year

	STR		MTR		Unadjusted analysis	Analysis adjusted by propensity score
	#	%	#	%		
Retention in care	502	80.7	295	72.7	OR 1.57; 95% CI 1.17-2.11; p=0.003	OR 1.49; 95% CI 1.10-2.02; p=0.011
Virologic suppression, first year	525	84.4	315	77.6	OR 1.56; 95% CI 1.14-2.15; p=0.006	OR 1.41; 95% CI 1.02-1.96; p=0.04
Suppressed on original regimen, first year	494	79.4	296	72.9	OR 1.43; 95% CI 1.07-1.92; p=0.016	OR 1.28; 95% CI 0.95-1.73; p=0.11
PDC>80% in first year*	205	33.0	122	30.1	OR 1.14; 95% CI 0.87-1.50; p=0.328	OR 1.04; CI 0.79-1.38, p=0.77

PDC, proportion of days covered.

* We could not account for transfers to other pharmacies, so this is a lower bound estimate of adherence