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Patterns of HIV Treatment Adherence do not Differ Between Male and Female Adolescents in Botswana

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Abstract

We hypothesized that longer and more frequent dosing gaps among boys in Botswana taking antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection compared to girls could account for previously seen gender-specific differences in outcomes. We monitored 154 male and 134 female adolescents for 2 years with medication event monitoring systems (MEMS). Median adherence was 95.6 % for males and 95.7 % for females ($p = 0.40$). There were no significant gender differences in the number of 7 day ($p = 0.55$) and 14 day ($p = 0.48$) dosing gaps. The median maximal gap was 7.7 days for males and 8.0 days for females ($p = 0.47$). These findings are not consistent with clinically meaningful gender differences in adherence.

Keywords

Antiretroviral therapy; ART; MEMS; Africa

Introduction

Adherence to antiretroviral therapy plays an important role in the global AIDS epidemic, particularly so among adolescents, and in resource-limited sub-Saharan African settings with

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflicts of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of all institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent and assent was obtained from all individual participants included in the study.

a high burden of HIV infections (1). In a previously published comparative effectiveness study from our tertiary pediatric HIV referral clinic in Botswana, rates of virologic failure (confirmed HIV viral load ≥ 400 copies/mL) among 156 boys on nevirapine were higher than those among 227 girls on nevirapine at 1, 2, and 5 years after treatment initiation [18.0 % (95 % CI 12.3–24.9 %), 24.4 % (95 % CI 17.9–31.9 %), and 30.1 % (95 % CI 23.1–38.0 %) vs 6.3 % (95 % CI 3.2–11.0 %), 10.3 % (95 % CI 6.2–15.8 %), and 14.3 % (95 % CI 9.5–20.4 %), respectively, although the interaction between drug regimen and sex was not statistically significant with $p = 0.25$] (2). Behavioral patterns that are more common in one gender than the other could drive adherence differences that are important to treatment outcomes. Families in Botswana commonly call on boys to leave the household for several days at a time to tend distant animal herds, whereas girls more often take on extensive chores within the home (3, 4). Variations in behavior between genders could drive effect modification of treatment outcomes if they lead boys to have more frequent or lengthy gaps between doses. We hypothesized that social factors affecting boys, including but not limited to out-of-town trips, may impact adherence by creating long gaps without access to medication.

The medication event monitoring system (MEMS) provides detailed dosing data for adherence monitoring using electronic pill bottle caps (5). MEMS findings from other settings have demonstrated the clinical significance of the longest gap between doses and suggested that the rate of failure increases greatly with 7–14 day treatment gaps (6). However, previous studies using MEMS to estimate adherence in Southern Africa have focused on percent adherence, without regard to timing of interruptions in therapy (7–9). Therefore, we aimed to compare adherence between boys and girls on antiretroviral therapy (ART), including number of 7 day and 14 day gaps between doses, and the longest observed gap between doses. We hypothesized that boys have longer and more frequent gaps between doses which could account for previously observed gender-specific differences in outcomes.

Methods

Adherence to once- or twice-daily ART was monitored with MEMS for 2 years during the study period of October 2012–January 2016 in an ongoing prospective study of 10–<20 year-old males and females taking ART at the Botswana-Baylor Children's Clinical Centre of Excellence, the same clinic in which the earlier study showed gender-specific outcome differences (2). Institutional review boards at the University of Botswana, Botswana Ministry of Health, University of Pennsylvania, and Baylor College of Medicine approved this study. All eligible clinic patients were offered enrollment sequentially until consent and assent were obtained for 300 patients. Local providers and study team members were blinded to MEMS data to avoid having patients respond to feedback by changing their pill-taking behavior. Periods when individual MEMS units malfunctioned as determined from technical analysis by the manufacturer were censored from the 2 year monitoring interval and re-analyzed as treatment gaps in a sensitivity analysis.

The primary outcomes were median adherence, number of dosing gaps of at least 7 days, number of dosing gaps of at least 14 days, and longest gap over the course of the 2 year

monitoring period. Mann–Whitney U tests were used to compare these adherence measures between boys and girls (10). Covariates were compared with Students t-tests or χ^2 -squared tests as appropriate. Ordinary least squares (OLS) regressions assessed for associations between demographic and clinical variables and the adherence measures. Demographic and clinical characteristics used in the multivariable analysis included age, years since diagnosis, years since treatment initiation, current ART regimen, number of prior regimens, WHO clinical and immunologic staging, and the presence and duration of censored periods and once-daily regimens, which were collected from clinic records, MEMS analysis and caregiver interviews. Variables collected from separate patient and family questionnaires included disclosure of serostatus to the patient by parents or healthcare workers, the adolescent's level of autonomy over medication-taking, and orphan status.

The possibility of confounding in the relationship between gender and adherence was examined by adding each covariate to the model one-by-one, and effect modification was examined by F-testing for joint significance of the interaction between gender and each covariate. Two-sided statistical tests with an alpha level of 0.05 were performed using Stata version 13 (StataCorp). The minimum detectable difference based on the first few months of preliminary monitoring data with an 80 % power was at least 6.3 % in overall adherence, 0.8 and 0.4 in the number of 7 and 14 day gaps per year, and 4.6 days in the longest gap between doses, respectively.

Results

Data from 154 females and 134 males were eligible for analysis (excluding 3 females and 9 males who had less than 2 year of monitoring). There were no statistically significant differences by gender in age (median 14.3 years), orphan status (55.9 % non-orphaned), or any other measured baseline covariates (Supplementary Appendix: Table A). Overall, median adherence was 95.6 % (IQR 75.4–100) with mean 84.3 % (standard deviation 22.0 %). In unadjusted analyses, there were no differences in median adherence, 7 day gaps, 14 day gaps, or longest gap by gender (Table 1).

Significantly more females than males had at least one censored period during which monitoring did not take place (9 females, 5.8 % versus 1 male, 0.8 %, $\chi^2 = 5.56$, $p = 0.02$). Sensitivity analysis incorporating censored periods as gaps magnified the observed gender differences, notably in the longest gap between doses (Table 1), but this difference did not achieve statistical significance. There was no significant association between the presence or length of censored periods and any of the primary outcomes. There was also no association between gender and any adherence measures even after controlling for potential confounders, including the presence or duration of censored periods (Supplementary Appendix: Tables B–E). Effect modification was apparent only due to orphaned status ($F = 4.5$ and $p = 0.01$ for overall adherence, $F = 5.9$ and $p = 0.003$ for 7 day gaps, $F = 4.8$ and $p = 0.009$ for 14 day gaps, and $F = 1.4$ and $p = 0.25$ for longest gap between doses), with male orphans ($N = 22$) having significantly worse adherence than female orphans ($N = 26$), and male non-orphans having significantly better adherence than female non-orphans (Supplementary Appendix: Figure A). This finding persisted when censored periods were re-analyzed as gaps ($F = 4.5$ and $p = 0.01$ for overall adherence, $F = 5.8$ and $p = 0.03$ for 7 day

gaps, $F = 4.8$ and $p = 0.009$ for 14 day gaps, and $F = 1.3$ and $p = 0.29$ for longest gap between doses).

Discussion

Although there is increasing evidence that adult males with HIV are more likely to have poor clinical outcomes, including defaulting from care (11, 12), our data do not support the hypothesis that different patterns of HIV medication adherence exist between male and female adolescents in Botswana. In our prior study, gender-specific differences in treatment outcomes were seen among patients on nevirapine, prompting this evaluation. Of note, however, similar findings were not seen among patients on efavirenz (2). We thought that, if males had longer gaps between doses than females, the lack of gender-specific outcomes among patients on efavirenz might be explained by increased permissiveness of efavirenz to longer treatment gaps. Previously, variants of the cytochrome 2B6 (CYP2B6) metabolizing gene that are common in black Africans, and in Botswana in particular, have been linked to increased serum concentrations of efavirenz (13).

The prior study finding gender differences in response to efavirenz versus nevirapine used data from 2002 to 2011. Since then, urbanization has been ongoing in Botswana, and providers at the study clinic have noted a subjective reduction in the prevalence of boys attributing poor adherence to trips to rural areas (2). Thus, cultural evolution could have extinguished gender-specific differences. Patients in this study were also on average 5 years older than in that prior study (IQR approximately 10–15 years versus 5–10 years). This age difference means that non-adherence behaviors could have changed as patients matured or received counseling interventions following initial virologic failure. It is also possible that patients with earlier poor adherence transferred out of or defaulted from the clinic prior to initiation of the current study.

Additionally, Hawthorne effect due to the MEMS monitors could have obscured non-adherence behaviors. Our power analysis using early data showed higher adherence with narrower variance, making our study's power lower than anticipated in this final analysis. Some non-adherence behaviors may also have been censored events if patients deliberately tampered with MEMS monitors to stop caregivers from discovering missed doses, even though patients were told that their treatment team and Botswana-based members of the study team were blinded to adherence data. Notably, censored periods were more common among girls, which if indicative of adherence differences would be more suggestive of the opposite of our hypothesized difference between sexes.

In the subset of double orphans, adherence was poorer among males. Prior studies have shown poorer adherence among double orphans overall with no evidence of differences by gender (14). Although this examination of orphan status was pre-planned, the possibility of type I error must be considered. Males and females may develop different relationships with adoptive parents that help or hinder adherence. Further research is needed to replicate and explore this finding.

Conclusions

This study did not observe gender-specific adherence differences in adolescent patients who were actively engaged in care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Adherence measures

	Female <i>n</i> = 154	Male <i>n</i> = 134	Test statistic	<i>P</i> value
<i>Primary analysis, median (IQR)</i>				
Overall adherence	95.7 % (72.1–100 %)	95.6 % (82.4–100 %)	<i>z</i> = −0.84	0.40
Number of gaps in 2 years				
7 days	0 (0–3)	0 (0–2)	<i>z</i> = 0.60	0.55
14 days	0 (0–1)	0 (0–1)	<i>z</i> = 0.71	0.48
Percent with at least one gap ^a				
7 days	70 (45.5 %)	57 (42.5 %)	$\chi^2 = 0.25$	0.62
14 days	49 (31.8 %)	38 (28.4 %)	$\chi^2 = 0.41$	0.52
Longest gap between doses (days)	7.7 (5.8–9.0)	8.0 (5.0–10.0)	<i>z</i> = 1.20	0.47
<i>Mean (standard deviation, 95 % CI): P value by t test</i>				
Overall adherence	82.9 % (23.6 %, 79.2–86.7 %)	86.0 % (20.1 %, 82.5–89.4 %)	<i>t</i> = −1.18	0.24
Number of gaps in 2 years				
7 days	3.4 (6.6, 2.4–4.5)	2.5 (5.0, 1.6–3.4)	<i>t</i> = 1.32	0.19
14 days	1.4 (3.3, 0.9–2.0)	1.2 (2.8, 0.7–1.6)	<i>t</i> = 0.74	0.46
Longest gap between doses (days)	16.9 (22.9, 13.3–20.6)	14.7 (26.9, 10.2–19.3)	<i>t</i> = 0.74	0.46
<i>Sensitivity analysis of censored periods as gaps</i>				
Overall adherence	94.7 % (72.1–100 %)	95.3 % (82.4–100 %)	<i>z</i> = −0.92	0.36
Number of gaps in 2 years				
7 days	0 (0–3)	0 (0–2)	<i>z</i> = 0.81	0.42
14 days	0 (0–1)	0 (0–1)	<i>z</i> = 1.08	0.28
Percent with at least one gap ^a				
7 days	74 (48.1 %)	58 (43.3 %)	$\chi^2 = 0.66$	0.42
14 days	54 (35.1 %)	39 (29.1 %)	$\chi^2 = 1.16$	0.28
Longest gap between doses (days)	6.5 (2.9–25.5)	5.7 (2.5–15.5)	<i>z</i> = 1.40	0.16
<i>Censored periods</i>				
At least one censored period ^a	9 (5.8 %)	1 (0.8 %)	$\chi^2 = 5.56$	0.02
Length of censored period (days)	23 (16–41)	97 (97–97)	<i>z</i> = −1.57	0.12
Including patients with 0 censored days ^b	0 (0–0)	0 (0–0)	<i>z</i> = 2.33	0.02
<i>Once-daily^c versus twice-daily dosing during monitoring</i>				
Ever on once daily regimen ^a	20 (13.0 %)	9 (6.7 %)	$\chi^2 = 3.11$	0.08
Always once daily ^d	9 (45.0 %)	5 (55.6 %)	$\chi^2 = 0.28$	0.60
Median length of once daily regimen (days) (N = 29)	474 (254–730)	730 (370–730)	<i>z</i> = −0.78	0.44

Unless otherwise specified, figures are median (IQR) with *P* value by Mann–Whitney test

^aNumber (%), with *P* value by Chi-squared

^bThis line examines the duration of censored periods including patients with no censored periods as having 0 censored days rather than excluding them from the comparison. For females, 95th and 99th percentiles were 7 and 58 days, respectively. For males, 95th and 99th percentiles were both 0 days

^cThese regimens were either single-pill efavirenz/emtricitabine/tenofovir (Atripla[®]) regimens or medications prescribed in lieu of ART during a period of patient or prescriber-initiated antiretroviral treatment interruption (commonly trimethoprim/sulfamethoxazole or a daily multivitamin)

^dAs a percentage of patients ever on once daily dosing, rather than a percentage of all patients