ORIGINAL ARTICLE

HIV Prevention Efforts and Incidence of HIV in Uganda

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ABSTRACT

BACKGROUND

To assess the effect of a combination strategy for prevention of human immunodeficiency virus (HIV) on the incidence of HIV infection, we analyzed the association between the incidence of HIV and the scale-up of antiretroviral therapy (ART) and medical male circumcision in Rakai, Uganda. Changes in population-level viral-load suppression and sexual behaviors were also examined.

METHODS

Between 1999 and 2016, data were collected from 30 communities with the use of 12 surveys in the Rakai Community Cohort Study, an open, population-based cohort of persons 15 to 49 years of age. We assessed trends in the incidence of HIV on the basis of observed seroconversion data, participant-reported use of ART, participant-reported male circumcision, viral-load suppression, and sexual behaviors.

RESULTS

In total, 33,937 study participants contributed 103,011 person-visits. A total of 17,870 persons who were initially HIV-negative were followed for 94,427 person-years; among these persons, 931 seroconversions were observed. ART was introduced in 2004, and by 2016, ART coverage was 69% (72% among women vs. 61% among men, P<0.001). HIV viral-load suppression among all HIV-positive persons increased from 42% in 2009 to 75% by 2016 (P<0.001). Male circumcision coverage increased from 15% in 1999 to 59% by 2016 (P<0.001). The percentage of adolescents 15 to 19 years of age who reported never having initiated sex (i.e., delayed sexual debut) increased from 30% in 1999 to 55% in 2016 (P<0.001). By 2016, the mean incidence of HIV infection had declined by 42% relative to the period before 2006 (i.e., before the scale-up of the combination strategy for HIV prevention) — from 1.17 cases per 100 person-years to 0.66 cases per 100 person-years (adjusted incidence rate ratio, 0.58; 95% confidence interval [CI], 0.45 to 0.76); declines were greater among men (adjusted incidence rate ratio, 0.46; 95% CI, 0.29 to 0.73) than among women (adjusted incidence rate ratio, 0.68; 95% CI, 0.50 to 0.94).

CONCLUSIONS

In this longitudinal study, the incidence of HIV infection declined significantly with the scale-up of a combination strategy for HIV prevention, which provides empirical evidence that interventions for HIV prevention can have a population-level effect. However, additional efforts are needed to overcome disparities according to sex and to achieve greater reductions in the incidence of HIV infection. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

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A combination strategy for the prevention of human immunodeficiency virus (HIV) is defined as the concurrent implementation of multiple interventions to reduce the incidence of HIV infection.[1] Most prevention packages in sub-Saharan Africa include antiretroviral therapy (ART) and medical male circumcision, along with provision of HIV testing and counseling, promotion of condom use, and other behavioral interventions.[2] The scale-up of such a combination strategy for HIV prevention has been an intense focus in the field of global health over the past decade.[3]

Modeling studies indicate that high coverage of ART and male circumcision could substantially reduce the incidence of HIV infection to low-endemic levels,[4,5] and could potentially even lead to its elimination.[6,7] However, the effectiveness of combination strategies for HIV prevention remains uncertain owing to challenges in increasing coverage of interventions and in accurately measuring changes in the population-level incidence of HIV infection.[8,9] Providing evidence of the population-level effectiveness of HIV prevention efforts is critical to understanding whether the current evidence-based interventions are sufficient to mitigate HIV infection and to guide allocation of resources.

Although previous research from South Africa has shown that increasing community ART coverage reduces individual-level risk of HIV infection, declines in the incidence of population-level HIV infection were not shown.[10,11] Other research from North America suggests that scale-up of ART has reduced the incidence of HIV infection, but these studies relied on modeled incidence and sentinel surveillance data.[9,12-14] The standard empirical method for assessing the incidence of HIV infection is the longitudinal measurement of HIV seroconversions in a population-based cohort.[8,9] However, such studies are rare despite the urgency to show relationships between changes in coverage of ART and male circumcision and the incidence of HIV infection over time.[4,5,15] To assess the effect of a combination strategy for HIV prevention on the incidence of HIV infection, we analyzed long-term trends in HIV incidence in Rakai, Uganda, on the basis of observed seroconversions and their associations with the scale-up of ART and male circumcision, population-level viral-load suppression, and sexual behaviors. Here, the combination strategy that was assessed included HIV counseling and testing, voluntary medical male circumcision, ART for persons living with HIV, the promotion of condom use, and interventions for behavioral change.

METHODS

COHORT DESCRIPTION

The Rakai Community Cohort Study (RCCS), established by the Rakai Health Sciences Program, is an open, population-based cohort of persons 15 to 49 years of age across multiple communities.[16] The RCCS is situated in Rakai District, which has a population of approximately 518,000 and is mostly rural with scattered trading centers.[17] The current study uses data from participants in 30 RCCS communities that were continuously evaluated from April 6, 1999, to September 2, 2016 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); data were collected with the use of 12 surveys.

To identify eligible participants, a household census enumerates all persons according to sex, age, and duration of residence, regardless of whether they are currently present or absent in the home. After the census, the RCCS surveys all residents who are present, who are within the eligible age range, and who have provided written informed consent. Participants are interviewed regarding demographic characteristics, sexual behaviors, ART use, and male circumcision status. Venous blood is obtained for HIV testing at the time of each survey (details on laboratory methods are provided in the Supplementary Appendix). The scale-up of the combination strategy for HIV prevention, which has been funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR),[18] began in earnest in the mid-2000s (details regarding the scale-up are provided in the Supplementary Appendix).

STATISTICAL ANALYSIS

We assessed the scale-up of the combination strategy for HIV prevention with descriptive statistics and logistic regression using person-visit data at each survey. Specifically, ART coverage was defined as the percentage of all HIV-positive participants who reported the use of ART, regardless of ART eligibility criteria; ART coverage was assessed overall and separately according to sex. Participant-reported use of ART in the cohort has been validated previously by the detection of antiretroviral drugs in plasma, with a specificity of 99% (95% confidence interval [CI], 96 to 100) and a sensitivity of 77% (95% CI, 70 to 83) and with no differences according to sex.[19] Male circumcision coverage at a given visit was defined as the percentage of men who reported having been circumcised. Participant-reported circumcision status has been validated previously from clinical records, with a specificity of 100%.[20] Viral-load suppression was defined as a viral load of less than 1000 RNA copies per milliliter, according to the recommendations of the World Health Organization.[21]

The unit of exposure for the incidence of HIV infection was person-intervals of follow-up between surveys among persons who were initially HIV-negative and who participated in at least two surveys. Cases of incident HIV infection were defined as cases in which persons tested HIV-seropositive for the first time after they had had an HIV-seronegative result at the previous RCCS visit; one missed visit was allowed. Incident infections were assumed to occur at the midpoint of the interval between two surveys. Changes in the incidence of HIV infection per 100 person-years were estimated with the use of a Poisson multivariate regression model with generalized estimating equations and an exchangeable correlation structure and are reported as incidence rate ratios with 95% confidence intervals.

To assess the effect of the combination strategy, the mean incidence of HIV infection at each visit interval after 2004 (i.e., beginning with the sixth survey) was compared with the mean incidence of HIV infection over the entire period before the availability of ART and the scale-up of medical male circumcision. The final multivariate model included individual-level information on demographics (sex, age, level of education, type of community of residence [agrarian or trading]), and sexual behaviors (number of sexual partners in the past year, sex with partners outside the community of residence, sex with nonmarital partners, condom use, and participant-reported genital ulcer disease). A categorical term for the community-level prevalence of HIV infection was included to adjust for variation in HIV exposure. Secondary analyses were stratified according to sex and were performed separately for circumcised and uncircumcised men. The incidence of HIV infection and individual-level risk were also assessed in relation to community-level measures of ART and male circumcision coverage and the prevalence of HIV viremia (details are provided in the Statistical Methods section in the Supplementary Appendix).

Sensitivity of the results to both selective participation and loss to follow-up was evaluated with the use of inverse probability weighting (see the Statistical Methods section in the Supplementary Appendix). To assess the potential effect of birth cohort on trends of HIV incidence, a term for each 5-year birth cohort was included in the multivariate model. The incidence of HIV infection was also assessed according to sex for each 5-year age group.

RESULTS

SURVEY PARTICIPATION

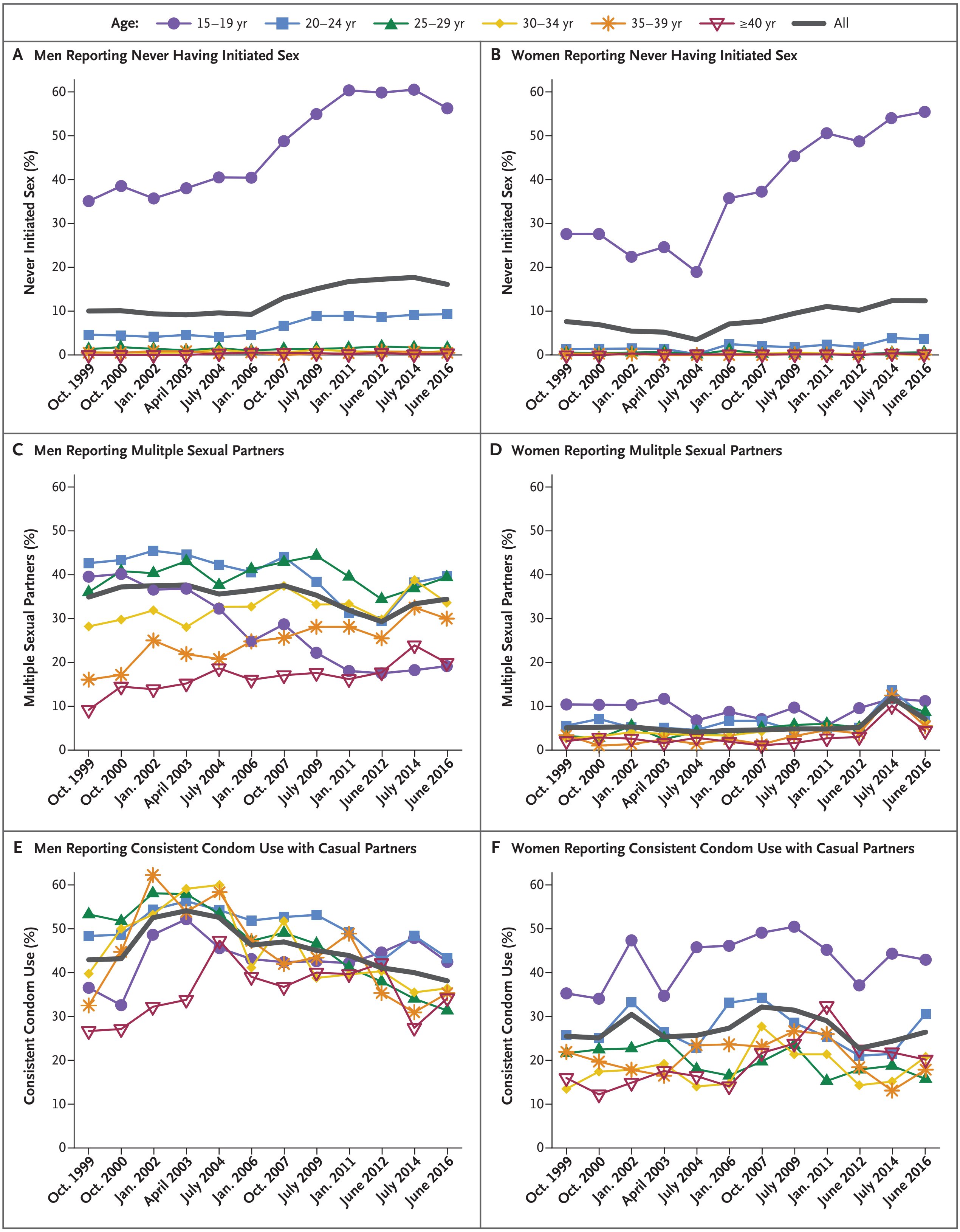
Table 1 shows summary data on study eligibility and participation for each of the 12 surveys. Overall, 33,937 individual participants contributed 103,011 person-visits, including 17,870 persons who were initially HIV-negative and contributed 58,344 person-intervals (consecutive visits from persons who were HIV-negative at the first of the two visits) for a total of 94,427 person-years of observation (incidence cohort). The mean participation rate among all persons who were eligible for the survey was 64% and did not vary substantially between surveys (range, 59 to 67); however, the reasons for nonparticipation and study dropout (e.g., travel or decision not to participate) changed over time (Tables S1 and S2 in the Supplementary Appendix). The percentage of persons who chose not to participate in the study declined steadily (from 21% to 0.5%) over the course of the analysis period, whereas the percentage of persons who were not present in the community at the time of the survey because of either work or school increased from 18% to 32%. The most common reasons for loss to follow-up were migration out of the study communities (42 to 63% of losses) and travel for work or school (25 to 33% of losses).

Participation and follow-up rates were significantly lower among younger persons than among older persons, among men than among women, and among persons living in trading centers than among persons living in agrarian communities, but these associations were stable over time. Persons with high-risk sexual behaviors were somewhat more likely to be lost to follow-up than persons with low-risk sexual behaviors, but this association was also constant over time (Figs. S2 through S4 in the Supplementary Appendix). The

Table 1. Eligibility, Participation, and Follow-up in the RCCS, According to Survey, 1999–2016.*

Survey No.	Interview Date†	Participated in Survey		HIV-Negative Participants Eligible for Incidence Cohort§	Eligible HIV-Negative Participants Who Migrated Out before Subsequent Survey	Incidence Cohort¶	Age-Eligible HIV-Negative Participants Followed	Age-Eligible and Resident-Eligible HIV-Negative Participants Followed‖	Yr Since Previous Survey Visit
		Eligible from Census‡	Eligible from Census and Present for Survey						
	median (range)	*no./total no. (%)*		*no.*	*no. (%)*	*no.*	*%*	*%*	*median (IQR)*
1	Oct. 1999 (April 1999–Feb. 2000)	5,992/9,869 (61)	5,992/8,125 (74)	—	—	—	—	—	—
2	Oct. 2000 (Feb. 2000–Feb. 2001)	6,732/10,448 (64)	6,732/8,567 (79)	5,183	546 (11)	3,760	73	93	1.0 (1.0–1.0)
3	Jan. 2002 (April 2001–May 2002)	7,340/11,316 (65)	7,340/9,176 (80)	7,277	1,677 (23)	4,540	62	82	1.3 (1.1–1.3)
4	April 2003 (July 2002–Aug. 2003)	6,856/11,436 (60)	6,856/8,603 (80)	7,905	2,167 (27)	4,555	58	80	1.2 (1.2–1.3)
5	July 2004 (Sep. 2003–Nov. 2004)	7,038/11,860 (59)	7,038/8,436 (83)	8,014	2,206 (28)	4,693	59	81	1.3 (1.2–1.3)
6	Jan. 2006 (Feb. 2005–June 2006)	8,097/12,528 (65)	8,097/9,137 (89)	7,768	2,159 (28)	4,867	63	87	1.5 (1.4–1.6)
7	Oct. 2007 (Aug. 2006–June 2008)	8,645/13,636 (63)	8,645/9,130 (95)	8,624	2,585 (30)	5,001	58	83	1.7 (1.6–1.8)
8	July 2009 (June 2008–Dec. 2009)	8,691/13,293 (65)	8,691/9,009 (96)	9,679	2,952 (30)	5,611	58	84	1.7 (1.6–1.8)
9	Jan. 2011 (Jan. 2010–June 2011)	9,643/14,629 (66)	9,643/9,949 (97)	9,686	2,894 (30)	5,742	59	85	1.6 (1.6–1.6)
10	June 2012 (Aug. 2011–May 2013)	10,588/16,007 (66)	10,588/10,846 (98)	10,300	3,032 (29)	6,176	60	85	1.6 (1.5–1.7)
11	July 2014 (July 2013–Jan. 2015)	11,379/17,477 (65)	11,379/11,566 (98)	11,419	3,875 (34)	6,277	55	83	2.0 (1.9–2.1)
12	Jan. 2016 (Jan. 2015–Sep. 2016)	12,010/18,065 (66)	12,010/12,308 (98)	12,908	4,017 (31)	7,122	55	80	1.6 (1.4–2.0)

* The incidence cohort was defined as persons who were initially HIV-negative and who participated in at least two consecutive surveys; one missed visit was allowed. IQR denotes interquartile range, and RCCS Rakai Community Cohort Study.
† The median interview date represents the middle of the survey period, and the range of interview dates represents the first and last interview dates in the given survey period.
‡ Residents included in the census who were between 15 and 49 years of age were eligible for the survey.
§ This category includes all age-eligible HIV-negative participants who participated in the previous survey and any HIV-negative participants who participated in the survey before the previous survey if the participant was absent at the most recent survey.
¶ The values are the number of persons who contributed to the incidence cohort during the given survey interval.
‖ The calculation excludes HIV-negative persons who migrated out before the survey.



Age: 15–19 yr 20–24 yr 25–29 yr 30–34 yr 35–39 yr ≥40 yr All
A Men Reporting Never Having Initiated Sex
B Women Reporting Never Having Initiated Sex
Never Initiated Sex (%)
C Men Reporting Mulitple Sexual Partners
D Women Reporting Mulitple Sexual Partners
Multiple Sexual Partners (%)
E Men Reporting Consistent Condom Use with Casual Partners
F Women Reporting Consistent Condom Use with Casual Partners
Consistent Condom Use (%)
Oct. 1999
Oct. 2000
Jan. 2002
April 2003
July 2004
Jan. 2006
Oct. 2007
July 2009
Jan. 2011
June 2012
July 2014
June 2016

Figure 1 (facing page). Sexual Behaviors Reported in the Rakai Community Cohort Study, 1999–2016.

Shown are the percentages of HIV-negative men and women who reported never having initiated sex (i.e., delayed sexual debut) (Panels A and B), the percentages of sexually active men and women who reported having multiple sexual partners (Panels C and D), and the percentages of men and women with casual (i.e., not classified as marital or long-term consensual unions) sexual partners who reported consistent condom use (Panels E and F), according to age group. The dates on the x axis represent the middle of each survey period from which the data were collected. The most substantial changes in sexual behaviors over time occurred among adolescent boys and girls 15 to 19 years of age who reported never having initiated sex and among adolescent boys who reported having multiple partners.

average population growth rate over the analysis period, calculated from the resident population included in the household census, irrespective of age, was 3.4% per year (95% CI, 3.2 to 3.6).

TEMPORAL TRENDS IN SEXUAL BEHAVIORS

Figure 1 shows age-specific sexual behaviors according to survey date among HIV-negative men and women. The most substantive changes in sexual behaviors occurred among adolescents 15 to 19 years of age, among whom the percentage who reported never having initiated sex (i.e., delayed sexual debut) increased from 30% in 1999 to 55% in 2016 overall (P<0.001) and from 35% (194 of 553) to 56% (679 of 1207) among adolescent boys and from 28% (209 of 757) to 55% (646 of 1165) among adolescent girls over the same time period (P<0.001 for both comparisons). Adolescent boys who initiated sex were also significantly less likely to report multiple sexual partners in the last survey than in the 1999 survey (19% in 2016 vs. 40% in 1999, P<0.001). There were no substantial changes over time in the percentage of women who had multiple sexual partners. Overall across age groups, the percentages of persons who reported consistent condom use with casual partners remained largely unchanged over time (Fig. 1E and 1F).

SCALE-UP OF ART AND CHANGES IN POPULATION HIV VIRAL-LOAD SUPPRESSION AND MALE CIRCUMCISION COVERAGE

The effects of the scale-up of biomedical HIV prevention interventions are shown in Figure 2. Participant-reported use of ART among all HIV-positive persons increased from 12% (118 of 1003 persons) in 2006 to 69% (1051 of 1526 persons) in 2016 (P<0.001). ART coverage was consistently higher among women than among men (P<0.001); however, the proportional increase in coverage over time was similar among men and women. By 2016, a total of 61% of HIV-positive men (285 of 466) and 72% of HIV-positive women (766 of 1060) reported use of ART; ART coverage was highest among older age groups in all surveys (Table S3A and Fig. S5 in the Supplementary Appendix).

HIV viral-load assays were performed in 96% of HIV-positive participants (1115 of 1160) in 2009 and in 99.9% of HIV-positive participants (1525 of 1526) in 2016. Viral-load suppression (defined as <1000 RNA copies per milliliter) among participants who reported ART use was observed in 94% (1228 of 1301 participants) and did not differ significantly according to sex (P=0.38) or survey visit (P=0.52). HIV viral-load suppression in all HIV-positive participants increased concomitant with increasing ART coverage over time. By 2016, a total of 75% of all HIV-positive persons (1151 of 1526), regardless of whether they reported ART use, had viral-load suppression; in contrast, 42% of all HIV-positive persons (464 of 1115) in 2009 had viral-load suppression (P<0.001) (Fig. 2B).

Population coverage of male circumcision increased significantly, from 15% (374 of 2518 men) in 1999 to 59% (3177 of 5361 men) in 2016 among all men (P<0.001) (Fig. 2C) and from 3% (77 of 2217) to 53% (2492 of 4666) among non-Muslim men who are not traditionally circumcised at birth (P<0.001). Male circumcision coverage increased both among HIV-positive and among HIV-negative men, with the highest coverage among younger men (Table S3B and Fig. S5 in the Supplementary Appendix).

The scale-up of ART and male circumcision occurred concurrently in all communities (Fig. 2D), and by 2016, coverage for both was high in all 30 RCCS communities. The median community-level ART coverage was 70% (interquartile range, 61 to 75), and the median community-level male circumcision coverage was 61% (interquartile range, 55 to 65).

CHANGES IN INCIDENCE OF HIV OVER TIME

Figure 3 shows the incidence of HIV infection in the whole population, among women, among men, and among circumcised and uncircumcised men. Over the course of the analysis period, a total of 931 seroconversions were observed; 549 (59%) of

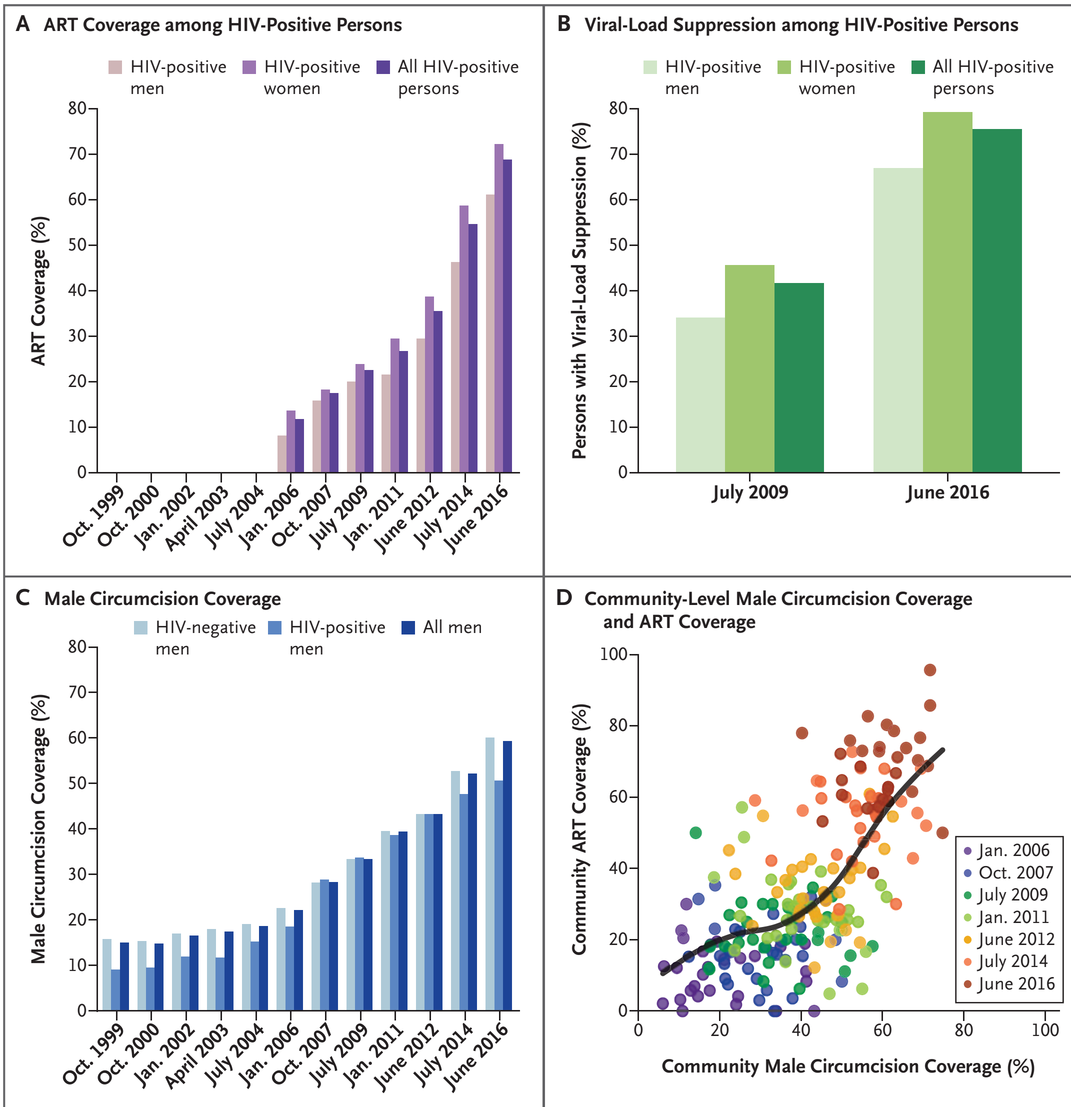


Figure 2. Scale-up of Biomedical HIV Interventions and Changes in Viral-Load Suppression in HIV-Positive Participants, 1999–2016.

Panel A shows the scale-up of antiretroviral therapy (ART) coverage, which was measured on the basis of participant-reported ART use, in human immunodeficiency virus (HIV)–positive study participants, according to sex, beginning in 2006. Panel B shows the percentages of HIV-positive persons, according to sex, who had viral-load suppression (<1000 RNA copies per milliliter) in 2009 and 2016. Panel C shows the scale-up of male circumcision coverage in men, irrespective of religion, according to HIV status. Panel D shows community-level male circumcision coverage versus community-level ART coverage for all 30 communities at each survey during the scale-up of the combination strategy for HIV prevention. A smoothing spline was fit to the smooth curve to assess trend. Scale-up of the interventions occurred simultaneously and both increased significantly over time in all communities.

these new infections occurred among women. The incidence of HIV infection was stable before the scale-up of combination HIV prevention and began to decline significantly in 2012 (Fig. 3 and Table 2, and Table S4 in the Supplementary Appendix). By 2016, the mean incidence of HIV infection had declined by 42%, from 1.17 cases per 100 person-years in the period before the scale-up to 0.66 cases per 100 person-years in 2016 (incidence rate ratio, 0.56; 95% CI, 0.44 to 0.72; adjusted incidence rate ratio, 0.58; 95% CI, 0.45 to 0.76). Similar trends in incidence were observed when the analyses were restricted to sexually active adults and to persons 20 years of age or older (Tables S5 and S6 in the Supplementary Appendix).

Declines in the incidence of HIV infection by 2016 relative to the period before the scale-up of the combination interventions for HIV prevention were greater among men (adjusted incidence rate ratio, 0.46; 95% CI, 0.29 to 0.73) than among women (adjusted incidence rate ratio, 0.68; 95% CI, 0.50 to 0.94). Overall, the incidence of HIV infection was lower among circumcised men than among uncircumcised men (adjusted incidence rate ratio, 0.62; 95% CI, 0.48 to 0.79), but the incidence declined significantly among both circumcised men (adjusted incidence rate ratio, 0.43; 95% CI, 0.19 to 0.99) and uncircumcised men (adjusted incidence rate ratio, 0.51; 95% CI, 0.29 to 0.88) by 2016 (Fig. 3 and Table 2, and Table S4 in the Supplementary Appendix).

Declines in the incidence of HIV infection were observed in the majority of age groups for both men and women, and among both men and women residing in trading communities and in agrarian communities; a notable exception was the subgroup of women who were 20 to 24 years of age (Fig. S6 in the Supplementary Appendix). Sensitivity analyses showed that the inclusion of birth cohort or inverse probability weighting for selective participation and follow-up did not change inferences regarding effects on trends in the incidence of HIV infection (Fig. S7 and Tables S7 and S8 in the Supplementary Appendix).

Although ART coverage and male circumcision coverage increased concurrently across RCCS communities (Fig. 2D, and Figs. S8 and S9 in the Supplementary Appendix), we also assessed the incidence of HIV infection and individual-level HIV risk as functions of ART coverage, population prevalence of HIV viremia, and male circumcision coverage within a participant's community of residence. These analyses showed declining HIV incidence and lower individual-level risk with increasing community ART coverage and male circumcision coverage and declining prevalence of viremia (Figs. S10 through S12 in the Supplementary Appendix).

DISCUSSION

In this study, the incidence of HIV infection declined significantly with the scale-up of a combination strategy for HIV prevention, which provides empirical evidence that HIV control efforts can have a substantial population-level effect. The declines in the incidence of HIV infection were probably a result of the scale-up of ART use and male circumcision, although reduced sexual activity in late adolescence may also have contributed. HIV incidence declined to a lesser degree among women than among men, which suggests that the combination of the direct effects of male circumcision and the indirect effects of ART use among women differentially benefited men. Additional efforts are needed to avert new infections in women, such as a further scale-up of ART use among men and the potential introduction of new interventions for primary prevention (e.g., preexposure prophylaxis, or PrEP).

Previously, we found that community levels of male circumcision and of ART use among women at modest coverage levels were associated with a lower community incidence of HIV infection among men than the incidence before these interventions.[22] In another study in rural South Africa, higher rates of ART coverage were associated with a lower risk of individual-level acquisition of HIV infection, but that study did not assess temporal declines in incidence of HIV infection or male circumcision coverage.[10] Our finding of a 42% reduction in the incidence of HIV infection to 0.66 cases per 100 person-years, relative to the incidence in the period before the scale-up, is substantial, but the incidence is still well above the incidence rate of 0.1 cases per 100 person-years, which is an estimated threshold for the elimination of HIV infection.[6,23]

From 2009 to 2016, the percentage of HIV-positive persons with viral-load suppression increased by 44%, which suggests that HIV viral-load suppression associated with ART use probably reduced HIV exposure to uninfected, opposite-sex partners, an assumption that is consistent with the findings from other studies.[12,13,24-26] By 2016, among HIV-positive persons, the percentage of participants who had viral-load suppression was 75%, which met one of the 2020 goals of the joint United Nations Program on HIV and AIDS (UNAIDS) 90-90-90 initiative, an initiative that modeling suggests could end the HIV epidemic by 2030.[27] Our results show that ambitious ART scale-up goals can be achieved. Similar results for viral-load suppression (71% of HIV-positive persons) have been reported in Botswana, al-

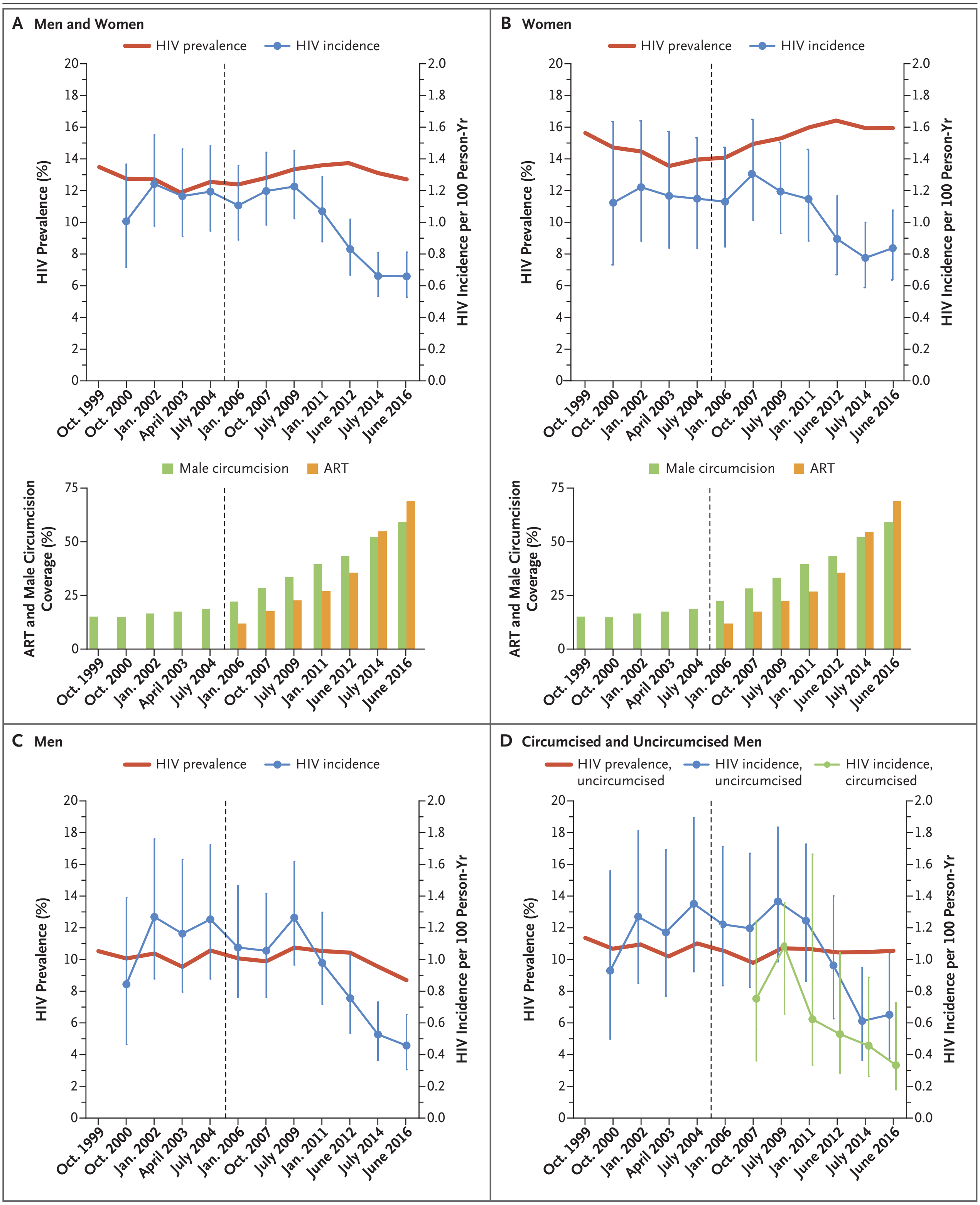

A Men and Women
HIV prevalence
HIV incidence
HIV Prevalence (%)
HIV Incidence per 100 Person-Yr
Oct. 1999
Oct. 2000
Jan. 2002
April 2003
July 2004
Jan. 2006
Oct. 2007
July 2009
Jan. 2011
June 2012
July 2014
June 2016
Male circumcision
ART
ART and Male Circumcision Coverage (%)
B Women
C Men
D Circumcised and Uncircumcised Men
HIV prevalence, uncircumcised
HIV incidence, uncircumcised
HIV incidence, circumcised

Figure 3 (facing page). Trends in the Incidence and Prevalence of HIV Infection in the Rakai Community Cohort Study, 1999–2016.

Shown are trends in the incidence and prevalence of HIV infection over the course of the analysis period among all initially HIV-negative men and women who had follow-up data (Panel A), among women only (Panel B), among men only (Panel C), and among men according to circumcision status (Panel D). The dotted line in each panel represents the time point at which the scale-up period of a combination strategy for HIV prevention (CHP) began. Vertical lines represent 95% confidence intervals for HIV incidence. The incidence of HIV infection is shown for circumcised men only beginning in 2007, after the recommendation by the World Health Organization that HIV-negative men undergo male circumcision to prevent HIV infection. The plots for ART and male circumcision coverage in Panels A and B are also included to show the temporal association between the scale-up of CHP and declines in HIV incidence.

though beneficial effects on HIV incidence rates in Botswana have not yet been reported.[28,29]

Male circumcision coverage increased steadily over time and reached 59% by 2016 but remained below the UNAIDS target of 80% coverage.[30] Scale-up of ART and male circumcision were highly correlated (Fig. 2D), so it is difficult to disaggregate their effects. Nevertheless, we attempted to address this issue empirically by assessing HIV incidence trends separately among men and women and among uncircumcised and circumcised men. Previous mathematical modeling studies have suggested that there are substantial, long-term, indirect effects of male circumcision on the incidence of HIV infection both among female partners and among uncircumcised men; however, these indirect benefits are unlikely to be realized until at least a decade after the prevalence of HIV declines as a result of the direct effects of male circumcision.[31] Therefore, the significant reductions in the incidence of HIV infection among women and among uncircumcised men that were observed in this study probably result from the population-level effect on HIV incidence of the increase in ART coverage over time. The sharpest declines in HIV incidence were observed among circumcised men — nearly twice the decline that was observed among uncircumcised men — which is probably because circumcised men benefit from the direct protective effect of male circumcision as well as from the indirect effect of female partners who are using ART. In comparison, the declines in the incidence of HIV infection among women and among uncircumcised men were more moderate, probably because these persons benefit largely from the reduced exposure afforded by their infected partner's use of ART. The percentage of persons who used ART was lower among HIV-positive men than among HIV-positive women, which would further attenuate benefits for women.[31]

Significant declines in the incidence of HIV infection were first observed in 2012, when ART coverage levels reached 36% and male circumcision coverage levels reached 43%. It would be tempting to conclude that these coverage levels represent threshold effects, but because interventions were scaled concurrently and the effect of interventions may be delayed, we cannot reliably make such inferences from these empirical data alone. The ability to define intervention thresholds would also depend on the proportion of infections that are introduced from outside the population of interest, a quantity that probably varies depending on geographic location.

We found reductions in sexual activity among both male and female adolescents 15 to 19 years of age. Previous studies conducted by the Rakai Health Sciences Program showed a decline in the incidence of HIV infection among 15-to-19-year-old girls that was associated with factors such as delayed sexual debut, which was coincident with an increased rate of enrollment in school.[32] However, given the fact that this age group represents only a small fraction of all incident HIV infections and that there were limited behavioral changes in older age groups, the reduction in sexual activity among adolescents probably has a modest effect on population-level HIV incidence. No significant changes over time in condom use were observed in any age group, which is a sobering finding, given the many years of efforts to promote the use of condoms and to facilitate access to condoms.

This study has several limitations. First, ART coverage, male circumcision coverage, and sexual behaviors were reported by the participants and may be subject to social desirability and other biases. However, there are no clear indications that any biases changed over time, and participant-reported ART use has been validated with high specificity in this population.[19] Second, viral-load testing was conducted on stored serum samples; such serum samples may be subject to RNA degradation over time, which could potentially result in an overestimation of viral-load suppression in the earlier surveys and an underestima-

Table 2. Incidence of HIV Infection before and during Scale-up of Combination Strategy for HIV Prevention in the RCCS.*

Survey (Survey No.)	Incident HIV Infections	Person-Years	HIV Incidence per 100 Person-Yr (95% CI)	Incidence Rate Ratio (95% CI)†	P Value	Adjusted Incidence Rate Ratio (95% CI)†‡	P Value
Total HIV incidence cohort (N=17,870)							
Pre-CHP (2 through 5)	254	21,765	1.17 (1.03–1.32)	—	—	—	—
Jan. 2006 (6)	86	7,773	1.11 (0.89–1.36)	0.95 (0.74–1.21)	0.66	0.94 (0.73–1.20)	0.61
Oct. 2007 (7)	105	8,769	1.20 (0.98–1.44)	1.02 (0.82–1.29)	0.84	1.00 (0.79–1.26)	0.99
July 2009 (8)	125	10,201	1.23 (1.02–1.45)	1.05 (0.85–1.30)	0.67	0.95 (0.76–1.18)	0.62
Jan. 2011 (9)	105	9,815	1.07 (0.88–1.29)	0.91 (0.73–1.15)	0.44	0.94 (0.74–1.19)	0.60
June 2012 (10)	86	10,352	0.83 (0.67–1.02)	0.71 (0.55–0.91)	0.006	0.72 (0.56–0.93)	0.01
July 2014 (11)	87	13,159	0.66 (0.53–0.81)	0.56 (0.44–0.72)	<0.001	0.60 (0.47–0.78)	<0.001
Jan. 2016 (12)	83	12,593	0.66 (0.53–0.81)	0.56 (0.44–0.72)	<0.001	0.58 (0.45–0.76)	<0.001
Women (N=9709)							
Pre-CHP (2 through 5)	145	12,409	1.17 (0.99–1.37)	—	—	—	—
Jan. 2006 (6)	50	4,425	1.13 (0.84–1.47)	0.97 (0.70–1.33)	0.84	0.98 (0.71–1.35)	0.90
Oct. 2007 (7)	65	4,978	1.31 (1.01–1.65)	1.12 (0.83–1.50)	0.46	1.10 (0.82–1.48)	0.52
July 2009 (8)	67	5,610	1.19 (0.93–1.50)	1.02 (0.76–1.36)	0.89	0.91 (0.68–1.23)	0.55
Jan. 2011 (9)	61	5,319	1.15 (0.88–1.46)	0.98 (0.73–1.32)	0.90	0.98 (0.72–1.33)	0.89
June 2012 (10)	50	5,587	0.89 (0.67–1.17)	0.77 (0.56–1.05)	0.10	0.75 (0.54–1.05)	0.096
July 2014 (11)	55	7,090	0.78 (0.59–1.00)	0.66 (0.49–0.90)	0.01	0.65 (0.47–0.91)	0.01
Jan. 2016 (12)	56	6,689	0.84 (0.64–1.08)	0.72 (0.53–0.97)	0.03	0.68 (0.50–0.94)	0.02
Men (N=8161)							
Pre-CHP (2 through 5)	109	9,356	1.17 (0.96–1.40)	—	—	—	—
Jan. 2006 (6)	36	3,348	1.08 (0.76–1.47)	0.92 (0.63–1.34)	0.66	0.90 (0.61–1.33)	0.60
Oct. 2007 (7)	40	3,791	1.06 (0.76–1.42)	0.90 (0.63–1.29)	0.57	0.89 (0.62–1.30)	0.56
July 2009 (8)	58	4,591	1.26 (0.97–1.62)	1.08 (0.78–1.48)	0.64	1.02 (0.73–1.42)	0.93
Jan. 2011 (9)	44	4,497	0.98 (0.72–1.30)	0.83 (0.59–1.18)	0.31	0.92 (0.63–1.33)	0.64
June 2012 (10)	36	4,765	0.76 (0.53–1.03)	0.64 (0.44–0.94)	0.02	0.70 (0.47–1.05)	0.08
July 2014 (11)	32	6,069	0.53 (0.37–0.73)	0.45 (0.30–0.67)	<0.001	0.54 (0.36–0.83)	0.005
Jan. 2016 (12)	27	5,904	0.46 (0.31–0.65)	0.39 (0.25–0.59)	<0.001	0.46 (0.29–0.73)	0.001
Uncircumcised men only (N=5660)							
Pre-CHP (2 through 5)	94	7,773	1.21 (0.98–1.47)	—	—	—	—
Jan. 2006 (6)	30	2,456	1.22 (0.83–1.71)	1.01 (0.67–1.52)	0.98	0.96 (0.63–1.46)	0.85
Oct. 2007 (7)	31	2,590	1.20 (0.82–1.67)	0.98 (0.66–1.48)	0.94	0.92 (0.61–1.4)	0.70
July 2009 (8)	40	2,927	1.37 (0.99–1.83)	1.12 (0.78–1.63)	0.54	1.00 (0.68–1.47)	0.99
Jan. 2011 (9)	32	2,571	1.24 (0.86–1.73)	1.02 (0.68–1.53)	0.92	1.00 (0.67–1.51)	0.98
June 2012 (10)	24	2,493	0.96 (0.63–1.40)	0.79 (0.50–1.24)	0.30	0.77 (0.49–1.22)	0.27
July 2014 (11)	17	2,779	0.61 (0.36–0.95)	0.50 (0.30–0.84)	0.009	0.46 (0.26–0.81)	0.007
Jan. 2016 (12)	15	2,303	0.65 (0.37–1.04)	0.53 (0.31–0.92)	0.02	0.51 (0.29–0.88)	0.02

* CHP denotes combination strategy for HIV prevention.

† The mean incidence of HIV infection at each visit interval after 2004 (i.e., beginning with the sixth survey) was compared with the mean incidence of HIV infection over the entire period before the availability of antiretroviral therapy and male circumcision.

‡ The final adjusted model included adjustment for age, sex (full cohort only), level of education, number of sexual partners in the past year, sex with partners outside the community of residence, sex with nonmarital partners, participant-reported genital ulcer disease, condom use with casual partners, type of community of residence (trading or agrarian), and HIV prevalence in the community.

tion of the magnitude of viral-load suppression over time.[33] Third, although the RCCS has relatively high participation rates as compared with other African population-based cohorts, there was substantial mobility among the participants, which reduced the rates of participation and follow-up.[34,35] However, rates of participation among persons who were present in the community increased over time, and sensitivity analyses to assess potential selection bias did not change our inferences. Fourth, we cannot rule out the possibility that unmeasured secular trends or other potential confounders explain the declines in the incidence of HIV infection. However, this observational study showed a strong temporal association between the scale-up of a combination strategy for HIV prevention and population-level declines in the incidence of HIV infection, as well as greater reductions in HIV incidence with higher coverage of interventions.

An important consideration is whether our estimates of service coverage and HIV incidence results can be generalized. Demographic and behavioral data in the RCCS are largely consistent with surveys of demographic and health data in the region.[36] The RCCS is also an open, population-based cohort with extensive migration in and out of the cohort, which probably minimized, but did not eliminate, potential Hawthorne effects (i.e., changes in behavior resulting from awareness of being observed) of repeat observations. The Rakai Health Sciences Program has conducted combination studies of HIV intervention and prevention, which may have increased ART and male circumcision coverage.[37-39] All participants in the RCCS are offered HIV testing services, which results in high coverage (98% in 2015). Although conditions in Rakai may have been favorable for rapidly scaling ART use and male circumcision services, the effect of these interventions on population-level incidence of HIV infection should be generalizable. Indeed, data from the National AIDS Control Program of the Uganda Ministry of Health indicate that a dramatic scale-up of a combination strategy for HIV prevention was also occurring nationally: in 2016, ART coverage was 68% and male circumcision coverage was 54% (Wiersma S: personal communication).

In summary, data from this longitudinal cohort in Rakai, Uganda, showed a 42% decline in the incidence of HIV infection that was associated with the scale-up of a combination strategy for HIV prevention. This decline provides evidence that HIV control efforts can have a population-level effect. Differential declines in the incidence of HIV infection according to sex indicate a need to strengthen prevention efforts to benefit women, including improvement in ART coverage among men and consideration of newer, primary prevention interventions. Intensification of HIV prevention efforts for both women and men, including key underserved populations such as migrants, as well as long-term surveillance, are needed.

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APPENDIX

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