Swaziland HIV Incidence Measurement Survey (SHIMS): a prospective national cohort study

Jessica Justman, Jason B Reed, George Bicego, Deborah Donnell, Keala Li, Naomi Bock, Alison Koler, Neena M Philip, Charmaine K Mlambo, Bharat S Parekh, Yen T Duong, Dennis L Ellenberger, Wafaa M El-Sadr, Rejoice Nkambule

Summary

Background Swaziland has the highest national HIV prevalence worldwide. The Swaziland HIV Incidence Measurement Survey (SHIMS) provides the first national HIV incidence estimate based on prospectively observed HIV seroconversions.

Methods A two-stage survey sampling design was used to select a nationally representative sample of men and women aged 18–49 years from 14 891 households in 575 enumeration areas in Swaziland, who underwent household-based counselling and rapid HIV testing during 2011. All individuals aged 18–49 years who resided or had slept in the household the night before and were willing to undergo home-based HIV testing, answer demographic and behavioural questions in English or siSwati, and provide written informed consent were eligible for the study. We performed rapid HIV testing and assessed sociodemographic and behavioural characteristics with use of a questionnaire at baseline and, for HIV-seronegative individuals, 6 months later. We calculated HIV incidence with Poisson regression modelling as events per person-years × 100, and we assessed covariables as predictors with Cox proportional hazards modelling. Survey weighting was applied and all models used survey sampling methods.

Findings Between Dec 10, 2010, and June 25, 2011, 11 897 HIV-seronegative adults were enrolled in SHIMS and 11 232 (94%) were re-tested. Of these, 145 HIV seroconversions were observed, resulting in a weighted HIV incidence of 2·4% (95% CI 2·1–2·8). Incidence was nearly twice as high in women (3·1%; 95% CI 2·6–3·7) as in men (1·7%; 1·3–2·1, p<0·0001). Among men, partner's HIV-positive status (adjusted hazard ratio [aHR] 2·67, 1·06–6·82, p=0·040) or unknown serostatus (aHR 4·64, 2·32–9·27, p<0·0001) in the past 6 months predicted HIV seroconversion. Among women, significant predictors included not being married (aHR 2·90, 1·44–5·84, p=0·0030), having a spouse who lives elsewhere (aHR 2·66, 1·29–5·45, p=0·0078), and having a partner in the past 6 months with unknown HIV status (aHR 2·87, 1·44–5·84, p=0·0030).

Interpretation Swaziland has the highest national HIV incidence in the world. In high-prevalence countries, population-based incidence measures and programmes that further expand HIV testing and support disclosure of HIV status are needed.

Funding President's Emergency Plan for AIDS Relief (PEPFAR) by the Centers for Disease Control and Prevention.

ICAP at Columbia University, Mailman School of Public Health, Columbia University, New York, NY, USA
(J Justman MD, N M Philip MPH, Y T Duong PhD, Prof W M El-Sadr MD); **Jhpiego, Washington, DC, USA**
(J B Reed MD); **US Centers for Disease Control and Prevention, Center for Global Health, Division of Global HIV/AIDS, Atlanta, GA, USA**
(G Bicego PhD, N Bock MD, B S Parekh PhD, D L Ellenberger PhD); **Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (K Li MS, D Donnell PhD) **Pact, Dar es Salaam, Tanzania** (A Koler MPH); **Clinton Health Access Initiative, Mbabane, Swaziland** (C K Mlambo PhD); **and Ministry of Health— Swaziland, Mbabane, Swaziland** (R Nkambule MPH)

Correspondence to:
Dr Jessica Justman, ICAP at Columbia University, Departments of Epidemiology and Medicine, Mailman School of Public Health, Columbia University, New York, NY 10032, USA
jj2158@columbia.edu

Introduction

Swaziland has the most severe HIV epidemic in the world, with a measured HIV prevalence of 26% among adults aged 15–49 years in 2006–07.[1] To combat this epidemic, in 2009, the Government of the Kingdom of Swaziland (GKOS) initiated support for scale-up of national HIV prevention and treatment programmes, including a voluntary medical male circumcision campaign.[2] The Swaziland HIV Incidence Measurement Survey (SHIMS) was designed to assess the effect of these programmes on HIV incidence by prospectively measuring HIV seroconversions in a household-based, nationally representative sample of adults before and after programme expansion.

The approach of "know your epidemic, know your response"[3] is crucial to effective HIV programmes, and having accurate and detailed HIV incidence estimates is fundamental to this approach. Incidence estimates allow identification of groups at the highest risk of new infections

and, when repeated, determine the effect of programmes over time. Although incidence estimates of large populations are often modelled from trends in HIV prevalence,[4] such modelled estimates provide little demographic detail. HIV incidence laboratory assays[5,6] are intended for use in cross-sectional surveys but have yet to achieve optimum performance.[7] HIV incidence estimates based on the gold standard of observed HIV seroconversions have not been available at a national level although they have been available from randomised clinical trials or observational cohorts restricted to subpopulations at increased risk of HIV.[8,9] We report the national estimate, before programme expansion, of HIV incidence based on population-level, prospectively observed seroconversions.

Methods

Study design and participants

A two-stage sampling design was used to obtain a cross-sectional, nationally representative sample of

Research in context

Evidence before this study
Swaziland's Demographic and Health Survey done in 2006–07 showed a severe generalised epidemic, with an HIV prevalence of 26% in 15–49 year olds. UNAIDS' modelled estimates of prevalence and incidence indicated a similarly severe epidemic. With a goal of reducing new HIV infections, Swaziland planned to scale up national treatment and prevention programmes. The Swaziland HIV Incidence Measurement Survey (SHIMS) was designed to assess HIV incidence before and after scale-up of these intervention programmes by measuring prospectively observed HIV seroconversion in a nationally representative adult cohort. A search of PubMed for studies published in English through to Nov 7, 2016, using the search terms "HIV incidence", "longitudinal cohort", and "nationally representative" confirmed no previous direct measurement of national HIV incidence using this method.
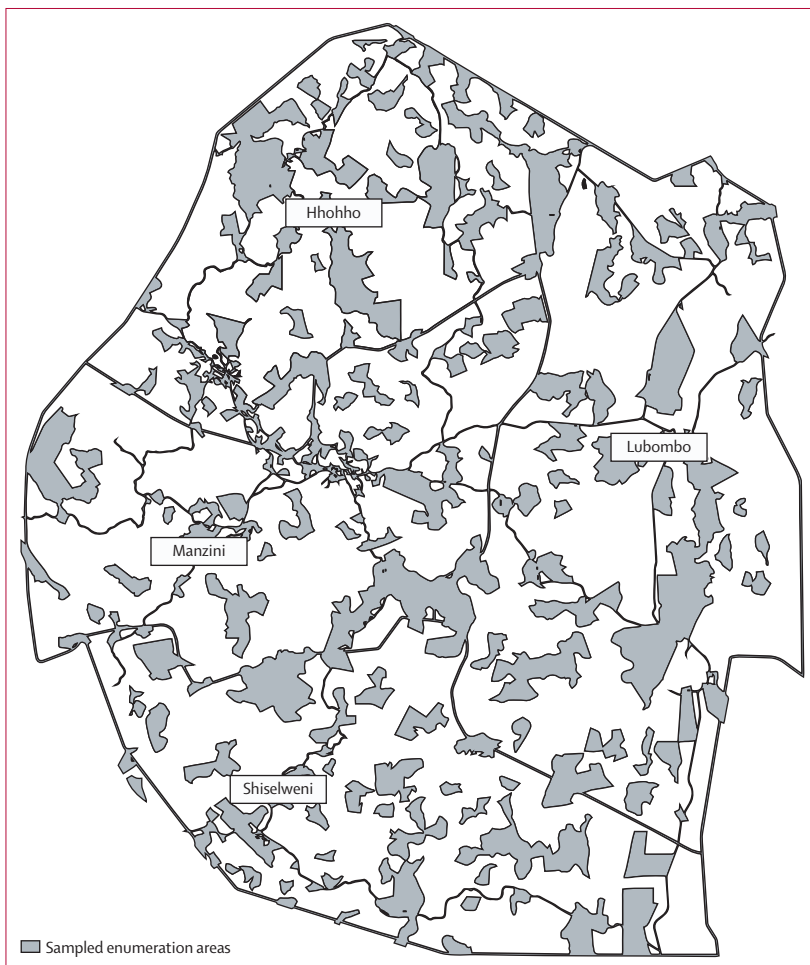
Added value of this study
This study reports the baseline results, before scale up of national interventions, of the first national HIV incidence measurement on the basis of prospectively observed seroconversion, the "gold standard" measure of the spread of infection. High retention rates, a rigorous HIV testing algorithm, and a large number of seroconverter cases permit an accurate and detailed description of HIV incidence in Swaziland, a country at the centre of the global HIV epidemic.

Implications of all the available evidence
As the global scale-up of antiretroviral treatment extends into its second decade, accurate and detailed knowledge of each country's epidemic is increasingly crucial to implement an effective local HIV response.

For the **SHIMS protocol** see http://shims.icap.columbia.edu/publications/type/study-protocol-case-review-forms

Figure 1: **Distribution of the 575 enumeration areas sampled in the Swaziland HIV Incidence Measurement Survey across the four regions of Swaziland**

adults aged 18–49 years in a survey of 14 891 households from 575 enumeration areas in Swaziland (figure 1), with household sample size calculations and other details as previously reported.[10] Each selected household was approached by study personnel trained in Good Clinical Practice[11] who asked responding heads of household to report the sex and age of all household members. All individuals aged 18–49 years who resided or had slept in the household the night before and were willing to undergo home-based HIV testing, answer demographic and behavioural questions in English or siSwati, and provide written informed consent were eligible for the study. We enrolled in the prospective HIV incidence cohort those HIV-seronegative individuals who consented to have a 6 month follow-up home-based HIV testing and counselling visit. The SHIMS protocol and consent forms were reviewed and approved by the GKOS Scientific and Ethics Committee and the institutional review boards at Columbia University Medical Center and the US Centers for Disease Control and Prevention.

Procedures
Study teams comprising one nurse and one or two counsellors did HIV counselling, venepuncture, and rapid HIV testing, provided condoms, and collected demographic, clinical, and behavioural information with questionnaires[12] administered during face-to-face interviews in a private location in or just outside the home. HIV test results were given to participants during the household visit. All HIV-seronegative individuals enrolled in the HIV incidence cohort had a 6 month follow-up visit, with similar procedures, including verification of participant identity and repeat HIV testing. At the baseline and 6 month follow-up interviews, information was obtained about sexual behaviours in the past 6 months and characteristics of the three most

recent sexual partners. Current pregnancy status in women was based on self-report. All individuals who tested HIV seropositive at either the baseline or follow-up visit were counselled and referred to HIV care as per national guidelines.

Rapid HIV testing was done in the field on whole blood samples obtained by venepuncture, as previously described.[10,13] Samples were initially tested with Determine HIV-1/2Ag/Ab Combo (Alere, Japan) and Determine-reactive samples were confirmed with

Uni-Gold HIV Test (Trinity Biotech, Ireland), following Swaziland's serial testing algorithm. All HIV-seronegative samples from the baseline visit, but not the follow-up visit, had a nucleic acid amplification test (NAAT) with pools of ten samples to identify individuals with virological evidence of acute HIV infection.[14,15] Individuals with NAAT-positive results had follow-up visits within 6 months to confirm seroconversion and were subsequently censored from the incidence analyses.[13]
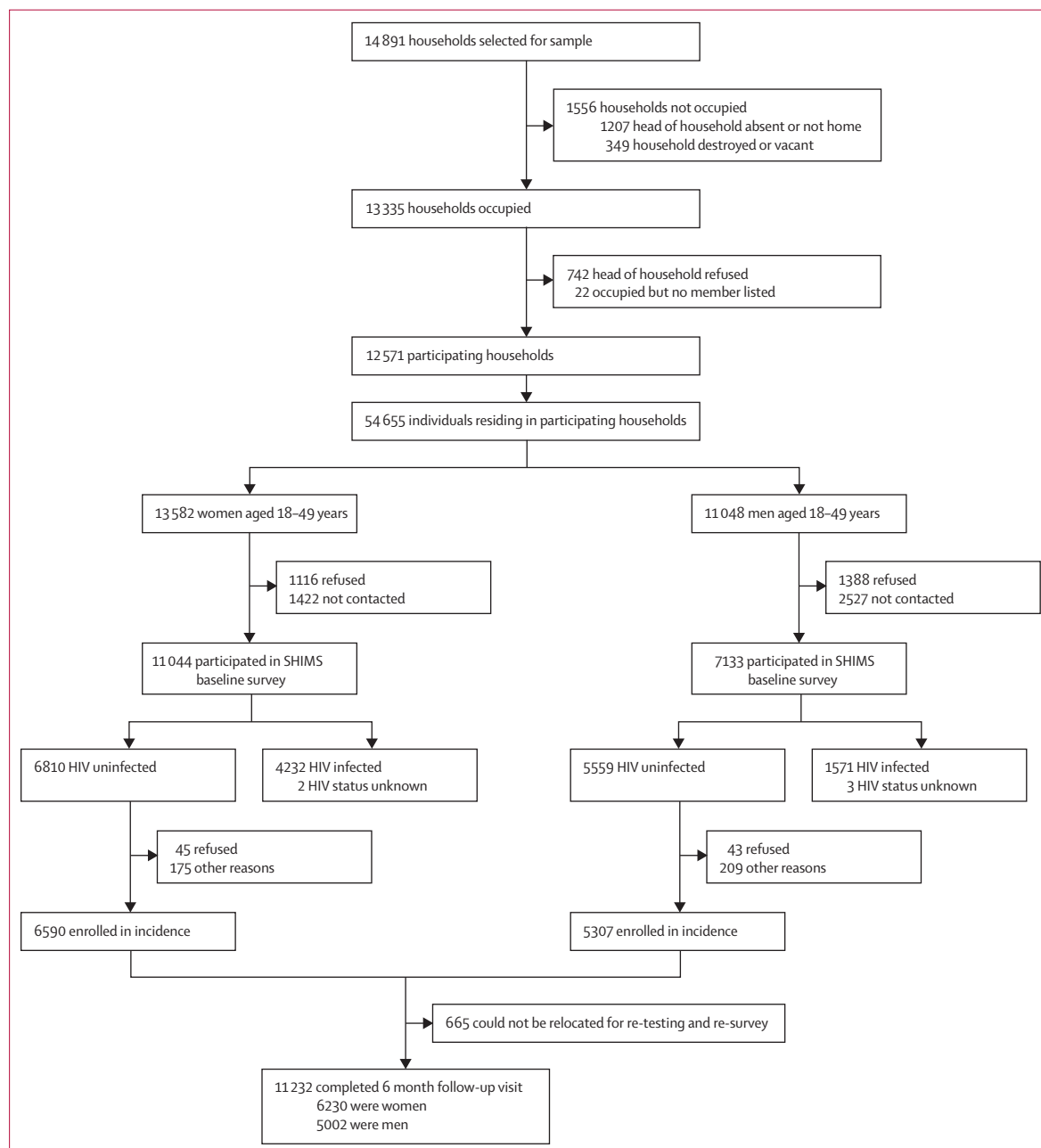
Figure 2: **Study flow diagram**
SHIMS=Swaziland HIV Incidence Measurement Survey.

	Total (n=11 232)	Men (n=5746)	Women (n=5486)
Age (years)*			
18–19	1671 (15%)	897 (16%)	774 (14%)
20–24	3330 (30%)	1775 (31%)	1555 (28%)
25–29	2139 (19%)	1207 (21%)	932 (17%)
30–34	1304 (12%)	729 (13%)	575 (10%)
35–39	1041 (9%)	480 (8%)	561 (10%)
40–44	892 (8%)	359 (6%)	533 (10%)
45–49	855 (8%)	299 (5%)	556 (10%)
Residence*			
Rural	7897 (70%)	4064 (71%)	3833 (70%)
Urban	3335 (30%)	1682 (29%)	1654 (30%)
Region*			
Hhohho	3280 (29%)	1680 (29%)	1600 (29%)
Lubombo	2213 (20%)	1184 (21%)	1029 (19%)
Manzini	3703 (33%)	1874 (33%)	1829 (33%)
Shiselweni	2036 (18%)	1008 (18%)	1028 (19%)
Education*†			
Did not attend	563 (5%)	271 (5%)	292 (5%)
Primary	2899 (26%)	1459 (25%)	1440 (26%)
Secondary	5845 (52%)	2945 (51%)	2900 (53%)
Tertiary (any level of education higher than secondary school)	1877 (17%)	1049 (18%)	828 (15%)
Employment*			
Employed	4413 (39%)	2667 (46%)	1746 (32%)
Unemployed, retired, or disabled	5104 (45%)	1971 (34%)	3133 (57%)
Other, refused, or missing	1715 (15%)	1108 (19%)	607 (11%)
Marital status*			
Not married	6639 (59%)	3992 (69%)	2647 (48%)
Married, living with partner	2820 (25%)	1200 (21%)	1620 (30%)
Married, partner stays elsewhere	1593 (14%)	494 (9%)	1099 (20%)
Lifetime sexual activity*‡			
Never had sex, as reported at both baseline and follow-up¶	1280 (11%)	885 (15%)	395 (7%)
Ever had sex	9855 (88%)	4788 (83%)	5067 (92%)
Sexual activity within the past 6 months (n=9855; 4788 male, 5067 female)*‡			
Sexual activity not reported at baseline or follow-up	858 (9%)	473 (10%)	385 (8%)
Sexual activity reported at baseline only	820 (8%)	424 (9%)	396 (8%)
Sexual activity reported at follow-up only	709 (7%)	449 (9%)	260 (5%)
Sexual activity reported at baseline and follow-up	7284 (74%)	3333 (70%)	3951 (78%)
Missing	184 (2%)	109 (2%)	75 (2%)
Number of sexual partners in the past 6 months (n=9855; 4788 male, 5067 female)‡			
0	1698 (17%)	909 (19%)	789 (16%)
1	7081 (73%)	2946 (62%)	4135 (82%)
≥2	967 (10%)	874 (18%)	93 (2%)
Condom use in the past 6 months (n=8048; 3820 male, 4228 female)‡			
Always	2329 (29%)	1317 (35%)	1012 (24%)
Sometimes	2847 (35%)	1416 (37%)	1431 (34%)
Never	2846 (35%)	1073 (28%)	1773 (42%)

(Table 1 continues on next page)

Statistical analysis

Probability of household selection within census enumeration areas of each of the four regions was designed to be proportional to population size and all household members were approached for selection. Corresponding design weights were then adjusted for non-response, within cross classification of age group, region, urban or rural living area, and sex, and post-stratification weights were calculated to match these same characteristics of the 2007 Swaziland census. Weights were scaled so that the weighted total matched the unweighted total number of participants. Proportions and 95% CIs were computed with survey sampling methods, weighted for sampling design,[10,16] non-response, and post-stratification, to achieve nationally representative findings.

Unless otherwise noted, all analyses were based on all those individuals who were enrolled in the incidence cohort and who completed a follow-up visit; similarly, unless otherwise indicated, for each variable, 1% of participants or less refused to answer the question, answered "I don't know", or had missing data, and these data were excluded. We used statistical methods for multistage surveys throughout, and all models were fitted with SAS, version 9.2. We used survey Poisson regression models to estimate seroincidence rates and CIs.

We analysed factors associated with the risk of seroconversion with survey proportional hazards, including number of sexual partners, marital status, condom use, knowledge of partner's HIV status, pregnancy, and circumcision status. To avoid imposing an assumption of constant HIV risk, we used the Cox proportional hazards model, rather than the Poisson regression model, to assess associations of baseline covariates with HIV seroincidence.

We fitted all regression models separately for men and women. Variables were included in the multivariable models when the covariate had a p value lower than 0·1 in the univariable model. For explanatory variables expected to be consistent over a 6 month period, such as age, marital status, and HIV testing history, the analyses used data collected at baseline; for variables of sexual history, sexual activity in the past 6 months, pregnancy, and male circumcision status, the analysis used data collected at baseline and follow-up. To estimate the risk of HIV seroconversion for covariates of sexual behaviour, such as number of partners in the past 6 months, the analysis used data reported at follow-up, during the period of risk of HIV seroconversion. Population attributable risk was computed with the adjusted hazard ratio (aHR) to estimate the relative risk.

Role of the funding source

The funder participated in study design, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 10, 2010, and June 25, 2011, study staff approached 14891 selected households from the four administrative regions of Swaziland (figure 1). Among the 13335 occupied households (figure 2), the head of household for 12571 (94%) households provided information about 54655 household members, of whom 24630 (45%) were eligible for inclusion in this study on the basis of age and residence. Of these, 18177 (74%) adults agreed to participate in the survey and undergo HIV testing; survey participation rates were higher in women (11044 [81%] of 13582) than in men (7133 [64%] of 11048). Of the 18172 participants with available HIV test results, 5803 (32%) were HIV seropositive and 13 were NAAT positive, as previously reported.[10,13] Among the remaining 12369 potentially eligible HIV-seronegative individuals, 11897 (96%) enrolled in the cohort and, of these, 11232 (94%) were successfully retained and retested for HIV at a 6 month follow-up visit which occurred between Aug 23, 2011, and Feb 4, 2012; the mean duration of follow-up was 6·5 (IQR 6·0–6·7) months.

Survey-weighted estimates show the demographic and behavioural profile of the population of HIV-seronegative adults in Swaziland in 2011 (table 1). The mean age was 28·3 years (27·4 years in men; 29·3 years in women), with about half of participants aged between 20–29 years. Most participants had completed either primary or secondary education, were living in rural areas, and were unemployed. About a third of the seronegative population reported no previous HIV testing.

Among those who reported ever having had sex, most reported at the follow-up visit having one sexual partner within the past 6 months and 967 (10%) of 9855 participants: 874 (18%) of 4788 men and 93 (2%) of 5067 women reported having two or more partners in the past 6 months. Among individuals reporting one or more partners in the past 6 months, most reported all partners as HIV negative, 917 (12%) of 8048 reported one or more HIV-positive partner, and 920 (11%) of 8048 reported having any partner with unknown HIV status. Among individuals reporting one or more partners in the past 6 months, only 24 (<1%) of 8048 reported anal sex, and most opted not to answer this question (data not shown). Potentially eligible HIV-seronegative adults who did not participate in the incidence cohort were less likely to be married (p=0·003), more likely to have two or more partners (p=0·002), and were less likely to have previously tested for HIV (p=0·015).

After applying survey weighting, 145 HIV seroconversions occurred during 6086 person-years of observation, corresponding to an annualised population incidence estimate of 2·4 per 100 person-years (95% CI 2·1–2·8). Incidence was nearly twice as high in women (3·1 per 100 person-years, 95% CI 2·6–3·7) as in men (1·7 per 100 person-years, 95% CI 1·3–2·1; p<0·0001) and patterns of incidence by demographic and behavioural characteristics varied by sex (table 2, figure 3).

	Total (n=11232)	Men (n=5746)	Women (n=5486)
(Continued from previous page)			
HIV status of sexual partners in the past 6 months (n=8048; 3820 male, 4228 female)‡			
All negative partners	6160 (77%)	2928 (77%)	3232 (76%)
Any HIV-positive partners	917 (11%)	401 (11%)	516 (12%)
Any partner with unknown status (and no known HIV-positive partners)	920 (11%)	466 (12%)	454 (11%)
Male circumcision status*‡			
Circumcised at baseline	..	1029 (18%)	..
Circumcised only at follow-up	..	338 (6%)	..
Uncircumcised at baseline and follow-up	..	4372 (76%)	..
Current pregnancy status*‡			
Pregnant at baseline or follow-up	..	..	671 (12%)
Not pregnant at both baseline and follow-up	..	..	4802 (88%)
HIV testing history* (n=11232; 5746 male, 5486 female)			
Any previous testing	7330 (65%)	2911 (51%)	4419 (81%)
No previous testing	3893 (35%)	2830 (49%)	1063 (19%)

Data are survey weighted. Numbers might not add to 100% because of rounding. *Indicates data were collected at baseline visit. †Education refers to highest level of education ever attended, whether or not that level was completed. ‡Indicates that data were collected at follow-up visit; unless otherwise indicated, for each variable, 1% or fewer participants refused to answer the question, answered "I don't know", or had missing data (in these cases data were excluded for the variable). ¶The variables "lifetime sexual activity" and "recent sexual activity" were constructed from responses to questions at both baseline and follow-up. There were 113 people who responded that they had "never had sex" at follow-up but had indicated at the baseline visit that they had been sexually active. These individuals were assigned to the category "sexual activity reported at baseline only" within the "recent sexual activity" variable.

Table 1: Demographic and behavioural characteristics of HIV-uninfected adults aged 18–49 years in Swaziland in 2011

HIV incidence in men peaked in those aged 30–34 years (3·1 per 100 person-years, 95% CI 1·9–5·1). HIV incidence was high in those reporting some condom use in the past 6 months (3·1 per 100 person-years, 2·1–4·3), two or more partners (3·8 per 100 person-years, 2·5–5·6), or a partner with unknown HIV status (7·0 per 100 person-years, 4·6–10·5). Age, employment status, sexual activity in the past 6 months, number of partners in the past 6 months, partner's HIV status, and condom use were included in the multivariable model for the men, and partner's HIV status in the past 6 months emerged as the only significant independent predictor of seroconversion for men (table 3). In analyses adjusted for sexual activity, number of partners and condom use, all in the past 6 months, as well as age and employment, the risk of seroconversion was markedly higher in those men reporting a partner who was either HIV positive (HR 2·67, 95% CI 1·06–6·82) or of unknown HIV status (4·64, 2·32–9·7, p<0·0001), compared with reporting only HIV-negative partners. Reporting an HIV-positive partner accounted for 16% of HIV incidence in men and a partner of unknown status 30%, on the basis of the calculated population attributable risk (data not shown).

	Men			Women		
	Number of seroconversions (unweighted)	Number of seroconversions (weighted)	Incidence per 100 person-years (95% CI)*	Number of seroconversions (unweighted)	Number of seroconversions (weighted)	Incidence per 100 person-years (95% CI)*
Overall	47	52·8	1·7 (1·3–2·1)	101	92·5	3·1 (2·6–3·7)
Age (years)†						
18–19	4	4·0	0·8 (0·4–1·9)	19	16·0	3·8 (2·6–5·6)
20–24	15	16·0	1·6 (1·1–2·5)	40	36·4	4·3 (3·3–5·6)
25–29	14	16·9	2·6 (1·7–4·0)	12	10·2	2·0 (1·2–3·2)
30–34	11	12·3	3·1 (1·9–5·1)	9	8·5	2·7 (1·6–4·8)
35–39	1	1·2	0·4 (0·1–2·2)	10	12·0	4·0 (2·2–7·3)
40–44	2	2·4	1·2 (0·4–3·9)	7	5·8	2·1 (1·1–3·9)
45–49	0	··	··	4	3·5	1·2 (0·5–2·7)
Residence†						
Rural	35	38·2	1·7 (1·3–2·2)	76	68·7	3·3 (2·7–4·0)
Urban	12	14·6	1·6 (1·0–2·6)	25	23·8	2·8 (2·0–3·8)
Region†						
Hhohho	12	13·9	1·5 (0·9–2·4)	24	20·5	2·4 (1·7–3·3)
Lubombo	11	10·7	1·6 (1·0–2·7)	24	19·3	3·5 (2·5–4·8)
Manzini	11	13·8	1·4 (0·8–2·3)	32	36·1	3·7 (2·7–5·0)
Shiselweni	13	14·4	2·6 (1·6–4·0)	21	16·6	3·0 (2·1–4·37)
Education†						
Did not attend	2	1·9	1·3 (0·4–4·0)	6	5·2	3·4 (1·7–6·5)
Primary	16	18·2	2·3 (1·5–3·4)	27	25·3	3·3 (2·4–4·5)
Secondary	21	23·2	1·4 (1·0–2·1)	63	55·2	3·5 (2·9–4·4)
Tertiary	8	9·5	1·6 (0·9–2·9)	4	6·0	1·3 (0·5–3·6)
Employment†						
Employed	30	34·9	2·4 (1·8–3·2)	29	26·2	2·8 (2·0–3·8)
Unemployed, retired, or disabled	14	14·8	1·4 (0·9–2·1)	63	58·6	3·5 (2·8–4·5)
Other, refused, or missing	3	3·0	0·5 (0·2–1·3)	9	7·8	2·4 (1·4–4·2)
Marital status†						
Not married	36	39·1	1·8 (1·4–2·4)	66	58·7	4·1 (3·3–5·0)
Married, living with partner	6	7·5	1·2 (0·6–2·2)	15	12·3	1·4 (0·9–2·2)
Married, partner stays elsewhere	5	6·2	2·3 (1·1–4·8)	20	21·5	3·7 (2·4–5·5)
Lifetime sexual activity†‡						
Never had sex, as reported at both baseline and follow-up	1	0·8	0·2 (0·0–0·9)	2	1·7	0·8 (0·2–2·4)
Ever had sex	46	51·9	2·0 (1·6–2·5)	99	90·9	3·3 (2·8–4·0)
Sexual activity within the past 6 months†‡(n=9855)						
Sexual activity not reported at baseline or at follow-up	0	··	··	1	1·0	0·5 (0·1–2·4)
Sexual activity reported at baseline only	1	1·8	0·8 (0·2–3·8)	5	3·9	1·8 (0·9, 3·7)
Sexual activity reported at follow-up only	5	5·4	2·2 (1·0–4·5)	11	9·1	6·5 (4·0, 10·5)
Sexual activity reported at both baseline and follow-up	39	43·6	2·4 (1·8–3·1)	81	76	3·6 (2·9, 4·3)
Number of sexual partners within the past 6 months‡(n=9855)						
0	1	1·8	0·4 (0·1–1·8)	6	4·8	1·1 (0·6–2·2)
1	29	32·0	2·0 (1·5–2·7)	87	80·8	3·6 (3·0–4·4)
2 or more	16	18·1	3·8 (2·5–5·6)	6	5·2	10·0 (5·0–19·2)
						(Table 2 continues on next page)

HIV incidence peaked in women in two age strata: 4·3 per 100 person-years (95% CI 3·3–5·6) in 20–24 year olds and 4·0 per 100 person-years (2·2–7·3) in 35–39 year olds (table 2, figure 3). HIV incidence was 4·1 per 100 person-years (3·3–5·0) in unmarried women, 3·7 per 100 person-years (2·4–5·5) in married women not living with their partner, and 1·4 per 100 person-years (0·9–2·2) in married women living with their partner.

	Men			Women		
	Number of seroconversions (unweighted)	Number of seroconversions (weighted)	Incidence per 100 person-years (95% CI)*	Number of seroconversions (unweighted)	Number of seroconversions (weighted)	Incidence per 100 person-years (95% CI)*
(Continued from previous page)						
Condom use in the past 6 months‡ (in those with one or more partners in the past 6 months)						
Always	11	12·5	1·7 (1·1–2·9)	22	19·4	3·5 (2·5–5·0)
Sometimes	21	23·3	3·1 (2·1–4·3)	39	34·5	4·4 (3·4–5·8)
Never	13	14·3	2·5 (1·6–3·9)	31	30·8	3·3 (2·4–4·5)
HIV status of sexual partners in the past 6 months‡ (in those with one or more partners in the past 6 months)						
All HIV-negative partners	20	22·7	1·4 (1·0–2·0)	54	48·0	2·8 (2·2–3·5)
Any HIV-positive partners	8	8·7	4·0 (2·2–7·0)	17	16·3	5·8 (3·9–8·7)
Any partner with unknown status (and no known HIV-positive partners)	16	18·1	7·0 (4·6–10·5)	20	19·5	8·0 (5·3–12·0)
Response missing (for all partners)	1	0·8	5·7 (1·1–26·6)	2	2·2	16·7 (5·1–47·7)
Male circumcision status†‡						
Circumcised at baseline	7	8·4	1·5 (0·8–2·8)	..	..	..
Circumcised only at follow-up	2	2·2	1·2 (0·4–4·0)	..	..	..
Uncircumcised at baseline and follow-up	37	41·4	1·7 (1·3–2·3)	..	..	..
Pregnancy status†‡						
Pregnant at baseline or follow-up	..	..	..	16	15·4	4·2 (2·6–6·9)
Not pregnant at both visits	..	..	..	84	76·1	2·9 (2·4–3·6)
HIV testing history†						
Any previous testing	28	32·6	2·0 (1·5–2·8)	80	74·2	3·1 (2·6–3·8)
No previous testing	19	20·2	1·3 (0·9–1·9)	21	18·3	3·2 (2·2–4·6)

Unless otherwise indicated for each variable, 1% or fewer participants refused to answer the question, answered "I don't know", or had missing data; these data were excluded for the variable. *Incidence estimates are based on weighted number of seroconversions. †Measured at baseline. ‡Measured at follow-up visit.

Table 2: Overall HIV incidence and HIV incidence by demographic and behavioural characteristics in Swaziland in 2011 (n=11 232)

Among women reporting sexual risk behaviours or partner characteristics associated with risk, incidence was increased: for example, two or more sexual partners in the past 6 months (HIV incidence was 10·0 per 100 person-years, 5·0–19·2) or not knowing the HIV status of a partner from the past 6 months, (8·0 per 100 person-years, 5·3–12·0).

Age, marital status, sexual activity, condom use, and partner's HIV status were included in the multivariable model for women, and marital status, sexual activity in the past 6 months, and partner's HIV status remained the significant independent predictors of seroconversion (table 3). The risk of HIV seroconversion was nearly three times higher in women who reported not being married than those who were married (HR 2·90, 95% CI 1·44–5·84, p=0·0030) or having a marital partner staying elsewhere than in those who live with their partner (2·66, 1·29–5·45, p=0·0078). Not being married or being married with a partner living elsewhere accounted for 50% and 25% of HIV incidence among women, respectively (data not shown). Reporting no sexual activity at either baseline or follow-up was protective, with an HR of 0·22 (95% CI 0·05–0·99, p=0·048). Reporting a partner in the past 6 months with HIV-positive status was associated with an increased risk of seroconversion (HR 1·78, 0·97–3·27, p=0·063); by

contrast, reporting a partner with unknown HIV status in the past 6 months predicted nearly three times the risk of seroconversion compared with reporting only HIV-negative partners (HR 2·87, 1·44–5·84, p=0·0030). Reporting any partner with unknown HIV status accounted for 16% of HIV incidence (data not shown).

Discussion

The national HIV incidence estimate from SHIMS, a prospective survey of adults in Swaziland, on the basis of observed seroconversions was 2·4% in 2011. Modelled estimates of HIV seroincidence have ranked Swaziland's HIV incidence as the highest globally for more than a decade, at 4·07% in 2001 and 2·66% in 2009.[17,18] Taking into account important differences in methods, the 2011 SHIMS estimate is consistent with previous modelled estimates, confirming that HIV incidence in Swaziland is alarmingly high but might be stable. Key subsets of the population, including women aged 20–24 years and 35–39 years and men aged 30–34 years, had incidence rates substantially higher than the national rate.

Few characteristics were independent predictors of HIV seroconversion in our study, emphasising the homogeneous nature of this generalised epidemic. For women, reporting no sexual activity at baseline or follow-up was protective, as might be expected; this
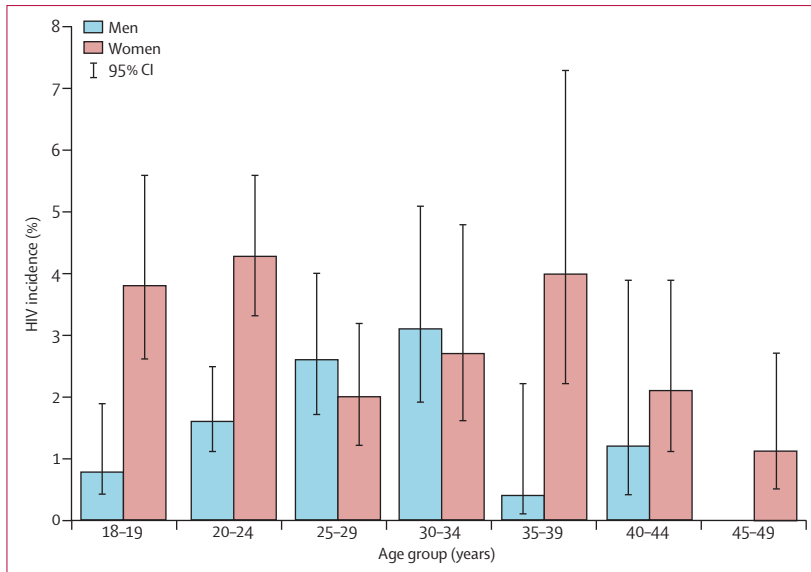
Figure 3: HIV incidence by age in Swaziland in 2011

The number of seroconverters permitted detailed assessment of predictors of HIV acquisition. Moreover, Swaziland's geographic location near other high prevalence countries in southern Africa make the results of this study highly relevant to the southern Africa region, the centre of the global HIV epidemic.

Study limitations include some imbalance in survey participation, with fewer men and fewer younger individuals taking part. The sex bias reflects the greater number of women than men in the overall Swaziland population (53% *vs* 47%[1]) and higher participation rates by women than men in the SHIMS household survey (81% *vs* 64%[10]). These sex and age biases, however, were reduced by the weighting of the data. Because we did not include injection drug use and men who have sex with men behaviours in the model, we were unable to quantify the attributable risk of these well known risk behaviours. The survey did not collect data for injection drug behaviours, but did collect data on anal sex; however, the non-response rate for this question was too high to permit inclusion in the proportional hazards model. The survey also collected data about the number of partners in the past 6 months, a behaviour associated with sex work; this variable was included in the model but was not a significant predictor. Because institutionalised individuals whose HIV incidence might be higher or lower than found in SHIMS were not included, the SHIMS estimates of HIV incidence might under-represent or over-represent actual HIV incidence.

HIV incidence was defined solely by seroconversion and NAAT testing was not conducted at follow-up; this approach might have led to a potential underestimate of overall incidence of almost 9% (ie, 2·4% *vs* 2·6%), assuming a similar number of acute cases at enrolment and follow-up. The study was not powered to determine independent predictors of HIV seroconversion, and this might explain why some factors previously linked with HIV protection or acquisition were not significant predictors of HIV acquisition, such as age in women and circumcision in men. Finally, although this was an observational study, risk-reduction counselling and the provision of condoms during the enrolment phase might have altered participants' risk behaviours and reduced the observed incidence rates below that of the rest of the national population.

SHIMS2, a cross-sectional, population-based HIV survey in Swaziland, has recently begun (Aug 30, 2016) and will assess the national estimate of HIV incidence after the 2009 programme expansion. As with other population-based HIV impact assessments,[24] the cross-sectional design of SHIMS2 will assess HIV incidence by taking advantage of advances in HIV incidence assays, namely the limiting antigen avidity assay combined with HIV RNA (viral load)[7] rather than prospectively observed seroconversions. Results should be available by late 2017 and, when available, will show whether the epidemic in Swaziland has improved or is

predictor, however, had only marginal statistical significance. For both women and men, a significant predictor of HIV acquisition was reporting a sex partner with unknown HIV status in the past 6 months. Although most (89%) of the sexually active, seronegative population of adults in Swaziland reported knowing the HIV status of partners they have been with in the past 6 months, only 65% of seronegative adults and 71% of the overall adult population in Swaziland[10] reported any HIV testing before participation in SHIMS. This discrepancy between knowledge of partner's status and the prevalence of reporting prior testing suggests it will be crucial to expand HIV testing through a wide range of approaches while encouraging HIV disclosure to partners.[19] The high population attributable risk observed with reporting partners in the past 6 months with unknown HIV status, and for women, being unmarried, also suggests the need to consider the use of pre-exposure prophylaxis,[20] expansion of voluntary medical male circumcision, and continued scale-up of treatment as prevention, with use of antiretroviral therapy at higher CD4 thresholds.[21–23]

Key strengths of this study included the systematic sampling of a household-based population, a high rate of participation in those sampled, and a high cohort retention rate. Although the study did not directly assess the role of migration and migrant labour on the epidemic, transient individuals who spent the previous night in someone's home were included in the sampled population. Additionally, having a partner who lives elsewhere, a characteristic which might indicate a partner involved in migrant labour, accounted for 25% of the HIV incidence in women. A rigorous HIV testing algorithm excluded seronegative individuals with acute HIV detected by NAAT testing at enrolment and determined the primary endpoint of HIV seroconversion.

	Men			Women		
	HR (95% CI) for univariable analysis	aHR (95% CI) for the multivariable analysis	p value for the multivariable analysis	HR (95% CI) for univariable analysis	aHR (95% CI) for the multivariable analysis	p value for the multivariable analysis
Age (years)*	p<0·0001	p<0·0001	..	p=0·16	p=0·43	..
18–19	1	1	..	1	1	..
20–24	1·74 (0·55–5·43)	0·90 (0·31–2·64)	0·85	1·09 (0·62–1·93)	1·11 (0·59–2·01)	0·76
25–29	2·76 (0·88–8·68)	0·82 (0·24–2·77)	0·75	0·53 (0·25–1·12)	0·59 (0·27–1·30)	0·19
30–34	3·52 (1·09–11·30)	1·10 (0·31–3·84)	0·88	0·76 (0·34–1·74)	0·89 (0·35–2·26)	0·80
35–39	0·49 (0·05–4·56)	0·15 (0·02–1·37)	0·092	1·29 (0·55–3·06)	1·58 (0·62–4·01)	0·33
40–44	1·33 (0·23–7·25)	0·45 (0·08–2·55)	0·37	0·63 (0·26–1·56)	0·90 (0·33–2·45)	0·84
45–49	..	0·00 (0·00–0·00)	<0·0001	0·41 (0·13–1·23)	0·66 (0·20–2·19)	0·50
Education*	p=0·74	..	..	p=0·34	..	..
Did not attend	1	..	..	1	..	..
Primary	1·71 (0·39–7·48)	..	..	0·87 (0·35–2·15)	..	..
Secondary	1·23 (0·28–5·32)	..	..	0·89 (0·38–2·08)	..	..
Tertiary	1·34 (0·28–6·41)	..	..	0·28 (0·06–1·24)	..	..
Employment*	p=0·034	p=0·24	..	p=0·59	..	..
Unemployed, retired, or disabled	1	1	..	1	..	..
Employed	1·77 (0·92–3·38)	1·59 (0·76–3·34)	0·22	0·84 (0·53–1·33)	..	..
Other, refused, or missing	0·44 (0·13–1·58)	0·58 (0·16–2·05)	0·40	0·73 (0·35–1·48)	..	..
Current marital status*	p=0·48	..	..	p=0·0030	p=0·0075	..
Married, living with partner	1	..	..	1	1	..
Married, partner stays elsewhere	2·07 (0·62–6·85)	..	..	2·99 (1·43–5·96)	2·66 (1·29–5·45)	0·0078
Not married	1·50 (0·63–3·60)	..	..	2·55 (1·44–4·51)	2·90 (1·44–5·84)	0·0030
Sexual activity in the past 6 months	p<0·0001	p=0·73	..	p<0·0001	p=0·056	..
Sexual activity reported at baseline and follow-up	1	1	..	1	1	..
Sexual activity reported at baseline only	0·18 (0·02–1·30)	0·62 (0·07–5·45)	0·66	0·33 (0·14–0·76)	0·46 (0·17–1·25)	0·13
Sexual activity at follow-up only	0·7 (0·27–1·79)	0·98 (0·4–2·42)	0·97	1·59 (0·85–3·00)	1·39 (0·71–2·73)	0·34
Sexual activity not reported at baseline or at follow-up	0·08 (0·01–0·61)	0·31 (0·04–2·42)	0·26	0·19 (0·05–0·79)	0·22 (0·05–0·99)	0·048
Number of partners in the past 6 months (of those who ever had sex) †	p=0·0043	p=0·48	..	p=0·11	..	..
1	1	1	..	1	..	..
2 or more	2·45 (1·32–4·56)	1·27 (0·65–2·48)	0·48	2·01 (0·86–4·73)	..	..
Condom use in the past 6 months†	p=0·0060	p=0·17	..	p=0·028	p=0·71	..
Always	1	1	..	1	1	..
Sometimes	3·06 (1·49–6·26)	1·91 (0·87–4·19)	0·11	1·89 (1·16–3·05)	1·14 (0·65–2·07)	0·65
Never	2·70 (1·23–5·91)	2·36 (0·93–5·98)	0·070	1·66 (0·97–2·85)	1·28 (0·71–2·32)	0·40
HIV status of sexual partners in the past 6 months (in those with one or more partners in the past 6 months)†	p<0·0001	p<0·0001	..	p<0·0001	p=0·0008	..
All HIV-negative partners	1	1	..	1	1	..
Any HIV-positive partners	3·93 (1·73–8·94)	2·67 (1·06–6·82)	0·040	2·48 (1·41–4·37)	1·78 (0·97–3·27)	0·063
Any partner(s) with unknown status (with no known HIV-positive partners)	6·28 (3·27–12·04)	4·64 (2·32–9·27)	<0·0001	3·71 (2·11–6·53)	2·87 (1·44–5·84)	0·0030

Univariable and multivariable models were each analysed separately for men and for women and HR and aHR from the multivariable models are shown. Those characteristics that were significant at or near p<0·10 in the univariable model were included in each multivariable model. Not shown are those characteristics for which p was greater than 0·10 in the univariable models for men and for women: region, geography (urban vs rural), and HIV testing history (any vs never) for men and for women; circumcision status for men; and pregnancy status for women. HR=hazard ratio. aHR=adjusted hazard ratio. *Measured at baseline visit. †Measured at follow-up visit.

Table 3: **Proportional hazards model of predictors of HIV seroconversion in Swaziland in 2011**

much the same. SHIMS2 and population-based HIV impact assessments will allow us to understand whether incidence remains the most suitable measure of a national HIV epidemic or whether other indicators, such as viral load suppression, will emerge as a more informative indicator.

Overall, this study is the first to report HIV incidence at a national level with the use of prospectively observed HIV seroconversion. The national HIV incidence in Swaziland of 2·4% is the highest national rate known. We found alarmingly high rates in men and women in specific age strata. In the context of Swaziland's treatment and male circumcision coverage, these high incidence rates warrant further expansion of treatment initiation criteria and male circumcision scale-up in Swaziland. Our findings show the value of detailed incidence measures in characterising those at highest risk of new infections and emphasise the need in high-prevalence countries for evidence-based HIV programmes that include frequent HIV testing, support for disclosure of HIV status, expansion of HIV treatment, and consideration of pre-exposure prophylaxis as public health priorities.

References
1. Central Statistical Office, Swaziland, and Macro International. Swaziland demographic and health survey 2006–07. Chapter 14: HIV prevalence and associated factors. http://www.measuredhs.com/publications/publication-fr202-dhs-final-reports.cfm (accessed Sept 23, 2015).
2. Partnership Framework on HIV and AIDS, 2009–2013. The Government of the Kingdom of Swaziland and the Government of the United States of America, 2009. http://www.pepfar.gov/documents/organization/124969.pdf (accessed Sept 23, 2015).
3. UNAIDS. Practical guidelines for intensifying HIV prevention: towards universal access: UNAIDS. 2007. http://data.unaids.org/pub/Manual/2007/20070306_Prevention_Guidelines_Towards_Universal_Access_en.pdf (accessed Aug 24, 2014).
4. Ghys PD, Garnett GP. The 2009 HIV and AIDS estimates and projections: methods, tools and analyses. *Sex Transm Infect* 2010; **86:** ii1–ii2.
5. Duong YT, Qui M, De AK, et al. Detection of recent HIV-1 infection using a new limiting-antigen avidity assay: potential for HIV-1 incidence estimates and avidity maturation studies. *PLoS One* 2012; **7:** e33328.
6. Konikoff J, Brookmeyer R, Longosz AF, et al. Performance of a limiting-antigen avidity enzyme immunoassay for cross-sectional estimation of HIV incidence in the United States. *PLoS One* 2013; **8:** e82772.
7. Kassanjee R, Pilcher CD, Keating SM, et al. Independent assessment of candidate HIV incidence assays on specimens in the CEPHIA repository. *AIDS* 2014; **28:** 2439–49.
8. Hodder SL, Justman J, Hughes JP, et al. HIV acquisition among women from selected areas of the United States: a cohort study. *Ann Intern Med* 2013; **158:** 10–18.
9. Nel A, Mabude Z, Smit J, et al. HIV incidence remains high in KwaZulu-Natal, South Africa: evidence from three districts. *PLoS One* 2012; **7:** e35278.
10. Bicego GT, Nkambule R, Peterson I, et al. Recent patterns in population-based HIV prevalence in Swaziland. *PLoS One* 2013; **8:** e77101.
11. US Food and Drug Administration. Clinical trials and human subject protection. http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/default.htm (accessed Feb 22, 2015).
12. **ICAP.** SHIMS website. http://shims.icap.columbia.edu/publications/type/study-protocol-case-review-forms (accessed Dec 14, 2014).
13. Duong YT, Mavengere Y, Patel H, et al. Poor performance of the determine HIV-1/2 Ag/Ab combo fourth-generation rapid test for detection of acute infections in a national household survey in Swaziland. *J Clin Microbiol* 2014; **52:** 3743–48.
14. Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. *N Engl J Med* 2005; **352:** 1873–83.
15. Pilcher CD, McPherson JT, Leone PA, et al. Real-time, universal screening for acute HIV infection in a routine HIV counseling and testing population. *JAMA* 2002; **288:** 216–21.
16. Ministry of Health, Government of the Kingdom of Swaziland. Swaziland Incidence Measurement Survey (SHIMS): first findings report, 2012. https://www.k4health.org/sites/default/files/SHIMS_Report.pdf (accessed Sept 23, 2015).
17. UNAIDS. Annex 1: HIV and AIDS estimates and data, 2009 and 2001. 2010. http://www.unaids.org/globalreport/documents/20101123_GlobalReport_Annexes1_em.pdf (accessed Nov 7, 2016).
18. Joint United Nations Programme on HIV/AIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. http://www.unaids.org/globalreport/documents/20101123_GlobalReport_Annexes1_em.pdf (accessed Sept 23, 2015).
19. Obermeyer CM, Baijal P, Pegurri E. Facilitating HIV disclosure across diverse settings: a review. *Am J Public Health* 2011; **101:** 1011–23.
20. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.
21. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.
22. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.
23. The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.
24. ICAP. PHIA Project web site. http://icap.columbia.edu/global-initiatives/the-phia-project/ (accessed Sept 1, 2016).