Impact of combination HIV interventions on HIV incidence in hyperendemic fishing communities in Uganda: a prospective cohort study

Joseph Kagaayi, Larry W Chang*, Victor Ssempijja, M Kate Grabowski, Robert Ssekubugu, Gertrude Nakigozi, Godfrey Kigozi, David M Serwadda, Ronald H Gray, Fred Nalugoda, Nelson K Sewankambo, Lisa Nelson, Lisa A Mills, Donna Kabatesi, Stella Alamo, Caitlin E Kennedy, Aaron A R Tobian, John S Santelli, Anna Mia Ekström, Helena Nordenstedt, Thomas C Quinn, Maria J Wawer, Steven J Reynolds*

Summary

Background Targeting combination HIV interventions to locations and populations with high HIV burden is a global priority, but the impact of these strategies on HIV incidence is unclear. We assessed the impact of combination HIV interventions on HIV incidence in four HIV-hyperendemic communities in Uganda.

Methods We did an open population-based cohort study of people aged 15–49 years residing in four fishing communities on Lake Victoria. The communities were surveyed five times to collect self-reported demographic, behavioural, and service-uptake data. Free HIV testing was provided at each interview, with referral to combination HIV intervention services as appropriate. From November, 2011, combination HIV intervention services were rapidly expanded in these geographical areas. We evaluated trends in HIV testing coverage among all participants, circumcision coverage among male participants, antiretroviral therapy (ART) coverage and HIV viral load among HIV-positive participants, and sexual behaviours and HIV incidence among HIV-negative participants.

Findings From Nov 4, 2011, to Aug 16, 2017, data were collected from five surveys. Overall, 8942 participants contributed 20 721 person-visits; 4619 (52%) of 8942 participants were male. HIV prevalence was 41% (1598 of 3870) in the 2011–12 baseline survey and declined to 37% (1740 of 4738) at the final survey ($p<0 \cdot 0001$). 3222 participants who were HIV-negative at baseline, and who had at least one repeat visit, contributed 9477 person-years of follow-up, and 230 incident HIV infections occurred. From the first survey in 2011–12 to the last survey in 2016–17, HIV testing coverage increased from 68% (2613 of 3870) to 96% (4526 of 4738; $p<0 \cdot 0001$); male circumcision coverage increased from 35% (698 of 2011) to 65% (1630 of 2525; $p<0 \cdot 0001$); ART coverage increased from 16% (254 of 1598) to 82% (1420 of 1740; $p<0 \cdot 0001$); and population HIV viral load suppression in all HIV-positive participants increased from 34% (546 of 1596) to 80% (1383 of 1734; $p<0 \cdot 0001$). Risky sexual behaviours did not decrease over this period. HIV incidence decreased from 3·43 per 100 person-years (95% CI 2·45–4·67) in 2011–12 to 1·59 per 100 person-years (95% CI 1·19–2·07) in 2016–17; adjusted incidence rate ratio (IRR) 0·52 (95% CI 0·34–0·79). Declines in HIV incidence were similar among men (adjusted IRR 0·53, 95% CI 0·30–0·93) and women (0·51, 0·27–0·96). The risk of incident HIV infection was lower in circumcised men than in uncircumcised men (0·46, 0·32–0·67).

Interpretation Rapid expansion of combination HIV interventions in HIV-hyperendemic fishing communities is feasible and could have a substantial impact on HIV incidence. However, incidence remains higher than HIV epidemic control targets, and additional efforts will be needed to achieve this global health priority.

Funding The National Institute of Mental Health, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Development, the National Cancer Institute, the National Institute for Allergy and Infectious Diseases Division of Intramural Research, Centers for Disease Control and Prevention Uganda, Karolinska Institutet, and the Johns Hopkins University Center for AIDS Research.

Lancet HIV 2019

Published Online September 15, 2019 http://dx.doi.org/10.1016/S2352-3018(19)30190-0

See Online/Comment http://dx.doi.org/10.1016/S2352-3018(19)30241-3

*Contributed equally

Rakai Health Sciences Program, Entebbe, Uganda (J Kagaayi MBChB, L W Chang MD, M K Grabowski PhD, R Ssekubugu MSPH, G Nakigozi MBChB, G Kigozi MBChB, D M Serwadda MBChB, Prof R H Gray MD, F Nalugoda PhD, Prof N K Sewankambo MBChB, Prof A A R Tobian MD, Prof M J Wawer MD); **Division of Infectious Diseases, Department of Medicine** (L W Chang, Prof T C Quinn MD, S J Reynolds MD) **and Department of Pathology** (M K Grabowski, Prof A A R Tobian), **Johns Hopkins School of Medicine, Baltimore, MD, USA; Makerere University School of Public Health, Kampala, Uganda** (J Kagaayi, D M Serwadda); **Social and Behavioral Interventions Program, Department of International Health** (L W Chang, C E Kennedy PhD) **and Department of Epidemiology** (L W Chang, M K Grabowski, Prof R H Gray, Prof M J Wawer), **Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research sponsored by the National Cancer Institute, Bethesda, MD, USA** (V Ssempijja ScM); **Makerere University School of Medicine, Kampala, Uganda** (Prof N K Sewankambo); **Centers for Disease Control and**

Introduction

UNAIDS, WHO, and the US President's Emergency Plan for AIDS Relief (PEPFAR) have emphasised the need to target HIV treatment and prevention resources to populations and locations with the highest HIV burden.[1–3] In Africa, HIV-hyperendemic geographical areas, sometimes referred to as hotspots,[3] include fishing communities, residents of urban slums, and periurban communities, in which priority and key populations, such as sex workers and migrant workers, are often overrepresented.[4–10] Many of these communities have also been underserved by HIV treatment and prevention services.[4,10]

Combination HIV interventions, including antiretroviral therapy (ART), voluntary medical male circumcision, HIV testing services, and behaviour-change interventions, have been shown to reduce HIV incidence in some lower risk populations in Africa.[11–14]

Prevention, Entebbe, Uganda (L Nelson MD, L A Mills MD, D Kabatesi MBChB, S Alamo MBChB); Department of Population and Family Health, Columbia Mailman School of Public Health, New York, NY, USA (Prof J S Santelli MD); Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden (Prof A M Ekström MD, H Nordenstedt MD); Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden (Prof A M Ekström); and Laboratory of Immunoregulation, Division of Intramural Research, National Institute for Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (Prof T C Quinn, S J Reynolds)

Correspondence to: Dr Larry W Chang, Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, MD 21205, USA lchang8@jhmi.edu

Research in context

Evidence before this study

We searched PubMed for longitudinal HIV cohort studies that included HIV hyperendemic communities in sub-Saharan Africa published from database inception up to Dec 1, 2018. Key search terms included "HIV or AIDS", "cohort", "observational", "fishing", "hotspot", "hyperendemic", and "Africa". No language limitation was used. This search identified studies reporting high levels of HIV seroprevalence and associated risk factors in varied hyperendemic communities; however, we found no studies reporting longitudinal HIV incidence and the population-level effects of HIV interventions in hyperendemic communities.

Added value of this study

To our knowledge, this is the first prospective study to provide evidence that combined HIV interventions, such as antiretroviral therapy (ART) and male circumcision, can be rapidly scaled up in HIV hyperendemic communities and can have a substantial effect on HIV incidence. We also provided supporting evidence for the population-level benefits of male circumcision in preventing HIV acquisition. Despite observing significant declines in HIV incidence, the incidence remained much higher than that needed for HIV epidemic control.

Implications of all the available evidence

The available evidence indicates the need for strong HIV surveillance programmes that regularly survey a range of community types, and additional population-level observational and modelling studies of heterogeneous communities to better understand the varied effects of HIV interventions in different risk settings. Further efforts are needed, such as increased ART and male circumcision scale-up, pre-exposure prophylaxis roll-out, and additional resources from national governments and international organisations, to achieve HIV epidemic control.

However, little is known about the impact of combination HIV interventions in HIV-hyperendemic geographical areas. Communities in these areas have specific social-behavioural, demographic, and structural characteristics, such as high levels of mobility, transactional sex, multiple sexual partnerships, alcohol use, and large proportions of men, that could hinder the scale-up of combination HIV interventions and moderate their effects.[4,7,15,16]

We did a prospective cohort study from 2011 to 2017 in four HIV-hyperendemic Lake Victoria fishing communities in Uganda (HIV prevalence of around 41%) to evaluate trends in coverage of combination HIV interventions and the effect of combination HIV interventions on HIV incidence.[4] This study was embedded within the Rakai Community Cohort Study (RCCS), a population-based, observational study of HIV incidence, sexual behaviours, and health service utilisation in south-central Uganda. Scale-up of combination HIV interventions has led to reductions in HIV incidence in nearby, lower-HIV-burden, agrarian and trading RCCS communities (HIV prevalence of around 13%);[11] however, scale-up of combination HIV interventions and HIV incidence trends in these high-burden fishing communities have not been reported.

Methods

Study design and participants

The RCCS, conducted by the Rakai Health Sciences Program, is an open (participants can age in and out of the cohort, and can also enter or exit the cohort on the basis of residency), population-based cohort of individuals aged 15–49 years in 40 communities located in Rakai and neighbouring districts of south-central Uganda.[4,11] RCCS methods have been reported previously.[4,11] In brief, the RCCS does a household census and interviews with consenting individuals to collect self-reported demographic, behavioural, and service-uptake data. Free HIV testing is provided at the time of interview, with referral to combination HIV intervention services as appropriate; HIV status is determined with a validated algorithm that incorporates three rapid HIV tests.[4,11] Blood samples are also taken for HIV confirmation and further tests (eg, HIV viral load). Established in 1994, the RCCS initially focused on rural agrarian and trading communities. In 2011, the four most populous Lake Victoria fishing communities in the region were added to the cohort. This study uses data from these four communities. Residency in the fishing villages was defined as living there for 1 month or longer, with the intention to stay.

This study was approved by the Research and Ethics Committee of the Uganda Virus Research Institute, the Ugandan Council of Science and Technology, and the Western Institutional Review Board.

Before November, 2011, the four fishing communities had little access to HIV services.[4] With support from PEPFAR and the Centers for Disease Control and Prevention Uganda, combination HIV intervention services were rapidly expanded, with Rakai Health Sciences Program as the lead implementer. For example, a new community-based HIV clinic was established in the largest of the four fishing communities and male circumcision was provided through mobile camps and referrals to outreach male circumcision facilities. From 2011 to 2013, ART was initiated in these communities at CD4 counts of less than 350 cells per µL. In 2013, fisherfolk were classified by the Ugandan Ministry of Health as a priority population in which ART should be started regardless of CD4 cell count (ie, a universal test-and-treat strategy).[17] The largest of the four fishing communities is the site of DREAMS programming, featuring HIV testing services, community mobilisation, economic and vocational strengthening, and condom promotion, as well as a community health worker programme promoting combination HIV intervention services.[18–21] All HIV services were provided free of charge to the recipient.

 www.thelancet.com/hiv Published online September 15, 2019 http://dx.doi.org/10.1016/S2352-3018(19)30190-0

	Census			Incidence cohort (HIV-negative participants)		
	Eligible	Eligible and present	Eligible, present, and participated	Eligible*	Migrated out before the next survey	Included in incidence cohort
Jan 20, 2012 (Dec 7, 2011–June 4, 2012)	5330	3913 (73%)	3870 (99%)	..	..	..
Sept 6, 2012 (Aug 16, 2012–March 18, 2013)	5910	4044 (68%)	3965 (98%)	2272	314 (14%)	1674 (74%)
Oct 8, 2013 (Sept 23, 2013–Jul 4, 2014)	6214	3947 (64%)	3926 (99%)	2539	535 (21%)	1735 (68%)
May 20, 2015 (April 23–Nov 13, 2015)	7191	4243 (59%)	4222 (>99%)	2581	516 (20%)	1752 (68%)
Jan 20, 2017 (Dec 21, 2016–Aug 14, 2017)	7462	4806 (64%)	4738 (99%)	2843	719 (25%)	1849 (65%)

Data are n or n (%). Survey dates are shown as the midpoint (range). *Includes all age-eligible HIV-negative participants from the most recent survey and any HIV-negative participants from the second most recent survey, if the participant was absent at the most recent survey.

Table 1: **Eligibility, participation, and follow-up by survey round**

Pre-exposure prophylaxis (PrEP) was not available in these communities at the time of these surveys.

Procedures

The four fishing communities were surveyed five times between Dec 7, 2011, and Aug 14, 2017. Viral load testing for all participants who were HIV-positive was done at baseline and at the final two surveys.

Self-reported combination HIV intervention coverage was assessed at each survey. ART coverage was defined as the proportion of all HIV-positive participants who self-reported ART use and was assessed overall and by sex and age groups. Self-reported ART use has been validated in this setting by plasma detection of antiretroviral drugs showing a specificity of 99% (95% CI 97–100) and sensitivity of 77% (70–83).[22] Male circumcision coverage was defined as the proportion of men who self-reported being circumcised. Self-reported male circumcision status has been previously validated from clinical records with 100% specificity.[23] Viral suppression was defined as less than 1000 copies per mL, according to WHO recommendations.[24]

The unit of exposure for HIV incidence was person-years of follow-up between surveys for individuals who were HIV-negative at their baseline and had at least one subsequent follow-up visit. HIV incident cases were individuals who first tested HIV-seropositive at a follow-up visit, allowing for up to one missed visit. HIV incidence was calculated per 100 person-years, with incident infections assumed to occur at the midpoint of the follow-up interval.

Statistical analysis

After validation of underlying assumptions, multivariable Poisson regression, with generalised estimating equations and an exchangeable correlation structure to account for repeated measurements, was used to estimate incidence rate ratios (IRRs) and 95% CIs. Mean incidence after scale-up of combination HIV interventions was compared with the baseline interval before scale-up.

The final multivariable model included variables previously shown to be associated with HIV incidence, including individual-level information on demographics

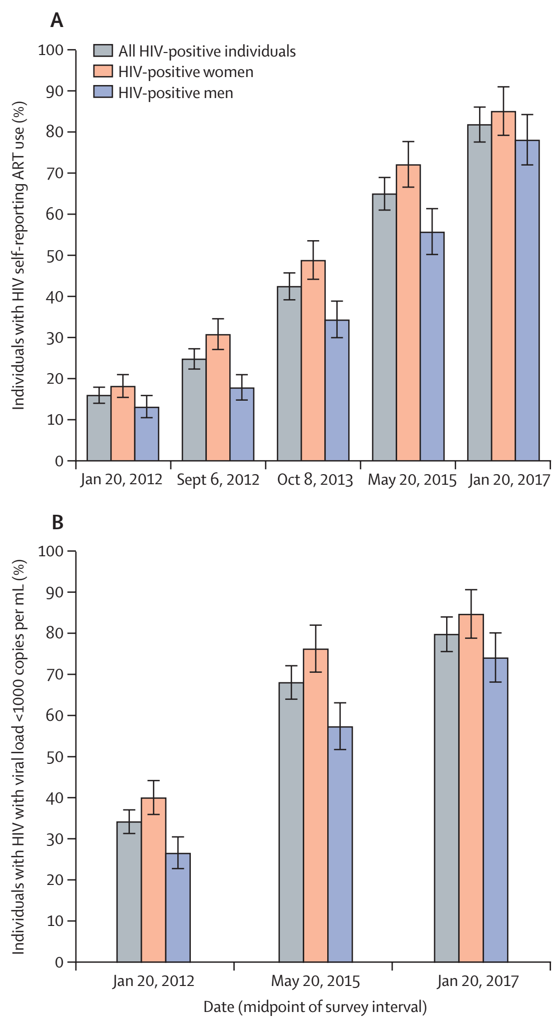

Figure 1: **ART coverage (A) and population viral load suppression (B)**
Error bars show 95% CIs. ART=antiretroviral therapy.

(sex, age, marital status, and education) and sexual behaviours (number of sexual partners in the previous 12 months, sex with partners outside the community of residence, sex with non-marital partners, condom use with

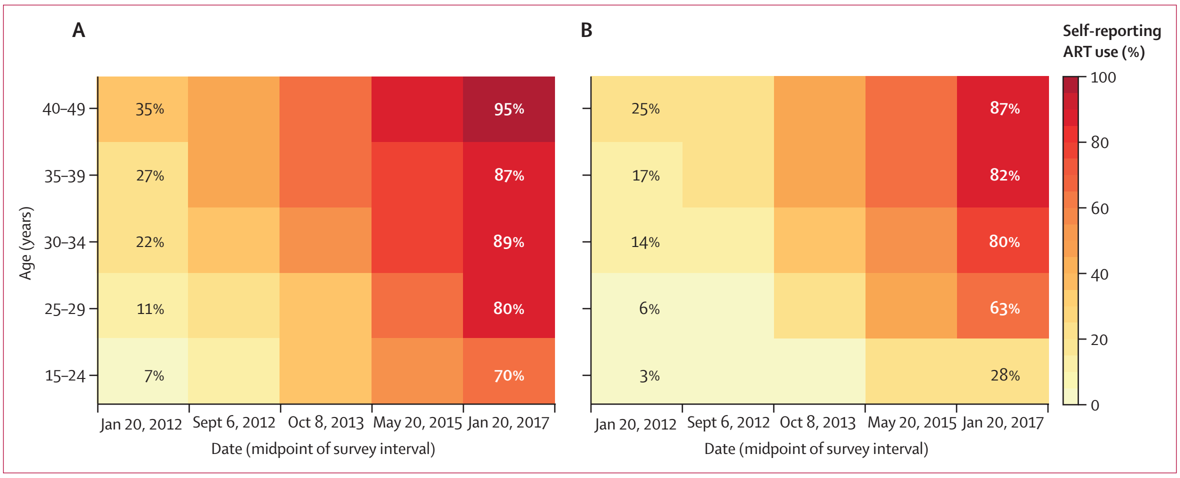

Figure 2: **ART coverage by age in women (A) and men (B)**
ART=antiretroviral therapy.

See Online for appendix

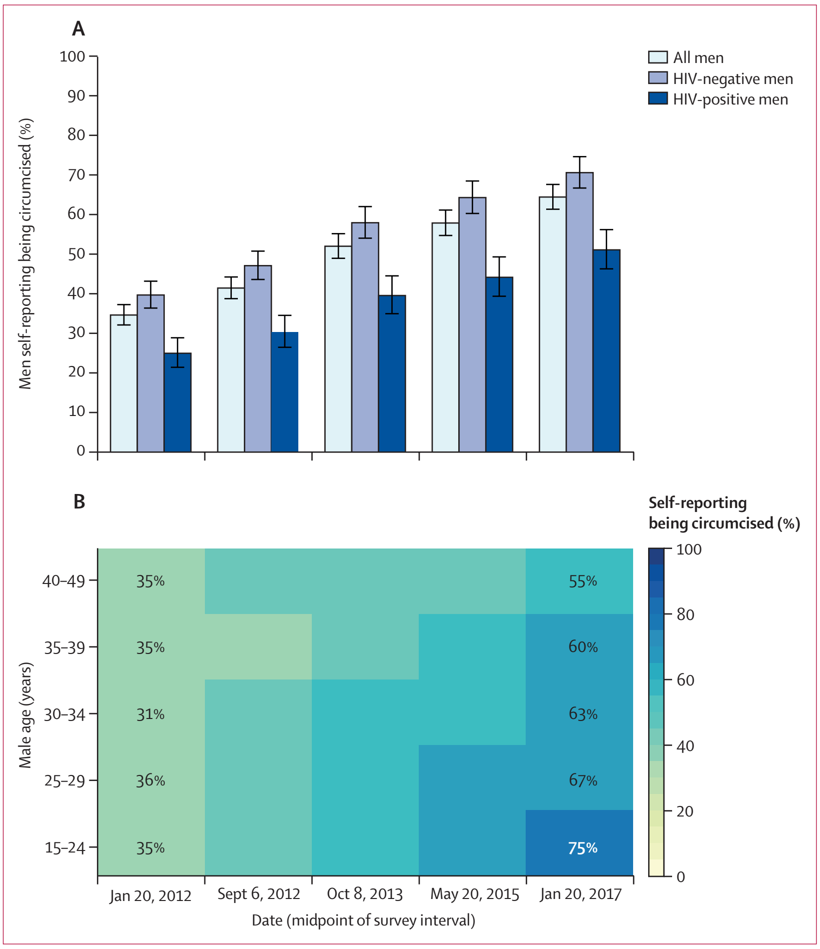

Figure 3: **Male circumcision coverage overall and by HIV status (A) and by age (B)**
Error bars show 95% CIs.

non-marital partners, and self-reported genital ulceration). Secondary analyses were stratified by sex, age group, and male circumcision status. Sensitivity of results to both selective participation and loss to follow-up were evaluated by use of inverse probability weighting (appendix p 14).[11] Analyses were done with STATA, version 15.

Role of the funding source

The US Centers for Disease Control and Prevention Uganda and the Karolinska Institutet contributed to study design, data interpretation, and analysis. All other funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JK, LWC, and SJR had overall scientific oversight, full access to all the data in the study, and final responsibility for the decision to submit for publication.

Results

From Nov 4, 2011, to Aug 16, 2017, data were collected from five surveys of people aged 15–49 years who were residing in four fishing communities on Lake Victoria. At baseline, the four study communities (appendix p 1) varied in size (census populations of individuals aged 15–49 years: n=600, n=605, n=1249, and n=2876) but they had a similar HIV prevalence (range 38–43%).[4] Over the five surveys, 8942 participants contributed a total of 20721 person-visits (table 1). 4619 (52%) of 8942 participants were men and the median age was 30 years (IQR 25–37). Overall, HIV prevalence was 41% (1598 of 3870) at the first cohort survey. 3222 participants who were HIV-negative at the baseline visit and had at least one follow-up visit (ie, the HIV incidence cohort) were followed up for a total of 9477 person-years, and 230 incident HIV infections occurred.

The number of eligible individuals in the four communities increased by 40% over the study period (table 1). The proportion of eligible residents who participated in the specific surveys ranged from 59% (4243 of 7191) to 73% (3913 of 5330) across survey rounds, but a similar composition by sex and age was maintained (appendix p 1). The major reason for non-participation was absence for work or school at the time of the survey, rather than refusal (appendix p 2). Among eligible individuals present in the community at the time of the first survey, 99% (3870 of 3913) participated, and participation rates were similar in all surveys (table 1). Among individuals who were HIV-negative, follow-up across surveys ranged from 65% (1849 of 2843) to 74% (1674 of 2272), with outmigration and absence for work or school contributing to almost all of the losses to follow-up (appendix p 3).

From 2011–12 to 2016–17, among HIV-negative participants, no significant changes were found in the proportion of individuals who were ever sexually active or in the number of non-marital sexual partners, overall or by sex. We found a small decrease in consistent condom use with non-marital sex partners, from 41% (340 of 832) at baseline to 35% (387 of 1120) by the last survey ($p<0\cdot0048$; appendix p 4). The proportion of respondents reporting ever having received an HIV test increased from 68% (2613 of 3870) in 2011–12 to 89% (3536 of 3965) by the second survey in 2012, and to 96% (4526 of 4738) by the final survey in 2016–17 ($p<0\cdot0001$; appendix p 5).

ART use increased from the 2011–12 baseline of 16% (254 of 1598) to 82% (1420 of 1740) in 2016–17 ($p<0\cdot0001$; figure 1A, appendix p 5). ART coverage was higher in women than in men at all surveys ($p<0\cdot0001$) and in 2016–17 85% (797 of 940) of women with HIV reported ART use compared with 78% (623 of 800) of men with HIV. Among HIV-positive individuals, population viral load suppression increased from 34% (546 of 1596) in 2011–12 to 80% (1383 of 1734) in 2016–17 ($p<0\cdot0001$; figure 1B, appendix p 5). Viral suppression was greater in women than men at each time-point ($p<0\cdot0001$).

In both men and women, ART coverage was lower in younger age groups (figure 2), but this differential was more pronounced and persistent in men than in women. For example, in 2016–17, ART coverage was 59 percentage points lower in men aged 15–24 years than in men aged 40–49 years; by contrast, the differential in women in the same age groups was 25 percentage points.

Overall, male circumcision coverage increased from 35% (698 of 2011) to 65% (1630 of 2525) over the study period ($p<0\cdot0001$; figure 3A, appendix p 5). Coverage was consistently higher in HIV-negative men than in HIV-positive men ($p<0\cdot0001$), but coverage in both groups increased over time. In 2011–12, male circumcision coverage was uniform and modest across age groups (figure 3B). However, in 2016–17, coverage was significantly greater in younger men than in older men (15–24 years *vs* 40–49 years; $p<0\cdot0001$).

Consistent decreases in HIV incidence at each study interval were observed in both sexes and were significantly lower at the last follow-up interval compared with baseline ($p=0\cdot0021$; figure 4, appendix p 6). HIV prevalence declined from 41% (1598 of 3870) at baseline to 37% (1740 of 4738; $p<0\cdot0001$) at the final survey (appendix pp 7–9).

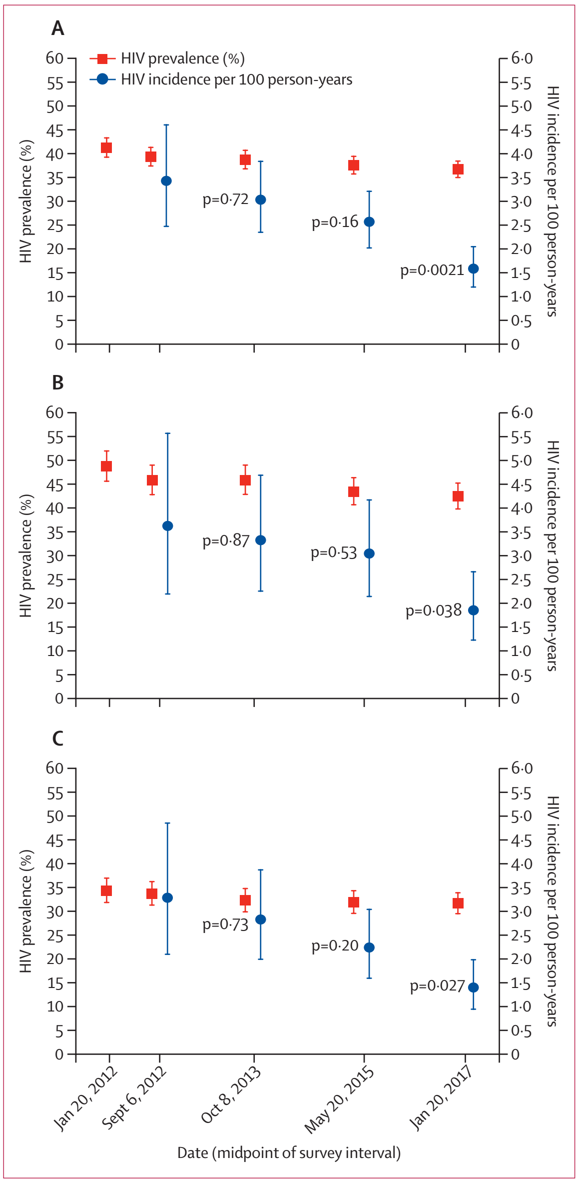

Figure 4: **HIV incidence and prevalence overall (A), in women (B), and in men (C)**
Error bars show 95% CIs.

Baseline HIV incidence in 2012 was 3·43 per 100 person-years (95% CI 2·45–4·67; table 2; appendix pp 10–13). In 2016–17, HIV incidence was 1·59 per 100 person-years (95% CI 1·19–2·07); adjusted IRR 0·52 (95% CI 0·34–0·79). Previous marriage, self-reported genital disease, and having more than one sex partner were associated with increased HIV incidence. Male circumcision and secondary or tertiary education were associated with decreased HIV incidence.

Decreases in HIV incidence from the baseline to the final survey interval (appendix p 6) were similar in men (adjusted IRR 0·53, 95% CI 0·30–0·93) and women (0·51, 0·27–0·96). Incident HIV infection

	Incident cases (n=230)	Person-years	Incidence per 100 person-years (95% CI)	Unadjusted analysis		Adjusted analysis	
				IRR (95% CI)	p value	Adjusted IRR (95% CI)	p value
Survey date, midpoint (range)							
Sept 6, 2012 (Aug 16, 2012–March 18, 2013)	40	1165·5	3·43 (2·45–4·67)	1	..	1	..
Oct 8, 2013 (Sept 23, 2013–Jul 4, 2014)	64	2108·1	3·04 (2·34–3·88)	0·88 (0·60–1·31)	0·54	0·93 (0·63–1·38)	0·72
May 20, 2015 (April 23–Nov 13, 2015)	72	2799·8	2·57 (2·01–3·24)	0·75 (0·51–1·10)	0·14	0·76 (0·51–1·12)	0·16
Jan 20, 2017 (Dec 21, 2016–Aug 14, 2017)	54	3403·7	1·59 (1·19–2·07)	0·46 (0·31–0·69)	0·0002	0·52 (0·34–0·79)	0·0021
Age (years)							
15–19	12	673·2	1·78 (0·92–3·11)	1	..	1	..
20–24	64	1831·2	3·49 (2·69–4·46)	1·96 (1·06–3·63)	0·032	1·40 (0·72–2·69)	0·32
25–29	68	2178·2	3·12 (2·43–3·96)	1·75 (0·95–3·24)	0·073	1·23 (0·63–2·42)	0·55
30–34	32	1842·4	1·74 (1·19–2·45)	0·97 (0·50–1·89)	0·94	0·66 (0·32–1·35)	0·26
35–39	31	1403·4	2·21 (1·50–3·14)	1·24 (0·64–2·42)	0·53	0·83 (0·40–1·73)	0·62
>39	23	1548·5	1·49 (0·94–2·23)	0·83 (0·41–1·67)	0·61	0·61 (0·29–1·30)	0·20
Sex							
Women	108	3915·5	2·76 (2·26–3·33)	1	..	1	..
Uncircumcised men	69	1926·2	3·58 (2·79–4·53)	1·30 (0·96–1·76)	0·094	0·95 (0·66–1·37)	0·78
Circumcised men	53	3635·3	1·46 (1·09–1·91)	0·53 (0·38–0·74)	0·0002	0·42 (0·28–0·64)	0·0098
Marital status							
Never married	24	1329·7	1·80 (1·16–2·69)	1	..	1	..
Married	126	6085·6	2·07 (1·73–2·47)	1·15 (0·74–1·78)	0·54	1·10 (0·56–2·16)	0·78
Previously married	80	2061·7	3·88 (3·08–4·83)	2·15 (1·36–3·40)	0·0011	1·99 (1·18–3·37)	0·0098
Education							
None	19	624·0	3·04 (1·83–4·75)	1	..	1	..
Primary	182	6842·4	2·66 (2·29–3·08)	0·87 (0·54–1·41)	0·58	0·82 (0·52–1·31)	0·41
Secondary or tertiary	29	2010·5	1·44 (0·97–2·07)	0·47 (0·26–0·85)	0·012	0·50 (0·28–0·89)	0·019
Sex with partners outside of the community in the past year							
None	162	6589·5	2·46 (2·09–2·87)	1	..	1	..
One or more	68	2887·5	2·36 (1·83–2·99)	0·96 (0·72–1·28)	0·77	0·85 (0·61–1·18)	0·32
Self-reported genital ulcer disease in the past year							
No	179	8531·8	2·10 (1·80–2·43)	1	..	1	..
Yes	51	945·2	5·40 (4·02–7·09)	2·57 (1·88–3·51)	<0·0001	1·88 (1·36–2·60)	0·0012
Number of sex partners in the past year							
None	6	685·0	0·88 (0·32–1·91)	1	..	1	..
One	103	5142·7	2·00 (1·64–2·43)	2·29 (1·00–5·22)	0·049	2·10 (0·81–5·48)	0·13
Two	62	2007·4	3·09 (2·37–3·96)	3·53 (1·52–8·18)	0·0033	4·02 (1·44–11·26)	0·0081
Three or more	59	1642·0	3·59 (2·74–4·64)	4·10 (1·77–9·52)	0·0010	4·64 (1·57–13·76)	0·0056
Non-marital relationships and condom use							
Stable partners only or no sex partners	124	6277·7	1·98 (1·64–2·36)	1	..	1	..
Non-stable partner, inconsistent use	71	2028·1	3·50 (2·73–4·42)	1·77 (1·32–2·38)	0·0001	1·06 (0·62–1·82)	0·82
Non-stable partner, consistent use	35	1171·2	2·99 (2·08–4·16)	1·51 (1·04–2·20)	0·031	0·98 (0·54–1·78)	0·95

IRR=incidence rate ratio.

Table 2: **Associations between individual characteristics and HIV incidence**

across all surveys was lower among circumcised men than among uncircumcised men (0·46, 0·32–0·67; figure 5, appendix p 11). Results did not change substantially with inclusion of inverse probability weights to account for selective participation and follow-up (appendix p 15).

Discussion

Rapid expansion of combination HIV intervention services in HIV-hyperendemic fishing communities in Uganda was feasible, and a concurrent reduction in HIV incidence was observed. Decreases in HIV incidence with combination HIV intervention scale-up have been reported in some lower-risk populations,[11,12,14] but to our knowledge this is the first report of prospectively observed declines in overall HIV incidence with rapid scale-up of combination HIV interventions in HIV-hyperendemic communities.

We previously reported a 42% (95% CI 24–55) reduction in HIV incidence to 0·66 per 100 person-years by 2016, compared with a period before combination HIV intervention scale-up (1999–2004), in an RCCS cohort of lower-risk agrarian and trading communities (HIV prevalence of around 13%).[11] In this previous study, ART coverage was 69%, HIV population viral load suppression was 75%, and male circumcision coverage was 59% by 2015–16, compared with 82%, 80%, and 65%, respectively, in the fishing communities in the current study in 2016–17. We previously observed greater decreases in HIV incidence in men than in women; however, this disparity was not observed in the fishing communities in the current study. Future modelling studies based on empirical population-level data are needed to better understand the individual contributions of combination HIV interventions to reductions in HIV incidence and the reasons for sex and community-level differences.

The SEARCH trial[12] assessed a universal test-and-treat, multidisease care model in both lower-risk rural communities and higher-risk fishing communities. HIV testing services and ART were rapidly scaled, with population viral load suppression reaching around 79% by year 3 of the study. Annual measured HIV incidence decreased by around 32% over three years, although there were no incidence differences between the two study groups.[12] POPART, a cluster-randomised trial in South Africa and Zambia,[25] found mixed results on the effect of a universal test-and-treat strategy on HIV incidence, despite reaching the first two of the 90-90-90 targets (90% of people with HIV knew their HIV status and 90% of people with diagnosed HIV infection were receiving ART) in both intervention groups. In western Kenya, a population-based cohort analysis found that HIV incidence in a lower-risk population (HIV prevalence of 12–15%) decreased by around 50% between 2011 and 2016, during which time combination HIV interventions were scaled up.[26] In population-based, nationally representative HIV impact assessments, HIV incidence measured with cross-sectional incidence assays also appears to be decreasing in several sub-Saharan African countries.[14,27] However, a separate cohort study in South Africa from 2004 to 2015 observed HIV incidence reductions only in men, and, surprisingly, found an increasing HIV incidence in women.[28] Continued reporting of HIV incidence-based impact evaluations will be needed to monitor and better understand the impact and sustainability of combination HIV interventions.

In this study, combination HIV interventions were rapidly scaled up in high-risk communities. However, important disparities were apparent. Self-reported ART use was more common among women than men, and among

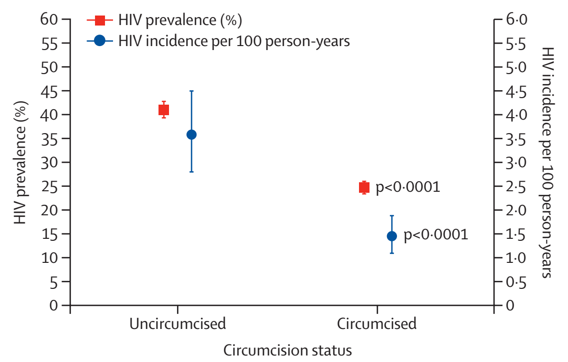

Figure 5: **HIV prevalence and incidence in men by circumcision status**
Error bars show 95% CIs.

older people than younger people, whereas younger men were more likely than older men to be circumcised. These findings are consistent with reports elsewhere in Africa.[2,29,30] Continued characterisation of hard-to-reach populations and targeted interventions are needed.[31]

Despite surpassing 90-90-90 goals and almost reaching 95-95-95 goals of around 86% population viral suppression,[2] HIV incidence in the Ugandan fishing communities remained 15-times higher than the suggested incidence required for HIV epidemic control (ie, 0·1 per 100 person-years) from previous modelling studies.[29,30] Of note, male circumcision increased in these communities to 65% coverage, but remained short of the UNAIDS and PEPFAR coverage goal of 80%.[1] Male circumcision in this study was strongly protective among men, decreasing their risk of HIV acquisition by around 54%. Thus, hyperendemic communities might need particularly high coverage levels of ART and male circumcision to achieve epidemic control; newer interventions, such as oral PrEP; or novel interventions, such as long-acting injectable PrEP or a vaccine.[32] Continued monitoring of these communities will also be needed to show sustainability of combination HIV intervention expansion, possibilities for further scale-up of combination HIV interventions, and the role of newer combination HIV interventions.

Our study had some limitations. Follow-up rates were moderate, mostly because of outmigration. However, study findings did not change with the use of inverse probability weights, suggesting that little bias due to selective follow-up was present. The study was also not able to show the effects of mortality, secular trends, or other potential unmeasured confounders that might have affected incidence declines. However, the strong temporal association between scale-up of combination HIV interventions and reductions in HIV incidence support causality. ART and male circumcision coverage were self-reported, which could have resulted in misclassification, although both measures have been validated in the Rakai setting.[22,23]

In summary, significant reductions in HIV incidence were found in HIV-hyperendemic fishing villages in which combination HIV interventions were scaled up, suggesting that existing HIV treatment and prevention interventions can be rapidly expanded and could potentially have a population-level impact on HIV incidence in high-burden settings. However, HIV incidence in this study setting remained higher than that needed for HIV epidemic control, and additional efforts will be needed to achieve this global health priority.

Contributors

JK, LWC, MKG, and SJR led the conceptualisation and design of the study. JK, LWC, RS, GN, GK, DMS, RHG, FN, NKS, AART, TCQ, MJW, and SJR oversaw data collection and laboratory testing. VS and MKG did the statistical analysis. All authors participated in interpretation of data, revising, and final approval of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

The study was funded by the National Institute of Allergy and Infectious Diseases (grant numbers U01AI100031, U01AI075115, R01AI110324, R01AI102939, R01AI128779, R01AI123002, and K01AI125086), the National Institute of Mental Health (grant numbers R01MH107275 and R01MH105313), the National Center for Child Health and Human Development (grant number R01HD091003), the National Institute for Allergy and Infectious Diseases Division of Intramural Research, the National Cancer Institute (contract number HHSN261200800001E), the Johns Hopkins University Center for AIDS Research (grant number P30AI094189), the Karolinska Institutet, and the President's Emergency Plan for AIDS Relief through the Centers for Disease Control and Prevention (cooperative agreement number NU2GGH000817). We thank the cohort participants, staff, and local community leaders who have made this study possible. We also thank the personnel at the Office of Cyberinfrastructure and Computational Biology at the National Institute of Allergy and Infectious Diseases for data management support. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies, nor does mention of trade names, commercial products, or organisations imply endorsement by the US Government.

References

1 Office of the US Global AIDS Coordinator and Health Diplomacy. PEPFAR 2018 Annual Report to Congress. April, 2018. http://www.pepfar.gov/documents/organization/279889.pdf (accessed April 30, 2019).

2 UNAIDS. Ending AIDS: progress towards the 90-90-90 targets. Global AIDS update 2017. Geneva: UNAIDS, 2017.

3 Lessler J, Azman AS, McKay HS, Moore SM. What is a hotspot anyway? *Am J Trop Med Hyg* 2017; **96:** 1270–73.

4 Chang LW, Grabowski MK, Ssekubugu R, et al. Heterogeneity of the HIV epidemic in agrarian, trading, and fishing communities in Rakai, Uganda: an observational epidemiological study. *Lancet HIV* 2016; **3:** e388–96.

5 Clift S, Anemona A, Watson-Jones D, et al. Variations of HIV and STI prevalences within communities neighbouring new goldmines in Tanzania: importance for intervention design. *Sexually Transmit Infect* 2003; **79:** 307–12.

6 Kimani J, McKinnon LR, Wachihi C, et al. Enumeration of sex workers in the central business district of Nairobi, Kenya. *PloS One* 2013; **8:** e54354.

7 Kiwanuka N, Ssetaala A, Mpendo J, et al. High HIV-1 prevalence, risk behaviours, and willingness to participate in HIV vaccine trials in fishing communities on Lake Victoria, Uganda. *J Int AIDS Soc* 2013; **16:** 18621.

8 Messina JP, Emch M, Muwonga J, et al. Spatial and socio-behavioral patterns of HIV prevalence in the Democratic Republic of Congo. *Soc Sci Med* 2010; **71:** 1428–35.

9 Wand H, Ramjee G. Targeting the hotspots: investigating spatial and demographic variations in HIV infection in small communities in South Africa. *J Int AIDS Soc* 2010; **13:** 41.

10 Tanser F, de Oliveira T, Maheu-Giroux M, Barnighausen T. Concentrated HIV subepidemics in generalized epidemic settings. *Curr Opin HIV AIDS* 2014; **9:** 115–25.

11 Grabowski MK, Serwadda DM, Gray RH, et al. HIV prevention efforts and incidence of HIV in Uganda. *N Engl J Med* 2017; **377:** 2154–66.

12 Havlir D, Charlebois E, Balzer L, et al. SEARCH community cluster randomized study of HIV "test and treat" using multi-disease approach and streamlined care in rural Uganda and Kenya. International AIDS Conference; Amsterdam; July 23–27, 2018 (abstr WEAX0106LB).

13 Karim SS. Assessing progress with HIV incidence in national cohorts. *Lancet HIV* 2017; **4:** e56–58.

14 Justman JE, Mugurungi O, El-Sadr WM. HIV population surveys: bringing precision to the global response. *N Engl J Med* 2018; **378:** 1859–61.

15 Lubega M, Nakyaanjo N, Nansubuga S, et al. Risk denial and socio-economic factors related to high HIV transmission in a fishing community in Rakai, Uganda: a qualitative study. *PloS One* 2015; **10:** e0132740.

16 Seeley JA, Allison EH. HIV/AIDS in fishing communities: challenges to delivering antiretroviral therapy to vulnerable groups. *AIDS Care* 2005; **17:** 688–97.

17 Uganda AIDS Commission. HIV and AIDS Uganda Country Progress Report 2014. Kampala: Uganda AIDS Commission, 2015.

18 Chang LW, Nakigozi G, Billioux VG, et al. Effectiveness of peer support on care engagement and preventive care intervention utilization among pre-antiretroviral therapy, HIV-infected adults in Rakai, Uganda: a randomized trial. *AIDS Behav* 2015; **19:** 1742–51.

19 Long A, Mbabali I, Hutton HE, et al. Design and implementation of a community health worker HIV treatment and prevention intervention in an HIV hot spot fishing community in Rakai, Uganda. *J Int Assoc Provid AIDS Care* 2017; **16:** 499–505.

20 Chang LW, Mbabali I, Kong X, et al. Impact of a community health worker HIV treatment and prevention intervention in an HIV hotspot fishing community in Rakai, Uganda (mLAKE): study protocol for a randomized controlled trial. *Trials* 2017; **18:** 494.

21 Office of the US Global AIDS Coordinator and Health Diplomacy. Dreaming of an AIDS-free future. November, 2018. https://www.pepfar.gov/documents/organization/287807.pdf (accessed April 30, 2019).

22 Grabowski MK, Reynolds SJ, Kagaayi J, et al. The validity of self-reported antiretroviral use in persons living with HIV: a population-based study. *AIDS* 2018; **32:** 363–69.

23 Kong X, Ndyanabo A, Nalugoda F, et al. The accuracy of women's reports of their partner's male circumcision status in Rakai, Uganda. *AIDS* 2013; **27:** 662–64.

24 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization, 2016.

25 Hayes RJ, Donnell DJ, Floyd S, et al. Impact of universal testing and treatment in Zambia and South Africa: HPTN071 (POPART). Conference on Retroviruses and Opportunistic Infections; Seattle, WA; March 4–7, 2019 (abstr 92).

26 Borgdorff MW, Kwaro D, Obor D, et al. HIV incidence in western Kenya during scale-up of antiretroviral therapy and voluntary medical male circumcision: a population-based cohort analysis. *Lancet HIV* 2018; **5:** e241–49.

27 Justman J, Reed JB, Bicego G, et al. Swaziland HIV Incidence Measurement Survey (SHIMS): a prospective national cohort study. *Lancet HIV* 2017; **4:** e83–92.

28 Vandormael A, Adam NA, Dobra A, de Oliveira T, Tanser F. Sharp decline in male HIV incidence in a rural South African population (2004–2015). Conference on Retroviruses and Opportunistic Infections; Boston, MA; March 4–7, 2018 (abstr 46).

29 Ghys PD, Williams BG, Over M, Hallett TB, Godfrey-Faussett P. Epidemiological metrics and benchmarks for a transition in the HIV epidemic. *PLoS Med* 2018; **15:** e1002678.

30 Galvani AP, Pandey A, Fitzpatrick MC, Medlock J, Gray GE. Defining control of HIV epidemics. *Lancet HIV* 2018; **5:** e667–70.

31 Bassett IV, Regan S, Mbonambi H, et al. Finding HIV in hard to reach populations: mobile HIV testing and geospatial mapping in Umlazi township, Durban, South Africa. *AIDS Behav* 2015; **19:** 1888–95.

32 Eisinger RW, Fauci AS. Ending the HIV/AIDS pandemic. *Emerg Infect Dis* 2018; **24:** 413–16.