PrEP uptake and HIV viral suppression when PrEP is integrated into Ugandan ART clinics for HIV-negative members of HIV-serodifferent couples: A stepped wedge cluster randomized trial

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Summary

Background Global scale-up of HIV pre-exposure prophylaxis (PrEP) includes services to HIV-negative people in partnerships with people living with HIV (serodifferent couples). Data are needed on HIV outcomes, including uptake and adherence to PrEP and antiretroviral treatment (ART), to describe the impact of integrating PrEP into an existing HIV program.

Methods Using a stepped-wedge cluster randomized trial design, we launched PrEP delivery for HIV-negative members of serodifferent couples in Uganda by integrating PrEP into existing ART programs for people living with HIV. The program provided PrEP training for ART providers, ongoing technical assistance, and a provisional supply chain mechanism for PrEP medication. Primary data on PrEP initiation, PrEP refills, ART initiation, and HIV viremia at 6 months (measured at 42-270 days) were collected through data abstraction of medical records from HIV-serodifferent couples sequentially enrolling at the ART clinics. Modified Poisson regression models, controlling for time and cluster, compared viral suppression (<1000 copies/ml) before and after launch of the PrEP program. This trial was registered at ClinicalTrials.gov, NCT03586128.

Findings From June 1, 2018-December 15, 2020, 1,381 HIV-serodifferent couples were enrolled across 12 ART clinics in Kampala and Wakiso, Uganda, including 730 enrolled before and 651 after the launch of PrEP delivery. During the baseline period, 99.4% of partners living with HIV initiated ART and 85.0% were virally suppressed at 6 months. Among HIV-negative partners enrolled after PrEP launched, 81.0% (527/651) initiated PrEP within 90 days of enrolling; among these 527, 11.2% sought a refill 6 months later. In our powered intent-to-treat analysis, 82.1% and 76.7% of partners living with HIV were virally suppressed, respectively, which was not a statistically significant difference (RR=0.94, 95% CI: 0.82-1.07) and was stable across sensitivity analyses.

Interpretation Integration of PrEP into ART clinics reached a high proportion of people in HIV-serodifferent relationships and did not improve the already high frequency of HIV viral suppression among partners living with HIV.

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Keywords: PrEP; Serodifferent couples; ART; Viral suppression; Stepped-wedge trial

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Research in context

Evidence before this study

Prior to this study, it was known that PrEP and ART are each highly effective methods for HIV prevention, including for HIV-serodifferent couples. Open-label evaluations found that using PrEP as a bridge to ART and viral suppression in couples was highly effective at preventing HIV transmission.

Added value of this study

This study is one of the first to evaluate the impact of widescale PrEP delivery when integrated into ART clinics and adds information about the impact of the PrEP component on the existing ART service. We find that PrEP can be delivered well and there is no meaningful impact on the ART component.

Implications of all the available evidence

The findings from our study indicate that ART clinics with programs for HIV-serodifferent couples are suitable environments for PrEP delivery. Integrating PrEP into the existing program is likely to result in good uptake of short-term PrEP use and likely to yield no change in the levels of viral suppression among the partners living with HIV who are using ART.

Introduction

Daily oral pre-exposure prophylaxis (PrEP) using tenofovir-based medication was integrated into normative guidelines for HIV prevention by the World Health Organization in 2015 and clinical guidance for its use in Uganda was published in 2016 by the Ministry of Health.[1,2] Today, PrEP is available at 260 facilities in Uganda and >175,000 people have ever been initiated on PrEP as part of the national programs.

Heterosexual HIV-serodifferent couples in Uganda — where one partner is living with HIV and the other is HIV-negative — have been integral to global efforts to understand HIV transmission and identify prevention modalities.[3–7] In Uganda PrEP guidance, HIV-serodifferent couples are recognized as a group to link to PrEP services. In stable monogamous couples, a priority HIV prevention strategy is for the partner living with HIV to initiate and sustain use of antiretroviral therapy (ART), yielding sustained HIV viral suppression and long-term prevention of HIV transmission to the HIV-negative partner.[8] There is, however, a short period after ART initiation when viremia is unsuppressed[9] and PrEP can be used as a "bridge" to ART use and HIV viral suppression, thereby affording near-immediate HIV protection while ART-taking behaviour becomes habitual and viremia subsides.[5] After this time, PrEP can be discontinued if discontinuation aligns with preferences and behaviours of both partners. This strategy afforded near complete protection in an open-label PrEP demonstration project with HIV-serodifferent couples.[5]

Since ART clinics are adept at HIV testing and many have programs to identify and support HIV-serodifferent couples, an early strategy in countries with generalized HIV epidemics has been to make PrEP available through ART clinics to members of key populations and HIV serodifferent couples.[10] This approach leverages the expertise of providers skilled in ART management and counseling with clear benefits to PrEP uptake and cost effectiveness.[11] However, programs and research to date have not assessed the ways in which PrEP provision integrated into ART clinics may have unanticipated benefits or consequences for ART programs. One hypothesis is that integrating PrEP into ART programs results in greater use of ART by partners living with HIV due to feelings of mutuality[12,13] and modeled behaviour.[14,15] Here, we report results from a stepped-wedge cluster randomized trial designed to evaluate PrEP initiation and persistence within a PrEP program in ART clinics in Kampala and Wakiso districts, Uganda and to statistically determine whether presence of the program could improve clinic-based levels of ART initiation and HIV viral suppression in persons living with HIV.

Methods

Study design and participants

The Partners PrEP Program was a stepped-wedge cluster randomized trial conducted within ART clinics at 12 public health facilities in Kampala and Wakiso districts, Uganda from June 2018 until December 2021. The stepped-wedge trial design was focused on testing the effect of the presence of an integrated couples-based PrEP program on ART initiation and adherence (measured through HIV viral suppression) in the partner living with HIV. The study commenced with a baseline period when none of the ART clinics had a couples-based integrated PrEP program in place (i.e., all were in the control/pre-intervention phase). Accrual progress was used to set the date for the beginning of each step. There were 3 total post-baseline steps and a different group of 4 clinics launched their PrEP program at the beginning of each step. HIV-serodifferent couples engaging with ART clinics at participating facilities could contribute data to the study if they were recently diagnosed as HIV serodifferent and if the HIV-negative partner was not using PrEP. Clinics identified couples through couples-based HIV testing and counseling and by encouraging clients living with HIV to bring their partners for HIV testing.

PrEP program intervention

Three elements defined the launch of the PrEP program: clinic-wide training on PrEP delivery, an initial

technical assistance visit by the training team to the clinic, and on-site availability of PrEP commodities, including lamivudine/tenofovir disoproxil fumarate (3TC/TDF) medication.[1] For PrEP training, clinic personnel responsible for HIV prevention and treatment counseling, oversight of medication provision, laboratory, and pharmacy were invited to a 2-day training delivered by PrEP-experienced research staff of the Infectious Diseases Institute Kasangati site. The training curriculum was adapted from the Uganda national PrEP training curriculum[16] to add elements specific to working with HIV serodifferent couples, testimonials from couples who have used PrEP, and adult learning techniques. Each clinic was trained separately at an offsite conference facility. Following the training, the training team completed a walk-through at the clinic where facility personnel highlighted the procedures and flow that couples would experience when coming to access couples counseling, PrEP, and ART. PrEP medication was then delivered to all 4 clinics within the group launching the PrEP program by the training team within a 2-day window of one another. (Efforts were made to deliver to all on the same day but distances between clinics often required 2 days.) PrEP provision could begin once commodities were in place. Once a clinic launched its PrEP program, the training team conducted monthly technical assistance visits, including troubleshooting problems with PrEP prescribing or counseling and conducting on-the-job training with new personnel.[17]

Once a facility had launched the integration of PrEP into its ART program, all HIV-negative members of newly and recently diagnosed HIV serodifferent couples were offered PrEP by trained facility nurses and counselors during routine service provision. PrEP was recommended to be used for at least 6 months after the partner living with HIV initiated ART. Counseling messages about PrEP followed a previously published framework and key messages that included discussions of HIV serodifference, PrEP and ART initiation and integrated use, and PrEP discontinuation.[18] Posters on the facility walls and outreach by community-based focal persons were additional methods used to identify HIV serodifferent couples and engage them for the program.

Randomization and masking

We employed a two-step process in which ART clinics were randomly assigned in a 1:1:1 ratio to one of three "clinic groups", and each of these was then assigned to launch the integrated PrEP program during step 1, 2, or 3. This was accomplished during a randomization event in September 2018 with attendance from members of each participating facility, members of the Uganda PrEP Technical Working Group, the Uganda Ministry of Health, and members of the research team. There was no masking for this study.

Procedures

Data were abstracted throughout the entire study period by trained research staff who were different from the training/technical assistance team. Data abstractors visited each facility at least once per month and reviewed 1) logbooks to identify all HIV serodifferent couples newly enrolled into the clinic since the last visit and 2) paper-based medical records for each individual to abstract data on demographics, PrEP and ART initiation and refills, and viral load among the partners living with HIV. Once a facility launched PrEP, additional data about HIV risk factors were available through the national PrEP client card for those who initiated PrEP. All data were abstracted into a web-based platform (REDCap, version 12.1.1, Vanderbilt University) using tablet computers.[19] Midway through the study, we implemented additional procedures for facility staff to call individuals without viral load results to understand reasons for the missing data. Information from these phone calls was captured in a separate database.

Data abstraction and phone calls to participants missing viral load data continued until at least 9 months after ART initiation had elapsed for each partner living with HIV, enabling potential ascertainment of the viral suppression outcome for all participants. At the end of study follow-up, the program was "handed over" to each facility, which entailed disseminating study results and explaining that the technical assistance team would remain available through virtual means if questions arose. PrEP commodities continued to be available through the Ministry of Health national PrEP program. Throughout the trial, key stakeholders were updated regularly via newsletters and meetings, which enabled close communication between the trial team, the Ministry of Health, key funders of PrEP and HIV prevention in Uganda (e.g., U.S. Centers for Disease Control and Prevention), and PrEP implementing partners.

Outcomes

This work describes the primary outcomes of PrEP initiation, 3- and 6-month PrEP persistence, ART initiation, and 6-month viral suppression. Each data point was ascertained through data abstraction of paper medical records at each ART clinic. Since medical records are kept on an individual level, this facilitated continued data capture for individuals whose partners dropped out of care. Viral load measurements were conducted as part of routine HIV care at the Central Public Health Laboratory in Uganda using the Abbott m2000 real-time HIV-1 or Roche COBAS Ampliprep assays.[20] Viral load data were available to the study team through the

centralized results database as well as through individual medical records.

PrEP initiation was defined as receiving PrEP within 3 months (90 days) of the couple being found to be HIV serodifferent (the later date of the two HIV test results establishing serodifference). ART initiation was defined as receiving ART medication within 3 months (90 days) of establishing serodifference. Viral suppression was defined as HIV RNA <1000 copies/mL 6 months from initiating ART[21] and we used a wide window of 42-270 days to accommodate a variation in the partner returning to the clinic for follow-up testing.

HIV seroconversion was not routinely monitored via clinical records. However, if a member of the data abstraction team came up on a clinical record noting seroconversion, the data were entered into the study database and summarized.

Statistical analysis

Study size was based on the ART initiation outcome and was determined by pilot data among HIV serodifferent couples in a prior PrEP trial indicating we could expect to observe 50% of people initiating ART during control periods, periods when only the standard of care was available.[22] Power calculations showed that with 12 clinics, 3 steps and 104 couples per clinic group (312 couples in total per step and 1248 couples in total), we would have 80% power to detect an increase in ART initiation from 50% to 65% within 3 months. Following the baseline step in which ART initiation was observed to be over 99%, a power calculation was performed for the outcome of viral suppression using the observed baseline step frequency (83.8%) and found that we would have 80% power to detect an increase in the proportion of people virally suppressed to 92.1%, accounting for 16% loss to follow-up.

Descriptive statistics were used to summarize participant characteristics and each outcome during the control and intervention periods. For analysis of the effect of the PrEP program on viral load of partners living with HIV, we pre-specified an intent-to-treat design using a modified Poisson generalized estimating equation (GEE) model – i.e., a GEE with binomial outcome, log-link, and robust standard errors – to calculate the relative risk (RR) of viral suppression during intervention versus control periods.[23–25] Upon recommendation from the external data monitoring committee, the primary analysis plan was updated to include values for viral suppression that were imputed for those without a 6-month viral load result based on reasons for missingness: participant transfers, those who attended a visit but never had blood drawn, and those without an available result from the laboratory were assigned to have viral suppression equal to the proportion virally suppressed among those with an available viral load at the same site and enrolled during the same step; all participants who did not attend any visit between 42 and 270 days post-ART initiation were assumed to be virally unsuppressed; participants who died were assigned a probability of 50% that they were suppressed since that cause of death was unknown for most. For participants who had a viral load measured between 270 and 365 days from ART initiation, suppression was imputed using the value available. Finally, for participants with no known reason for missing data, viral suppression was imputed using a probability of suppression equal to the weighted average of the probabilities that were used for all other missingness reasons in the same clinic-step. In addition to the reason-specific imputation, two additional models were constructed assuming that participants missing viral load data were either all virally suppressed or all virally unsuppressed. We then performed a non-pre-specified sensitivity analysis where we excluded all data from participants who enrolled when their facility was in the control period and whose viral load was measured during the intervention period. We also looked separately at the intervention effect solely during step 1 and step 2. We also conducted a sensitivity analysis excluding participants enrolled in the step prior to the program launch. Each model adjusts for the partial confounding by time and corrects for the small number of clusters using Fay and Graubard's method.[26,27]

Prior to our program, PEPFAR-supported PrEP programs in these facilities were targeted only to "key populations" that excluded members of HIV serodifferent couples. Therefore, we assumed that baseline PrEP use was zero and we did not calculate any effect of the intervention on changes in PrEP use.

Approvals for the trial, including access to de-identified data from patient clinical records, were obtained from the Uganda National HIV/AIDS Research Committee (ARC 194), the Uganda National Council for Science and Technology (HS 2381), and the University of Washington Human Subjects Division (STUDY00000320). Local administration approval to access de-identified data was also obtained from Kampala Capital City Authority and Wakiso District. Thus, individual consent was not required. An independent data monitoring committee reviewed data from the project on an annual basis, with a focus on study execution and feasibility. The trial was registered with clinicaltrials.gov, NCT03586128. The CONSORT checklist and extension for cluster randomized trials was consulted during manuscript preparation to ensure that all relevant information was included [28]. The full trial protocol is available as a supplement to this manuscript.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, interpretation, or writing of the manuscript. The corresponding author had full access to all

of the data and had final responsibility for the decision to submit for publication.

Results

Twenty-four ART clinics were approached and 12 were purposively selected to participate, which represented large and small ART clinics in peri-urban and urban settings (Figure 1). A total of 1381 HIV serodifferent couples were enrolled during the study period, including 730 during the control period and 651 during the intervention period (Table 1). The median age of all participants was 28 years (interquartile range [IQR] 24-34), 61.5% of partners living with HIV were women and most couples were married (77.6%). Among partners living with HIV, 38.3% had a CD4 count ≥500 cells/mm^3, 93.7% had WHO Stage 1 or 2 HIV disease. The baseline phase lasted for 265 days, step 1 lasted 196 days, step 2 lasted 176 days and step 3 lasted 371 days. Overall, 24.6% of HIV-negative partners and 74.6% of partners living with HIV returned to their facility at least once during the follow up period. Most visits (97.3%) were attended on different days by individual members of a couple.

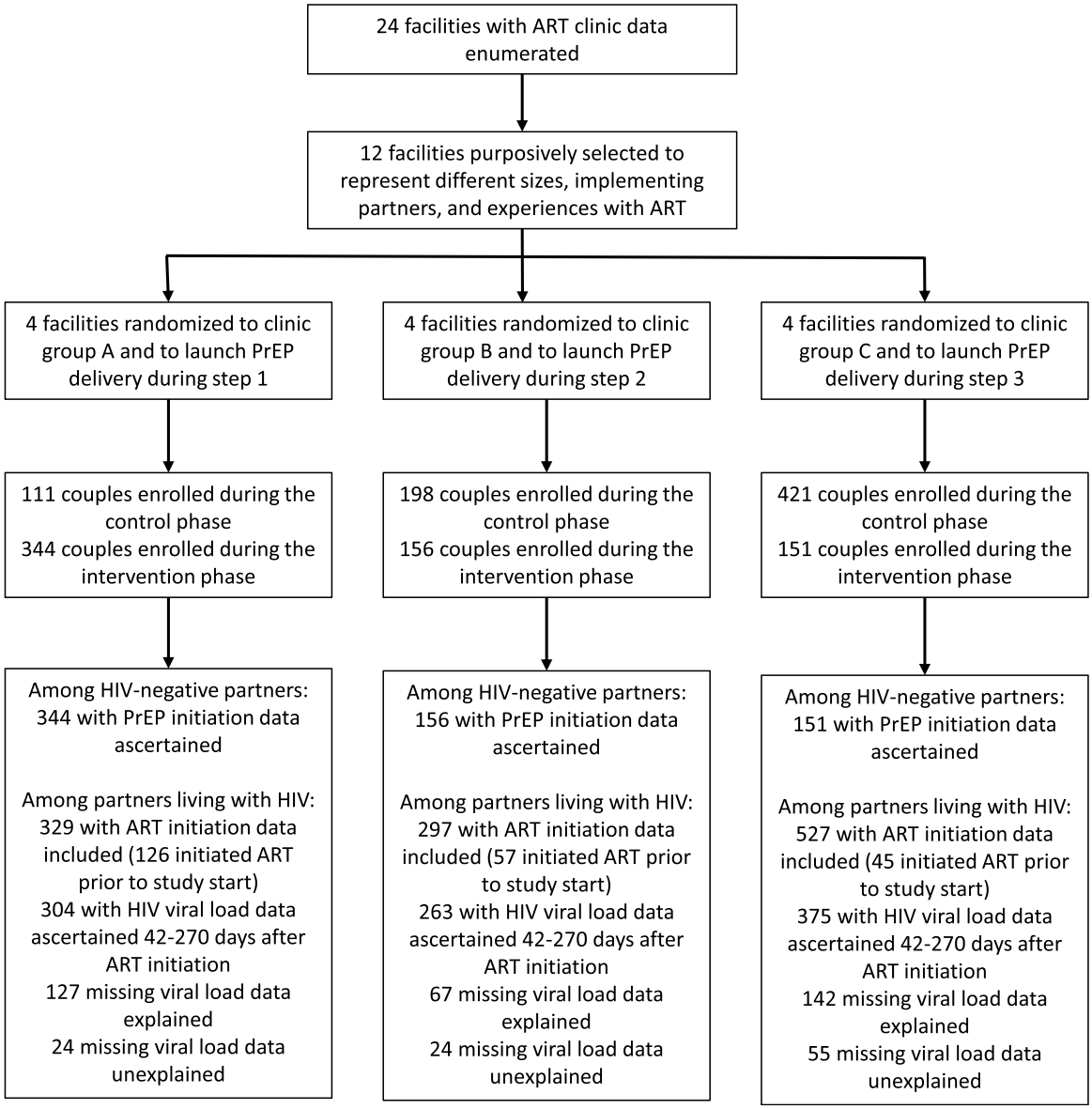

Figure 1. Trial profile. Flow of facility selection and resulting numbers of couples and individual partners with data available for analyses.

	Group A		Group B		Group C		Total	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Partners living with HIV								
Participants enrolled	111	344	198	156	421	151	730	651
Age in years, median (IQR)	28·0 (23·2, 35·0)	27·0 (23·0, 3·20)	29·0 (25·0, 36·1)	28·7 (23·0, 35·0)	28·0 (23·5, 34·0)	27·0 (22·0, 33·0)	28·0 (24·0, 35·0)	27·0 (23·0, 33·0)
Female sex	67 (60·4%)	216 (62·8%)	107 (54·0%)	99 (63·5%)	261 (62·0%)	99 (65·6%)	435 (59·6%)	414 (63·6%)
Married	82 (83·7%)	210 (70·0%)	119 (77·3%)	92 (74·8%)	303 (80·2%)	113 (85·6%)	504 (80·0%)	415 (74·8%)
CD4+ count, cells/mm3, median (IQR)	419·0 (265·5, 602·0)	396·0 (270·0, 588·0)	445·5 (277·8, 704·8)	504·0 (279·0, 778·0)	392·5 (234·5, 567·5)	456·0 (234·5, 674·5)	407·0 (242·0, 603·0)	430·0 (265·0, 658·0)
WHO HIV Stage 1-2	99 (95·2%)	321 (95·3%)	187 (96·4%)	150 (96·8%)	372 (90·1%)	137 (92·6%)	658 (92·5%)	608 (95·0%)
Days from HIV diagnosis to enrollment (median (IQR))	0 (0, 0)	0 (0, 7)	0 (0, 0)	0 (0, 3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 5)
ART Initiated	111 (100%)	343 (99·7%)	198 (100%)	156 (100%)	414 (98·3%)	150 (99·3%)	723 (99·0%)	649 (99·7%)
Days from ART initiation to enrollment (median (IQR))	0 (0, 0)	0 (0, 6)	0 (0, 0)	0 (0, 2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 3)
HIV-negative partners								
Participants enrolled	111	344	198	156	421	151	730	651
Age in years (median (IQR))	28·0 (25·0, 33·0)	28·0 (24·0, 33·0)	29·5 (25·0, 35·0)	30·0 (25·0, 36·0)	28·0 (25·0, 34·0)	30·0 (25·0, 35·0)	28·0 (25·0, 34·8)	29·0 (25·0, 34·0)
Female sex	44 (39·6%)	128 (37·2%)	91 (46·0%)	57 (36·5%)	160 (38·0%)	52 (34·4%)	295 (40·4%)	237 (36·4%)

***Table 1*: Characteristics of partners living with HIV and HIV-negative partners enrolled by clinic group and intervention status.**
Missing data from 196 missing marital status, 668 missing CD4 count and 30 missing WHO stage are not shown.

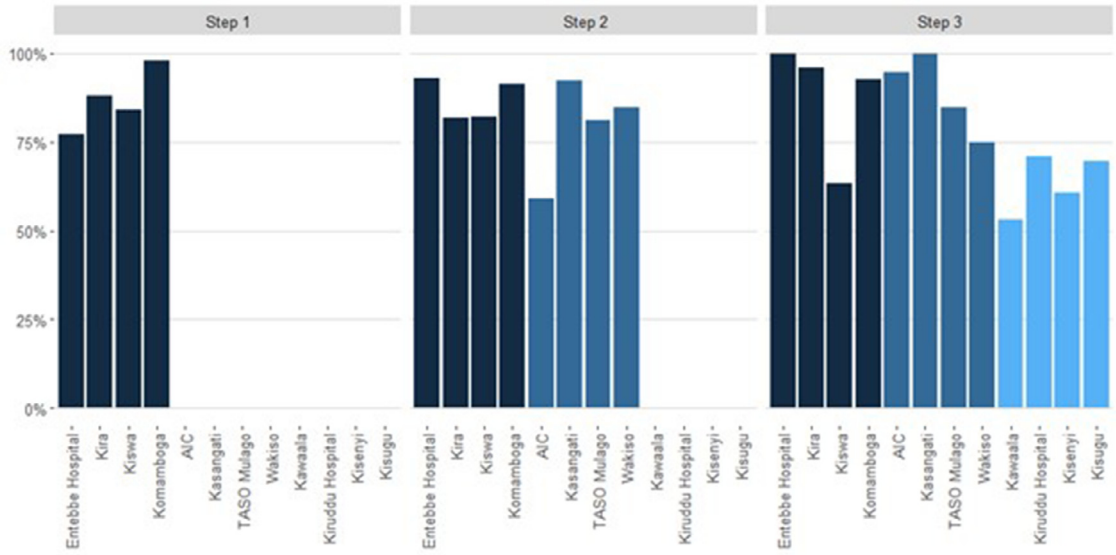

Figure 2. Pre-exposure prophylaxis (PrEP) initiation during periods when each facility was distributing PrEP. Facilities launching PrEP delivery during Step 1 are shown in darkest blue, facilities launching in Step 2 are in medium blue, and Step 3 in light blue.

Following the intervention launch, PrEP initiation by HIV-negative partners was 81.0% overall and >50% at each facility during each step (Figure 2). For clinic group A, which was the first to launch, PrEP initiation was 89.2% across all trial steps (307/344 people, Supplementary Table 1) with a range from 77.8% to 94.1% across its four clinics. Group B clinics had 82.1% of HIV-negative partners initiate PrEP (128/156 people) with a range from 75.6% to 96.4% across its four clinics and Group C had 60.9% (92/151 people) with a range from 53.1% to 71.0% across its four clinics. In addition to 527 people who initiated PrEP through the Partners PrEP Program, 20 people initiated PrEP through another program and were incorporated into the program once PrEP delivery began, bringing the total PrEP users to 547. Among 547 people who started PrEP, 42.4% received a refill at month 1, 38.6% at month 2, 10.8% at month 6, and by month 9, only 3.5% received a refill (Figure 3). Among those who received a refill at month 1, 47.8% received a refill at month 3, 22.4% at month 6 and 7.3% at month 9.

ART initiation was high with 99.2% of all partners living with HIV starting ART within 90 days of enrollment, including 228 (16.5%) that started prior to enrollment (60 of these people started ART 1-7 days before enrollment, 18 initiated 8-14 days before enrollment, 42 initiated 15-30 days before enrollment, and 108 initiated 31-365 days before enrollment). High levels of ART initiation were consistent across steps and clinic groups (Supplementary Table 2). Among partners living with HIV, 68.2% had a viral load result ascertained within 42-270 days from ART initiation (median time between ART initiation and viral load measurement=143.5 days, IQR 98-189). Among people with viral load data abstracted, 91.8% of those enrolled during a control period and 83.3% of those enrolled during an intervention period were virally suppressed. Using imputation to include the full set of participants, 82.1% of control and 76.7% of intervention participants were estimated to be virally suppressed (RR = 0.94, 95% CI = 0.82-1.07; Table 2 and Supplementary Table 3). Results from all sensitivity analyses were similar, including when all participants with missing viral loads were assumed to be unsuppressed (RR=0.93, 95% CI 0.78-1.09) or suppressed (RR=0.92, 95% CI 0.83-1.03), and when excluding people who enrolled during a control phase and had their viral load measured during the intervention phase (RR=0.96, 95% CI 0.78-1.19). In step 1 alone, there was a trend towards a higher frequency of viral suppression in the control period (80.2% in control period and 69.0% in intervention period, RR=0.86, 95% CI 0.74-1.0) and there was no significant difference in control and intervention periods when step 2 was analysed unto itself (77.1% control and 78.2% intervention, RR=1.01, 95% CI 0.82-1.26). In our analysis where we excluded participants enrolled in the step prior to the program launch, results were nearly identical to the analysis of step 1 alone. Three seroconversions were identified during the course of the program among people who had initiated PrEP; one was known to have missed multiple doses and two had no data available about their PrEP use prior to the date of their HIV positive test result.

Discussion

In this stepped-wedge cluster randomized trial of a novel PrEP program in ART clinics, we found that integrating PrEP resulted in high PrEP uptake, frequent

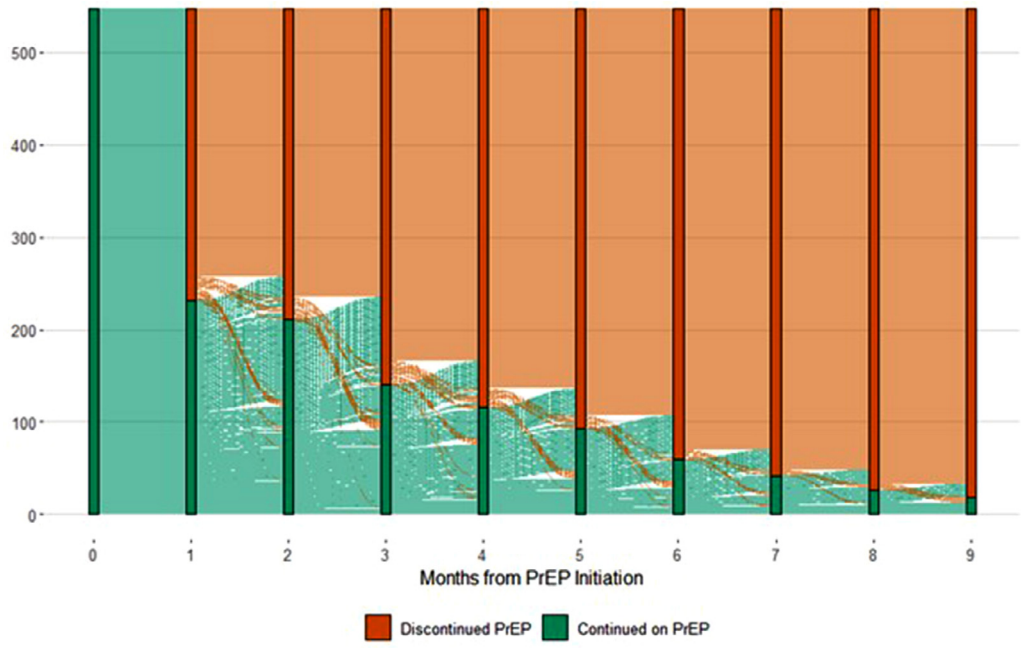

Figure 3. Longitudinal pre-exposure prophylaxis (PrEP) continuation, discontinuation, and restarts by month from initiation. Each HIV-negative partner is represented by one line moving from left to right through Month 0 to 9. Green portions of the line are periods with PrEP use and orange portions are periods without PrEP use.

Effect of intervention on HIV viral suppression	HIV viral suppression during control periods	HIV viral suppression during intervention periods	RR (95% CI)	p-value
Primary Analysis[1]	599/730 (82·1%)	499/651 (76·7%)	0·94 (0·82, 1·07)	0·28
Assuming missing are unsuppressed	457/730 (62·6%)	370/651 (56·8%)	0·93 (0·78, 1·09)	0·30
Assuming missing are suppressed	689/730 (94·4%)	577/651 (88·6%)	0·92 (0·83, 1·03)	0·12
Excluding those enrolled during control period with viral load assessed after intervention began[1,2]	369/450 (82·0%)	499/651 (76·7%)	0·96 (0·78, 1·19)	0·66
Change over time[1]				0·26
Effect during step 1 (Group A vs. Group B + Group C clinics)	186/232 (80·2%)	78/113 (69·0%)	0·86 (0·74, 1·00)	
Effect during step 2 (Groups A + B vs. Group C clinics)	101/131 (77·1%)	151/193 (78·2%)	1·01 (0·82, 1·26)	

***Table 2*: Statistical comparison and estimation of effect of intervention on viral suppression in the partner living with HIV.**
Viral suppression is defined by having fewer than 1000 viral copies/mL at 6 months (42 to 270 days) after initiating ART. Participants who did not initiate ART are assumed to be unsuppressed.
For participants missing a viral load within 270 days but with a viral load measured between 270 and 365 days from ART initiation (*n*=42), suppression was imputed using the viral load taken 270-365 days post-ART initiation.
[1] Missing values were imputed using reasons for missingness as follows:
- Participant transferred to a different clinic (*n*=154): p equal to the proportion virally suppressed among those with an available viral load at the same site and enrolled during the same step.
- Follow-up visit not attended (*n*=98): all assumed to be unsuppressed.
- Follow-up visit attended but blood not taken (*n*=17): p equal to the proportion virally suppressed among those with an available viral load at the same site and enrolled during the same step.
- Participant death (*n*=14): p=0.5.
- Lack of available result from laboratory (*n*=8): p equal to the proportion virally suppressed among those with an available viral load at the same site and enrolled during the same step.
- No known reason (*n*=103): p equal to the weighted average of p used for all other missingness reasons in the same clinic-step.
[2] Exclusion incorporated a two-week grace period; if a participant who enrolled during a control period was assessed <=14 days after the intervention was introduced at the site, the assessment is not excluded, whereas if assessed >14 days after, the assessment is excluded.

PrEP discontinuation by 6 months, no change in the already high frequency of ART uptake, and no statistically significant change in 6-month HIV viral suppression. The intervention was intended to provide immediate HIV protection to HIV-negative members of HIV serodifferent couples and potentially enhance ART initiation and viral suppression in partners living with HIV. Although we did not see the hypothesized increase in ART uptake and HIV viral suppression in people living with HIV whose partners had access to an integrated PrEP program, we observed higher than expected levels of ART initiation overall, often at 99%, and HIV viral suppression. In this context of high ART use in the population, the integrated PrEP program did not have any substantial effect on ART initiation or viral suppression outcomes.

ART programs in Uganda have been instrumental in the country's near-achievement of UNAIDS goals for 90-90-90 and progress towards these goals has advanced significantly since 2017 when our study was planned[29,30] and sample sizes were calculated, which potentially led to underpowering our ART initiation outcome. Nevertheless, our study may be among the first to evaluate the impact of a PrEP program on ART outcomes measured on partners of PrEP users and our research design facilitated important efforts to monitor and track results of routinely conducted viral load testing. In Kenya, a PrEP program designed for HIV serodifferent couples that was delivered at a national scale focused on PrEP outcomes. This program also found high frequency of PrEP initiation (mean PrEP initiations per month=7.5 during intervention periods) and high rates of PrEP discontinuation by HIV-negative partners at 6 months (34% of all PrEP initiators).[10] High discontinuation by 6 months that was observed in the Kenya program, as well as our Uganda program, was expected since PrEP discontinuation among HIV serodifferent couples is warranted when the partner living with HIV achieves sustained use of ART and there are no other potential sources of transmission.

Stepped-wedge designs have utility for evaluating pragmatic implementation and permit rollout to occur in an organized manner with each set of facilities gaining experience with the new intervention before more facilities begin. However, the interpretation of results can suffer if the intervention becomes available to participants through other means while the study is ongoing. Through the financial support of the U.S. PEPFAR program, PrEP delivery in Uganda grew dramatically in late 2019, before PrEP delivery was launched in the facilities assigned to step 3. Although it was not targeted to ART clinics nor HIV-serodifferent couples, it resulted in a greater number of facility staff with PrEP training and familiarity. During data abstraction, we identified newly enrolled HIV-serodifferent couples who received PrEP through PEPFAR-supported programs whom we had to exclude from our study (the largest numbers were in two step 3 facilities with 180-210 couples, data not shown). By analyzing couples enrolled during steps 1 and 2 only, we attempted to isolate periods prior to the large PEPFAR PrEP rollout, however we did not find that there was substantial difference in the results.

We must also acknowledge the impact of the COVID-19 pandemic on our trial. Originally slated to be approximately 6 months long, step 3 was elongated to 12 months in order to accrue a sufficient number of couples. In Uganda, lockdown regulations that restricted use of public and private transportation and attendance at health facilities created challenges for couples to reach ART clinics. Clinics facilitated ART distribution to individuals with stable ART adherence through neighborhood distribution programs and many added PrEP distribution into this program.[31] This resulted in improved access during the early days of the pandemic, but it was challenging for the study team to abstract data on PrEP and ART use since data capture systems were often not linked to individuals' medical records.

While a strength of our study was leveraging existing public health data, we lacked HIV viral load data from ~30% of our participants and needed to collect additional data on the reasons for missingness to impute estimates of viral suppression. Through our statistical modeling, we were able to estimate the impact of the imputation and were reassured to see that the results for differences in viral suppression were similar in all scenarios. We chose to include all ART clinic clients and their partners in our study, including those who initiated ART prior to, at enrollment, and during the course of the study, reflecting real world conditions where PrEP is introduced into ART clinics without regard to the ongoing ART program and to increase generalizability represented by the cohort. Finally, our sensitivity analyses to isolate different periods of time when the program was running included many fewer participants and were not powered, thus their results should be interpreted cautiously.

Novel PrEP products are on the horizon and Ugandans participated in trials to test their efficacy and safety, paving the way for regulatory review and potential integration of long-acting injectable cabotegravir and the dapivirine vaginal ring into HIV prevention guidelines.[32-35] As their integration is considered, a similar stepped-wedge design could be used to evaluate PrEP uptake, choice, and switching between PrEP products by numerous groups of people with substantial HIV risk. Importantly, this trial also provided an opportunity for numerous PrEP stakeholders to come together to discuss study progress, creating a forum to share experiences with PrEP implementation and broad goals for national rollout. This level of community engagement will be instrumental to continue as novel products are rolled out.

In summary, we found that integrating a PrEP program into existing ART clinics was feasible and yielded

positive outcomes with PrEP and ART for members of HIV-serodifferent couples. Future rollout of novel HIV prevention interventions could draw on the same methodologies and be extended to incorporate people with additional risk factors for HIV who are seeking care in existing public health programs.

Contributors

All authors had full access to the data and had final responsibility for the decision to submit for publication.
RH conceptualized and designed the study, obtained funding, interpreted the data, wrote the initial draft of the manuscript, and was responsible for the decision to submit the manuscript.
TRM designed the study and was involved in data collection.
KT conceptualized and designed the study, had access to and verified the underlying data, and interpreted the data.
FN was involved in data collection.
LN was involved in data collection.
JK was involved in data collection.
DT was involved in data collection.
EF had access to and verified the underlying data.
AM had access to and verified the underlying data and interpreted the data.
NCW interpreted the data.
MAW interpreted the data.
JS conceptualized and designed the study and interpreted the data.
ITK interpreted the data.
HK interpreted the data.
JMB conceptualized and designed the study and interpreted the data.
AM conceptualized and designed the study and interpreted the data.

Data sharing statement

The study protocol, statistical plan, and data from the Partners PrEP Program are available by contacting the International Clinical Research Center at the University of Washington (icrc@uw.edu).

Declaration of interests

JMB reports being an employee of Gilead Sciences, with salary and stock/options, outside the submitted work. All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101611.

References

1 Ministry of Health RoU. *Technical Guidance on Pre-Exposure Prophylaxis (PrEP) for Persons at High Risk of HIV in Uganda*. Kampala, Uganda: Ministry of Health; 2016.
2 World Health Organization. *Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*. Geneva, Switzerland: World Health Organization; 2015.
3 Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010;362(5):427–439.
4 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367(5):399–410.
5 Heffron R, Ngure K, Odoyo J, et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. *Gates Open Research*. 2017;1:3.
6 Kahle EM, Hughes JP, Lingappa JR, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. *J Acquir Immune Defic Syndr*. 2013;62(3):339–347.
7 Mugwanya KK, Donnell D, Celum C, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. *Lancet Infect Dis*. 2013;13(12):1021–1028.
8 Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830–839.
9 Mujugira A, Celum C, Coombs RW, et al. HIV transmission risk persists during the first 6 months of antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2016;72(5):579–584.
10 Irungu EM, Mugwanya KK, Mugo NR, et al. Integration of pre-exposure prophylaxis services into public HIV care clinics in Kenya: a pragmatic stepped-wedge randomised trial. *Lancet Global Health*. 2021;9(12):e1730–e1739.
11 Irungu EM, Sharma M, Maronga C, et al. The incremental cost of delivering PrEP as a bridge to ART for HIV serodiscordant couples in public HIV care clinics in Kenya. *AIDS Res Treatment*. 2019;2019:4170615.
12 Ware NC, Pisarski EE, Nakku-Joloba E, et al. Integrated delivery of antiretroviral treatment and pre-exposure prophylaxis to HIV-1 serodiscordant couples in East Africa: a qualitative evaluation study in Uganda. *J Int AIDS Soc*. 2018;21(5):e25113.
13 Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *J Acquir Immune Defic Syndr*. 2012;59(5):463–468.
14 Mujugira A, Baeten J, Kidoguchi L, et al. High levels of viral suppression among East African HIV-infected women and men in

serodiscordant partnerships initiating antiretroviral therapy with high CD4 counts and during pregnancy. *AIDS Res Hum Retroviruses*. 2017.
15 Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84(2):191–215.
16 Djomand G, Bingham T, Benech I, et al. Expansion of HIV preexposure prophylaxis to 35 PEPFAR-supported early program adopters, October 2016-September 2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(8):212–215.
17 Thomas D, Mujugira A, Ortblad K, et al. A pragmatic approach to identifying implementation barriers and facilitators for a novel pre-exposure prophylaxis (PrEP) delivery model at public facilities in urban Uganda. *Implement Sci Commun*. 2022;3(1):7.
18 Morton JF, Celum C, Njoroge J, et al. Counseling framework for hiv-serodiscordant couples on the integrated use of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention. *J Acquir Immune Defic Syndr*. 2017;74(Suppl 1):S15–s22.
19 Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
20 Aisu S, Nyegenye W, Bigira V, et al. Quality assurance as an integral component of diagnostic testing in clinical laboratories and point-of-care testing: the Uganda experience. *Afr J Lab Med*. 2016;5(2):447.
21 Uganda Ministry of Health. *Consolidated guidelines for prevention and treatment of HIV in Uganda*. Ministry of Health, Republic of Uganda; 2016.
22 Mujugira A, Celum C, Thomas KK, et al. Delay of antiretroviral therapy initiation is common in East African HIV-infected individuals in serodiscordant partnerships. *J Acquir Immune Defic Syndr*. 2014;66(4):436–442.
23 Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007;28(2):182–191.
24 Hughes JP, Granston TS, Heagerty PJ. Current issues in the design and analysis of stepped wedge trials. *Contemp Clin Trials*. 2015;45(Pt A):55–60.
25 Yelland LN, Salter AB, Ryan P. Performance of the modified Poisson regression approach for estimating relative risks from clustered prospective data. *Am J Epidemiol*. 2011;174(8):984–992.
26 Fay MP, Graubard BI. Small-sample adjustments for Wald-type tests using sandwich estimators. *Biometrics*. 2001;57(4):1198–1206.
27 Thompson JA, Hemming K, Forbes A, Fielding K, Hayes R. Comparison of small-sample standard-error corrections for generalised estimating equations in stepped wedge cluster randomised trials with a binary outcome: a simulation study. *Stat Methods Med Res*. 2021;30(2):425–439.
28 Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. *BMJ*. 2012;345:e5661. https://doi.org/10.1136/bmj.e5661.
29 Ministry of Health Uganda, ICAP, PEPFAR, US Centers for Disease Control and Prevention, Westat. Uganda Population-Based HIV Impact Assessment. UPHIA 2016-2017. Available at: https://phia.icap.columbia.edu/wp-content/uploads/2018/07/3430%E2%80%A2PHIA-Uganda-SS_NEW.v14.pdf. Accessed 15 August 2018. 2018.
30 Ministry of Health Uganda. *Uganda Project Population-Based HIV Impact (UPHIA)*. New York, NY: ICAP at Columbia University; 2022. Available from: https://phia.icap.columbia.edu/countries/uganda/.
31 Zakumumpa H, Tumwine C, Milliam K, Spicer N. Dispensing antiretrovirals during Covid-19 lockdown: re-discovering community-based ART delivery models in Uganda. *BMC Health Serv Res*. 2021;21(1):692.
32 Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med*. 2016;375(22):2121–2132. https://doi.org/10.1056/NEJMoa1506110.
33 Baeten JM, Palanee-Phillips T, Mgodi NM, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. *Lancet HIV*. 2021;8(2):e87–e95.
34 Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med*. 2016;375(22):2133–2143.
35 Delany-Moretlwe S, Hughes J, Bock P, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: interim results from HPTN 084. HIVR4P Virtual Conference; 27 January 2021.