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Depression and incident HIV in adolescent girls and young women in HPTN 068: Targets for prevention and mediating factors

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Running head: Depression and incident HIV in South Africa

Abstract

The human immunodeficiency virus (HIV) epidemic among adolescent girls and young women (AGYW) in sub-Saharan Africa is a critical public health problem. We assessed whether depressive symptoms in AGYW were longitudinally associated with incident HIV, and identified potential social and behavioral mediators. Data came from a randomized trial of a cash transfer conditional on school attendance among AGYW (ages 13 – 21) in rural Mpumalanga Province, South Africa during 2011-2017. We estimated the relationship between depressive symptoms and cumulative HIV incidence using a linear probability model, and assessed mediation using inverse odds ratio weighting. Inference was calculated using the non-parametric bootstrap. AGYW with depressive symptoms had higher cumulative incidence of HIV compared to those without (risk difference = 3.5 [95% CI 0.1, 7.0]). The strongest individual mediators of this association were parental monitoring and involvement (indirect effect = 1.6 [95% CI 0.0, 3.3]) and reporting a partner would hit her if she asked him to wear a condom (indirect effect = 1.5 [95% CI -0.3, 3.3]). All mediators jointly explained two-thirds (indirect effect = 2.4 [95% CI 0.2, 4.5]) of the association between depressive symptoms and HIV incidence. Interventions addressing mental health may reduce risk of acquiring HIV among AGYW.

Keywords: depression; HIV/AIDS; adolescent health; South Africa

Every hour, 30 adolescents are infected with the human immunodeficiency virus (HIV) (1). In 2016, the global number of adolescents aged 10-19 living with HIV rose to 2.1 million, a 30% increase since 2005 (1). Three in four new HIV infections among adolescents occur in sub-Saharan Africa (1), and adolescent girls are especially burdened. The ratio of adolescent girl to boy incident HIV infection in sub-Saharan Africa was almost 3:1 in 2017 (2). Understanding risk factors during adolescence *before* infection is thus crucial to inform prevention strategies.

The most common method of HIV transmission worldwide, at almost 70% of infections, is unprotected heterosexual intercourse (3). Therefore, age at sexual debut, choice of partner, and risky sexual behavior are key targets for prevention (4). However, given limited success in reducing HIV incidence, there is increasing recognition of the critical need to address upstream factors that shape risky behaviors (5–8).

Long standing evidence demonstrates a link between depression and HIV in sub-Saharan Africa (9,10). Depression is known to influence treatment adherence and mortality among HIV-infected individuals (11,12). Furthermore, a high prevalence of depressive disorders has been reported at the time of HIV testing (13) and among HIV-infected individuals in South Africa (14–16). It is understood that a diagnosis of HIV can contribute to depression (17), given that it is a life-threatening illness, requiring lifelong management and medication. The stigma of HIV likely contributes further to depression (18) and concerns about losing a job, a partnership or, in the case of pregnancy, the prospect of the infant acquiring HIV, add more stress (19).

However, the possibility of depression as a risk factor for HIV incidence in sub-Saharan Africa has not been examined to date. Depressive symptoms have been linked to increased risk of HIV incidence among men who have sex with men in the United States (20,21), but the relationship has not previously been tested among adolescent girls and young women (AGYW) in sub-Saharan Africa, though a number of plausible pathways exist. Depressive symptoms among young South African

women are associated with increased alcohol use and risky sexual behaviors (22–25), both considered to be risk factors for HIV (3,26,27). The association between depression and risky sexual behaviors may be related to sexual abuse as child or sexual assault as an adolescent/adult (28). Furthermore, depression may lead to use of sex as a coping mechanism to regulate negative emotions, may increase a young woman's attempt to please her partners (4,29), and may contribute to a lack of efficacy or power in sexual relationships (30–32). Depressive symptoms are also associated with reduced educational attainment (33), another known risk factor for HIV in this population (26,27,34), and limited involvement or engagement in community life (35). Finally, depression in adolescence can be associated with poor relationships with parents and can reduce parental closeness or involvement (36–38), which may in turn put girls at greater risk due to lower parental monitoring and advice.

Existing evidence linking depression to risky sexual behavior and HIV infection in sub-Saharan Africa relies on cross sectional studies that leave the direction of causality unclear (i.e., is depression a cause or consequence of risky sexual behavior/HIV?) (9,10,14,17,39–41). In the current study, we utilised unique longitudinal data to test the hypothesis that depressive symptoms in early adolescence are associated with incident HIV infection. Furthermore, we investigated whether a range of social and behavioral factors mediated the relationship between depressive symptoms and incident HIV. This study was conducted using the HIV Prevention Trials Network (HPTN) 068 cohort, a longitudinal study of AGYW in South Africa. We hypothesized that depressive symptoms in adolescence would increase HIV incidence, and this would be explained, at least in part, by behavioral mediators. As depression is common and potentially modifiable in low and middle-income countries (42), it represents a promising prevention target.

METHODS

Participants

This cohort of AGYW was established in 2012 as part of an National Institutes of Health-funded randomized controlled trial (HPTN 068) to estimate the effects of cash transfers conditional on school attendance on HIV incidence among adolescent girls in rural Mpumalanga Province, South Africa (26). Participants included 2,533 women in grades 8-11 (aged 13-21) at baseline. Eligibility criteria required the girls to be unmarried, not pregnant at enrolment, and to be able to read. They and their parent/guardian were also required to be able to open a bank account. All households with eligible AGYW in the study area were recruited; only 7% did not participate due to either parent/guardian or participant refusal (43). The study did not exclude girls who tested positive for HIV infection at baseline in order to avoid undesired disclosure of HIV status. Additional details on the study recruitment and enrolment have been previously published (26,43). Participants were followed annually for up to four years, with additional graduation and post-intervention follow-up visits that resulted in follow-up duration of up to six years. Retention during the study period was approximately 91% (26). Participants completed detailed surveys about their economic and health behaviors, attitudes regarding social norms, and life experiences, and provided blood samples to test for HIV each year. Surveys about household composition and wealth were also undertaken with the participant's head of household, providing rich longitudinal cohort data with HIV incidence at multiple time points throughout adolescence.

Institutional Review Board approval for this study was obtained from the University of North Carolina at Chapel Hill, the University of the Witwatersrand Human Research Ethics Committee, and the Mpumalanga Province Health Research and Ethics Committee. Approval for analytic work was also obtained by the University of California, Berkeley, and the University of California, San Francisco.

Exposure definition

To assess depressive symptoms, we used a 10-item short form of the Children's Depression Inventory scale (44) administered at the baseline visit. The reduced scale has comparable results with the full scale and has previously been used in South Africa (45–47); the full scale has been

validated in sub-Saharan Africa (48). Each question had three levels and, following standard practice, we coded the most positive response as 0, the middle response as 1, and the most negative response as 2. We summed the items over the 10 questions and we dichotomized the index at 7, which is the prorated equivalent of the recommended cut off at 19 from the full 27-item Children's Depression Inventory, which is used to identify adolescents with depressive disorders in non-clinical samples (44,45). In a validation study of the short-form Children's Depression Inventory in Rwanda, the sensitivity and specificity were 0.64 and 0.97, respectively, for the cut-off value of 7 (48).

Outcome definition

HIV status was determined at each follow-up visit by administering two parallel rapid HIV tests (the Determine HIV-1/2 test [Alere Medical Co, Matsudo-shi, Chiba, Japan] and the US Food and Drug Administration (FDA)-cleared Uni-gold Recombigen HIV test [Trinity Biotech, Bray, County Wicklow, Ireland]). If one or both tests were reactive or positive, confirmatory HIV testing was done with the FDA-cleared GS HIV-1 western blot assay (Bio-Rad Laboratories Inc, Redmond, WA, USA). A detailed description of study visit and laboratory procedures are published elsewhere (26). Cumulative incidence of HIV was evaluated from the second through the fifth follow-up visits, which spanned a period of up to six years.

Mediator definitions

We examined the following possible mediators, assessed at the first follow-up visit, which was approximately a year after the measurement of depressive symptoms. They included health and sexual behaviors, indicators of relationship power, and family or social involvement. Health and sexual behaviors included alcohol use more than once a month, number of partners in the past 12 months, unprotected sex in the past 3 months, and purchased or received birth control or condoms in the past month. Indicators of relationship power included a recent sexual partner $\geq$5 years older, engaged in transactional sex in the past 12 months, a partner who would hit her if she asked him to use a condom, a partner who would be angry if she asked him to use a condom, a partner who

would suspect she was cheating if she asked him to use a condom, low power according to the Sexual Relationship Power Scale (49), and intimate partner violence in the past 12 months. Family and social involvement mediators included having an average of > 5 days of missed school per month during the past year, attended > 80% of school days between follow-up visits, parental monitoring and involvement in girl's life (a detailed description of this measure is provided in Web Appendix 1), and the number of community organizations of which the girl was a member.

We chose these mediators based on literature that had identified these factors as behaviors that could be affected by depressive symptoms, may modify HIV risk, and could plausibly be targeted by interventions.

Analytical Plan

To establish temporal ordering between depressive symptoms, mediators and HIV, we excluded AGYW who were HIV infected at the baseline or first follow-up visit (n=113, 4.5%). We considered mediators from the first annual follow-up visit to ensure temporality between depression at the baseline visit and mediators (Figure 1). HIV incidence was included from the second to the fifth annual follow-up visits, which spanned a period of up to six years.

We controlled for baseline covariates that may have affected depressive symptoms, HIV incidence, and the mediators based on theory and prior literature. These included household food insecurity, per capita household consumption, percent of household members receiving a government grant, adverse and positive life events, orphan status, maternal and paternal educational attainment, pregnancy history, age, and trial arm. Detailed definitions of the covariates are available in Web Appendix 2.

We estimated the effect of depressive symptoms on cumulative HIV incidence using a linear probability model to estimate parameters on the additive (risk difference) scale (50,51). For the mediation analyses, we estimated natural direct and indirect effects using inverse odds-ratio

weighting and considered multiple mediators (52,53). This method uses the invariance property of the odds ratio to create weights that block the association between depression and the mediator(s), thus isolating the natural direct effect of depression (i.e., the effect that does not go through the mediator(s)). Some strengths of this approach, in contrast to other available mediation methods (54,55), are that it allows multiple mediators to be considered simultaneously and allows for interactions between depression and the mediators. The natural indirect effect, the association of depression with HIV via the mediator(s), is the difference between the total effect and the natural direct effect.

To account for covariate missingness we used multiple imputation with 30 imputed datasets (56). The non-parametric bootstrap was used to calculate 95% Wald-type confidence intervals (CI). We estimated direct and indirect effects for each mediator separately and all mediators jointly. We conducted a sensitivity analysis using inverse probability of censoring weights to assess whether loss to follow up affected our results. We also conducted a quantitative bias analysis using results on the risk ratio scale to assess how strong mediator-outcome confounding would need to be to change our results (57). A full description of this procedure is provided in Web Appendix 3.

All analyses were performed using R version 3.4 (58).

RESULTS

Main effects

There were 2,533 AGYW included in the study; of these, 118 were excluded as a result of having no information on HIV status (n=5, 0.2%) or were HIV positive at baseline or the first follow-up visit (n=113, 4.5%). This resulted in a sample size of 2,415. The prevalence of depressive symptoms and incidence of HIV varied across the baseline covariates (Table 1), but overall, 18.2% of AGYW were classified as having depressive symptoms at baseline, and the cumulative incidence of HIV after the first follow-up visit was 0.072 (Table 2). AGYW with depressive symptoms had 0.107

cumulative HIV incidence over the years of follow up, compared to 0.065 cumulative incidence among those without depressive symptoms (Table 2). After adjustment for covariates, depressive symptoms at baseline were associated with higher cumulative incidence of HIV (risk difference = 3.5 [95% CI 0.1, 7.0)] (Table 3).

Mediation

Estimates of mediation parameters between depressive symptoms and HIV are presented in Table 3. The estimated natural direct effect on the risk difference scale of depressive symptoms on incident HIV considering all mediators jointly was 1.1 (-2.1, 4.4), while the estimated natural indirect effect considering all mediators was 2.4 (0.2, 4.5), suggesting that the mediators explain about two-thirds of the absolute association between depressive symptoms and HIV when considered jointly. The remaining estimate of the natural direct effect suggests that depressive symptoms may also increase the risk of HIV through biological or other behavioral mechanisms not examined here.

The mediators that individually explained the largest portion of the association between depressive symptoms and HIV incidence were parental monitoring and involvement and reporting that a partner would hit her if she asked him to wear a condom. The next strongest mediators were missing 5 or more days of school on average per month in the past year, having unprotected sex in the past 3 months, reporting her partner would assume she was cheating or become angry if she asked him to use a condom, and experiencing intimate partner violence in the past 12 months. Having a partner 5 or more years older, engaging in transactional sex, and the number of community organizations AGYW were involved with mediated the smallest portions of the overall association. The results did not meaningfully change when we used inverse probability of censoring weights to control for differential loss to follow up (Web Table 1).

We conducted a quantitative bias analysis on the risk ratio scale for the amount of unobserved mediator-outcome confounding that could change the results, focusing on the

mediation analysis that considered all mediators jointly (Web Table 2). We found that unobserved confounding would need to be strong in order to alter our findings (Web Tables 3 and 4).

DISCUSSION

This study examined the association of depressive symptoms with HIV incidence among AGYW in South Africa, a population bearing a large burden of HIV/AIDS and the highest number of incident cases in the region hardest hit by the epidemic. We found prevalence of depressive symptoms of 18.2% in this young adolescent population, which was almost twice the prevalence recorded in a nationally-representative survey of adults in South Africa (59). Previous evidence in sub-Saharan Africa showed that HIV infection increased risk of depression (15,18,40), and depression reduced treatment adherence and survival among HIV positive individuals (10,11,41). Cross-sectional studies also suggested a co-occurrence of depression and HIV (14,39). The findings of this study suggest that having depressive symptoms in adolescence may also increase risk of HIV infection. To our knowledge, this is the first demonstration that depression is longitudinally related to HIV acquisition among AGYW in sub-Saharan Africa. The results are especially important given the high burden of depression among adolescents and point to areas for prevention strategies.

Because depression has been linked to lower condom use (30), and unprotected sex is the main route of HIV transmission in South Africa (60), we considered mediators that might connect depressive symptoms to behaviors that could influence risk of HIV. Mediators considered in this study, including alcohol use, school attendance, parental monitoring and involvement, community participation, sexual behaviors, and sexual relationship power, jointly explained about two-thirds of this association. Parental monitoring and involvement and reporting fear that a partner would hit her if she requested he use a condom were responsible for the largest estimated individual mediation effects. However, we acknowledge that these mediators represent complex behaviors whose development may have preceded and contributed to the manifestation of depressive symptoms. In this study, we were not able to disentangle all the interconnections between these

complicated emotional and social factors over time, but by measuring them at distinct visits we attempted to capture meaningful temporal connections between them and their relationships to HIV incidence.

Evidence indicates that parental monitoring and involvement can influence HIV risk. Parental involvement has been linked to reduced sexual activity and risky sexual behavior among adolescents in sub-Saharan Africa (61,62), and parental communication around sexuality and sexual risk-taking with adolescent children has been tied to improved self-efficacy and interpersonal communication about sex, especially among AGYW (36). Positive parenting has been identified as an important contributor to adolescent physical and mental health in sub-Saharan Africa (63–65), but the directional relationship between parental involvement and child mental health and behavior is less well-studied. However, evidence from the United States indicates that the relationship between parental monitoring and child behavior is bi-directional (37) and that the direction of the relationship changes as children age into adolescence (38). For example, increased parental monitoring has been associated with lower childhood depression (66), but during adolescence, child behavior can also affect parental monitoring and parenting behaviors (38). Our results suggest that lack of parental monitoring and involvement plays an important role in mediating the association of adolescent depressive symptoms with HIV incidence, such that depression leads to less involvement from parents, which then increases risk of HIV. However, it is also possible that parental monitoring and involvement earlier in a child's life influences later parental behavior, in addition to depressive symptoms and risky sexual behaviors.

Having gender-based power imbalances in sexual relationships has been tied to increased risk of acquiring HIV and other STIs in South Africa (67,68), and has also been associated with inconsistent condom use (31). Previous work has shown South African men who were physically violent toward a partner were more likely to be HIV positive, increasing HIV risk for those partners (69). Prior work has found that young HIV-infected women with low sexual relationship power are at

increased risk of depression in sub-Saharan Africa (32), and the results of this study indicate that AGYW with depressive symptoms may be more vulnerable to relationships in which they have less power or control over decision making. One of the largest estimated mediation effects was observed for AGYW reporting a partner would hit her if she requested he use a condom. Having a partner who would assume infidelity or become angry if she requested he use a condom during sex and experiencing intimate partner violence in the past 12 months also had some of the largest estimated mediation effects. These results indicate that depressive symptoms may reduce the ability of AGYW to negotiate condom use during sex and increase their risk of HIV. Depression may also be associated with choosing sexual partners who are less open to negotiation or who are more likely to commit intimate partner violence.

In South Africa, children's mental health has been linked to school attendance and other educational outcomes (70). Furthermore, remaining in school and educational attainment during adolescence are protective against for HIV incidence among AGYW in South Africa (34). School attendance was inversely related to both depressive symptoms and HIV incidence in this cohort, and missing more than 5 days of school on average per month was among the largest estimated individual mediation effects.

There were some limitations to this work. Although we were able to control for a large set of social, economic, and demographic covariates, residual confounding is always a concern in observational studies. Our total effect estimates assume there is no unmeasured confounding between the exposure and outcome. Additional assumptions for causal inference are positivity, consistency, and the stable unit treatment value assumption. Furthermore, our measurements of depressive symptoms and social and behavioral factors were self-reported. This could introduce same-source bias, in which measurement error is correlated because, for example, depressive symptoms could affect a young woman's perception of parental monitoring or recall of past behavior. This is a limitation for the measurement of our exposure and mediators, but not the

outcome, as HIV status was determined by blood test. In addition, while our sample included a large cohort of AGYW, we nonetheless had limited power to detect natural direct and indirect effects, particularly for a rare outcome. Detection of mediation effects tend to be underpowered with sample sizes designed for main effects only (71). Furthermore, when estimating natural direct and natural indirect effects there are several assumptions that need to be considered beyond those in a total effect analysis. In particular, in addition to concern about confounding between the exposure and outcome, there must also be no confounding of the exposure and the mediator, and the mediator and the outcome. We conducted a quantitative bias analysis to assess how strong unmeasured mediator-outcome confounding would need to be to invalidate our results and found strong confounding would be necessary, increasing our confidence in the findings.

Our results suggest that interventions that improve mental health among AGYW may also improve HIV prevention efforts. They suggest the importance of incorporating family support and educational or empowerment initiatives around condom use, negotiating condom use with respect to gender-based sexual relationship power, and addressing male norms around condom use in prevention programming. While depression is a modifiable public health problem, access to mental healthcare services in South Africa is currently quite poor. Nevertheless, relatively low-cost interventions, delivered by lay workers in the community, have been shown to be effective in low- and middle-income countries, such as the rural South African context (72–74). Such interventions in adolescence, targeting depression as well as parental relationships and addressing social and structural factors that encourage women to participate in sexual relationships with gender-based power dynamics, could help prevent young women from acquiring HIV.

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Abbreviations:

HIV Prevention Trials Network (HPTN)

Adolescent girls and young women (AGYW)

Human immunodeficiency virus (HIV)

Confidence interval (CI)

References

1. Children and AIDS: Statistical Update [Internet]. UNICEF; 2017 [cited 2018 Aug 25]. Available from: https://data.unicef.org/wp-content/uploads/2017/11/HIVAIDS-Statistical-Update-2017.pdf

2. Adolescent HIV prevention [Internet]. UNICEF; 2018 [cited 2018 Aug 25]. Available from: https://data.unicef.org/topic/hivaids/adolescents-young-people/

3. Shaw GM, Hunter E. HIV transmission. Cold Spring Harb Perspect Med. 2012 Nov 1;2(11).

4. Lara LAS, Abdo CHN. Age at Time of Initial Sexual Intercourse and Health of Adolescent Girls. J Pediatr Adolesc Gynecol. 2016 Oct;29(5):417–23.

5. Harrison A, Colvin CJ, Kuo C, Swartz A, Lurie M. Sustained High HIV Incidence in Young Women in Southern Africa: Social, Behavioral, and Structural Factors and Emerging Intervention Approaches. Curr HIV/AIDS Rep. 2015 Jun 1;12(2):207–15.

6. Ramjee G, Daniels B. Women and HIV in Sub-Saharan Africa. AIDS Res Ther. 2013 Dec 13;10(1):30.

7. UNAIDS. On the Fast-Track to end AIDS by 2030: Focus on location and population [Internet]. 2015 [cited 2018 Aug 25]. Available from: http://www.unaids.org/en/resources/documents/2015/FocusLocationPopulation

8. UNAIDS. Prevention Gap Report [Internet]. 2016 [cited 2018 Aug 25]. Available from: http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf

9. Bernard C, Dabis F, Rekeneire N de. Prevalence and factors associated with depression in people living with HIV in sub-Saharan Africa: A systematic review and meta-analysis. PLOS ONE. 2017 Aug 4;12(8):e0181960.

10. Abas M, Ali G-C, Nakimuli-Mpungu E, Chibanda D. Depression in people living with HIV in sub-Saharan Africa: time to act. Trop Med Int Health. 2014 Dec 1;19(12):1392–6.

11. Nakimuli-Mpungu E, Bass JK, Alexandre P, Mills EJ, Musisi S, Ram M, et al. Depression, Alcohol Use and Adherence to Antiretroviral Therapy in Sub-Saharan Africa: A Systematic Review. AIDS Behav. 2012 Nov 1;16(8):2101–18.

12. Antelman G, Kaaya S, Wei R, Mbwambo J, Msamanga GI, Fawzi WW, et al. Depressive Symptoms Increase Risk of HIV Disease Progression and Mortality Among Women in Tanzania. JAIDS J Acquir Immune Defic Syndr. 2007 Apr 1;44(4):470.

13. Kagee A, Saal W, De Villiers L, Sefatsa M, Bantjes J. The prevalence of common mental disorders among South Africans seeking HIV testing. AIDS Behav. 2017 Jun;21(6):1511–7.

14. Myer L, Smit J, Roux LL, Parker S, Stein DJ, Seedat S. Common Mental Disorders among HIV-Infected Individuals in South Africa: Prevalence, Predictors, and Validation of Brief Psychiatric Rating Scales. AIDS Patient Care STDs. 2008 Feb 1;22(2):147–58.

15. Olley BO, Gxamza F, Seedat S, Theron H, Taljaard J, Reid E, et al. Psychopathology and coping in recently diagnosed HIV/AIDS patients--the role of gender. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2003 Dec;93(12):928–31.

16. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012 [Internet]. HSRC Press; 2014 [cited 2018 Sep 7]. Available from: http://repository.hsrc.ac.za/handle/20.500.11910/2490

17. Simoni JM, Safren SA, Manhart LE, Lyda K, Grossman CI, Rao D, et al. Challenges in Addressing Depression in HIV Research: Assessment, Cultural Context, and Methods. AIDS Behav. 2011 Feb 1;15(2):376–88.

18. Simbayi LC, Kalichman S, Strebel A, Cloete A, Henda N, Mqeketo A. Internalized stigma, discrimination, and depression among men and women living with HIV/AIDS in Cape Town, South Africa. Soc Sci Med. 2007 May 1;64(9):1823–31.

19. Brittain K, Mellins CA, Phillips T, Zerbe A, Abrams EJ, Myer L, et al. Social Support, Stigma and Antenatal Depression Among HIV-Infected Pregnant Women in South Africa. AIDS Behav. 2017 Jan 1;21(1):274–82.

20. Koblin BA, Husnik MJ, Colfax G, Huang Y, Madison M, Mayer K, et al. Risk factors for HIV infection among men who have sex with men. AIDS. 2006 Mar 21;20(5):731.

21. MIMIAGA MJ, O'CLEIRIGH C, BIELLO KB, ROBERTSON AM, SAFREN SA, COATES TJ, et al. The effect of psychosocial syndemic production on 4-year HIV incidence and risk behavior in a large cohort of sexually active men who have sex with men. J Acquir Immune Defic Syndr 1999. 2015 Mar 1;68(3):329–36.

22. Abler LA, Sikkema KJ, Watt MH, Eaton LA, Choi KW, Kalichman SC, et al. Longitudinal cohort study of depression, post-traumatic stress, and alcohol use in South African women who attend alcohol serving venues. BMC Psychiatry. 2014 Aug 6;14:224.

23. Davis EC, Rotheram-Borus MJ, Weichle TW, Rezai R, Tomlinson M. Patterns of Alcohol Abuse, Depression, and Intimate Partner Violence Among Township Mothers in South Africa Over 5 Years. AIDS Behav. 2017 Nov 1;21(2):174–82.

24. Onah MN, Field S, van Heyningen T, Honikman S. Predictors of alcohol and other drug use among pregnant women in a peri-urban South African setting. Int J Ment Health Syst. 2016 May 4;10:38.

25. Parry CDH, Tomlinson M, Bryant K, Rotherham-Borus MJ. Fresh Perspectives on the Alcohol and HIV Nexus: A Call for Action in an Era of Increased Opportunities and Challenges. AIDS Behav. 2017 Nov 1;21(2):121–5.

26. Pettifor A, MacPhail C, Hughes JP, Selin A, Wang J, Gómez-Olivé FX, et al. The effect of a conditional cash transfer on HIV incidence in young women in rural South Africa (HPTN 068): a phase 3, randomised controlled trial. Lancet Glob Health. 2016 Dec 1;4(12):e978–88.

27. McKinnon LR, Karim QA. Factors Driving the HIV Epidemic in Southern Africa. Curr HIV/AIDS Rep. 2016 Jun 1;13(3):158–69.

28. Tyler KA. Social and emotional outcomes of childhood sexual abuse: A review of recent research. Aggress Violent Behav. 2002 Nov 1;7(6):567–89.

29. Littleton HL, Grills AE, Drum KB. Predicting risky sexual behavior in emerging adulthood: examination of a moderated mediation model among child sexual abuse and adult sexual assault victims. Violence Vict. 2014;29(6):981–98.

30. Nduna M, Jewkes RK, Dunkle KL, Shai NPJ, Colman I. Associations between depressive symptoms, sexual behaviour and relationship characteristics: a prospective cohort study of young women and men in the Eastern Cape, South Africa. J Int AIDS Soc. 2010 Nov 15;13:44.

31. Pettifor AE, Measham DM, Rees HV, Padian NS. Sexual Power and HIV Risk, South Africa1. Emerg Infect Dis. 2004 Nov;10(11):1996–2004.

32. Hatcher AM, Tsai AC, Kumbakumba E, Dworkin SL, Hunt PW, Martin JN, et al. Sexual Relationship Power and Depression among HIV-Infected Women in Rural Uganda. PLOS ONE. 2012 Dec 26;7(12):e49821.

33. Hamad R, Fernald LCH, Karlan DS, Zinman J. Social and economic correlates of depressive symptoms and perceived stress in South African adults. J Epidemiol Community Health. 2008 Jun 1;62(6):538–44.

34. Pettifor AE, Levandowski BA, MacPhail C, Padian NS, Cohen MS, Rees HV. Keep them in school: the importance of education as a protective factor against HIV infection among young South African women. Int J Epidemiol. 2008 Dec 1;37(6):1266–73.

35. Tomita A, Burns JK. A multilevel analysis of association between neighborhood social capital and depression: Evidence from the first South African National Income Dynamics Study. J Affect Disord. 2013 Jan 10;144(1):101–5.

36. Bastien S, Kajula L, Muhwezi W. A review of studies of parent-child communication about sexuality and HIV/AIDS in sub-Saharan Africa. Reprod Health. 2011 Sep 24;8:25.

37. Pardini DA. Novel Insights into Longstanding Theories of Bidirectional Parent–Child Influences: Introduction to the Special Section. J Abnorm Child Psychol. 2008 Jul 1;36(5):627–31.

38. Bradley RH, Corwyn R. From parent to child to parent…: paths in and out of problem behavior. J Abnorm Child Psychol. 2013 May;41(4):515–29.

39. Spies G, Seedat S. Depression and resilience in women with HIV and early life stress: does trauma play a mediating role? A cross-sectional study. BMJ Open. 2014 Feb 1;4(2):e004200.

40. Olley BO, Seedat S, Stein DJ. Persistence of psychiatric disorders in a cohort of HIV/AIDS patients in South Africa: a 6-month follow-up study. J Psychosom Res. 2006 Oct;61(4):479–84.

41. Rabkin JG. HIV and depression: 2008 review and update. Curr HIV/AIDS Rep. 2008 Nov;5(4):163–71.

42. Cuijpers P, Karyotaki E, Reijnders M, Purgato M, Barbui C. Psychotherapies for depression in low- and middle-income countries: a meta-analysis. World Psychiatry Off J World Psychiatr Assoc WPA. 2018 Feb;17(1):90–101.

43. Pettifor A, MacPhail C, Selin A, Gómez-Olivé FX, Rosenberg M, Wagner RG, et al. HPTN 068: A Randomized Control Trial of a Conditional Cash Transfer to Reduce HIV Infection in Young Women in South Africa—Study Design and Baseline Results. AIDS Behav. 2016 Sep;20(9):1863–82.

44. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull. 1985;21(4):995–8.

45. Cluver L, Gardner F, Operario D. Psychological distress amongst AIDS-orphaned children in urban South Africa. J Child Psychol Psychiatry. 2007 Aug 1;48(8):755–63.

46. Sharer M, Cluver L, Shields J. Mental health of youth orphaned due to AIDS in South Africa: biological and supportive links to caregivers. Vulnerable Child Youth Stud. 2015 Apr 3;10(2):141–52.

47. Cluver LD, Orkin M, Gardner F, Boyes ME. Persisting mental health problems among AIDS-orphaned children in South Africa. J Child Psychol Psychiatry. 2012 Apr 1;53(4):363–70.

48. Binagwaho A, Fawzi MCS, Agbonyitor M, Nsanzimana S, Karema C, Remera E, et al. Validating the Children's Depression Inventory in the context of Rwanda. BMC Pediatr [Internet]. 2016 Feb 22 [cited 2018 Mar 16];16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4762156/

49. Pulerwitz J, Gortmaker SL, DeJong W. Measuring Sexual Relationship Power in HIV/STD Research. Sex Roles. 2000 Apr 1;42(7–8):637–60.

50. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math Model. 1986 Jan 1;7(9):1393–512.

51. Laan MJ van der, Robins JM. Unified Methods for Censored Longitudinal Data and Causality. New York, New York: Springer Science & Business Media; 2003. 424 p.

52. Tchetgen Tchetgen EJ. Inverse odds ratio-weighted estimation for causal mediation analysis. Stat Med. 2013 Nov 20;32(26):4567–80.

53. Nguyen QC, Osypuk TL, Schmidt NM, Glymour MM, Tchetgen Tchetgen EJ. Practical Guidance for Conducting Mediation Analysis With Multiple Mediators Using Inverse Odds Ratio Weighting. Am J Epidemiol. 2015 Mar 1;181(5):349–56.

54. Valeri L, Vanderweele TJ. Mediation Analysis Allowing for Exposure–mediator Interactions and Causal Interpretation: Theoretical Assumptions and Implementation With Sas and Spss Macros. Psychol Methods. 2013 Jun 1;18(2):137–50.

55. Petersen ML, Sinisi SE, van der Laan MJ. Estimation of Direct Causal Effects. Epidemiology. 2006 May;17(3):276.

56. Rubin DB. Multiple Imputation for Nonresponse in Surveys. Hoboken, New Jersey: John Wiley & Sons; 2004. 326 p.

57. Ding P, Vanderweele TJ. Sharp sensitivity bounds for mediation under unmeasured mediator-outcome confounding. Biometrika. 2016 Jun 1;103(2):483–90.

58. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2017. Available from: https://www.R-project.org/

59. Tomlinson M, Grimsrud AT, Stein DJ, Williams DR, Myer L. The epidemiology of major depression in South Africa: Results from the South African Stress and Health study. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2009 May;99(5 Pt 2):367–73.

60. Sarkar DNN. Barriers to condom use. Eur J Contracept Reprod Health Care. 2008 Jan 1;13(2):114–22.

61. Biddlecom A, Awusabo-Asare K, Bankole A. Role of Parents in Adolescent Sexual Activity and Contraceptive Use in Four African Countries. Int Perspect Sex Reprod Health. 2009;35(2):72–81.

62. Puffer ES, Green EP, Sikkema KJ, Broverman SA, Ogwang-Odhiambo RA, Pian J. A church-based intervention for families to promote mental health and prevent HIV among adolescents in rural Kenya: Results of a randomized trial. J Consult Clin Psychol. 2016 Jun;84(6):511–25.

63. Lachman J, Cluver L, Boyes M, Kuo C, Casale M. Positive parenting for positive parents: HIV/AIDS, poverty, caregiver depression, child behavior and parenting in South Africa. AIDS Care. 2014 Mar;26(3):304–13.

64. Meinck F, Cluver LD, Orkin FM, Kuo C, Sharma AD, Hensels IS, et al. Pathways From Family Disadvantage via Abusive Parenting and Caregiver Mental Health to Adolescent Health Risks in South Africa. J Adolesc Health Off Publ Soc Adolesc Med. 2017 Jan;60(1):57–64.

65. Sherr L, Macedo A, Cluver LD, Meinck F, Skeen S, Hensels IS, et al. Parenting, the other oldest profession in the world - a cross-sectional study of parenting and child outcomes in South Africa and Malawi. Health Psychol Behav Med. 2017;5(1):145–65.

66. Murphy DA, Marelich WD, Herbeck DM, Payne DL. Family Routines and Parental Monitoring as Protective Factors Among Early and Middle Adolescents Affected by Maternal HIV/AIDS. Child Dev. 2009;80(6):1676–91.

67. Jewkes RK, Dunkle K, Nduna M, Shai N. Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. The Lancet. 2010 Jul 3;376(9734):41–8.

68. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntryre JA, Harlow SD. Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. The Lancet. 2004 May 1;363(9419):1415–21.

69. Jewkes R, Sikweyiya Y, Morrell R, Dunkle K. The Relationship between Intimate Partner Violence, Rape and HIV amongst South African Men: A Cross-Sectional Study. PLoS ONE [Internet]. 2011 Sep 14 [cited 2019 Jun 10];6(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3173408/

70. Orkin M, Boyes ME, Cluver LD, Zhang Y. Pathways to poor educational outcomes for HIV/AIDS-affected youth in South Africa. AIDS Care. 2014 Mar 4;26(3):343–50.

71. Kenny DA, Judd CM. Power Anomalies in Testing Mediation. Psychol Sci. 2014 Feb 1;25(2):334–9.

72. Hamdani SU, Ahmed Z, Sijbrandij M, Nazir H, Masood A, Akhtar P, et al. Problem Management Plus (PM+) in the management of common mental disorders in a specialized mental healthcare facility in Pakistan; study protocol for a randomized controlled trial. Int J Ment Health Syst. 2017 Jun 8;11(1):40.

73. Patel V, Weiss HA, Chowdhary N, Naik S, Pednekar S, Chatterjee S, et al. Lay health worker led intervention for depressive and anxiety disorders in India: impact on clinical and disability outcomes over 12 months. Br J Psychiatry J Ment Sci. 2011 Dec;199(6):459–66.

74. Turner EL, Sikander S, Bangash O, Zaidi A, Bates L, Gallis J, et al. The effectiveness of the peer-delivered Thinking Healthy PLUS (THPP+) Program for maternal depression and child socioemotional development in Pakistan: study protocol for a randomized controlled trial. Trials [Internet]. 2016 Sep 8 [cited 2018 Sep 7];17(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5017048/

Table 1. Descriptive statistics for baseline covariates, severe depressive symptoms, and HIV incidence for the HPTN 068 cohort during 2011-2017, Mpumalanga, South Africa

Covariates	N	Depressive Symptoms (%)	HIV positive (%)
Orphaning status[a]			
Single orphan (1 parent deceased)	567	19.5	8.1
Double orphan (2 parents deceased)	105	20.8	10.2
Household economic status			
Food insecure[b]			
No	2,022	17.9	7.7
Yes	393	19.5	10.1
Total household per capita expenditure deciles[b]			
1	242	16.4	9.6
2	235	17.0	8.6
3	240	21.5	7.6
4	244	15.5	6.6
5	246	20.9	7.3
6	242	19.0	8.8
7	241	20.7	12.6
8	239	17.4	8.4
9	240	18.0	7.6
10	246	15.4	3.7
More than 25% of household receiving a government grant[b]			
No	560	14.8	7.0
Yes	1,855	19.2	8.4
Maternal education[c]			
No school	443	18.7	8.0
Some primary	480	21.8	9.4
Completed primary	111	23.0	7.1
Some high school	716	17.9	9.9
Completed high school	570	16.0	5.6
University or technikon	94	7.1	3.0
Paternal education			
No school	499	17.9	9.4
Some primary	433	21.3	9.2
Completed primary	125	20.7	8.5
Some high school	553	17.6	8.4
Completed high school	687	17.3	7.0
University or technikon	118	13.2	2.1

Any negative life event[b]			
No	1,772	17.8	8.2
Yes	643	19.3	7.8
Any positive life event[b]			
No	1,965	18.4	7.8
Yes	450	17.1	9.3
Demographics			
Ever been pregnant			
No	2,211	16.6	7.5
Yes	204	35.4	15.0
Age at baseline			
13	269	15.2	6.3
14	482	13.5	5.5
15	527	18.1	7.5
16	505	16.1	8.7
17	358	18.6	10.0
18	163	34.7	11.4
19	79	31.4	11.9
20+	32	28.2	19.2
Trial arm			
Control	1212	17.3	8.3
Intervention	1203	19.1	7.9

HTPN is the HIV Prevention Trials Network, HIV is the Human Immunodeficiency Virus.

[a] This category does not sum to the total because it does not include participants for whom both parents are still living.

[b] Details on measurement and definitions of these variables are available in Web Appendix 2.

[c] The total for this category does not sum to the total due to rounding across multiply imputed data sets.

Table 2. HIV incidence by exposure status and year of follow-up for the HPTN 068 cohort from 2011-2017, Mpumalanga, South Africa

	Total				No depressive symptoms				Depressive symptoms			
Years of follow up	Number of HIV cases	Observed person-years at risk[a]	Cases/person-years	Cumulative incidence[b]	Number of HIV cases	Observed person-years at risk	Cases/person-years	Cumulative incidence[b]	Number of HIV cases	Observed person-years at risk	Cases/person-years	Cumulative incidence[b]
2	22	2329	0.009	0.009	16	1906	0.008	0.008	6	423	0.014	0.014
3	43	2136	0.020	0.027	27	1747	0.015	0.022	16	389	0.041	0.050
4	42	1913	0.022	0.044	34	1570	0.022	0.039	8	343	0.023	0.068
5	36	1336	0.027	0.059	26	1093	0.024	0.052	10	243	0.041	0.091
6	32	671	0.048	0.072	25	547	0.046	0.065	7	124	0.056	0.107
Total	175	8385	0.021	0.072	128	6863	0.019	0.065	47	1522	0.031	0.107

HTPN is the HIV Prevention Trials Network, HIV is the Human Immunodeficiency Virus.

[a] The total observed person-years at risk at the second year of follow-up is N=2329 rather than the total N=2415 because 86 were lost to follow-up before the second year.

[b] Cumulative incidence includes all cases up through the relevant year of follow up.

Table 3. Estimated total effects of depressive symptoms on HIV incidence and estimated natural direct and indirect effects with several mediators in the HPTN 068 cohort during 2011-2017, Mpumalanga, South Africa

Mediators	Natural direct effect	95% CI	Natural indirect effect	95% CI
Health and school behaviors				
Alcohol use in the past month	2.40	-1.0, 5.8	1.10	-0.4, 2.7
More than 5 days of missed school on average per month in the past year	2.10	-1.3, 5.4	1.40	-0.2, 3.1
High school attendance between rounds (>80%)	2.30	-1.1, 5.7	1.20	-0.4, 2.8
Parental monitoring and involvement	1.90	-1.3, 5.0	1.60	0.0, 3.3
Community engagement (number of community organizations involved in)	2.60	-0.9, 6.1	0.90	-0.7, 2.5
Sexual behaviors and self-efficacy				
Had a recent sexual partner 5 years or more older than oneself	2.50	-0.9, 5.9	1.00	-0.5, 2.6
Number of partners in the past 12 months (0, 1, 2 or more)	2.30	-1.1, 5.7	1.20	-0.4, 2.9
Had unprotected sex in the past 3 months	2.20	-1.2, 5.5	1.40	-0.3, 3.0
Engaged in transactional sex in the past 12 months	2.50	-1.0, 6.0	1.00	-0.6, 2.6
Sexual relationship power: partner would hit me if I requested he use a condom	2.00	-1.3, 5.2	1.50	-0.3, 3.3
Sexual relationship power: partner would be angry if I requested he use a condom	2.20	-1.1, 5.6	1.30	-0.4, 3.0
Sexual relationship power: partner would assume I'm cheating if I ask him to use a condom	2.20	-1.2, 5.5	1.40	-0.3, 3.0
Low power according to sexual relationship power scale	2.30	-1.0, 5.6	1.20	-0.4, 2.9
Experienced intimate partner violence in the past 12 months	2.20	-1.1, 5.5	1.30	-0.3, 2.8
Purchased birth control or condoms	2.40	-1.0, 5.7	1.20	-0.4, 2.7
All mediators	1.10	-2.1, 4.4	2.40	0.2, 4.5

HTPN is the HIV Prevention Trials Network, HIV is the Human Immunodeficiency Virus, CI is confidence interval.

The estimated total effect risk difference and 95% confidence interval was 3.5 (0.1, 7.0).

Estimates are adjusted for household consumption, food insecurity, any negative or positive events, the percent of the household receiving a government grant, orphaning status, maternal and paternal educational attainment, pregnancy history, age at baseline, and arm of the trial.

Figure 1. Timeline of depressive symptoms measurement, mediator assessment, and HIV testing over the course of the study.