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Jonathan Mermin
Joshua Musinguzi
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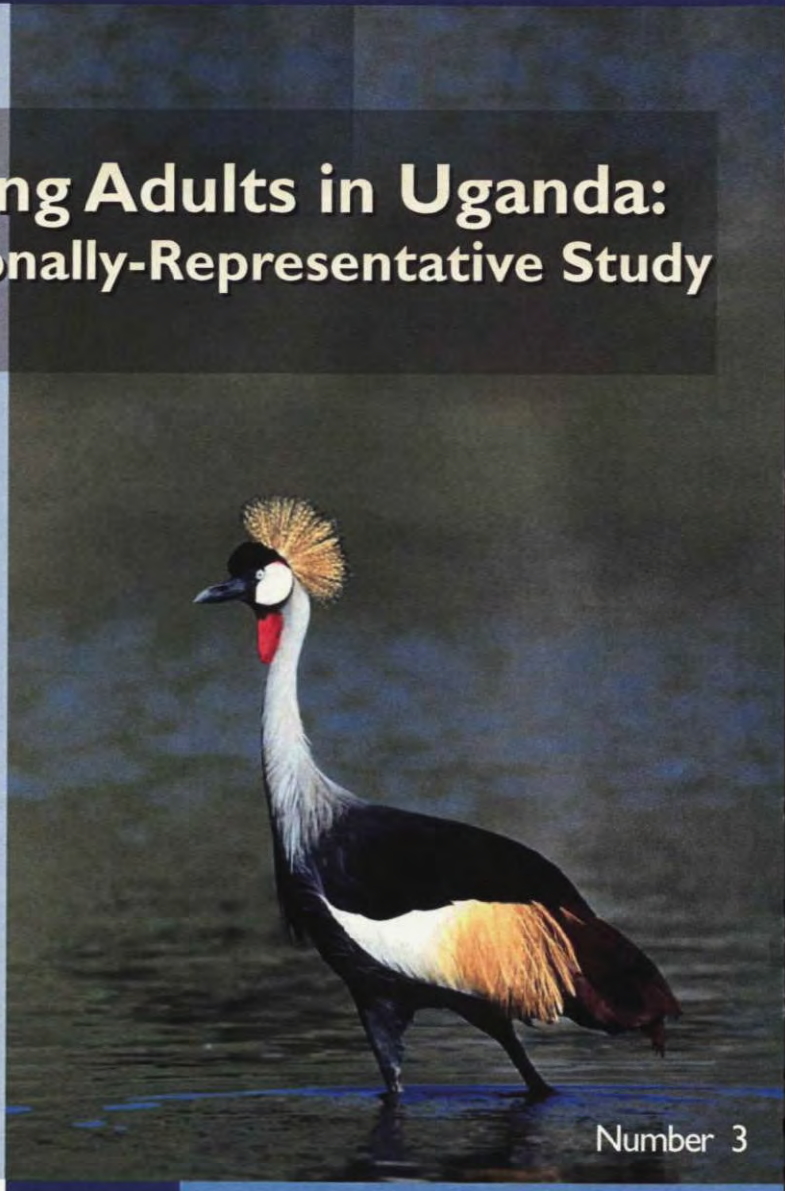

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Based on further analysis of the 2004-05 Uganda HIV/AIDS Sero-Behavioural Survey

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Jonathan Mermin[1]
Joshua Musinguzi[2]
Alex Opio[2]
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John Paul Ekwaru[1]
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Robert Downing[1]
Rebecca Bunnell[1]

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Corresponding author: Jonathan Mermin, CDC-Kenya, Kenya Medical Research Institute, P.O. Box 606-00621, Village Market, Nairobi, Kenya, Phone: +254-20-271-3008 / +254-722-721783, email: jhm7@cdc.gov

[1] CDC-Uganda, Global AIDS Program, National Center for HIV, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention (CDC), Entebbe, Uganda
[2] Uganda Ministry of Health

ABSTRACT

Background: HIV programs can be improved from knowing risk factors associated with HIV acquisition. However, HIV prevalence data poorly reflect HIV incidence in countries that have changing epidemics.

Methods: We analyzed data from a 2004-05, nationally representative, population-based interview survey of adults aged 15-59 years old in Uganda. Blood samples were tested for HIV, syphilis, and herpes simplex virus type 2 (HSV-2). We tested HIV-seropositive specimens with the BED IgG capture-based enzyme immunosorbent assay that identifies infections for which seroconversion occurred on average in the preceding 155 days. We calculated incidence values using a normalized optical density (OD-n) of 0.8 and established adjustments.

Findings: A total of 11,454 women and 9,905 men age 15-59 years were eligible; 90% of women and 84% of men provided blood specimens. After testing, 172 (16%) of 1,092 HIV infections were characterized as recent. Accounting for sampling design and variation in specificity due to stage of infection, weighted incidence was 1.9 infections per 100 person years (95%CI 1.59-2.21). Sixty-five percent (65%) occurred among married people, 26% among divorced or widowed, 9% among never married, and 77% occurred among people ≥25 years of age.

In multivariate analysis, recent HIV infection was associated with the number of sexual partners in the past year (>2 partners compared with none (OR 2.5 [1.3-4.6]), HSV-2 (OR 3.9 [2.6-5.8]), and being an uncircumcised man (OR 2.5 [1.2-5.5]). Among married participants, 84% of recent infections occurred in people who reported no sexual partners outside of marriage in the previous year. Sex without condoms with outside partners was associated with recent infection (OR 3.3 [1.7-6.3]). The risk of recent infection was similar for people who used condoms with partners outside of marriage and those who did not have outside partners (OR 1.0 [0.3-2.7]). Among 74 married participants with recent infection for whom HIV testing was also conducted for their spouse, 38% of recent infections occurred among people whose spouse had long-standing HIV infection, 13% had a spouse with recent HIV infection, and 49% had an uninfected spouse.

Interpretation: The majority of incident HIV infections in Ugandan adults occurred among married people and those ≥25 years. At least half of new infections among married participants were acquired from their spouse. National prevention efforts should include married men and women who are at increased risk because of both existing HIV-discordance and sexual partnerships outside of marriage.

KEY WORDS: HIV, incidence, prevalence, risk factors, BED assay, sexual behavior, Uganda, behavior, condoms

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INTRODUCTION

Implementing effective HIV prevention programs requires information about risk factors that are associated with HIV acquisition. Data should reflect the current country-specific epidemiology of the epidemic. However, HIV prevalence data, the most commonly used information to direct programs, reflect infections that occurred from a few weeks to over a decade prior to the time of testing. In changing HIV epidemics, prevalence data do not reflect incidence, which is the measure of how many new infections occurred over a period of time(1;2). In addition, although prevalence data from routine, anonymous antenatal clinic testing(2;3) and cross-sectional sampling of specific populations(4;5) have often been used to approximate incidence, they are vulnerable to selection bias (6;7), may not represent infections among older people and men, often have limited behavioral data, and present difficulties distinguishing the temporal relationship between potential risk factors and HIV infection. Repeat testing in large population cohorts(8-10), overcomes many of these obstacles, including allowing identification of individuals with recent infection(11;12). However, cohorts are expensive to maintain, are not geographically representative, and may be subject to participation biases, intervention effects, and differential loss to follow-up. Nationally representative cross-sectional surveys that include HIV testing overcome challenges to generalizability, but have been limited to estimating HIV prevalence(6).

HIV incidence has recently been estimated using laboratory-based assays that distinguish between recent and long-term HIV infections(13-17). One of the advantages of a laboratory test is that it can be applied to specimens collected during cross-sectional studies for surveillance purposes(15) and avoids some of the biases inherent in repeatedly testing participants in cohorts(17). Although a previous incidence assay(16) had different performance characteristics for non-B HIV-1 subtypes that are common in many regions of the world, a new enzyme immunosorbent assay specifically designed to have similar sensitivity across subtypes has been developed(14;18) (BED assay, Calypte Biomedical, Lake Oswego, Oregon), and applied to populations in Thailand(13), Cambodia(19), South Africa (DHS), China, Zimbabwe, and North America(20).

The HIV epidemic in Uganda has progressed from initial concentrations of infection among higher-risk groups to a generalized epidemic(1), and risk factors for infection may also have changed. In the 1990's, Uganda experienced nationwide declines in HIV prevalence among antenatal clinic attendees(3) and voluntary counseling and testing clients(21), in addition to reduced incidence and prevalence within population-based cohorts in the Masaka(9) and Rakai(8) districts. These declines have been attributed to increased age of sexual debut(3;22), reductions in sexual partnerships outside of marriage(22), and increased use of condoms(3;23). However, the proportion of incident HIV infections countrywide occurring in traditional higher risk groups, such as young sexually active women, may have shifted, resulting in increased HIV incidence among groups of people who are not

the focus of current prevention programs and for whom data are limited, such as married couples and people aged >35 years. Yet, these groups may contain large proportions of people with incident HIV nationwide.

To assist with program planning, we estimated the current incidence of HIV infection in Uganda and determined demographic and behavioral risk factors associated with recent HIV infection We tested with the BED incidence assay HIV-reactive sera from adult participants 15-59 years old included in the 2005 Uganda HIV/AIDS Sero-Behavioral Survey (UHSBS).

METHODS

Survey design, sampling, and participation

We analyzed data from the 2005 UHSBS, a nationally representative, population-based survey involving adults aged 15-59 years old and children <5 years. Details of the sampling design, survey implementation, and laboratory procedures have been reported elsewhere (24). Briefly, data were collected on behavioral, social, and demographic indicators and venous blood samples were obtained for testing for HIV, syphilis, and herpes simplex virus type 2 (HSV-2). Dried blood spots from fingersticks were collected from adults who refused venous blood draw and from children. Separate informed consent was provided by respondents for interviews and blood sampling. For analyses, we present data only regarding adults.

Laboratory testing

Testing for HIV, syphilis, and HSV-2, was conducted using standard testing and quality-control procedures. HIV testing was performed using two HIV enzyme immunosorbent assays (EIA), based on different antigens (Murex 1.2.0, Abbott; Vironostica Uniform II Plus O, Biomerieux). Specimens with equivocal or discordant test results were retested with the same EIAs, and, if still discordant, were resolved by Western blot testing. All HIV-positive specimens and 5% of negative specimens were re-tested at a different laboratory using the same testing algorithm. Equivocal results were resolved by repeat testing at a third laboratory. For syphilis testing, rapid plasma reagin (RPR) testing was conducted in the field and if requested at the time of interview, results were provided by a nurse to participants the next day. Treatment with benzathine penicillin was provided for titers >1:8. Syphilis testing was repeated using RPR and *Treponemal pallidum* haemaglutination assay testing [TPHA] in the laboratory and results from this testing were used in analyses. HIV test results were not provided to participants; however, vouchers were provided for free HIV counseling and testing at a local or mobile testing site. Specimens were tested for HSV-2 using indirect EIA (Kalon Biological HSV-2 IgG, Guildford, UK). Laboratory test results for individuals were anonymously linked to questionnaire information through bar codes.

To determine recent HIV infections, we tested all HIV-1-seropositive specimens with the BED IgG capture-based enzyme immunosorbent assay that identifies infections for which seroconversion occurred during the past 155 days (95%CI 146-165 days)(14;18). Sera were diluted 1/100 and incubated on goat-antihuman IgG-coated microwell plates to allow capture of HIV and non-HIV IgG. HIV-specific IgG was detected by a multisubtype-derived branched peptide (BED-biotin), followed by streptavidin-peroxidase. For each run, optical density values were normalized using a calibrator specimen. Specimens with a normalized optical density (OD-n) of ≤ 1.2 during initial testing were retested in triplicate and the mean value was used as a final result. Samples positive on BED assay testing were categorized as "recent". Because data indicated that use of a cut-off OD-n of 0.8 without

adjustment may overestimate HIV incidence, we calculated absolute incidence values accounting for established sensitivity and varying specificity in relation to time from initial infection. We repeated risk factors analyses using a conservative OD-n cut-off of 0.4, a value derived empirically from maximizing concordance between the BED assay and an HIV avidity assay (Dr.Bharat Parekh, personal communication). BED test results were not provided to participants, as the assay has only been validated for population-level testing.

Data analysis.

Data were double entered using CSPro (ORC Macro, Calverton, MD), and analyzed using SAS (SAS Institute, Cary, NC, USA). Analyses of overall and group-specific incidence were weighted to account for the sampling design to provide national estimates, and annual incidence rates and 95% confidence intervals (CI) were calculated using established formulas (14) adjusting for missing results (Appendix 1).

To evaluate associations between potential risk factors and recent infection, we compared people with recent infection with the population uninfected with HIV. Separate multivariate logistic regression models were developed for sexually active, married participants and the entire population. Multivariate results are presented unless otherwise specified, and weighted results used in analyses. Demographic variables of age, sex, and rural or urban residence were retained in all models because they were associated with HIV prevalence. Other variables were retained if they were statistically significant at $p<0.05$. Population attributable risk for individual factors was calculated using the equation $PAR = P (OR - 1)/[1+P(OR - 1)] * 100$. P is the proportion of the population with a particular risk factor, and OR is the adjusted odds ratio from multivariate logistic regression models.

The survey protocol was approved by the Institutional Review Boards of the Uganda Virus Research Institute and ORC Macro, and by the Uganda National Council of Science and Technology and the Centers for Disease Control and Prevention (CDC).

RESULTS

We collected information from 9,529 households in 417 sample enumeration areas. A total of 11,454 women and 9,905 men age 15–59 years were eligible for individual interviews and blood sample collection. Of the eligible women and men, individual questionnaires were completed for 95% of women and 89% of men, and blood specimens were collected for 90% of women and 84% of men.

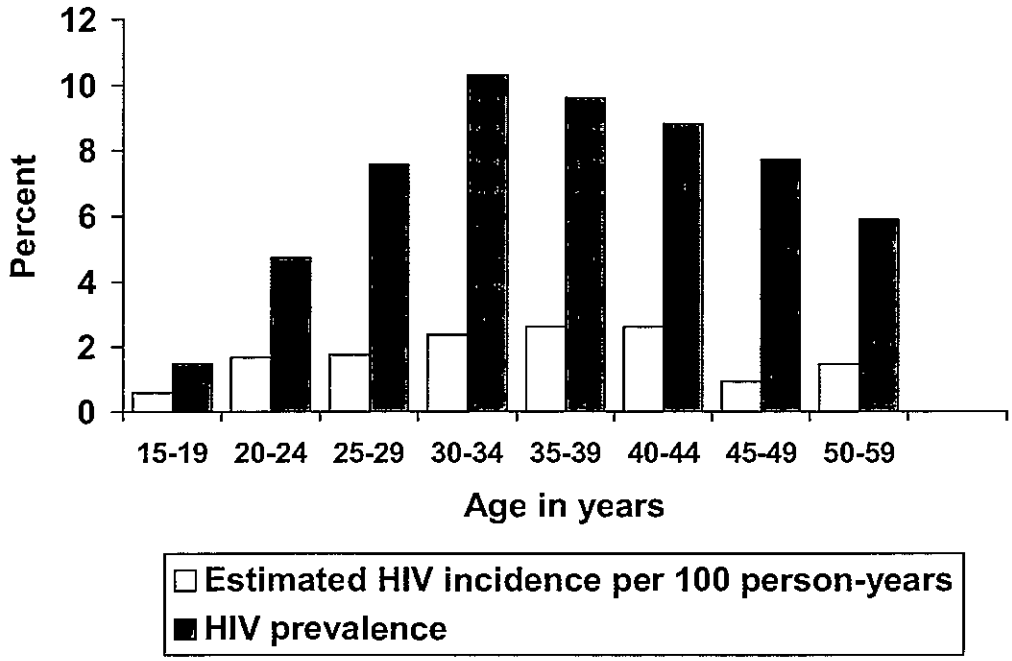
Among 18,525 participants screened for HIV, 1,092 were HIV-infected. Of these, 172 (16%) infections were categorized as recent. Weighted HIV prevalence was 6.3%; weighted incidence was 1.9 infections per 100 person years (95% confidence interval 1.59-2.21). HIV incidence was higher among women than men (2.2 vs. 1.5 per 100 person-years), and higher for people ≥25 years of age than <25 years (2.4 vs. 1.1 per 100 person-years), currently married than never married people (2.1 vs. 0.8 per 100 person-years), and varied by household wealth and geographic region (Table 1).

Table 1 HIV incidence in different demographic groups, Uganda, 2005

	Total screened	HIV infected	Weighted HIV prevalence	Recent HIV infections	Proportion of infections recent	Weighted incidence per 100 person years	95%CI
Sex							
Male	8,298	397	5.2	65	16	1.5	(1.10-1.94)
Female	10,227	695	7.3	107	15	2.2	(1.76-2.68)
Age in years							
15-24	6,959	189	2.9	39	21	1.1	(0.75-1.53)
25-34	5,380	440	8.9	63	14	2.4	(1.73-3.07)
35-59	6,186	463	8.1	70	15	2.4	(1.78-3.00)
Current marital status							
Never married	4,970	73	1.6	16	22	0.8	(0.40-1.14)
Married	11,201	635	6.1	111	17	2.1	(1.63-2.47)
Widowed	911	209	24.7	24	11	5.3	(2.73-7.85)
Divorced	1,353	172	13.3	21	12	3.3	(1.71-4.79)
Education							
Primary or less	14,265	843	6.5	136	16	1.9	(1.58-2.30)
Secondary or more	4,259	249	5.9	36	14	1.8	(1.14-2.38)
Residence							
Rural	15,493	799	5.7	132	17	1.8	(1.44-2.10)
Urban	3,032	293	10.1	40	14	2.6	(1.63-3.61)
Wealth index							
Lowest	3,532	131	4.5	20	15	1.3	(0.63-1.89)
Lower	3,942	197	5.7	31	16	1.4	(0.81-1.99)
Middle	3,365	185	5.9	35	19	2.1	(1.37-2.87)
Higher	3,395	213	6.4	35	16	2.3	(1.49-3.01)
Highest	4,291	366	8.5	51	14	2.3	(1.58-3.02)
Region							
North Central	1,945	158	8.1	40	25	4.7	(3.10-6.20)
Southwest/West	4,028	265	6.5	42	16	2.0	(1.32-2.60)
Central/Kampala	5,724	441	7.6	57	13	1.9	(1.42-2.44)
Eastern/Northeast	4,100	170	4.5	27	16	1.2	(0.58-1.74)
West Nile	2,728	58	2.2	6	10	0.2	(-0.13-0.43)
Overall	18,525	1,092	6.4	172	16	1.9	(1.59-2.21)

Of all incident infections, 65% occurred among married people, 9% among single people, and 26% among divorced or widowed people. In addition, 77% occurred among people ≥25 years of age, and 77% occurred among people living in a rural area of the country. Of all incident infections, 67% occurred among people who reported having had only one sexual partner in the previous year (81% of women and 49% of men), and 20% among people who reported only one lifetime partner (29% of women and 7% of men). HIV incidence and prevalence increased with age of participants; however, the proportion of prevalent infections that were recent was greatest at younger ages (Figure 1).

Figure 1 Estimated HIV incidence and prevalence among adults in Uganda, 2005



In multivariate analysis, adjusting for demographic, behavioral, and biological factors, having a recent HIV infection was associated with: the number of sexual partners in the last year (OR 2.5 [1.3-4.6]; having had ≥2 partners compared with none); having HSV-2 infection (OR 3.9 [2.6-5.8]); having had a sexually transmitted infection in the last year (OR 1.7 [1.2-2.3]); and being an uncircumcised man (OR 2.5 [1.2-5.5]). Widowhood, geographic region, and sex were also factors (Table 2).

Table 2 Risk factors associated with recent HIV infection among adults aged 15-59 years, Uganda, 2005

Variable	Number at risk	Number of recent infections	Weighted incidence per 100 person-years	95%CI	Unadjusted OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value	Population attributable risk[1]
Sex									
Male	7,966	65	2 1	(1.61 - 2.62)					
Female	9,639	107	3.0	(2 50 - 3 60)	1.4(1.1 - 1.9)	0 0225	2.4(1.1 - 5.3)	0.0253	
Age in years									
15-24	6,809	39	1.4	(1 02 - 1 93)	0.4(0.3 - 0 6)	0.0000	1 2(0 8 - 2 0)	0.3879	
25-34	5,003	63	3.4	(2.66 - 4.29)	1 1(0.8 - 1 5)	0.6944	1 3(0 9 - 1.9)	0.1749	
35–59	5,793	70	3 3	(2.59 - 4.07)					
Current marital status									
Never married	4,913	16	0.9	(0.55 - 1.43)					
Married	10,677	111	2 7	(2 24 - 3 23)	3.1(1.9 - 5 2)	0 0000	1.2(0.6 - 2 4)	0 5784	
Widowed	726	24	8.6	(5.66 - 12 51)	10 4(5.6 - 19.3)	0.0000	4 5(2.0 - 10.2)	0.0003	12.7
Divorced	1,202	21	4 8	(3.14 - 7 10)	5.6(3.0 - 10 5)	0 0000	2.6(1.2 - 5 4)	0 0114	9.9
Education									
Primary or less	13,558	136	2 6	(2.23 - 3.09)					
Secondary or more	40,46	36	2.4	(1.76 - 3 29)	0 9(0.7 - 1 3)	0 6817			
Residence									
Rural	14,826	132	2 3	(1.98 - 2.75)					
Urban	2,779	40	4.0	(2.89 - 5 44)	1.6(1 1 - 2.3)	0 0132	1 4(0 8 - 2 2)	0.2003	
Wealth index									
Lowest	3,421	20	1 8	(1 11 - 2.69)					
Middle	10,208	101	2 5	(2 08 - 3 03)	1.4(0.9 - 2 3)	0 1534	1.1(0.6 - 1 7)	0 8319	
Highest	3,976	51	3 3	(2.52 - 4.31)	1.8(1 1 - 3 0)	0 0275	1.3(0.7 - 2 3)	0 4315	
Region									
Central/Kampala	5,340	57	2 7	(2.10 - 3.34)					
North Central	1,827	40	5 5	(3.97 - 7.50)	2 1(1 4 - 3 1)	0.0003	2.7(1 7 - 4 2)	0 0000	15 0
East/Northeast	3,957	27	1 8	(1 15 - 2 68)	0.7(0.4 - 1.1)	0 1315	1.2(0.7 - 2.0)	0 4972	
Southwest/West	3,805	42	2 6	(1.94 - 3 48)	1.0(0.7 - 1.5)	0 8189	1.5(1.0 - 2.3)	0 0553	
West Nile	2,676	6	0 6	(0 17 - 1.47)	0.2(0.1 - 0 6)	0 0037	0.1(0.0 - 0.9)	0 0393	

Continued

Table 2- *Continued*

Variable	*Number at risk*	*Number of recent infections*	*Weighted incidence per 100 person-years*	*95%CI*	*Unadjusted OR (95%CI)*	*p-value*	*Adjusted OR (95%CI)*	*p-value*	*Population attributable risk*[1]
Number of sex partners in past year									
0	4,999	28	1.5	(1.01 - 2.10)					
1	10,756	116	2 8	(2.35 - 3 35)	1.9(1.3 - 2 9)	0.0016	1.4(0.8 - 2 3)	0 2190	
2+	1,756	28	4.3	(2.94 - 5.97)	2.9(1.7 - 4.8)	0.0000	2.5(1.3 - 4.6)	0.0053	13.1
Age at first sex									
Never had sex	2,610	2	0 16	(0.01 - 0 62)	0 1(0 0 - 0 3)	0.0003			
<15 yrs old	2,518	29	2 9	(1.99 - 4 07)	1.0(0.6 - 1.7)	0.9205			
15-17 yrs old	6,314	78	3.3	(2.63 - 4.03)	1.1(0.7 - 1.7)	0.6960			
18-19 yrs old	3,420	38	2 8	(1.99 - 3 81)	1.0(0 6 - 1 6)	0.9023			
20+ yrs old	2,611	25	2 8	(1 89 - 4 05)					
Lifetime number of sex partners									
0	2,610	2	0 16	(0 01 - 0 62)					
1	4,810	34	1.8	(1.27 - 2 54)	11 0(2 4 - 50.8)	0 0021			
2	3,294	32	2 5	(1.75 - 3 49)	14.7(3.2 - 68.2)	0.0006			
3	2,239	30	3 6	(2.52 - 5 02)	21.9(4.7 - 101 3)	0 0001			
4+	4,305	69	4 1	(3 26 - 5 12)	25 1(5 5 - 113 3)	0 0000			
HSV-2 infection									
Negative	9,607	32	0 9	(0 63 - 1 25)					
Positive	7,236	140	4.7	(3.93 - 5 46)	5.4(3.7 - 7.9)	0.0000	3 9(2 6 - 5 8)	0 0000	55 5
Reported sexually transmitted disease in past year									
No	13,938	101	1 9	(1 60 - 2 34)					
Yes	3,574	71	4 9	(3 89 - 6 10)	2 6(1.9 - 3.5)	0.0000	1.7(1.2 - 2.3)	0.0021	12 5
Sypbilis									
No	16,451	164	2 5	(2.16 - 2 92)					
Yes	578	8	3 7	(1 69 - 7 02)	1.4(0 7 - 2.8)	0.3786			

Continued...

Table 2- *Continued*

Variable	Number at risk	Number of recent infections	Weighted incidence per 100 person-years	95%CI	Unadjusted OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value	Population attributable risk[†]
Circumcision									
Man circumcised									
Yes	1,983	7	1 1	(0.47 - 2 00)					
No	5,935	58	2.4	(1.86 - 3.12)	2.2(1.1 - 4.6)	0.0269	2.5 (1.2 - 5 5)	0 0180	33 6
Female respondent	9,639	107	3 0	(2 50 - 3 60)	2 7(1 4 - 5.5)	0.0044	1.0	.	
Blood transfusion									
Received in past year	491	3	2 5	(0 84 - 5 57)					
Did not receive in past year	17,114	169	2.6	(2.23 - 2.99)	1 1(0 4 - 2.7)	0.8301			
Number of injections by health professional in past year									
0	9,727	78	2 2	(1 75 - 2 68)	0 6(0 5 - 0.9)	0.0051			
1	1,273	11	2.4	(1 29 - 4 12)	0 7(0 4 - 1 3)	0 2347			
2	1,385	15	2 8	(1 64 - 4.51)	0 8(0 5 - 1.4)	0.4963			
3+	4,819	65	3 4	(2.68 - 4 32)					
Pregnancy									
Woman pregnant									
Yes	8,480	96	3 0	(2.49 - 3 65)	1.4(1.1 - 2.0)	0.0216			
No	1,036	11	3 2	(1 71 - 5.34)	1 5(0.8 - 2.7)	0.2246			
Male respondent	7,966	65	2 1	(1.61 - 2.62)					
Religion									
Moslem	2,354	14	1.7	(1.01 - 2 76)					
Christian	14,902	154	2 7	(2.32 - 3.15)	1.6(1.0 - 2.7)	0.0760			
Other or no religion	208	3	3.3	(0.55 - 10.35)	2.1(0 5 - 7 8)	0 2909			

[†]Calculated for potentially modifiable risk factors associated with recent HIV infection

Potential factors not statistically associated with recent infection included education, wealth, urban residence, religion, current employment, age at first sex, lifetime number of sexual partners, current pregnancy, syphilis infection, drinking alcohol by respondent or partner before last sexual activity, having received a blood transfusion in the previous year, and number of medical injections in previous year.

Among sexually active, married participants, recent HIV infection was associated with having sexual partners outside of marriage, lack of condom use, reported STDs in the last one year, circumcision and HSV-2 infection (Table 3). Sex without condoms with partners outside of marriage was associated with an increased risk of recent HIV infection (OR 3.3 [1.7-6.3]) compared with people who had no outside partners. The risk of incident HIV infection was similar for people who used condoms with outside partners and those who did not have any partners outside of marriage (OR 1.0 [0.3-2.7]). Among sexually active, married participants, 84% of recent infections occurred in people who reported no sexual partners outside of marriage in the previous year: 98% among women and 67% among men. Restricting the analysis to 74 married participants with recent infection for whom HIV testing was also conducted for their spouse, 38% of incident infections occurred among people whose spouse had long-standing HIV infection, 13% had a spouse with recent HIV infection, and 49% had a spouse who was uninfected.

Table 3 Risk factors associated with recent HIV infection among sexually active, married adults aged 15-59 years, Uganda, 2005

Factor	Number at risk	Number of recent infections	Weighted incidence per 100 person-years	95%CI	Unadjusted OR (95%CI)	*p*-value	Adjusted OR (95%CI)*	*p*-value	Population attributable risk
Condom use during last sex with partners outside marriage in last year									
Never used condom with outside partners	397	12	7.8	(4.24 - 13.24)	3.3(1.8 - 6.0)	0.0001	3.3(1.7 - 6.3)	0.0002	8.6
Used condom with at least one partner	414	5	2.3	(0.69 - 5.65)	0.9(0.3 - 2.5)	0.8743	1.0(0.3 - 2.7)	0.9675	
No outside partner	9,371	89	2.4	(1.97 - 2.98)					
HSV-2 infection									
Negative	4,903	20	1.1	(0.69 - 1.67)					
Positive	4,911	86	4.1	(3.27 - 5.03)	3.9(2.4 - 6.4)	0.0000	4.0(2.4 - 6.8)	0.0000	60.0
Reported sexually transmitted disease in past year									
No	7,607	61	2.1	(1.66 - 2.72)					
Yes	2,578	45	4.0	(2.96 - 5.34)	2.0(1.4 - 2.9)	0.0004	1.6(1.0 - 2.4)	0.0354	13.2
Circumcision									
Man circumcised									
Yes	1,120	3	0.8	(0.22 - 2.14)					
No	3,249	45	3.4	(2.50 - 4.56)	4.0(1.4 - 11.5)	0.0087	4.3(1.3 - 14.3)	0.0190	51.3
Female	5,817	58	2.6	(1.99 - 3.31)	3.0(1.1 - 8.4)	0.0367	1.0(- .)		

*Adjusting for sex, age, rural residence, religion, geographical region,, and household wealth Factors not associated with incident infection included educational level, current employment, age at first sex, lifetime number of sexual partners, polygynous or monogynous marriage, syphilis, blood transfusion in past year, number of medical injections in past year, circumcision, current pregnancy, and drinking alcohol by respondent or partner before last sex

We repeated the risk factor analysis using a 0.4 n-OD cut-off for the BED assay and found similar results to when a 0.8 cut-off was used. That is, incident HIV infection was associated with: HSV-2 infection (OR 4.0 vs. 3.9); being an uncircumcised man (OR 2.6 vs. 2.5); having $\geq$2 sexual partners in the last 12 months compared to none (OR 4.1 vs. 2.5); and living in the north-central region compared with Kampala (OR 3.0 vs. 2.7).

The population attributable risk (PAR) for incident infection was substantial for several potentially modifiable factors. For example, the PAR for having more than one sexual partner in the past year was 13%, and being an uncircumcised man was 34% (Table 2). For sexually active, married participants, the PAR for not using a condom with partners outside of marriage was 9%, and for prevalent HSV-2 infection, it was 60%.

DISCUSSION

The majority of incident HIV infections in a nationally-representative sample of Ugandan adults occurred among married people and those aged 25 years or older. In addition, among married participants about half of new infections occurred among those who had a spouse with HIV infection. These data highlight the need to expand HIV prevention efforts to include not only young, single people, but also older, married people among whom the majority of new infections occur.

Several risk factors for infection provide prevention opportunities. Over half of all new HIV infections in Uganda could potentially be prevented if the risks associated with having multiple sexual partners, not using condoms with partners outside of marriage, and lack of circumcision were eliminated. Programs promoting faithfulness are increasingly a part of prevention efforts in Africa, and are likely to be most fruitful among couples where both partners have been tested and are uninfected. Consistent condom use has been associated with an 80% reduction in HIV transmission (25), and is particularly effective with partners outside marriage and within HIV-discordant couples.

Eighty-four percent of recent infections among married people occurred in those reporting no sexual partners outside of marriage in the past year, supporting the hypothesis that transmission within marriage is an important driving force in the HIV epidemic. In a sub-analysis among 72 couples for whom HIV status was known for both partners and at least one partner had recent HIV infection, 51% of recent infections occurred among people whose spouse had HIV. The difference in these self-reported and biological estimates may reflect reluctance among some participants to report outside relationships, or a limited sample size and reduced precision for the couple analysis. In either case, for at least one-half of all recent infections among married people, infection was likely to have come from a spouse. For some, partners may have been infected with HIV before marriage, as the majority of spouses reported monogamy and most had an infection that was outside the window period of the BED assay. These data support the importance of HIV testing for married couples who often assume that they are not at risk of acquiring HIV from their spouse, especially if the relationship is monogamous.

One randomized controlled trial in South Africa found that adult male circumcision was associated with a 61% reduction in the risk of HIV acquisition(26). Two additional randomized trials are currently being implemented in Kenya and Uganda. If these findings support the benefits of circumcision on HIV prevention, then efforts should be made to operationalize programs in areas of high incidence. Prevalent HSV-2 infection has been associated with increased risk of HIV acquisition and transmission(27;28). It has also been cited as a potential driving force of the epidemic in Uganda(28) and elsewhere in Africa(30). Most behavioral interventions focused on preventing HIV infection should also prevent HSV-2. However, 44% of Ugandans were infected with HSV-2, raising

the question as to whether acyclovir suppressive therapy might be useful in preventing HIV transmission from people with HSV-2 and HIV co-infection living with uninfected partners, a hypothesis currently being examined in a randomized trial.

Young women in Uganda experienced a higher risk of incident HIV infection than young men, and throughout their lives men were more likely to have sexual partners outside of marriage. These differences highlight the potential benefit of focusing specific interventions on changing social norms, such as power differentials between men and women regarding sex and reproductive choice, social expectations regarding sex, access to financial resources and education, and sexual violence. The high rate of recent HIV infection among divorced people may reflect some of these imbalances. The increased odds of recent infection among widows may result from some of the same factors as well as a high risk for HIV transmission during end-stage HIV disease when a person's viral load is high.

The response rate to this nationally-representative survey was high; 90% of women and 84% of men participated, supporting the generalizability of the findings. However, we had a limited sample of recent infections. This resulted in relatively wide confidence intervals around incidence estimates, and may have resulted in our identifying only major risk factors for infection. There may have been some misclassification of HIV incident infections. The BED assay has previously overestimated incidence when using a 0.8 n-OD value. To account for this, we adjusted absolute incidence measurements using standard procedures. The BED assay is likely to have an increased frequency of false positive results during long-standing infections, which might have increased the estimated incidence in older age groups. In support of its use, the HIV incidence estimate using the BED assay for the Southwest-West region of 2.0 per 100 person years is comparable to the rate of 1.7 per 100 person years found in a large population-based cohort in Rakai District, Uganda in 2002-3 (31). There is internal consistency to the estimates. A higher proportion of HIV infections were reactive on the assay among youth compared with older people (15% vs. 9%). And, the number of sexual partners in the previous year was associated with incident infection whereas number of lifetime sexual partners was not. In addition, the highest incidence was noted in the North-Central region of the country, twice as high as the central Kampala region, even though HIV prevalence was comparable. The North-Central region of Uganda is experiencing a civil war, and it is plausible that HIV incidence may be higher than in other areas, and potentially increasing. Lastly, associations among incident HIV infection and HSV-2, circumcision, and number of sexual partners in the past year are reasonable from an epidemiologic perspective. These data support the supposition that we are identifying incident rather than prevalent infections. These data support the benefits of using nationally-representative, population-based HIV surveys for evidence-based program planning.

A national HIV incidence of 1.9 per 100 person years is high compared with a prevalence of 6.3%, and may indicate increasing incidence rates, particularly in certain regions of the country. As noted previously(1), stable HIV prevalence can mask changes in HIV incidence. This may be especially relevant as antiretroviral therapy becomes increasingly available and HIV prevalence begins to rise due to declines in HIV-associated mortality. However, our confidence intervals are relatively large and assessment of trends in incidence will require a repeat national survey.

The HIV epidemic in Uganda may portend the future for other countries in Africa. HIV prevalence peaked in Uganda in the early 1990's and in other countries in East Africa several years later(32). In Uganda, HIV prevalence appears to have stabilized for the past few years, and many countries in West and Central Africa have mature HIV epidemics with unchanging prevalence(32). Improved prevention programs are necessary to reduce HIV prevalence, especially during a time when care and antiretroviral treatment programs are increasing survival. Prevention efforts should focus on evidence-based behaviors that are known to prevent infection, such as reduced number of sexual partners (22), condom use (25), and delayed age of sexual debut(22). Efforts should also explore new approaches, such as reducing transmission from people with known HIV infection (Positive Prevention) (33) and increasing routine HIV counseling and testing in clinical and community settings (34). Other interventions, such as circumcision and acyclovir prophylaxis, may have a substantial impact if found effective in clinical trials and implemented on a wide-scale, particularly in countries like Uganda where the attributable risk associated with lack of circumcision and HSV-2 infection is large. Cross-sectional, nationally-representative serologic surveys are useful for providing information for monitoring the HIV epidemic and program planning.

Despite current prevention efforts, 3.1 million new HIV infections occurred in 2004 in sub-Saharan Africa (35). New initiatives to prevent HIV infection should be at a scale comparable to current programs improving access to antiretroviral therapy (36). Without this, countries in Africa are likely to experience continued, if not worsening, HIV epidemics.

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APPENDIX

Formulas for calculating adjusted, weighted incidence and 95% confidence intervals.

$$I = \frac{(365/W) \times S \times f \times N_{inc}}{N_{neg} + (365/W) \times S \times f \times N_{inc}/2} \times 100$$

95% Confidence interval $= I \pm 1.96 \frac{I}{\sqrt{S \times f \times N_{inc}}}$

Where:

f is a factor adjusting for missing BED assay results from HIV-positive specimens

$$f = \frac{N_{inc}}{(N_{pos} - N_{mis})}$$

S adjusts for varying specificity from time of HIV infection

$$S = \frac{(f \times N_{inc}/N_{pos}) + (SP2 - 1)}{((f \times N_{inc}/N_{pos}) \times (SS - SP1 + 2 \times SP2 - 1))}$$

W = Window period (155 days)
N_{inc} = Weighted number of recent infections (BED positive)
N_{neg} = Weighted number of HIV seronegative specimens
N_{pos} = Weighted number of HIV-positive specimens
N_{mis} = Weighted number of HIV positive specimens with missing BED results

To compute weighted incidence estimates we computed weighted numbers as follows:

$N_{pos} = \sum wp$ where $p = 1$ for HIV positive, 0 otherwise
$N_{inc} = \sum w\theta$ where $\theta = 1$ for BED positive, 0 otherwise
$N_{mis} = \sum w\psi$ where $\psi = 1$ for HIV positive with missing BED results, 0 otherwise
$N_{neg} = \sum w\phi$ where $\phi = 1$ for HIV negative, 0 otherwise

and w is the individual weight.