HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2015 October 1; 70(2): 212–217. doi:10.1097/QAI.0000000000000715.

Age-Disparate Partnerships and Risk of HIV-1 Acquisition among South African Women Participating in the VOICE Trial

Jennifer E. Balkus[1,2], **Gonasagrie Nair**[3], **Elizabeth T. Montgomery**[4], **Anu Mishra**[5], **Thesla Palanee-Phillips**[6], **Gita Ramjee**[7], **Ravindre Panchia**[8], **Pearl Selepe**[9], **Barbra A. Richardson**[1,5], **Zvavahera M. Chirenje**[10], and **Jeanne M. Marrazzo**[11]

[1]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center; Seattle, WA, USA

[2]Department of Global Health, University of Washington; Seattle, WA, USA

[3]CAPRISA/University of KwaZulu-Natal, Durban, South Africa

[4]RTI International, San Francisco, CA, United States

[5]Department of Biostatistics, University of Washington; Seattle, WA, USA

[6]University of Witwatersrand, Johannesburg, South Africa

[7]South African Medical Research Council, Durban, South Africa

[8]Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Johannesburg, South Africa

[9]The Aurum Institute, Klerksdorp, South Africa

[10]UZ-UCSF, Harare, Zimbabwe

[11]Department of Medicine, University of Washington; Seattle, WA, USA

Abstract

A recent analysis from South Africa reported no association between age-disparate relationships and HIV-1 acquisition. We assessed the association between male partner age and HIV-1 acquisition among South African women participating in the VOICE trial. Of 4,077 women enrolled, 3,789 had complete data; 26% and 5% reported having a partner >5 and >10 years older at enrollment, respectively. Reporting a partner >5 years older (HR=1.00; 95% CI 0.74, 1.35) or >10 older (HR=0.92; 95% CI 0.49, 1.74) was not associated with HIV-1 acquisition. These data corroborate recent reports and may suggest a shift in local epidemiology of heterosexual HIV-1 transmission.

*Correspondence: Jennifer E. Balkus, PhD, MPH, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N., M2-C200, P.O. Box 19024, Seattle, WA 98109-1024, Phone: +1 206 667 7149, jbalkus@fhcrc.org.

These data were presented in part at the HIV Research for Prevention meeting, held 27th -31th October 2014 in Cape Town, South Africa

Potential Conflicts of Interest: All authors declare no commercial or other associations that might pose a conflict of interest relevant to the submitted work.

Keywords

HIV-1 in women; age-disparate relationships; male partner; South Africa; sexual behavior

Introduction

In many African countries, women account for more than half of those living with HIV-1 and young women (<25 years old) are up to five times more likely to be HIV-1 infected compared to their male peers.[1-3] A combination of biological, behavioral, social and structural factors may impact young women's susceptibility to HIV-1 infection.[4] Engagement in age-disparate relationships, where the male partner is substantially older than the female partner, has been hypothesized as one of the drivers of this higher burden of HIV-1 among young women.[5-10] Evidence in support of this hypothesis comes from surveillance data showing consistent sex-age disparities in HIV prevalence, [2,3,11,12] where the prevalence of HIV is greater among young women compared to young men, and from epidemiologic studies that report that age-disparate relationships are common among young women. [3,13,14] In South Africa, a country which continues to have the greatest HIV-1 burden globally,[2] population based surveys of women aged 15-24 reported that 33-39% of respondents had a partner >5 years older.[3,13] Campaigns to reduce or eliminate age-disparate relationships have been a prominent part of HIV-1 prevention strategies in this region and other high incidence settings.[15-17] Although cross-sectional studies have reported an association between age-disparate relationships and HIV in women,[7,14,18] data from prospective studies provide limited and conflicting evidence regarding the contribution of age-disparate relationships to HIV-1 acquisition in South Africa and other African countries.[15,18] A recent analysis of data collected between 2003-2012 from >2,400 women in KwaZulu-Natal, South Africa observed no association between age-disparate relationships and HIV-1 acquisition in this high-incidence region.[15] These data may suggest a shift in local epidemiology of heterosexual HIV-1 transmission, but require confirmation. Our objective was to assess the association between age-disparate relationships and HIV-1 acquisition risk among South African women participating in the VOICE trial.

Methods

VOICE was a randomized placebo-controlled trial that assessed the safety and effectiveness of oral tenofovir disoproxil fumarate (TDF), oral TDF plus emtricitabine (TDF-FTC), and vaginal 1% tenofovir (TFV) gel for HIV-1 prevention in women (#NCT00705679). Detailed methods have been described previously.[19] Briefly, between 2009-2012, 5,029 women from three countries (Uganda, South Africa and Zimbabwe) were enrolled and followed monthly. Eligible women were 18-45 years old, HIV-1-uninfected, not pregnant, sexually active, and willing to use highly effective contraception. All participants provided written informed consent and all institutional review boards and relevant regulatory authorities approved the trial at each site.

At monthly visits, blood was collected through venipuncture for HIV-1 testing. Structured face-to-face interviews were used to collect data on sexual behaviors, vaginal washing and

contraceptive use. Demographic characteristics of the primary partner, including partner age as reported by the participant, were assessed at enrollment. At quarterly visits, audio computer-assisted self-interviews were conducted to collect additional sexual behavior data, including a change in the primary partner in the last three months. Planned follow-up was for a minimum of 12 months and up to 36 months, depending on enrollment date. However, the data safety and monitoring board recommended the TDF arm and the TFV arm be discontinued for futility. Participants in the TDF-FTC and oral placebo arms continued participation until planned study exit (August 2012).

HIV-1 infection status was determined using a standardized algorithm.[20] Rapid testing was performed using Determine HIV 1/2 (Abbott Diagnostic Division; Hoofddorp, Netherlands), OraQuick® (Orasure Technologies; Bethlehem, Pennsylvania, USA), or Uni-Gold Recombigen® HIV test (Trinity Biotech; Wicklow, Ireland). Western blot was performed on samples with any positive HIV-1 rapid result (Genetics Systems HIV-1 Western Blot kit, BioRad Laboratories; Hercules, CA, USA).

This analysis assessed the association between having an older primary partner at enrollment (age-disparate relationship) and HIV-1 acquisition risk within the first year of follow-up among women enrolled at South African sites (Durban area, Johannesburg area and Klerksdorp). Due to potential differences in measured and unmeasured factors by country and low HIV incidences in Uganda and Zimbabwe[19], we limited our analysis population *a priori* to women enrolled in South Africa. Primary partner was defined as, "*A man you have sex with on a regular basis or who you consider to be your main partner*." Participants who reported that they did not have a primary partner at enrollment were excluded from this analysis since questions about partner characteristics were only asked of women who reported a primary partner. Two categorizations of age-disparity (as reported by the participant at enrollment) were used: (1) partner more than 5 years older than participant; (2) partner more than 10 years older than participant. Participants could respond that they did not know their partner's age. Those who indicated "don't know" were retained in the analysis and evaluated as a separate exposure category, since we hypothesized that lack of knowledge may be reflective of a new or less stable partnership and potentially associated with increased HIV-1 risk. Secondary analyses were performed to assess partner age as a continuous variable. The primary outcome was HIV-1 infection within one year of VOICE enrollment. Cox proportional hazards models stratified by study site were used to assess the association between age-disparate relationship status at enrollment and time to HIV-1 infection. Participant follow-up was censored at one year from enrollment since we hypothesized that characteristics assessed at baseline would be predictive up to one year from assessment. Baseline factors associated with age-disparate relationship status and HIV-1 acquisition were considered for inclusion in the multivariable model.[21] Data were available at quarterly visits regarding a change in primary partner in the last three months. Since data on partner age was not collected for subsequent partners, nor were specimens available to link new infections to specific partners, a sensitivity analysis was conducted censoring women when a change in primary partner was reported (no longer having a primary partner or a new primary partner). The above analyses were repeated stratifying by participant age at enrollment (<25 years versus ≥25 years). All statistical tests were assessed

using a 2-sided α of 0.05. Analyses were conducted using Stata version 12.0 (StataCorp, Inc., College Station, TX) and R (R Foundation for Statistical Computing; Vienna, Austria).

Results

Of 4,077 HIV-1-uninfected South African participants enrolled in VOICE, 22 had acute HIV-1 infection detected at enrollment and 34 did not return for follow-up. In addition, 148 participants did not report having a primary partner at baseline and 84 were missing data for important baseline factors and were excluded, leaving 3,789 participants for analysis. Select characteristics at enrollment are presented in Table 1. The majority of participants were <25 years old and not married or living with their primary partner. Approximately one-quarter (999 [26%]) reported having a primary partner >5 years older and 183 (5%) reported that their primary partner was >10 years older. The proportion of participants who reported that their partner was >5 years older did not differ by participant age category (chi-squared p-value=0.36); however, a higher proportion of participants ≥25 years old reported having a partner >10 years older (p<0.001) [Table 1].

There were 243 seroconversions over 3,344 person-years of follow-up (HIV-1 incidence per 100 person-years (p-yrs)=7.27; 95% confidence interval [CI] 6.41, 8.24). Among participants who reported having a primary partner >5 years older the HIV-1 incidence was 7.68/100 p-yrs versus 7.12/100 p-yrs among participants whose primary partner was <5 years older (hazard ratio [HR]=1.10; 95% CI 0.82, 1.45). Results were similar for participants who reported having a primary partner >10 years older (Table 2). A small proportion (2%) of participants did not know their primary partner's age. Among participants who did not know their partner's age, HIV-1 incidence did not differ compared to those who did not report an age-disparate relationship. Effect estimates for all analyses remained unchanged after adjusting for potential confounders. Findings were also similar when partner age difference was considered as a continuous variable. A one-year increase in partner's age was not associated with risk of HIV-1 acquisition in univariate (HR=1.00; 95% CI 0.96, 1.03) and multivariable models (adjusted HR=1.01; 95% CI 0.97, 1.05). After stratifying by participant age at enrollment, all categorizations of age-disparate relationships (>5 years, >10 years, or continuous variable) continued to not be associated with increased risk of HIV-1 acquisition (Table 2).

There were 790 (21%) participants who reported a partnership change within one year of enrollment. Among those reporting a change, median time to partner change was 5.5 months (interquartile range 2.8-8.3). In sensitivity analyses where follow-up was censored at the visit where the participant reported she no longer had a primary partner or reported a change in primary partner, there were 194 seroconversions over 3,005 p-yrs of follow-up (HIV-1 incidence per 100 p-yrs = 6.46; 95% 5.61, 7.43). Consistent with the primary analysis, age-disparate relationships were not associated with HIV-1 acquisition in the overall study population nor when stratified by participant age at enrollment. Furthermore, the effect estimates were unchanged following adjustment for potential confounders (Table 2).

Discussion

In this secondary analysis of prospective data from South African women participating in an HIV-1 prevention trial, the incidence of HIV-1 infection did not differ among women who reported being in an age-disparate relationship at enrollment versus those that did not. Findings were consistent after adjustment for potential confounding factors, stratification by participant age at enrollment and in sensitivity analyses that censored follow-up when a woman reported that she no longer had a partner or reported a change in partner.

Our results are consistent with research from the Africa Centre in South Africa, which reported no association between age-disparate relationships and HIV-1 risk among women living in rural KwaZulu-Natal.[15] South African women participating in VOICE were similar to women participating in the Africa Centre study with regard to potential HIV risk factors including age, not being married, and having a partner >5 years or >10 years older.[15] The overall HIV-1 incidence was nearly identical and very high (VOICE=7.27/100 p-yrs versus Africa Centre=7.75/100 p-yrs), demonstrating the urgent need for effective HIV-1 prevention interventions for women in this region. There are also several notable differences in the populations that should be considered when comparing the results of these studies. The Africa Centre was a longitudinal cohort study that included women aged 15-29 and censored follow-up when participants reached age 30, whereas VOICE was a clinical trial that enrolled women aged 18-45, although the majority of VOICE participants were <25 year old. In addition, follow-up in the Africa Centre study was up to 9 years with surveys administered annually, allowing for assessment of new partnerships over time. In VOICE, partner age was only assessed at enrollment; therefore our analysis is limited to the primary partnership reported at enrollment into the trial. Lastly, Africa Centre study participants were all enrolled from rural KwaZulu-Natal. VOICE enrolled the majority of its South African participants from the KwaZulu-Natal region (areas within ∼50 kilometers of Durban) and also included women from other areas of South Africa. Despite these differences in population and study design, findings from these two studies are remarkably similar and further suggest that age-disparate relationships may not be a driver of the current HIV-1 epidemic among young women in South Africa.

Although the prevalence of HIV is higher among older men, it is possible that same-age sexual relationships among young men and women could be driving high endemic levels of HIV and incidence among young women. In South Africa, young men are more likely to be newly infected with HIV and are less likely to be on antiretroviral therapy compared to older HIV-infected men,[22,23] thus increasing the potential infectiousness of HIV-infected young men. In addition, mathematical modeling of the population-level impact of behavior change on HIV incidence in generalized epidemics suggests that, in the absence of other behavioral changes, a decrease in age-disparate relationships does not substantially alter the spread of HIV within a sexual network.[24] Regardless of partner age, young women in South Africa, particularly in the KwaZulu-Natal region, continue to have one of the highest HIV incidences globally and should be considered a priority population for scale up of effective HIV prevention interventions, such as pre-exposure prophylaxis.[10] In addition, continued epidemiological surveillance and research into the dynamic and culturally-defined risk factors for HIV among young men and women in this region remains critical.

The findings from this study should be interpreted in the context of several strengths and limitations. Strengths included assessment of data collected in the course of a clinical trial with high retention and inclusion of women from several geographic regions within South Africa. The large sample size and number of HIV-1 infections allowed for ample statistical power as demonstrated by the narrow confidence intervals surrounding the effect estimates. Quarterly evaluation of relationship status combined with monthly HIV-1 testing reduced the potential for misclassification due to partnership changes in our sensitivity analysis. However, since data on partner characteristics were only collected at enrollment, we were unable to include information on subsequent primary partners in our analysis. Data were not collected on the age of non-primary sexual partners; therefore our findings do not extend to age-disparate relationships with non-primary partners. Lastly, this study included women enrolled in a biomedical HIV-1 prevention trial, thus the findings may not generalizable to women in the general population.

In summary, among South African women enrolled in a large HIV-1 prevention trial, report of being in an age-disparate relationship at enrollment was common, but not associated with HIV-1 acquisition within one year. There continues to be an urgent need for interventions to reduce the HIV-1 incidence among young women in this region.

Acknowledgments

Funding: The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We sincerely thank the women who participated in this study. We gratefully acknowledge the MTN-003 study team and study sites for their work on data and sample collection and the Statistical Center for their work on data management.

References

1. UNAIDS. UNAIDS World AIDS Day report. 2011
2. UNAIDS. UNAIDS report on the global AIDS epidemic. 2013
3. Pettifor AE, Rees HV, Kleinschmidt I, et al. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. AIDS. Sep 23; 2005 19(14):1525–1534. [PubMed: 16135907]
4. UNAIDS. [accessed 19 April 2014] Combination HIV Prevention: Tailoring and Coordinating Biomedical, Behavioural and Structural Strategies to Reduce New HIV Infections. A UNAIDS Discussion Paper. 2010. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/JC2007_Combination_Prevention_paper_en.pdf
5. Leclerc-Madlala S. Age-disparate and intergenerational sex in southern Africa: the dynamics of hypervulnerability. AIDS. Dec; 2008 22(Suppl 4):S17–25. [PubMed: 19033752]
6. UNAIDS. [accessed 15 July 2014. 2004] Facing the Future Together: Report of the Secretary General's Task Force on Women, Girls and HIV/AIDS in Southern Africa. http://data.unaids.org/publications/irc-pub06/jc380-facingfuture_en.pdf
7. Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. Lancet. Jun 1; 2002 359(9321):1896–1903. [PubMed: 12057552]

8. Kaiser R, Bunnell R, Hightower A, et al. Factors associated with HIV infection in married or cohabitating couples in Kenya: results from a nationally representative study. PLoS One. 2011; 6(3):e17842. [PubMed: 21423615]

9. WHO. [accessed 15 July 2014] National AIDS programmes : a guide to indicators for monitoring and evaluating national HIV/AIDS prevention programmes for young people. 2004. http://www.who.int/hiv/pub/epidemiology/napyoungpeople.pdf

10. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. Journal of the International AIDS Society. 2015; 18(2 Suppl 1):19408. [PubMed: 25724504]

11. Shisana, O.; Rehle, T.; Simbayi, LC., et al. South African national HIV prevalence, incidence and behaviour survey, 2012. Cape Town: HSRC Press; 2014.

12. Katz I, Low-Beer D. Why has HIV stabilized in South Africa, yet not declined further? Age and sexual behavior patterns among youth. Sex Transm Dis. Oct; 2008 35(10):837–842. [PubMed: 18607312]

13. Maughan-Brown B, Kenyon C, Lurie MN. Partner Age Differences and Concurrency in South Africa: Implications for HIV-Infection Risk Among Young Women. AIDS Behav. Jul 22.2014

14. Luke N. Age and economic asymmetries in the sexual relationships of adolescent girls in sub-Saharan Africa. Studies in family planning. Jun; 2003 34(2):67–86. [PubMed: 12889340]

15. Harling G, Newell ML, Tanser F, Kawachi I, Subramanian SV, Barnighausen T. Do Age-Disparate Relationships Drive HIV Incidence in Young Women? Evidence from a Population Cohort in Rural KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. Aug 1; 2014 66(4):443–451. [PubMed: 24815854]

16. South African National AIDS Council. [accessed 15 July 2014] National Strategic Plan on HIV, STIs and TB 2012-2016. http://www.sanac.org.za/nsp/the-national-strategic-plan

17. KwaZulu-Natal Department of Health. [accessed 15 July 2014] Sugar Daddy Campaign. http://www.kznhealth.gov.za/sugardaddy.htm

18. Kelly RJ, Gray RH, Sewankambo NK, et al. Age differences in sexual partners and risk of HIV-1 infection in rural Uganda. J Acquir Immune Defic Syndr. Apr 1; 2003 32(4):446–451. [PubMed: 12640205]

19. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. In press.

20. Microbicide Trials Network. [Accessed April 10, 2014] MTN-003: Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women. 2010. http://www.mtnstopshiv.org/sites/default/files/attachments/MTN-003_FINAL_Version_2.0_31DEC2010.pdf

21. Nair, G.; Balkus, JE.; Marrazzo, JM., et al. Baseline predictors of HIV-1 acquisition among women participating in MTN-003 (VOICE). Conference on Opportunistic Infections and Retroviruses; Boston, MA. 2014.

22. Tromp N, Michels C, Mikkelsen E, Hontelez J, Baltussen R. Equity in utilization of antiretroviral therapy for HIV-infected people in South Africa: a systematic review. International journal for equity in health. Aug 1.2014 13(1):60. [PubMed: 25078612]

23. Muula AS, Ngulube TJ, Siziya S, et al. Gender distribution of adult patients on highly active antiretroviral therapy (HAART) in Southern Africa: a systematic review. BMC public health. 2007; 7:63. [PubMed: 17459154]

24. Hallett TB, Gregson S, Lewis JJ, Lopman BA, Garnett GP. Behaviour change in generalised HIV epidemics: impact of reducing cross-generational sex and delaying age at sexual debut. Sex Transm Infect. Aug; 2007 83(Suppl 1):i50–54. [PubMed: 17314125]

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2016 October 01.

Table 1

Participant and participant-reported partner characteristics at VOICE enrollment[1]

	All women N= 3,789		Age < 25 years N= 2,143		Age ≥ 25 years N= 1,646	
Participant characteristics						
Age < 25 years	2,143	(57)	--	--	--	--
Married or living with husband/primary sex partner	830	(22)	221	(10)	609	(37)
Some secondary school education or higher[2]	3,648	(96)	2,095	(98)	1,553	(94)
Earns own income	2,238	(59)	1,100	(51)	1,138	(69)
Number of live births[3]						
0	678	(18)	579	(27)	99	(6)
1	1,850	(49)	1,229	(57)	621	(38)
>1	1,260	(33)	335	(16)	925	(56)
Alcohol use in the past 3 months						
≥ 2 times	112	(3)	64	(3)	48	(3)
≤ 1 time	876	(23)	576	(27)	300	(18)
None	2,801	(74)	1,503	(70)	1,298	(79)
Any curable STI detected[4]	789	(21)	554	(26)	235	(14)
HSV-2 seropositive	1,765	(47)	751	(35)	1,014	(62)
More than one vaginal sex partner in the past three months[5]	794	(21)	457	(21)	337	(20)
Study arm						
Oral tenofovir	749	(20)	433	(20)	316	(19)
Oral Truvada	748	(20)	397	(19)	351	(21)
Oral placebo	762	(20)	445	(21)	317	(19)
Vaginal tenofovir gel	763	(20)	432	(20)	331	(20)
Vaginal placebo gel	767	(20)	436	(20)	331	(20)
Study regions[6]						
Durban area	2,976	(79)	1,708	(80)	1,268	(77)
Johannesburg area	582	(15)	291	(14)	291	(18)
Klerksdorp	231	(6)	144	(7)	87	(5)
Participant reported partner characteristics						
Primary partner >5 years older than participant						

	All women N= 3,789		Age < 25 years N= 2,143		Age ≥ 25 years N= 1,646	
Yes	999	(26)	552	(26)	447	(27)
Don't know partner age	80	(2)	41	(2)	39	(2)
No	2,710	(72)	1,550	(72)	1160	(70)
Primary partner >10 years older than participant						
Yes	183	(5)	78	(4)	105	(6)
Don't know partner age	80	(2)	41	(2)	39	(2)
No	3,526	(93)	2,024	(94)	1502	(91)
Primary partner has other partners						
Yes	426	(11)	200	(9)	226	(14)
Don't know	2,294	(61)	1,346	(63)	948	(58)
No	1,069	(28)	597	(28)	472	(29)
Primary partner provides financial or material support	3,053	(81)	1,663	(78)	1,390	(84)
Primary partner has some secondary school education or higher						
Yes	3,510	(93)	2,042	(95)	1,468	(89)
Don't know	167	(4)	69	(3)	98	(6)
No	112	(3)	32	(1)	80	(5)

[1] Data presented as N (%) or median (IQR)

[2] Four observations missing.

[3] One observation missing.

[4] *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, or syphilis detected at baseline

[5] Participants were required to have at least one sex act in the last three months in order to enroll in the trial, therefore all women reported at least one sex partner.

[6] Participants were enrolled from 8 sites in the Durban area (Bothas Hill, Chatsworth, eThekwini, Isipingo, Overport, Tongaat, Umkomaas) 2 sites in the Johannesburg area (Hillbrow and Soweto) and 1 site in Klerksdorp

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2016 October 01.

Table 2

Association between age-disparate relationship and HIV-1 infection within one year

	HIV infections/person-years	HIV incidence[1] (95% CI)		Univariate model[2] HR (95% CI)		Multivariable model[3] HR (95% CI)	
Primary analysis							
All participants	243/3343.57	7.27	(6.41, 8.24)				
Primary partner >5 years older							
Yes	67/871.84	7.68	(6.05, 9.76)	1.10	(0.82, 1.45)	1.17	(0.88, 1.56)
Don't know partner age	5/70.36	7.11	(2.96, 17.07)	0.97	(0.40, 2.37)	0.98	(0.40, 2.39)
No	171/2401.37	7.12	(6.13, 8.27)	1.00	-	1.00	-
Primary partner >10 years older							
Yes	10/160.43	6.23	(3.35, 11.58)	0.87	(0.46, 1.64)	1.01	(0.53, 1.92)
Don't know partner age	5/70.36	7.11	(2.96, 17.07)	0.94	(0.39, 2.29)	0.94	(0.38, 2.28)
No	228/3112.78	7.32	(6.43, 8.34)	1.00	-	1.00	-
Participants < 25 years	172 /1877.54	9.16	(7.89, 10.64)				
Primary partner >5 years older							
Yes	47/480.43	9.78	(7.35, 13.02)	1.09	(0.78, 1.53)	1.13	(0.80, 1.59)
Don't know partner age	4/35.30	11.33	(4.25, 30.19)	1.17	(0.43, 3.18)	1.13	(0.41, 3.09)
No	121/1361.81	8.89	(7.43, 10.62)	1.00	-	1.00	-
Primary partner >10 years older							
Yes	7/67.04	10.44	(4.98, 21.90)	1.16	(0.54, 2.48)	1.24	(0.57, 2.68)
Don't know partner age	4/35.30	11.33	(4.25, 30.19)	1.14	(0.42, 3.11)	1.10	(0.41, 3.01)
No	161/1775.20	9.07	(7.77, 10.58)	1.00	-	1.00	-
Participants ≥ 25 years	71/1466.03	4.84	(3.84, 6.11)				
Primary partner >5 years older							
Yes	20/391.41	5.11	(3.30, 7.92)	1.09	(0.65, 1.83)	1.27	(0.75, 2.16)
Don't know partner age	1/35.06	2.85	(0.40, 20.25)	0.64	(0.09, 4.64)	0.67	(0.09, 4.95)
No	50/1039.56	4.81	(3.65, 6.34)	1.00	-	1.00	-
Primary partner >10 years older							
Yes	3/93.39	3.21	(1.03, 9.96)	0.63	(0.20, 2.01)	0.75	(0.23, 2.41)
Don't know partner age	1/35.06	2.85	(0.40, 20.25)	0.61	(0.08, 4.41)	0.62	(0.09, 4.55)
No	67/1337.58	5.00	(3.94, 6.36)	1.00	-	1.00	-

	HIV infections/person-years	HIV incidence[1] (95% CI)		Univariate model[2] HR (95% CI)		Multivariable model[3] HR (95% CI)	
Sensitivity analysis[4]							
All participants	194/3005.35	6.46	(5.61, 7.43)				
Primary partner >5 years older							
Yes	52/784.52	6.63	(5.05, 8.70)	1.06	(0.77, 1.46)	1.15	(0.83, 1.59)
Don't know partner age	4/59.02	6.78	(2.54, 18.06)	1.01	(0.37, 2.75)	1.09	(0.40, 2.96)
No	138/2161.81	6.39	(5.40, 7.54)	-	-	-	-
Primary partner >10 years older							
Yes	9/127.96	7.03	(3.66, 13.52)	1.00	(0.51, 1.96)	1.20	(0.61, 2.37)
Don't know partner age	4/53.34	7.50	(2.81, 19.98)	1.00	(0.37, 2.70)	1.06	(0.39, 2.87)
No	148/2526.68	5.86	(4.98, 6.88)	-	-	-	-
Participants < 25 years	139/1671.60	8.32	(7.04, 9.81)				
Primary partner >5 years older							
Yes	40/430.26	9.29	(6.47, 9.68)	1.19	(0.82, 1.73)	1.25	(0.86, 1.82)
Don't know partner age	3/29.34	10.22	(3.30, 31.70)	1.15	(0.36, 3.64)	1.18	(0.37, 3.76)
No	96/1211.90	7.92	(6.49, 9.68)	-	-	-	-
Primary partner >10 years older							
Yes	6/61.10	9.82	(4.41, 21.86)	1.20	(0.53, 2.74)	1.30	(0.56, 3.00)
Don't know partner age	3/29.34	10.22	(3.20, 31.70)	1.10	(0.35, 3.48)	1.13	(0.36, 3.57)
No	130/1581.16	8.22	(6.92, 9.76)	-	-	-	-
Participants ≥ 25 years	55/1333.74	4.12	(3.17, 5.37)				
Primary partner >5 years older							
Yes	12/354.16	3.39	(1.92, 5.97)	0.79	(0.41, 1.50)	0.90	(0.47, 1.73)
Don't know partner age	1/29.68	3.37	(0.47, 23.92)	0.78	(0.11, 5.70)	0.90	(0.12, 6.74)
No	42/949.91	4.42	(3.27, 5.98)	-	-	-	-
Primary partner >10 years older							
Yes	3/71.14	4.10	(1.32, 12.72)	0.92	(0.29, 2.96)	1.10	(0.34, 3.61)
Don't know partner age	1/29.68	3.37	(0.47, 23.92)	0.82	(0.1, 5.98)	0.93	(0.13, 6.94)
No	51/1222.84	4.17	(3.17, 5.49)	-	-	-	-

HR = hazard ratio; CI = confidence interval.

[1] Per 100 person-years.

[2] Stratified by site.

[3] Models for all participants adjusted for age, married or living with a partner, partner provides financial or material support, partner has other partners, any curable STI at baseline, HSV-2 status and alcohol use, and stratified by site. Models stratified by participant age adjusted for married or living with a partner, partner provides financial or material support, partner has other partners, any curable STI at baseline, HSV-2 status and alcohol use, and stratified by site.

[4] Sensitivity analysis censored women when a change in primary partner was reported (no longer having a primary partner or a new primary partner).

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2016 October 01.