HHS Public Access

Author manuscript

AIDS Behav. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

AIDS Behav. 2015 November ; 19(11): 2044–2048. doi:10.1007/s10461-015-1061-7.

Prediction of HIV Virologic Failure among Adolescents Using the Pediatric Symptom Checklist

Elizabeth D. Lowenthal[1,2], **Tafireyi Marukutira**[3], **Ontibile Tshume**[3], **Jennifer Chapman**[2], **Gabriel M. Anabwani**[3], and **Robert Gross**[4]

[1]University of Pennsylvania Perelman School of Medicine Departments of Pediatrics and Epidemiology, Philadelphia, PA USA

[2]Children's Hospital of Philadelphia, Philadelphia, PA USA

[3]Botswana-Baylor Children's Clinical Centre of Excellence, Gaborone, Botswana

[4]University of Pennsylvania Perelman School of Medicine Departments of Medicine and Epidemiology

Abstract

Psychosocial dysfunction is a risk factor for treatment non-adherence among children and adolescents. A previous study showed that high scores on the Pediatric Symptom Checklist (PSC) were associated with a history of HIV virologic failure. We assessed whether high scores on the PSC could predict virologic failure in HIV-infected youth. Caregivers of 234 adolescents between the ages of 10 and 16 years were asked to complete a PSC at baseline. Elevated PSC scores were associated with virologic failure in the subsequent 6 months. PSC scores may help guide resource utilization when viral load monitoring is limited.

Keywords

HIV; virologic failure; adolescents; Pediatric Symptom Checklist; Psychosocial dysfunction

INTRODUCTION

An estimated 3.3 million children worldwide are infected with HIV, 90% of whom live in sub-Saharan Africa (1). As the HIV epidemic matures and more children are accessing antiretroviral treatment, large numbers of HIV-infected children are aging into adolescence. Limiting their morbidity and mortality is dependent on maintaining adherence to lifelong antiretroviral treatment (2). Unfortunately, adolescents have higher rates of poor treatment adherence and virologic treatment failure than both younger children and older adults (3–7). In a South African study, more than a quarter of adolescents who achieved virologic suppression had virologic rebound within 12 months and fewer than 15% maintained 100% adherence by pharmacy refill during that time (6). In the United States, only 54% of adolescents who initiate antiretroviral therapy achieve viral suppression (7). Self-reported

CORRESPONDING AUTHOR: Elizabeth Lowenthal, MD, MSCE, 3535 Market Street, Room 1513, Philadelphia, PA 19104, lowenthale@email.chop.edu.

adherence, which is typically over-estimated, has been reported between 40 and 84% in HIV-infected adolescents (8).

Psychosocial dysfunction is a risk factor for non-adherence (9). In sub-Saharan Africa in particular, psychosocial problems and poor drug adherence have been cited as the greatest threats to the continued therapeutic success of perinatally HIV-infected children (10). Psychosocial support services are limited in busy clinics in resource-poor settings, creating an urgent need to find ways to target the youth at highest risk (11).

The Pediatric Symptom Checklist (PSC) is a simple psychosocial screening tool that was designed to help pediatricians in busy office practices select children who are likely to have psychosocial difficulties and thus could benefit from further evaluation (12). Designed for use among youth between the ages of 6 and 16 years (13) in the United States, the PSC has been adapted for use in other settings, including Botswana (14). Parents/caregivers are asked to scores 35 items related to their child's behavior or emotions as "never," "sometimes," or "often" present. Example items include "distracted easily," "feels hopeless," and "does not listen to rules." The PSC includes questions related to attention, internalizing and externalizing problems and alerts to a higher level of risk for emotional, social, or behavioral difficulties. It is not diagnostic of any specific psychiatric or social problem.

High PSC scores have previously been associated with a *history of* virologic failure among HIV-infected children and adolescents (15). In a prior study of older children and adolescents in Northern Botswana, 17% had positive PSC scores. In high-prevalence, low-resource settings where most HIV-infected children and adolescents live, a screening tool that could predict patients at highest risk of failure *before* failure occurs would allow for enhanced targeting of these children for behavioral interventions. We aimed to determine whether high scores on the PSC predict which adolescents will have virologic failure in the subsequent 6 months.

METHODS

Adolescents (aged 10–16 years) receiving treatment through the Botswana National HIV Treatment Program at the Botswana-Baylor Children's Clinical Centre of Excellence (COE) were followed prospectively. The Botswana-Baylor COE provides HIV treatment for children living in and around the capital city, Gaborone, and also serves as a referral center for more complicated pediatric and adolescent HIV cases. All adolescents included in this study were part of a longitudinal observational adherence study which enrolled 300 treatment-experienced adolescents between 10 and <20 years of age; 150 on protease inhibitor (PI)-based antiretroviral therapy, and 150 on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy. The caregivers of all adolescents were asked to complete the parent-report PSC measure at the study entry visit with the help of a research assistant. The PSC took approximately 5 minutes to complete for each child. PSC scores were dichotomized (≥20 defined as 'positive') based on prior data (14). Plasma HIV RNA levels were obtained from the adolescents every 3 months. Caregivers' unwillingness or inability to complete the PSC was classified as a positive score. Virologic failure was defined as HIV RNA ≥400 copies/ml after 3 or 6 months of study enrollment. Subject characteristics were

compared using t-tests or Wilcoxon rank-sum tests for continuous data and chi-squared tests for categorical data. A chi-squared test assessed for difference in virologic failure rates between those with/without a positive PSC. Logistic regression was used to evaluate the association between virologic failure and continuous PSC scores as well as to assess for confounding in the dichotomous comparison.

As a secondary analysis, we evaluated the association between virologic failure and PSC scores among adolescents who had passed their 16th birthday.

RESULTS

Among the 234 adolescents between 10 and 16 years of age evaluated, the median age was 12.7 years (IQR 11.4–14.2). The adolescents' demographic and clinical characteristics are outlined in Table I by PSC score group. A small majority (125 (53%)) of the adolescents in the primary analysis group were on PI-based antiretroviral therapy.

Of those on PIs, 72% were on second-line treatment. There was no significant difference between PSC score groups in terms of age, time on treatment, sex, orphan status, baseline clinical stage, baseline immunologic status, or treatment regimen.

Twenty four adolescents entered the study with detectable viral loads. Of those, 11 achieved undetectable viral loads during the observation period without a regimen change. One (PSC negative group) was determined to have high level resistance to the antiretroviral regimen based on genotypic resistance testing. Twelve (10 (4.7%) in the PSC negative group and 2 (9.1%) in the PSC positive group) had not had an undetectable viral load or resistance test during the observation period.

Forty patients (17%) had virologic failure during the 6 months of follow-up and 22 (9%) had a positive PSC (20 due to meeting the cut-off score requirement and 2 due to parental refusal to complete the test). 9 (41%) patients with a positive PSC had virologic failure compared with 31 (15%) of those with a negative PSC, p=0.002. The specificity of the PSC for ruling out virologic failure was 0.93 (95% confidence interval (CI) 0.89–0.96). However, the sensitivity (0.23, 95% CI 0.11–0.39) was poor. The positive likelihood ratio was 3.4 (95% CI 1.5–7.3) and the negative likelihood ratio was 0.83 (95% CI 0.70–0.99). The risk of VF increased by 6% for every 1-point increase in PSC score (p=0.02, see Figure). One of the two patients whose caregiver refused to complete the PSC had virologic failure. Adjusting for age minimally changed the odds of failure with a positive PSC (from 4.0 to 3.9). Of the factors listed in Table I, only age was associated with virologic failure. The odds ratio for failure with increasing age (per year) was 1.35 (1.09–1.69, p=0.007).

Secondary Analysis

Among the 66 adolescents who were over 16 years of age, 20 (30%) had virologic failure and 20 had a positive PSC. Among the 20 older adolescents with positive PSC scores, 8 (40%) were classified as positive due to parental refusal to complete the assessment. Five (25%) older adolescents with a positive PSC had virologic failure compared with 15 (33%) of those with a negative PSC, p=0.54.

DISCUSSION

Adolescents between 10 and 16 years of age with higher scores on the PSC were more likely to later have virologic failure. Unfortunately, most patients with virologic failure would not be identified by a positive PSC. Therefore, the PSC should not be considered a substitute for virologic testing. Yet, the PSC may help us to prioritize patients for virologic testing in resource-limited settings. Among 10–16 year olds in our cohort, the pretest odds of having virologic failure were 0.21 ((probability of virologic failure (0.17))/(1-probability of virologic failure)). The posttest odds increased to 0.68 (likelihood ratio (3.4) * pretest probability) for those with a positive PSC. Thus, having a positive PSC score meaningfully increased the odds of having virologic failure among 10–16 year olds in our cohort. In clinical practice where resources are limited, it may save precious resources to not order a viral load for a patient with odds of 0.21 of having virologic failure. Meanwhile, the need for a viral load in a patient with 0.68 odds of failure would seem compelling. Of course, the determination of whether the PSC should be used in any clinical setting should depend on the expense associated with obtaining frequent viral loads compared with the costs of missing virologic failure.

Furthermore, the likelihood that intervening early will change treatment outcomes when psychosocial problems are detected should be considered. The PSC is not meant to be diagnostic of any particular problem. Rather, it reflects parents' perceptions of the child's overall psychosocial functioning. Since adherence behaviors are mediated by complex psychosocial factors and adherence is the prime determinant of virologic treatment outcomes, it makes sense that detecting problems with psychosocial functioning would often signal increased likelihood of poor virologic outcomes. It remains to be determined whether focusing support resources on patients with high PSC scores would improve virologic outcomes.

Within the adolescent age group, older age has been consistently related to poor adherence (4, 16, 17). In our cohort, we also saw higher failure rates among those youth who were over the age of 16 years. Recent stressful life events, repeating a grade in school, and having a diagnosis of depression or anxiety have also been associated with poor treatment adherence among children and adolescents with HIV (17). Having a parent or caregiver present at clinical visits appears to be protective of adherence and treatment outcomes among adolescents (18, 19). Adherence has been inconsistently associated with gender (17, 18, 20, 21) and orphan/caregiver status (21–23). Lack of caregiver involvement was incorporated into our definition of a positive PSC as we classified non-completion of the PSC as a positive score. However, only two patients in our 10–16 year old group did not have a parent complete the PSC. Among the adolescents between 17 and 20 years of age, 40% of positive PSC scores were classified as positive due to parental refusal to complete the assessment.

Both CD4 count and adherence assessments have been evaluated as tools to help predict virologic failure. Compared with viral load testing, CD4 counts are less expensive and more readily available in most low-resource settings (24). However, changes in CD4 count lag behind changes in viral load and a patient may have longstanding virologic failure with development of antiretroviral medication resistance before immunologic failure can be

confirmed. Furthermore, immunologic failure brings with it increased immediate risk of poor clinical outcomes. Bisson et al. showed that among adults in Botswana pharmacy refill data was superior to CD4 count as a better predictor of virologic failure (25). However, given that in adolescence, responsibility for medication-taking may precede responsibility for obtaining refills, the predictive value of pharmacy refill data in adolescents cannot be assumed."

Our observational cohort is limited to adolescents since this age group is at the highest risk of poor adherence and virologic failure. By setting this age restriction, we lost the ability to assess the utility of the PSC for predicting virologic failure among children under the age of 10 years. Thus, while the PSC was designed for use among children as young as 6 years of age, we cannot comment on whether or not high scores among children <10 years of age would be equally useful for predicting risk of virologic failure. Although we had relatively few adolescents over 16 years of age, the PSC did not appear to distinguish between those with and without virologic failure when used among adolescents who were older than those for whom the PSC was designed.

Since our study was performed in a pediatric and adolescent specialty center where >95% of patients are believed to have been perinatally infected with HIV, the generalizability of the findings to behaviorally-infected adolescents is uncertain. The generalizability of these study results may also be limited by the fact that our patients, unlike most in resource-limited settings, received regular virologic testing. Botswana guidelines allow for regimen-switches when patients have persistent virologic failure without strong evidence of ongoing poor adherence (26). Therefore, most patients in our setting do not have longstanding virologic failure prior to switching from a first-line treatment regimen to a second-line treatment regimen. In settings with more limited viral load access, patients would be more likely to develop high-level resistance to their regimens during prolonged periods of non-adherence. This would limit their ability to suppress their viral loads later if they became adherent to treatment recommendations. Under those conditions, the specificity of the PSC for determining near-term virologic failure risk would be lower. The generalizability of our findings may be limited further by the fact that no services were offered in our study based on the results of the PSC screening. In settings in which families learn that scores would influence the availability of limited resources such as viral load testing, scores might be biased by the desire to qualify for receipt of these limited resources. Regardless, even if viral load testing becomes cheap and easy, development of better prediction tools for those at higher risk of virologic failure should remain a priority.

Acknowledgments

The study team would like to thank the patients and families who are taking part in the Ba Nana (Setswana for Adolescent) Study. We would also like to thank the study and clinical staff at the Botswana-Baylor Children's Clinical Centre of Excellence in Gaborone, the Botswana Ministry of Health, and the Baylor International Pediatric AIDS Initiative. Funding to establish this longitudinal cohort was provided through a PEPFAR Public Health Effectiveness grant. Study-specific funding for this analysis was provided through NIH K23 MH095669 to Dr. Lowenthal. Dr. Gross' effort was supported by the Penn Center for AIDS Research (CFAR), an NIH-funded program (P30 AI 045008). Thanks to Diana Idarraga Rico for assistance with the Spanish translation of the abstract.

The authors would like to thank the adolescents and families at the Botswana Baylor Children's Clinical Centre of Excellence who shared their experiences as part of the Ba Nana (adolescent) Adherence Study and the Botswana-

Baylor staff, especially the Ba Nana Study staff. Dr. Lowenthal is supported through a career development award from the National Institute of Mental Health (K23 MH095669). This study was also supported by a CDC-PEPFAR Public Health Effectiveness Grant. Dr. Gross receives support from P30 A1 045008 from the Penn Center for AIDS Research. The funders did not play a role in study design, analysis, or decision to publish.

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS report on the global AIDS epidemic 2013. 2013 Nov.2013
2. 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 Jul; 14(7):627–39. [Review]. [PubMed: 24406145]
3. Evans D, Menezes C, Mahomed K, Macdonald P, Untiedt S, Levin L, et al. Treatment outcomes of HIV-infected adolescents attending public-sector HIV clinics across Gauteng and Mpumalanga, South Africa. AIDS Res Hum Retroviruses. 2013 Jun; 29(6):892–900. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. [PubMed: 23373540]
4. Bygrave H, Mtangirwa J, Ncube K, Ford N, Kranzer K, Munyaradzi D. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. PLoS One. 2012; 7(12):e52856. [PubMed: 23285204]
5. Bakanda C, Birungi J, Mwesigwa R, Nachega JB, Chan K, Palmer A, et al. Survival of HIV-infected adolescents on antiretroviral therapy in Uganda: findings from a nationally representative cohort in Uganda. PLoS One. 2011; 6(4):e19261. Research Support, Non-U.S Gov't. [PubMed: 21559441]
6. Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. J Acquir Immune Defic Syndr. 2009 May 1; 51(1):65–71. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. [PubMed: 19282780]
7. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS. 2014 Mar; 28(3):128–35. [Review]. [PubMed: 24601734]
8. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. J Int AIDS Soc. 2013; 16:18579. Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S Review. [PubMed: 23782477]
9. Whetten K, Shirey K, Pence BW, Yao J, Thielman N, Whetten R, et al. Trauma history and depression predict incomplete adherence to antiretroviral therapies in a low income country. PLoS One. 2013; 8(10):e74771. Research Support, N.I.H Extramural. [PubMed: 24124455]
10. Ferrand R, Lowe S, Whande B, Munaiwa L, Langhaug L, Cowan F, et al. Survey of children accessing HIV services in a high prevalence setting: time for adolescents to count? Bull World Health Organ. 2010 Jun; 88(6):428–34. Research Support, Non-U.S. Gov't]. [PubMed: 20539856]
11. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. Lancet. 2007 Sep 8; 370(9590):859–77. Research Support, Non-U.S. Gov't Review]. [PubMed: 17804063]
12. Jellinek MS, Murphy JM, Burns BJ. Brief psychosocial screening in outpatient pediatric practice. J Pediatr. 1986 Aug; 109(2):371–8. Research Support, U.S. Gov't, P.H.S. [PubMed: 3734977]
13. Jellinek MS, Murphy JM, Robinson J, Feins A, Lamb S, Fenton T. Pediatric Symptom Checklist: screening school-age children for psychosocial dysfunction. J Pediatr. 1988 Feb; 112(2):201–9. Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. [PubMed: 3339501]
14. Lowenthal E, Lawler K, Harari N, Moamogwe L, Masunge J, Masedi M, et al. Validation of the Pediatric Symptom Checklist in HIV-infected Batswana. J Child Adolesc Ment Health. 2011 Jan 1; 23(1):17–28. [PubMed: 22685483]
15. Lowenthal E, Lawler K, Harari N, Moamogwe L, Masunge J, Masedi M, et al. Rapid psychosocial function screening test identified treatment failure in HIV+ African youth. AIDS Care. 2012; 24(6):722–7. Research Support, N.I.H Extramural. [PubMed: 22292411]

16. Williams PL, Van Dyke R, Eagle M, Smith D, Vincent C, Ciupak G, et al. Association of site-specific and participant-specific factors with retention of children in a long-term pediatric HIV cohort study. Am J Epidemiol. 2008 Jun 1; 167(11):1375–86. Multicenter Study Research Support, N.I.H., Extramural]. [PubMed: 18413359]
17. Williams PL, Storm D, Montepiedra G, Nichols S, Kammerer B, Sirois PA, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics. 2006 Dec; 118(6):e1745–57. Research Support, N.I.H., Extramural]. [PubMed: 17101712]
18. Gross R, Bandason T, Langhaug L, Mujuru H, Lowenthal E, Ferrand R. Factors associated with self-reported adherence among adolescents on antiretroviral therapy in Zimbabwe. AIDS Care. 2014 Oct 22.:1–5.
19. Lowenthal E, Marukutira T, Tshume O, Chapman J, Nachega JB, Anabwani G, et al. Parental Absence from Clinic Predicts HIV Treatment Failure in Adolescents. JAMA Pediatrics. 2015 In Press.
20. Ndiaye M, Nyasulu P, Nguyen H, Lowenthal ED, Gross R, Mills EJ, et al. Risk factors for suboptimal antiretroviral therapy adherence in HIV-infected adolescents in Gaborone, Botswana: a pilot cross-sectional study. Patient Prefer Adherence. 2013; 7:891–5. [PubMed: 24049440]
21. Zoufaly A, Fillekes Q, Hammerl R, Nassimi N, Jochum J, Drexler JF, et al. Prevalence and determinants of virological failure in HIV-infected children on antiretroviral therapy in rural Cameroon: a cross-sectional study. Antivir Ther. 2013; 18(5):681–90. Research Support, Non-U.S Gov't. [PubMed: 23502762]
22. Ugwu R, Eneh A. Factors influencing adherence to paediatric antiretroviral therapy in Portharcourt, South- South Nigeria. Pan Afr Med J. 2013; 16:30. [PubMed: 24570791]
23. Sivapalasingam S, Mendillo M, Ahmed A, Mwamzuka M, Said S, Marshed F, et al. The importance of caregivers in the outcome of pediatric HIV management, Mombasa, Kenya. AIDS Care. 2014 Apr; 26(4):425–33. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. [PubMed: 24090313]
24. Ford N, Meintjes G, Pozniak A, Bygrave H, Hill A, Peter T, et al. The future role of CD4 cell count for monitoring antiretroviral therapy. Lancet Infect Dis. 2014 Nov 19.
25. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS Med. 2008 May 20.5(5):e109. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. [PubMed: 18494555]
26. Ministry of Health of Botswana. Botswana National HIV/AIDS Treatment Guidelines. Gaborone: Ministry of Health of Botswana; 2012.

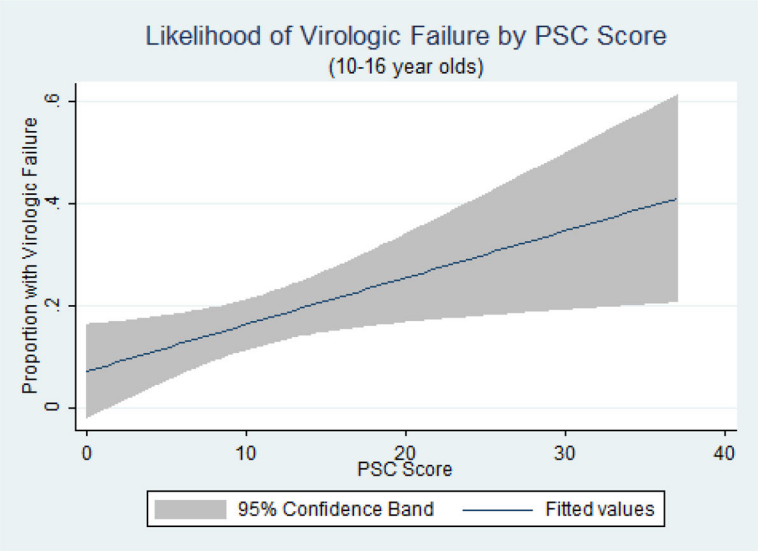

FIGURE 1.
Likelihood of Virologic Failure by PSC Score (10–16 year olds)

Table I

Subject Characteristics (N=234)

	PSC Negative (N=212)	PSC Positive (N=22)	p- value
	Median (IQR)		
Age in years	13.1 (11.9–14.5)	12.6 (11.4–14.1)	0.38
Years on treatment	8.5 (6.0–10.2)	7.5 (4.9–10.6)	0.17
	Number (%)		
Male Sex	108 (51)	7 (32)	0.09
Orphan status			
Non-orphans	144 (68)	15 (68)	0.68
Maternal orphans	24 (11)	1 (5)	
Paternal orphans	19 (9)	2 (9)	
Double orphans	25 (12)	4 (18)	
WHO Clinical Stage			
1	68 (32)	6 (27)	0.93
2	98 (46)	12 (55)	
3	28 (13)	2 (9)	
4	17 (8)	2 (9)	
missing	1 (1)	0 (0)	
WHO Immunologic Stage			
1	86 (41)	9 (41)	0.51
2	52 (25)	4 (18)	
3	58 (27)	5 (23)	
4	13 (6)	3 (14)	
missing	3 (1)	1 (4)	
Antiretroviral regimen			
NNRTI-based	115 (54)	10 (46)	0.43
PI-based	97 (46)	12 (54)	
Suspected mode of HIV acquisition			
Perinatal/breastfeeding	201 (95)	22 (100)	0.73
Blood transfusion	4 (2)	0	
Unknown/other	7 (3)	0	