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Adherence to antiretroviral therapy, stigma and behavioral risk factors in HIV-infected adolescents in Asia

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Abstract

We studied behavioral risks among HIV-infected and uninfected adolescents using an audio computer-assisted self-interview. A prospective cohort study was initiated between 2013 and 2014 in Malaysia, Thailand, and Vietnam. HIV-infected adolescents were matched to uninfected adolescents (4:1) by sex and age group (12–14 and 15–18 years). We enrolled 250 HIV-infected (48% male; median age 14.5 years; 93% perinatally infected) and 59 uninfected (51% male; median age 14.1 years) adolescents. At enrollment, HIV-infected adolescents were on antiretroviral therapy (ART) for a median (IQR) of 7.5 (4.7–10.2) years, and 14% had HIV-RNA >1000 copies/mL; 19% reported adherence <80%. Eighty-four (34%) HIV-infected and 26 (44%) uninfected adolescents reported having ever smoked cigarettes or drunk alcohol ($p=0.13$); 10% of HIV-infected and 17% of uninfected adolescents reported having initiated sexual activity; 6 of the HIV-infected adolescents had HIV-RNA >1000 copies/mL. Risk behaviors were common among adolescents, with few differences between those with and without HIV.

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Disclosure Statement

The authors declare no conflicts of interest related to this study.

Keywords

HIV; adolescents; Asia; adherence; stigma

Introduction

A large proportion of adolescents living with HIV have been infected through vertical transmission ("Global Consultation on Strengthening the Health Sector Response to Care, Support, Treatment and Prevention for Young People Living with HIV, 2008,"). They face important challenges with regards to the need for long-term care, adherence to antiretroviral therapy (ART), how to manage disclosure of their HIV status, and transition to adult life. Studies of youth living with HIV in the US have demonstrated high rates of substance use and high-risk sexual behaviour (Naar-King, Kolmodin, Parsons, & Murphy, 2010; Naar-King, Parsons, Murphy, Kolmodin, & Harris, 2010; Nugent et al., 2010; Tanney, Naar-King, Murphy, Parsons, & Janisse, 2010). Stigmatization and discrimination are additional concerns that can cause delays in seeking and adhering to healthcare (Lieber, Li, Wu, Rotheram-Borus, & Guan, 2006).

The study of these broad challenges faced by HIV-infected adolescents and their impact on treatment outcomes is necessary to help identify appropriate psychosocial support and interventions. Yet, collecting accurate information related to these sensitive issues is challenging in a formal healthcare setting. Previous studies involving behavioral and culturally sensitive data have shown that results can significantly vary, depending on the data collection methodology used (Estes et al., 2010; Jaya, Hindin, & Ahmed, 2008). As a tool for independent and/or anonymous data collection, the audio computer-assisted self-interview (ACASI) has been found to provide younger users with a greater sense of privacy and comfort, reducing bias in responses, and has been shown to have higher acceptability than paper-based or oral interviews when collecting sensitive data (Dolezal et al., 2012; Langhaug et al., 2011).

We aimed to study risk behaviors, ART adherence, and perceived stigma and discrimination among Asian HIV-infected adolescents, and HIV-uninfected controls using an ACASI-based questionnaire.

Methods

Study design and study population

We conducted a prospective, observational cohort study among HIV-infected adolescents followed in the TREAT Asia Pediatric HIV Observational Database (TAPHOD) of IeDEA Asia-Pacific (Kariminia et al., 2011) and HIV-uninfected adolescents (controls). Among a total of 16 HIV treatment sites in six countries involved in TAPHOD, 9 participated in the present study, from Malaysia (three sites), Thailand (four sites) and Vietnam (two sites). The HIV-uninfected controls were recruited from other clinics (e.g., general pediatrics) at participating sites, and through outreach services. Uninfected control patients were all matched and enrolled at the same sites and same countries as the HIV-infected adolescents.

HIV-infected and -uninfected adolescents aged between 12 to 18 years and HIV-infected adolescents disclosed to about their HIV status were eligible for enrollment. The HIV-infected children were matched to the HIV-uninfected children by sex and age bands (12–14 years and 15–18 years) in a ratio of 4:1.

ACASI and data collection

During an earlier pilot phase, a study-specific ACASI was developed (Prasitsuebsai W et al., 2012) based on a version created for the US NIH Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (Mellins CA et al.). It was further revised for use in the present study and included a maximum of 84 questions on general demographics, sexual behavior, substance use, and violence, with additional questions on adherence to ART and stigmatization among HIV-infected adolescents. The ACASI was developed in English, and then translated and recorded in the participants' local languages, which were Malay, Thai, and Vietnamese. For the HIV-infected participants, data on their treatment history and other HIV clinical information were collected from the parent TAPHOD cohort. The methods for data collection for that study have previously been described, and include data collected during routine clinical care (Kariminia et al., 2011).

As part of the consent process, participants were informed that questions asking about violence (e.g., at home, school) would be included in the ACASI, and that they had the option to refuse to answer any of the questions. However, if the participant responded that violence had been experienced, the software included an automatic alert notification for study staff that would trigger a post-ACASI individual discussion to determine the nature and seriousness of the violence (minor, moderate, serious) and organize physical examination, counseling, referral, and additional follow-up, according to the hospital's violence management protocols and as needed. In addition, site staff reported post-ACASI management plans to the study coordinating center for further tracking.

Participants were asked to complete the anonymous ACASI questionnaire on a tablet computer in a private area, and study staff were available to answer questions during the session. After reaching the end of the ACASI, the participant handed the tablet back to the study staff who checked for notifications (per above) prior to closing the individual session. ACASI response files were electronically transferred in real time or at regular intervals to the data team at the study management center for cleaning and analysis, depending on local internet access.

Statistical consideration

The sample size of the control group was determined based on the outcome of initiating sexual activity. Using findings from the pilot phase of the study in which 11% of the HIV-infected adolescents compared to 48% of uninfected adolescents had reported engaging in sexual activity, (Prasitsuebsai W et al., 2012) enrolling 60 HIV-uninfected controls for 250 HIV-infected adolescents would provide over 95% power to detect a difference in sexual debut between the two groups, at a two-sided significance level of 5%.

Demographic and clinical characteristics were summarized in medians (interquartile range, IQR) and proportions, as appropriate. The correlation significance between HIV-infected

and HIV-uninfected adolescents was calculated by using chi-square test for categorical variables. If a sample size was small, Fisher's exact test was used to identify correlation among groups. Wilcoxon rank-sum test was used to calculate the difference of quantitative variables among two groups. SAS version 9.3 (SAS Institute Inc, Cary, NC, USA) and Stata version 12 (Statacorp, College Station, TX, USA) were used for data analyses.

Ethical considerations

All participating study sites and the study coordinating centers (HIV-NAT, Thai Red Cross AIDS Research Centre, Thailand; TREAT Asia, amfAR/The Foundation for AIDS Research, Thailand) obtained institutional review board (IRB) approvals for study participation. Caregivers for patients under 18 years and patients 18 or more years of age were asked to give consent; those under 18 were asked to provide assent when this was required by the local site IRB.

Results

Socio-demographic characteristics

Between July 2013 and March 2014, a total of 309 adolescents (250 HIV-infected adolescents, and 59 –uninfected controls) were enrolled in the study and included in the analysis; 178 participants (58%) were from Thailand, 77 (25%) from Vietnam, and 54 (17%) from Malaysia (Table 1). Among the HIV-infected participants, 52% were female and the median age was 14.5 years. Of the HIV-uninfected participants, 49% were female and the median age was 14.1 years. Fewer HIV-infected than -uninfected adolescents lived with their biological parents (24% vs. 59%; $p < 0.001$). Almost all (95% both groups) were currently in school or vocational training. Less than one-fifth (18% HIV-infected vs. 10% HIV-uninfected, $p = 0.13$) were working to support themselves.

Clinical characteristics and stigma in HIV-infected adolescents (n=250)

Among the HIV-infected adolescents, almost all (93%) were perinatally infected, and the remainder were enrolled in care at the age of 8 (IQR 6–11) years. All (100%) were currently on ART, with a median age at ART initiation of 7 (4–10) years. The median (IQR) duration of ART was 7.5 (4.7–10.1) years, and 154 (62%) were currently taking non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (Table 2). The median CD4 of the 96% with testing was 676 (484–884) cells/mm³, and 27 (22 – 32)%. Of the 194 (78%) of adolescents with available HIV RNA results at their most recent clinic visits before enrollment, 28 (14%) had HIV RNA >1000 copies/mL and 160 (83%) had HIV RNA <400 copies/mL.

Of those with HIV, half were responsible for managing their own medicines; 19% reported overall ART adherence at less than 80% for the last month, and 39% reported having difficulties taking daily ART. The main difficulties reported included pill fatigue (42%), the scheduled dosing time (35%), the number of pills (26%), and the size of the pills (25%; not mutually exclusive). The median age when the patients reported they first knew they were infected with HIV was 10 (6–12) years. The majority (65%) reported they were told by their doctors; the rest were told by either their parent(s) or primary caregiver. Few HIV-infected

adolescents reported problems of stigmatization at home (7%) or school (9%). No episodes of serious violence were reported within the past six months in either group.

Sexual behavior – all adolescents

A non-statistically significant lower percentage of infected adolescents (10% vs. 17% of uninfected; $p=0.16$) reported having initiated sexual activity. The majority of those who were sexually active in both groups had their first sexual intercourse before the age of 15 years (31% HIV-infected vs. 50% HIV-uninfected; $p=0.19$). About one-third of sexually active adolescents in both groups reported never or intermittently using condoms (28% HIV-infected vs. 30% HIV-uninfected, $p=0.91$); 26% of HIV-infected and 38% of uninfected adolescents had >1 partner within the past three months ($p=0.54$); 23/26 (88%) HIV-infected and all 10 (100%) uninfected adolescents were using at least one method of birth control. Six of 24 (25%) sexually active HIV-infected adolescents with HIV RNA testing had levels >1000 copies/mL at their most recent clinic visits. Only HIV-infected adolescents (15% of those sexually active) reported a history of sexual transmitted diseases, and few (2–3%) of either group reported an experience of unsafe or unplanned sexual activity after substance use.

Substance abuse – all adolescents

Eighty-four (34%) HIV-infected and 26 (44%) uninfected adolescents had ever either smoked cigarettes or drunk alcohol ($p=0.13$). The HIV-uninfected group had done so earlier but the difference was not statistically significant (median age 15 vs. 13 years [$p=0.25$] for alcohol; 14 vs. 12.5 year [$p=0.66$] years for smoking). The HIV-infected group tended to use marijuana less than the uninfected group (3% vs. 9%; $p=0.07$). Few (0.4% vs. 3%; $p=0.1$) had ever tried others drugs, including inhalants, amphetamines, methamphetamine, cocaine, or heroin.

Discussion

To our knowledge, this is the first regional cohort study of risk behaviors in HIV-infected adolescents in Asia using an ACASI tool. As the study questionnaire dealt with sensitive personal information, the use of the confidential ACASI platform is thought to have optimized the accuracy of the information collected. Although there were few statistically significant differences between the groups, our study found that substantial proportions of both HIV-infected and -uninfected control adolescents reported risk-taking behaviors.

Adolescents with HIV infection are at high risk of treatment failure from challenges in ART adherence, which stem from several factors. In this cohort, 38% of HIV-infected adolescents reported difficulties in taking daily ART, and 19% reported adherence below 80%. These participants were mostly perinatally HIV-infected adolescents who had been taking ART for several years. The most common adherence challenge reported was pill fatigue, and more specifically of “feeling bored” with taking ART on a daily basis. Other studies have similarly reported (Parianti, Bangsberg, Verdon, & Gardner, 2009; Parruti et al., 2006) adherence to be a major concern in adolescents after long-term ART, with pill burden and duration on treatment being significant factors associated with adherence problems. Previous

studies on disclosure have found inconsistent impact of disclosure on adherence (Gyamfi, Okyere, Appiah-Brempong, Adjei, & Mensah, 2015; Nichols, Steinmetz, & Paintsil, 2016). As our study included only adolescents who had been disclosed to about their HIV status, this was not a parameter affecting adherence.

Another factor which has been associated with poor ART adherence is stigmatization (Lyimo et al., 2014; Reisner et al., 2009). Depression, low self-esteem or psychiatric disorders can be consequences of stigmatization (Kingori et al., 2012; White et al., 2012), which in turn can lead to poor health outcomes together with non-adherence (Sweeney & Venable, 2015). The proportion of people living with HIV facing stigma, and the extent of stigma endured, have been shown to vary, but stigma remains a persistent factor limiting access and uptake of HIV care services, as well as the quality of life of people living with HIV (Kingori et al., 2012; Li, Murray, Suwanteerangkul, & Wiwatanadate, 2014; Pichon, Rossi, Ogg, Krull, & Griffin, 2015). In the present study, the low numbers of participants reporting problems with stigmatization was unexpected and encouraging, but we did not assess the extent of onward disclosure to extended family members or other social contacts.

Understanding factors impacting youth adherence are essential to guide interventions to improve long-term treatment outcomes. As models of differentiated service delivery are implemented in national programs in low- and middle-income settings (Grimsrud, Barnabas, Ehrenkranz, & Ford, 2017), greater advocacy is needed to promote tailored care for adolescents due to their greater risk for loss to follow-up and treatment failure. Perinatally infected youth in school have less flexible scheduling options for clinic visits (Nsanzimana et al., 2017), and are coping with prolonged ART durations that lead to the reports of treatment fatigue observed in our study. Models that focus on adults will be inadequate to address the unique problems of youth. (Yang et al., 2017)

Studies of young people living with HIV in the US have demonstrated major psychosocial challenges of growing up with HIV, including substance use, and high-risk sexual behavior (Naar-King S, Kolmodin K, Parsons JT, & D, Apr 2010; Naar-King S, Parsons JT, Murphy D, Kolmodin K, & DR, May 2010; Nugent NR et al., Mar-Apr 2010; Tanney MR, Naar-King S, Murphy DA, Parsons JT, & H, Jan 2010). A few studies examining similar issues have been conducted in Thailand (Lee B & P, Jul-Aug 2009; Oberdorfer, Louthrenoo, Puthanakit, Sirisanthana, & Sirisanthana, 2008; Oberdorfer et al., 2006), but not on a regional level in Asia. Our data on risk behaviors varied from other reports from Western and Asian countries where both our infected and uninfected participants had lower rates of risk behaviors, including drug abuse, early sexual engagement, and unprotected sex (Elkington et al., 2012; Saingam, Assanangkornchai, & Geater, 2012; Sychareun, Thomsen, Chaleunvong, & Faxelid, 2013). Although less than 20% in both groups reported having initiated sexual activity, the majority of those had their first sexual activity before 15 years of age. Notably, 75% admitted to receiving education on safe sex practices, and although 64% used at least one method of birth control, 30% used condoms only intermittently.

In addition to early sexual engagement and unsafe sex practices, substance use is another major risk behavior in adolescents. Findings from the US and other cohorts revealed higher numbers of HIV-uninfected adolescents having used alcohol and other illegal drugs

(Elkington et al., 2012; Saingam et al., 2012; Sychareun et al., 2013). Our study also found that uninfected adolescents more frequently reported substance use than infected adolescents. These findings urge us to identify interventions to reduce these risk behaviors among both HIV-infected and HIV-uninfected adolescents to prevent further transmission of HIV and sexually transmitted diseases.

Our study had limitations that prevent broad generalization of the results. The socio-economic and cultural contexts between the three countries are markedly different, especially with regards to religion and economic systems. These factors impact social acceptability and feasibility of different risk-taking behaviors, and could have resulted in biased reporting by the adolescents. Another limitation was that study sites are tertiary-care referral centers in urban settings, and youth may have different behaviors from those living in rural areas. Matching criteria for the control patients did not include socio-economic status, which could have influenced outcomes, given that families coping with HIV in our setting may be more likely to also have lower income levels (Puthanakit et al., 2010). In addition, our power calculation was based on a difference in initiation sexual activity in the pilot study that was higher than what we observed in this study. This likely limited our power to detect significant differences between the HIV-infected and uninfected groups, a factor that would need to be further assessed through subsequent follow-up research.

Conclusions

In conclusion, our study demonstrates that sexual and substance use risk behaviors and ART adherence issues are common among adolescents in our region. The use of a tablet-based, self-administered ACASI was feasible across these socio-cultural settings in Southeast Asia. The results help inform our understanding of these risk behaviors in the context of long-term ART management, and can be used to guide adherence interventions as well as prevention and harm reduction efforts during adolescence.

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Table 1
Reports of substance abuse, sexual behaviour, and violence among Asian HIV-infected and -uninfected adolescents at enrolment

	HIV-infected			HIV-uninfected			p
	Total	Male	Female	Total	Male	Female	
Demographics							
Number of participants	250	121 (48)	129 (52)	59	30 (51)	29 (49)	
Age	14.5 (13.3–15.7)	14.3 (13.3–15.4)	14.6 (13.3–15.8)	14.1 (13–16)	14.3 (13–16.5)	13.8 (12.5–15.5)	0.54
Country of residence							
Malaysia	42 (17)	17 (14)	25 (19)	12 (20)	6 (20)	6 (21)	
Thai	147 (59)	71 (59)	76 (59)	31 (53)	16 (53)	15 (52)	
Vietnam	61 (24)	33 (27)	28 (22)	16 (27)	8 (27)	8 (28)	
Mother alive (%)	126 (58)	61 (59)	65 (58)	49 (96)	24 (92)	25 (100)	<0.001
Father alive (%)	95 (44)	46 (44)	49 (44)	41 (80)	22 (85)	19 (76)	<0.001
Sexual behavior							
Ever received information on sexual education	184 (74)	86 (72)	98 (77)	44 (75)	24 (80)	20 (69)	0.95
Ever had sexual intercourse	26 (10)	3 (2)	23 (18)	10 (17)	4 (13)	6 (21)	0.16
First sexual activity at <15 years old	8 (31)	1 (33)	7 (30)	5 (50)	2 (50)	3 (50)	0.19
More than 1 partner within the past 3 months	6 (26)	0 (0)	6 (26)	3 (38)	3 (75)	0 (0)	0.54
Ever had symptoms of a sexually transmitted infection	4/25 (15)	1 (33)	3 (14)	0/10 (0)	0 (0)	0 (0)	0.18
Always use condoms during sexual activity	18/25 (72)	2 (67)	16 (73)	7/10 (70)	4 (100)	3 (50)	0.91
Never or intermittently use condoms	7/25 (28)	1 (33)	6 (27)	3/10 (30)	0 (0)	3 (50)	0.91
Females who had started their menstrual period	97 (75)	NA	97 (75)	24 (83)	NA	24 (83)	0.39
Females who had ever been pregnant	1 (4)	NA	1 (4)	1 (17)	NA	1 (17)	0.29
Substance abuse							

p	HIV-uninfected			HIV-infected		
	Total	Male	Female	Total	Male	Female
Demographics						
Ever tried an alcoholic beverage (%)	25 (42)	16 (53)	9 (31)	80 (32)	40 (33)	40 (31)
Ever smoked cigarettes (%)	10 (17)	7 (23)	3 (10)	24 (10)	20 (17)	4 (3)
Ever tried marijuana (%)	5 (9)	5 (17)	0 (0)	8 (3)	5 (4)	3 (2)
Ever used other illegal drugs (%)	2 (3)	2 (7)	0 (0)	1 (0.4)	1 (1)	0 (0)
Violence						
Had ever been forced to have any sexual interaction within the past 6 months	0 (0)			0 (0)		
Had ever been physically abused by a friend, teacher, or family member within the past 6 months	0 (0)			0 (0)		

Note: P-value for testing difference among HIV-infected and HIV-uninfected adolescents

Table 2

Characteristics of Asian HIV-infected adolescents (n=250)

	Total	Male	Female
N	250	121	129
Age at ART initiation	7 (4–10)	7 (3–10)	7 (4–10)
HIV exposure N (%)			
Perinatal	234 (93)	116 (96)	118 (91)
Blood products/sexual abuse	2 (1)	0 (0)	2 (2)
Unknown	14 (6)	5 (4)	9 (7)
Median (IQR) duration on ART, years	7.1 (4.7–10.2)	7.1 (4.9–10.8)	7.0 (4.7–10.2)
Median (IQR) current CD4 cell count, cells/mm ³	676 (484–884), n=240	676 (520–886), n=117	677 (470–882), n=123
Median (IQR) current CD4 percentage	27 (22–32), n=231	26 (22–30), n=113	29 (22–33), n=118
ART regimens (%)			
NNRTI-based	154 (62)	73 (60)	81 (63)
PI-based	81 (32)	41 (34)	40 (31)
Others	15 (6)	7 (6)	8 (6)
HIV-RNA <400 copies/mL, N (%)	160 (83), n=194	79 (86)	81 (79)
HIV-RNA >1000 copies/mL, N (%)	28 (14), n=194	10 (11)	18 (18)

IQR: interquartile range; ART: antiretroviral therapy; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor