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Original article

Quality of Caregiver-Adolescent Relationship on HIV, Herpes Simplex Virus Type-2, and on Pregnancy Among Young Women in South Africa Enrolled in HIV Prevention Trials Network 068

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A B S T R A C T

Purpose: Adolescent girls and young women (AGYW) are at an increased risk of acquiring HIV and HSV-2, and unintended pregnancies are high in AGYW. Despite the protective impact of caregiver-adolescent relationships on risk behaviors, less attention has been paid to the association of these relationships and sexually transmitted infections (STIs) and pregnancy.
Methods: We used longitudinal data from HIV Prevention Trial Network 068, which was conducted among 2,533 AGYW (13 – 20 years) over 5 years in Agincourt, South Africa. Kaplan-Meier and Cox models were used to estimate the effect of quality of caregiver-adolescent relationships (caring and closeness) on STIs and pregnancy. Also, we assessed effect measure modification by age (14–19 vs. 20–25 years) for STI risk using stratum-specific estimates and likelihood ratio tests, with a p value <.1 indicative of effect measure modification.
Results: There were no significant differences in the hazard of HIV by our exposures (caring: hazard ratio (HR): 1.03, 95% CI: 0.75, 1.42; closeness: HR: 0.80, 95% CI: 0.57, 1.11). Among 14–19-year-olds, those who reported caregiver caring were less likely to acquire HSV-2 (HR: 0.69, 95% CI: 0.51, 0.94, likelihood ratio tests= 3.89, p-value = .0487), in contrast, there were no significant differences among 20 – 25-year-olds. AGYW who reported high-quality relationships had a lower hazard of pregnancy incidence (caring: HR: 0.79, 95% CI: 0.68, 0.93; closeness: HR: 0.76; 95% CI: 0.64, 0.91).
Discussion: Positive caregiver-adolescent relationships are associated with reduced risk of HSV-2 among younger AGYW and pregnancy incidence.
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IMPLICATIONS AND CONTRIBUTIONS

This study contributes to literature on adolescent girls and young women (AGYW) in rural South Africa, showing that positive caregiver-adolescent relationships are associated with reduced Herpes simplex virus type 2 risk among younger AGYW and pregnancy incidence. Family-centered interventions should be promoted to build positive caregiver-adolescent relationships as a strategy to reduce AGYW's STI risk and unplanned pregnancies.

In South Africa (SA) young people are at an increased risk of acquiring human immunodeficiency viruses (HIV), particularly adolescent girls and young women (AGYW) as they are 2 to 3 times more likely to be infected with HIV [1] and also acquire HIV 5 to 7 years earlier compared to male peers [2,3]. Herpes simplex

Conflicts of interest: The authors have no conflicts of interest to declare.

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virus type 2 (HSV-2) increases the risk of HIV acquisition [4,5], and its prevalence globally is estimated to be the highest in sub-Saharan Africa ranging from 22% to 87% [6]. AGYW are disproportionately affected by HSV-2 [7,8], with a prevalence of 29.2% and 10.0% in young (15 − 26 years) females and males, respectively [9]. In addition to HIV and HSV-2, pregnancies are a concern in AGYW in SA [10]. Among adolescent girls (15–19 years), 16% have begun childbearing [11], and 10–19-year-old females contribute to 12.4% of all registered births [12]. Also, there are urban-rural disparities in pregnancy among AGYW − rural women are likely to have more pregnancies, and pregnancies are likely to occur 2 years earlier among rural women compared to urban women [13]. Given the high levels of HIV, HSV-2, and pregnancy in AGYW, there is a need to understand why young women continue to be at risk for these outcomes.

Research supports that when young people feel connected to caregivers, risk behaviors are mitigated. In particular, positive caregiver-adolescent relationships are associated with delayed sexual debut [14,15], safer sex [14,15], and reduced sexual activity [16]. According to the attachment theory, the attachment between a child and a caregiver develops in infancy and influences development, behaviors, and decision-making skills throughout the life course [17,18]. Thus, there is a possibility that positive caregiver-adolescent relationships indirectly affect pregnancy risk and sexually transmitted infection (STI) risk through promoting safer sexual behaviors among AGYW [14–16,19]. Moreover, less attention has been paid to the relationship between the quality of caregiver-adolescent relationships and health outcomes associated with risk behaviors, such as STIs and pregnancy. Therefore, in this study we aimed to understand the association between caregiver-adolescent relationships and HIV, HSV-2, and pregnancy incidence in a cohort of rural, SA adolescent girls.

We used rich longitudinal data from the HIV Prevention Trials Network (HPTN) 068 study of SA AGYW (median age at baseline = 15 years). The use of longitudinal data gives us an advantage of being able to explore whether caregiver-adolescent relationships influence HIV or HSV-2 and pregnancy incidence, as adolescent girls transition to early adulthood. We hypothesized that AGYW who perceive higher levels of caregiver caring and closeness will have a lower risk of STIs and pregnancy compared to those who perceive lower levels of caregiver caring and closeness.

Methods

Study sample

For this analysis, we used data from the HIV Prevention Trials Network (HPTN) 068 study, a phase III randomized controlled trial that aimed to assess whether providing cash transfers (conditional on 80% school attendance) to AGYW and their households reduced the risk of HIV acquisition among young women (previously described [20]). The parent study included females who at enrolment were as follows: (1) aged 13–20 years; (2) registered for high school in grades 8–11; (3) not married; (4) not pregnant; (5) had a parent or guardian in the household; and (6) resided in Agincourt Health and Demographic Surveillance System study area. Agincourt is a rural community located in Mpumalanga, SA, which has high HIV prevalence and HIV or acquired immunodeficiency syndrome mortality [21,22]– in 2013, over 40% of deaths were attributable to HIV [23]. In addition, agincourt experiences high levels of labor migration with approximately 31% male and 19% female migrants [24]. As a result, children are often left behind in the care of a single parent [25] or an extended family member [26]. In the HPTN 068 study conducted in rural SA among young women, 28% of the participants were a single or double orphan [20,27], and 63.6% of them lived with a single parent or nonbiological caregiver at study enrollment [20].

For this study, we excluded participants with no follow-up visits after the baseline visit given that this is a longitudinal assessment. We also excluded participants who were prevalent HIV cases at baseline from all analyses because the parent study examined the impact of a conditional cash transfer on school attendance on HIV infection [27] and also to allow us to assess HIV incidence. We further excluded baseline HSV-2 cases for the HSV-2 analysis to assess HSV-2 incidence, and similarly, for the pregnancy analysis we excluded AGYW who had ever been pregnant before study enrollment for the pregnancy analysis to allow us to assess pregnancy incidence.

AGYW were seen annually, and up to 4 visits were conducted from 2011 to 2015 (T_0–T_3). At each visit, participants completed an audio computer-assisted self-interview (ACASI) and a blood draw for HIV and HSV-2 testing. Participants completed the interview and study procedures at a “weekend camp”, which was partially administered by a trained fieldworkers and by partially by the participant. Parents or guardians completed a computer-assisted personal interview annually. AGYW exited the main trial upon high school graduation. Follow-up was 1 to 3 years from baseline (T_1–T_3) based on the participant’s grade at study enrolment. For some participants who missed a visit or graduated during the study, additional HIV and HSV-2 testing was done close to the AGYW’s graduation date. Further, a poststudy visit was conducted in 2016–2017 (T_4), where a behavioral survey and HIV and HSV-2 testing. The ethical approval for this secondary analysis was obtained from the University of North Carolina at Chapel Hill Institutional Review Board.

Measures or variables

We examined the association between the quality of caregiver-adolescent relationships and HIV, HSV-2, and pregnancy incidence. The quality of caregiver-adolescent relationship (caring and closeness) was measured by asking AGYW their perceptions of their relationship with their primary caregiver (parent or guardian); it was measured annually in the main study (T_0–T_3). The primary caregiver was conceptualized as the adult most responsible for taking care of the participant. The participants were first asked to identify their caregiver before questions about the quality of caregiver-adolescent relationship were asked. Caregiver caring was captured by asking “how much do you feel that [your caregiver] cares about you?”, with possible response options of “very much”, “somewhat”, or “not at all.” Caregiver caring was conceptualized as feelings of concern, interest, and empathy. For analyses, this question was operationalized as a binary measure by collapsing levels, “somewhat” and “not at all” into one level to avoid sparse data (0 (or No) = “not at all” or “somewhat”, and one (or Yes) = “very much”). Caregiver closeness was captured by asking “how close do you feel to [your caregiver]?”, with possible response options of “very close”, “somewhat close”, and “not at all close.” Caregiver closeness was conceptualized as having an emotional connection, feelings of trust and affection. For analyses, this question was

operationalized as a binary measure by collapsing "somewhat" and "not at all close" to avoid sparse data (0 (or No) = "somewhat close" or "not at all close", and one (or Yes) = "very close"). The questions assessing the quality of adolescent relationships were adapted from Add Health [28].

We explored 2 STIs (HIV and HSV-2) and a pregnancy. We defined incident HIV as the first positive HIV test among those who were HIV-negative at enrollment. Screening for HIV infection was performed in parallel using 2 different HIV rapid tests: (1) Determine HIV-1/2 test (Alere Medical Co., Ltd, Matsudo-shi, Chiba, Japan), and (2) Food and Drug Administration-cleared Uni-gold Recombigen HIV test (Trinity Biotech PLC, Bray, Co. Wicklow, Ireland). Incident HSV-2 infection was defined as the first positive HSV-2 test among those who were HSV-2 negative at enrollment. Testing for HSV-2 was performed using the Herpes Simplex Virus Type 2 IgG ELISA assay (Kalon Biological, LTD Guilford, UK). Further details on diagnostic testing procedures are reported elsewhere [27]. Pregnancy is a dichotomous self-report measure of the first report of pregnancy among AGYW who had never been pregnant at baseline. Young women were asked if they have ever been pregnant at each visit (T_0–T_3), and at follow-up visits, they were asked if they have been pregnant in the last 12 months (T_1–T_3). AGYW responded to this question using ACASI.

Statistical analysis

To examine the relationship between the quality of caregiver-adolescent relationships on incident HIV, HSV-2, and pregnancy, we used Kaplan–Meier and Cox models. In these analyses, time-varying exposures and covariates were lagged to predict outcomes at the following visit, allowing us to determine how quality of the caregiver–adolescent relationship at time t affects outcomes of interest reported at time t + 1. The participants were followed from origin (study baseline) until the first-reported outcome while in the study or date of censoring. Participants were censored if they migrated, were lost to follow-up, or reached the end the study period. We administratively censored those who did not acquire the outcome at the date of their last questionnaire or test. Once a young woman had reported the outcome of interest, they were removed from the risk set at the date of her first-reported outcome. For AGYW with an additional HIV and HSV-2 test conducted near graduation, we carried forward data from the most recent survey. We used time in years since age 13 (until 21 years), and we allowed AGYW who were older than 13 years at baseline as late entries.

To illustrate how the risk of the outcome varies over time by exposure group, we used the complement of the Kaplan–Meier survival function. To estimate the hazard ratio for the relationship between the quality of caregiver-adolescent relationship and the first report of a given outcome, we used Cox proportional hazards models, which can handle late entry, time-varying exposure, and time-varying covariates [29,30]. We evaluated the proportional hazards assumption using plots of the cumulative hazard functions for each group and also by testing the product term between exposure and time. We also assessed effect measure modification (EMM) by age (adolescents 14–19 years and young adults 20–25 years [31]) in the association between the quality of caregiver-adolescent relationship and STI risk. We used stratum-specific estimates and likelihood ratio tests (ERTs) to compare models with and without interaction terms between the exposure and the potential modifier (with a p-value $<.1$ indicative of EMM) [32].

For all models, directed acyclic graphs were used to identify a minimally sufficient set of confounders for each exposure-outcome relationship. In the quality of caregiver and HIV and HSV-2 associations, confounders included age, intervention assignment (cash transfer study arm), orphan status, and school dropout. In addition, for the quality of caregiver and pregnancy relationship, confounders included age, intervention assignment, and orphan status (see Table S1). To account for confounding, we used inverse probability of treatment weights. We created weights using logistic regression models to estimate each woman's probability of exposure (caring or closeness) and also each woman's probability of exposure conditional on confounders over time. We used exposure stabilized weights [33]. To account for time-varying confounding being affected by prior exposure, we structured weights to be conditional on prior exposure and covariates. Less than 10% of AGYW had missing information for exposures or covariates. We carried forward covariate data from the most recent prior visit to address missing data. Moreover, we used a robust variance estimator for creating confidence intervals for hazard ratios, and used Efron's approximation method to account for tied data.

Results

Of the 2,533 young women, we excluded AGYW who were HIV positive at baseline (n = 81) and who did not have at least 1 additional visit postbaseline (n = 70). Our analyses included 2,382 young women for the HIV incidence outcome. For the HSV-2 analysis, we further excluded 93 participants from the HIV cohort analysis who were HSV-2 positive at baseline, resulting in a total of 2,289 young women. In addition, from the HIV cohort we excluded 196 participants who reported ever being pregnant at baseline, ending with a total of 2,186 young women in the incident first pregnancy cohort.

At baseline (Table 1), most of the participants reported positive quality of caregiver-adolescent relationships (77.63% felt their caregiver cares very much and 82.45% felt very close to their caregiver). Participants who that felt their caregiver cares about them very much had a lower percentage of high mean depression scores (2.96 vs. 4.88), transactional sex (2.76% vs. 7.16%), sexual debut (23.19% vs. 36.66%), being in age-disparate relationships (4.61% vs. 8.79%), being in a concurrent relationship (39.09% vs. 47.43%), having had a sexual partner in last 12 months (23.23% vs. 37.50%), having had unprotected sex in last 3 months (6.58% vs. 12.45%), cohabitating (15.72% vs. 22.70%), and having ever been pregnant (7.15% vs. 12.30%) at baseline compared to participants who reported "no or somewhat", when asked if their caregiver cares about them. In addition, participants who felt their caregiver cares about them very much had a higher percentage of having both parents at home (42.53% vs. 39.56%), having a female caregiver (81.09% vs. 75.64%), and a lower percentage of being a single or double orphan (29.13% vs. 33.08%). Further, AGYW who reported that their caregiver somewhat or did not care about them had similar levels of household wealth, conditional cash transfer intervention arm assignment, and primary caregiver compared to AGYW who reported feeling that their caregiver cares about them. We observed similar patterns with the second measure of quality of caregiver-adolescent relationships (feels close to caregiver).

Table 1
Baseline characteristics of adolescent girls & young women aged 13–21 years in Agincourt, South Africa (2011–2012)[a]

	Total		Caregiver cares[b]				Feels close to caregiver[b]			
	(N = 2,382)		Yes (N = 1,849)		No (N = 521)		Yes (N = 1,964)		No (N = 404)	
	N	%	N	%	N	%	N	%	N	%
Age in years, mean (range)	15.48 (13–21)		15.40 (13–21)		15.74 (13–21)		15.48 (13–21)		15.47 (13–20)	
13–15	1,263	53.02	1,008	54.52	250	47.98	1,049	53.41	205	50.74
16–18	1,009	42.36	775	41.91	228	43.76	824	41.96	181	44.80
19–21	110	4.62	66	3.57	43	8.25	91	4.63	18	4.46
Randomization arm	1,217	51.09	935	50.57	277	53.17	991	50.46	219	54.21
Household wealth (assets)										
Low	601	25.27	438	23.73	156	30.00	479	24.43	117	29.03
Middle-to-low	630	26.49	505	27.36	124	23.85	519	26.47	108	26.80
Middle	585	24.60	448	24.27	135	25.96	482	24.58	100	24.81
High	562	23.63	455	24.65	105	20.19	481	24.53	78	19.35
Children's depression inventory, mean (range)	3.38 (0 –16)		2.96 (0–16)		4.88 (0–16)		3.12 (0–15)		4.62 (0–16)	
Children's manifest anxiety, mean (range)	4.49 (0–14)		4.29 (0–14)		5.20 (0–14)		4.31 (0–14)		5.36 (0–14)	
Transactional sex	82	3.68	48	2.76	34	7.16	64	3.48	18	4.8
Sexual debut	625	26.27	428	23.19	191	36.66	501	25.55	119	29.46
Age-disparate relationship	130	5.55	84	4.61	45	8.79	99	5.12	30	7.58
Concurrent relationship	239	41.78	154	39.09	83	47.43	177	38.39	61	55.96
Had sexual partner(s) in last 12 months	621	26.45	424	23.23	192	37.50	525	26.26	123	30.3
Unprotected sex in last 3 months	187	7.91	121	6.58	64	12.45	144	7.38	41	10.3
HSV-2 prevalence	93	3.90	67	3.62	24	4.61	74	3.77	18	4.46
Living with partner	106	17.79	64	15.72	42	22.70	78	16.25	28	24.78
Ever pregnant	196	8.33	131	7.15	63	12.30	156	8.04	38	9.48
Single or double orphan	712	29.89	538	29.13	172	33.08	577	29.42	132	32.6
Parent at home										
Both parent	865	41.69	686	42.53	178	39.56	737	43.25	126	35.29
Neither or one parent	1,210	58.31	927	57.47	272	60.44	967	56.75	231	64.71
Primary caregiver										
Mother or father	1,774	74.48	1,379	74.58	389	74.66	1,466	74.64	298	73.76
Non-parent (caregiver)	608	25.52	470	25.42	132	25.34	498	25.36	106	26.24
Gender of caregiver										
Female	1,897	79.64	1,462	81.09	385	75.64	1,560	81.38	283	72.01
Male	271	11.38	187	10.37	79	15.52	197	10.28	70	17.81
Unknown	214	8.98	154	8.54	45	8.84	160	8.35	40	10.18

[a] Missing at baseline: caregiver cares N = 12; close to caregiver N = 14; SES N = 4; depressive symptoms N = 117; anxiety N = 34; transactional sex N = 154; sexual debut N = 3; age-disparate relationship N = 38; concurrency N = 1810; had sexual partner in last 12 months N = 34; unprotected sex N = 19; live with partner N = 1,786; pregnant N = 28; orphan status N = 3; parent at home N = 307. Prevalent HIV cases were excluded.
[b] Caregiver cares: Yes = "very much", No = "not at all" or "somewhat"; Feels close to caregiver: Yes = "very close", No = somewhat close" or "not at all close".

There were 207 incident HIV cases that occurred over the study period. The cumulative incidence of HIV increased with age from 0.41% at age 15%–35.01% at age 25. The risk of HIV increased over time in both groups (Figure 1). After accounting for confounding, there was no difference in hazard of HIV (HR: 1.03, 95% CI: 0.75, 1.42) between those who said their caregiver cares for them very much and those who said "no or somewhat", when asked if their caregiver cares about them (Table 2). However, caregiver closeness was protective for HIV although not statistically significant (HR: 0.79, 95% CI: 0.57, 1.11). Moreover, there was no indication of EMM by age for the relationship between the quality of caregiver-adolescent relationships and HIV incidence (Table 3).

Over the study period, there were 424 incident HSV-2 cases. The cumulative incidence of HSV-2 was 0.76% at 14 years and 58.40% at 25 years. The risk of HSV-2 increased over time in both exposure groups (Figure 2). Young women (Table 2) who felt their caregiver cares about them very much had a similar hazard of HSV-2 (HR: 0.88, 95% CI: 0.70, 1.09) compared to young women who said "no or somewhat", when asked if their caregiver cares about them. Caregiver closeness was protective for HSV-2 (HR: 0.79, 95% CI: 0.62, 1.00). In addition, among adolescents (14–19 years), participants (Table 3) who felt their caregiver cares about them very much had a lower hazard of HSV-2 compared to those who reported "no or somewhat", when asked if caregiver cares about them (HR: 0.69, 95% CI: 0.51, 0.94, likelihood ratio test= 3.89, p value = .0487). Among those who were 20–25 years, the hazard of HSV-2 was similar between those who felt their caregiver cares very much and those who felt "no" or "somewhat" (HR: 1.07, 95% CI: 0.79, 1.45). In contrast, there was no indication of EMM between the second measure of relationship quality, caregiver closeness, and risk of HSV-2 by age groups (likelihood ratio test= 1.57, p value = .2100).

There were 798 incident pregnancy cases during the study period. Pregnancy incidence was 2.25% at age 14% and 80.90% at age 25. Pregnancy increased over time (Figure 3) and was higher in the group with lower levels of quality of caregiver-adolescent relationships ("no or somewhat") compared to the group with higher levels of quality of caregiver-adolescent relationship ("very much"), especially for the "feels close" to caregiver measure. Participants who felt their caregiver cares about them very much had a lower hazard of incident pregnancies (HR: 0.79, 95%

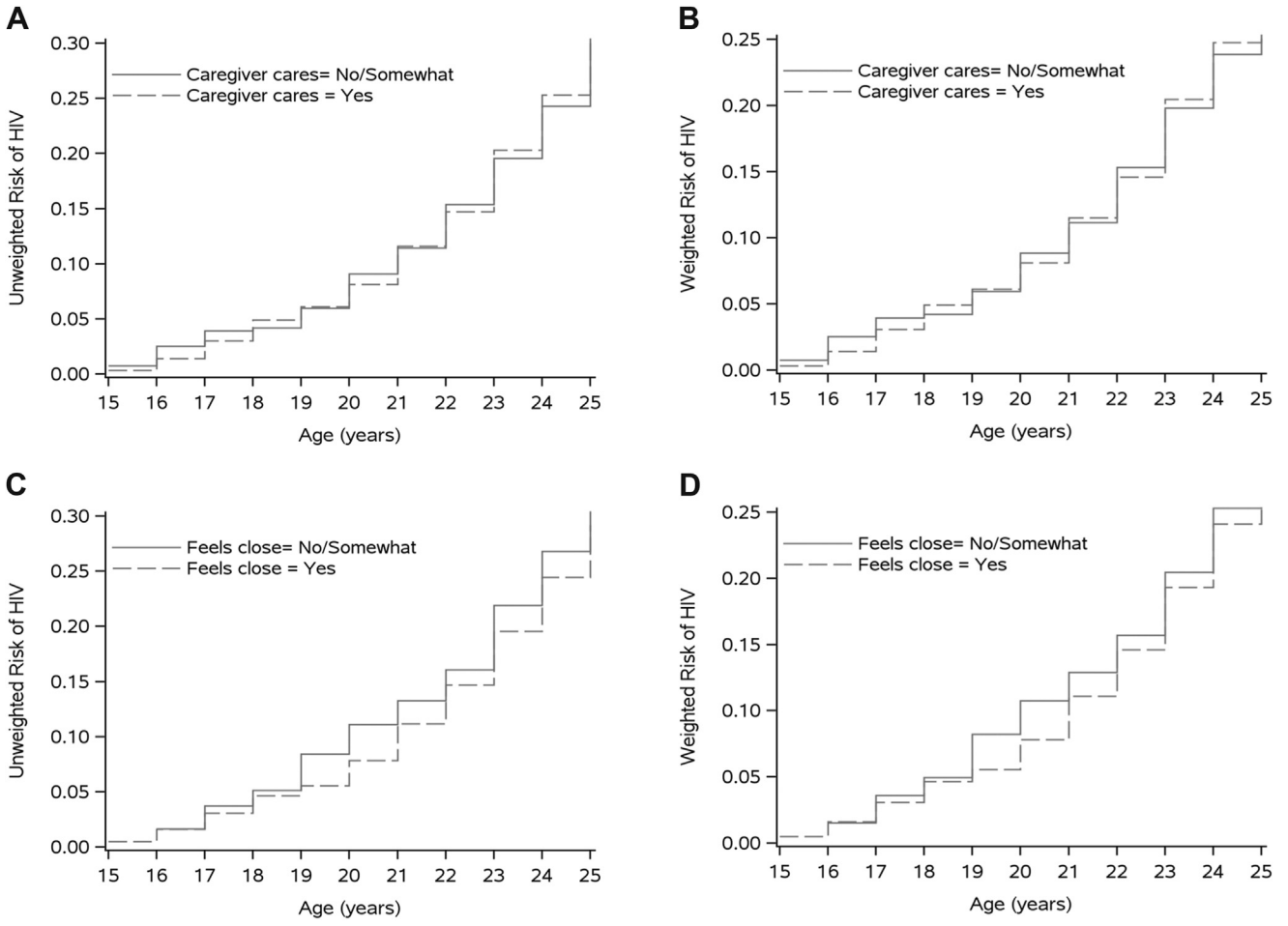


Figure 1. Survival curves for the relationship between caregiver-adolescent relationships and risk of HIV among young women aged 13–25 enrolled in HIV prevention trials network (HPTN) 068 (2011–2017). A & C) Unweighted; B & D) Weighted. Adjusted curves weighted for the following covariates: age, conditional cash transfer treatment arm, orphan status, and school dropout. Solid lines represent participants with low-quality caregiver-adolescent relationships (no/somewhat). Dashed lines represent individuals with high-quality caregiver-adolescent relationship (yes).

CI: 0.68, 0.93) than in AGYW who said "no or somewhat" when asked if their caregiver cares about them (Table 2). In addition, the weighted hazard of pregnancy over the study period was lower among those who reported feeling very close to caregiver (HR: 0.76, 95% CI: 0.64, 0.91) compared to the group that reported "no or somewhat" when asked if they felt close to their caregiver.

Discussion

In this cohort of adolescent girls followed over multiple years in rural SA, we observed that those who had more caring and/or closer relationships with their caregiver were less likely to experience a first pregnancy during the study. In addition, among adolescents (14–19 years), those who reported that their caregiver cares for them very much were less likely to acquire HSV-2. However, there was no association between the quality of caregiver-adolescent relationships and HIV acquisition.

Study findings support our hypothesis that higher levels of quality caregiver-adolescent relationships are associated with reduced risk of HSV-2 among younger AGYW and pregnancy incidence compared to lower levels of quality of caregiver-adolescent relationships. Not much attention has been paid to the relationship between the quality of caregiver-adolescent relationships and risk of STIs. Previous studies on caregiver-adolescent relationship and STIs, such as HIV, have primarily looked at STI risk behavior and not at the risk of STI acquisition [16,34]. For instance, a longitudinal study among African American adolescents, who had their biological mother as the primary caregiver, found that adolescents who had greater mother-adolescent communication had a reduced risk of HIV [34]. However, in this study HIV risk was operationalized using HIV risk behavior questions and not using HIV test results. In our study, we did not find significant differences of risk of incident HIV infection between those who had higher levels of quality of caregiver-adolescent relationships and those with lower levels. In terms of HSV-2 incidence, among adolescents (14–19 years), we found that the hazard of HSV-2 was lower among those who reported that their caregiver cares about them very much compared to those who said "no or somewhat", when asked if their caregiver cares. In terms of pregnancy, our results showing that higher levels of quality of caregiver-adolescent relationships are protective against first teenage pregnancy are consistent with prior literature. A review of over 20 non-African studies supports

Table 2
Hazard ratios for the relationship between caregiver-adolescent relationships and HIV, HSV-2, and pregnancy incidence among adolescent girls and young women in HTPN 068 (2011–2017)

	Number of events	Person-years of follow-up	Unadjusted		Weighted	
			Hazard ratio	(95% CI)	Hazard ratio	(95% CI)
HIV						
Caregiver cares						
Yes	154	8,446	1.01	(0.74, 1.38)	1.03	(0.75, 1.42)
No	53	2,560	1	-	1	-
Feels close to caregiver						
Yes	162	9,086	0.77	(0.56, 1.07)	0.80	(0.57, 1.11)
No	45	1,916	1	-	1	-
HSV-2						
Caregiver cares						
Yes	302	8,446	0.86	(0.69, 1.07)	0.87	(0.70, 1.09)
No	117	2,560	1	-	1	-
Feels close to caregiver						
Yes	333	9,086	0.79	(0.62, 1.00)	0.79	(0.62, 1.00)
No	86	1,916	1	-		-
Pregnancy						
Caregiver cares						
Yes	586	7,840	0.79	(0.67 0.93)	0.79	(0.68, 0.93)
No	202	2,281	1	-	1	-
Feels close to caregiver						
Yes	629	8,369	0.77	(0.64, 0.91)	0.76	(0.64, 0.91)
No	160	1,748	1	-	1	-

CI = robust confidence intervals. Adjusted for the following covariates: *HIV & HSV-2*: age, CCT intervention, orphan status, school dropout. *Pregnancy*: age, CCT intervention, orphan status.

that positive parent-child relationships are associated with decreased risk of adolescent pregnancy [19]. Our results align with these studies using evidence from longitudinal data to show a relationship between the quality of caregiver-adolescent relationships, inclusive of both parental and nonparental guardians, and the risk of first pregnancy among AGYW in SA.

Our data is a little less compatible with the hypothesis of the effect of HSV-2 and HIV. Although precision between our estimates varies due to differences in the number of events, overall, the direction of our effect estimates is consistent with our hypothesis and our effect estimates are comparable in magnitude.

Positive quality of caregiver-adolescent relationships are crucial, because caregivers influence AGYW's development over the life course, including decision-making skills and behaviors [17,35,36]. The quality of caregiver-adolescent relationships may indirectly influence pregnancy and STI risk through promoting safer sexual behaviors, such as delayed sexual debut, fewer sexual partners, and/or consistent use of contraceptives or protection [14–16,19]. Furthermore, caregivers are a central source of assuring AGYW that they matter [37]. According to Elliott, "mattering" serves as a "safety net", especially during adolescence [37] and as a personal motivator that encourages behaviors which are approved by people who matter, such as caregivers, thereby encouraging AGYW to avoid from engaging in unsafe and/or self-destructive behaviors [38].

To our knowledge, this is the first study to assess the longitudinal association between the quality of caregiver-adolescent relationships and HIV and HSV-2 incidence measured using methods to test for confirmation of infection via blood samples. In our study, we used data from a randomized controlled trial, which might limit the generalizability of our results to other populations outside of the study context. For instance, at

Table 3
Hazard ratios for the relationship between caregiver-adolescent relationships and STIs stratified by age among adolescent girls & young women in HTPN 068

	Unadjusted		LRT (*p*-value)	Weighted		LRT (*p*-value)
	Hazard ratio	(95% CI)		Hazard ratio	(95% CI)	
HIV						
Caregiver cares						
Age: ≤19 years	1.14	(0.69, 1.88)	0.38 (0.536)	1.14	(0.69, 1.88)	0.28 (0.599)
Age: ≥20 years	0.93	(0.62, 1.40)	-	0.96	(0.63, 1.46)	-
Feels close to caregiver						
Age: ≤19 years	0.75	(0.52, 1.09)	0.07 (0.793)	0.77	(0.53, 1.12)	0.14 (0.705)
Age: ≥20 years	0.84	(0.41, 1.72)		0.90	(0.44, 1.86)	
HSV-2						
Caregiver cares						
Age: ≤19 years	0.68	(0.50, 0.93)	3.88 (0.0490)	0.69	(0.51, 0.94)	3.89 (0.0487)
Age: ≥20 years	1.05	(0.78, 1.41)	-	1.07	(0.79, 1.45)	
Feels close to caregiver						
Age: ≤19 years	0.94	(0.65, 1.34)	1.80 (0.1803)	0.93	(0.65, 1.33)	1.57 (0.2100)
Age: ≥20 years	0.68	(0.49, 0.93)		0.68	(0.50, 0.94)	

CI = robust confidence intervals. Adjusted for the following covariates: *HIV & HSV-2*: age, CCT intervention, orphan status, school dropout.

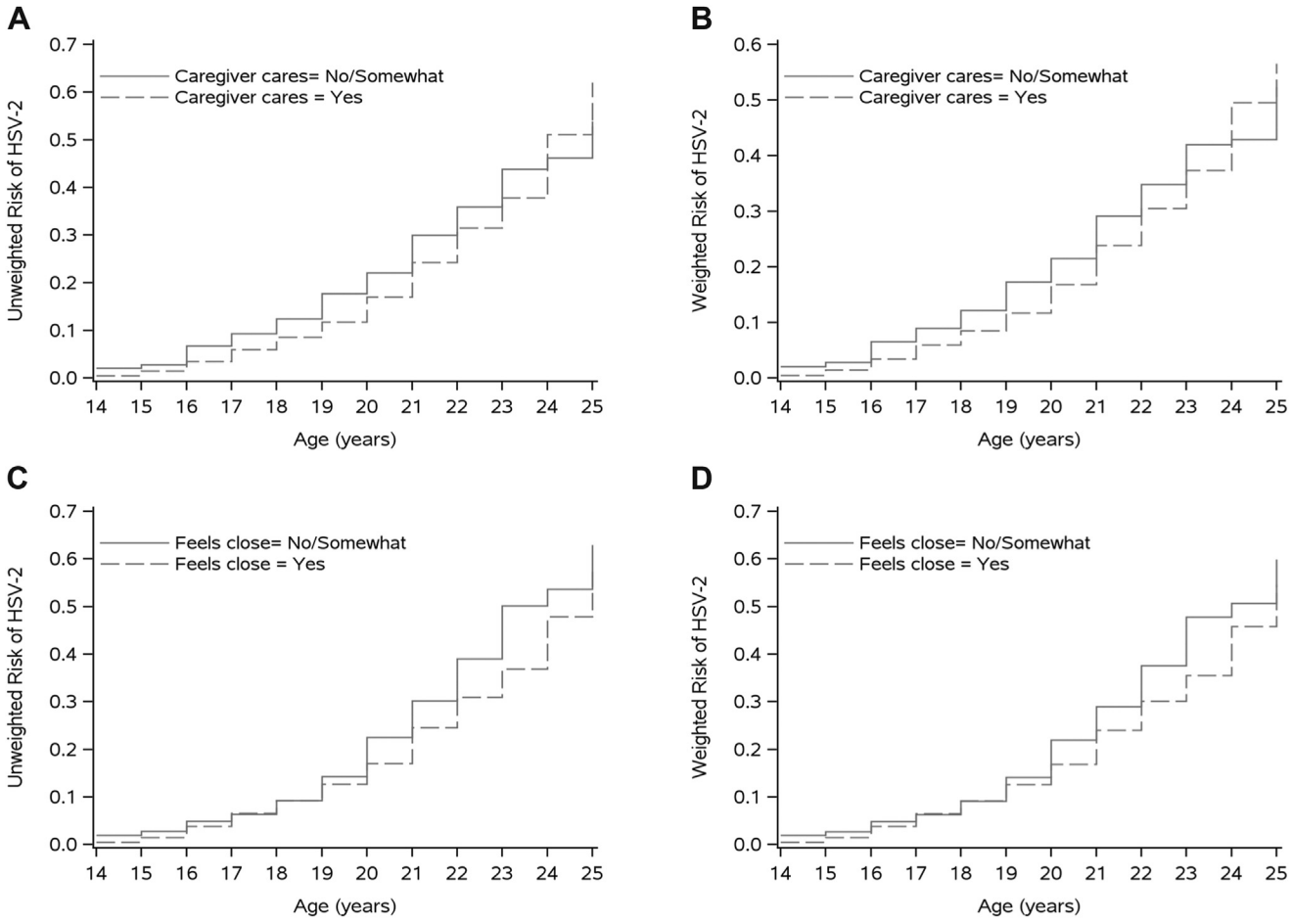


Figure 2. Survival curves for the relationship between caregiver-adolescent relationships and risk of HSV-2 among young women aged 13–25 enrolled in HPTN 068 (2011–2017). A & C) Unweighted; B & D) Weighted. Adjusted curves weighted for the following covariates: age, CCT treatment arm, orphan status, and school dropout. Solid lines represent participants with low-quality caregiver-adolescent relationships (no/somewhat). Dashed lines represent individuals with highquality caregiver-adolescent relationship (yes).

enrollment, all AGYW were enrolled in school and might be different from those who are not enrolled in school. However, in SA, enrolment rates for high school remain high [39]. Also, participants needed to have a parent or guardian in order to be enrolled in the study, therefore, might have more caregiver support than the general population. In the parent study, HIV and HSV-2 testing were measured at each study visit, and the exact date of infection is unknown. Thus, we can only say that the infection occurred within the interval between the previous visit and the current visit. However, it is not common for AGYW to have been tested in between the study visits, because testing for HIV and/or HSV-2 does not occur regularly in the community [40,41].

Information on the quality of caregiver-adolescent relationships and pregnancy was collected by self-report and might be misreported. However, we expect bias in reporting to be reduced because interviews were conducted using ACASI, which has been shown to reduce bias and reluctance to respond to sensitive questions [42]. Additionally, self-reported measures of caregiver-adolescent relationships are necessary to understand their impact on health [37]. As a limitation, we acknowledge that the first occurrence of pregnancy might be a desirable outcome, especially for young women (20–24 years). Moreover, we did not use a tool to assess the quality of caregiver-adolescent relationships; instead, we used 2 independent questions. Validated instruments adapted for SA are needed to better understand quality adolescent-caregiver relationships and their influence on sexual reproductive health. Further, in this study, we assessed the quality of caregiver-adolescent relationships from the perspective of the adolescents; however, it would have been beneficial to administer similar questions to the caregivers. Further, we allowed late entries for AGYW older than 13 years, thus making the assumption that those who were observed from age 13 years accurately represent the experiences of AGYW who would have entered the study later (>13 years). AGYW needed to be enrolled in school to participate in the main study; therefore, those who entered the study late (>13 years) might have a protective factor keeping them in school, such as having stronger relationships with their caregivers.

Our study adds to the literature focused on AGYW in rural SA by providing evidence for the relationship between quality of caregiver-adolescent relationships and STIs and pregnancy. In addition, our study uses longitudinal data, which allowed us to identify incident outcomes. Strengthening the quality of caregiver-adolescent relationships may mitigate unsafe sexual behaviors in AGYW and ultimately reduce the risk of unintended

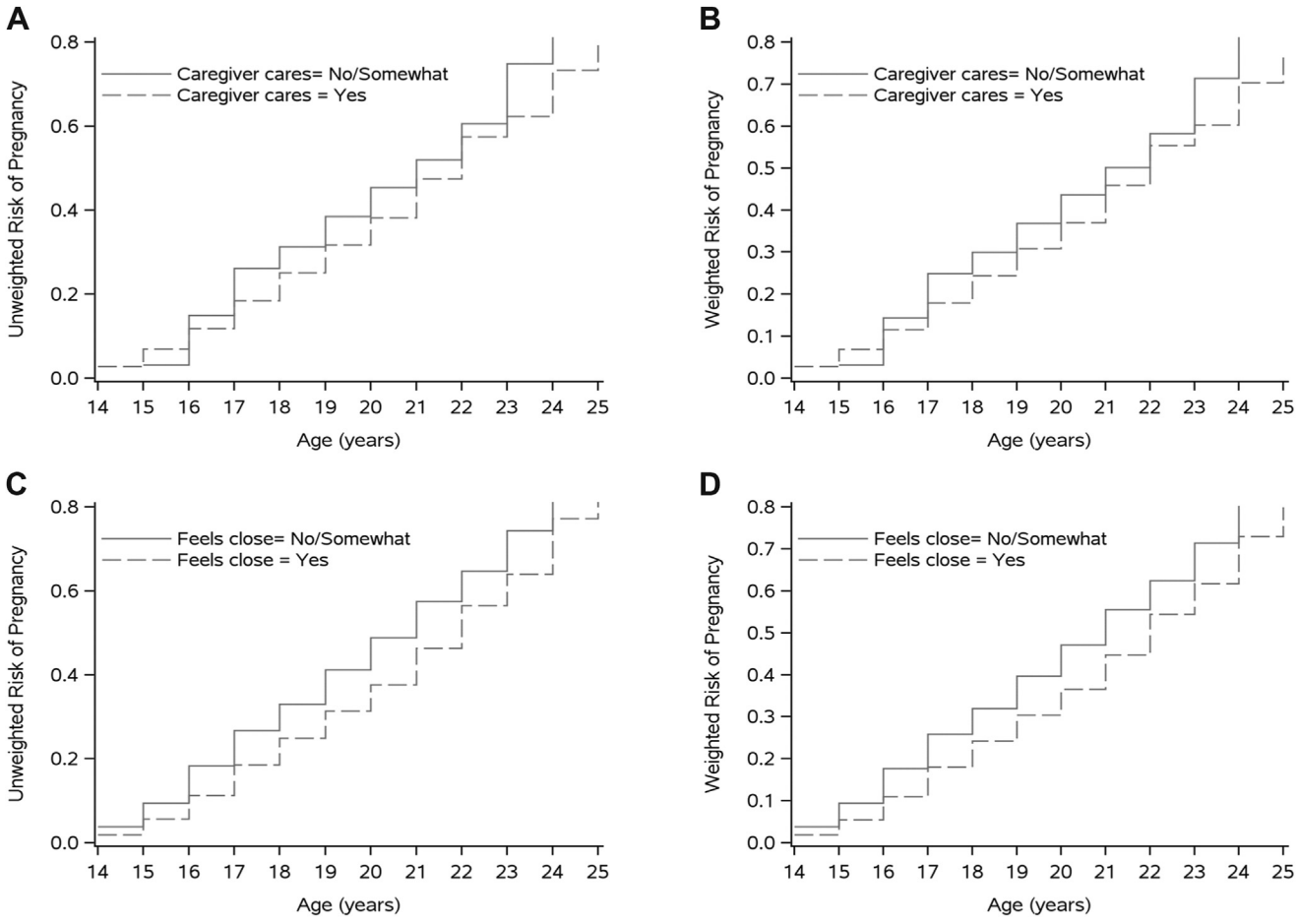


Figure 3. Survival curves for the relationship between caregiver-adolescent relationships and incidence pregnancy among young women aged 13–25 enrolled in HPTN 068 (2011–2017). A & C) Unweighted; B & D) Weighted. Adjusted curves weighted for the following covariates: age, CCT treatment arm, and orphan status. Solid lines represent participants with low-quality caregiver-adolescent relationships (no/somewhat). Dashed lines represent individuals with high-quality caregiver-adolescent relationship (yes).

adolescent pregnancy and/or HIV/HSV-2. We urge further research to assess if the association between quality caregiver-adolescent relationships, STIs, and pregnancy risk is mediated by sexual risk behaviors. Family-centered interventions should be promoted in order to build positive quality of caregiver-adolescent relationships as a strategy to reduce AGYW's STI risk and unplanned adolescent pregnancies. Additionally, we recommend interventions geared toward developing support systems for adolescents, especially orphans, to address the needs of adolescents. Moreover, interventions promoting long-term contraceptive methods and the use of HIV prevention strategies, such as pre-exposure prophylaxis, would be beneficial in reducing unintended pregnancies and the risk of STIs.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jadohealth.2024.08.015.

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