

Original article

Adolescent and Adult Participation in an HIV Vaccine Trial Preparedness Cohort in South Africa

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See Editorial p. 1

Abstract

Purpose: The importance of involving adolescents in HIV prevention trials has been recognized, but there have been few experiences reported from sub-Saharan Africa. We analyzed adult and adolescent data from a cohort study conducted to assess the feasibility of involving adolescents and adults in HIV vaccine-related studies.

Methods: Two hundred HIV-negative participants aged 16 to 40 years were enrolled, including 86 (43%) adolescents. At baseline, sexual risk behavior and willingness to participate (WTP) in future HIV vaccine trials questionnaires were administered. Three monthly HIV counseling, pregnancy, HIV and syphilis tests were performed. Risk questionnaires were repeated at 6 months and WTP at 12 months.

Results: No significant difference in retention between adults (83%) and adolescents (87%) was noted ($p = .58$). Initially, more adults (40%) reported WTP compared to adolescents (13%) ($p < .001$). At the end of the study both groups reported higher levels of WTP; increasing to 40% among adolescents. HIV incidence during the study was 9.2 infections per 100 person-years (95% confidence interval [CI]: 4.4–19.2) among adolescents compared to 5.8 (95% CI 2.6–12.9) in adults ($p = .42$).

Conclusions: Retention of high-risk HIV-negative adolescents in a cohort study is feasible. Following education, adolescents reported improved WTP. The high HIV incidence rate in adolescents highlights the importance of including this group in prevention trials. © 2008 Society for Adolescent Medicine. All rights reserved.

Keywords:

Adolescents; HIV; HIV vaccines

Internationally, there are an estimated 10 million young people between the ages of 15 and 24 years living with HIV, and most of those infected live in sub-Saharan Africa [1]. Half of all new HIV infections occur in the 10–24 year age group, and each day 7000 youth become infected [2]. In

South Africa the national prevalence of HIV in under 20 year olds is reported to be 16% [3]. With the recognition that the HIV epidemic is youth-driven, there has been a growing awareness of the need to include adolescents in HIV prevention trials, including vaccine trials. It has been suggested that the best strategy to curb the HIV crisis is the effective vaccination of this high-risk group [4].

The scientific rationale [5], the ethico-legal [4,6,7], clinical [4,8], and socio-behavioral [9] issues related to adolescent involvement in HIV vaccine trials have recently been

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highlighted. Although there are few practical experiences in this area, theoretical concerns have been raised regarding the ability to recruit and retain adolescents into long-term vaccine efficacy studies, as well as adolescents' attitudes toward participating in this research [8,9]. However, to date, most vaccine preparedness research and clinical trials have focused on adult volunteers. One of the few reports of recruiting and retaining adolescents in longitudinal HIV research comes from the REACH study, which followed HIV-positive and HIV-negative adolescents in the United States [10]. Retention at the end of the study was 87%, but the retention data for HIV-positive and HIV-negative participants were not reported separately. To our knowledge, there have been no adolescent HIV preparedness cohort experiences reported in sub-Saharan Africa or other resource-limited settings.

Similarly, very few studies have reported adolescent willingness to participate (WTP) in HIV vaccine trials. Although WTP has been associated with lower levels of education [11], there are conflicting data published on the impact of vaccine knowledge on WTP. In 1994, research from an HIV vaccine preparedness trial in the United States reported a decrease in WTP among men who have sex with men following education about HIV vaccines and vaccine trials [12]. Similarly, a recent study from the United States reported a significant drop in willingness to participate among adolescent volunteers following an information presentation [13], although this contrasts with the reported experience in one Indian study [14]. Generally, there is little published data on this issue from sub-Saharan Africa [15], and especially regarding adolescents. One cross-sectional survey performed among adolescents in a South African township found high levels of willingness to participate in HIV vaccine trials (79%), but the misconceptions about HIV vaccines described in this study suggest concerns about basic understanding of vaccine trial involvement [16].

We performed an HIV vaccine trial preparatory study among adolescents and adults in a periurban township in South Africa. Given the importance of including adolescents in HIV vaccine research, and the lack of data around this topic in sub-Saharan Africa where a number of HIV vaccine trials are planned, we report findings of the comparison of retention, knowledge of vaccines, WTP in future HIV vaccine trials, changes in reported sexual risk behavior, and HIV incidence rates between adults and adolescents participants in the cohort.

Methods

The cohort study took place at a HIV vaccine trial site based in a periurban community outside Cape Town, South Africa. The study site has a population of approximately 13,500, predominantly Xhosa-speaking individuals. HIV prevalence in this community is high: 23% in the adult population [17] and 11% among those aged 11 to 19 years [16].

Volunteers were eligible for the study if they were 16 to 40 years of age, HIV-negative, not pregnant or breast feeding, and available for 12 months of follow-up. Screening and enrolment both occurred at the initial study visit. Following enrolment, demographic, sexual risk behavior, and WTP in future HIV vaccine trials questionnaires were administered. Syphilis testing was also carried out at baseline.

Three monthly visits were performed thereafter, with HIV counseling and testing, risk reduction counseling, and pregnancy and syphilis testing repeated at each visit. Sexual risk questionnaires were administered 6 monthly and WTP was reassessed at 12 months. Social harms, defined as any possible experiences of stigma and discrimination the participant may have encountered as a result of study participation, were recorded at each visit following enrolment. Study participants also attended two 1.5-hour educational group workshops on HIV, vaccines, and vaccine trials. These education sessions were held during the course of the study, after the baseline sexual risk and WTP questionnaires were administered and prior to the administration of the 12-month questionnaires. All questionnaires as well as education sessions were administered in Xhosa or English, by a trained interviewer.

The study was approved by the University of Cape Town's Research Ethics Committee. Following a detailed explanation about the study, all participants provided written consent. As no experimental product was involved, the research ethics committee waived the requirement for parental consent for participants aged 16 to 20 years.

Data were analyzed using STATA 9.0 (College Station, TX). In analysis, adolescents were defined as participants aged 16 to 20 years. A general vaccine knowledge score was calculated as the number of correct answers to five close-ended questions regarding the following basic vaccine-related concepts: prevention (one item), route of administration (two items), design (one item), and availability to general population (one item). HIV vaccine knowledge was calculated as the number of correct answers to seven close-ended questions pertaining specifically to the following HIV vaccine-related concepts: aim of HIV vaccine (two items), availability to general population (one item), efficacy (one item), infectivity (one item), and target population (two items). Reliability of the knowledge scales was assessed using Cronbach's alpha test. Bivariate analysis employed Student's *t*- and Fisher's exact tests, as appropriate; for intraindividual comparisons of measures taken at baseline and 12 months, McNemar's chi-square and paired *t*-tests were used. Separate survival analyses, including Kaplan-Meier tables and Cox's proportional hazards models, were used to determine factors associated with either incident HIV infection or loss to follow-up in the cohort. The date of HIV incidence was estimated as the midpoint between the last HIV negative and first HIV-positive test. All statistical tests are two-sided at $\alpha = 0.05$.

Table 1
Demographic characteristics

	Adults (n = 115)		Adolescents (n = 85)		<i>p</i> Value	Total (n = 200)	
	n	%	n	%		n	%
Age range (mean)	21–39	(27)	16–20	(18)		16–39	(23)
Gender							
Male	30	26	12	14		42	21
Female	85	74	73	86	.040	158	79
Race							
Black	112	100	82	96		194	99
Other	0	0	1	1	.244	1	1
Language							
Xhosa	110	96	83	98		193	97
Other	5	4	2	2	.222	7	4
Housing							
Formal	8	7	7	8		15	8
Informal	106	93	78	92	.748	184	92
Education							
Below Grade 8	29	26	20	24		49	25
Grade 8 or higher	82	74	64	76	.712	146	75
Employment							
Employed	44	57	9	11		53	27
Unemployed/other	69	61	75	88	<.001	144	73
Relationship status							
Single	10	9	15	18		25	13
Partner	105	91	69	82	.054	174	87

Results

Two hundred HIV-negative participants were enrolled between November 2003 and April 2004. Adolescents comprised 43% of the study sample; 34 (17%) were 16 to 17 years of age, and 51 (26%) between 18 and 20 years. All results are presented as a comparison of adults with adolescents (Table 1). The majority of participants from both the adult (74%) and adolescent (86%) groups were female and most participants reported having a sexual partner.

Overall, 169 participants completed 12 months of follow-up (Table 2), with no significant difference in retention rates between adults (83%) and adolescents (87%) ($p = .58$). Most attrition (58%) occurred immediately after the initial screening and enrolment visit. The reasons for attrition were: participant moved out of the community ($n = 16$), lost to follow-up for unknown reason ($n = 5$), incorrect locator data ($n = 4$), gained employment, and were unable to attend appointments ($n = 3$), withdrew because of fear of a positive HIV result ($n = 2$) or imprisonment ($n = 1$). There was no difference between adolescents' reasons for dropout versus those of adults. In an unadjusted analysis, retention was significantly associated with female gender in both the adult and adolescent groups ($p = .007$ and $p = .001$, respectively). Good baseline knowledge of HIV vaccines and reported WTP in HIV vaccine trials were both weakly associated with good retention ($p = .047$ and $p = .045$, respectively). Reported alcohol use was a significant risk factor for attrition in adults ($p = .006$), but not in adoles-

cents ($p = .845$). In a multivariate model adjusted for education and HIV vaccine knowledge, the association between female gender and better retention persisted (hazard ratio 0.28; 95% CI 0.13–0.61; $p = .001$). No social harms were reported in either group during the course of the study.

At study entry, adults had significantly better knowledge of both general vaccines ($p < .001$) and HIV vaccines ($p = .002$), with mean scores of 3.3 and 1.7, respectively, compared with adolescents whose mean scores were 2.4 and 0.7, respectively. Over the course of the study, the adults' general vaccine knowledge and HIV vaccine specific knowledge improved significantly ($p < .001$ and $p = .002$, respectively), with mean scores of 3.9 and 3.7, respectively, as did the adolescents' general vaccine knowledge and HIV vaccine-specific knowledge scores ($p < .001$ for both mean scores), with mean scores of 4.0 and 3.0, respectively. At the end of the 12-month follow-up period, there was no significant difference between the general vaccine and HIV vaccine knowledge between the two age groups ($p = .39$ and $p = .72$, respectively). Internal consistency of both knowledge scales was high (Cronbach's alpha = 0.91 for general vaccine knowledge scale and 0.98 for vaccine specific knowledge scale).

Similarly, at the start of the study significantly more adults (40%) reported willingness to participate in future HIV vaccine trials compared with adolescent participants (13%) ($p < .001$). Both groups reported significantly higher levels of WTP by the end of the study: 63% of adults stated

Table 2
Retention

	Adults (n = 115)		Adolescents (n = 85)		p Value
	Retained	Lost to follow-up	Retained	Lost to follow-up	
Retained in the cohort	95 (83%)		74 (87%)		
Predictors of retention					
Gender					
Male	20 (67%)	10 (33%)	7 (58%)	5 (42%)	<.001
Female	75 (88%)	10 (12%)	67 (92%)	6 (8%)	
Education					
Below Grade 8	26 (90%)	3 (10%)	16 (80%)	4 (20%)	.894
Grade 8 or higher	66 (80%)	16 (20%)	58 (91%)	6 (9%)	
Relationship status					
Single	7 (70%)	3 (30%)	14 (93%)	1 (7%)	.890
Partner	88 (84%)	17 (16%)	60 (87%)	9 (13%)	
Baseline General vaccine knowledge score					
<Mean score	12 (67%)	6 (33%)	25 (83%)	5 (17%)	.088
≥Mean score	83 (86%)	14 (14%)	47 (90%)	5 (10%)	
Baseline HIV vaccine knowledge score					
<Mean score	60 (78%)	17 (22%)	62 (86%)	10 (14%)	.047
≥Mean score	35 (92%)	3 (8%)	10 (100%)	0 (0%)	
Baseline WTP					
WTP	41 (91%)	4 (9%)	11 (100%)	0 (0%)	.045
Not WTP	53 (77%)	16 (23%)	61 (86%)	10 (14%)	
Perception of own risk for HIV acquisition					
Perceived self to be at risk	62 (87%)	9 (13%)	37 (88%)	5 (12%)	.284
Did not perceived self to be at risk	33 (77%)	10 (23%)	36 (88%)	5 (12%)	
Alcohol use in last 12 months					
Yes	7 (54%)	6 (46%)	6 (86%)	1 (14%)	.012
No	72 (86%)	12 (14%)	60 (88%)	8 (12%)	

that they would be willing to participate in future HIV vaccine trials (odds ratio [OR] 3.50 CI: 1.55–8.89), and 40% of adolescents reported willingness (OR 28.0, CI: 4.63–1144); this increase over time was significantly greater among adolescents ($p = .036$). As with vaccine knowledge, at the end of the 12-month study, there was no significant difference in reported WTP between adults and adolescents ($p = .489$). In both the adult and adolescent groups, increasing HIV vaccine knowledge was significantly associated with greater willingness to participate as reported at both the start and end of the study ($p < .001$ for both groups at both time points).

Sexual risk behaviors reported at baseline and repeated at month 6 and month 12 are presented in Table 3. Low levels of high risk behaviors such as sex in exchange for commodities ($n = 2$), forced sex ($n = 2$), and sex related to alcohol or drug use ($n = 3$) were reported at baseline by both adults and adolescents, and this remained consistent throughout the study (data not shown). There was a significant increase in the number of participants who knew their partner's HIV status at month 12 compared with baseline (OR for all ages: 4.36; 95% CI: 2.23–9.32), and this increase was of similar magnitude for both adult and adolescents. Reported condom use at last sexual encounter did not change significantly over the course of the study in either

the adult or adolescent groups (OR for all ages: 1.08; 95% CI: 0.60–1.97).

Thirteen incident HIV infections were identified during the follow-up period; the overall HIV infection rate in this cohort was 7.2 per 100 person years (95% CI: 4.2–12.4). The highest infection rate was noted in the first 90-day interval (17.3 infections per 100 person years; 95% CI: 8.7–34.7), with a steady fall-off thereafter (Figure 1). The incidence of HIV was slightly higher among adolescents compared with adults (incidence rates per 100 person years and 95% CI: 9.2; 4.4–19.2 and 5.8; 2.6–12.9, respectively), although this did not reach statistical significance ($p = .42$). HIV infection was not associated with any participant demographic characteristics or sexual risk behaviors (not shown). During the course of the study 12% of both female adult ($n = 10$) and adolescent ($n = 9$) participants became pregnant, and 13% of all adults ($n = 15$) and 9% of all adolescents ($n = 8$) acquired syphilis infection. There was no statistical difference between the two age groups in these findings ($p = .65$ and $p = .43$, respectively).

Discussion

This study demonstrates that recruitment and retention of high-risk HIV-negative adolescents and young adults into HIV vaccine trials is feasible in this setting. The retention of

Table 3
Sexual risk behaviors

	Adults (n = 115)		Adolescents (n = 85)		p Value
	N	%	N	%	
Age of sexual debut (mean)	12–25	(16.8)	12–18	(15.4)	
Number of sexual partners ever (mean)	1–31	(5.2)	1–16	(3.08)	
Ever used a condom	88	77	61	74	.627
Ever had STD	80	70	31	37	<.001
Month 0					
Number of sexual partners in 6 months (mean)	0–6		1–4		
Mean	2.2		1.3		
Condom use at last sexual encounter	38	33	33	43	.146
HIV-positive sexual partner—yes	2	2	0	0	.494
Symptom/sign of STI in past 6 months	47	41	23	28	.050
Are you at risk of HIV infection	71	62	42	51	.102
Persons you are having sex with at risk?	70	66	44	56	.184
Similar lifestyle at risk—yes	77	68	43	52	.025
Month 6					
	Adults (n = 83)		Adolescents (n = 63)		
Number of sexual partners in 6 months (mean)	0–6	(1.12)	0–3	(1.07)	
Condom use at last sexual encounter	24	29	32	53	.003
HIV-positive sexual partner—yes	1	1	0	0	.644
Symptom/sign of STI	14	17	13	21	.410
Are you at risk of HIV infection	29	35	14	23	.107
Persons you are having sex with at risk?	29	36	14	23	.088
Similar lifestyle at risk—yes	30	36	14	23	.079
Month 12					
	Adults (n = 92)		Adolescents (n = 65)		
Number of sexual partners in 6 months (mean)	1–2	(1.07)	1–2	(1.15)	.103
Condom use at last sexual encounter	32	35	29	47	.136
HIV-positive sexual partner—yes	2	2	1	2	.857
Symptom/sign of STI	9	10	9	14	.431
Are you at risk of HIV infection	48	52	37	57	.556
Persons you are having sex with at risk?	48	52	37	57	.556
Similar lifestyle at risk—yes	48	52	37	57	.556

STI = sexually transmitted infection; STD = sexually transmitted disease.

adolescents was comparable to that of adults in this study and equivalent to rates reported in the developed world [10]. The high rate of loss to follow-up immediately after the initial study visit suggests that separating screening and enrolment visits, as is standard in HIV vaccine trial designs, may be a particularly useful strategy. A similar fall-off in volunteers who initially expressed interest at prescreening and then failed to attend screening appointments has been reported in research from Thailand [18]. Separate screening and enrolment visits would help ensure commitment to the study, allow ambivalent volunteers the opportunity to make a decision, and allow for confirmation of accurate locator data.

Poor baseline knowledge of vaccines was in keeping with previous research in this population [16]. The significant increase observed in HIV and vaccine-related knowledge scores in both the adult and adolescent groups may be attributed to the education programs organized for the study participants as well as the community-wide program. Good

baseline HIV vaccine knowledge was associated with better retention, indicating the potential importance of good information sessions prior to enrolment for vaccine trials.

This is one of the few studies to examine changes in WTP in HIV vaccine research in sub-Saharan Africa. Our data showed that WTP in future HIV vaccine trials increased in both adults and adolescents during the study, and that this increase was strongly associated with HIV vaccine knowledge. Interestingly, this association is in keeping with previous research from India [14], but contrasts with research from the United States, suggesting that increased knowledge of HIV vaccines is associated with reduced WTP [12,13]. The finding suggests that education and improved knowledge about HIV vaccines and research may improve WTP in this setting, particularly among adolescents. One caution is that this data reports WTP among study volunteers and may not reflect WTP in the general community because in consenting to participate in the cohort, participants have already indicated willingness to par-

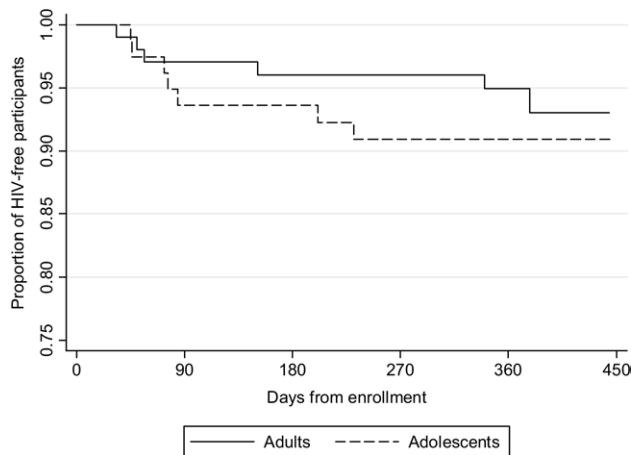


Figure 1. Kaplan-Meier survival graph for HIV incident infection rate for adults and adolescents over the course of the study.

ticipate in biomedical research, and may thus bias WTP positively. In addition, it is unknown how reported WTP will translate into actual WTP when an HIV vaccine trial is offered.

Although one marker of risk behavior improved over the course of the study (knowledge of partner's HIV status), there was no significant change in most aspects of risk behavior. These markers of risk behavior remained the same despite the comprehensive risk reduction counseling provided by a trained nurse practitioner at each study visit. More research on the effectiveness of methods for risk reduction counseling in a developing context is necessary.

The estimated HIV incidence in a target population is an important factor in the design of vaccine trials [19,20] and these data are among the first to be published on the HIV incidence in adolescents at a potential HIV vaccine trial site. The incidence rate of HIV infection was high in this setting, and at least as high in adolescents as adults, highlighting the importance of including young people in HIV vaccine trials and other forms of prevention research. Analysis of risk factors for incident HIV infection was limited by the small numbers of new infections.

The data reported here are based on a small cohort, and although this study community is typical of periurban populations in South Africa, the generalizability of these data remains unclear. At the time of the study, the South African Children's Act required parental consent for the participation of children under 21 years of age in research studies; this has recently been amended to children under 18 years. The enrolment of adolescents in this study was simplified by the fact that parental consent was waived and was potentially easier than it would be when assisted consent is required, as will be the case for adolescent HIV vaccine trial participants in South Africa. Further investigation into this potential barrier to adolescent involvement into trials is needed. Finally,

study questionnaires were interviewer administered, which may have led to a social desirability bias, potentially contributing to an underreporting of high risk sexual risk activities and overreporting of WTP.

In summary, these data suggest that the recruitment and retention of high-risk HIV-negative adolescents in a long-term cohort study is feasible in this setting. The rates of both HIV incidence and retention in the cohort are similar in adolescents and adults. Education may play a critical role in the willingness of adolescents to take part in future HIV vaccine trials.

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