Published in final edited form as:
AIDS Care. 2012 June ; 24(6): 722–727. doi:10.1080/09540121.2011.644233.

Rapid psychosocial function screening test identified treatment failure in HIV+ African youth

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Abstract

Psychosocial dysfunction in older children and adolescents is common and may lead to non-adherence to HIV treatments. Poor adherence leads to HIV treatment failure and the development of resistant virus. In resource-limited settings where treatment options are typically limited to only one or two available lines of therapy, identification of individuals at highest risk of failure before failure occurs is of critical importance. Rapid screening tools for psychosocial dysfunction may allow for identification of those children and adolescents who are most likely to benefit from limited psychosocial support services targeted at preventing HIV treatment failure. The Pediatric Symptom Checklist (PSC) is used in high resource settings for rapid identification of at-risk youth. In 692 HIV-infected treated children (ages of 8-<17 years) in Botswana, having a high score on the PSC was associated with having virologic failure (OR 1.7, 95% CI 1.1–2.6). The PSC may be a useful screening tool in pediatric HIV.

Keywords

HIV; adolescents; treatment failure; psychosocial dysfunction; Africa

Introduction

More than two million children worldwide are infected with HIV, approximately 90% of whom live in sub-Saharan Africa (UNAIDS, 2009; UNICEF, 2010). Among children who have aged into adolescence with HIV in sub-Saharan Africa, psychosocial problems and poor drug adherence are cited as the greatest challenges to their continued success (Ferrand R, 2010). When compared to adults and younger children, HIV-infected adolescents demonstrate the highest rates of poor medication adherence and treatment failure (Appleby

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et al., 2005; Crockett, Weinman, Hankins, & Marteau, 2009; DeLaMora, Aledort, & Stavola, 2006; Khan et al., 2009; Ledlie, 2001; Mellins, Brackis-Cott, Dolezal, & Abrams, 2004; Murphy et al., 2005; Murphy et al.; Murphy et al., 2003; Nachega et al., 2009; Reisner et al., 2009; Vijayan, Benin, Wagner, Romano, & Andiman, 2009). Higher rates of HIV treatment non-adherence in youth are often related to psychosocial problems (Bauman, Silver, Draimin, & Hudis, 2007; Cluver, Gardner, & Operario, 2007; DeLaMora et al., 2006). As older children and adolescents gain autonomy over their medication-taking, their psychosocial problems may play an increasing role in influencing treatment outcomes (Ledlie, 2001; Mellins et al., 2004). If so, by measuring psychosocial dysfunction in these youth we might identify those at highest risk of treatment failure. This is of particular importance in busy clinics in resource-limited settings where limited psychosocial support resources need to target patients at highest risk (Prince M et al., 2007).

We therefore sought to determine whether a simple screening test for psychosocial problems holds promise for identifying older children and adolescents at greatest risk of HIV treatment failure in busy clinics in resource-limited settings in Botswana treated according to national guidelines (*Botswana National HIV AIDS Treatment Guidelines*, 2008) including non-nucleoside reverse transcriptase inhibitor-based regimens as first line and boosted protease inhibitor based regimens as second line if first line fails. Located in Southern Africa, Botswana has approximately 1.7 million people with a large burden of HIV (Stover, Fidzani, Molomo, Moeti, & Musuka, 2008). Antiretroviral therapy has resulted in HIV-infected infants surviving through adolescence, even in resource-limited settings (Bolton-Moore et al., 2007; Kline et al., 2004). UNAIDS estimates that Botswana has ~16,000 HIV infected children aged 0–14 years (UNAIDS, 2011).

Given limited resources to support HIV-infected adolescents, in whom adherence is the greatest challenge, we need to identify those at greatest risk of treatment failure to intervene before HIV resistance emerges and they clinically deteriorate. Rapid screening tests can be used to identify populations at greatest risk of problems related to mental health and social difficulties and have been used extensively in the U.S. (Eisert, Sturner, & Mabe, 1991; Sturner, 1991). The Pediatric Symptom Checklist (PSC) was developed in the U.S. to allow for rapid identification of individuals between the ages of 6 and 16 years who would benefit most from detailed evaluation and treatment of emotional and behavioral problems (Jellinek & Murphy, 1988; Jellinek, Murphy, & Burns, 1986; Jellinek et al., 1988). The PSC is a 35 item parent-report tool with symptom ratings of never, sometimes or often present (scored 0, 1, or 2) and graded by simple addition of items. It takes less than 10 minutes to complete and can be administered without assistance to parents and caregivers with elementary-level education. A briefer, 17-item version is also available (Borowsky, Mozayeny, & Ireland, 2003; Duke, Ireland, & Borowsky, 2005; Gall, Pagano, Desmond, Perrin, & Murphy, 2000; Gardner, Lucas, Kolko, & Campo, 2007).

The PSC has been used in many different cultural contexts and has been translated into other languages including Japanese, Spanish, German and Dutch (Ishizaki, 2000; Jutte, Burgos, Mendoza, Ford, & Huffman, 2003; Reijneveld, Vogels, Hoekstra, & Crone, 2006; Thun-Hohenstein & Herzog, 2008). Translated versions have been tested in the appropriate ethnic groups with different score cut-offs proving appropriate in different settings. For the Japanese version, the optimal cut-off score is 17 (Ishizaki, 2000). For the Dutch version, a cut-off of 25 is recommended (Reijneveld et al., 2006). Part of our study included determining the most appropriate cut-off score for the Setswana PSC (Lowenthal et al., 2011). We now report on the association between high scores on the PSC and virologic outcomes among HIV-infected older children and adolescents in Botswana.

Methods

We culturally-adapted a Setswana translation of the PSC utilizing a team of 8 bilingual (Setswana-English) professionals. We then piloted the tool in a population similar to the study population and confirmed the tool's internal consistency and factor structure in Batswana children and adolescents. We determined the optimal score cutoff for the Setswana PSC using receiver operator characteristic (ROC) analyses (Hanley & McNeil, 1982). ROC curves were generated by determining the sensitivity and specificity of each potential PSC score cut-off with respect to dichotomized parent reports of concern about the child. Binomial exact 95% confidence intervals were generated for sensitivity and specificity at each cut point and areas under the ROC curves were calculated.

We then sought to determine whether having a high PSC score was associated with virologic treatment failure among HIV-infected children and adolescents in this African setting. We targeted HIV-infected children on combination antiretroviral therapy (cART) for ≥6 months since those who would achieve complete viral suppression should do so by this time. Virologic failure was defined as a confirmed HIV-1 viral load >400 copies/ml after 6 months on first-line treatment. We assessed whether children with virologic failure had higher PSC scores using Wilcoxon rank sum test in unadjusted analyses and using linear regression to adjust for potential confounders, including demographic and clinic characteristics. We assessed the association between having a PSC score above the cut-off value and having virologic failure using a chi-squared test in unadjusted analyses and using logistic regression to adjust for potential confounders. We also assessed each individual PSC question for a trend of higher likelihood of failure with increasing score using a non-parametric test of trend.

Results

We enrolled 692 participants all of whom initiated cART with non-nucleoside reverse transcriptase-based therapy at least 6 months prior to enrollment (median age=11.9 years (IQR 10.2–13.6, range 8–16.9); median treatment duration=56 months (IQR 37–72, range 6–134); 50.3% female) from Francistown and Maun, Botswana. More than 90% of subjects were perinatally HIV-infected with 12 (1.7%) reportedly infected via breastfeeding and 1 (0.1%) infected via rape. Orphan status was common (52.6%) with 102 (28%) being double-orphans, 261 (72%) being single-orphans, but only 18 (5%) residing in an orphanage. Most children (98.7%) had been enrolled in school with 96% being within 2 years of the age-appropriate grade level. The median age at initiation of cART was 7.4 (IQR 5.4–9.3) years. At baseline 48% were CDC immune category 3 and 6.8% were CDC immune category 3 at the time of enrollment in our study. Virologic failure had occurred in 161 (23.3%) patients at some time in their treatment history.

A score cut-off of 20 on the PSC was chosen based on the ROC curve analysis. The chosen cut-off gave us an accuracy of 92% for correctly classifying subjects according to our standard measure. Using the cut-off score of 20, 120 (17.3%) patients had high scores. The median PSC score for those with virologic failure was 12 (IQR 7–19) and the median for those without virologic failure was 10 (IQR 5–16, $p<0.01$). A scatter plot with a fitted line showing the proportion of subjects with each PSC score who had virologic failure demonstrates increasing proportions with virologic failure among those with higher PSC scores (Figure 1). Virologic failure was more common among those with a PSC score ≥20 (31.7%) than among those with a PSC score of <20 (21.5%, unadjusted OR 1.7, 95% CI 1.1–2.6; sensitivity 23%, specificity 85%, PPV 32%, NPV 78%). The results were not significantly altered by controlling for demographic or clinical factors, including age, age at

initiation of cART, sex, nadir CD4, orphan status, primary caregiver, and HIV disclosure status.

From the full-length (35 question) PSC, 9 questions had a statistically significant test of trend for a higher likelihood of failure in those with higher scores at the 0.05 level and 6 questions had a statistically significant test of trend at the 0.01 level. Table 1 shows the distribution of test scores and results from the test of trend for the 17 questions that make up the brief-report version of the PSC. Questions which tended to be scored higher among patients with virologic failure were mainly related to attention/executive dysfunction, and depressive symptoms.

Discussion

Psychosocial dysfunction as measured by the PSC is related to treatment failure among HIV-infected youth in Botswana. Because of our study's cross-sectional design, we cannot comment on causality. Psychosocial dysfunction may have played a role in causing treatment failure, may be the result of treatment failure, or both. If psychosocial dysfunction is found in longitudinal studies to precede treatment failure, then by screening for psychosocial dysfunction, those children and adolescents at highest risk of virologic failure in resource-limited settings might be identified. Because the sensitivity and specificity were insufficiently high, the PSC score cannot be used to either rule out or rule in the diagnosis of virologic failure, and is not a substitute for virologic monitoring. However, if found in longitudinal studies to be a predictor of virologic failure, the PSC could easily be utilized in resource-limited settings to allow for prioritization of scarce psychosocial support resources to target children and adolescents at the highest risk of treatment failure.

Further studies need to be done to assess whether high scores on the PSC can predict poor adherence and treatment failure before poor outcomes are recognizable. If proven to be a useful predictor of poor outcomes, translation and cultural-adaptation of the test for use in other linguistic and cultural groups would be recommended. Another major limitation of our study is that other factors contributing to failure were not investigated. The "low risk group" still had a >20% virologic failure rate, suggesting that further studies to address the factors contributing to poor outcomes among older children and adolescents in resource-limited settings are urgently needed (Ferrand R, 2010).

Acknowledgments

The authors would like to thank the clinic staff, patients and families who helped to make this study possible. This research was supported by a grant for the Penn Center for AIDS Research (CFAR), an NIH-funded program (P30 AI 045008).

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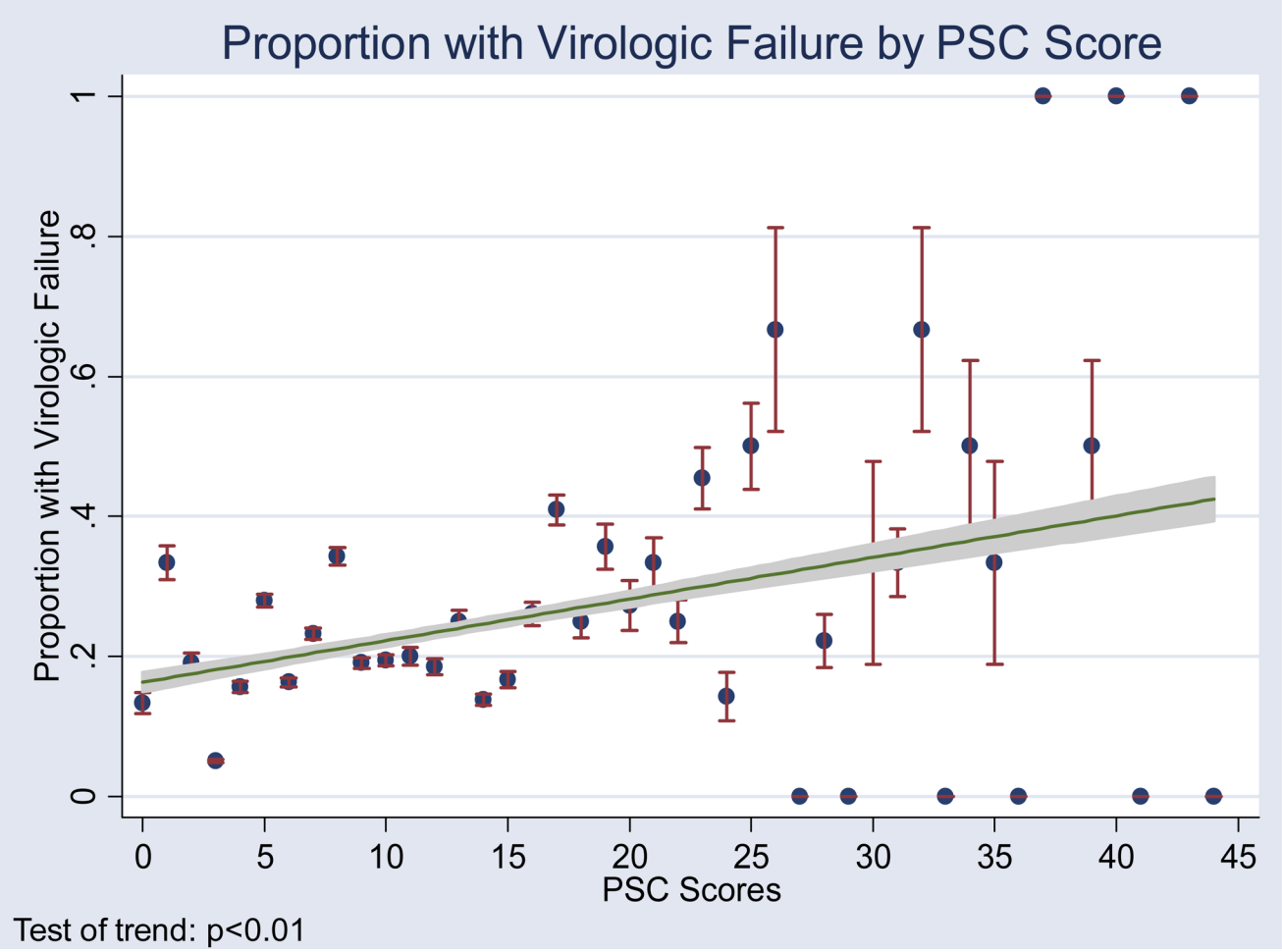

Figure 1.
Proportion of subjects with virologic failure by PSC score

Table 1

Distribution of PSC brief report item scores

PSC Question	Number (percent) without (N=530) and with (N=162) virologic failure who answered never (0), sometimes (1), or often (2) for each PSC question			Test of Trend p-value
		No Virologic Failure	Virologic Failure	
Worries a lot	(0)	424 (80)	109 (67)	**0.008**
	(1)	64 (12)	37 (23)	
	(2)	42 (8)	16 (10)	
Seems to be having less fun	(0)	446 (84)	122 (75)	**0.005**
	(1)	64 (13)	29 (18)	
	(2)	16 (3)	11 (7)	
Feels sad, unhappy	(0)	389 (73)	102 (63)	**0.003**
	(1)	120 (23)	46 (28)	
	(2)	21 (4)	14 (9)	
Feels bad about him or her self	(0)	470 (89)	109 (67)	**0.002**
	(1)	41 (8)	37 (23)	
	(2)	19 (4)	16 (10)	
Does not listen to rules	(0)	465 (88)	127 (78)	**0.002**
	(1)	50 (9)	24 (15)	
	(2)	15 (3)	11 (7)	
Distracted easily	(0)	348 (66)	83 (51)	**0.012**
	(1)	118 (22)	57 (35)	
	(2)	64 (12)	22 (14)	
Daydreams too much	(0)	354 (67)	92 (56)	**0.013**
	(1)	130 (25)	48 (30)	
	(2)	46 (8)	22 (14)	
Does not understand other people's feelings	(0)	391 (74)	105 (65)	**NS**
	(1)	59 (11)	28 (17)	
	(2)	80 (15)	29 (18)	
Teases others	(0)	458 (86)	140 (86)	**NS**
	(1)	54 (10)	17 (11)	
	(2)	18 (4)	5 (3)	
Blames others for his or her troubles	(0)	471 (89)	140 (86)	**NS**
	(1)	47 (9)	18 (11)	
	(2)	12 (2)	4 (3)	
Takes things that do not belong to him or her	(0)	471 (89)	140 (86)	**NS**
	(1)	43 (8)	19 (12)	
	(2)	16 (3)	3 (2)	
Refuses to share	(0)	395 (74)	118 (73)	**NS**
	(1)	46 (9)	20 (12)	

PSC Question	Number (percent) without (N=530) and with (N=162) virologic failure who answered never (0), sometimes (1), or often (2) for each PSC question			Test of Trend p-value
		No Virologic Failure	Virologic Failure	
	(2)	89 (17)	24 (15)	
Fidgety, unable to sit still	(0)	417 (79)	131 (81)	**NS**
	(1)	87 (16)	22 (14)	
	(2)	26 (5)	9 (5)	
Acts as if driven by motor	(0)	451 (85)	134 (83)	**NS**
	(1)	54 (10)	21 (13)	
	(2)	25 (5)	7 (4)	
Feels hopeless	(0)	464 (88)	137 (85)	**NS**
	(1)	34 (6)	17 (10)	
	(2)	32 (6)	8 (5)	
Has trouble concentrating	(0)	353 (67)	95 (59)	**NS**
	(1)	110 (21)	39 (24)	
	(2)	67 (13)	28 (17)	
Fights with other children	(0)	467 (88)	147 (91)	**NS**
	(1)	45 (9)	10 (6)	
	(2)	18 (3)	5 (3)	