Original Investigation

Association of Medical Male Circumcision and Antiretroviral Therapy Scale-up With Community HIV Incidence in Rakai, Uganda

Xiangrong Kong, PhD; Godfrey Kigozi, MB, ChB, PhD; Joseph Ssekasanvu, MS; Fred Nalugoda, PhD; Gertrude Nakigozi, MD, MPH; Anthony Ndyanabo, MSc; Tom Lutalo, MS; Steven J. Reynolds, MD, MPH; Robert Ssekubugu, MHS; Joseph Kagaayi, MB, ChB, PhD; Eva Bugos, BS; Larry W. Chang, MD, MPH; Pilgrim Nanlesta, PhD; Grabowski Mary, PhD; Amanda Berman, MSPH, MPhil; Thomas C. Quinn, MD; David Serwadda, MB, ChB, MMed, MPH; Maria J. Wawer, MD, MSH; Ronald H. Gray, MD, MSc

IMPORTANCE Medical male circumcision (MMC) and antiretroviral therapy (ART) are proven HIV prevention interventions, but there are limited data on the population-level effect of scale-up of these interventions in sub-Saharan Africa. Such evaluation is important for planning and resource allocation.

OBJECTIVE To examine whether increasing community MMC and ART coverage was associated with reduced community HIV incidence in Rakai District, Uganda.

DESIGN, SETTING, AND PARTICIPANTS Using person-level data from population-based surveys conducted from 1999 through 2013 in 45 rural Rakai communities, community-level ART and MMC coverage, sociodemographics, sexual behaviors, and HIV prevalence and incidence were estimated in 3 periods: prior to the availability of ART and MMC (1999-2004), during early availability of ART and MMC (2004-2007), and during mature program scale-up (2007-2013).

EXPOSURES Community MMC coverage in males and ART coverage in HIV-positive persons of the opposite sex based on self-reported MMC status and ART use.

MAIN OUTCOMES AND MEASURES Adjusted incidence rate ratios (IRRs) for sex-specific community HIV incidence estimated using multivariable Poisson regression with generalized estimating equations.

RESULTS From 1999 through 2013, 44 688 persons participated in 1 or more surveys (mean age at the first survey, 24.6 years [range, 15-49]; female, 56.5%; mean survey participation rate, 92.6% [95% CI, 92.4%-92.7%]). Median community MMC coverage increased from 19% to 39%, and median community ART coverage rose from 0% to 21% in males and from 0% to 26% in females. Median community HIV incidence declined from 1.25 to 0.84 per 100 person-years in males, and from 1.25 to 0.99 per 100 person-years in females. Among males, each 10% increase in community MMC coverage was associated with an adjusted IRR of 0.87 (95% CI, 0.82-0.93). Comparing communities with MMC coverage more than 40% (mean male community incidence, 1.03 per 100 person-years) with communities with coverage of 10% or less (mean male incidence, 1.69 per 100 person-years), the adjusted IRR was 0.61 (95% CI, 0.43-0.88). For each 10% increase in female self-reported ART coverage, there was no significant reduction in male HIV incidence (adjusted IRR, 0.95 [95% CI, 0.81-1.13]). Comparing communities with female ART coverage more than 20% (mean male incidence, 0.87 per 100 person-years) to communities with female ART coverage of 20% or less (mean male incidence, 1.17 per 100 person-years), the adjusted IRR was 0.77 (95% CI, 0.61-0.98). Neither MMC nor male ART coverage was associated with lower female community HIV incidence.

CONCLUSIONS AND RELEVANCE In Rakai, Uganda, increasing community MMC and female ART coverage was associated with lower community HIV incidence in males. If similar associations are found elsewhere, this would support further scale-up of MMC and ART for HIV prevention in sub-Saharan Africa.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Xiangrong Kong, PhD, Johns Hopkins, Bloomberg School of Public Health, 627 N Washington St, Baltimore, MD 21205 (xkong4@jhu.edu).

Randomized trials have shown that medical male circumcision (MMC) reduces male HIV acquisition by 50% to 60%,[1-3] and that early initiation of antiretroviral therapy (ART) reduces HIV transmission by more than 90% in HIV-discordant couples.[4] Mathematical modeling suggests that these interventions could mitigate the HIV epidemic in sub-Saharan Africa,[5-7] but there is limited empirical evidence for the population-level effects of these interventions on HIV incidence in real-world programs.

MMC provides direct protection against male HIV acquisition by removing the foreskin, which is rich in HIV target cells.[8-10] The potential effect of MMC on population-level HIV incidence depends on this biological effect, the level of MMC coverage, risk profiles of men accepting MMC, and whether behavioral disinhibition occurs following circumcision.

ART indirectly protects an HIV-negative partner by reducing the viral load of the HIV-positive person.[4,11] The effects of ART on population-level incidence depends on the proportion of HIV-positive persons taking ART, which is contingent on the guidelines for ART initiation, the proportion of eligible persons who initiate treatment, the proportion of persons on treatment who are virologically suppressed, and the likelihood that an HIV-uninfected person has relationships with a virologically suppressed HIV-positive partner. Early ART initiation was highly efficacious in reducing HIV transmission in HIV-discordant couples who disclosed their HIV results,[4] but in general populations, the effects of ART on HIV incidence are likely to be lower because rates of HIV disclosure, ART coverage, and exposures to HIV-positive partners on ART are likely to be more variable.

A community-based study was conducted to assess the associations between MMC and ART coverage and community HIV incidence in Rakai, Uganda, using longitudinal population-based data prior to the availability of MMC and ART, and following the scale-up of these interventions.

Methods

The study was approved by the Scientific Ethics Committee of the Uganda Virus Research Institute, the Uganda National Council of Science and Technology, the Committee on Human Research at Johns Hopkins University Bloomberg School of Public Health, and the Western Institutional Review Board. Written informed consent was obtained at cohort enrollment and follow-up visits. The Rakai Health Sciences Program conducts HIV-related surveillance and provides HIV prevention and clinical services in rural Rakai district, south central Uganda. The area has had a generalized heterosexual HIV epidemic since the 1970s. Data for this analysis are derived from the 1999-2013 Rakai Community Cohort Study, a longitudinal open cohort of persons aged 15 through 49 years. The study has been described in detail elsewhere.[12] In brief, population-based surveys were conducted approximately every 12 to 18 months. A census preceded each survey to identify eligible community residents for survey participation. Each participant received a permanent identification number used to link data between databases. Experienced same-sex interviewers used structured questionnaires to collect information on sociodemographics, sexual behaviors, general health, male circumcision status, and long-term medication use including ART. Venous blood was collected for HIV testing.

HIV was detected using 2 enzyme immunoassays (Murex HIV-1.2.0, Abbott, and Vironostika HIV-1/2 PlusO, Bioméreux), with confirmation of discordant enzyme immunoassay results and of seroconversions by Western blot assay (Vitek, BioMérieux), polymerase chain reaction (Abbott RealTime HIV-1, Abbott), or both. Rapid tests were introduced in 2009 using Alere Determine (Alere) and STAT-PAK (Chembio) run in parallel with Uni-Gold (Trinity Biotech) as a tiebreaker, and results were confirmed by enzyme immunoassays for all seroconverters, with Western blot or polymerase chain reaction as needed.

Free HIV counseling and testing was offered to all participants, and HIV-positive persons were linked to care. ART became available in 2004, supported by the President's Emergency Plan for AIDS Relief (PEPFAR). The criteria for ART initiation evolved from a CD4 level higher than 250 cells/mm^3 (2004 to mid-2011) to a CD4 level higher than 350 cells/mm^3 (mid-2011 to 2013). Approximately 15% of the male population are Muslims and practice infant circumcision, and prior to 2004, only 5% of non-Muslim men were circumcised. During 2004 through 2006, a randomized trial of MMC for HIV prevention enrolled 4996 HIV-negative men from the Rakai district (the majority were from outside the cohort study communities), half of whom received immediate MMC after randomization.[3] After trial completion, control participants were offered circumcision. In late 2007, free MMC services were scaled up with PEPFAR funding via fixed facilities and mobile surgical camps throughout Rakai.

Statistical Analyses

This analysis was confined to 45 Rakai communities under surveillance since 1999, including 15 communities surveyed until 2011 and 30 communities surveyed until 2013. The communities were defined in 1994 by local council administrative areas and were separated by distance or natural obstacles. They remain separate administrative units despite expansions in recent years. Availability of MMC and ART services varied over time, and the data were divided into 3 periods: period 1 (mid-1999 to mid-2004), prior to the availability of ART or MMC; period 2 (mid-2004 to late-2007), when MMC was provided via trial and posttrial services and the ART program was initiated; and period 3 (late 2007 to mid-2013), when scale-up of both services matured. The surveys occurred continuously throughout the year, with communities surveyed in the same order during each survey round. The survey in a given round provides the end points and person-time for the preceding interval, as well as the baseline observations and start of person-time measurement for the succeeding interval of observation. Therefore, the end of a period also serves as the beginning of the next period, and there are no fixed dates for the beginning and end of the periods used.

For each community, sex-specific HIV incidence was calculated as the number of incident cases divided by the total person-years at risk during each period. Person-years for incident cases were estimated from the date of the first HIV-negative visit and the date of infection (estimated as the midpoint between the last seronegative and first seropositive test dates). Person-years for persistently HIV-negative persons were estimated from the first and last visit dates during each period. Community incidence was estimated over each period rather than in each intersurvey interval, in part to reflect the changes in ART and MMC coverage and because of the limited number of incident events during an intersurvey interval in low-risk communities.

The primary exposures were community-level MMC coverage in males and ART coverage among HIV-positive persons of the opposite sex in each period. Self-reported MMC status and ART use were used to estimate coverage in each survey, and were then summarized into community-level exposures by periods (eMethods in the Supplement). Pearson correlation coefficient was calculated to assess the correlation between community MMC coverage in men and ART coverage among HIV-positive persons of each sex.

To adjust for potential confounding by community characteristics, for each period sex-specific, community-level age distributions, proportions reporting multiple sex partners, and proportions of sexually active persons reporting nonuse (ie, never-use) of condoms in the past year were assessed. Community HIV prevalence in the opposite sex was included as a measure of community HIV exposure. Additionally, to adjust for temporal changes not captured by the aforementioned factors, an indicator variable for periods was used as a surrogate of unmeasured societal change over study periods (eMethods in the Supplement).

Poisson log-linear models were used to estimate incidence rate ratios (IRRs) of community-level, sex-specific HIV incidence associated with the exposures: the logarithm of the community HIV incidence rate for a period was modeled as a linear function of the exposures. Robust variance estimates based on generalized estimating equations were used to account for correlation between repeated observations in the same communities. The primary exposure variables of MMC and ART coverage were analyzed as continuous variables to estimate the IRRs associated with each 10% increment in coverage on community HIV incidence. Additionally, MMC coverage was modeled as a categorical variable (≤10%, >10-≤20%, >20-≤30%, >30-≤40%, and >40%); and ART coverage was categorized as 20% or less vs more than 20% upon considering the variable's distribution (a cutoff of 15% was also explored). The associations between community-level exposures and HIV incidence were estimated in bivariable models, followed by multivariable models including variables significant at a *P* value of .10 or less in bivariable analyses. All main multivariable analyses included both the primary exposures of MMC and ART coverage. Additionally, the potential multiplicative associations of MMC and ART coverage with HIV incidence were explored via a multivariable model including both the main terms of the primary exposure variables and their interaction term.

Because MMC and ART coverage were correlated over time, to avoid collinearity, sensitivity analyses were also conducted using multivariable models, which included only MMC or ART coverage while adjusting for other confounders. Another sensitivity analysis was performed using data from the 30 communities consistently observed from 1999 through 2013. Additionally, further sensitivity analyses were conducted using ART coverage estimated from the Rakai Health Sciences Program's clinic records (eMethods in the Supplement).

Model diagnostics were based on aggregated residuals.[13] SAS (SAS Institute), version 9.3, was used for the regression modeling, and *P* values were based on 2-sided Wald tests with a significance level of .05.

Results

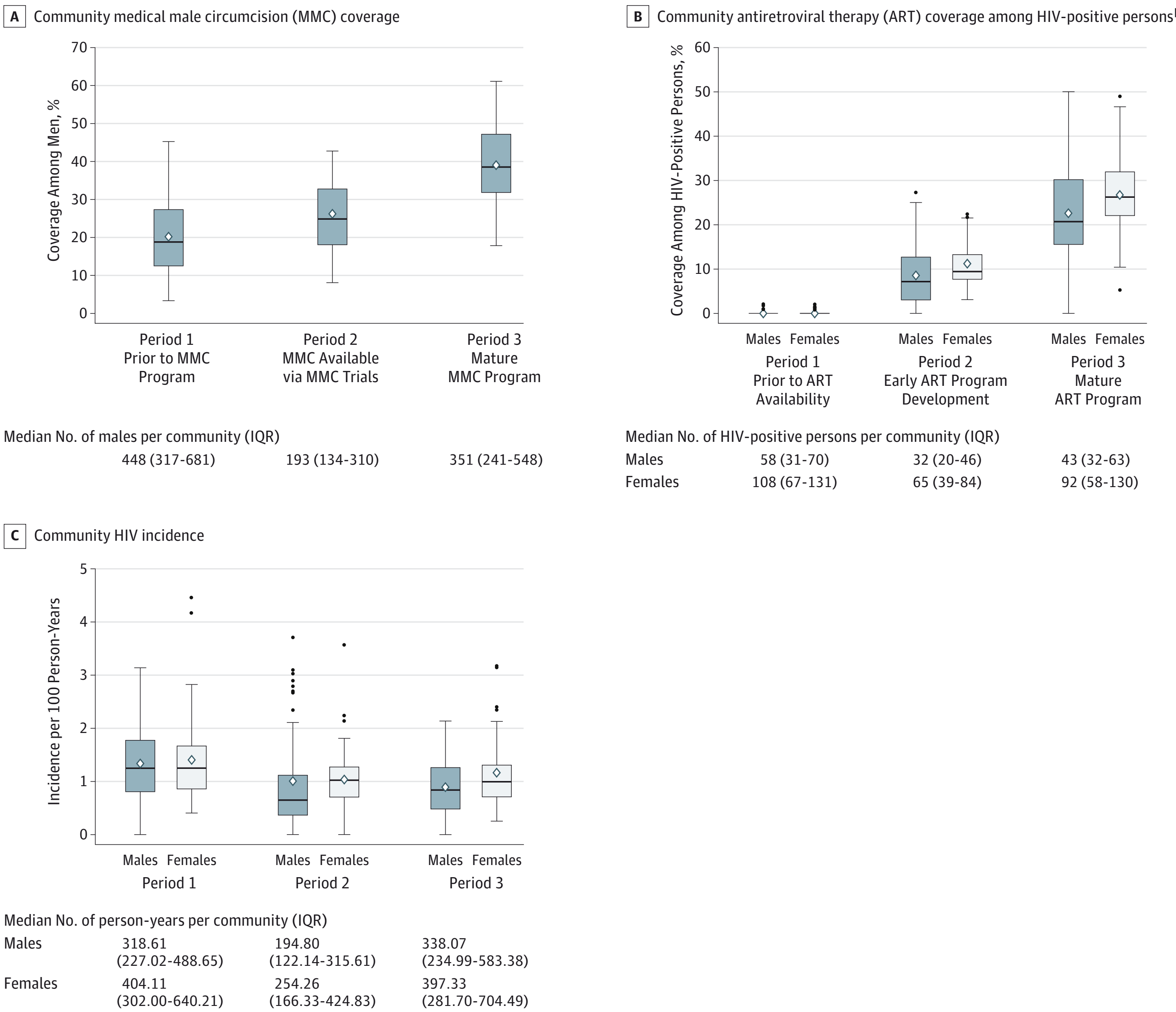
Ten survey rounds were conducted between 1999 and 2013: 44 688 persons participated in 1 or more surveys (mean age at the first survey, 24.6 years [range, 15-49]; female, 56.5%). The mean participation rate was 92.6% (95% CI, 92.4%-92.7%) among age-eligible residents present at time of survey; and among these participants, 94.7% provided a blood sample for HIV testing, and 62.6% participated in at least 1 follow-up survey.

The **Figure** presents distributions of MMC and ART coverage and HIV incidence in the 45 communities by sex and the 3 periods. It shows substantial variability in coverage and incidence across communities. Both MMC and ART coverage increased over time and were correlated (Pearson correlation coefficient: MMC with female ART coverage, 0.53 [95% CI, 0.40-0.64], $P < .001$; MMC with male ART coverage, 0.48 [95% CI, 0.34-0.60], $P < .001$).

Table 1 summarizes the distributions of community-level exposures for males by period. The median community MMC coverage increased from 18.8% (interquartile range [IQR], 12.5%-27.3%) in period 1 to 38.5% (IQR, 31.9%-47.2%) in period 3, and median ART coverage in HIV-positive males increased from 0% (IQR, 0%-0%; range, 0%-2.1%) to 20.7% (IQR, 15.6%-30.2%). The proportions of men aged 20 through 24 years and 25 through 29 years decreased, whereas the proportions aged 35 through 39 years and 40 through 49 years increased over time. In period 3, the proportion of males reporting multiple sex partners declined, but the proportion of sexually active males reporting nonuse of condoms increased. Median male community HIV prevalence was approximately 9% to 10% in all periods, whereas median male community HIV incidence declined by 32.8% from 1.25 (IQR, 0.81-1.77) per 100 person-years to 0.84 (IQR, 0.48-1.26) per 100 person-years from period 1 to period 3.

Median community ART coverage in HIV-positive females increased from 0% (IQR 0%-0%; range, 0%-2.0%) in period 1 to 26.3% (IQR, 22.0%-31.9%) in period 3 (Table 1). The proportion of women aged 20 through 24 years declined, and the proportions aged 30 through 34 years and 35 through 39 years increased over time. The proportion of female self-reported multiple partnerships did not vary over time, but the median proportion of sexually active females reporting nonuse of condoms declined from 74.2% (IQR, 69.8%-77.9%) to 68.4% (IQR, 64.7%-71.5%) from period 1 to period 3. Female median community HIV prevalence remained relatively stable (approximately 13%-14%), and female community HIV inci-

Figure. Distributions of Community-Level MMC Coverage in Males, ART Coverage, and HIV Incidence by Sex in the 45 Communities in Rakai, Uganda, Over 3 Periods[a]



ART indicates antiretroviral therapy; MMC, medical male circumcision. In each box plot, the top and bottom of the boxes indicate the interquartile range; the horizontal black line indictes the median; the diamond indicates the mean; and the lower and upper whiskers are the lowest and highest values of the data that are not outliers. Any circle outside the whiskers is an outlier (ie, the data value is greater than 1.5 interquartile ranges away from the first and third quartiles). Surveys occurred continuously throughout the year, with communities surveyed in the same order during each survey round. The survey in a given round provides the end points and person-year for the preceding interval, as well as the baseline observations and start of person-year measurement for the succeeding interval of observation. Therefore, the end of a period also serves as the beginning of the next period, and there are no fixed dates for the beginning and end of the periods used.

[a] For each period, distribution of data for 45 communities is shown by the box plot. For period 3, data for 15 communities were from surveys conducted up to 2011, and data for the other 30 communities were from surveys conducted up to 2013. Period 1 was from mid-1999 to mid-2004. Period 2 was from mid-2004 to late 2007. Period 3 was from late-2007 to mid-2013.

[b] ART initiation criteria evolved from CD4 level less than 250 cells/mm^3 during 2004-2011 to CD4 level less than 350 cells/mm^3 during 2011-2013.

dence declined by 20.8% from 1.25 (IQR, 0.86-1.67) per 100 person-years in period 1 to 0.99 (IQR, 0.71-1.31) per 100 person-years in period 3.

Table 2 presents the unadjusted IRR and adjusted IRR for male community HIV incidence. Each 10% increase in MMC coverage was associated with an adjusted IRR of 0.87 (95% CI, 0.82-0.93), $P < .001$. When modeled as a categorical variable, the observed mean community HIV incidence rate was 1.03 per 100 person-years in communities with MMC coverage more than 40% and 1.69 per 100 person-years in communities with MMC coverage of 10% or less, and the adjusted IRR was 0.61 (95% CI, 0.43-0.88), $P = .007$. Each 10% increase in female self-reported ART coverage was associated with reduced male HIV incidence in bivariable analysis, but this was not statistically significant after adjustment (adjusted IRR, 0.95 [95% CI, 0.81-1.13], $P = .58$). However, when modeled as a categorical

Table 1. Distributions of Sex-Specific Community-Level Characteristics of the 45 Communities by Period[a]

	Median (IQR)[b]		
	Period 1 (mid-1999 to mid-2004)	Period 2 (mid-2004 to late-2007)	Period 3 (late 2007 to mid-2013)
Community-Level Characteristics in Males			
MMC coverage in males, %[c]	18.8 (12.5-27.3)	25.0 (18.1-32.8)	38.5 (31.9-47.2)
ART coverage in HIV+ males, %	0 (0-0) (range, 0-2.1)	7.1 (3.0-12.7)	20.7 (15.6-30.2)
Male age distribution, %			
15-19 y	18.4 (16.0-20.9)	16.7 (13.4-20.0)	20.7 (17.8-24.2)
20-24 y	21.2 (18.8-24.7)	18.6 (17.0-21.0)	16.4 (14.7-18.0)
25-29 y	21.2 (19.2-22.8)	20.3 (17.7-22.9)	16.9 (15.5-19.1)
30-34 y	16.2 (14.8-18.1)	17.1 (15.5-20.1)	16.8 (14.3-18.9)
35-39 y	10.3 (8.6-12.3)	12.5 (10.4-14.0)	14.1 (12.0-15.2)
40-49 y	12.1 (10.4-14.2)	13.5 (12.0-15.5)	15.0 (13.7-17.2)
Males reporting multiple partnerships in the past year, %	40.0 (36.4-43.2)	37.3 (35.1-44.1)	32.0 (29.2-36.3)
Sexually active males reporting no condom use in the past year, %	47.5 (43.3-53.0)	45.3 (41.5-51.0)	50.9 (46.8-54.9)
Male HIV prevalence, %	10.4 (7.7-13.6)	9.4 (7.7-12.2)	10.1 (7.7-11.9
Total person-years in males	318.61 (227.02-488.65)	194.80 (122.14-315.61)	338.07 (234.99-583.38)
Male HIV incidence, per 100 person-years	1.25 (0.81-1.77)	0.65 (0.37-1.12)	0.84 (0.48-1.26)
No. of males per community[d]	448 (317-681)	193 (134-310)	351 (241-548)
Community-Level Characteristics in Females			
ART coverage in HIV+ females, %	0 (0-0) (range, 0-2.0)	9.4 (7.7-13.3)	26.3 (22.0-31.9)
Female age distribution, %			
15-19 y	18.3 (16.4-20.0)	15.5 (12.8-17.2)	16.9 (14.1-20.2)
20-24 y	25.1 (23.2-27.1)	22.0 (19.9-25.7)	18.5 (16.3-20.3)
25-29 y	20.5 (18.9-23.6)	22.6 (20.3-24.4)	20.2 (17.6-22.0)
30-34 y	12.4 (11.5-13.9)	15.3 (14.1-17.8)	17.5 (16.0-20.0)
35-39 y	9.5 (8.2-11.2)	9.2 (8.1-11.1)	12.2 (10.7-13.5)
40-49 y	13.2 (11.0-15.6)	14.9 (11.8-17.2)	14.1 (12.0-16.2)
Females reporting multiple partnerships in the past year, %	4.9 (3.8-6.1)	4.5 (3.5-5.9)	4.7 (3.9-5.8)
Sexually active females reporting no condom use past year, %	74.2 (69.8-77.9)	68.7 (62.1-71.6)	68.4 (64.7-71.5)
Female HIV prevalence, %	14.0 (12.3-16.4)	13.5 (10.9-16.3)	14.8 (12.2-18.3)
Total person-years in females	404.11 (302.00-640.21)	254.26 (166.33-424.83)	397.33 (281.70-704.49)
Female HIV incidence, per 100 person-years	1.25 (0.86-1.67)	1.02 (0.70-1.27)	0.99 (0.71-1.31)
No. of females per community[d]	644 (406-927)	283 (170-422)	477 (303-693)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; MMC, medical male circumcision.

[a] Including 15 communities surveyed from 1999 through 2011 and 30 communities surveyed from 1999-2013.

[b] The surveys occurred continuously throughout the year, with communities surveyed in the same order during each survey round. The survey in a given round provides the end points and person-time for the preceding interval, as well as the baseline observations and start of person-time measurement for the succeeding interval of observation. Therefore, the end of a period also serves as the beginning of the next period, and there are no fixed dates for the beginning and end of the periods used.

[c] MMC scale-up was mainly targeted on non-Muslim males as Muslims practice infant circumcision. The composition of Muslims and non-Muslims was stable in Rakai: non-Muslim males constituted 85.1%, 84.3%, and 84.5% of the male population in period 1, 2 and 3, respectively.

[d] The number of males and females for a community during a period was the sum of the number of males or females in all survey rounds in the period. Overall, there were 11 409 males and 15 166 females who participated in at least 1 survey round in period 1, 9376 males and 12 076 females who participated in at least 1 survey in period 2, and 12 068 males and 15 149 females who participated in at least 1 survey in period 3.

variable, the observed mean male incidence rate was 0.87 per 100 person-years in communities with female ART coverage more than 20% and 1.17 per 100 person-years in communities with female ART coverage of 20% or less (adjusted IRR, 0.77 [95% CI, 0.61-0.98], *P* = .03). Each 10% increase in female community HIV prevalence was associated with increased male incidence (adjusted IRR, 1.44 [95% CI, 1.17-1.77]). Changes in community male age composition and increase in the proportion of men reporting multiple sex partners were not significantly associated with male incidence after adjustment. Periods were significantly associated with HIV incidence in bivariable analysis, but the association was not significant after adjustment. The model including the interaction between MMC and female ART coverage showed no significant multiplicative associations (interaction *P* = .36). Because MMC and female ART coverage were correlated over time, they were also modeled separately in a sensitivity analysis (eTable 1 in the Supplement), which yielded similar results on the adjusted IRRs for MMC and ART coverage.

Table 3 presents the IRRs for female community HIV incidence. Each 10% increase in male MMC coverage was associated with lower female incidence in bivariable analysis, but there was no significant association after adjustment (adjusted IRR, 1.00 [95% CI, 0.93-1.06]). Categorized MMC coverage was not associated with lower female incidence. Each 10% increment in male ART coverage was significantly associated with lower female incidence in bivariable analysis, but this was not significant after adjustment (adjusted IRR, 0.98 [95% CI, 0.89-1.08], *P* = .67). Categorized male ART coverage more than 20% compared with 20% or less was not signifi-

Table 2. Incidence Rate Ratios of Community-Level HIV Incidence in Males From Bivariable and Multivariable Models Using Data From the 45 Communities[a]

		Bivariable Model		Full Multivariable Model[b]	
		IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Each 10% increment in…					
MMC coverage		0.85 (0.79-0.92)	<.001	0.87 (0.82-0.93)	<.001
Self-reported female ART coverage		0.89 (0.82-0.97)	<.001	0.95 (0.81-1.13)	.58
HIV prevalence in females		1.57 (1.31-1.87)	<.001	1.44 (1.17-1.77)	<.001
Percentage of males aged					
15-19 y		0.91 (0.72-1.15)	.43	NA[c]	
20-24 y		1.66 (1.27-2.16)	.002	1.34 (0.89-2.03)	.17
25-29 y		1.28 (0.95-1.73)	.10	0.99 (0.62-1.57)	.96
30-34 y		0.86 (0.61-1.23)	.42	NA[c]	
35-39 y		0.68 (0.46-1.00)	.05	1.07 (0.63-1.82)	.79
40-49 y		0.63 (0.45-0.88)	.007	0.95 (0.69-1.30)	.75
Males reporting multiple sex partners in the past year, %		1.29 (1.10-1.51)	.002	1.22 (0.99-1.51)	.07
Sexually active males reporting no condom use in past year, %		0.87 (0.76-0.99)	.03	0.93 (0.80-1.07)	.32
Period[d]					
1 (mid-1999 to mid-2004)		Reference		Reference	
2 (mid-2004 to late-2007)		0.71 (0.55-0.91)	.007	0.88 (0.57-1.36)	.56
3 (late 2007 to mid-2013)		0.69 (0.57-0.84)	<.001	1.32 (0.79-2.20)	.29
Modeled as a Categorical Variable					
MMC coverage, %	Observed community HIV incidence rate per 100 person-years, mean (95% CI)				
≤10	1.69 (1.05-2.33)	Reference		Reference	
>10-≤20	1.19 (0.86-1.52)	0.71 (0.48-1.06)	.09	0.89 (0.64-1.26)	.53
>20-≤30	1.01 (0.75-1.28)	0.54 (0.38-0.77)	<.001	0.65 (0.47-0.92)	.002
>30-≤40	0.93 (0.68-1.17)	0.54 (0.37-0.77)	<.001	0.72 (0.50-1.05)	.09
>40	1.03 (0.71-1.35)	0.49 (0.34-0.72)	<.001	0.61 (0.43-0.88)	.007
ART coverage in females, %[e]					
≤20	1.17 (0.99-1.35)	Reference		Reference	
>20	0.87 (0.68-1.07)	0.75 (0.60-0.92)	.007	0.77 (0.61-0.98)	.03

Abbreviations: ART, antiretroviral therapy; IRR, incidence rate ratios; MMC, medical male circumcision; NA, not applicable.

[a] Including 15 communities surveyed from 1999-2011 and 30 communities surveyed from 1999 through 2013.

[b] The full multivariable model included the primary exposures of MMC coverage in males and ART coverage in HIV-positive females, as well as covariates of community HIV prevalence in females, proportions of men in age groups of 20-24, 25-29, 35-39, and 40-49, proportion of males reporting multiple sex partnership, proportion of sexually active males reporting no condom use, and the indicator variable for period.

[c] Not applicable in the multivariable model because the *P* value more than .10 in bivariable models.

[d] The surveys occurred continuously throughout the year, with communities surveyed in the same order during each survey round. The survey in a given round provides the endpoints and person-time for the preceding interval, as well as the baseline observations and start of person-time measurement for the succeeding interval of observation. Therefore, the end of a period also serves as the beginning of the next period, and there are no fixed dates for the beginning and end of the periods used.

[e] When ART coverage in females was categorized as more than 15% vs 15% or less, the adjusted IRR was 0.76 (95% CI, 0.57-1.02), *P* = .07.

cantly associated with lower female incidence (adjusted IRR, 0.86 [95% CI, 0.72-1.03], *P* = .11). Each 10% increase in male community HIV prevalence was associated with higher female incidence (adjusted IRR, 1.30 [95% CI, 1.01-1.67]), and a higher proportion of females reporting multiple sexual partners was strongly associated with higher female community incidence (adjusted IRR, 1.96 [95% CI, 1.25-3.06]). Community female age composition, nonuse of condoms, and periods were not associated with female incidence after adjustment. The model including the interaction between MMC and male ART coverage showed no significant multiplicative associations (interaction *P* = .21). The sensitivity analysis that modeled ART or MMC coverage separately yielded similar adjusted IRRs for ART and MMC coverage with female community incidence (eTable 2 in the Supplement).

Results from the sensitivity analysis of the 30 communities observed continuously from 1999 through 2013 were similar to those reported above (eTables 3 and 4 in the Supplement). Results based on ART coverage estimated from clinic records (eTables 5-8 in the Supplement) did not affect most findings, but using the 45 communities and ART coverage estimated from clinic records categorized male ART coverage more than 20% compared with 20% or less as associated with lower female incidence (adjusted IRR, 0.80 [95% CI, 0.65-0.98], *P* = .03; eTable 6 in the Supplement). eTable 9 in the Supplement summarizes the distributions of community-

Table 3. Incidence Rate Ratios of Community-Level HIV Incidence in Females From Bivariable and Multivariable Models Using Data From the 45 Communities[a]

		Bivariable Model		Full Multivariable Model[b]	
		IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Each 10% increment in…					
MMC coverage		0.94 (0.89-0.99)	.02	1.00 (0.93-1.06)	.92
Self-reported male ART coverage		0.92 (0.87-0.98)	.01	0.98 (0.89-1.08)	.67
HIV prevalence in males		1.62 (1.31-2.01)	<.001	1.30 (1.01-1.67)	.05
Percentage of females aged					
15-19 y		0.94 (0.76-1.18)	.61	NA[c]	
20-24 y		1.42 (1.20-1.69)	<.001	1.31 (0.94-1.82)	.11
25-29 y		1.24 (0.94-1.63)	.12	NA	
30-34 y		0.77 (0.62-0.96)	.02	0.95 (0.72-1.26)	.71
35-39 y		0.71 (0.47-1.06)	.10	1.04 (0.71-1.52)	.85
40-49 y		0.67 (0.47-0.96)	.03	1.10 (0.83-1.45)	.50
Females reporting multiple sex partners in the past year, %		2.54 (1.58-4.09)	<.001	1.96 (1.25-3.06)	.003
Sexually active females reporting no condom use in the past year, %		0.90 (0.78-1.06)	.20	NA[c]	
Period[d]					
1 (mid-1999 to mid-2004)		Reference		Reference	
2 (mid-2004 to late-2007)		0.83 (0.68-1.01)	.07	0.94 (0.73-1.22)	.65
3 (late 2007 to mid-2013)		0.80 (0.69-0.94)	.005	1.03 (0.73-1.45)	.85
Modeled as a Categorical Variable					
MMC coverage, %	Observed community HIV incidence rate per 100 person-years, mean (95% CI)				
≤10	1.15 (0.71-1.60)	Reference		Reference	
>10-≤20	1.33 (1.12-1.54)	1.00 (0.66-1.50)	.99	1.16 (0.79-1.72)	.45
>20-≤30	1.18 (0.94-1.42)	0.96 (0.67-1.40)	.85	1.22 (0.86-1.74)	.27
>30-≤40	0.96 (0.74-1.17)	0.78 (0.54-1.13)	.19	1.03 (0.72-1.47)	.88
>40	1.39 (0.97-1.81)	0.87 (0.59-1.28)	.47	1.15 (0.82-1.63)	.41
ART coverage in males, %[e]					
≤20	1.20 (1.06-1.34)	Reference		Reference	
>20	1.19 (0.88-1.50)	0.82 (0.69-0.98)	.03	0.86 (0.72-1.03)	.11

Abbreviations: ART, antiretroviral therapy; IRR, incidence rate ratio; MMC, medical male circumcision; NA, not applicable.

[a] Including 15 communities surveyed from 1999 through 2011 and 30 communities surveyed from 1999 through 2013.

[b] The full multivariable model included the primary exposures of MMC coverage in males and ART coverage in HIV-positive males, as well as covariates of community HIV prevalence in males, proportions of women in age groups of 20-24, 30-34, 35-39, and 40-49, proportion of females reporting multiple sex partnership, and the indicator variable for period.

[c] Not applicable in the multivariable model because the *P* value more than .10 in bivariable models.

[d] The surveys occurred continuously throughout the year, with communities surveyed in the same order during each survey round. The survey in a given round provides the end points and person-time for the preceding interval, as well as the baseline observations and start of person-time measurement for the succeeding interval of observation. Therefore, the end of a period also serves as the beginning of the next period, and there are no fixed dates for the beginning and end of the periods used.

[e] When ART coverage in males was categorized as more than 15% vs 15% or less, the adjusted IRR was 0.98 (95% CI, 0.79-1.20), *P* = .82.

level characteristics for the 30 communities observed continuously from 1999 through 2013. The eFigure in the Supplement shows the comparison between self-reported and clinic-based community ART coverage estimates.

Discussion

To our knowledge, this is the first study to concurrently assess the associations of community ART and MMC coverage with population-level HIV incidence. Increasing community-level coverage of MMC was associated with significant reductions in male community HIV incidence. For example, in communities with MMC more than 40%, male HIV incidence was 0.66 per 100 person-years lower than in communities with MMC coverage 10% or less. This difference is substantial to these communities and suggests that increasing MMC coverage more than 40% could reduce male incidence by approximately 39% at a population-level. This is comparable with the estimated reduction in individual HIV acquisition risk associated with comparable ART coverage in South Africa.[14] Because MMC provides direct protection against male HIV acquisition, this association is plausible and consistent with the estimated associations of increasing MMC coverage with male HIV prevalence from cross-sectional analyses in South Africa.[15] Female community HIV incidence was not significantly associated with male MMC coverage during the study period, consistent with mathematical models suggesting that the HIV prevention benefits of MMC to women accrue over longer periods.[7]

In adjusted analyses, ART coverage more than 20% in the opposite sex was significantly associated with lower community HIV incidence in males, but not in females. This potentially reflects the higher ART coverage in females than in males (Figure and Table 1), as reported elsewhere in sub-Saharan Africa.[16] Additionally, men initiate ART at a later stage of disease than women,[16] potentially increasing the duration of female exposure to infectious partners. The ART coverage achieved during this study was modest: even in period 3 (2007-2013), the median community ART coverage among HIV-infected persons was only 20.7% in males and 26.3% in females. This partly reflects the World Health

Organization (WHO) guidelines for ART initiation during the study time: for example, only 32% of HIV-positive persons had CD4 counts less than 350 cells/mm^3 in 2011-2013, and some delayed ART initiation for personal and social reasons.[17,18]

A South African study assessed the associations between ART coverage among HIV-infected persons within 3 km of a HIV-negative individual and the individual-level risk of HIV acquisition.[14] Significant associations were only observed with ART coverage more than 30%, which is higher than the median coverage in Rakai communities during the study period. Additionally, only 26% to 46% of the eligible South African participants contacted provided a blood sample for HIV testing, which may have affected estimates of the associations between ART coverage and incidence.[19] The Mombasa female sex workers study in Kenya reported that each 10% increase in ART coverage among all HIV-infected persons in the region was associated with a 23% reduction of HIV acquisition risk in female sex workers, but such regional coverage may not accurately reflect exposure among the male partners of the sex workers.[20] Neither the South African nor the Mombasa study assessed the associations of MMC coverage with HIV incidence.

This community-based ecologic analysis is subject to "ecologic fallacy," whereby associations observed at a population level may not hold at an individual level. However, the efficacy of MMC and ART on individual-level HIV risk was established by earlier clinical trials.[1-4] The objective of this study was to assess the associations of these interventions with HIV incidence at a population-level. As Smith and colleagues[21] noted, ecologic studies "are the first of many steps in the path from science to policy." Strengths of this study include that the data were derived from an established cohort with high participation rates, and reflected a wide range of service coverages. Few programs in sub-Saharan Africa have population-based data on service coverages and HIV incidence, which are critical for the empirical evaluation of the effect of HIV prevention programs under real-world settings. Additionally, ART coverage based on self-reports provided similar estimates to those validated from clinical records.

This study has limitations. First, it is an observational study, and potential unmeasured confounding may lead to biased estimates of the associations. Second, sexual networks in Rakai are wider than the community of residence, thus use of community-level MMC and ART coverage may underestimate associations. However, prior Rakai studies suggest that more than 60% of HIV infections are from relationships within the community,[22] and community HIV prevalence in the opposite sex was predictive of community incidence in both men and women, suggesting that community-based measures reflect the predominant HIV exposures. Third, study power was limited by the use of 45 communities as the units of observation; however, statistically significant findings for MMC did not change in the sensitivity analysis using the subset of 30 communities. Fourth, MMC and ART coverage was estimated from self-reports, which may introduce misclassification bias. However, a prior study indicated high accuracy of men's self-reported MMC status[23]; and sensitivity analysis showed similar results when using ART coverage estimated from clinical records. Additionally, this study considered heterosexual transmission as the predominant mode of HIV transmission. Transmissions due to homosexual intercourse or contaminated injections could not be evaluated, although these are less common in rural Rakai.

Findings from this study have public health implications. WHO estimates that 9.1 million men have been circumcised from 2007 through 2014 in the 14 priority countries. MMC coverage in sub-Saharan Africa is estimated to be around 44%,[24] which, based on the findings from this study, is likely to have had an effect on male HIV incidence. There are approximately 25.8 million people living with HIV in sub-Saharan Africa, of whom approximately 41% were on ART in 2014.[25] However, there are wide variations in MMC and ART coverage,[24,25] and both fall short of UNAIDS targets. Economic modeling indicates the potential cost-effectiveness of jointly scaling up MMC and ART for HIV prevention,[5] but international resources for treatment and prevention have remained relatively flat since 2008.[26]

Conclusions

In Rakai, Uganda, increasing community MMC and female ART coverage was associated with lower community HIV incidence in males. If similar associations are found elsewhere, this would support further scale-up of MMC and ART for HIV prevention in sub-Saharan Africa.

ARTICLE INFORMATION

Author Affiliations: Department of Epidemiology, Johns Hopkins, Bloomberg School of Public Health, Baltimore, Maryland (Kong, Ssekasanvu, Bugos, Chang, Mary, Wawer, Gray); Department of Biostatistics, Johns Hopkins, Bloomberg School of Public Health, Baltimore, Maryland (Kong); Rakai Health Sciences Program, Entebbe, Uganda (Kigozi, Ssekasanvu, Nalugoda, Nakigozi, Ndyanabo, Lutalo, Ssekubugu, Kagaayi, Serwadda, Wawer, Gray); Johns Hopkins School of Medicine, Baltimore, Maryland (Reynolds, Chang, Quinn); Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland (Reynolds, Quinn); Population Council, Washington, DC (Nanlesta); Center for Communications Programs, Johns Hopkins, Baltimore, Maryland (Berman); School of Public Health, Makerere University, Kampala, Uganda (Serwadda).

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Study concept and design: Kong, Quinn, Serwadda, Wawer, Gray.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kong, Gray.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kong, Gray.
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Administrative, technical, or material support: Kong, Nalugoda, Nakigozi, Ndyanabo, Lutalo, Reynolds, Ssekubugu, Kagaayi, Bugos, Chang, Nanlesta, Grabowski, Serwadda, Wawer.
Study supervision: Kong, Kigozi, Ssekubugu, Quinn, Serwadda, Wawer.

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