OPEN

The association of exposure to DREAMS on sexually acquiring or transmitting HIV amongst adolescent girls and young women living in rural South Africa

Nondumiso Mthiyane[a,b], Kathy Baisley[a,g], Natsayi Chimbindi[a,b,c], Thembelihle Zuma[a,b,c], Nonhlanhla Okesola[a], Jaco Dreyer[a], Carina Herbst[a], Theresa Smit[a], Siva Danaviah[a], Nuala McGrath[a,c,d], Guy Harling[a,b,c,e,f], Lorraine Sherr[b], Janet Seeley[a,c,g], Sian Floyd[g], Isolde Birdthistle[g] and Maryam Shahmanesh[a,b,c]

Objective: We investigate how risk of sexually acquiring or transmitting HIV in adolescent girls and young women (AGYW) changed following the real-world implementation of DREAMS (Determined, Resilient, Empowered, AIDS free, Mentored and Safe) HIV prevention programme.

Design: A representative population-based prospective cohort study of AGYW living in rural KwaZulu-Natal.

Methods: Between 2017 and 2019, we interviewed a random sample of AGYW aged 13–22 years annually. We measured exposure to DREAMS as self-reported receipt of an invitation to participate and/or participation in DREAMS activities that were provided by DREAMS implementing organizations. HIV and herpes simplex virus type 2 (HSV-2) statuses were ascertained through blood tests on Dried Blood Spot (DBS). We used multivariable regression analysis to assess the association between exposure to DREAMS and risk of acquiring HIV: measured as incident HSV-2 (a proxy of sexual risk) and incident HIV;and the risk of sexually transmitting HIV: measured as being HIV positive with a detectable HIV viral load ($\geq$50 copie/ml) on the last available DBS. We adjusted for sociodemographic, sexual relationship, and migration.

Results: Two thousand one hundred and eighty-four (86.4%) of those eligible agreed to participate and 2016 (92.3%) provided data for at least one follow-up time-point. One thousand and thirty (54%) were exposed to DREAMS;HIV and HSV-2 incidence were 2.2/100 person-years [95% confidence interval (CI) 1.66–2.86] and 17.3/100 person-years (95% CI 15.5–19.4), respectively. There was no evidence that HSV-2 and HIV incidence were lower in those exposed to DREAMS: adjusted rate ratio (aRR) 0.96 (95% CI 0.76–1.23 and 0.83 (95% CI 0.46–1.52), respectively. HIV viral load was detectable for 169 (8.9%) respondents;there was no evidence this was lower in those exposed to DREAMS with an adjusted risk difference, compared with those not exposed to DREAMS, of 0.99% (95% CI–1.52 to 3.82]. Participants who lived in peri-urban/urban setting were more likely to have incident HIV and transmissible HIV. Both HSV-2 incidence and the transmissible HIV were associated with older age and ever having sex. Findings did not differ substantively by respondent age group.

[a]Africa Health Research Institute, KwaZulu-Natal, South Africa, [b]Institute for Global Health, University College London, London, UK, [c]University of KwaZulu-Natal, Durban, [d]University of Southampton, Southampton, UK, [e]MRC/Wits Rural Public Health & Health Transitions Research Unit (Agincourt), University of the Witwatersrand, Gauteng, South Africa, [f]Department of Epidemiology & Harvard Centre for Population and Development Studies, Harvard T.H. Chan School of Public Health, Boston, USA, and [g]London School of Hygiene and Tropical Medicine, London, UK.

Correspondence to Maryam Shahmanesh, UCL, Institute for Global Health, 3rd floor Mortimer Market Centre, Capper Street, London WC1E 6JB, UK.

Tel: +44 7776185572; e-mail: m.shahmanesh@ucl.ac.uk

Received: 5 February 2021; revised: 28 October 2021; accepted: 4 January 2022.

DOI:10.1097/QAD.0000000000003156

Conclusion: DREAMS exposure was not associated with measurable reductions in risk of sexually acquiring or transmitting HIV amongst a representative cohort of AGYW in rural South Africa

AIDS 2022, **36** (Suppl 1):S39–S49

Keywords: adolescent girls and young women, combination HIV prevention, HIV, HIV viral load, HSV-2

Introduction

South Africa has an estimated 7.7 million people living with HIV – the highest number of any country globally; HIV remains the leading cause of death. Despite highly efficacious and cost-effective HIV prevention tools, HIV incidence has remained stubbornly high, especially in KwaZulu-Natal (KZN) where we have shown an annual incidence of 8% amongst women aged 20–24 years [1,2]. There is an urgent need to reduce the impact of the HIV epidemic in adolescent girls and young women (AGYW) [3].

There have long been calls to scale-up evidence-based combination structural, behavioural, and biomedical HIV prevention interventions [4–8]. This has been reinvigorated by evidence that 'layering', that is, providing multiple interventions together, can accelerate progress towards the Sustainable Development Goals in adolescents [9]. In response, the US Presidents' Emergency Plan for AIDS Relief with others, supported the 'DREAMS (Determined, Resilient, Empowered, AIDS free, Mentored and Safe) Partnership', a multisectoral package of interventions to reduce HIV incidence amongst AGYW, hereafter referred to as DREAMS [10,11]. The aim of DREAMS was to reduce HIV incidence through strengthening existing HIV testing, prevention, and linkage to care interventions and the introduction of evidence-based interventions for gender-based violence, family and caregiving, social asset building, and cash transfers for AGYW [10,12,13].

DREAMS in South Africa was implemented with high-level oversight by government and funders, through local implementing partners who were resourced to deliver defined and target-focused packages of interventions to AGYW in selected geographic areas [14,15]. Two of the pathways through which we hypothesized DREAMS would reduce HIV amongst AGYW was through reducing sexual risk and reducing the prevalence of transmissible HIV amongst AGYW and their male partners [12,16].

Between 2016 and 2018, we evaluated DREAMS rollout in a poor rural district in northern KZN, South Africa, with a high burden of HIV [16]. We present the prespecified analysis of the impact of the real-world implementation of the DREAMS combination prevention intervention on the incidence of herpes simplex virus type 2 (HSV-2, as a measure of sexual risk), HIV incidence and detectable HIV viral load (as a measure of sexually transmissible HIV) in AGYW.

Methods

Study design

As part of a multicounty DREAMS impact evaluation, we conducted a cohort study to evaluate the impact of exposure to DREAMS on risk of sexually acquiring or transmitting HIV amongst a representative sample of ~2000 AGYW in a DREAMS district of rural South Africa. In 2017, a random sample of AGYW, stratified by age and geographical area, were enrolled from the Africa Health Research Institute (AHRI) demographic surveillance area [17] and followed up annually for 2 years.

Setting and population

The AHRI demographic Surveillance System is situated in the uMkhanyakude district in rural northern KZN, which is mostly rural and poor with high levels of HIV and youth unemployment (over 85% of those aged 18–24 years are unemployed) [17]. DREAMS was rolled-out in 2016 and delivered until the end of 2018 In uMkhanyakude [13,14].

In 2017, the AHRI demographic surveillance was used as a sampling frame to identify and invite a random sample of 3013 AGYW, stratified by age (13–17 and 18–22) and area. This longitudinal cohort was followed prospectively at three specific time points over a 2-year study period: baseline, 12, and 24 months, to study the influence of exposure to DREAMS on HIV outcomes and sexual risk [16]. Up to six contact attempts (at home and by phone) were made at each study time point by a team of experienced researchers.

Data collection

Following informed consent, researchers collected data in the local language (isiZulu) using a structured quantitative questionnaire programmed in REDCap onto a tablet computer [16]. They used interviewer-administered and self-administered tablet-assisted interviews. The interview included questions on sociodemographics, general health, sexual relationships, awareness and uptake of DREAMS, migration, and gender norms. Interviewers took a Dried Blood Spot (DBS) at baseline and follow-up. They were consented separately for HSV-2 testing on DBS and storage of DBS for future testing, that included for sexually transmitted infections. At the end-line survey, informed consent was obtained separately for DBS, HSV-2 testing, HIV antibody and viral load testing, and retrospective HIV antibody testing on stored DBS. All participants were also offered point-of-care HIV testing and linkage to services. Those who were not found at end-line survey but had provided consent for their DBS to be stored and tested for future testing that included sexually transmitted infections, as approved by a research ethics committee, were included in the retrospective HIV antibody testing and viral load testing. For sexual behaviour questions, violence and other sensitive questions, participants were given the tablet to complete a self-interview; the research assistants were available to provide support and referral as required.

Laboratory

We used the HerpeSelect2 ELISA IgG assay (FOCUS Diagnostics, Cypress, California, USA) for the qualitative detection of human IgG class antibodies to HSV-2 on DBS samples collected on Whatman 903 filter cards [18]. A 6 mm diameter punch of a DBS spot was incubated overnight in 150 μL Assay Diluent and the assay was performed with 50 μL of the eluent in accordance with the manufacturer's instructions. Following optimization studies comparing DBS with plasma samples, we multiplied the mean cut-off calibrator absorbance values by a factor of 1.5 before determining the index value for each sample [19,20].

We retrieved samples from participants who had consented to be tested for HIV and tested them using the Genscreen ULTRA HIVAg-Ab ELISA immunoassay (BioRad, Marnes-la-Coquette, France). A 4.7 mm punch spot of DBS was incubated overnight, the eluate was assayed as per the manufacturer's instructions. Optical density measurements were read using an ELx800 Universal microplate reader (BioTek, Vermont, USA) and calculations were performed using the Gen5 v3.03 (BioTek).

HIV viral loads were measured on all serology positive samples. Nucleic acid extraction was performed using the automated EasyMag magnetic bead-based extraction protocol on the Nuclisens easyMAG instrument (bio-Merieux, Marcy l'Etoile, France). 2 × 50 mm DBS spots were incubated in the NucliSens Lysis Buffer (2 ml) for 1 h with rotation. The supernatant was transferred to the onboard consumables containing magnetic silica beads and an internal control. The eluted nucleic acids were aliquoted for testing using the Generic HIV Charge Viral assay (Biocentric, Bandol, France). The quantitative qPCR assay was performed using the CFX-96 Touch instrument and analysed using the CFX Manager Software v3.0. Standard curves were calculated per run while baselines were set manually.

All laboratory tests underwent internal and external quality control. An incident HSV-2 or HIV individual was defined as having been negative at baseline and positive at follow-up. Those who were equivocal at follow-up were not considered seroconversions.

Measures

Exposure definitions

Exposure to DREAMS intervention was defined as self-reported receipt of an invitation to participate in DREAMS activities and/or participation in DREAMS activities that were provided by known DREAMS implementing organizations in the baseline (2017) and/or 2018 interview. Eleven organisations were receiving DREAMS funding to deliver 28 different interventions, grouped into categories: HIV testing services; condom promotion and provision; expanding contraception mix; post violence care; PrEP for young women who sell sex; social asset building; social protection; parenting/caregiver programmes; community mobilisation and norms change; and targeting male partners of AGYW [13,14]. Of the AGYW who were invited to participate in DREAMS activities (2017 and/or 2018), 88.2% received three or more interventions and 96.3% received two or more interventions [13].

Outcome definitions

For HIV and HSV-2 incidence analysis, we included participants who had at least two or more test results with the first test being negative. The seroconversion dates were estimated at the midpoint between the date of the last negative and first positive test result. All participants who remained negative throughout the study were censored at their last negative test date. Transmissible HIV was defined as being HIV positive with a detectable HIV viral load ($\geq$50 copies/ml) on their last available DBS. Those who only provided a DBS at baseline were excluded.

Explanatory variables included age and other socio-demographic variables: level of education (in school or completed school), geographic area (urbanicity); household wealth index calculated using principal component analysis based on household asset ownership and access to safe drinking water and sanitation; food insecurity defined as any report of reducing the size of food portions or skipping meals by any member of a household as there was not enough money to buy food in the past 12 months; and migration status (defined as ever having moved outside or within the surveillance area since the age of 13). A composite categorical variable with three levels (coded as 0 if never had sex, 1 if ever had sex but never pregnant and 2 if ever pregnant) was generated to measure sexual and pregnancy history. All explanatory variables were measured at baseline in 2017.

Statistical analysis

We calculated the proportion of AGYW who were enrolled and consented to either HSV-2 or HIV testing at baseline and follow-up. HIV, HSV-2, and transmissible viral load prevalence were calculated at baseline, and at follow-up among participants who have at least one follow-up HIV or HSV-2 test results. A directed acyclic graph (DAG) was constructed to identify a set of variables to adjusted for to control for confounding when estimating the association between DREAMS exposure and the outcome [21]. In the DAG, we included individual and household characteristics, DREAMS exposure and the outcome variable to show the hypothesized causal links between these variables. We conducted multivariable regression analysis (adjusted for confounders identified in the DAG) to measure the effect of DREAMS exposure on HIV incidence, HSV-2 incidence, and transmissible HIV. We calculated HIV and HSV-2 incidence per 100 person-years and used a multivariable Poisson regression model, adjusting for potential confounders identified in the DAG, to estimate the rate ratio of the outcome comparing AGYW with exposure to DREAMS compared with those without exposure. Follow-up time was split up according to an AGYW's current age, distinguishing the age groups 13–14, 15–17, 18–19 and 20–24 years, when controlling for age group in multivariate analysis.

For transmissible HIV, which was measured cross-sectionally, we first performed a classic logistic regression to explore the association of the explanatory variables that were identified in the DAG with prevalence of transmissible HIV. We then used logistic regression to predict the percentage of AGYW with the outcome in two counterfactual scenarios that all AGYW were invited to DREAMS vs. no AGYW were invited to DREAMS. We first estimated the 'propensity to be invited to DREAMS' by fitting a logistic regression model with 'exposure to DREAMS' as the outcome and explanatory variables that were identified in the DAG as potential confounding variables for the association between DREAMS and the outcome. We then fitted two separate logistic regression models, one among AGYW who were invited to DREAMS and one among AGYW who were not invited to DREAMS; the outcome variable was transmissible HIV and the explanatory variables were age group and the propensity score. After fitting these two models, we used the first to predict the probability of the outcome (transmissible HIV) for all AGYW under the scenario that all were invited to DREAMS, and the second to predict the probability of the outcome for all AGYW under the scenario that none were invited to DREAMS. We calculated the average of these probabilities for each of the two alternative scenarios, and from that estimated the difference between them, with 95% confidence intervals estimated using bootstrapping. We checked the robustness of the 'propensity-score regression adjustment' estimates by comparing them with predictions from a multivariable logistic regression model of the outcome on explanatory variables, with estimates from stratification on the propensity score, and with "inverse probability of treatment" weighting' (IPTW) based on the propensity score. Item-specific missing data was uncommon; we used analysis-specific complete case analysis.

Ethics approval

Approval of the DREAMS Partnership impact evaluation protocol was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BFC339/ 19), the AHRI Somkhele Community Advisory Board, and the London School of Hygiene & Tropical Medicine Research Ethics Committee (REF11835). Additional ethical approval for secondary data analysis was attained from University College London (18321/001). Written consent was provided from participants aged 18 years or older, and for participants below 18 years of age, written parental consent, and participant assent was obtained.

Results

Participants

Figure 1 shows that 2184 (86.4%) of those eligible agreed to participate in the cohort. $n = 1853$ (84.8%) and 1712 (78.4%) were retained at year 1 and year 2 follow-up respectively; $n = 2016$ (92.3%) had at least one follow-up survey. Consent to HSV-2 and HIV testing was high (92–95%) in all rounds.

At baseline (Table 1), median age was 16 years, three quarters were still attending school, 31% described food insecurity, 64% lived in rural areas, and 20% had migrated since the age of 13 years. The majority (59%) had not yet reported sex. Those who had at least one follow-up HSV-2 or HIV test results were younger, more likely to be in school and less likely to have migrated or had sex compared with those not contributing follow-up data (Table 1). The majority (54%) of AGYW included in follow-up analysis had been exposed to DREAMS (Table 1).

Exposure to DREAMS and HIV and herpes simplex virus type 2 outcomes

Table 1 shows $n = 1030$ (54%) were invited to or received DREAMS in 2017 and/or 2018. $n = 259$ (11.8%) were HIV-positive at baseline (either knew their status or tested positive on DBS); 70 (6.1%) and 189 (18.2%) of 13–17 and 18–22-year-olds, respectively. Overall HIV incidence was 2.2/100 person-years 95% CI (1.66–2.86) and HSV-2 incidence was 17.3/100 person-years 95% CI

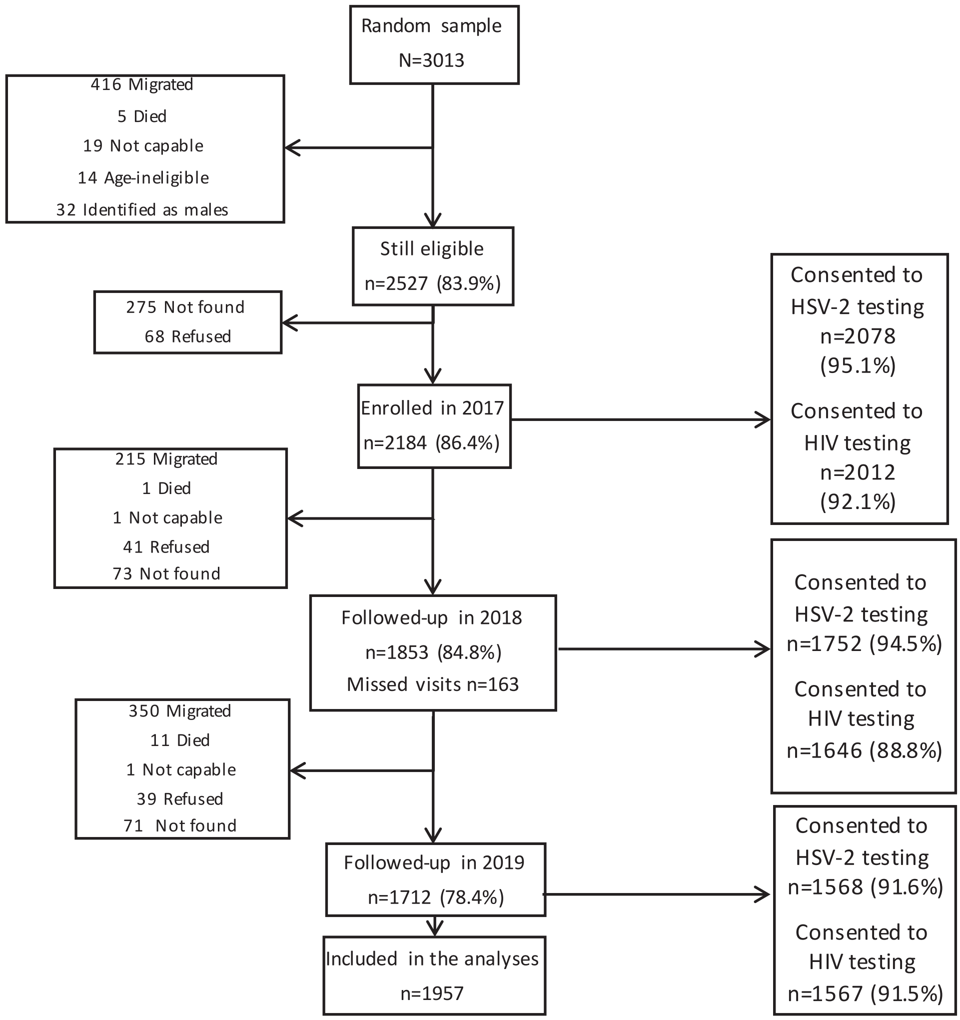

Fig. 1. Flow chart of cohort recruitment and follow-up 2017–2019.

(15.5–19.4). $n = 169$ (8.9%) had a detectable HIV viral load at last measure.

HIV and herpes simplex virus type 2 incidence by DREAM exposure

HIV incidence was 2.75 (1.91–3.96)/100 person-years in those unexposed to DREAMS, compared with 1.73 (1.15–2.60)/100 person-years in those exposed to DREAMS. After adjusting for potential confounding factors, there was no evidence of an association between DREAMS exposure and HIV incidence: adjusted rate ratio (adjRR) 0.83; 95% CI of 0.46–1.52. Findings in the younger age group (aged 13–17) and the older age group (18–22) were similar (Fig. 2a). Beyond age, the only characteristic (Table 2) for which there was evidence of association with HIV incidence was peri-urban/urban setting adjRR 1.89: 95% CI (1.05–2.39).

HSV-2 incidence was 18.8 (15.9–22.1)/100 person-years in those unexposed to DREAMS, compared with 16.3 (14.0–18.9)/100 person-years in those exposed to DREAMS. As with HIV incidence, there was no evidence of an association between DREAMS exposure and HSV-2incidenceafter adjusting for potential confounding factors: adjRR 0.96: 95% CI 0.76–1.23. Findings in the younger age group (aged 13–17 years) and the older age group (18–22 years) were similar (Fig. 2a).

Age and ever having sex were the only factors that remained associated with HSV-2 incidence after adjustment (Table 3).

Transmissible HIV by DREAMS exposure

Prevalence of transmissible HIV was 87/865 (10.1%) in those who had not received DREAMS compared with 82/1030 (8.0%) in those who had received DREAMS, with no evidence of a DREAMS effect after adjusting for potential confounding factors using multivariable logistic regression: adjOR 1.14; 95% CI 0.79–1.64. Those who lived in a peri-urban/urban area, were out of school and had not completed secondary education at baseline, had

Table 1. Characteristics of adolescent girls and young women who were enrolled and consented to herpes simplex virus type 2 or HIV testing.

	All AGYW	AGYW consent HSV-2/HIV testing baseline (2017)	AGYW consented to HSV-2/HIV testing at follow-up (2018/2019)			
	n (%)	*n* (%)	All *n* (%)	Invited/received DREAMS by 2018 *n* (%)	Never Invited/ received DREAMS by 2018 *n* (%)	Chi-square test *P* value
Total	**2184**	**2078 (95.1)**	**1957 (89.6)**	**1056 (54.0)**	**901 (46.0)**	
Age group						<0.001
13–14	460 (21.1)	445 (20.4)	435 (22.2)	261 (24.7)	174 (19.3)	
15–17	688 (31.5)	667 (30.5)	638 (32.6)	430 (40.7)	208 (23.1)	
18–19	475 (21.7)	442 (20.2)	413 (21.1)	200 (18.9)	213 (23.6)	
20–22	561 (25.7)	524 (24.0)	471 (24.1)	165 (15.6)	306 (34.0)	
Currently in school						<0.001
No	540 (24.7)	498 (22.8)	443 (22.6)	140 (13.3)	303 (33.6)	
Yes	1644 (75.3)	1580 (72.3)	1514 (77.4)	916 (86.7)	598 (66.4)	
Age and education						<0.001
13–17 or 18–22 and in school	1664 (76.3)	1600 (73.3)	1529 (78.2)	924 (87.5)	605 (67.2)	
18–22 and not completed secondary	188 (8.6)	175 (8.0)	161 (8.2)	52 (4.9)	109 (12.1)	
18–22 and completed secondary	330 (15.1)	301 (13.8)	266 (13.6)	80 (7.6)	186 (20.7)	
Socio-economic status						0.009
Low	727 (35.1)	700 (32.1)	674 (35.8)	398 (38.9)	276 (32.2)	
Middle	747 (36.0)	717 (32.8)	677 (36.0)	354 (34.6)	323 (37.6)	
High	600 (28.9)	558 (25.5)	530 (28.2)	271 (26.5)	259 (30.2)	
Food insecurity						0.077
No	1497 (68.7)	1419 (65.0)	1342 (68.8)	742 (70.5)	600 (66.7)	
Yes	682 (31.3)	656 (30.0)	610 (31.3)	311 (29.5)	299 (33.3)	
Geographic area						<0.001
Rural	1388 (64.1)	1325 (60.7)	1252 (64.6)	724 (69.2)	528 (59.1)	
Peri-urban/urban	777 (35.9)	734 (33.6)	687 (35.4)	322 (30.8)	365 (40.9)	
Migrated/moved						<0.001
No	1781 (81.5)	1703 (78.0)	1616 (82.6)	911 (86.3)	705 (78.2)	
Yes	403 (18.5)	375 (17.2)	341 (17.4)	145 (13.7)	196 (21.8)	
Ever had sex, ever pregnant						<0.001
Never had sex	1273 (58.7)	1209 (55.4)	1174 (60.4)	722 (68.6)	452 (50.7)	
Ever sex, never pregnant	308 (14.2)	293 (13.4)	264 (13.6)	122 (11.6)	142 (15.9)	
Ever pregnant	588 (27.1)	563 (25.8)	507 (26.1)	209 (19.8)	298 (33.4)	
HIV prevalence						<0.001
Negative	1776 (81.3)	1623 (74.3)	1669 (85.3)	920 (87.1)	749 (83.1)	
Positive	236 (10.8)	270 (12.4)	288 (14.7)	136 (12.9)	152 (16.9)	
Did not consent	172 (7.9)					
HSV-2 prevalence						<0.001
Negative	1525 (69.8)	1116 (51.1)	1153 (58.9)	665 (63.0)	488 (54.2)	
Positive	553 (25.3)	777 (35.6)	804 (41.1)	391 (37.0)	413 (45.8)	
Did not consent	106 (4.9)					
Transmissible viral load						0.158
<50	1835 (91.2)	1733 (79.3)	1785 (91.2)	972 (92.0)	813 (90.2)	
≥50	139 (6.9)	160 (7.3)	172 (8.8)	84 (8.0)	88 (9.8)	
Insufficient sample (not testable)	38 (1.9)					

AGYW, adolescent girls and young women;DREAMS, Determined, Resilient, Empowered, AIDS free, Mentored and Safe;HSV-2, herpes simplex virus type 2.

migrated, and who had sex or had been pregnant were more likely to have transmissible HIV (Table 4). The propensity-score adjusted analysis, to compare the scenarios that all versus no AGYW were exposed to DREAMS (Fig. 2b), similarly found no evidence of an effect of DREAMS on transmissible HIV, with an estimated difference in the percentage with a detectable HIV viral load of 0.99%: 95% CI (−1.52 to 3.82)%. Findings about the association between DREAMS exposure and transmissible HIV were similar in the younger age group (aged 13−17 years) and the older age group (18−22 years).

Discussion

In this representative cohort of women aged 13−22 years, half of whom were invited to DREAMS (all of whom

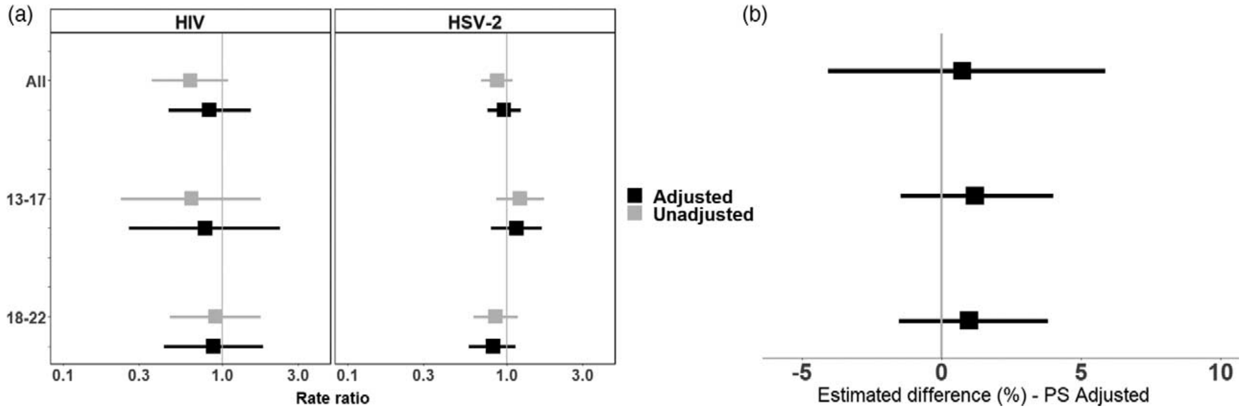

Fig. 2. Comparing incident HIV, herpes simplex virus type 2, and transmissible HIV between DREAMS exposed and unexposed adolescent girls and young women.

received at least one of the combination HIV prevention interventions) [13], we found no evidence that exposure to DREAMS was associated with reduction in sexual risk as evidenced by HSV-2 incidence. After 2 years of exposure to DREAMS combination prevention, there was no evidence of impact on HIV incidence or transmissible HIV (defined as detectable HIV viral load). Women who lived in peri-urban/urban areas, had recently left school, had a history of migration and were sexually active were at most risk of poor HIV outcomes.

It is plausible that overall declines in HIV incidence, attributable to a reduction in levels of untreated HIV infection among male sexual partners of AGYW may

Table 2. Association between DREAMS and HIV incidence among adolescent girls and young women.

	Person-years	*n* HIV-positive	Incidence rate	Unadjusted rate ratio (95% CI)	Age-adjusted rate ratio (95% CI)	Fully adjusted rate ratio (95% CI)	Likelihood ratio (LR) *P* value
Invited or received DREAMS in 2017/2018							0.549
No	1054	29	2.8	1	1	1	
Yes	1329	23	1.7	0.63 (0.36–1.09)	0.78 (0.44–1.36)	0.83 (0.46–1.52)	
Current age							0.449
13–17	1439	15	1.0	1		1	
18–19	475	19	4.0	2.57 (1.23–5.39)		1.74 (0.73–4.15)	
20–24	469	18	3.8	3.50 (1.81–6.76)		1.40 (0.51–3.84)	
Geographic area							0.034
Rural	1528	25	1.6	1	1	1	
Peri-urban/urban	830	27	3.3	1.99 (1.15–3.43)	1.96 (1.14–3.38)	1.89 (1.05–3.39)	
Socio-economic status							0.316
Low	838	23	2.7	1	1	1	
Middle	811	16	2.0	0.72 (0.38–1.36)	0.71 (0.37–1.34)	0.66 (0.34–1.28)	
High	649	11	1.7	0.62 (0.30–1.27)	0.63 (0.31–1.29)	0.60 (0.28–1.29)	
Age and education							0.358
13–17 or 18–22 and in school	1962	34	1.7	1	1	1	
18–22 and not completed secondary	148	9	6.1	3.51 (1.68–7.32)	1.96 (0.85–4.54)	1.79 (0.73–4.38)	
18–22 and completed secondary	272	9	3.3	1.91 (0.92–3.99)	1.06 (0.45–2.48)	0.98 (0.39–2.46)	
Food insecurity							0.674
No	1671	31	1.9	1	1	1	
Yes	706	21	3.0	1.60 (0.92–2.79)	1.27 (0.72–2.24)	1.14 (0.62–2.11)	
Ever had sex, ever pregnant							0.278
Never had sex	1568	18	1.1	1	1	1	
Ever sex, never pregnant	266	7	2.6	2.29 (0.96–5.48)	1.68 (0.64–4.41)	1.54 (0.58–4.10)	
Ever pregnant	537	24	4.5	3.89 (2.11–7.17)	2.78 (1.26–6.14)	2.02 (0.85–4.78)	
Migrated/moved							0.174
No	2036	36	1.8	1	1	1	
Yes	347	16	4.6	2.61 (1.45–4.70)	1.85 (0.99–3.46)	1.60 (0.81–3.16)	

CI, confidence interval;DREAMS, Determined, Resilient, Empowered, AIDS free, Mentored and Safe;HSV-2, herpes simplex virus type 2.

Table 3. Association between DREAMS and herpes simplex virus type 2 incidence among adolescent girls and young women.

	Person years	*n* HSV-2 positive	Incidence rate	Unadjusted rate ratio (95% CI)	Age adjusted rate ratio (95% CI)	Fully adjusted rate ratio (95% CI)	LR *P* value
Invited or received DREAMS in 2017/2018							0.759
No	741	139	18.8	1	1	1	
Yes	1032	168	16.3	0.87 (0.69–1.09)	0.99 (0.79–1.25)	0.96 (0.76–1.23)	
Current age							0.002
13–14	519	57	11.0	1		1	
15–17	656	94	14.3	1.66 (1.09–2.55)		1.56 (1.02–2.40)	
18–19	322	85	26.4	2.68 (1.73–4.15)		2.17 (1.36–3.46)	
20–24	276	71	25.7	3.30 (2.16–5.05)		2.55 (1.53–4.25)	
Geographic area							0.084
Rural	1126	212	18.8	1	1	1	
Peri-urban/urban	628	94	15.0	0.79 (0.62–1.01)	0.79 (0.62–1.01)	0.80 (0.62–1.03)	
Socio-economic status							0.751
Low	639	122	19.1	1	1	1	
Middle	584	102	17.5	0.92 (0.70–1.19)	0.94 (0.72–1.22)	0.95 (0.73–1.24)	
High	484	73	15.1	0.79 (0.59–1.06)	0.82 (0.61–1.09)	0.89 (0.66–1.20)	
Age and education							0.505
13–17 or 18–22 and in school	1515	241	15.9	1	1	1	
18–22 and not completed secondary	74	25	33.7	2.12 (1.40–3.20)	1.24 (0.79–1.96)	1.09 (0.67–1.76)	
18–22 and completed secondary	184	41	22.3	1.40 (1.01–1.95)	0.82 (0.56–1.20)	0.83 (0.56–1.23)	
Food insecurity							0.531
No	1256	193	15.4	1	1	1	
Yes	510	114	22.4	1.45 (1.15–1.83)	1.23 (0.97–1.56)	1.08 (0.84–1.39)	
Ever had sex, ever pregnant							0.028
Never had sex	1278	171	13.4	1	1	1	
Ever sex, never pregnant	161	49	30.5	2.28 (1.66–3.13)	1.68 (1.18–2.37)	1.62 (1.13–2.33)	
Ever pregnant	323	85	26.3	1.97 (1.52–2.55)	1.36 (0.98–1.87)	1.34 (0.95–1.89)	
Migrated/moved							0.895
No	1546	257	16.6	1	1	1	
Yes	227	50	22.0	1.33 (0.98–1.80)	0.98 (0.72–1.35)	1.02 (0.73–1.43)	

CI, confidence interval; DREAMS, Determined, Resilient, Empowered, AIDS free, Mentored and Safe; LR, Likelihood ratio.

have prevented us from showing small reductions in HIV incidence attributable to DREAMS itself [22,23]. However, we also found that DREAMS did not impact on sexual risk or prevalence of transmissible HIV, the two pathways through which we hypothesized DREAMS would reduce HIV incidence. This is consistent with other findings from our setting, that is, that DREAMS did not affect any of the behavioural drivers of sexual risk, including condom use, transactional sex or number of sexual partners. It remains to be investigated if DREAMS exposure had an impact on transmissible HIV amongst male partners in our setting.

These disappointing findings may in part be explained by the fact that DREAMS exposure was greater in younger than older AGYW: those still in school and who had not yet reached sexual debut even during the follow-up period. Key outcomes, on the other hand, were more common in older age groups: those who had left school and had a history of migration. It is plausible that over a longer follow-up period, and as this younger cohort age into their sexual debut, we will start to observe an impact of earlier exposure to DREAMS [14,24].

Our analysis confirms the importance of structural factors in driving HIV risk and poor outcomes [5,9,25,26]. We found that young women who have left the relative protection of school and who had a history of migration were more vulnerable to poor sexual health and HIV outcomes. DREAMS, whilst emphasizing some aspects of social asset building, such as cash transfers and school grants, had limited income generation and training activities that appeal to young women transitioning from school into employment [14,15]. Moreover, our process evaluation suggested that retention in curricular-based interventions to change social and gender norms was challenging for young women [14,15,27,28]. Our findings support calls for more radical and fundamental structural interventions to build social capital and create a more enabling environment for young women who are not in education, employment, or training [14,29,30].

DREAMS, whilst ambitious in scope, did not explicitly tackle the well described barriers to AGYW accessing sexual reproductive and HIV treatment services within primary healthcare settings [27,28,31]. Implementing partners delivered community-based HIV testing (which increased testing uptake) but not sexual and reproductive health or HIV care [15]. Work from both our group and others have consistently found that young men and women (aged <30 years) often do not access HIV care, even after diagnosis [32,33]. A similar pattern is seen in sexual and reproductive health seeking, and this has led to

Table 4. Logistic regression: association between DREAMS and transmissible HIV among adolescent girls and young women aged 13–22 years.

	Total	*n* with viral load ≥50 (%)	Unadjusted OR (95% CI)	Age-adjusted OR (95% CI)	Fully adjusted OR (95% CI)	LR *P* value
Invited or received DREAMS, 2017/2018						
No	865	87 (10.1)	1	1	1	
Yes	1030	82 (8.0)	0.77 (0.56–1.06)	0.99 (0.71–1.38)	1.14 (0.79–1.64)	0.477
Age group, 2017						
13–14	433	10 (2.3)	0.13 (0.06–0.25)		0.37 (0.15–0.90)	
15–17	623	43 (6.9)	0.40 (0.27–0.60)		1.01 (0.55–1.84)	
18–19	404	48 (11.9)	0.73 (0.49–1.08)		0.94 (0.59–1.51)	
20–22	435	68 (15.6)	1		1	0.071
Geographic area						
Rural	1214	86 (7.1)	1	1	1	
Peri-urban/urban	663	82 (12.4)	1.85 (1.35–2.55)	1.86 (1.35–2.57)	1.91 (1.34–2.72)	<0.001
Socioeconomic status, 2017						
Low	653	64 (9.8)	1	1	1	
Middle	656	59 (9.0)	0.91 (0.63–1.32)	0.92 (0.63–1.34)	0.86 (0.58–1.29)	
High	513	37 (7.2)	0.72 (0.47–1.09)	0.76 (0.50–1.17)	0.71 (0.45–1.13)	0.356
Food insecurity, 2017						
No	1308	96 (7.3)	1	1	1	
Yes	582	73 (12.5)	1.81 (1.31–2.50)	1.42 (1.02–1.98)	1.20 (0.83–1.73)	0.329
Age and education, 2017						
13–17 or 18–22 and in school	1497	99 (6.6)	1	1	1	
18–22 and not completed secondary	152	42 (27.6)	5.39 (3.58–8.12)	3.13 (1.91–5.11)	2.96 (1.72–5.10)	
18–22 and completed secondary	245	28 (11.4)	1.82 (1.17–2.84)	1.05 (0.62–1.77)	1.05 (0.60–1.84)	<0.001
Migrated/moved, 2017						
No	1571	115 (7.3)	1	1	1	
Yes	324	54 (16.7)	2.53 (1.79–3.59)	1.66 (1.15–2.41)	1.50 (1.00–2.25)	0.05
Ever had sex, ever pregnant composite variable, 2017						
Never had sex	1158	51 (4.4)	1	1	1	
Ever sex, never pregnant	249	45 (18.1)	4.79 (3.12–7.34)	3.16 (1.95–5.13)	2.55 (1.52–4.30)	
Ever pregnant	476	69 (14.5)	3.68 (2.52–5.38)	2.27 (1.41–3.65)	1.79 (1.06–3.00)	0.002

CI, confidence interval; DREAMS, Determined, Resilient, Empowered, AIDS free, Mentored and Safe; LR, Likelihood ratio; OR, odds ratio.

a high burden of sexually transmitted infections [34] and teenage pregnancy [27]. Despite the growing evidence on the effectiveness of community-based HIV care [35], particularly for adolescents living with HIV [36–38], HIVand sexual reproductive care in DREAMS remained facility-based. This may partly account for the limited effect of exposure to DREAMS on HIV viral load amongst the AGYW (Supplementary Table, http:// links.lww.com/QAD/C430; Supplementary Figure, http:// links.lww.com/QAD/C431).

Finally, we looked at the effect of any DREAMS exposure on sexual behaviour and HIV outcomes in AGYW but not at the effect of different amounts of exposure, different patterns of layering, or the fidelity of the intervention content. In work presented elsewhere, we have shown that exposure and layering increased with time and that over 80% of those invited received at least three interventions [13]. Our in-depth ethnographic mapping, however, illustrated some of the challenges that multiple implementing partners faced in scaling-up this complex and multifaceted intervention [15,28] and the competing priorities for out of school women making it difficult for them to engage, either fully or at all, in curriculum-based interventions [14,27]. It is, therefore, plausible that longer and more sustained DREAMS like combination prevention intervention, led by AGYW that also integrates employability and livelihoods into the curriculum-based interventions, would have greater impact [29].

Strengths and limitations

The strength of our study was our ability to prospectively measure exposure to the DREAMS intervention and biological measures of sexual risk and HIV in a representative sample of AGYW. With over 80% response rate and over 90% contributing to the outcome, we are confident that our sample is representative of the experience of DREAMS roll out amongst AGYW in this poor rural community of South Africa. However, our study was observational and we cannot exclude the possibility that those who are exposed to DREAMS are systematically different to those who are not in ways that impact on the outcome but which we did not capture sufficiently in our data collection or account for in our analyses. We attempted to measure key dimensions of sexual risk at baseline, and adjusted for these in our analyses, but we may not have fully accounted for these differences, and if so, there will be residual confounding. Given that for all outcomes the proportion with a poor outcome was lower among those exposed to DREAMS than among those not exposed, it is possible that systematic channelling bias may have masked a real effect of DREAMS exposure. Another limitation is that we did not track ‘dose’ of exposure and counted any invitation or participation in a DREAMS intervention as an exposure.

In conclusion, in this evaluation of a real-world scale-up of a promising combination HIV prevention intervention, we did not find a short-term effect (over 2 years) of DREAMS exposure on sexual risk or HIV outcomes in a representative cohort of AGYW. Sexually active young women who had left school, had a history of migration and were residing in small urban and peri-urban areas had worse sexual risk and HIVoutcomes. This suggests a need to improve engagement of older adolescents and young women in DREAMS and DREAMS like interventions with more fundamental structural interventions that build social capital and strengthen health systems for older adolescents and young women.

Acknowledgements

The authors acknowledge the AHRI research team including the research assistants (B. Mbatha, D. Mkhwanazi, K. Ngobese, N. Buthelezi, G. Buthelezi, N. Fakude, N. Mbatha, S. Nsibande, S. Ntshangase, S. Mnyango, Th. Dlamini, Z. Cumbane, Z. Mathenjwa, M.Zikhali, N. Mpanza, S. Xulu, X. Ngwenya, Zakhele Xulu, Z. Mthethwa, S. Hlongwane) and research administrators, especially A. Jalazi and S. Mbili, for their commitment to the study. We also extend our appreciation to our research community including the community advisory boards in uMkhanyakude district. We also thank the AHRI Clinical Laboratory Staff for their role in preparation of clinical specimen kits, processing and testing of samples.

Consent for publication: not applicable.

Availability of data and materials: the datasets generated and/or analyzed during the current study are available in the AHRI repository and will be made available prior to publication

Funding: this work was supported by the Bill & Melinda Gates Foundation, Grant Number OPP1136774 and

OPP1171600 and the National Institutes of Health under award number 5R01MH114560-03, Africa Health Research Institute is supported by a grant from the Wellcome Trust (Grant numbers 082384/Z/07/Z and 210479/Z/18/Z). The AHRI population surveillance is partially funded by DSI-MRC South Africa Population Research Network. G.H. is supported by a fellowship from the Wellcome Trust and Royal Society (210479/Z/18/Z). N.M. is a recipient of an NIHR Research Professorship award (Ref: RP-2017-08-ST2-008). Funding bodies were not involved in the design of the study, data collection, analysis, or interpretation of the data. This research was funded in part by Wellcome Trust (Grant numbers 082384/Z/07/Z and 210479/Z/18/Z). For the purpose of open access the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Authors' contributions: M.S., I.B., and S.F. conceived and designed the study. M.S. prepared the first and final draft of the manuscript, N. Mthiyani conducted all the statistical analysis and contributed to the first and all drafts of the manuscript. N.C. and C.H. managed the project, developed, and piloted the data collection tools, training, and implementation. J.D. led all aspects of data management, curating, and quality control. S.F., K.B., G. H., and N. McGrath, supported data analysis and interpretation. All authors read and commented on iterations of the manuscript and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

References

1. Chimbindi N, Mthiyane N, Birdthistle I, Floyd S, McGrath N, Pillay D, *et al*. **Persistently high incidence of HIV and poor service uptake in adolescent girls and young women in rural KwaZulu-Natal, South Africa prior to DREAMS.** *PLoS One* 2018; **13**:e0203193.
2. Human Sciences Research Council (HSRC). The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017 HIV Impact Assessment Summary Report. In. Edited by Press H. Cape Town; 2018.
3. UNAIDS. HIV prevention among adolescent girls and young women Putting HIV prevention among adolescent girls and youngwomen on the Fast-Track and engaging men and boys. In: UNAIDS 2016.
4. 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.
5. Pettifor A, Stoner M, Pike C, Bekker L-G. **Adolescent lives matter: preventing HIV in adolescents.** *Current opinion in HIV and AIDS* 2018; **13**:265–273.
6. Gupta GR, Parkhurst JO, Ogden JA, Aggleton P, Mahal A. **Structural approaches to HIV prevention.** *Lancet* 2008; **372**:764–775.
7. Pronyk PM, Kim JC, Abramsky T, Phetla G, Hargreaves JR, Morison LA, *et al*. **A combined microfinance and training intervention can reduce HIV risk behaviour in young female participants.** *AIDS* 2008; **22**:1659–1665.
8. Wagman JA, Gray RH, Campbell JC, Thoma M, Ndyanabo A, Ssekasanvu J, *et al*. **Effectiveness of an integrated intimate partner violence and HIV prevention intervention in Rakai, Uganda: analysis of an intervention in an existing cluster randomised cohort.** *Lancet Glob Health* 2015; **3**: e23–e33.
9. Cluver LD, Orkin FM, Campeau L, Toska E, Webb D, Carlqvist A, Sherr L. **Improving lives by accelerating progress towards the UN Sustainable Development Goals for adolescents living with HIV: a prospective cohort study.** *Lancet Child Adolesc Health* 2019; **3**:245–254.
10. *DREAMS working together for an AIDS free future for girls and women.* Washington DC: Office of the U.S. Global AIDS Coordinator; 2018.
11. *Dreaming of an AIDS-Free Future.* Washington D.C, USA: Office of the U.S. Global AIDS Coordinator; 2018.
12. Saul J, Bachman G, Allen S, Toiv NF, Cooney C, Beamon TA. **The DREAMS core package of interventions: a comprehensive approach to preventing HIV among adolescent girls and young women.** *PLoS One* 2018; **13**:e0208167.

13. Gourlay A, Birdthistle I, Mthiyane NT, Orindi BO, Muuo S, Kwaro D, *et al*. **Awareness and uptake of layered HIV prevention programming for young women: analysis of population-based surveys in three DREAMS settings in Kenya and South Africa.** *BMC Public Health* 2019; **19**:1417.
14. Chimbindi N, Birdthistle I, Floyd S, Harling G, Mthiyane N, Zuma T, *et al*. **Directed and target focused multisectoral adolescent HIV prevention: Insights from implementation of the 'DREAMS Partnership' in rural South Africa.** *J IntAIDS Soc* 2020; **23 (Suppl 5)**:e25575.
15. Chimbindi N, Birdthistle I, Shahmanesh M, Osindo J, Mushati P, Ondeng'e K, *et al*. **Translating DREAMS into practice: early lessons from implementation in six settings.** *PloS one* 2018; **13**: e0208243.
16. Birdthistle I, Schaffnit SB, Kwaro D, Shahmanesh M, Ziraba A, Kabiru CW, *et al*. **Evaluating the impact of the DREAMS partnership to reduce HIV incidence among adolescent girls and young women in four settings: a study protocol.** *BMC Public Health* 2018; **18**:912.
17. Gareta D, Baisley K, Mngomezulu T, Smit T, Khoza T, Nxumalo S, *et al*. **Cohort profile update: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey.** *Int J Epidemiol* 2021; **50**:33–34.
18. Arvin A, Prober C. **Herpes simplex viruses.** In: Murray P, Baron E, Pfaller M, Tenover F, Yolkenet R,editors. *Manual of clinical microbiology*. 6th ed. Washington DC: ASM; 1995. pp. 876–883.
19. Delany-Moretlwe S, Jentsch U, Weiss H, Moyes J, Ashley-Morrow R, Stevens W, *et al*. **Comparison of Focus HerpeSelect and Kalon TM HSV-2 gG2 ELISA serological assays to detect herpes simplex virus type 2 (HSV-2) antibodies in a South African population.** *Sex Transm Infect* 2009; **86**:46–50.
20. Ashley-Morrow R, Nolkamper J, Robinson N, Bishop N, Smith J. **Performance of Focus ELISA test for herpes simplex virus type 1 (HSV-1) and HSV-2 antibodies among women in ten diverse geographicallocations.** *ClinMicrobiol Infect* 2004; **10**:530–536.
21. Greenland S, Pearl J, Robins JM. **Causal diagrams for epidemiologic research.** *Epidemiology* 1999; **10**:37–48.
22. Shahmanesh M, Baisley K, Wambiya E, Khagayi S, Mulwa S, Ziraba A, et al. Reaching young men: Evaluating the impact of DREAMS on HIV testing, care and prevention among young men in three diverse settings. In: AIDS 2020. San Francisco; 2020.
23. Vandormael A, Akullian A, Siedner M, de Oliveira T, Barnighausen T, Tanser F. **Declines in HIV incidence among men and women in a South African population-based cohort.** *Nat Commun* 2019; **10**:5482.
24. Gibbs A, Campbell C, Maimane S. **Can local communities 'sustain' HIV/AIDS programmes? A South African example.** *Health Promot Int* 2015; **30**:114–125.
25. Pettifor A, Lippman SA, Gottert A, Suchindran CM, Selin A, Peacock D, *et al*. **Community mobilization to modify harmful gender norms and reduce HIV risk: results from a community cluster randomized trial in South Africa.** *J Int AIDS Soc* 2018; **21**:e25134.
26. Ranganathan M, Heise L, Pettifor A, Silverwood RJ, Selin A, MacPhail C, *et al*. **Transactional sex among young women in rural South Africa: prevalence, mediators and association with HIV infection.** *J Int AIDS Soc* 2016; **19**:20749.
27. Zuma T, Seeley J, Mdluli S, Chimbindi N, McGrath N, Floyd S, *et al*. **Young people's experiences of sexual and reproductive health interventions in rural KwaZulu-Natal, South Africa.** *Int J Adolesc Youth* 2020; **25**:1058–1075.
28. Zuma T, Seeley J, Sibiya LO, Chimbindi N, Birdthistle I, Sherr L, Shahmanesh M. **The changing landscape of diverse HIV treatment and prevention interventions: experiences and perceptions of adolescents and young adults in rural KwaZulu-Natal, South Africa.** *Front Public Health* 2019; **7**:336.
29. Mannell J, Willan S, Shahmanesh M, Seeley J, Sherr L, Gibbs A. **Why interventions to prevent intimate partner violence and HIV have failed young women in southern Africa.** *J Int AIDS Soc* 2019; **22**:e25380.
30. Campbell C. **Social capital, social movements and global public health: fighting for health-enabling contexts in marginalised settings.** *Soc Sci Med* 2020; **257**:112153.
31. Nkosi B, Seeley J, Chimbindi N, Zuma T, Kelley M, Shahmanesh M. **Managing ancillary care in resource-constrained settings: dilemmas faced by frontline HIV prevention researchers in a rural area in South Africa.** *Int Health* 2020; **12**:543–550.
32. Baisley KJ, Seeley J, Siedner MJ, Koole K, Matthews P, Tanser F, *et al*. **Findings from home-based HIV testing and facilitated linkage after scale-up of test and treat in rural South Africa: young people still missing.** *HIV Med* 2019; **20**:704–708.
33. Iwuji CC, Orne-Gliemann J, LarmarangeJ, Balestre E, Thiebaut R, Tanser F, *et al*. **ANRS 12249 TasP Study Group. Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial.** *Lancet HIV* 2018; **5**:e116–e125.
34. Francis SC, Mthiyane TN, Baisley K, McHunu SL, Ferguson JB, Smit T, *et al*. **Prevalence of sexually transmitted infections among young people in South Africa: A nested survey in a health and demographic surveillance site.** *PLoS Med* 2018; **15**: e1002512.
35. Dave S, Peter T, Fogarty C, Karatzas N, Belinsky N, Pant Pai N. **Which community-based HIV initiatives are effective in achieving UNAIDS 90-90-90 targets? A systematic review and meta-analysis of evidence (2007-2018).** *PLoS One* 2019; **14**:e0219826.
36. Mavhu W, Willis N, MufukaJ, Bernays S, Tshuma M, Mangenah C, *et al*. **Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial.** *Lancet Glob Health* 2020; **8**:e264–e275.
37. Kanters S, Park JJ, Chan K, Ford N, Forrest J, Thorlund K, *et al*. **Use of peers to improve adherence to antiretroviral therapy: a global network meta-analysis.** *J IntAIDS Soc* 2016; **19**:21141.
38. Bernays S, Tshuma M, Willis N, Mvududu K, Chikeya A, Mufuka J, *et al*. **Scaling up peer-led community-based differentiated support for adolescents living with HIV: keeping the needs of youth peer supporters in mind to sustain success.** *J Int AIDS Soc* 2020; **23 (Suppl 5)**:e25570.