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Variations in HIV Risk by Young Women's Age and Partner Age Disparity in Rural South Africa (HPTN 068)

Hillary M. Topazian, MSc,[a] Marie C. D. Stoner, PhD,[b] Jessie K. Edwards, PhD,[a] Kathleen Kahn, PhD,[c,d,e] Francesc Xavier Gómez-Olivé, PhD,[c,d] Rhian Twine, PhD,[c] James P. Hughes, PhD,[f,g] Myron S. Cohen, MD,[h] and Audrey Pettifor, PhD[a,b,c]

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Background: Nearly all population-level research showing positive associations between age-disparate partnerships and HIV acquisition among adolescent girls and young women (AGYW) has classified age disparity as ≥5 or ≥10 years. We describe variations in 1-year risk of HIV infection after exposure to sexual partner(s) of continuous age disparities.

Methods: Longitudinal data from the HPTN 068 randomized trial in South Africa were used to estimate 1-year risk of HIV infection at various age pairings. The parametric g-formula was used to estimate risk at up to 5 annual time points, stratified by maximum partner age difference, maximum partner age, and AGYW age.

Results: AGYW reported an older partner in 86% of 5351 age pairings. The 1-year risk of HIV infection rapidly increased with maximum partner age difference among girls ages 13–14 years, from 0·01 with a same-age partner, to 0·21 with a partner 10 years older, and 0·24 with a partner 15 years older. A gradual increase occurred among AGYW ages 15–16 years, up to 0·13 with a partner 15 years older, and 0·09 among AGYW 17–18 years with partners 8–11 years older. Risk of HIV infection among AGYW ages 19–21 years remained relatively constant across maximum partner age differences.

Conclusions: Age differences between AGYW and their sexual partners have a greater effect on HIV-risk infection in younger compared with older AGYW. Considering both the age of an AGYW and her sexual partners provides granular insight into identifying key groups for HIV transmission prevention efforts.

Key Words: adolescent girls and young women, South Africa, HIV, age-disparity

(*J Acquir Immune Defic Syndr* 2020;83:350–356)

INTRODUCTION

High HIV prevalence remains a serious problem among young women in South Africa. Population-based data from 2017 report a prevalence of 5·8% among female adolescents 15–19 years of age, increasing rapidly to 15·6% among young women 20–24 years, and to 27·5% among those 25–29 years.[1] Males have a much lower HIV prevalence than females within the same age group (4·7%, 4·8%, 12·4%, respectively).[1] Differences in HIV prevalence by gender are hypothesized to stem from adolescent girls and young women (AGYW) having sex with older men, connecting them to sexual networks with high HIV prevalence.[2] High-risk behaviors such as transactional sex and alcohol use are associated with age-disparate partnerships,[3] and biological factors also play a role in increasing risk of HIV in women.[4]

Nationally representative data from South Africa in 2009, 2012, and 2017 consistently show that a third (34%–36%) of AGYW ages 15–19 years or 16–24 years of age are at least 5 years younger than their sexual partners.[2,5] Population-level research examining the association between age-disparate partnerships and HIV acquisition has produced mixed results. Among South African women, cross-sectional

Received for publication September 26, 2019; accepted December 2, 2019.

From the [a]Department of Epidemiology, University of North Carolina, Chapel Hill, NC; [b]Carolina Population Center, University of North Carolina, Chapel Hill, NC; [c]MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [d]INDEPTH Network, Accra, Ghana; [e]Epidemiology and Global Health Unit, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [f]Department of Biostatistics, University of Washington, Seattle, WA; [g]Fred Hutchinson Cancer Research Center, Seattle, WA; and [h]Institute for Global Health and Infectious Diseases, University of North Carolina School of Medicine, Chapel Hill, NC.

Supported by award numbers UM1 AI068619 (HPTN Leadership and Operations Center), UM1AI068617 (HPTN Statistical and Data Management Center), UM1AI068613 (HPTN Laboratory Center), and R01 MH110186 from the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health, and the National Institute on Drug Abuse of the National Institutes of Health (NIH). This work was also supported by R01MH087118 and R24HD050924 to the Carolina Population Center. Additional funding was provided by the Division of Intramural Research, NIAID, and NIH. The Agincourt Health and Socio-Demographic Surveillance System is supported by the University of the Witwatersrand and Medical Research Council, South Africa, and the UK Wellcome Trust (Grants 058893/Z/99/A, 069683/Z/02/Z, 085477/Z/08/Z, and 085477/B/08/Z). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors have no conflicts of interest to disclose.

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Correspondence to: Audrey Pettifor, PhD, Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27599 (e-mail: apettif@email.unc.edu).

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studies identified increased odds of HIV with a partner greater than 5 years older,[6,7] whereas some prospective studies found no such association among partnerships with age differences greater than 5 or 10 years at enrollment.[8,9] Assessment of partner age rather than age difference has demonstrated associations between risk of HIV acquisition among women and male partners ages 25–34 years.[10] Phylogenetic linkage and HIV prevalence results support the hypothesis that the main source of HIV transmission to AGYW ages 15–25 years comes from older men ages 25–40 years.[11]

Research on age-disparate partnerships has traditionally classified age disparity as a binary variable, usually categorized as an age difference of at least 5 or 10 years between a participant and her sexual partner(s).[7–9,12] Few studies have measured age disparity using flexible models[13,14] and research classifying age disparity as a continuous variable has assumed a constant change in the effect estimate for every year of partner age difference.[7,8] Yet, other cut points to classify age disparity may be more appropriate, as increasing or decreasing periods of risk exist within age-disparity categories of <5 years or ≥ 5 years.[13] The extent of age disparity can also vary depending on AGYW age, with older AGYW tending to have smaller age differences with their sexual partners as compared to younger AGYW.[14]

Previous evidence from the HIV Prevention Trials Network (HPTN) 068 cohort in South Africa demonstrated a higher risk of HIV infection among AGYW with age-disparate partnerships ≥ 5 years as compared to AGYW with no age-disparate partnerships, even after accounting for transactional or condomless sex.[15] Building upon this research, the objective of the present analysis was to determine how the 1-year risk of becoming newly infected with HIV changes after exposure to sexual partners of different ages, and how this risk is modified by AGYW age in the HPTN 068 cohort. To investigate the association between age pairings and HIV, we modeled risk of HIV by AGYW age, partner age difference, and partner age. Consideration of both AGYW age and partner age presents a multifaceted approach to identify key groups for HIV prevention efforts.

METHODS

Study Design and Population

The HPTN 068 study is a longitudinal phase III individually randomized controlled trial examining the effect of cash transfers, conditional on school attendance, on HIV acquisition among AGYW in South Africa.[16,17] To be eligible, AGYW had to be between the ages of 13–20 years, enrolled in grades 8–11, not married or pregnant, and have a parent/guardian in the household.[17] A total of 2537 AGYW were enrolled from the health and sociodemographic surveillance system site of the MRC/Wits-Rural Public Health and Health Transitions Research Unit (Agincourt) in rural Bushbuckridge, Mpumalanga province, South Africa, in 2011 and 2012. HIV prevalence in this region was 5.5% in girls ages 15–19 years, and 27.0% in young women ages 20–24 years around the time of study enrollment.[18] Peak HIV prevalence in this population occurred in adults ages 35–39 years, 45.3% in men and 46.1% in women. Our analysis includes AGYW who were HIV negative at enrollment and had at least 1 follow-up test. Given the 47 incident HIV infections among those who reported never having had sex, AGYW were included regardless of reported sexual history.

Participants were followed annually from enrollment until study completion in 2015 or until high school graduation, whichever came first. During study visits, participants completed an audio computer-assisted self-interview and underwent HIV testing if they had tested negative at their previous visit. Some participants had an additional HIV test around the time of their expected high school graduation or at study completion to capture extra person time. Only HIV test information within 6 months of the previous visit was retained, and audio computer-assisted self-interview data carried forward from the previous interview. For all other visits, we carried forward missing covariate information from the last observation, except for sexual behavior information, as we did not expect answers to vary dramatically and missing data were minimal ($<10\%$). A postintervention visit was also conducted 1–2 years after the end of the main trial.

IRB approval for this study was obtained from the University of North Carolina at Chapel Hill and the University of the Witwatersrand Human Research Ethics Committee.

Exposure, Outcome, and Covariate Assessment

Partner age difference was defined as the difference between a study participant's age and the age of up to 3 self-reported sexual partners at each study visit. The main exposure was classified as the maximum age differences of these partners; previous analyses conducted using both mean and maximum partner age differences showed similar results.[15] Incident HIV infection was defined as a new diagnosis of HIV after study enrollment. HIV testing was performed using 2 HIV rapid tests with a confirmatory Western blot.[17]

Fixed and time-varying covariates were selected using directed acyclic graph analysis and a review of the literature.[15] We included time-varying self-report of any alcohol use, time-varying household socioeconomic status according to a principal components analysis of household assets measured in quartiles, time-varying multiple sexual partners, and time-varying AGYW age. We also adjusted for randomized cash transfer intervention assignment at baseline from the main HPTN 068 study,[16,17] although this did not have an effect on incident HIV infection.[15] Transactional sex and condomless sex were not included in the model because they are mediators on the pathway between partner age and HIV infection. To better guide our simulation, we also created a time-varying indicator for having had sex, assuming that AGYW who did not report any sexual partners did not have sex over the indicated period. Other descriptive covariates included enrolled in school or completion of grade 12, double orphan, ever pregnant, age at first vaginal sex, number of sex partners in the last 12 months, children's depression inventory score ≥ 7, and low sexual relationships power score (South African adaptation of the Sexual Relationship Power Scale; score in lower third of the distribution).[19] All covariate

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information was taken from the visit before the study visit where a participant was tested for HIV, except for sexual partner age difference, which refers to partners over the preceding 1 year.

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Statistical Analysis

We used the parametric g-formula to simulate how 1-year risk of HIV infection varies over AGYW age and partner age after removing the effect of confounding factors. The parametric g-formula has been described elsewhere,[20,21] and additional information can be found in the Appendix (see Technical Methods, Supplemental Digital Content, http://links.lww.com/QAI/B415). Briefly, we first modeled the conditional probabilities of time-varying maximum partner age difference, acquisition of HIV, and covariates, with flexible pooled regression models using the observed data. We next drew a large Monte Carlo sample of 950,000 AGYW drawn with replacement from the observed data and retained each AGYW's baseline age and randomized cash transfer intervention assignment. We then used coefficients from the pooled regression models above to simulate time-varying confounders, maximum partner age difference, and HIV outcomes. Conditional probabilities were estimated at up to 5 time points, one for each annual study visit. Once a participant tested positive for HIV or turned 21 years of age, she was simulated as exiting the risk set.

We used logistic regression to obtain predicted probabilities of HIV by AGYW age, partner age difference, and partner age group in the simulated data set. Bootstrapping provided 95% confidence intervals. All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC) and R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 2362 AGYW were included in this analysis. Of these, the majority were enrolled between ages 13 and 16 years (1748 of 2362; 74.0%) (Table 1). There was a low prevalence of any reported alcohol use (153 of 2351; 6.5%) and depression (415 of 2249; 18.5%). Low sexual relationship power scores (372 of 599; 62.1%) were observed across the entire cohort at baseline.

When accounting for all 10,148 baseline and follow-up study visits in our original data, the frequency of sexual activity risk behaviors ranged widely by age group; girls ages 13–14 years reported unprotected sex acts in the previous 3 months at only 9 of 958 (0.9%) study visits, as opposed to at 137 of the 554 (24.7%) visits among AGYW ages 21–22 years (Table 2). Girls ages 13–14 years reported no sex partners in the previous year at the majority (886 of 955; 92.8%) of study visits, in contrast to older AGYW ages 21–22 and 23–26 years who indicated one or more sex partners at the majority of study visits (ages 21–22: 401 of 554, 72.4%; ages 23–26: 62 of 87, 71.3%). AGYW reported the age of their sexual partner(s) at over a third of all study visits (3767 of 10,148; 37.1%). There were 193 seroconversions over the study period.

TABLE 1. Baseline Characteristics of AGYW Enrolled in HPTN 068 in Agincourt, South Africa, From 2011– 2012, and Included in This Analysis (N = 2362)

	N (%)/Median (IQR)
Sample size	2362
Age at baseline	
13–14	739 (31.3)
15–16	1009 (42.7)
17–18	505 (21.4)
19–21	109 (4.6)
Household socioeconomic status	
Low	599 (25.4)
Middle to low	627 (26.6)
Middle	575 (24.4)
High	557 (23.6)
Cash transfer intervention arm	1215 (51.4)
Enrolled or completed school	2257 (95.6)
Double orphan	102 (4.4)
Ever pregnant	192 (8.2)
Age at first vaginal sex	16 (15–16)
Any alcohol use	153 (6.5)
Children's depression inventory score ≥7	415 (18.5)
Low Sexual Relationship Power Score (SRPS)	372 (62.1)

Missing values: socioeconomic status (4, 0.2%), orphan (27, 1.1%), pregnant (26, 1.1%), age first sex (1,772, 75.0%), alcohol (11, 0.5%), depression (113, 4.8%), and low power (1,763, 74.6%).

Participants were HIV negative at enrollment and had at least 1 follow-up test. Percentages were calculated based on all available data for each variable; missing counts are displayed below.

IQR, interquartile range.

There were 5351 total partner pairings in our original data, with each AGYW reporting up to 3 partners per study visit (Fig. 1). The majority (5132; 95.9%) of these partner-age pairings were reported at a visit where a participant tested HIV negative, and 219 (4·1%) at a visit where an incident HIV infection was recorded. The reported partner was older than the participant in 4408 of 5132 (85.9%) age pairings at a visit when the participant was HIV negative and 196 of 219 (89.5%) age pairings at a visit where an incident HIV infection was reported. The median maximum partner age difference was 3 years (interquartile range: 1–4) at visits when no HIV infection occurred and 3 years (interquartile range: 2–6) when an incident HIV infection took place. Information on 1-year risk of HIV among various age pairings can be found in the Appendix (see Tables 1 and 2, Supplemental Digital Content, http://links.lww.com/QAI/B415).

In the observed data, the 1-year risk of HIV infection increased as AGYW age increased, from 0.00 at ages 13 and 14 years (0 of 265; 0 of 698), to 0.09 at age 23 years (7 of 75) (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B415). The 1-year risk of HIV infection among AGYW also independently increased as partner age increased, from 0.00 at maximum partner ages 15 and 16 years (0 of 29, 0 of 67), to 0.12 at age 30 years (3 of 26).

In our simulated data, the age difference between an AGYW and her sexual partners seemed to have a more

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TABLE 2. Study Visit Characteristics of AGYW in Agincourt, South Africa, From 2011–2017, Stratified by Age at Study Visit (N = 2362)

	AGYW Age						
	13–14	15–16	17–18	19–20	21–22	23–26	All
	N (%)/Median (IQR)	N (%)/Median (IQR)	N (%)/Median (IQR)	N (%)/Median (IQR)	N (%)/Median (IQR)	N (%)/Median (IQR)	N (%)/Median (IQR)
No. of total study visits	963 (9.5)	3058 (30.1)	3574 (35.2)	1872 (18.5)	589 (5.8)	89 (0.9)	10,148
No. of seroconversions in the next yr	5	59	83	38	7	1	193
Risk of HIV in the next 1 yr	0.01	0.02	0.03	0.04	0.07	0.33	0.02
Maximum partner age difference (yr)	3 (2–5)	3 (2–4)	3 (1–4)	3 (1–5)	3 (1–5)	3 (2–4)	3 (1.8–4)
Household socioeconomic status							
Low	196 (20.4)	547 (18.1)	547 (15.5)	255 (13.7)	66 (11.3)	9 (10.2)	1620 (16.1)
Middle to low	230 (24.0)	776 (25.7)	962 (27.3)	463 (24.9)	145 (24.9)	16 (18.2)	2592 (25.8)
Middle	268 (27.9)	834 (27.6)	1084 (30.8)	551 (29.6)	169 (29.0)	35 (39.8)	2942 (29.3)
High	266 (27.7)	868 (28.7)	932 (26.4)	590 (31.7)	203 (34.8)	28 (31.8)	2888 (28.8)
Unprotected sex acts in the last 3 mo	9 (0.9)	143 (5.2)	326 (11.8)	319 (19.7)	137 (24.7)	18 (20.7)	952 (10.9)
No. of sex partners in the last 12 mo							
0	886 (92.8)	2179 (78.8)	1599 (58.1)	647 (40.0)	153 (27.6)	25 (28.7)	5489 (62.9)
1	59 (6.2)	489 (17.7)	926 (33.6)	746 (46.2)	316 (57.0)	49 (56.3)	2585 (29.6)
>1	10 (1.0)	98 (3.5)	229 (8.3)	223 (13.8)	85 (15.3)	13 (14.9)	658 (7.5)
Received money or gifts in exchange for sex	7 (0.7)	119 (4.0)	365 (10.8)	332 (19.1)	133 (24.1)	22 (26.2)	978 (10.1)
Any alcohol use	42 (4.4)	194 (6.4)	297 (8.4)	217 (11.8)	72 (12.5)	10 (11.6)	832 (8.3)

Missing in each strata: AGYW age (3, 0.0%), risk of HIV (4, 0.4%; 99, 3.2%; 396, 11.1%; 1014, 54.2%; 484, 82.2%; 86, and 96.6%), maximum partner age [902, 93.7%; 2427, 79.4%; 2085, 58.3%; 766, 40.9%; 170, 28.9%; and 31, 34.8% (no partner reported)], socioeconomic status (3, 0.3%; 33, 1.1%; 49, 1.4%; 13, 0.7%; 6, 1.0%; and 1, 1.1%), unprotected sex (5, 0.5%; 282, 9.2%; 801, 22.4%; 251, 13.4%; 35, 5.9%; and 2, 2.2%), sexual partners (8, 0.8%; 292, 9.5%; 820, 22.9%; 256, 13.7%; 35, 5.9%; and 2, 2.2%), exchange sex (17, 1.8%; 110, 3.6%; 199, 5.6%; 130, 6.9%; 38, 6.5%; and 5, 5.6%), and alcohol (4, 0.4%; 13, 0.4%; 30, 0.8%; 36, 1.9%; 14, 2.4%; and 3, 3.4%).

Participants were followed annually from enrollment to study completion in 2014 or until high school graduation, whichever came first. A postintervention visit was also conducted 1 to 2 years after the end of the main trial and was included in the analysis.

IQR, interquartile range.

pronounced effect on risk of HIV in younger as compared to older AGYW, after controlling for multiple partners, alcohol use, and wealth. The 1-year risk of HIV infection rapidly increased as age disparity increased among girls ages 13–14 years, from 0.01 with a partner of the same age, to 0.21 with a partner 10 years older, and 0.24 with a partner 15 years

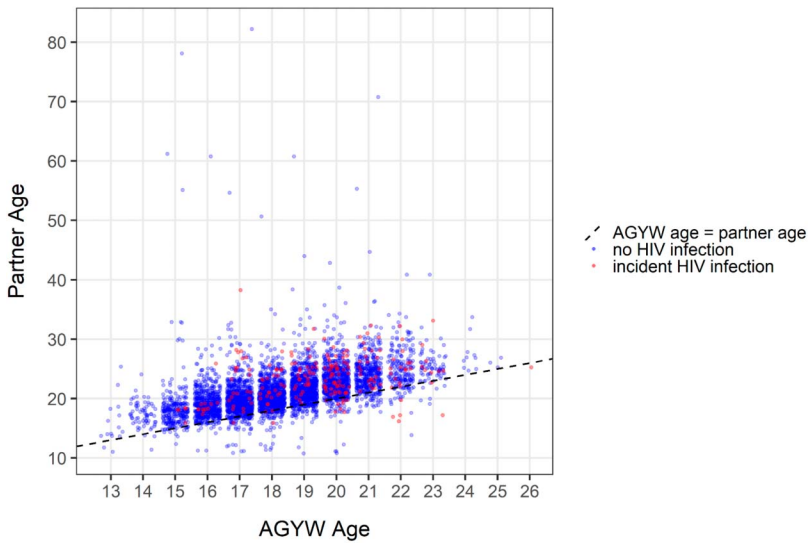


FIGURE 1. Scatterplot of reported age pairings (N = 5351) and associated incident HIV infections at all study visits. Each AGYW could report up to 3 sexual partners per study visit. Only 124 of the 193 total infections are shown; the remaining cases were missing data on partner age. The dashed line indicates points where AGYW age would equal partner age. Age is a discrete variable measured in years; a small amount of random variation is added to each pairing's location to reduce overplotting. full color online

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older (Fig. 2; see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B415). More gradual increases were observed among AGYW ages 15–16, with a 0.01 1-year risk of HIV infection with a partner of the same age, 0.11 with a partner 10 years older, and 0.10 with a partner 15 years older. AGYW ages 17–18 years had a 1-year risk of HIV of 0.02 with a same-age partner, a maximum risk of 0.09 when with partners 8–11 years older, and a lower risk of 0.07 with a partner 15 years older. Partner age difference did not substantially change the risk of HIV in young women ages 19–21 years; estimates remained relatively constant from same-age partners at 0.05, up to a maximum of 0.11 when paired with partners 7–9 years older, and fell to 0.02 when with a partner 15 years older.

After stratifying by maximum partner age difference in the simulated data, the 1-year risk of HIV infection among AGYW ages 13–14 years was lowest when paired with partners 0–4 years older (0.02–0.03) and highest with partners 5–9 years older (0.12–0.13) (Fig. 3A). Among AGYW ages 15–18 years, the 1-year risk of HIV was lowest with younger partners (0.01–0.02) and highest with partners ≥10 years older (0.08–0.15). Among AGYW ages 19 and 20 years, the 1-year risk was lowest with partners 0–4 years older (0.04–0.06), and highest with partners 5–9 years older (0.08–0.10). Among AGYW age 21 years, the 1-year risk was lowest with partners 0–4 years older (0.08) and highest with younger partners (0.13).

Crude partner age showed a large association with risk of HIV in girls' ages 13–16 years, ranging from 0.01 among 14 year olds paired with partners under 15 years of age, to 0.15 among 15 year olds paired with partners ages 25–29 years (Fig. 3B). Variation in risk decreased among AGYW ages 17–19 years, with lowest risk estimates when paired with partners ages 15–19 years (0.02–0.03), and highest risk when paired with partners ages 25–29 years (0.09). Partner age and partner age difference both seemed to be less associated with risk of HIV among young women ages 20–21 years, ranging from a risk of 0.06–0.08 with partners 20–24 years of age, to 0.10–0.11 with partners 25–29 years.

DISCUSSION

Results illustrate that the association between partner age disparity and 1-year risk of HIV infection has a much more pronounced effect in younger than in older AGYW, after controlling for multiple partners, alcohol use, and wealth. In our study population, sexual partnerships with older men led to a dramatically higher risk of HIV acquisition among girls ages 13–14 years, a moderately higher risk of HIV acquisition in AGYW ages 15–16 years, and a marginally elevated risk of HIV among AGYW ages 17–18 years. The 1-year risk of HIV among AGYW ages 19–21 years was high in partnerships with younger men and with moderately older men, but fell with significantly older partners. Focusing an analysis solely on partner age differences incorrectly assumes that the effects of age disparity are constant across all AGYW ages.

Our results are somewhat consistent with previous research examining age pairings in KwaZulu-Natal, South Africa, showing that reported partner age failed to

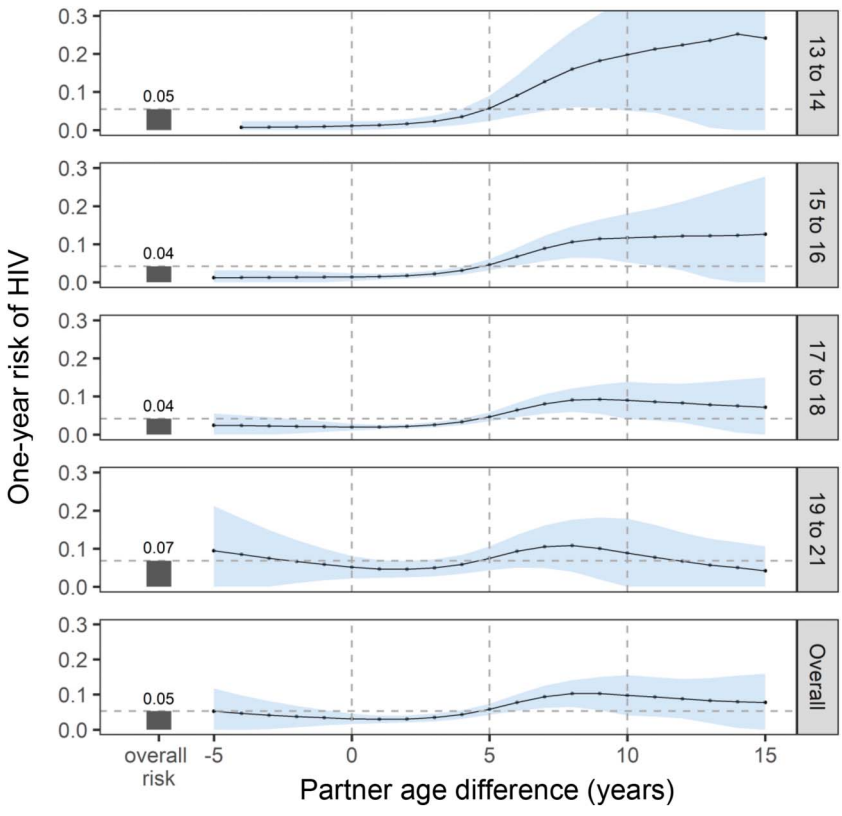


FIGURE 2. AGYW risk of HIV in the next 1 year (and 95% confidence intervals) at various maximum partner age differences in the simulated data set (N = 950,000). Risk estimates are stratified by AGYW age group (years). Vertical dashed lines indicate maximum partner age differences of 0, 5, and 10 years. Bars indicate absolute risk of HIV in each AGYW age group, only among AGYW who were assigned partners in the simulation, regardless of partner age. Estimates from pairings in the 13–14 years stratum with a partner age difference less than 0 or greater than or equal to 10 years, and estimates from pairings in all strata with partner age differences above 12 years are extrapolated from sparse data in the observational cohort and should be interpreted with caution. full color online

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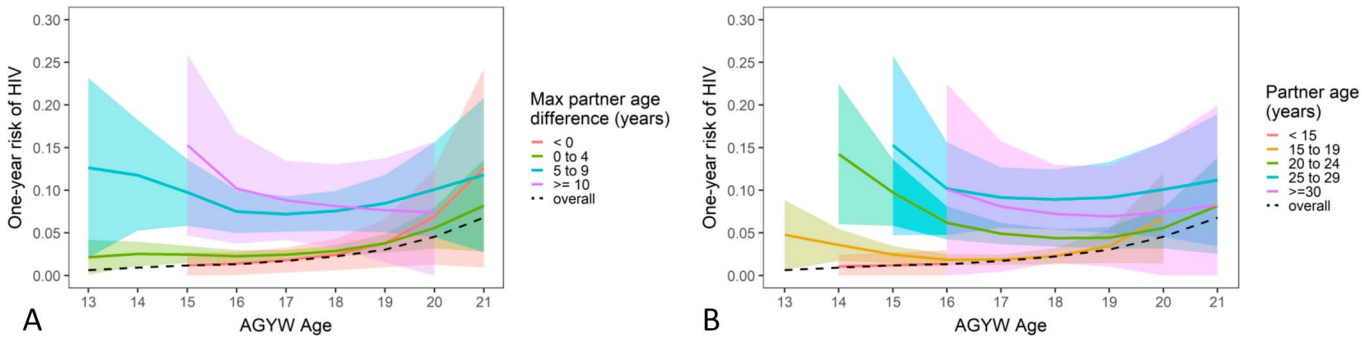


FIGURE 3. AGYW risk of HIV in the next 1 year (and 95% confidence intervals) at various age pairings in the simulated data set (N = 950,000). A, Risk estimates are stratified by maximum partner age difference (years). B, Risk estimates are stratified by maximum partner age (years). Pairings between AGYW and partner age strata with fewer than 5 counts in the observed data are removed to avoid extrapolation from sparse data. Absolute risk was derived from the overall simulated cohort, regardless of if a sexual partner was reported or not. full color online

demonstrate a linear relationship with HIV incidence.[10] HIV incidence was highest among AGYW ages 15–24 years who had older partners ages 30–34 years, followed by those with partners ages 25–29 years. In our cohort, most high HIV-risk estimates occurred between AGYW ages 15–18 years with sexual partners ages 25 years and older. Our results also align with research from Malawi, indicating that partner age did not demonstrate a linear relationship with HIV probability among women ages 18–49 years.[13] A cross-sectional study in KwaZulu-Natal found that among AGYW younger than 25 years of age with HIV, 62% were phylogenetically linked with partners ages 25–40 years, a group in which HIV prevalence was over 40%.[11] Although directionality was inferred from prevalence gradients and with no support from longitudinal data, it was hypothesized that HIV transmission could be galvanized by sexual partnerships in which older men concurrently partnered with older women ages 25–40 years in whom HIV prevalence was nearly 60%. The same transmission cycle could be occurring among the Agincourt rural study population. Interestingly, AGYW in our cohort ages 19–21 years were at a higher risk of HIV when paired with younger partners (<0 years age difference) than when paired with partners 0–4 years older, similar to findings among women ages 18–49 years in Malawi.[13]

Age-disparate partnerships in sub-Saharan Africa result from social and economic factors. In some cases, AGYW can be motivated by increased social status and may view older men as a means to obtain financial support and economic stability, often resulting in less power to negotiate safe sex practices.[4,22] Biological factors also play a role in increasing risk of HIV infection, including a greater mucosal surface area in women and vaginal practices or substances, which disrupt the microbiome and epithelial tissue, facilitating HIV transmission.[4,23] Men may be motivated to partner with AGYW through the virgin-cure myth, "sexual rejuvenation" believed to be obtained through younger partners, and traditional gender roles.[22] Further research is necessary to characterize the specific behaviors and motivations of older men who partner with AGYW in rural South Africa.

Globally, women also tend to partner with older men,[24] and reducing the risks of age-disparate relationships is challenging. UNAIDS recommendations for AGYW ages 15–24 years in high HIV incidence settings include incentives to keep girls in school and social and behavioral change activities to address sexual behavior, HIV-risk perception, gender norms, power, and gender-based violence.[25] Pre-exposure prophylaxis (PrEP) can be an effective intervention and integrated alongside reproductive health services.[26] Previous research among the HPTN 068 cohort has shown that school attendance reduces HIV risk by preventing greater numbers of sexual partnerships and partnerships with older men.[27,28] Programs such as DREAMS and "She Conquers" support school attendance in South Africa, primarily targeting young women ages 15–24 years for retention and tracing and describing their male sexual partners for HIV intervention purposes.[29,30] Specifically targeting men ages 15–34 years could further reduce infections, such as through HIV testing, linkage to care, and circumcision, which has low uptake among male partners of young women in certain locales.[31]

A primary limitation of this analysis is the potential misreporting of sexual behaviors; although HIV is not only transmitted sexually, there were 47 incident HIV infections detected in AGYW who stated they had never had sex. Other research in rural South Africa has identified underreporting of age-disparate partnerships among AGYW <25 years of age with a sensitivity of 74% and specificity of 90% for correctly reporting a partner ≥5 years older.[32] If comparable misreporting occurred in our study, we would underestimate the influence of age-disparate partnerships on HIV risk. Second, we found several unusually young and old partners reported, with age ranging from 11 to 82 years. Speculatively, these outliers could be the result of errors in data entry or misreporting by AGYW who may not have known their partner's actual age. To diminish the influence of outliers, we limited the youngest sexual partners in our model to 10 years of age and removed pairings with limited observations from the figures to reduce the extent of model inference into areas where no original data exist. A third limitation is the potential for unmeasured confounding. We created flexible models, including interactions between known confounders and time, but residual confounding or model misspecification may exist. Finally, the study population was limited to a select group taking part in a randomized trial and

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who were enrolled in school at baseline; results may not be broadly generalizable to AGYW in rural South Africa. Nevertheless, methods can be translated to populations that would benefit from a more granular determination of age pairings most at risk for HIV transmission. Grouping our analysis by standard age-disparity definitions of <5 and ≥ 5 years would have missed important variations in risk of HIV with older partners and the increased 1-year risk of HIV among older AGYW with younger partners.

This study presents a unique accumulation of longitudinal sexual partnership data among a cohort of AGYW in rural South Africa. Our methodology allowed us to move beyond binary constraints to assess both AGYW age and partner age in 1-year increments, while accounting for time-varying covariates. We showed that 1-year risk of HIV infection in AGYW changes after exposure to partners of different ages, and that this relationship is modified by AGYW age. Future studies should model age-disparity flexibly and stratify by AGYW age. Since our analysis observed AGYW annually and did not track sexual partners, we are unable to determine the transmitting partner and the risk of transmission per act, despite few reports of multiple partners (658 of 8735 study visits; 7.5%). Future research should characterize older partners of AGYW in the target population. Defining both the level of risk and proportion of pairings that contribute to the most HIV infections are important steps in targeting interventions to slow the HIV transmission cycle in this high prevalence region.

ACKNOWLEDGMENTS

The authors thank the HPTN 068 study team and all trial participants.

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