RATE AND DETERMINANTS OF VIROLOGIC FAILURE IN HIV-INFECTED YOUTH RECEIVING FIRST-LINE EMTRICITABINE/ TENOFOVIR DISOPROXIL FUMARATE/ EFAVIRENZ (ATRIPLA®) COMPARED TO OTHER ANTIRETROVIRAL DRUG REGIMENS

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ABSTRACT

Objectives. The primary objective of the study was to determine whether first-line once-daily Emtricitabine/ Tenofovir disoproxil fumarate/Efavirenz (Atripla®) is associated with a lower rate of virologic failure compared with alternative first-line regimens in HIV-infected youth. The secondary objective was to identify predictors of virologic failure in the overall study sample and in the Atripla® group.

Methods. Fifty two HIV-infected youth followed at an urban HIV clinic, ages 17-25, not pregnant, with no history of prevention of mother-to-child transmission of HIV, starting their first-line antiretroviral regimen, and with at least 12 weeks of follow-up on their regimen were eligible to be included in a retrospective review of medical charts. The main outcome was virologic failure, defined as having a viral load over 400 copies/ml after 12 weeks of therapy or failure to ever reach this threshold.

Results. No significant difference in the rate of virologic failure was found between the two treatment groups. Overall, 52% of patients failed their first-line regimen. The only significant independent predictor of virologic failure was history of AIDS. Tobacco use was associated with failure in the Atripla® group. No significant difference was noted in time to failure after the start of either Atripla® or an alternative regimen. Development of resistance mutations and adherence levels did not significantly differ between the two regimen groups. However, adherence levels were significantly lower in those who failed their regimen compared to those who did not.

Conclusions. Our data do not support the hypothesis that rate of virologic failure in a simple, once-daily, first-line Atripla® regimen is lower compared to alternative regimens in our HIV-infected youth population. Adherence and psychosocial factors are important determinants of first-line regimen success and require particular consideration before offering Atripla®.

Keywords: HIV, adolescents, teens, adherence, virologic failure, treatment failure, antiretroviral therapy, HAART

INTRODUCTION

Despite continued advances in public health infrastructure, health education, and antiretroviral therapeutics, the HIV/AIDS epidemic continues to afflict the most vulnerable age groups of our population – children and adolescents. In the United States (US), several sources reported a high inci-

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dence of HIV infection in youth (1-3). In 2010, the Centers for Disease Control (CDC) estimated that in the US over 12200 incident cases of HIV occurred in young adults aged 13-24, representing 26% of all new infections (3). The majority of these infections occurred in ethnic minority youth populations, especially blacks (57%, 7000) and Hispanic/Latino (20%, 2390) (3). Of particular concern is the estimation that 60% of youth in the US are not aware that they are HIV-infected (3). Worldwide, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS), adolescents (10-19 years) are the only age group in which AIDS mortality has increased between 2001 and 2012 (4). These statistics emphasize the continued gravity of HIV/AIDS in our youth populations and the need to scale-up strategies of testing and counseling, access and adherence to antiretroviral (ARV) therapy.

It has been well established that adherence to highly active antiretroviral therapy (HAART) in youth is a strong predictor of therapeutic effectiveness, and that non-adherence increases the risk of opportunistic infections, disease progression, and death (5,6). Several studies explored the relationship between regimen complexity and HAART adherence (5-9). Data, however, has been conflicting, making this relationship difficult to evaluate. In a 6-month longitudinal study of 24 HIV-positive children being treated with HAART, Martin *et al*. (5) found that regimen complexity was not significantly correlated with patient demographics nor HIV-1 RNA viral load, CD4 percentages, or absolute CD4 counts. However, at both 3 month and 6 month time points, children with more complex regimens were more adherent to therapy. Williams *et al*. (7) used a cross-sectional evaluation of over 2000 patients from the Pediatric AIDS Clinical Trials Group and found no association of adherence with medication burden. However, this study also showed that there was a nearly twofold increase in the odds of non-adherence for youth receiving ≥ 3 nucleoside reverse transcriptase inhibitors (NRTIs) as compared with patients on HAART. Studies by Van Dyke *et al*. (8) and Maggiolo *et al*. (9) concluded that more complex regimens are associated with poorer adherence in children and adults, respectively.

Atripla® (Efavirenz, Tenofovir, Emtricitabine) is a one pill, once-daily HAART regimen released in 2006 as a solution for high pill burden (10). The combination of EFV, TDF, and 3TC has been shown to be effective and safe in treating HIV infected adolescents (11-15) and recommended as first-line therapy in this age group by US HIV guidelines (16).

The primary objective of this study was to assess the likelihood of virologic failure in HIV-infected youth starting their first antiretroviral treatment with Atripla® compared to other antiretroviral regimens. The secondary objective was to identify predictors of overall virologic failure and in the Atripla® subset of our study population. We hypothesized that Atripla® is associated with lower rate of virologic failure, longer time to failure, better virologic response, and lower number of antiretroviral resistance mutations.

METHODS

Study sample

The study design was a retrospective cohort study with data collected from medical records of adolescent patients followed at the Thomas Street Clinic. As one of the largest free standing HIV treatment centers in the US, Thomas Street Clinic offers multi-disciplinary care for HIV infected adolescents and adults. The Adolescent Clinic at Thomas Street Clinic, founded in 2003, provides care for HIV infected youth ages 14-24, and is staffed by a physician, nurse practitioner, registered nurse and multiple case managers. Transportation to and from appointments is provided. Patients can access a wide range of services including: well-woman care, psychiatry, substance abuse counseling, nutrition and physical therapy as well as other medical specialties.

Subjects that were ARV-experienced patients of the Adolescent Clinic were included in the study. Those patients who only took ARV medication for mother-to-child prevention of HIV transmission were excluded. Out of the ARV-experienced patients, we identified the first-line regimen and compared patients initiated on Atripla® with patients initiated on a different HAART regimen with respect to virologic failure.

This study has been approved by the Institutional Review Board (IRB) of the Baylor College of Medicine, Houston, Texas. Informed consent for retrospective chart review was waived by the IRB. Informed consent was obtained prior to administration of the adherence survey.

Data collection

Baseline demographics (age, gender, race/ethnicity), behaviors (history of alcohol use, illicit drug use, smoking), medical history (history of psychiatric illness, sexually transmitted infections (STIs), opportunistic infections, or AIDS), CD4

cell count, viral load, and HIV genotyping were abstracted from the clinic electronic medical record system. Four follow-up times were defined as follows: time point 1 (3-8 weeks post-regimen initiation), time point 2 (9-14 weeks), time point 3 (15-20 weeks), time point 4 (more than 21 weeks). These time points were chosen based on the recommended schedule of visits following treatment initiation at the Thomas Street Clinic. Complete information on the variables listed above was available for each patient for two up to four follow-up time points. For each subject, follow-up began when the subject was initiated on combination antiretroviral therapy at the TSC and ended when virologic failure occurred with a first-line regimen or when the subject was switched to a second line regimen. For subjects who did not demonstrate virologic failure, follow-up occurred through 2010. The data collection process took place in 2009-2010. HIV genotyping was performed for all subjects at the beginning of follow-up and at the date of suspected virologic failure.

Definitions of variables

The once-daily combination of Emtricitabine/Tenofovir disoproxil fumarate/Efavirenz, commercially available as Atripla® (Bristol-Myers Squibb Company/Gilead Sciences, Inc.) was the exposure of interest in our retrospective cohort study. Based on exposure to Atripla® as a first-line ARV regimen, the study sample was divided in two groups: one initiated on Atripla®, and one initiated on a different regimen.

The primary endpoint of the study was virologic failure, defined as a viral load higher than 400 copies/ml after 12 weeks of therapy or failure to ever reach this threshold. Time to virologic failure was calculated as the first of at least two sequential viral load measurements over 400 copies/ml, recorded after 12 weeks on therapy. Time to failure was considered zero for those who never achieved virologic suppression during follow-up.

Race/ethnicity was self-reported. History of AIDS was defined as CD4 cell count less than 200 cells/uL and/or presence of an AIDS defining illness, according to the 1993 CDC Revised Classification System for HIV Infection (17).

A modified version of the Brief Medication Questionnaire (BMQ) (18) was used to quantify adherence to a particular regimen. Originally developed in the context of hypertension, the BMQ has been adapted and validated for studying adherence in many chronic diseases, including HIV (19). Informed consent was obtained before administration of this instrument to a randomly chosen subgroup of the study sample (twenty patients). Administration of the BMQ provided for calculation of the Adherence Risk Scale (ARS). The ARS resulted in a score of 0-4. ARS scores of 3 or 4 indicate poor adherence, whereas scores of 1 or 2 indicate a better level of adherence. Adherence was also assessed for all study participants using an average of physician rated level of adherence during three medical visits within the follow-up period. This was calculated as a percent between 0 and 100, based on the number of missed pills recalled by the patient.

Statistical analysis

Baseline differences between the two groups were assessed using the Pearson chi square or Fischer's exact test (for categorical variables), the t test (for normally distributed continuous variables) or the Mann-Whitney test (for continuous variables with skewed distributions).

In order to identify predictors of virologic failure, either in the entire cohort or in the Atripla® group, multivariable logistic regression modeling was used, following the method described by Hosmer and Lemeshow (20). Univariable analyses were performed to investigate the crude associations between virologic failure and potential predictor variables: baseline CD4 cell count and viral load, ethnicity, age, history of psychiatric illness, history of AIDS, history of opportunistic infections and sexually transmitted diseases, smoking or alcohol consumption. According to the Hosmer and Lemeshow method, variables that were significant at the p=0.25 level were included in the multivariable model. Because of the small sample size, continuous variables, such as viral load and CD4 cell count, were dichotomized. Thresholds at 100,000 RNA copies/ml for viral load and at 200 cells/µl for the CD4 were considered clinically relevant. The contribution of each variable to the multivariable model was examined using a stepwise procedure with backward elimination followed by a likelihood ratio test. Once the significant variables were identified, interactions and collinearity were evaluated. Goodness of fit of the final model was assessed using the Hosmer and Lemeshow test.

Descriptive statistics were performed for the CD4 measurements across time points between the two regimen groups. Week since baseline CD4 measurement was derived from the recorded date at baseline, time point 1 and time point 2. If the day information was missing but month and year were available, the 15th of the month was used to calculate the time. The linear mixed model was applied

and time was treated as a continuous variable. More specifically, the fixed effects included regimen, week and regimen by week interaction. We applied the random intercept to account for the correlation among repeated measurements from the same subject. For sensitivity analysis, we refitted the model by excluding two observations with time outliers.

Statistical analyses were performed with the statistical software STATA IC 11.1 (Stata Corps, College Station, TX). The level of statistical significance was set at 0.05.

RESULTS

Baseline cohort characteristics

Out of 155 adolescent patients seen at the Adolescent Clinic of the Thomas Street Clinic, 52 were eligible for inclusion in our retrospective medical record analysis. Of these, 30 (58%) initiated their antiretroviral therapy on Atripla®, and the remaining 22 were started on another regimen.

Of fifty two patients, 76.9% were African American, and 92.3% were males. The median age of the study sample was 21, the median CD4 cell count at regimen initiation was 281 cells/ul, and the median baseline viral load was 69,296 RNA copies/ml (equivalent to 4.84 $\log_{10}$ RNA copies/ml). Fifty eight percent of patients had a history of smoking, 58% had used alcohol sometime in their life, 58% had abused drugs, 60% had a history of opportunistic infections, 67% had had at least one sexually transmitted disease, 50% had a history of AIDS, 52% had a history of psychiatric illness, and 75% were men who have sex with men (MSM). Three patients had baseline K103N mutations and were initiated on a different regimen than Atripla® (Lopinavir/ritonavir + Emtricitabine + Tenofovir disoproxil fumarate or Emtricitabine + Tenofovir disoproxil fumarate + Ritonavir + Atazanavir). A comparison of baseline characteristics of the two study groups is shown in Table 1. There were significantly more males initiated on Atripla® (p = 0.02).

Predictors of virologic failure

Twenty seven subjects failed their regimen (52%). Out of these, 11 were on Atripla® (36.7% of those initiated on Atripla®), and 16 were on another regimen (73% of those initiated on another regimen). Statistically significant bivariate associations were observed between treatment failure and regi-

TABLE 1. *Baseline cohort characteristics*

Characteristic	Initiated on Atripla® (n=30)	Initiated on another regimen (n=22)	p value
Male, n (%)[a]	30 (100)	18 (81.8)	0.02
Ethnicity			
African American	24	16	
Hispanic	6	4	0.35
White	0	2	
Age			
Range	17-24	17-25	
Mean ± SD	20.7 ± 1.9	20.7 ± 2.1	0.92
Median, IQR	21, 20-22	20, 19-23	
CD4 cell count			
Range (cells/µl)	7-680	7-738	
Mean ± SD	276.8 ± 160.2	249.7 ± 213.8	0.53
Median, IQR	295, 223-354	238.5, 67-394	
HIV viral load ($\log_{10}$ RNA copies/ml)			
Range	2.6-5.9	2-5.6	
Mean ± SD	4.7 ± 1.1	4.2 ± 1.2	0.06
Median, IQR	5.1, 3.7-5.5	4.5, 3.6-5.1	
History tobacco use, n (%)	14 (50)	16 (76.2)	0.06
History of alcohol use, n (%)	17 (58.6)	13 (59.1)	0.81
History of illicit drug abuse, n (%)	17 (56.6)	13 (59.1)	0.86
History of psychiatric illness, n (%)	14 (46.6)	13 (59.1)	0.38
History of AIDS, n (%)	12 (40)	14 (63.6%)	0.09
History of opportunistic infections, n (%)	16 (53.3%)	15 (68.2)	0.28
History of STI, n (%)	22 (73.3)	13 (59.1)	0.39

Note: [a] (%) = percent of the total number of subjects with existing data on a given variable within regimen group. SD = standard deviation, IQR = interquartile range, STI = sexually transmitted infection(s)

men, tobacco use, history of AIDS, and baseline CD4 count (Table 2).

After fitting the multivariable model and following the stepwise backward elimination procedure, only the following variables were kept in the final model: regimen, AIDS history and baseline viral load (Table 2). After adjusting for history of AIDS and baseline viral load, the odds of treatment failure in those initiated on a different regimen were five times as high those started on Atripla®; however, this result did not reach statistical significance (p=0.05; 95% confidence interval: [1, 25.76]). The only significant independent predictor of virologic failure was history of AIDS. The multivariable model was a good fit for the data, as assessed by the Hosmer-Lemeshow goodness-of-fit test (p=0.02). The likelihood ratio test for the overall model was significant (p=0.002), and the coefficient of determination (R^2) was 0.22. Therefore, 22% of the variation in treatment failure can be explained by the variables included in the model.

When examining potential predictors of treatment failure in the Atripla® group of the study sample, only tobacco use reached statistical significance in univariable logistic regression analysis (p=0.01). However, baseline viral load groups and substance abuse were also good candidates for a multivariable model at the 0.25 level of significance. Adjusted and unadjusted odds ratios of failure are shown in Table 3. Tobacco use remained the only significant predictor of virologic failure in the multivariable model (p=0.04).

Regarding time to virologic failure, subjects who were initiated on Atripla® had a lower average (26.4 ± 36 weeks) and median (20 weeks) time to failure compared to those initiated on a different regimen (average: 29.5 ± 27.8 weeks, median: 26 weeks), but this result did not reach statistical significance (p=0.58).

The evolution of CD4 cell counts over time is shown in Table 4. No significant difference could be detected between the two treatment groups (ns, p=0.71). However, after exclusion of two outliers, there was a trend in difference in the change of CD4 count across time between the two regimen groups, with those initiated on Atripla® experiencing a higher and faster increase in CD4 counts over time compared to those initiated on another regimen.

Based on genotyping results at the end of the follow-up period, the group initiated on a different regimen had 1.6 times higher odds of developing any resistance mutation than the Atripla® group (not significant, p=0.43). However, patients initiated on Atripla® were twice as likely to develop the K103N mutation compared to those who started HAART on a different regimen (not significant, p=0.28). In addition, among the 27 patients who failed their regimen, those initiated on Atripla® had1.75 times the odds of developing either M184V or the K103N resistance mutations compared with those initiated on another regimen (not significant, p=0.49).

In the context of our adolescent and young population, adherence could be an important predictor of regimen failure. Adherence was measured cross-sectionally and prospectively in a random group of twenty patients using the BMQ questionnaire, a validated instrument. These patients had an average

TABLE 2. *Predictors of treatment failure in the cohort*

Predictor variable	Unadjusted odds ratio (95% confidence interval)	p value	Adjusted odds ratio (95% confidence interval)	p value
Regimen				
Atripla®	1 (reference)		1 (reference)	
Another regimen	4.6 (1.39-15.24)	0.01	5.07[a] (1.0-25.76)	0.05
Baseline viral load				
≤ 100,000 copies/ml	1 (reference)		1 (reference)	
> 100,000 copies/ml	2.29 (0.74-7.08)	0.15	4.07[b] (0.83-20.10)	0.08
Baseline CD4 cell count				
≥ 200 cells/µl	1 (reference)		-	
< 200 cells/µl	7.54 (1.81-31.37)	0.005	-	-
History of AIDS				
No	1 (reference)		1 (reference)	
Yes	4.25 (1.33-13.56)	0.02	4.48[c] (1.17-17.15)	0.03
History of tobacco use				
No	1 (reference)		-	
Yes	4.55 (1.27-14.82)	0.02	-	-

Note: adjusted for the presence of [a]history of AIDS and baseline viral load, [b]regimen and history of AIDS, [c]regimen and baseline viral load. The cells corresponding to CD4 subgroups and history of tobacco are empty because these variables were not included in the final model of virologic failure prediction.

TABLE 3. *Predictors of treatment failure in the Atripla® group*

Predictor variable	Unadjusted odds ratio (95% confidence interval)	p value	Adjusted[a] odds ratio (95% confidence interval)	p value
Baseline viral load				
≤100,000 copies/ml	1 (reference)		1 (reference)	
>100,000 copies/ml	2.66 (0.51-13.88)	0.24	4.36 (0.56-3.51)	0.16
History of illicit drug abuse				
No	1 (reference)		1 (reference)	
Yes	3.42 (0.65-17.93)	0.14	1.2 (0.14-10.13)	0.87
History of tobacco use				
No	1 (reference)		1 (reference)	
Yes	9.9 (1.53-63.68)	0.02	12.31 (1.21-125.44)	0.04

Note: [a] adjusted for the presence of the other variables in the table

TABLE 4. *Descriptive statistics on three sequential CD4 count measurements*

Regimen	Time point	N	Mean ± SD (cells/µl)	Median	Range
Atripla®	Baseline	29	276.8 ± 160.2	295	7-680
	Time point 1	26	406.7 ± 215.6	396.5	40-870
	Time point 2	20	476.2 ± 189.3	475	72-797
Other regimen	Baseline	22	249.7 ± 213.8	238.5	7-738
	Time point 1	20	306.2 ± 192.4	284.5	40-605
	Time point 2	16	310.6 ± 167	262.5	56-720

baseline CD4 count of 217.4 ± 164.7 cells/µl, an average baseline viral load of 198,989.1 ± 201,951.8 copies/ml, nine of them had a history of AIDS, fourteen had started antiretroviral therapy on Atripla®, and nine of them failed their initial regimen (out of whom four had been initiated on Atripla®). We could not detect a significant difference in ARS scores between the two treatment groups (p=0.60). However, patients with ARS scores of 3 or 4 had 18 times higher odds of failing their regimen than the ones with ARS scores of 1 or 2 (p=0.03, 95% CI: [1.26, 255.74]). Physician rated adherence was available for 37 patients. We could not detect a significant difference in adherence levels between the two regimen groups (89.18 ± 21.97% in Atripla® group vs. 91.88 ± 14.84% in the other regimens group, p=0.74). However, those who failed had a significantly lower average adherence compared to those who did not fail (80.1 ± 26.4% vs. 96.5% ± 11.3%, p=0.01). In the Atripla® group, those who failed had a significantly lower average adherence compared to those who did not fail (74.88 ± 31% vs. 95.94 ± 12.1%, p=0.01).

DISCUSSION

Our results do not support the hypothesis that the rate of virologic failure is lower in HIV-infected youth who start their first-line therapy with the once daily administered Atripla® compared to alternative regimens. Notably, over half of the total cohort of 52 patients failed their first-line antiretroviral regimen. This is an unusually high level for a first-line regimen, compared to other studies in both adults and children, in which failure ranged from 14% to 31.6% (21-24).

In our adolescent population, history of AIDS was the only significant independent predictor of virologic failure. Although baseline viral load has been known to be a significant predictor of failure in children or adults starting their first-line therapy (25-27), the predictive value of AIDS history is not so clear; at least one study argues against it in a retrospective cohort study in patients over 18 years of age in Mexico (28).

Psychosocial factors, such as tobacco use or illicit drug use were also associated with increased failure of therapy. Although behavioral factors have been studied in association with adherence to therapy, few studies have attempted to characterize the direct impact of these factors on treatment failure, especially in HIV-infected youth. In a study conducted in antiretroviral-naïve adults initiating HAART, a composite score of mental illness and substance abuse probability at baseline was used to predict virologic and immunologic failure (29). The predicted probability of any mood, anxiety, or substance disorder (be it drug or alcohol abuse)

was associated with virologic failure (hazard ratio=1.22, 95% confidence interval: [1.06, 1.40]).

In our study, baseline viral load, history of AIDS and tobacco use could only explain 22% of the variability in virologic failure observed in our cohort. This may be due to residual confounding resulting from dichotomizing significant predictors, such as viral load and CD4 cell count, or to lack of inclusion of other covariates, such as adherence. Due to the small sample size and the substantial number of missing data for adherence, we were not able to assess the contribution of this variable to the prediction of virologic failure in our cohort.

Adherence was significantly lower in patients who experienced virologic failure, regardless of which regimen they were on. Adherence has been widely recognized as fundamental for the success of antiretroviral therapy (30-34), and levels over 95% are recommended for achieving viral suppression (16). Interestingly, adherence was very similar between those who were taking a once-daily regimen and those who had a more complex regimen. In a long follow-up study of chronic antiepileptic drug use, adherence significantly started to decline only with use of four or more medications per day (35). Further studies are needed to elucidate what level of complexity of antiretroviral regimens will begin to have an impact on adherence and clinical outcomes.

This study has several limitations. The observational design may not be appropriate for a comparison of two types of antiretroviral regimens, as it is prone to selection and information bias, as well as confounding by indication. It is likely that the choice of Atripla® over another type of regimen did not occur randomly, but was influenced by a series of baseline factors (CD4 count, viral load, HIV genotype, comorbidities, psychiatric background, and history of adherence) that could have been associated with the outcome. However, this was a preliminary, exploratory study within the Thomas Street Clinic, designed to inform future prospective study designs with more extensive control over assignment of antiretroviral regimen, baseline and follow-up data collection. Although medical records were abstracted for all the youth under care at the clinic, the sample size was rather small. The size of the sample did not permit investigation of viral load and CD4 count as continuous predictors of virologic failure, which would have provided useful guidelines for a first-line regimen in youth infected with HIV. The small sample size also decreased the precision of our estimates, as reflected by the large 95% confidence intervals around some of our parameter estimates. Another limitation of the study is the retrospective nature of data collection. Data were missing on a few essential variables, such as adherence, or later time point viral load and CD4 cell counts. Recording of psychosocial factors was oversimplified to presence or absence. The choice of the virologic failure definition, based on previous studies in the United States, limits the applicability and generalizability of our results. However, the sample studied closely mirrors the fastest growing group of HIV infected youth in the US: young African American men who have sex with men.

The observed lack of difference in treatment failure when considering the complexity of a regimen provides those prescribing HIV medications with additional information when choosing a first-line therapy. If pill burden does not significantly change adherence (as implied in this study), consideration should be given to more robust regimens where single point mutations are less likely to decrease efficacy. While more recent guidelines encourage prompt initiation of ART in HIV infected adolescents and adults, the results of our study prompt us to recommend careful consideration to risk factors for failure in HIV infected youth, such as psychosocial factors or AIDS-defining illnesses.

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