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Uptake and virologic outcomes of single versus multi-tablet antiretroviral regimen among treatment naïve youth in the HIV Research Network

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Abstract

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Objective—Several single tablet regimens (STR) are now available and are recommended for first line antiretroviral therapy (ART), however STR use for youth with HIV (YHIV) has not been systematically studied. We examined the characteristics associated with initiation of STR versus multi-tablet regimens (MTR) and the virologic outcomes for youth with non-perinatally acquired HIV (nPHIV).

Methods—Retrospective cohort study of nPHIV youth ages 13–24 initiating ART between 2006 and 2014 at 18 U.S. HIV clinical sites in the HIV Research Network was performed. The outcomes measured were initiation of STR versus MTR, virologic suppression (VS) at 12 months, and time to VS. Demographic and clinical factors associated with initiation of STR versus MTR ART and VS (<400 copies/mL) at 12 months after initiation were assessed using multivariable logistic regression. Cox proportional hazards regression was used to assess VS within the first year.

Results—Of 987 youth, 67% initiated STR. Of the 589 who had viral load data at 1 year, 84% of those on STR versus 67% of those on MTR achieved VS ($p < 0.01$). VS was associated with STR (AOR 1.61 [1.01–2.58]), white (AOR 2.41 [1.13–5.13]) or Hispanic race/ethnicity (2.38 [1.32–4.27]), and baseline CD4 count 350–500 cells/mm3 (AOR 1.94 [1.18–3.19]) and >500 cells/mm3 (AOR 1.76, 95% CI 1.0–3.10). STR was not associated with a shorter time to VS compared to MTR (HR 1.07 [0.90–1.28]).

Conclusion—Use of STR was associated with greater likelihood of sustained VS 12 months after ART initiation in YHIV.

Keywords

HIV; youth; adherence; antiretroviral therapy; single tablet

INTRODUCTION

Compared to adults, youth with HIV (YHIV) have poorer retention in care, antiretroviral therapy (ART) adherence, and HIV virologic suppression (VS) (1)· Multiple barriers to medication adherence have been identified, including environmental barriers, such as unstable housing, poor health literacy, and under-employment, and barriers related to cognitive development, stigma, and co-morbid mental health issues and/or substance use (2,3)· In adults with HIV, lower pill burden has been shown to be associated better adherence and VS (4). Simplification to a once daily single tablet regimen (STR) first became available in 2006 with the introduction of efavirenz/emtricitabine/tenofovir disoproxil fumarate (5). Studies have shown that use of STR is associated with better adherence to ART and VS, when compared to multi-tablet regimens (MTR) (6). Additionally STR have been shown to improve quality of life in adult patients and improve cost effectiveness compared to MTR (7–9). The Department of Health and Human Services (DHHS) HIV treatment guidelines for adults and adolescents highlight the importance of using STR when appropriate to minimize pill burden and aid in adherence (10). This recommendation is based on data from studies in adults. STR have been shown to improve adherence outcomes in other groups at high risk for non-adherence, such as homeless and marginally housed adults (11). However, there is

no specific data available on the use of STR in YHIV, where factors affecting adherence may be complex and adherence has been shown to be lower than for adults (12,13).

Given the unique challenges that YHIV face, it is presumed that the increasing use of STR may increase adherence and VS through decreased pill burden. However, this has not been previously examined specifically in YHIV. The aim of this study is to evaluate the uptake of STR in YHIV and virologic outcomes for YHIV initiating ART with STR vs. MTR.

METHODS

This was a retrospective cohort study examining uptake of STR and comparing STR and MTR ART initiation in YHIV. Eligible patients were recruited from HIV clinics participating in the HIV Research Network (HIVRN), a consortium of 18 U.S. clinic sites that provide primary and subspecialty care to children, youth, and adults distributed across the United States (14). As described previously, HIVRN sites abstract specified data elements from patients' medical records, including demographic data, service utilization, medications, and laboratory tests; abstracted data are assembled into a single database after quality assurance review (14). The Johns Hopkins University School of Medicine Institutional review board (IRB) and the IRBs of each participating institution approved the collection and use of these data for analysis. Data from 13 sites were analyzed, 4 of which were pediatric sites. Patients were included in the analysis if they were between the ages of 13 and 24 with non-perinatally acquired HIV (nPHIV) and initiated ART between 2006 and 2014, with documented viral load > 400 copies/mL at the time of ART initiation. Patients were included if they had no documented history of ART use. Patients with perinatally acquired HIV were excluded.

Statistical analysis

Three separate outcomes were measured: 1) Factors associated the initiation of STR versus MTR, 2) VS at 12 months after ART initiation, and 3) Time to VS. STR were defined as efavirenz/emtricitabine/tenofovir disoproxil fumarate, emtricitabine/rilpivirine/tenofovir disoproxil fumarate, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, or abacavir/dolutegravir/lamivudine. VS was defined as HIV viral load < 400 copies/mL at 12 months, using the viral load measurement closest to 12 months within 9–15 months after initiation. To assure that the viral load outcome was being associated with the regimen type that was first initiated, patients were excluded if they changed treatment (STR to MTR or MTR to STR) within 9 months after first ART initiation; 9 months chosen because it was the minimum time point for assessment of viral load. For viral load outcome analysis, patients who initiated ART in 2014 were excluded as they lacked 12-month follow up data. Additionally, viral suppression was measured as time to first VS within the first 12 months of ART initiation.

Demographic and clinical characteristics of ART-naïve patients initiating ART with either STR or MTR regimens were assessed using the Chi-squared test for categorical variables and Wilcoxon rank sum test for continuous variables. Univariate and multivariable logistic regression was used to assess the factors associated with initiation of STR versus MTR and factors associated with VS at 12 months after ART initiation. Cox proportional hazard

models were used to compare time to initial viral suppression (<400 copies/mL) over the 12 months after initiation of ART. The final multivariable and Cox proportional hazards models included gender, race/ethnicity, HIV risk factor, clinical site (pediatric versus adult), CD4 count at ART initiation, viral load at ART initiation, year of ART initiation, and ART exposure history. The proportional hazards assumption was assessed graphically. Analyses were performed with STATA version 14 software (StataCorp, TX).

RESULTS

A total of 987 YHIV were initiated on ART between 2006 and 2014 and were included in this analysis. The majority were male (84%), African American (62%), and had male-to-male sex (MSM) as an HIV risk factor (75%) with a median age of 22 years (IQR 20–23 years). Overall 661 (67%) initiated STR and 326 (33%) initiated MTR. Of the STR initiated, 69% were efavirenz/emtricitabine/tenofovir disoproxil fumarate, 19% emtricitabine/rilpivirine/tenofovir disoproxil fumarate, 11% elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, and 1% abacavir/dolutegravir/lamivudine.

In univariate analyses, patients were more likely to be initiated on a STR if they were male, MSM, had a CD4 count greater than 200 cells/mm^3, or were initiated in 2010 or 2013–2014 (Table 2). In multivariable analysis, patients were more likely to be started on STR if they were male (adjusted odds ratio (AOR) 5.10 [2.80–9.28]), had CD4 count 200–250 cells/mm^3 (AOR 1.955 [1.01–2.37]) or >500 cells/mm^3 (AOR 1.72 [1.05–2.82]) compared to CD4 <200 cells/mm^3, or initiated ART in 2013 (AOR 2.49 [1.06–5.83]) or 2014 (AOR 2.77 [1.14–6.74]) compared to 2006.

A total of 846/987 (86%) patients initiated ART between 2006–2013. Of those, 42 who changed from STR to MTR and 13 who changed from MTR to STR within 9 months of initiation were excluded from analysis because of the change in regimen type. Of the remaining 791 patients, at total of 589 (75%) had an HIV viral load measurement at 12 months. There was no difference in availability of viral load data at 12 months between the STR group and the MTR group (76% versus 72%, p=0.20). At 12 months after ART initiation, 83% (322/388) of those on STR versus 73% (146/201) of those on MTR had VS (unadjusted OR 1.84 [1.22–2.76]). For the 388 patients on STR with viral load data at 12 months, STR consisted of 80% efavirenz/emtricitabine/tenofovir disoproxil fumarate, 14% emtricitabine/rilpivirine/tenofovir disoproxil fumarate, and 7% elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil.

In the multivariate logistic regression model, initiation of a STR was associated with VS at 12 months (AOR 1.61 [1.01–2.58]) (Table 2). VS was also associated with White race (AOR 2.41 [1.13–5.13]) and Hispanic ethnicity (2.38 [1.32–4.27]) (compared to Black), and CD4 350–500 cells/mm^3 (AOR 2.90 [1.49–5.65]) and 500 cells/mm^3, (3.36 [1.56–7.22) compared to <200 cells/mm^3. Care at a pediatric center had a trend to association with VS (AOR 2.32 (0.97–5.55). There was no difference in likelihood of VS among the different STR.

Of those who initiated ART from 2006–2013, 747 had at least one follow up viral load measurement after ART. Within the first 12 months, those initiated maintained on a STR

achieved first measurement of VS at a faster rate compared to those initiated on a MTR in the unadjusted model (HR 1.22 [1.03–1.44]). After adjusting for covariates, the median time to VS was shorter (77 days, [68–85 days]) in the STR compared to the MTR group (91 days, [77–103 days]), however, this was not statistically significant (HR 1.07 [0.90–1.28]).

DISCUSSION

In this multisite cohort, YHIV initiating STR were more likely to achieve VS 12 months after initiation than YHIV who initiated MTR. These results are similar to results seen in prior studies focused on adult populations (6,15). In addition, STR initiation was associated with male gender, higher CD4 count, and initiation of ART in 2013 and 2014.

The association of STR initiation and male gender likely occurred because of heightened concern for teratogenicity of the efavirenz component of the most commonly prescribed STR during the study period. This association is unlikely to be seen with the other STR agents.

There may be the perception that those with CD4 count <200 cells/mm^3 may require a more complex ART regimen than was available as a STR, such as the use of protease inhibitors, and this may explain the increased likelihood of STR use in those with higher baseline CD4 count. Higher likelihood of STR use in patients with higher CD4 counts has been shown in other cohort studies focused on adult patients (15).

Patients were more likely to initiate STR if ART was initiated in 2013 or 2014, which reflects an increase in available STR options with FDA approval of emtricitabine/rilpivirine/tenofovir disoproxil fumarate in 2011, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in 2012 and abacavir/dolutegravir/lamivudine in 2014.

YHIV were seen in either adult or pediatric sites. Care at a pediatric center, while not associated with initiation of STR, had a trend to association with virologic suppression. This finding is consistent with other data published from the HIVRN showing higher rates of treatment discontinuation and lost to follow up at adult versus pediatric care sites (16,17). It is likely that there are factors (youth friendly services, etc.) associated with pediatric care sites that support adherence to ART and maintenance of virologic suppression.

A strength of our study is that we evaluated YHIV being followed at HIV clinical sites under non-trial-based conditions with a clinic diversity. However, while HIVRN demographics closely resemble those of PLHIV in the U.S., our sample is not nationally representative. Additionally, factors, such as mental health or substance abuse co-morbidities are not measured by HIVRN, so were not examined. Our analysis of VS was limited to those with a 12-month measure of viral load. It is unknown whether the patients who did not have follow up viral load testing achieved virologic suppression as we do not have data on whether those patients engaged in care at other sites or disengaged from care. Additionally, regimen type changes after 9 months were not recorded. Lastly, 72% of the STR used during the study period was efavirenz/emtricitabine/tenofovir disoproxil fumarate, which with the development of newer regimens with fewer side effects, such as teratogenicity, likely does not reflect current STR use. Though no difference was noted in terms of regimen type and

virologic suppression, the small numbers of the other regimens make it difficult to compare. The limited number of patients <18 years make the results less generalizable to the younger population.

Overall, this study shows increasing uptake of STR over time among YHIV and that use of STR in YHIV was associated with virologic suppression. These results support U.S. adult and adolescent guidelines recommending STR to improve adherence and virologic suppression. Use of STR is one component of the complex comprehensive care that this challenging group requires.

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Table 1:

Baseline clinical and demographic characteristics for youth living with HIV enrolled in the HIV Research Network initiated on single tablet regimen and multi-tablet regimen antiretroviral therapy

Characteristic	STR 661 (67%)	MTR 326 (33%)	Total 987	P value
Median Age (range, IQR)	22 (15–24, 20–23)	22 (16–24, 20–23)	22 (15–24, 20–23)	0.20
Sex/Gender				**<0.001**
Female	60 (9)	100 (31)	160 (16)	
Male	601 (91)	226 (69)	827 (84)	
Race				0.47
Black	410 (62)	204 (63)	614 (62)	
White	79 (12)	48(15)	127 (13)	
Hispanic	142 (21)	63 (19)	205 (21)	
Other	30 (5)	11 (3)	41 (4)	
Risk Factor				**<0.001**
MSM	537 (81)	199 (61)	736 (75)	
Heterosexual	103 (16)	107 (33)	210 (21)	
Other	21 (3)	20 (6)	41 (4)	
Site				0.83
Adult	589 (89)	289 (89)	878 (89)	
Pediatric	72 (11)	37 (11)	109 (11)	
CD4 count (cells/mm3)				**0.03**
<200	97 (15)	72 (22)	169 (17)	
200–350	210 (32)	101 (31)	311 (32)	
350–500	183 (28)	84 (26)	267 (27)	
>500	171 (26)	69 (21)	240 (24)	
Viral load (copies/ml)				0.68
400–9,999	130 (20)	70 (21)	200 (20)	
10,000–49,999	206 (31)	92 (28)	298 (30)	
50,000–99,9999	117 (18)	54 (17)	171 (17)	
>100,000	208 (31)	110 (34)	318 (32)	
Year				**<0.001**
2006	16 (2)	16 (4)	32 (3)	
2007	20 (3)	10 (3)	30 (3)	
2008	36 (5)	29 (9)	65 (7)	
2009	65 (7)	29 (9)	65 (7)	
2010	79 (12)	33 (10)	112 (11)	
2011	96 (15)	67 (21)	163 (17)	
2012	122 (18)	64 (19)	186 (19)	
2013	148 (22)	45 (14)	193 (20)	

Characteristic	STR 661 (67%)	MTR 326 (33%)	Total 987	P value
2014	108 (16)	33 (10)	141 (14)	

Bolded P value statistically significant. STR, single tablet regimen; MTR, multi-tablet regimen; IQR, interquartile range; MSM, men who have sex with men; IDU, injection drug use; ART, antiretroviral therapy

Table 2:

Univariate and multivariable logistic regression of factors associated with initiation of single tablet regimen (STR) and virologic suppression at 1 year in youth living with HIV enrolled in the HIV Research Network

	Initiation of STR n=987		**Virologic Suppression at 1 year n=951**	
	Univariate (OR) 95%CI	**Multivariable (AOR) 95% CI**	**Univariate (OR) 95%CI**	**Multivariable (AOR) 95% CI**
STR	----	----	**1.84 (1.22–2.76)**	**1.61 (1.01–2.58)**
Male	**4.43 (3.11–6.31)**	**5.10 (2.80–9.28)**	**2.29 (1.39–3.75)**	1.52 (0.63–3.70)
Pediatric Site	0.95 (0.63–1.45)	0.60 (0.36–0.97)	1.84 (0.85–3.98)	2.32 (0.97–5.55)
HIV risk factor				
Heterosexual	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
MSM	**2.80 (2.04–3.84)**	0.89 (0.51–1.54)	**1.77 (1.10–2.82)**	0.87 (0.39–1.94)
Other	1.09 (0.56–2.13)	0.65 (0.31–1.41)	0.67 (0.26–1.75)	0.43 (0.15–1.22)
Race				
Black	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
White	0.82 (0.55–1.22)	0.72 (0.847–1.12)	**2.34 1.16–4.73)**	**2.41 (1.13–5.13)**
Hispanic	1.12 (0.79–1.58)	0.98 (0.68–1.42)	**2.00 (1.14–3.46)**	2.38 (1.32–4.27)
Other	1.36 (0.67–2.76)	1.02 (0.48–2.15)	3.18 (0.73–13.91)	3.13 (0.66–14.99)
CD4 count (cells/mm^3)				
<200	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200–350	**1.54 (1.04–2.27)**	**1.55(1.01–2.37)**	**1.71 (1.01–2.89)**	1.71 (0.96–3.03)
350–500	**1.62 (1.08–2.41)**	1.43 (0.91–2.25)	**2.88 (1.60–5.20)**	**2.90 (1.49–5.65)**
>500	**1.84 (1.22–2.78)**	**1.72 (1.05–2.82)**	**3.67 (1.87–7.22)**	**3.36 (1.56–7.22)**
Viral load (copies/mL)				
400–9,999	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
10,000–49,999	1.20 (0.82–1.76)	1.15 (0.75–1.75)	1.25 (0.69–2.27)	1.29 (0.68–2.47)
50,000–99,9999	1.17 (0.76–1.80)	0.99 (0.62–1.60)	1.02 (0.53–2.00)	1.08 (0.52–2.26)
>100,000	1.02 (0.70–1.48)	0.99 (0.64–1.53)	0.94 (0.54–1.64)	1.22 (0.64–2.34)
Year				
2006	1.0(ref)	1.0(ref)	1.0(ref)	1.0(ref)
2007	2.00 (0.72–5.59)	1.78 (0.59–5.36)	1.24 (0.33–4.65)	1.38 (0.34–5.66)
2008	1.24 (0.53–2.89)	1.01 (0.41–2.53)	1.14 (0.41–3.22)	1.07 (0.35–3.20)
2009	1.24 (0.53–2.89)	0.96 (0.38–2.39)	1.07 (0.38–2.98)	0.97 (0.32–2.94)
2010	**2.39 (1.07–5.35)**	1.70 (0.71–4.07)	1.46 (0.56–3.84)	1.01 (0.35–2.87)
2011	1.43 (0.67–3.06)	0.97 (0.43–2.23)	**2.30 (0.86–6.14)**	1.58 (0.55–4.55)
2012	1.91 (0.89–4.06)	1.26 (0.55–2.90)	**2.43 (0.93–6.39)**	1.29 (0.44–3.73)
2013	**3.29 (1.52–7.10)**	**2.49 (1.06–5.83)**	**2.08 (0.80–5.39)**	0.99 (0.34–2.88)
2014	**3.27 (1.48–7.25)**	**2.77 (1.14–6.74)**	----	----

Bold values statistically significant. STR, single tablet regimen; CI, confidence interval; OR; odds ratio; AOR, adjusted odds ratio; MSM, men who have sex with men; IDU, injection drug use; ART, antiretroviral therapy