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Brief Report: Apparent Antiretroviral Over-adherence by Pill Count is Associated with HIV Treatment Failure in Adolescents

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Abstract

Pill counts with calculated adherence percentages are used in many settings to monitor adherence, but can be undermined by patients discarding pills to hide non-adherence. Pill counts suggesting that >100% of prescribed doses were taken can signal “pill dumping.” We defined “over-adherence” (OA) among a cohort of 300 HIV-infected adolescents as having >1/3 of pill counts with >100% adherence during a year of follow-up. Apparent over-adherence was more common in those with virologic failure than those with suppressed viral loads (33% vs 13%, χ^2 $p=0.001$). Pill count adherence repeatedly >100% may identify HIV-infected adolescents at increased risk of treatment failure.

Keywords

Adolescents; adherence monitoring; resource-limited settings; antiretroviral therapy

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Introduction

Adolescents with HIV and other chronic diseases are frequently poorly adherent to essential medications.¹⁻³ Due in part to adherence challenges, HIV is currently the second-leading cause of death among adolescents worldwide and the leading cause of adolescent deaths in Africa.⁴ While in resource-rich settings, HIV viral loads are routinely available, the cost of routine laboratory monitoring is prohibitive in many settings.⁵ Monitoring adherence is a major challenge,⁶ despite the fact that such monitoring is a primary method of identifying individuals at risk of disease progression, particularly in places where biomarkers cannot be routinely measured. Adherence monitoring can also identify problems before treatment failure occurs.

Counting pills and calculating an adherence percentage when patients come for refills can help with assessments of medication adherence.⁷ Comparing the number of pills that would remain if the patient had taken all prescribed doses to the number of pills actually remaining can facilitate detection of missed doses. Furthermore, pill counts done as part of routine clinical care during the first six months of HIV treatment have been shown to improve medication adherence and clinical outcomes during the first year of treatment.⁸ In Botswana, a high HIV-prevalence setting in sub-Saharan Africa, pill counts are frequently utilized and more doses than needed by the expected return date are provided in case of difficulty in reaching clinic as planned for refills. When pills remain that should have been taken before a refill visit, clinic staff know that those pills were not ingested and can engage patients in discussions regarding their adherence barriers. However, when patients anticipate pill counts, they may remove pills without ingesting them in order to make their adherence appear desirably high.⁹ In these cases, adherence measurements may be more than 100% (apparent “over-adherence”).

Prior to initiating this study, we observed anecdotally that various adherence measures were disparate in some adolescents. By more objective measures such as microelectronic monitors, some had very poor adherence, yet they frequently had pill counts suggesting either perfect or “greater than perfect” adherence (more pills missing from the bottle than would have been taken if adherence had been perfect). Adolescents may be particularly prone to falsifying pill counts in order to make it appear that they are adhering well to their medications. Adolescents are more likely than adults to self-report socially-desirable rather than true behaviors. Delaney-Black et al. observed that teens were approximately ten-fold more likely than adults to report that they were not using illicit drugs despite biological evidence to the contrary.¹⁰ If adolescents with particularly poor adherence are motivated to hide their poor adherence by falsifying pill counts (discarding pills or leaving “excess” pills at home) in order to avoid detection, noting repeated apparent “over-adherence” might help to identify this risk group. Additional resources might then be prudently utilized to both increase laboratory monitoring and to provide appropriate non-judgmental counseling.

We hypothesized that repeated pill counts implying apparent “over-adherence” would be associated with detectable HIV viral loads among adolescents receiving treatment for HIV infection.

Methods

Participants

300 HIV-infected adolescents (10-<20 years old) with a minimum of 6 months of treatment experience were enrolled in an ongoing observational adherence study at the Botswana-Baylor Children's Clinical Centre of Excellence in Gaborone, Botswana beginning in October, 2012. Since virologic response only reliably occurs with adherence when the virus is susceptible to the regimen, adolescents were excluded if baseline resistance tests showed that their virus was not susceptible to their regimen or if susceptibility was uncertain, defined by: 1) never having an undetectable viral load during study follow-up and 2) HIV resistance test results being unavailable. Adolescents were also excluded if their follow-up period was less than 12 months.

In addition to quarterly study visits, study participants obtained standard-of-care monitoring and treatment per the Botswana National HIV Treatment Guidelines, including HIV viral load testing every three months.¹¹ Pill counts were obtained with every medication refill per the clinic protocol. Medication refill frequency was determined by the pharmacy staff and treatment team based on patient needs (e.g., those who live far away may come less frequently for refills) and treatment team desires to see patients more frequently for monitoring. Most patients were given a four to six week supply at each refill. Adolescents were seen every three months for an adherence questionnaire administered by a research assistant. Data from the first twelve months of follow-up were included in this analysis.

Measures

HIV Viral load

Each adolescent was classified as having a detectable HIV viral load if any plasma viral load measurement during the year of follow-up was ≥ 400 copies/mL.

Pill Count Adherence

Pill count adherence percentage was calculated at every medication refill as follows: $((\text{quantity dispensed} - \text{quantity remaining}) / (\text{pills prescribed per day} * \text{days since last refill})) * 100$. Pill counts were calculated separately for all antiretroviral drug formulations in each patient's regimen. However, for the primary analysis, a single reference drug was chosen. For most patients, the non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine) or the protease inhibitor (ritonavir-boosted lopinavir) was the reference drug. For patients who took a twice daily nucleoside reverse transcriptase inhibitor with a once a day non-nucleoside reverse transcriptase inhibitor, one of the twice daily drugs was considered the reference drug. Adolescents were classified as apparent "over-adherers" (OA) if at least 33% (1 in 3) of their reference drug pill count suggested $>100\%$ adherence. We also recorded whether the pill counts for other drugs in the regimen differed from that of the reference drug by more than 5%.

Microelectronic Adherence Data

Medication Event Monitoring Systems (MEMS, ©2014 MeadWestvaco)¹² caps were placed on each adolescent's reference medication bottle to record each date and time the bottle was opened. All individuals (staff, patients, families) at the clinical site were blinded to the MEMS data in order to minimize incentives for patients to open their medication bottles when doses were not taken and eliminate the possibility of punitive measures tied to MEMS data. We averaged MEMS data over the one year interval for each adolescent. MEMS adherence was considered a "gold standard" and was compared to the pill count adherence group.¹³ The maximum MEMS adherence per day was the number of doses prescribed per day.

Data analysis

Normality was assessed graphically and using Shapiro-Wilk test. Continuous variables were compared between groups using Wilcoxon Rank Sum test or Student's T test, as appropriate. Chi-squared test was used to compare dichotomous variables. Multivariable logistic regression was used to model the association between having a detectable viral load (> 400 copies/mL) during the year of follow-up and over adherence. The model evaluated for confounding by age, sex, and time on treatment.

Data were collected and stored using REDCap Software, Version 5-6-3.¹⁴ STATA versions 11 and 12 software were used for statistical analyses.¹⁵

Ethical Considerations

The study was approved by the Botswana Health Research Development Committee and Institutional Review Boards at the University of Pennsylvania and Baylor College of Medicine. Written informed consent was obtained from a parent or guardian of each adolescent study participant and assent was obtained for each adolescent participant. The study authors have no conflicts of interest relevant to this publication.

Results

289 subjects were included in the analyses. Eleven potential study subjects were excluded for the following reasons: 3- high grade resistance to the antiretroviral regimen; 5- unknown suppression status; 3- <12 months of follow-up time. Subject characteristics are summarized in **Table 1**. The range of ages was 10.1-19.9 years at study entry with ages skewed toward younger adolescents. Time on treatment at study entry ranged from 6 months to 11.5 years. The median number of pill counts during the twelve month monitoring interval was 9 (interquartile range (IQR) = 8-10) and did not differ between adherence groups ($p=0.32$). Overall, the range of individuals' average pill count adherence percent values for the reference drug was large (80%-106%), but median pill count adherence did not differ between the adolescents with and without a detectable viral load (Table 1). The difference between the pill count for the reference drug and for every other drug in the regimen was <5% for 87% of visits.

48 adolescents were classified as OA and 16 of those (33%) had virologic failure. In contrast, only 33 (13%) of the 241 adolescents who were not classified as OA had virologic failure ($p=0.001$). Similarly, median MEMS adherence was lower in the OA group compared with those not in the OA group (87.2% (IQR 48.2-98.7) versus 95.4% (IQR 86.6-98.8), $p=0.003$).

Over-adherence remained significantly associated with a detectable viral load in the multivariate model. There was no confounding by age, sex, or time on treatment. The odds of having a detectable viral load were 3.3-fold higher among OA patients compared with non-OA patients (95% CI 1.5-4.2, $p=0.002$). Unfortunately, the sensitivity of the OA classification for detecting patients with virologic failure was poor (33%, 95% CI 20-48%). The specificity was 87% (95% CI 82-91%). Differences in the odds of virologic failure across alternate OA definitions (from 5% of pill counts $>100\%$ to 50% of pill counts $>100\%$) are outlined in supplemental digital content.

Discussion

We found that with routine pill count assessments among treatment-experienced patients who are accustomed to receiving feedback about their pill counts, those who frequently have pill counts that imply $>100\%$ adherence are at higher risk of treatment failure. Prior adherence studies have defined patients as “hypocompliers,” “eucompliers,” and “hypercompliers.” “Eucompliance” has been defined as anywhere between 80% and 119% adherence by pill count.¹⁶ However, our data suggest that consistently having adherence just over 100% defines a group of adolescents that is less likely to be taking medications reliably.

Attempting to hide non-adherence by falsifying pill counts characterizes a type of behavior termed demand bias, a form of social desirability bias that results from subjects correctly perceiving that the pill counts aim to identify non-adherence and attempting to “outsmart” the system by altering their pill counts.¹⁷ Clinic staff at our study site attempt to counsel patients in non-judgmental ways. However, fear of negative judgments or punishment would be expected to increase demand bias.

While having more pills remaining than expected reveals non-adherence, the converse may not be true; “perfect” pill counts may not indicate that the medications were consumed. Consistent with prior published data, pill count values minimally exceeding 100% were treated at our study site as if they indicated “good” adherence. Our study shows, however, that patients who exhibit a pattern of repeatedly having pill counts that suggest $>100\%$ adherence are more likely than those without $>100\%$ pill count adherence measurements to have poor adherence. Our data demonstrate that meeting the threshold of $>100\%$ adherence more than every third visit should raise concern for poor-adherence. The odds of virologic failure in those patients are considerably higher than among those who do not exhibit the OA pattern. However, the sensitivity of the OA definition for identifying virologic failure is poor. The sensitivity and specificity of the OA definition are limited by significant risk of misclassification. Poorly adherent patients who remove pills prior to clinic-based pill counts in order to appear more adherent are not identified by the over-adherence measure if they are meticulous about counting their pills. In the absence of more costly measures, patients with

deceitful behavior who are particularly good at deception cannot easily be distinguished from patients who consistently have perfect adherence.

“Punitive counseling” of patients who consistently come in with more pills missing than expected might lead these patients to more carefully mask their non-adherence, decreasing the likelihood that over-adherence would be detected. On the other hand, sharing pills with other HIV-infected individuals could also introduce a risk of misclassifying adherent patients as “over-adherers.” Since Botswana offers free antiretroviral medication to HIV-infected citizens, pill sharing likely accounts for less misclassification in our population than in some other settings.

MEMS adherence was lower in the “over-adherent” group. This suggests that the increased risk of treatment failure in those groups is due to lower adherence. There are some limitations to the use of MEMS to measure adherence. First, patients may have opened their bottles and not taken the medications. However, that likelihood was minimized by blinding all staff at the study site to the MEMS data. Also, MEMS data may over-estimate true adherence by recording openings at the time of pharmacy refills and “curiosity openings.”⁹

These study findings are not generalizable to settings in which routine pill counts are not performed. However, since routine pill counts can both improve adherence⁸ and help to identify non-adherence, they are appropriate to pursue in settings in which the availability of more objective measures of adherence is limited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HIV	Human immunodeficiency virus
MEMS	Microelectronic adherence monitoring
OA	Over-adherent
VF	Virologic Failure

References

1. Borus JS, Laffel L. Adherence challenges in the management of type 1 diabetes in adolescents: prevention and intervention. *Curr Opin Pediatr*. 2010; 22(4):405–411. [PubMed: 20489639]

2. Shemesh E, Annunziato RA, Arnon R, Miloh T, Kerkar N. Adherence to medical recommendations and transition to adult services in pediatric transplant recipients. *Curr Opin Organ Transplant*. 2010; 15(3):288–292. [PubMed: 20445451]
3. Hudelson C, Cluver L. Factors associated with adherence to antiretroviral therapy among adolescents living with HIV/AIDS in low- and middle-income countries: a systematic review. *AIDS Care*. 2015; 27(7):805–816. [PubMed: 25702789]
4. World Health Organization. *Health for the World's Adolescents: A second chance in the second decade*. Geneva: WHO. 2014
5. Keebler D, Revill P, Braithwaite S, et al. Cost-effectiveness of different strategies to monitor adults on antiretroviral treatment: a combined analysis of three mathematical models. *Lancet Glob Health*. 2014; 2(1):e35–43. [PubMed: 25104633]
6. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *Lancet Infect Dis*. 2014
7. San Lio MM, Carbin R, Germano P, et al. Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique. *Clin Infect Dis*. 2008; 46(10):1609–1616. [PubMed: 18419498]
8. Achieng L, Musangi H, Billingsley K, et al. The use of pill counts as a facilitator of adherence with antiretroviral therapy in resource limited settings. *PLoS One*. 2013; 8(12):e67259. [PubMed: 24339861]
9. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. *Journal of acquired immune deficiency syndromes*. 2006; 43:Suppl 1, S79–87.
10. Delaney-Black V, Chiodo LM, Hannigan JH, et al. Just say “I don’t”: lack of concordance between teen report and biological measures of drug use. *Pediatrics*. 2010; 126(5):887–893. [PubMed: 20974792]
11. Ministry of Health of Botswana. 2012 Botswana National HIV & AIDS Treatment Guidelines. Ministry of Health of Botswana; Gaborone: 2012.
12. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. *Drugs*. 1995; 49(3):321–327. [PubMed: 7774509]
13. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA*. 1989; 261(22):3273–3277. [PubMed: 2716163]
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42(2):377–381. [PubMed: 18929686]
15. Stata Statistical Software: Release 11 [computer program]. College Station, TX: StataCorp LP. 2009.
16. Rudd P, Byyny RL, Zachary V, et al. The natural history of medication compliance in a drug trial: limitations of pill counts. *Clin Pharmacol Ther*. 1989; 46(2):169–176. [PubMed: 2667837]
17. Sawyer AG. Demand Artifacts in Laboratory Experiments in Consumer Research. *Journal of Consumer Research*. 1975; 1:20–30.
18. World Health Organization. [September 8, 2014] WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related Disease in Adults and Children. 2007. <http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf>.

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Table 1

Subject Characteristics

	All (N=289)	Undetectable HIV viral load (N=239)	Detectable HIV viral load (N=50)	P-value
Female	151 (52%)	124 (52%)	27 (54%)	0.79
Age, years Median (IQR)	13.2 (11.7-15.5)	12.9 (11.5-14.8)	15.4 (14.0-17.7)	<0.01
Years on Treatment Median (IQR)	7.5 (5.4-8.8)	7.5 (5.0-8.7)	7.7 (6.1-9.5)	0.24
Baseline WHO Clinical Status¹				
Stage 4	22 (7.6%)	18 (7.5%)	4 (8.0%)	0.18
Stage 3	34 (11.8%)	32 (13.4%)	2 (4.0%)	
Stage 2	131 (45.3%)	110 (46.0%)	21 (42.0%)	
Stage 1	99 (34.3%)	76 (31.8%)	23 (46.0%)	
Missing	3 (1.0%)	3 (1.3%)	0	
Baseline Immunologic Status²				
Stage 4	17 (5.8%)	15 (6.3%)	2 (4.0%)	0.07
Stage 3	74 (25.6%)	64 (26.8%)	10 (20.0%)	
Stage 2	64 (22.2%)	58 (24.3%)	6 (12.0%)	
Stage 1	128 (44.3%)	98 (41.0%)	30 (60.0%)	
Missing	6 (2.1%)	4 (1.7%)	2 (4.0%)	
Over adherent group	48 (16.6%)	32 (13.4%)	16 (32.0%)	<0.01
Median Pill Count Adherence (IQR)	98.7 (95.7-99.9)	98.8 (96.2-99.9)	97.7 (93.7-100.2)	0.33
Proportion of Pill Counts >100% (IQR)	0.13 (0-0.25)	0.13 (0-0.25)	0.20 (0.09-0.38)	0.03
Median MEMS adherence (IQR)	94.7 (83.8-98.8)	96.7 (90.1-99.1)	61.4 (42.3-86.9)	<0.01

¹Baseline WHO Clinical Stages were defined according to published standards, indicating the patient's worst ever HIV-related clinical disease.¹⁸ Stage 4 indicates that the patient has a history of severe HIV-related illness and Stage 1 indicates that the patient has been asymptomatic or had only persistent generalized lymphadenopathy.

²Baseline Immunologic Status was defined according to published WHO standards, indicating the patient's lowest CD4+ T-lymphocyte count or percent. Stage 4 indicates severe immunologic suppression, Stage 3 indicates advanced immunologic suppression, Stage 2 indicates mild immunologic suppression, and Stage 1 indicates insignificant immunologic suppression.