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Thirty years of change in HIV incidence among adults in the Kyamulibwa General Population Cohort in rural southwest Uganda, 1989–2021

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ABSTRACT

Objectives: To document the changes in HIV incidence over thirty years in Kalungu district, Uganda.

Methods: Since 1989, residents aged ≥ 15 years old have been tested for HIV, and data were collected on HIV risk factors annually and later, biennially in the Kyamulibwa open cohort. In the 2019–2021 survey, people living with HIV self-reported on knowledge of their HIV status, antiretroviral therapy (ART) use, and their most recent viral load data were obtained from health facilities. The HIV seroconversion dates were randomly imputed between the last negative and first positive test dates using a uniform distribution.

Results: Among 20,959 residents who were HIV-negative, 669 seroconverted within 176,659 person-years. Data showed a downward trend in age-adjusted HIV incidence over 30 years ($P < 0.001$) even though HIV prevalence steadily increased with ART availability from 2004. Comparing 1990–1992 and 1996–1998, HIV incidence declined by 43% (0.79 to 0.45/100 person-years, $P = 0.002$). Between 1999 and 2011, the incidence remained stable at 0.49/100 person-years (95% confidence interval: 0.41–0.58) in men but slowly increased in women (average age-adjusted hazard ratio = 1.13 per 3 years, 95% confidence interval: 1.03–1.24; trend P -value = 0.02). After 2011, however, the incidence trends reversed and continued to decline in men and women and in all age groups.

Conclusion: Facilitating HIV testing and timely ART initiation, and supporting ART adherence must be emphasized alongside sustainable prevention measures.

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Introduction

The long-term changes in HIV incidence can highlight broad patterns to inform efforts for stopping the spread of HIV. Empirical evidence and mathematical models have shown declining HIV incidence in eastern and southern Africa [1,2]. However, remarkable variations between and within countries were noted in rates and

trends in a systematic review and meta-analysis of HIV incidence in sub-Saharan Africa [1]. Furthermore, the estimated number of new HIV acquisitions in 2021 remained three times more than the global target, and sub-Saharan Africa disproportionately accounted for 59% of the new acquisitions [2]. Therefore, there is an urgent need to share lessons to accelerate the reduction of new HIV acquisitions and the resulting morbidity and mortality.

Population-level HIV incidence declines have been associated with a combination of effective interventions, which can be concurrently implemented to prevent HIV acquisition and transmission [3,4]. These have included HIV counseling and testing (HCT);

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HIV risk reduction behavioral interventions, including condom use and voluntary medical male circumcision; and the use of antiretroviral drugs for prevention of mother to child transmission, pre-exposure prophylaxis, postexposure prophylaxis (PEP), and treatment as prevention. The development of these interventions was based on lessons learned over the long-term global HIV response.

In Uganda, intensive and extensive efforts to create public awareness of HIV risk were credited for earlier declines in HIV incidence [5]. These efforts are likely to have influenced the quick adaptation of safer sexual behaviors when combined with witnessing many HIV-related deaths of close community members in high-prevalence communities before the introduction of antiretroviral therapy (ART). However, these community attitudes toward risk behavior are likely to have changed with changes in underlying populations and availability of ART, which decreased mortality among people living with HIV (PLHIV).

Although ART was introduced to enable PLHIV to live longer, evidence later showed that ART reduced the risk of HIV transmission [6]. As a result, the emphasis shifted to the promotion of treatment as prevention, leading to the effective implementation of the test-and-treat policy in 2017. This policy aimed at immediate ART initiation, regardless of an individual's clusters of differentiation (CD4) count or World Health Organization clinical staging. In addition, combination HIV prevention has been scaled up in Uganda, leading to substantial declines in HIV incidence [7,8]. For example, 78% of the 1.3 million adult PLHIV were estimated to be on ART in 2020, whereas 57.5% of men aged 15–49 years had been circumcised [9]. In one population-based study, the scale-up of combination HIV prevention (ART and male circumcision coverage) during the 2006–2016 period was shown to be associated with a 42% decline in HIV incidence by 2016 compared with the period before 2006, but the incidence remained high at about 0.6/100 person-years in men and women combined [7].

To avoid reversing the gains in HIV control, it is important to have a better understanding of long-term HIV incidence patterns and the key HIV prevention components that can be concurrently implemented and emphasized. Using data from an open population cohort in Kyamulibwa, Kalungu district in rural Uganda, we documented changes in HIV incidence over 30 years alongside changes in sexual behavior, in the HIV prevention and treatment landscape, mortality, and progress toward the Joint United Nations Programme on HIV/AIDS (UNAIDS) fast-track targets to end AIDS by 2030.

Methods

Cohort description

The Kyamulibwa General Population Cohort (GPC) has been running since 1989 for the surveillance of HIV in Kalungu district, rural southwest Uganda. Now, the GPC incorporates research on noncommunicable diseases with over 23,000 residents [10]. [Figure 1](#) shows the map of the study area with a cluster of 15 villages established in 1989, which was expanded to 25 villages in 1999. Also shown are the government-run health facilities and a study clinic run by the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI) and London School of Hygiene and Tropical Medicine Uganda Research Unit, which offers free general health care to residents. The study activities in GPC have been previously described in detail and include community mobilization, annual house-to-house census of all households (capturing new births, migrants, and deaths), and the subsequent health surveys for all consenting adults [10–12].

Over time, some study procedures have changed. Initially, consenting residents provided samples for HIV serology annually at

their homes, and those who wanted to know their test results were referred to GPC counselors. The HIV test results were usually returned within 1–2 weeks. From 2012, however, residents were invited to attend the health survey at temporary village hubs biennially after the house-to-house census within each village. In addition, HIV test results were given to participants on the same day of hub attendance, and all participants now receive their results at each survey after counseling. Participants who failed to make it to the hubs were actively followed up by the mobilization team. Health survey participation ranged between 61% and 89%, with most surveys having a participation proportion of over 70%. HIV status determination followed the prevailing Uganda Ministry of Health (MoH) testing algorithm at any time [13]. Participants diagnosed with HIV were referred for HIV care (before and after ART availability) and for treatment at a health facility of their choice, when ART became available. At the end of each round, the GPC team discusses outcomes on health conditions with members of each village separately.

HIV prevention services

In addition to survey HIV tests, free HIV testing and counseling, and support for PLHIV have been offered since establishing the GPC [11]. Condoms have been promoted and distributed during the survey, at the clinic, and during community mobilization activities. Individuals in this study area, as in other areas, have been exposed to HIV control efforts by the Uganda MoH programs, including those providing HIV information, education, and behavioral change communication. For example, since 2011 free voluntary medical male circumcision has been promoted in the study area including schools, and delivered at a government-run health facility located within the study area at least twice a year. Although PEP and pre-exposure prophylaxis are available at health centers, only PEP is offered at the study clinic.

HIV care and treatment

Participants are offered free general health care at the study clinic ([Figure 1](#)). Since 1990, those diagnosed with HIV were enrolled into a clinical cohort in which they were treated for opportunistic infections and offered positive prevention counseling before ART became available [14]. The clinic was accredited by Uganda MoH to offer ART in 2004 and became the main ART provider to PLHIV in the study area. HIV care, treatment, and support services are provided according to prevailing national guidelines and policies. The time points when changes in ART eligibility thresholds were implemented are indicated within the figures showing HIV incidence and prevalence trends.

Data collection

In each of the 26 completed surveys, consenting residents provided blood samples for HIV testing. Data were collected on sociodemographics, sexual behavior (*i.e.*, age at sexual debut, sexual activity, and condom use at last sex with casual sexual partners in the last 12 months), male circumcision, and other health indices at different surveys through standard questionnaires administered by trained survey interviewers [10]. In the 2019–2021 survey, PLHIV also reported on whether they knew their HIV status, were on ART, and their HIV viral load data were obtained from the facilities where they accessed ART. Data for each resident were linked using a unique identifier.

Statistical analysis

The analyses were restricted to participants aged 15 years and above at the time of each survey. The HIV incidence rates were

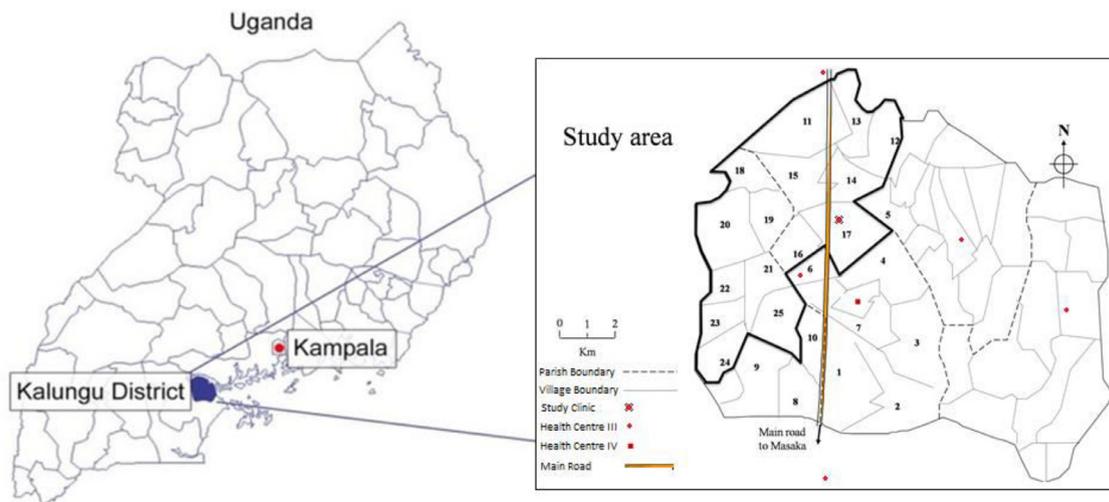


Figure 1. Map of Uganda showing the Kiyambwa General Population Cohort study area in Kalungu district. The study area is composed of 25 villages defined by administrative boundaries (In bold are the initial 15 villages established in 1989 and the other numbered villages were added in 1999).

estimated among people with an initial negative HIV test result as the ratio of the number of people who seroconverted to the total number of person-years at risk. The person-years were calculated from the date of joining the study area to their last HIV-negative test (for out-migrants, lost-to-follow-up, death) or seroconversion date (seroconverters). Gaps in follow-up were allowed if individuals out-migrated but later returned to the study area. For each seroconverter, the seroconversion date was randomly imputed between their last HIV-negative and first HIV-positive test dates using a uniform distribution [15,16]. The imputations were repeated 70 times to account for random error because the exact seroconversion dates were unknown and HIV incidence estimates were summarized using Rubin rules [17]. Statistical tests to assess whether changes in HIV incidence were significant were based on Poisson regression models adjusted for the time-varying age.

For HIV prevalence trends, the longitudinal nature of HIV serostatus data allowed making assumptions where residents had no recorded serostatus before an HIV-negative test result or after an HIV-positive result. Participants were assumed to be HIV-negative for the entire time before their first negative test result while those with a positive HIV test result were assumed to be positive in the subsequent period. These assumptions, however, tend to bias the prevalence estimates downward in the initial period and upward in the most recent period [15]. To reduce this bias and given that later rounds were biennial, participants whose first HIV test was positive were assumed to have been HIV-positive within the preceding 2 years while residing in the area. Residents with a negative last test were assumed to be HIV-negative in the subsequent 3 years if they were still residing in the area. Otherwise, participants were assigned an unknown HIV status. A sensitivity analysis assessing these assumptions was conducted, excluding these periods of pre-HIV-positive and post-HIV-negative.

The HIV incidence trends were interpreted in view of related changes in HIV prevalence, time to first sex, condom use at last casual sex, male circumcision, mortality rates, and progress toward the UNAIDS fast-track testing and treatment targets. The reported age at first sex for each individual at different time points were reconciled into a single age at first sex; but some caution would still be needed in interpreting these findings. The time to first sex was based on the reconciled age at first sex analyzed using survival analysis. For mortality rates, the follow-up time for residents ended at either the date of death or their last observation, whichever came first.

Estimating progress toward the UNAIDS 95-95-95 targets was only based on the 2019-2021 survey, in which PLHIV self-reported knowledge of HIV status and ART use, and had linked viral load data. For the first 95, the denominator was the number of residents who self-reported being HIV-positive or had tested HIV-positive within GPC by July 2021. The numerator was the number of PLHIV who self-reported knowing their HIV status, but to avoid underestimation due to nondisclosure of HIV status, the reports were cross-checked with linked individual data on previous HIV test results and ART use [18]. The second 95 was defined as the proportion of people who self-reported currently being on ART among PLHIV who knew their HIV status in the first 95. The third 95 was defined as the number of people currently on ART with suppressed viral loads (<1000 copies/ μl). The confidence intervals (CIs) were based on the logit transformation of proportions.

Ethics

Approvals are sought for each survey round from the UVRI Research and Ethics Committee (most recent: GC/127/710) and the Uganda National Council for Science and Technology (SS 4981). The participants provided written informed consent at each round and those aged <18 years additionally required parental consent.

Results

Cohort description

A total of 236,300 person-years of residency were contributed by 36,156 participants (54% women) aged 15 years and above (Table 1). The highest proportion of the person-years (58%) were contributed by participants who were residents at the start of surveillance, whereas 6% of person-years (15,075) were contributed by those born in the study area after the start of surveillance. A higher proportion of women than men were in-migrants (57% vs 47%) and joined while aged 15-24 years (31% vs 22%). Approximately 18% ($n = 6470$) of residents did not ever test for HIV as part of the GPC, whereas 5% ($n = 1803$) tested positive at their first HIV test.

By 2021, 10,839 participants aged 15+ years were residents, and 63% ($n = 6808$) participated in the most recent serosurvey (Table 2). The participation over time was consistently above 60% but was higher among women than men (2019-2021 survey: 72% among women, 52% among men). The demographic, behavioral,

Table 1

Description of residents in the study area aged at least 15 years participating in the Kyamulibwa General Population Cohort (GPC) in southwest Uganda between 1989 and 2021.

Characteristic	MEN AND WOMEN			MEN			WOMEN		
	Participants, n	Person-years (%)	Mean Person-years	Participants, n	Person-years (%)	Mean Person-years	Participants, n	Person-years (%)	Mean Person-years
Observed follow-up^a	36,156	236,300	6.5	16,511	111,676	6.8	19,645	124,625	6.3
Gaps in follow-up	7,314	22,558	2.2	3,450	10,759	2.2	3,864	11,799	2.2
Entry into study area									
Baseline recruitment	13,379	137,030 (58.0)	10.2	6,701	70,050 (62.7)	10.5	6,678	66,981 (53.7)	10.0
Birth	3,723	15,075 (6.4)	4.0	1,937	8,252 (7.4)	4.3	1,786	6,823 (5.5)	3.8
In-migration	19,035	84,123 (35.6)	4.4	7,866	33,353 (29.9)	4.2	11,169	50,770 (40.7)	4.5
Age at entry (years)^b									
0-14	15,343	77,342 (32.7)	5.0	7,719	42,686 (38.2)	5.5	7,624	34,656 (27.8)	4.5
15-24	9,752	58,182 (24.6)	6.0	3,709	23,512 (21.1)	6.3	6,043	34,670 (27.8)	5.7
25-34	4,725	39,484 (16.7)	8.4	2,138	18,028 (16.1)	8.4	2,587	21,456 (17.2)	8.3
35-54	4,147	41,746 (17.7)	10.1	1,936	18,377 (16.5)	9.5	2,211	23,369 (18.8)	10.6
55+	2,187	19,537 (8.3)	8.9	1,007	9,063 (8.1)	9.0	1,180	10,474 (8.4)	8.9
First HIV test result									
Negative	27,883	211,323 (89.4)	7.6	12,802	99,579 (89.2)	7.8	15,081	111,744 (89.7)	7.4
Positive	1,803	9,195 (3.9)	5.1	601	3,347 (3.0)	5.6	1,202	5,848 (4.7)	4.9
Never tested	6,470	15,783 (6.7)	2.4	3,108	8,750 (7.8)	2.8	3,362	7,032 (5.6)	2.1
Status at last survey									
Still resident	10,839	119,957 (50.8)	11.1	4,973	55,233 (49.5)	11.1	5,866	64,724 (51.9)	11.0
Died	3,063	28,186 (11.9)	9.2	1,554	15,372 (13.8)	9.9	1,509	12,814 (10.3)	8.5
Out-migrated	20,963	81,433 (34.5)	3.9	9,353	37,562 (33.6)	4.0	11,610	43,871 (35.2)	3.8
Lost to follow-up	1,291	6,725 (2.8)	5.2	631	3,508 (3.1)	5.6	660	3,216 (2.6)	4.9

^a Includes all participants regardless of HIV-status.

^b Joined the study area within this age-group but analysis left censored at age 15 years for residents who joined before their 15th birthday.

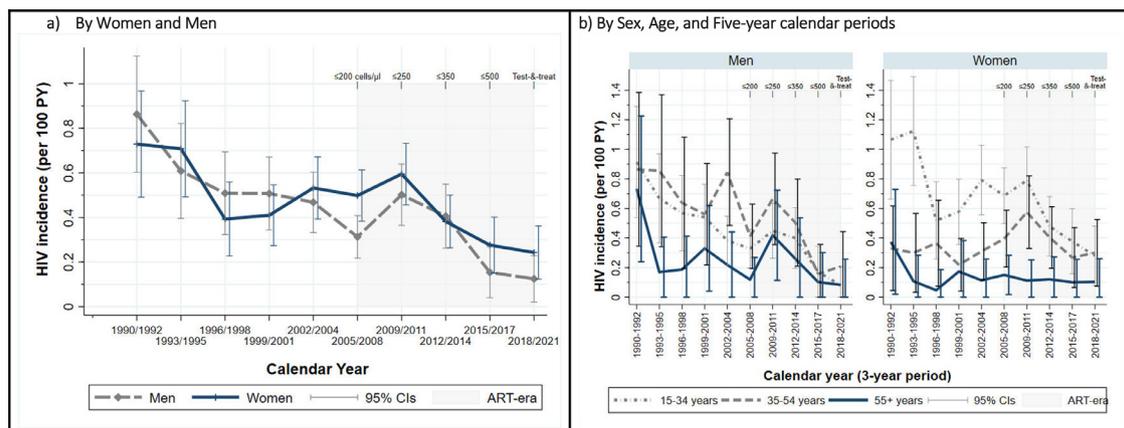


Figure 2. HIV incidence trends (a) and age-specific patterns (b) in men and women aged at least 15 years in the Kyamulibwa General Population Cohort in southwest Uganda, 1989–2021.

ART, antiretroviral therapy; CI, confidence interval; PY, person-years.

and self-reported HIV characteristics for the 2019–2021 survey are shown in Table 2.

HIV incidence trends

Participants who initially tested HIV-negative ($n = 20,959$, 54% women) contributed 176,659 person-years and 669 seroconversions (58% in women). HIV incidence estimates have shown a downward trend over the 30 years since the early 1990s (age-adjusted $P < 0.001$, Figure 2a). In men, HIV incidence declined by 88% (95% CI: 71%–95%, adjusted by age) from 0.96/100 person-years (95% CI: 0.70–1.32) in 1990–1992 to 0.12/100 (95% CI: 0.05–0.26) in 2018–2021. In women, the corresponding HIV incidence decline was 60% (95% CI: 28–78%, adjusted by age) from 0.68/100 (95% CI: 0.48–0.97) to 0.26/100 (95% CI: 0.16–0.40).

The rates of change in HIV incidence, however, varied over time, by sex and by age. Between 1990 and 1998, there was an accelerated decline in HIV incidence, which did not differ between men and women (age-adjusted interaction $P = 0.48$, [Figure 2a]). In

this period, HIV incidence declined by 41% (from 0.86 to 0.51/100 person-years, $P = 0.001$) in men and 47% (0.73 to 0.39/100 person-years, $P = 0.015$) in women. Between 1998 and 2004, HIV incidence was stable in men at an average of 0.49/100 person-years (95% CI: 0.41–0.58), fell by 37% to 0.31/100 person-years (95% CI: 0.22–0.41) in 2005–2008 ($P = 0.02$), then returned to the incidence rate of 0.50/100 person-years (95% CI: 0.36–0.64) in 2009–2011. In the 2005–2008 period, the maximum proportion of survey participation in men was 57%, which later increased to 66% in the subsequent period of 2009–2011. The drop in HIV incidence in 2005–2008 was likely related to the high proportion of men who did not participate in that period. In women, however, there was a steady increase in HIV incidence from 1999–2001 until 2009–2011 (average age-adjusted hazard ratio = 1.13 per 3 years, 95% CI: 1.03–1.24; trend $P = 0.02$). In the period of 2009–2011, there was no evidence to suggest a difference in the HIV incidence rate between men and women ($P = 0.38$).

After the ART eligibility thresholds changed from ≤ 250 cells/ μ l to ≤ 350 cells/ μ l, the HIV incidence trend in both men and women

Table 2
Characteristics of participants aged at least 15 years in the health survey of the Kyamulibwa General Population Cohort conducted between June 2019 and July 2021 in southwest Uganda.

Characteristic	MEN AND WOMEN	MEN, n (%)	WOMEN, n (%)
Number of respondents	6808	2596	4212
Age of respondent (years)			
15-24	1598 (23.5)	530 (20.4)	1068 (25.4)
25-34	1332 (19.6)	524 (20.2)	808 (19.2)
35-54	2371 (34.8)	948 (36.5)	1423 (33.8)
55+	1507 (22.1)	594 (22.9)	913 (21.7)
Marital status			
Never married	1550 (22.8)	687 (26.5)	863 (20.5)
Currently married	3650 (53.6)	1496 (57.6)	2154 (51.1)
Divorced/separated	1031 (15.1)	358 (13.8)	673 (16.0)
Widowed	577 (8.5)	55 (2.1)	522 (12.4)
Religion			
Catholic	4007 (58.9)	1537 (59.3)	2470 (58.6)
Anglican	766 (11.3)	307 (11.8)	459 (10.9)
Other Christian	327 (4.8)	110 (4.2)	217 (5.2)
Muslim	1706 (25.1)	640 (24.7)	1066 (25.3)
Education level			
<Primary 5	1474 (21.7)	526 (20.3)	948 (22.5)
Primary 5-7	2934 (43.1)	1188 (45.8)	1746 (41.5)
Secondary 1-4	1801 (26.5)	600 (23.1)	1201 (28.5)
Secondary 5 and above	598 (8.8)	281 (10.8)	317 (7.5)
Tribe			
Baganda	5188 (76.2)	1989 (76.7)	3199 (75.9)
Rwandese	1011 (14.9)	396 (15.3)	615 (14.6)
Other	607 (8.9)	209 (8.1)	398 (9.4)
Reported pregnancy status (15-54 years old)			
No	2375 (56.4)		2375 (56.4)
Yes	189 (4.5)		189 (4.5)
Question not asked	1648 (39.1)		1648 (39.1)
Ever had sex (16-21 years old)¹			
Yes	-	-	410 (50.7)
No	-	-	399 (49.3)
Alcohol intake frequency, last 12 months			
5-7 days/week	258 (12.0)	216 (18.4)	42 (4.3)
1-4 days/week	515 (24.0)	362 (30.9)	153 (15.8)
1-3 days/month	614 (28.7)	327 (27.9)	287 (29.6)
<once a month	755 (35.2)	268 (22.8)	487 (50.3)
Self-reported knowing HIV status²			
Yes	4461 (65.5)	1570 (60.5)	2891 (68.6)
No	2347 (34.5)	1026 (39.5)	1321 (31.4)
HIV test status			
Negative	5798 (85.2)	2232 (86.0)	3566 (84.7)
Positive	602 (8.8)	203 (7.8)	399 (9.5)
Unknown	408 (6.0)	161 (6.2)	247 (5.9)
Self-reported receiving ART³			
Yes	535 (98.9)	176 (98.9)	359 (98.9)
No	6 (1.1)	2 (1.1)	4 (1.1)
ART provider³			
GPC study clinic	294 (55.1)	110 (62.9)	184 (51.3)
Study area HC III ⁴	105 (19.7)	26 (14.9)	79 (22.0)
Study area HC IV	51 (9.6)	17 (9.7)	34 (9.5)
Other healthcare facilities	84 (15.7)	22 (12.6)	62 (17.3)

¹ Asked for only young women aged 16 to 21 years at this medical survey.

² Self-reported knowledge of HIV status among all survey participants regardless of HIV status.

³ ART - antiretroviral therapy. ⁴ HC - Health Centre.

was changed and the declines continued when the ART eligibility threshold was further changed to ≤ 500 cells/ μ l in 2015-2017 (comparing the incidence in 2009-2011 and 2015-2017: in men, $P = 0.01$; in women, $P = 0.001$). Compared with 2015-2017, however, the HIV incidence seemed to have reduce only slightly when the test-and-treat policy was implemented during 2018-2021 in men ($P = 0.57$) and in women ($P = 0.72$). In this most recent period, there was no evidence to suggest that HIV incidence was substantially higher in women than in men ($P = 0.12$).

In women, HIV incidence was consistently higher in those aged 15-34 years than in other age groups but similar across age groups in the more recent time point. In the early 1990s, HIV incidence was disproportionately high among young women aged 15-34 years and particularly in those aged 15-24 years (Figure 2b). In

the later 1990s, the incidence remarkably fell in young women ($P = 0.01$) but remained stable for other age groups. From the early 2000s, however, the incidence steadily increased in women aged 15-34 and 35-54 years until the 2009-2011 period. In both age groups, the trend was reversed after the ART eligibility thresholds changed from ≤ 250 cells/ μ l to ≤ 350 cells/ μ l, and the incidence declines continued with further changes to ≤ 500 cells/ μ l. When the test-and-treat policy was implemented, HIV incidence reduced only slightly in those aged 15-34 years but not in those aged 35-54 years. In women aged 55 years and above, HIV incidence has been stable and consistently lowest over the observation period.

In men, HIV incidence was consistently highest in those aged 35-54 years and lowest among those aged 55+ years but similar across age groups in more recent time points. From 1990-1992 to

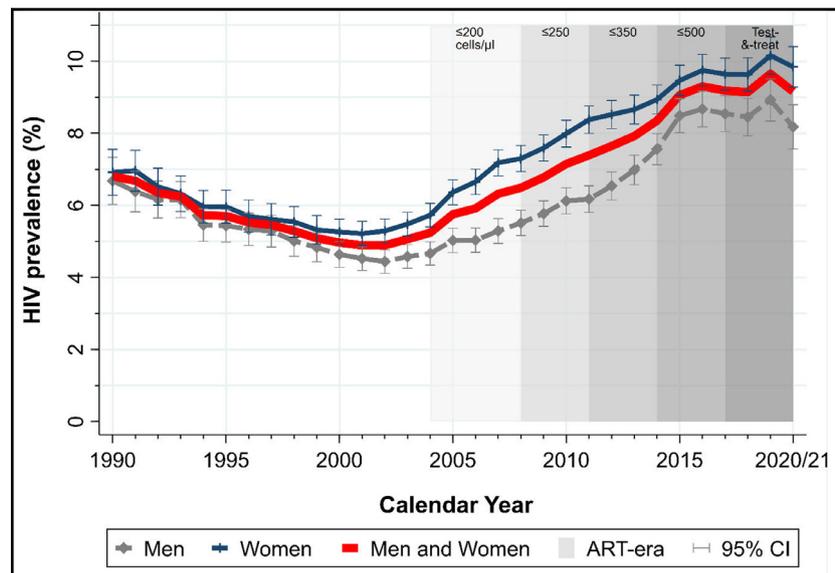


Figure 3. HIV prevalence trends among men and women aged at least 15 years in the Kyamulibwa General Population Cohort in southwest Uganda between 1989 and 2021. ART, antiretroviral therapy; CI, confidence interval.

2005–2008, HIV incidence steadily declined among men aged 15–34 years and in those aged 35–54 years; but there was a spike in 2002–2004 for those aged 35–54 years. Compared with 2005–2008, HIV incidence increased slightly in 2009–2011 among men of all ages but was not statistically significant at 5% level. However, the incidence trend was reversed in all ages after the ART eligibility thresholds changed from ≤ 250 cells/ μl to ≤ 350 cells/ μl , and the incidence declines continued with further changes to ≤ 500 cells/ μl as was the case among women.

HIV prevalence trends

Overall, the HIV prevalence slowly declined from 8% in 1989/90 to an average of 5% between 2000 and 2004, before steadily increasing in the ART era until 2015, where it has flattened at about 10% (Figure 3). This prevalence trend pattern did not differ between men and women; although, the prevalence remained consistently higher among women since 1998. Before ART introduction, the individual-year HIV prevalence was strongly correlated with individual-year HIV incidence rates in both men (Pearson correlation coefficient, $r = 0.85$, $P < 0.001$) and women ($r = 0.77$, $P = 0.001$). After ART introduction, the rate of increase in HIV prevalence was faster for women than men until the ART eligibility was changed from ≤ 250 cells/ μl to ≤ 350 cells/ μl ($P < 0.001$). In the period when the ART eligibility was ≤ 350 cells/ μl , however, the rate of increase in HIV prevalence was much higher in men than women before leveling off for both sexes in the period when the ART eligibility threshold was ≤ 500 cells/ μl .

All-cause mortality trends

All-cause mortality was disproportionately high among PLHIV but markedly declined after ART introduction and subsequently, with changes in the ART eligibility thresholds that led to more PLHIV initiating treatment (Figure 4a). After 2 years of ART availability in this setting, mortality declined by 63% (9.6/100 to 3.6/100 person-years) in male PLHIV and by 51% (6.5–3.2/100 person-years) in female PLHIV. Overall age-specific mortality rates reduced with calendar periods corresponding to increases in ART eligibility thresholds (Figure 4b).

Male circumcision, condom use, and time to first sex

The proportion of men who were circumcised slowly increased from 24% in 2000/2001 to 28% in 2008/2009, then to 33% in 2012/2013, and 41% in 2014/2015 (Figure 5). At all the time points, the prevalence of male circumcision decreased with age. Between 2000 and 2015, the proportion of males circumcised had doubled in men aged 15–24 and 25–34 years and was 53% higher in those aged 35–49 years. Approximately 25% of all men were Muslim.

The proportion of individuals reporting condom use at last sex with a casual partner seemed to decline from 60% in 1997, then remain unchanged in men at an average of 52%. In women, the proportion increased steadily from 38% in 1997 to 53% in 2014 (Figure 6). The reported time to first sex by birth cohort is shown for both men and women in Figure 7. Over time, data showed that the time to first sex increased in women from a median of 16.6 years in the birth cohort of 1950–1954 to 18.6 years in the 2000–2004 birth cohort ($P < 0.001$). In the 2000–2004 birth cohort, 60% reported not having had sex by 18 years compared with less than 50% in the previous birth cohorts. In men, however, the reported time to first sex did not seem to change (range: 18–18.5 years) but an increasingly higher proportion reported delaying initiating sex ($P = 0.03$).

Progress toward the 95-95-95 UNAIDS targets

In both men and women, nearly all PLHIV who knew their HIV status reported being on ART (99%); 91% of those on ART achieved viral suppression (Figure 8), but a sizable proportion of PLHIV did not know their HIV status (18% in male PLHIV, 14% in female PLHIV). The proportion of PLHIV with unknown HIV status was higher among those aged 15–24 years than those aged ≥ 25 years (men [45% vs 17%, $P = 0.03$]; women [22% vs 13%, $P = 0.10$]).

Discussion

In this setting, there was a downward trend in HIV incidence over three decades since the early 1990s, even though HIV prevalence steadily increased with ART availability. However, the rates of decline in HIV incidence varied over time by sex and age of residents. A key hallmark in the HIV response was implementing the

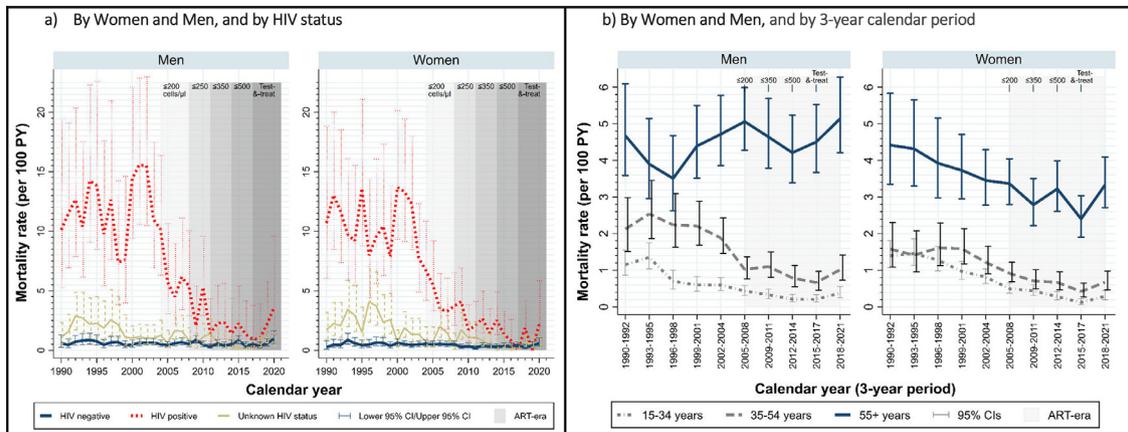


Figure 4. Mortality trends in men and women by HIV status and by age categories in the Kyamulibwa General Population Cohort in southwest Uganda between 1989 and 2021. ART, antiretroviral therapy; CI, confidence interval; PY, person-years.

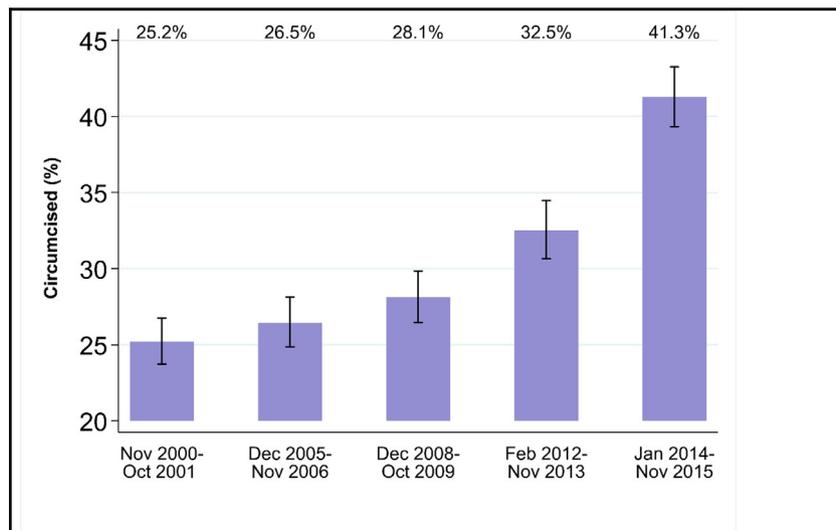


Figure 5. Changes in reported circumcision status among males aged 15 years and above in the Kyamulibwa General Population Cohort in southwest Uganda (2000-2015).

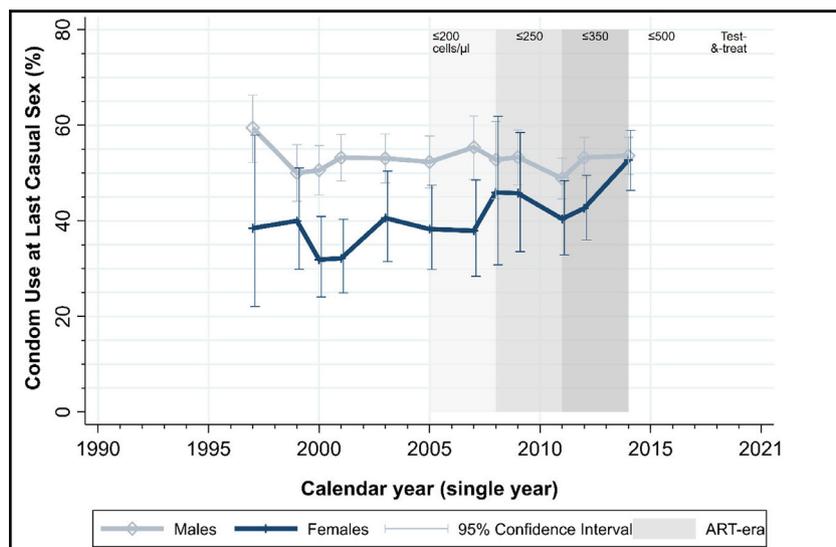


Figure 6. Changes in self-reported condom use at last sex with a casual partner in the Kyamulibwa General Population Cohort in southwest Uganda (1997-2014). ART, antiretroviral therapy.

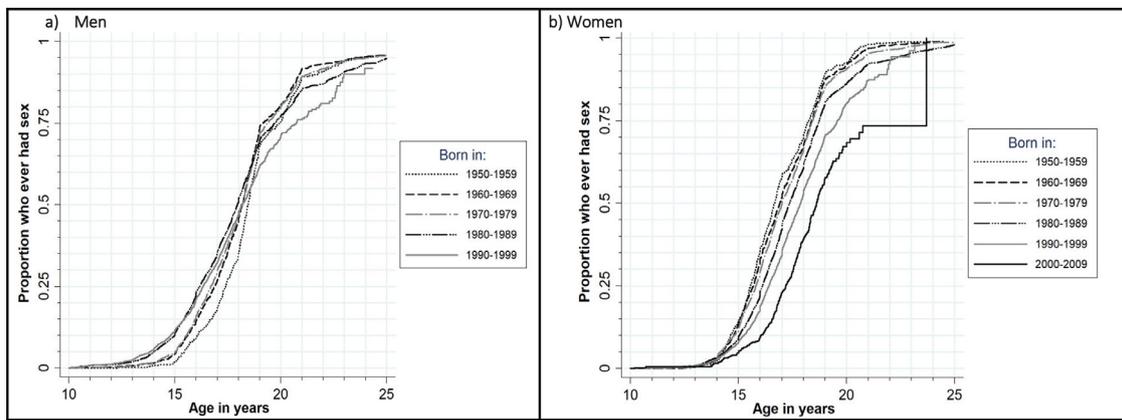


Figure 7. Time to first sex for men and women born since 1950, by 10-year birth cohorts in the Kyamulibwa General Population Cohort in southwest Uganda.

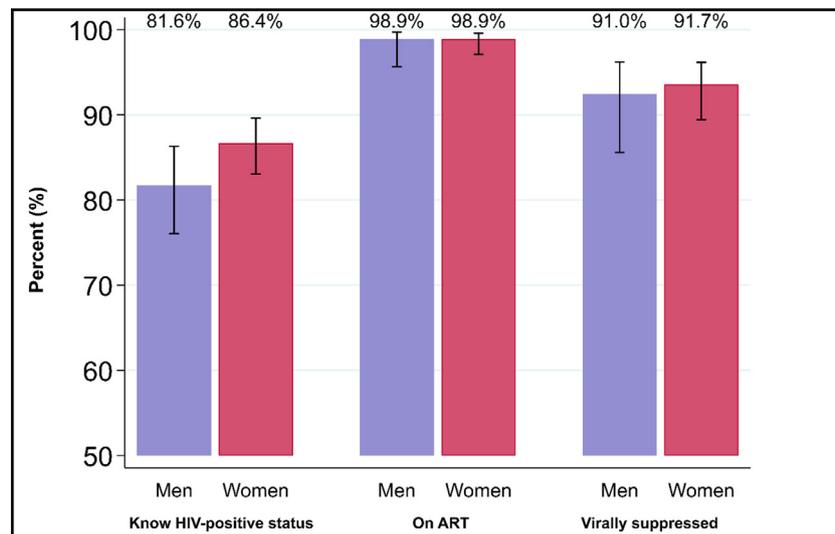


Figure 8. Progress toward the 95-95-95 UNAIDS targets among men and women in the Kyamulibwa General Population Cohort (data collected between June 2019 and July 2021). ART, antiretroviral therapy.

changes in ART eligibility thresholds from ≤ 250 to ≤ 350 cells/ μ l and upward, which substantially scaled up the ART coverage with each change. With these changes, the rising HIV incidence trend in women between 2001 and 2011 was reversed and the stable trend in men declined, and the incidence is at its lowest in the most recent time point. HIV control in this setting was likely facilitated by the regular opportunities and support for HCT, rapid ART initiation, and active support for ART adherence, alongside other HIV prevention measures (messaging, circumcision, condoms).

The initial declines in HIV incidence through the 1990s are likely explained by a combination of factors, including structural factors, individual behavioral changes, and the witnessing of many close community members die of AIDS [5,19,20]. Epidemiological evidence suggests an interrelationship between HIV-related mortality, HIV prevalence, and incidence in the absence of ART [19,21]. In particular, a high prevalence of untreated HIV infection has been shown to be associated with an increased risk of HIV acquisition [21]. This link might explain the declining HIV incidence in the 1990s in our study when PLHIV experienced high mortality resulting in a steady decline in HIV prevalence and thus impacting incidence.

Changes in sexual behavior might have also impacted initial HIV incidence trends following Uganda’s HIV response since the mid-1980s, which focused on mass education and awareness campaigns

on HIV/AIDS, facilitated by extensive social mobilization and political leadership [5,22–24]. For example, between 1989 and 1995, the percentage of people who reported at least one casual partner dropped from 35% to 15% in men and from 16% to 6% in women [25]. In this study area, condom use has been promoted, and free condoms were distributed during mobilization, in the health surveys, and at the study clinic since the start of the cohort. Our proportion of reported condom use at last sex with a casual partner in 1997 is consistent with figures from the Uganda demographic and health survey [26]. Since then, however, the proportion of reported condom use at last casual sex remained unchanged in men but slowly increased in women to a level similar to that in men. Furthermore, the HIV incidence trends are likely to have been impacted by increasing delays in initiating first sex, particularly among young women. It is likely that behavioral changes might have been accelerated by the high mortality and morbidity rates that were witnessed in the community among PLHIV before ART was introduced. However, it is difficult to tell how the positive prevention counseling for PLHIV in this setting since the early 1990s might have contributed to earlier HIV incidence trends [11,14].

After ART introduction, the mortality dropped sharply among PLHIV and HIV incidence slowly increased in women and remained stable in men until 2011. During this period, ART was initiated mainly among people with more advanced HIV disease [27] given

that the thresholds for ART initiation were CD4 cell counts of ≤ 200 cells/ μl at the start, then ≤ 250 in 2008, and ≤ 350 cells/ μl in 2011. Although the combination of ART and cotrimoxazole prophylaxis reduced mortality among PLHIV [28,29], there was likely a high risk of HIV transmission from over 60% of PLHIV who had not yet been initiated on ART [27]. The increase in HIV incidence among women during this period suggests that women might not have benefited substantially from the HIV preventive benefits of ART and prevention counseling among men as much as men did from women. A lower proportion of men than women participated in the survey (an average of 55% in men vs 67% in women) and therefore were less likely to know their HIV status earlier. In addition, men also delayed initiating ART and were more likely to drop out of HIV care than women, undermining the potential preventive benefit of ART for women [30]. There was no evidence suggesting increased risky sexual behavior during this period of early ART availability.

The downward HIV incidence trends after 2011 are consistent with findings that showed declining HIV incidence in SSA [1]. In our study, these HIV incidence declines are likely a result of the combined HIV preventive benefits of earlier ART initiation and subsequently, expanded ART coverage among PLHIV and expanded male circumcision coverage. There was a rise by over 10% in the proportion of PLHIV on ART as result of the expansion of the threshold for ART initiation to ≤ 350 cells/ μl and to ≤ 500 cells/ μl . In 2011, free voluntary medical male circumcision became available to the community and has been delivered through government health centers, and actively promoted in the community since 2012. This intervention substantially increased male circumcision coverage but remained only half of the UNAIDS target of 80%. These findings are similar to those in the neighboring Rakai district, which found an impact of modest coverage levels of male circumcision and ART on community-level HIV incidence trends [7].

The introduction of test-and-treat in 2017 did not seem to substantially influence population-level HIV incidence likely because a considerable proportion of PLHIV was already on ART. These stable incidence trends in the most recent time points with no indication of increasing mortality trends among PLHIV might explain the flattening HIV prevalence in the most recent period at about 11% in women and 9% in men. However, this high HIV prevalence is not positively correlated with HIV incidence because of the reduced risk of HIV transmission as a result of high ART coverage in this setting. Further declines in HIV incidence might be possible with interventions for HIV prevention among people at the highest risk, continued earlier diagnosis of PLHIV, and rapid ART initiation, as well as ensuring higher levels of viral suppression and actively promoting male circumcision.

Some of our findings might not be generalizable to populations beyond the study population. For example, regular HIV testing for all residents (at least every 2 years) in the GPC presented repeated opportunities for PLHIV to know their HIV status, resulting in a higher proportion of individuals who know their status than in other settings, particularly among men. Although high rates of undisclosed HIV status have been reported in household surveys, the potential for underestimating the first 95 in this study due to nondisclosure was likely reduced by cross-checking their reports with linked data on previous HIV test results and ART use [18]. The proportions of PLHIV on ART and those achieving viral suppression, however, are comparable to the national estimates [2]. Our estimates of HIV incidence and prevalence before ART introduction might have been conservative given the observed high mortality rates among people with unknown HIV status. Another limitation concerns self-reported data which must be interpreted with caution given social desirability and other reporting biases, such as recall bias. However, a key strength of this study was the ability

to use longitudinal data for cross-checking and defining key metrics.

In conclusion, the accelerated declines in HIV incidence after the changes in ART eligibility to higher CD4 cell counts starting with 350 cells/ μl were enabled by regular HCT opportunities in this setting. The findings in this study reinforce the need for enabling HCT, particularly among young men and women, rapid ART initiation to maintain a high ART coverage, and support for ART adherence for viral suppression, alongside sustainable HIV prevention measures.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Ethical approval

Approvals are sought for each survey round from the Uganda Virus Research Institute Research and Ethics Committee (most recent: GC/127/710) and the Uganda National Council for Science and Technology (SS 4981). The participants provided written informed consent at each round and those aged <18 years additionally required parental consent.

Author contributions

I.K, J.M, and R.N conceptualised the idea. I.K conducted statistical analysis and wrote the first draft of the paper. J.M is the project leader of the cohort and manages day-to-day study activities. A.A supported in reviewing the statistical analyses. R.M provided data management support. E.R, P.K, J.S, and R.N provided overall guidance on the paper. All authors contributed to the drafts of the paper until the final version.

References

- [1] Joshi K, Lessler J, Olawore O, Loevinsohn G, Bushey S, Tobian AAR, et al. Declining HIV incidence in sub-Saharan Africa: a systematic review and meta-analysis of empiric data. *J Int AIDS Soc* 2021;24:e25818. doi:10.1002/jia2.25818.
- [2] UNAIDS. UNAIDS global AIDS update 2022, https://www.unaids.org/sites/default/files/media_asset/2022-global-aids-update-summary_en.pdf; 2022 (accessed 06 December 2022).
- [3] Chang LW, Serwadda D, Quinn TC, Wawer MJ, Gray RH, Reynolds SJ. Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects. *Lancet Infect Dis* 2013;13:65–76. doi:10.1016/S1473-3099(12)70273-6.
- [4] Hayes RJ, Donnell D, Floyd S, Mandla N, Bwalya J, Sabapathy K, et al. Effect of universal testing and treatment on HIV incidence—HPTN 071 (PopART). *N Engl J Med* 2019;381:207–18. doi:10.1056/NEJMoa1814556.
- [5] Slutkin G, Okware S, Naamara W, Sutherland D, Flanagan D, Carael M, et al. How Uganda reversed its HIV epidemic. *AIDS Behav* 2006;10:351–60. doi:10.1007/s10461-006-9118-2.
- [6] Williams BG, Lima V, Gouws E. Modelling the impact of antiretroviral therapy on the epidemic of HIV. *Curr HIV Res* 2011;9:367–82. doi:10.2174/157016211798038533.
- [7] Grabowski MK, Serwadda DM, Gray RH, Nakigozi G, Kigozi G, Kagaayi J, et al. HIV prevention efforts and incidence of HIV in Uganda. *N Engl J Med* 2017;377:2154–66. doi:10.1056/NEJMoa1702150.
- [8] Uganda AIDS Commission. The national HIV and AIDS research agenda for 2020/21. Kampala: Uganda AIDS Commission 2021.

- [9] Uganda Ministry of Health. Release of preliminary results of the 2020 Uganda population-based HIV impact assessment (UPHIA). <https://www.health.go.ug/cause/release-of-preliminary-results-of-the-2020-uganda-population-based-hiv-impact-assessment/>; 2020 [accessed 06 December 2022].
- [10] Asiki G, Murphy G, Nakiyingi-Miiri J, Seeley J, Nsubuga RN, Karabarinde A, et al. The general population cohort in rural south-western Uganda: a platform for communicable and non-communicable disease studies. *Int J Epidemiol* 2013;**42**:129–41. doi:10.1093/ije/dys234.
- [11] Seeley J, Wagner U, Mulemwa J, Kengeya-kayondo J, Mulder D. The development of a community-based HIV/AIDS counselling service in a rural area in Uganda. *AIDS Care* 1991;**3**:207–17. doi:10.1080/09540129108253064.
- [12] Shafer LA, Biraro S, Nakiyingi-Miiri J, Kamali A, Ssematimba D, Ouma J, et al. HIV prevalence and incidence are no longer falling in southwest Uganda: evidence from a rural population cohort 1989–2005. *AIDS* 2008;**22**:1641–9. doi:10.1097/QAD.0b013e32830a7502.
- [13] Nunn AJ, Biryahwaho B, Downing RG, van der Groen G, Ojwiya A, Mulder DW. Algorithms for detecting antibodies to HIV-1: results from a rural Ugandan cohort. *AIDS* 1993;**7**:1057–61. doi:10.1097/00002030-199308000-00005.
- [14] Morgan D, Malamba SS, Maude GH, Okongo MJ, Wagner HU, Mulder DW, et al. An HIV-1 natural history cohort and survival times in rural Uganda. *AIDS* 1997;**11**:633–40. doi:10.1097/00002030-199705000-00011.
- [15] Vandormael A, Dobra A, Bärnighausen T, de Oliveira T, Tanser F. Incidence rate estimation, periodic testing and the limitations of the mid-point imputation approach. *Int J Epidemiol* 2018;**47**:236–45. doi:10.1093/ije/dyx134.
- [16] Kasamba I, Nash S, Seeley J, Weiss HA. Human immunodeficiency virus incidence among women at high-risk of human immunodeficiency virus infection attending a Dedicated Clinic in Kampala, Uganda: 2008–2017. *Sex Transm Dis* 2019;**46**:407–15. doi:10.1097/OLQ.0000000000000978.
- [17] Rubin DB. *Multiple imputation for nonresponse in surveys*. Chichester: John Wiley & Sons; 2004.
- [18] Rentsch CT, Reniers G, Machemba R, Slaymaker E, Marston M, Wringe A, et al. Non-disclosure of HIV testing history in population-based surveys: implications for estimating a UNAIDS 90-90-90 target. *Glob Health Action* 2018;**11**:1553470. doi:10.1080/16549716.2018.1553470.
- [19] Macintyre K, Brown L, Sosler S. It's not what you know, but who you knew": examining the relationship between behavior change and AIDS mortality in Africa. *AIDS Educ Prev* 2001;**13**:160–74. doi:10.1521/aeap.13.2.160.19736.
- [20] Ntozi JP, Kirunga CT. HIV/AIDS, change in sexual behaviour and community attitudes in Uganda. *Health Transit Rev* 1997;**7**:157–74.
- [21] Slaymaker E, Todd J, Urassa M, Herbst A, McGrath N, Newton R, et al. HIV incidence trends among the general population in eastern and southern Africa 2000 to 2014. *J Int AIDS Soc* 2018;**21**:e25148 Oral abstracts of the 22nd International AIDS Conference, 23–27 July 2018, Amsterdam, the Netherlands'. doi:10.1002/jia2.25148.
- [22] Okware S. Review of social challenges of heterosexual transmission of HIV/AIDS in Uganda. *AIDS Updates - Recent Advances and New Perspectives*. London: IntechOpen Limited; 2021.
- [23] Wilson D. Partner reduction and the prevention of HIV/AIDS. *BMJ* 2004;**328**:848–9. doi:10.1136/bmj.328.7444.848.
- [24] Green EC, Halperin DT, Nantulya V, Hogle JA. Uganda's HIV prevention success: the role of sexual behavior change and the national response. *AIDS Behav* 2006;**10**:335–46 discussion 347–50. doi:10.1007/s10461-006-9073-y.
- [25] UNAIDS. Epidemiological fact sheets on HIV and sexually transmitted infections: United States. https://data.unaids.org/publications/fact-sheets01/uganda_en.pdf; 2004 [accessed 28 May 2022].
- [26] Uganda Bureau of Statistics (UBOS) and ORC Macro *Uganda Demographic and Health Survey 2000-2001*. Calverton, Maryland, USA: UBOS and ORC Macro; 2001.
- [27] Kazooba P, Kasamba I, Baisley K, Mayanja BN, Maher D. Access to, and uptake of, antiretroviral therapy in a developing country with high HIV prevalence: a population-based cohort study in rural Uganda, 2004–2008. *Trop Med Int Health* 2012;**17**:e49–57. doi:10.1111/j.1365-3156.2012.02942.x.
- [28] Kasamba I, Baisley K, Mayanja BN, Maher D, Grosskurth H. The impact of antiretroviral treatment on mortality trends of HIV-positive adults in rural Uganda: a longitudinal population-based study, 1999–2009. *Trop Med Int Health* 2012;**17**:e66–73. doi:10.1111/j.1365-3156.2012.02841.x.
- [29] Mermin J, Lule J, Ekwaru JP, Malamba S, Downing R, Ransom R, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet* 2004;**364**:1428–34. doi:10.1016/S0140-6736(04)17225-5.
- [30] Nakigozi G, Makumbi F, Reynolds S, Galiwango R, Kagaayi J, Nalugoda F, et al. Non-enrollment for free community HIV care: findings from a population-based study in Rakai. *Uganda. AIDS Care* 2011;**23**:764–70. doi:10.1080/09540121.2010.525614.