Adaptive HIV pre-exposure prophylaxis adherence interventions for young women in Johannesburg, South Africa: a sequential multiple-assignment randomised trial

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Summary

Background Adherence to daily oral pre-exposure prophylaxis (PrEP) is low among African young women, and layered support strategies are needed to improve PrEP adherence in this population. We aimed to evaluate potentially scalable adherence-support strategies for young women aged 18–25 years who initiated PrEP in Johannesburg, South Africa.

Methods We conducted a sequential multiple-assignment randomised trial at Ward 21 of the Wits Reproductive Health and HIV Institute clinical research site, affiliated with University of the Witwatersrand, Johannesburg, South Africa. Participants were eligible if they were assigned female sex at birth, aged 18–25 years, not living with HIV, sexually active, newly initiating PrEP, had regular access to a mobile telephone, and could read. Using sequentially numbered, sealed, opaque envelopes containing group allocation, a staff member assigned enrolled participants (1:1) to receive one of two adherence-support interventions: once per week two-way SMS communication or participation in a WhatsApp peer-support group. Participants assigned to WhatsApp were put into groups with approximately 25 participants, during which they were prompted by staff facilitators to discuss any challenges with PrEP use or other events happening in their lives. The allocation sequence was generated by the data manager using random numbers with variable block sizes between 10 and 14. Only trial investigators were masked to participant intervention assignments; participants, people giving interventions, people assessing outcomes, and people analysing data were not masked to group assignment. All enrolled participants were offered PrEP (ie, co-formulated, once per day oral emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg). The primary outcome was high PrEP adherence at month 9, defined as concentration of tenofovir diphosphate on dried blood sample of 700 fmol per punch or more. At month 3, participants with low PrEP adherence were randomly assigned to a secondary, intensified intervention of issue-focused counselling once per month or drug-level feedback counselling based on PrEP drug concentrations at months 3 and 6. The protocol was registered at ClinicalTrials.gov (NCT04038060) and the trial is complete.

Findings Participants were enrolled and followed up between May 16, 2019, and Jan 25, 2022. From May 16, 2019, to Jan 29, 2021, 401 participants were screened and 360 were enrolled and initiated PrEP. 180 (50%) were randomly assigned to two-way SMS and 180 (50%) were randomly assigned to WhatsApp support groups. At month 9, 34 (20%) of 174 participants in the two-way SMS arm had tenofovir diphosphate 700 fmol per punch or more, compared with 32 (18%) of 174 in the WhatsApp arm (relative risk 1·06, 95% CI 0·69–1·64; p=0·78). At month 9, four (5%) of 76 participants in the drug-level feedback arm had tenofovir diphosphate 700 fmol per punch or more, compared with three (4%) of 76 participants in the monthly counselling arm (1·33, 0·31–5·76; p=0·70). 22 serious adverse events were reported during the trial, but were all deemed unrelated to the trial.

Interpretation PrEP adherence did not differ across interventions among young women in Johannesburg, South Africa. Future research is needed on whether and how to scale-up PrEP support for young women in resource-constrained settings.

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Introduction

Daily oral HIV pre-exposure prophylaxis (PrEP) co-formulated with tenofovir and emtricitabine is an effective HIV-prevention strategy in sub-Saharan Africa when taken with high adherence.[1] Despite high PrEP uptake among young women aged 18–25 years in sub-Saharan Africa, PrEP projects during 2020–22 found waning continuation and adherence in this population in South Africa, Kenya, and Zimbabwe.[2–4] Although approximately 90% of young women in southern and eastern Africa who are offered PrEP in trials and implementation projects choose to initiate, only 18–55% continue up to 6 months and less than 15% continue up to 24 months.[4–6] Multiple factors affect oral PrEP use in African young women, such as difficulty with habit formation, side-effects, depressive symptoms, challenges

Research in context

Evidence before this study

We searched PubMed from database inception to June 30, 2023, for articles published in English using the search terms ("HIV" AND "pre-exposure" AND "prophylaxis" AND "PrEP" AND "adolescent*" OR "girl*") AND "adherence". We also conducted the search without the term "adherence". We searched relevant conference abstracts in English from the Conference on Retroviruses and Opportunistic Infections, HIV Research for Prevention, and the International AIDS Conference from the past 5 years using the same search terms. Only articles and abstracts focused on PrEP adherence interventions for young women were considered. HIV incidence remains high in African young women. Pre-exposure prophylaxis (PrEP) is an effective HIV-prevention intervention when used consistently during periods of HIV risk, but some projects and trials have found low adherence to and continuation of oral PrEP among these women. Multiple individual, interpersonal, and contextual factors affect their adherence to and continuation of PrEP (eg, side-effects, depressive symptoms, stigma, and frequency of clinic visits and contact with health-care staff). Various PrEP adherence-support interventions have been developed for adolescent populations worldwide, such as SMS reminders and supportive messages, in-person and virtual adherence-support groups, psychosocial counselling, and targeted feedback. However, these approaches have generally been evaluated individually and there is no evidence on the strategy or combination of strategies most effective in supporting African young women adhere to PrEP.

Added value of this study

To our knowledge, we conducted the first sequential, multiple-assignment, randomised trial of stepped PrEP adherence-support interventions. PrEP adherence did not differ across interventions among young women in Johannesburg, South Africa. However, we estimated PrEP adherence at month 9 to be higher than has been shown in other similar cohorts in South Africa, Kenya, Zimbabwe, and Namibia, even with trial visits occurring during the COVID-19 pandemic. Four (1%) of 360 young women acquired HIV during our trial, a lower HIV incidence than in the general population of Johannesburg. Our high retention rate shows that a sequential multiple-assignment randomised trial design is feasible and efficient when exploring PrEP implementation in resource-constrained settings.

Implications of all the available evidence

PrEP programmes could consider our findings as a proof-of-concept on how to potentially offer differentiated PrEP-adherence support. Alternatives to daily oral PrEP, such as long-acting HIV-prevention products, might support PrEP adherence for young women who want to use biomedical prevention but have challenges taking daily oral PrEP. Future research on how, whether, and when to scale-up PrEP-adherence support is needed to inform cost-effective and efficient PrEP delivery in resource-constrained settings and to improve the public health effects of PrEP among young women in sub-Saharan Africa.

with social support, stigma, concerns about product disclosure, fears or experiences of gender-based violence, and frequency of clinic visits and contact with health-care staff.[7–9] There are still knowledge gaps in understanding and addressing barriers to PrEP use, and these gaps need to be overcome in order to maximise the public health effects of PrEP for this population.

Differentiated PrEP provision can simplify and adapt PrEP delivery to reduce burdens on clients and the health system. Although various PrEP-adherence interventions have been developed and tested among adolescents worldwide, such as one-way or two-way SMS reminders and supportive messages, in-person and virtual adherence-support groups, person-centred psychosocial counselling, and adapted feedback based on PrEP-adherence data (ie, drug-level feedback counselling), few have been evaluated with objective adherence as the outcome.[5,10] Therefore, there is a need to rigorously evaluate these PrEP-adherence interventions. The HPTN 082 trial provided preliminary data on the effectiveness of two-way SMS and adherence-support groups, offered via PrEP adherence-support services for 451 young women in South Africa and Zimbabwe.[4] An unpublished secondary latent class analysis of trial data found that 59% of participants had high response rates to SMS messages in the first 3 months of PrEP use, 82% of participants with high PrEP adherence also had high SMS response rates, and 67% of participants attended monthly PrEP adherence-support groups. 77% of participants with high PrEP adherence attended these groups regularly, although participants reported challenges with attending groups in person and suggested virtual peer groups as a way to overcome transportation and scheduling issues. In a qualitative analysis of interviews with 67 participants from the HPTN 082 trial, they described the acceptability of two-way SMS as a way to strengthen communication between participants and health-care staff, whereas adherence-support groups were described as offering social and emotional peer support and modelling to influence behaviour change.[9] SMS was preferred by young women who wanted short, weekly, clinical check-ins; WhatsApp was preferred by young women who sought more normative experiences around PrEP use from others in their community.[9] Both offer relatively affordable, simple, and scalable approaches to PrEP-adherence support, but have never been compared to assess their relative effects.

There is no evidence on the optimal strategy that is most responsive to the needs of African young women.

In HPTN 082, some participants chose to not engage with the two-way SMS or adherence-support groups, had low PrEP adherence, and might have needed additional support.[4] Drug-level feedback counselling was offered to everyone in the intervention arm at months 2 and 3, but did not increase the proportion of young women with high adherence at month 6 (21% in the standard-care arm *vs* 22% in the drug-level feedback arm).[4] In MTN-034/REACH, there was high adherence to oral PrEP in 57% of young women from South Africa, Zimbabwe, and Uganda who received monthly counselling and various PrEP adherence-support options (eg, drug-level feedback counselling and SMS reminders).[11] However, implementing these interventions for all young women irrespective of need is resource intensive. An alternative approach would be to offer simplified and decentralised adherence support to all PrEP clients and reserving more resource-intensive, clinic-based support for clients with adherence challenges.

We aimed to evaluate potentially scalable adherence-support strategies for young women aged 18–25 years who initiated PrEP in Johannesburg, South Africa.

Methods

Trial design and participants

We conducted a sequential multiple-assignment randomised trial at Ward 21 of the Wits Reproductive Health and HIV Institute clinical research site, affiliated with University of the Witwatersrand, Johannesburg, South Africa. The protocol was registered at ClinicalTrials.gov (NCT04038060) and approved by ethics review boards at the University of the Witwatersrand and the University of Washington (Seattle, WA, USA).[12] The trial is complete.

We recruited participants through posters, presentations in clinic waiting rooms, and individual discussions at primary care facilities. Participants were eligible if they were assigned female sex at birth (assessed via national identification card and self-report), aged 18–25 years, not living with HIV, sexually active, newly initiating PrEP, had regular access to a mobile telephone, and could read. Participants provided written informed consent in their preferred language before participation.

Randomisation and masking

Using sequentially numbered, sealed, opaque envelopes containing group allocation, a staff member (NP or NN) assigned enrolled participants (1:1) to receive one of two initial adherence-support interventions: once per week two-way SMS communication or participation in a WhatsApp peer-support group.[12] The allocation sequence was generated by the data manager (CG) using random numbers with variable block sizes between 10 and 14 in SAS version 9.4. CG developed and maintained the study database and ran all analyses for this Article.

Only trial investigators (CC, SD-M, and JV) were masked to participant intervention assignments. Investigators were not informed of intervention assignments and did not have access to the full study database during recruitment. Participants, people giving interventions, people assessing outcomes, and people analysing data were not masked to group assignment. The success of masking was not assessed.

Procedures

All enrolled participants were offered PrEP (ie, co-formulated, once per day oral emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg) and received adherence counselling aligned with South African national guidelines.[13] Participants also completed computer-assisted self-interviews on HIV risk factors and behaviours via study provided tablets with REDCap. Study staff (NP or NN) logged into REDCap and opened the participant record, then handed the tablet to the participant. The staff member was available to answer any questions as needed and to help with any technical issues with the tablet. The self-interview consisted of HIV risk perception (ie, the nine-item HIV Perception and Salience scale),[14] social support (ie, the Functional Social Support Questionnaire),[15] intimate partner violence (ie, the four-item WHO violence questionnaire),[16] depressive symptoms (ie, the ten-item Center for Epidemiologic Studies—Depression scale),[17] HIV stigma (ie, six questions from previous PrEP projects with African young women),[2,4] traumatic stress (ie, the four-item Primary Care PTSD Screen scale),[18] alcohol use (ie, the Alcohol Use Disorders Identification Test–Concise),[19] self-esteem (ie, the Rosenberg self-esteem scale),[20] and Vaginal and Oral Interventions to Control the Epidemic risk score.[21] Computer-assisted self-interviews occurred at month 1 follow-up and once every 3 months thereafter.

All participants received training for secure management of mobile telephone devices and communications. Participants were then assigned to their primary intervention and scheduled to return for follow-up visits at months 1, 2, 3, 6, and 9, at which they were assessed for HIV using point-of-care rapid tests. Participants with reactive HIV tests were taken off PrEP and linked to HIV treatment after confirmatory testing. Dried blood spots were collected at months 2, 3, 6, and 9 by trained laboratory staff via a finger prick and intraerythrocytic tenofovir diphosphate concentrations (ie, a cumulative measure of PrEP dosing)[22] were quantified at the University of Cape Town (Cape Town, South Africa). At any visit when either participant-driven or provider-driven discontinuation of PrEP was reported, the trial clinician (NP) completed a PrEP-discontinuation case-report form, noting date of discontinuation, reason, and whether discontinuation was temporary or permanent. Temporary discontinuations were updated with date of re-start. Discontinuation procedures were informed by South African PrEP-delivery guidelines.[13] Serious adverse events, instances of creatinine clearance less than 60 mL per min, PrEP tolerability or side-effects

that led to PrEP discontinuation, and social harms associated with participation were recorded by NP and reported to ethics review boards as required.

Participants assigned to two-way SMS received messages one per week asking, "Are you well, girlfriend?", based on WelTel and HPTN 082 approaches.[4,12,23] Participants who responded "No" received a telephone call from a PrEP counsellor or clinician (NP, SM, or MM) within 24 h of responding. Those who did not respond within 24 h automatically received a second message, which was a repeat of the first. Participants who did not respond to either message received a follow-up call within 24 h of the second non-response.

Participants assigned to WhatsApp were put into groups with approximately 25 participants. Groups were moderated by a staff facilitator (PZ), who introduced monthly themed topics (eg, based on local holidays or trending issues in the news) to stimulate discussion. Groups also had the opportunity to meet in person once every 3 months for about 2 h.[12] Each month, facilitators developed a plan that consists of activities and topics such as "Ladies Night" or "Ask a Doctor", games, and memes to stimulate discussions. The topics were informed by participants, public holidays, and issues trending in social media and the news. During group meetings, conversations developed organically from those activities and topics and were focused broadly on things happening in the lives and relationships of participants. Specific discussions about PrEP adherence which were largely participant led.

At month 3, participants with low PrEP adherence, indicated by tenofovir diphosphate less than 500 fmol per punch from a dried blood spot sample at their month 2 visit or by missing PrEP refills at months 1 or 2, were randomly assigned to a secondary, intensified intervention of issue-focused counselling once per month or drug-level feedback counselling based on PrEP drug concentrations at months 3 and 6. We used a cutoff of 500 fmol per punch, corresponding to about 2–3 PrEP doses per week, to measure whether a participant responded or did not respond to their primary intervention.[14] This cutoff differed from the level of tenofovir diphosphate defining PrEP adherence in our primary analysis (ie, 700 fmol per punch) as the cutoff of 500 fmol per punch is a more sensitive threshold to classify consistent dosing after 2 months of PrEP use and ensured that we were able to allocate additional adherence-support resources to young women who had the greatest difficulty taking PrEP regularly. We also used missed visits as an indicator of not responding to the intervention; those who missed visits also missed their PrEP refills and could be presumed to have low PrEP adherence. Secondary randomisation occurred at month 3 and followed the same procedures, with participants assigned (1:1) to either drug-level feedback counselling at months 3 and 6 or issue-focused counselling at visits at months 4, 5, 7, and 8.[12] Participants who were randomly assigned to secondary interventions at month 3 also continued to receive their primary intervention throughout follow-up. Secondary randomisation assignments were stratified by primary-intervention arm and we generated variable block sizes between 8–10 in SAS version 9.4.

On the basis of tenofovir diphosphate in dried blood spot samples obtained at month 2, participants assigned to drug-level feedback received counselling at month 3 in person and after month 6 via telephone. Counselling after month 6 was provided on the basis of dried blood spot samples taken at the month 6 visit. Participants with tenofovir diphosphate less than the limit of quantification (ie, <16 fmol per punch) were asked whether they were still interested in taking PrEP and, if so, what support could be provided. Those with tenofovir diphosphate between 16 and 499 fmol per punch received counselling on the importance of taking PrEP consistently and barriers to taking PrEP were explored. Those with tenofovir diphosphate 500 fmol per punch or more were encouraged to continue taking PrEP regularly for HIV prevention.[12] Drug-level feedback counselling was conducted by MM and SM at the trial site; they had previous experience in problem-solving and motivational interviewing with African young women using PrEP. Clinicians received 2-day training on drug-level feedback counselling and the trial protocol. A subset of drug-level feedback counselling sessions were recorded and reviewed by JV, NP, NN, and NN-K, who provided feedback on counselling sessions as needed.

Participants assigned to monthly issue-focused counselling were asked to return to the clinic site or Ward 21 at months 4, 5, 7, and 8 to receive counselling on topics of their choosing and relevant to their PrEP adherence (eg, relationships, depression, or financial planning). They were also given the option to complete counselling visits via telephone. Counselling was grounded in an interactive, participant-led, problem-solving, cognitive-behavioural approach, with manuals adapted from HPTN 082 and MTN-034/REACH.[4,11] Each session was 20–60 min, and a subset of sessions were recorded to monitor fidelity. Issue-focused counselling was also conducted by MM and SM. These counsellors had experience in issue-focused counselling from HPTN 082 and MTN-034/REACH, on which manuals were based, and they completed 1-week training on issue-focused-counselling procedures. A subset of counselling sessions were recorded and reviewed by JV, NP, NN, and NN-K, for supervision and feedback.

Outcomes

The primary outcome was high PrEP adherence at month 9, defined as concentration of tenofovir diphosphate on dried blood sample of 700 fmol per punch or more, consistent with taking 4–7 pill doses per week and almost 100% PrEP efficacy.[22] The secondary outcome was the short-term effect of two-way SMS communication or participation in a WhatsApp peer-support group on concentrations of tenofovir diphosphate at month 2.

Statistical analysis

This trial had 84% power to detect a 15% difference in concentrations of tenofovir diphosphate between the two-way SMS and WhatsApp peer-support group arms among 350 young women who initiated PrEP. Assuming that 70–105 participants in each primary intervention arm would not respond to treatment and would therefore be randomly assigned again, the trial had 79–95% power to detect a 30% difference in tenofovir diphosphate concentrations between secondary-counselling intervention arms (appendix p 1).

For the primary intention-to-treat (ITT) analysis, we used a Poisson regression to compare PrEP adherence at month 9 with a threshold of 700 fmol per punch between the two-way SMS and WhatsApp peer-support group arms. We also used a Poisson regression for the secondary ITT analysis to compare the effect of the primary interventions on PrEP adherence at month 2. Participants with missing tenofovir diphosphate were assigned to the low-adherence group.

To compare the effect of our primary interventions on PrEP adherence in the subset of young women who remained engaged and interested in PrEP, we conducted a modified ITT analysis with participants who were randomly assigned and returned for at least one trial visit between month 1 and month 3. Our per-protocol analyses comparing PrEP adherence by primary intervention excluded participants who did not fully receive the two-way SMS or WhatsApp interventions because they opted out of their assigned interventions or because of investigator removal, as well as those with missing dried blood samples for tenofovir diphosphate testing. We believed the per-protocol analysis would provide additional insights into the effect of our interventions specifically among young women with continued interest in PrEP and in engagement with the intervention approaches.

To compare differences in the effect of the secondary interventions (ie, drug-level feedback counselling *vs* monthly issue-focused counselling) on PrEP adherence, we conducted an ITT analysis of adherence at month 9 using Poisson regression without adjustment for or stratification on the primary intervention arm. We used the same procedures related to missing data and loss to follow-up. To assess whether people who did or did not respond to these interventions differed in HIV risk and continuing need for PrEP at month 3, we used logistic regression to assess associations between HIV risk factors at enrolment and month 1 (ie, predictors) and subsequent randomisation again at month 3 (ie, outcome). We defined HIV risk as a binary variable based on South African guidelines for PrEP eligibility (eg, condomless sex and at least one sexual partner).[24] We also conducted a modified ITT analysis with the subset of participants who returned for a visit between month 1 and month 3. The per-protocol analysis excluded participants who did not receive drug-level feedback counselling or monthly counselling and those with missing dried blood samples and tenofovir diphosphate.

Finally, we assessed the optimal adherence-support strategy among four embedded dynamic treatment strategies (ie, two-way SMS followed by monthly counselling, two-way SMS followed by drug-level feedback counselling, WhatsApp followed by monthly counselling, and WhatsApp followed by drug-level feedback counselling) for people who did not respond to the intervention. We used a weighted and replicated approach to account for non-response, re-randomisation, and overlap in intervention assignments (eg, the same participants in the SMS intervention were represented twice in two of the four interventions).[25] Weighting accounted for over-representation of people who responded, whereas replicating responder observations across the two embedded dynamic treatment strategies with the same first-line treatment accounted for one participant being able to be in two treatment strategies. We modelled replicated data for our primary analysis with a weighted, generalised estimating-equation model with log-link function, fitted with robust SEs and an independent working-correlation matrix in which clusters were individual participants. Using this model, we estimated the proportion of participants with tenofovir diphosphate 700 fmol per punch or more, and corresponding 95% CIs, for each of the four embedded dynamic treatment strategies at month 9 (appendix pp 2–4).

We used person-years were used to calculate the denominator for HIV incidence on the basis of the length of time each individual was followed up in our study, with participants censored at the time of HIV seroconversion or trial termination.

For secondary analyses, we constructed a risk-prediction tool to estimate the probability of PrEP adherence at month 9 (appendix p 5) and explored changes in socio-behavioural characteristics over time (appendix p 6).

We conducted a sensitivity analysis excluding all missing outcome data and explored whether missing data were different between the two arms.

We did all analyses using R version 4.2 and SAS version 9.4.

See Online for appendix

Role of the funding source

The funder of the trial had no role in trial design, data collection, data analysis, data interpretation, or writing of the report.

Results

Participants were enrolled and followed up between May 16, 2019, and Jan 25, 2022. From May 16, 2019, to Jan 29, 2021, 401 participants were screened and 360 were enrolled and initiated PrEP. 180 (50%) were randomly assigned to two-way SMS and 180 (50%) were randomly assigned to WhatsApp support groups (figure). At month 3, 85 (47%) of 180 participants in the two-way SMS

group and 70 (39%) of 180 participants in the WhatsApp group were categorised as not responding to treatment and randomly assigned again to the second-level intervention. 12 (3%) of 360 participants (ie, six in two-way SMS and six in WhatsApp) discontinued the trial before month 9 and were not included in the primary analysis. Despite the COVID-19 pandemic, 172 (88%) of 196 participants who responded and 107 (69%) of 155 participants who did not respond completed their month-9 visit. Tenofovir diphosphate concentrations were available for 132 (73%) of 180 participants in the two-way SMS arm and 134 (74%) of 180 participants in the WhatsApp arm at month 9. PrEP discontinuations did not differ by arm; 19 (11%) of 180 participants in the two-way SMS arm and 18 (10%) of 180 participants in the WhatsApp arm had at least one PrEP discontinuation (p=0·87).

Participant baseline characteristics were balanced by primary intervention arm (table 1). Median age at enrolment overall was 21·0 years (IQR 20·0–23·0). At enrolment, 255 (71%) of 360 participants had had a primary sexual partner in the past 3 months and 113 (31%) had a curable STI (table 1).

At month 9, 34 (20%) of 174 participants in the two-way SMS arm had tenofovir diphosphate 700 fmol per punch or more, compared with 32 (18%) of 174 in the WhatsApp arm (relative risk [RR] 1·06, 95% CI 0·69–1·64; p=0·78; table 2). Results were similar for the modified ITT (1·09,

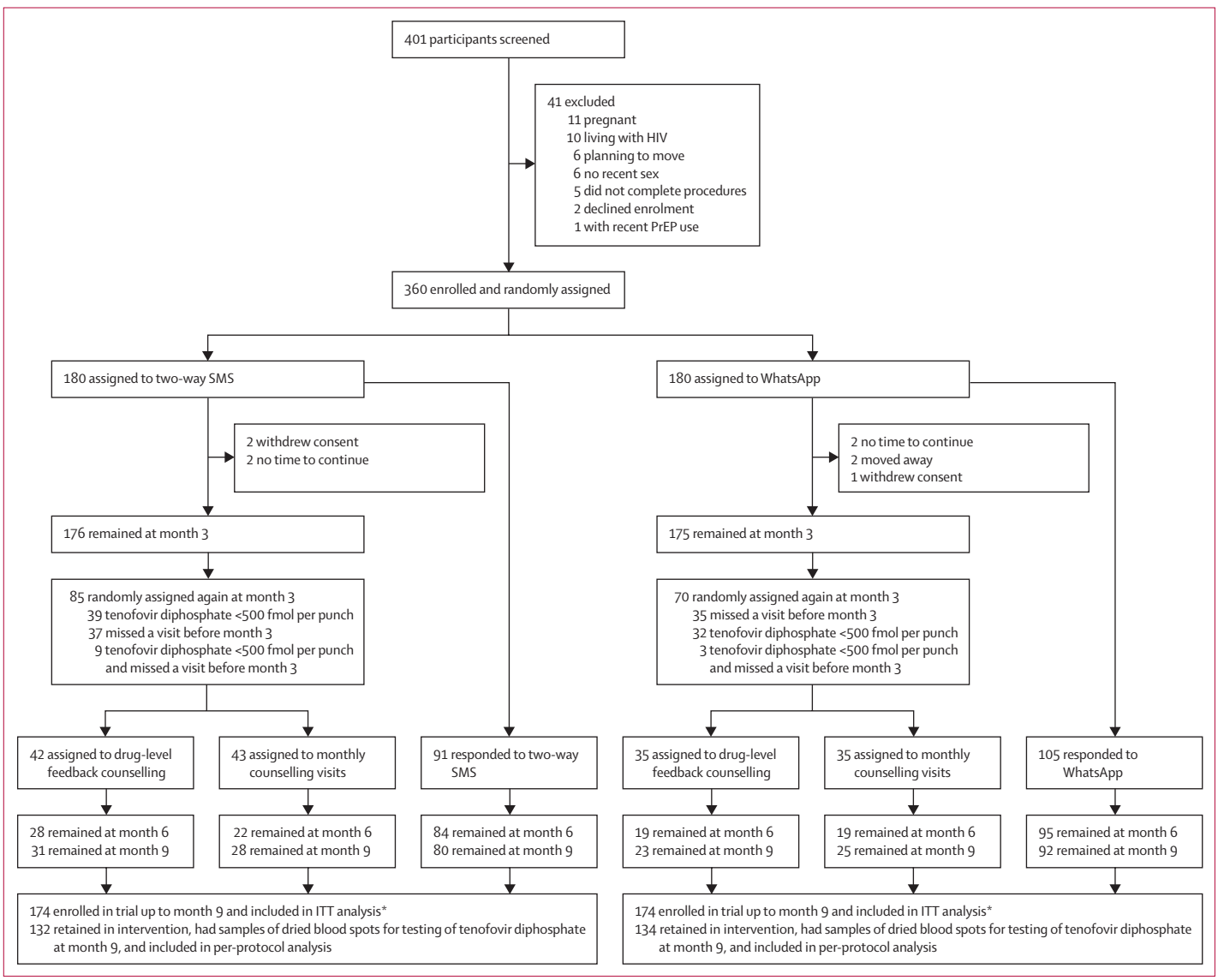

Figure: **Trial profile**
ITT=intention to treat. PrEP=pre-exposure prophylaxis. *12 participants (six per arm) dropped out before their final visit at month 9 and were not included in the ITT analysis. Nine participants dropped out immediately after enrolment and initial randomisation; two participants attended the visit at month 1 and were randomly assigned again in absentia at month 3, but did not attend any visits after month 1 or complete any trial procedures; and one participant was randomly assigned again at month 3 but was found to have seroconverted before that visit.

0·70–1·69; p=0·70) and per-protocol analyses (1·08, 0·71–1·64; p=0·72; table 2).

2 months after PrEP initiation, 196 (55%) of 360 young women had tenofovir diphosphate less than 700 fmol per punch. In a secondary analysis comparing PrEP adherence at month 2 between the two primary intervention arms, 78 (43%) of 180 in the two-way SMS arm and 86 (48%) of 180 in the WhatsApp arm had tenofovir diphosphate 700 fmol per punch or more (RR 0·91, 95% CI 0·72–1·13; p=0·40; table 2). Neither of the primary interventions affected short-term adherence in the modified ITT (0·89, 0·72–1·10; p=0·29) or per-protocol analyses either (0·94, 0·77–1·14; p=0·54).

155 (43%) of 360 participants who did not respond to initial interventions were randomly assigned again to either drug-level feedback counselling or monthly issue-focused counselling at month 3. 85 (47%) of 180 participants in the SMS arm and 70 (39%) of 180 in the WhatsApp arm were randomly assigned again (figure). 72 (47%) of 155 participants were randomly assigned again due to a missed visit between months 1 and 3, 71 (46%) due to tenofovir diphosphate less than 500 fmol per punch in month 2 dried blood samples, and 12 (8%) had both a missing visit and tenofovir diphosphate less than 500 fmol per punch. There was no association between baseline HIV risk at enrolment (odds ratio [OR] 0·93, 95% CI 0·52–1·66; p=0·80) or month 1 (1·06, 0·69–1·63; p=0·78) and not responding to the interventions at month 3.

At month 9, four (5%) of 76 participants in the drug-level feedback arm had tenofovir diphosphate 700 fmol per punch or more, compared with three (4%) of 76 participants in the monthly counselling arm (RR 1·33, 95% CI 0·31–5·76; p=0·70; table 3). PrEP adherence at month 9 did not vary between drug-level feedback and monthly counselling arms in the modified ITT (1·36, 0·24–7·87; p=0·73) or per-protocol analyses (1·36, 0·32–5·77; p=0·68; table 3).

The probability of high PrEP adherence at month 9 did not vary across the four embedded dynamic treatment strategies (p=0·94; table 4). Among 264 participants with a dried blood sample available at month 9, we estimated tenofovir diphosphate 700 fmol per punch to be 27% (95% CI 19–36) in participants who received two-way SMS alone or two-way SMS then drug-level feedback, 25% (18–34) in those who received two-way SMS alone or two-way SMS then monthly counselling, 24% (17–33) in those who received WhatsApp alone or WhatsApp then drug-level feedback, and 24% (17–33) in those who received WhatsApp alone or WhatsApp then monthly counselling.

22 serious adverse events were reported during the trial (table 5): 14 (64%) hospitalisations for conditions unrelated to the trial or PrEP, five (23%) pregnancy-related issues, two (9%) attempted drug overdoses on PrEP, and one (5%) death. All serious adverse events were deemed unrelated to the trial.

Four (1%) of 360 participants acquired HIV during our trial, an HIV incidence of 1·1 (95% CI 0·3–2·9) per 100 person-years. All four participants were in the two-way SMS arm; one responded to the intervention, two did not respond to the intervention and were assigned to drug-level feedback counselling, and one did not respond to the intervention and was assigned to monthly counselling. In three of these four participants, tenofovir

	WhatsApp	Two-way SMS	Total
Assigned female sex at birth	180/180 (100%)	180/180 (100%)	360/360 (100%)
Age, years	21·5 (20·0–23·0)	21·0 (20·0–23·0)	21·0 (20·0–23·0)
Highest education			
No schooling	1/180 (1%)	1/180 (1%)	2/360 (1%)
Primary school	26/180 (14%)	20/180 (11%)	46/360 (13%)
Secondary school	136/180 (76%)	144/180 (80%)	280/360 (78%)
University	17/180 (9%)	15/180 (8%)	32/360 (9%)
Number of sexual partners in the past 3 months*	2·0 (1·0–2·0)	2·0 (1·0–2·0)	2·0 (1·0–2·0)
Had a primary sexual partner in the past 3 months	130/180 (72%)	125/180 (69%)	255/360 (71%)
Age difference with primary partner			
Within 2 years of own age	29/120 (24%)	33/111 (30%)	62/231 (27%)
3–10 years older	86/120 (72%)	71/111 (64%)	157/231 (68%)
11–20 years older	5/120 (4%)	7/111 (6%)	12/231 (5%)
HIV status of primary partner			
Negative	67/130 (52%)	64/120 (53%)	131/250 (52%)
Positive	1/130 (1%)	4/120 (3%)	5/250 (2%)
Unknown	62/130 (48%)	52/120 (43%)	114/250 (46%)
Primary partner had other partners			
Yes	57/130 (44%)	53/119 (45%)	110/249 (44%)
No	21/130 (16%)	25/119 (21%)	46/249 (18%)
Unknown	52/130 (40%)	41/119 (35%)	93/249 (37%)
Number of vaginal sexual acts in the past 3 months†	4·0 (2·0–7·0)	4·0 (2·0–7·0)	4·0 (2·0–7·0)
Any transactional sex in the past 3 months	42/171 (25%)	38/164 (23%)	80/335 (24%)
Condom use with vaginal sex in the past month			
Never	33/153 (22%)	41/153 (27%)	74/306 (24%)
Rarely	30/153 (20%)	26/153 (17%)	56/306 (18%)
Sometimes	47/153 (31%)	56/153 (37%)	103/306 (34%)
Often	23/153 (15%)	18/153 (12%)	41/306 (13%)
Always	20/153 (13%)	12/153 (8%)	32/306 (10%)
HIV risk perception and salience score‡	19·0 (16·0–22·0)	19·0 (15·0–21·0)	19·0 (15·0–22·0)
VOICE risk score§	8·0 (6·0–8·0)	8·0 (6·0–8·0)	8·0 (6·0–8·0)
PrEP stigma score¶	8·0 (6·0–10·0)	8·0 (6·0–10·0)	8·0 (6·0–10·0)
Social support score‖	31·0 (27·0–33·0)	31·0 (27·0–34·0)	31·0 (27·0–33·0)
Any intimate partner violence in the past year**	97/180 (54%)	98/180 (54%)	195/360 (54%)
Rosenberg self-esteem score††	19·0 (17·0–23·0)	19·0 (16·0–23·0)	19·0 (17·0–23·0)
Depressive symptoms‡‡	102/178 (57%)	83/177 (47%)	185/355 (52%)
Any traumatic stress symptoms§§	100/180 (56%)	106/179 (59%)	206/359 (57%)
Harmful or hazardous alcohol use¶¶	114/179 (64%)	115/178 (65%)	229/357 (64%)

(Table 1 continues on next page)

diphosphate was less than the lower limit of detection at the visit when HIV seroconversion was detected. For the remaining participant who seroconverted at month 9, tenofovir diphosphate was 2190 fmol per punch at the visit when seroconversion was detected. Tenofovir diphosphate was 1323 fmol per punch at the month-2 visit and we have no further drug-level data from visits before month 9. Three of the four participants had no resistance mutations, including the participant with high tenofovir diphosphate, and one had a nucleoside reverse transcriptase inhibitor mutation (ie, Lys219Glu) unrelated to tenofovir or emtricitabine.

Discussion

In our sequential multiple-assignment randomised trial evaluating adaptive PrEP-support strategies, PrEP adherence did not differ across interventions among young women in Johannesburg, South Africa. PrEP adherence also did not differ between four embedded dynamic treatment strategies. Sequential multiple-assignment randomised trials are useful to assess stepped adherence-support models by providing data on optimal timing of intervention switches, criteria prompting escalation or de-escalation of services, and outcomes from adaptive interventions while controlling for confounding.

2 months after PrEP initiation, 196 (55%) of 360 young women had tenofovir diphosphate less than 700 fmol per punch, consistent with PrEP dosing four or more times per week and a value associated with HIV protection in an analysis of adolescent girls and women aged 15–69 years taking oral tenofovir-based PrEP.[26] However, PrEP adherence decreased across the four treatment strategies throughout our trial, even with more PrEP-adherence support for people who did not respond to the intervention, and did not differ across four embedded dynamic treatment strategies. Nevertheless, PrEP adherence at month 2 and estimated PrEP adherence at month 9 in this trial were higher than in the POWER demonstration project and HPTN 082.[2–4] The effect of our interventions on PrEP adherence could not be quantified without a standard-of-care comparison group, but were likely insufficient to overcome individual and interpersonal barriers to PrEP use (eg, concerns about side-effects, pill reminders, or challenges with social support). Despite our interventions not differing from one another in their effect on PrEP adherence, our trial was a successful implementation of a sequential multiple-assignment randomised trial to evaluate different PrEP-adherence interventions, a feasible and efficient trial design to guide future PrEP implementation.

Previous studies evaluating the effect of two-way SMS messages for PrEP adherence have reported mixed results. In a quasi-experimental study, pregnant and postpartum women in Kenya had higher PrEP uptake and persistence after receiving two-way SMS support messages than before.[27] By contrast, a trial of young

	WhatsApp	Two-way SMS	Total
(Continued from previous page)			
Contraceptive use			
Oral	13/180 (7%)	12/180 (7%)	25/360 (7%)
Injectable	46/180 (26%)	45/180 (25%)	91/360 (25%)
Implant	15/180 (8%)	8/180 (4%)	23/360 (6%)
Intrauterine device	1/180 (1%)	3/180 (2%)	4/360 (1%)
Condoms	38/180 (21%)	39/180 (22%)	77/360 (21%)
None	67/180 (37%)	73/180 (41%)	140/360 (39%)
Had a curable STI (ie, gonorrhoea, chlamydia, trichomonas, or syphilis)	51/180 (28%)	62/180 (34%)	113/360 (31%)

Data are n/N (%) or median (IQR). PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. VOICE=Vaginal and Oral Interventions to Control the Epidemic. *n=166 in Whatsapp group, n=157 in SMS group, and n=323 total. †n=339. ‡Possible range 9–36, with higher values indicating greater risk perception. §Calculated on the basis of age, marital status, whether the primary partner provided financial or marital support, whether the primary partner had other partners, and alcohol use. We used the modified version of the VOICE risk score that does not include curable STI as a component. ¶Possible range 0–18, with higher values indicating greater endorsement of PrEP stigma. ||Possible range 10–40, with higher values indicating greater feelings of social support. **Assessed physical, emotional, and sexual violence or being made to feel unsafe by an intimate partner. ††Possible range 0–30. ‡‡Possible range 0–30, with scores of 10 or more indicating increased depressive symptoms. §§Participants who endorsed at least three of four items were considered to have traumatic stress symptoms. ¶¶Possible range 0–12, with scores of 3 or more indicating harmful or hazardous alcohol use.

Table 1: **Demographic and behavioural characteristics of participants at enrolment, by primary intervention arm**

	Month 2 (secondary outcome)				Month 9 (primary outcome)			
	Two-way SMS	WhatsApp	Relative risk (95% CI)*	p value	Two-way SMS	WhatsApp	Relative risk (95% CI)*	p value
ITT analysis (n=360 at month 2; n=348 at month 9)†								
Tenofovir diphosphate ≥700 fmol per punch	78/180 (43%)	86/180 (48%)	0·91 (0·72–1·13)	0·40	34/174 (20%)	32/174 (18%)	1·06 (0·69–1·64)	0·78
Modified ITT analysis (n=325 at month 2; n=320 at month 9)‡								
Tenofovir diphosphate ≥700 fmol per punch	78/164 (48%)	86/161 (53%)	0·89 (0·72–1·10)	0·29	34/163 (21%)	30/157 (19%)	1·09 (0·70–1·69)	0·70
Per-protocol analysis (n=359 at month 2; n=347 at month 9)§								
Tenofovir diphosphate ≥700 fmol per punch	78/137 (57%)	86/142 (61%)	0·94 (0·77–1·14)	0·54	34/132 (26%)	32/134 (24%)	1·08 (0·71–1·64)	0·72

Data are n/n (%), unless otherwise stated. ITT=intention to treat. PrEP=pre-exposure prophylaxis. *Reference for all relative risks is the WhatsApp arm. †Included all randomly assigned participants who had not left the trial by months 2 or 9. Participants with missing tenofovir diphosphate data were assigned to <700 fmol per punch. ‡Included all randomly assigned participants who had not left the trial by months 2 or 9 and had attended at least one trial visit between month 1 and the decision to randomly assign participants again at month 3. §Included all randomly assigned participants who remained in the SMS or WhatsApp interventions throughout the entire follow-up; excluded participants who opted out of the interventions, who were removed from the interventions by trial staff, who were lost to follow-up, and who did not have samples of dried blood spots available for testing of tenofovir diphosphate.

Table 2: **PrEP adherence at months 2 and 9, by primary intervention arm**

women in Kenya found no effect of daily two-way SMS messages on PrEP adherence, despite high acceptability and feasibility.[28] In a qualitative sub-study of that trial, participants described challenges with two-way SMS that included privacy concerns, SMS fatigue, telephone loss, poor telephone network, and lack of electricity.[29] In our own qualitative analysis using data from this trial, participants described similar technological challenges with a two-way SMS intervention, and the issues of telephone access, privacy, and network connectivity also applied to a WhatsApp intervention.[30] In-person PrEP adherence-support groups, which informed our WhatsApp model, were liked by adolescent girls and young women in South Africa and Tanzania as they were safe spaces to share problems with PrEP use or in relationships, as well as reducing social isolation.[31] However, these in-person groups did not increase PrEP continuation and were difficult to schedule and coordinate.[10] We included two-way SMS and WhatsApp as our primary interventions because they would involve less participant burden and clinic-based procedures than the counselling interventions and we thought that they would improve PrEP adherence through increased participant knowledge, social support, and participant empowerment through direct communication from a provider-like figure in the SMS arm and through peer support in the WhatsApp arm. However, they were both still time-intensive for staff monitoring the messages and could have been too similar to affect PrEP adherence. Future work is needed to assess optimal approaches to implementing WhatsApp groups as an alternative support model.

Previous studies evaluating the effect of second-line counselling interventions, such as drug-level feedback and problem-focused counselling, have also reported mixed findings on effectiveness, acceptability, and feasibility. The HPTN 082 trial did not find an effect of drug-level feedback counselling informed by tenofovir diphosphate on PrEP adherence during a 6-month period.[4] However, the counselling was acceptable and HIV incidence in the cohort was lower than expected.[4,30] The implementation of drug-level feedback counselling via data from dried blood samples is limited by the time between collection of the sample and counselling received based on the result. This time lag might weaken the effect on of the intervention on PrEP adherence. However, a urine point-of-care assay for real-time adherence monitoring and drug-level feedback could mitigate these challenges.[32]

Few studies have evaluated the effect of enhanced problem-focused counselling or monthly visits on PrEP adherence among African young women. PrEP demonstration projects have consistently reported declines in PrEP adherence in this population as they move from a monthly to 3-monthly visit schedule.[3–6] Pilot trials of enhanced counselling based on problem-solving techniques have reported high acceptability and fidelity, as well as some signal of possible effectiveness, in improving medication adherence for adolescents and young people aged 15–22 years in the USA and Zimbabwe.[33,34] These pilot trials highlight the promise of and challenges with counselling interventions to promote PrEP adherence and offer insights into how future PrEP programmes could implement these approaches with greater success. Considering the high rates of depression and trauma symptoms seen in our population and in HPTN 082,[4] more targeted mental health services might be needed to improve overall wellbeing and engagement with HIV prevention services. We chose drug-level feedback and monthly counselling as our second-line interventions because of high acceptability in HPTN 082[4] and because they were more time-intensive and resource-intensive than WhatsApp and SMS. They also allowed for directed problem-solving about specific adherence barriers. However, again, these approaches might have been too similar in their mechanism of action to detect a difference in PrEP adherence and we were restricted in studying the effect of these interventions due to low retention in people who did not respond to the interventions. Individual and

	Drug-level feedback counselling	Monthly counselling	Relative risk (95% CI)*	p value
ITT analysis (n=152)†				
Tenofovir diphosphate ≥700 fmol per punch	4/76 (5%)	3/76 (4%)	1·33 (0·31–5·76)	0·70
Modified ITT analysis (n=124)‡				
Tenofovir diphosphate ≥700 fmol per punch	3/65 (5%)	2/59 (3%)	1·36 (0·24–7·87)	0·73
Per-protocol analysis (n=99)§				
Tenofovir diphosphate ≥700 fmol per punch	4/49 (8%)	3/50 (6%)	1·36 (0·32–5·77)	0·68

PrEP=pre-exposure prophylaxis. *Reference for all relative risks is the monthly counselling arm. †Included all randomly assigned participants who had not left the trial by month or 9. Participants with missing tenofovir diphosphate data were assigned to <700 fmol per punch. ‡Included all randomly assigned participants who had not left the trial by month 9 and had attended at least one trial visit between month 1 and the decision to randomly assign participants again at month 3. §Included all randomly assigned participants who remained in the drug-level feedback or monthly counselling interventions throughout the entire follow-up; excluded participants who opted out of the interventions, who were removed from the interventions by trial staff, who were lost to follow-up, and who did not have samples of dried blood spots available for testing of tenofovir diphosphate.

Table 3: **PrEP adherence at month 9 among 155 participants who did not respond to the primary intervention, by secondary intervention arm**

	Estimated adherence (95% CI)	p value
Global	..	0·94
SMS alone or SMS then monthly counselling for 134 participants	0·25 (0·18–0·34)	..
SMS alone or SMS then drug-level feedback counselling for 133 participants	0·27 (0·19–0·36)	..
WhatsApp alone or WhatsApp then monthly counselling for 140 participants	0·24 (0·17–0·33)	..
WhatsApp alone or WhatsApp then drug-level feedback counselling for 140 participants	0·24 (0·17–0·33)	..

We defined high PrEP adherence as tenofovir diphosphate ≥700 fmol per punch. PrEP=pre-exposure prophylaxis.

Table 4: **Estimated PrEP adherence at month 9 for embedded dynamic treatment strategies among participants who had available data**

	Patient identification number	Onset date	Severity	Related to PrEP	PrEP status	Resolution date
Death due to complications with a molar pregnancy	29–0223	June 4, 2020	Grade 5, death	Not related	Permanently discontinued	NA
Ectopic pregnancy	29–0025	Oct 9, 2019	Grade 4, potentially life threatening	Not related	Continued	Oct 18, 2019
PrEP overdose related to suicide attempt	29–0090	Oct 28, 2019	Grade 4, potentially life threatening	Not related	Temporarily discontinued	Nov 28, 2019
PrEP overdose related to suicide attempt	29–0183	Sept 2, 2020	Grade 4, potentially life threatening	Not related	Temporarily discontinued	Sept 8, 2020
Hospitalisation due to headache	29–0001	Not reported	Grade 3, severe	Not related	Permanently discontinued	Dec 20, 2019
Hospitalisation due to high-risk pregnancy	29–0029	June 4, 2020	Grade 3, severe	Not related	Permanently discontinued	June 5, 2020
Hospitalisation for abscess	29–0075	Sept 28, 2019	Grade 3, severe	Not related	Continued	Oct 5, 2019
Hospitalisation for anaemia	29–0117	July 19, 2020	Grade 3, severe	Not related	NA as not taking PrEP at time of event	July 21, 2020
Hospitalisation for spontaneous pregnancy loss	29–0120	Dec 5, 2019	Grade 3, severe	Not related	Continued	Dec 7, 2019
Hospitalisation for severe pre-eclampsia	29–0154	Aug 11, 2020	Grade 3, severe	Not related	Continued	Aug 1, 2020
Hospitalisation for wrist laceration after vehicle accident	29–0183	Nov 27, 2020	Grade 3, severe	Not related	Continued	Dec 4, 2020
Hospitalisation for anaemia	29–0196	July 24, 2020	Grade 3, severe	Not related	Continued	July 26, 2020
Hospitalisation for soft tissue injuries after vehicle accident	29–0256	March 28, 2021	Grade 3, severe	Not related	Continued	March 29, 2021
Hospitalisation for traumatic brain injury and follow-up assessment from vehicle accident	29–0256	Not reported	Grade 3, severe	Not related	Continued	Not reported
Hospitalisation for incomplete miscasrriage	29–0272	May 11, 2021	Grade 3, severe	Not related	NA as not taking PrEP at time of event	May 11, 2021
Hospitalisation for knee dislocation	29–0314	March 10, 2021	Grade 3, severe	Not related	Continued	March 12, 2021
Hospitalisation for pelvic inflammatory disease	29–0329	Feb 3, 2021	Grade 3, severe	Not related	Continued	Feb 4, 2021
Hospitalisation for tonsilitis	29–0371	May 9, 2021	Grade 3, severe	Not related	Continued	May 12, 2021
Hospitalisation for COVID-19	29–0372	June 22, 2021	Grade 3, severe	Not related	Temporarily discontinued	July 4, 2021
Hospitalisation for deep vein thrombosis	29–0401	Aug 13, 2021	Grade 3, severe	Not related	Temporarily discontinued	Aug 27, 2021
Hospitalisation for worsening deep vein thrombosis	29–0401	Oct 11, 2021	Grade 3, severe	Not related	NA as not taking PrEP at time of event	Oct 12, 2021
Hospitalisation for traumatic brain injury and follow-up assessment from vehicle accident	29–0256	Not reported	Grade 3, severe	Not related	Continued	Not reported

NA=not applicable.

Table 5: **Serious adverse events recorded during the trial**

interpersonal adherence-support interventions alone are probably insufficient to promote PrEP initiation among African young women or to facilitate adherence among them if they desire biomedical HIV prevention. For young women who might desire biomedical HIV prevention products but who have challenges with daily oral PrEP use, we believe that long-acting PrEP formulations could improve PrEP coverage and reduce HIV incidence.

43% of participants in our trial were randomly assigned again at month 3, primarily due to missed visits in the first 2 months. Other PrEP implementation programmes with African young women have similarly reported large, early drop-offs in PrEP persistence and adherence.[3–5] In the PrEP SMART trial, adolescent girls and young women in South Africa with low or no PrEP adherence had low retention returning to the clinic for more intensive, in-person, clinic-based counselling interventions.[30] Although the COVID-19 pandemic could have contributed to reluctance to attend clinics, these results could indicate little desire for clinic-based counselling among young women with existing PrEP challenges and potentially highlight the value of de-medicalised PrEP delivery. Trials of stepped-adherence interventions to support young people living with HIV and pregnant and postpartum people engaging in PrEP will add key insights to the field.[35] Moreover, promising findings on community-based, differentiated models of PrEP-adherence support offer new approaches that could be used to re-engage African young women who struggle returning to clinic and adhering to PrEP.[36]

The strengths of this trial include an innovative design to explore the effectiveness of different PrEP adherence-support interventions. Our team was experienced in delivering adherence-support interventions and we were able to adapt our procedures to offer remote PrEP delivery and counselling as needed.

There are several limitations of this trial. First, retaining participants who had low adherence was difficult after the initial interventions, resulting in less retention in participants assigned to the monthly counselling and drug-level feedback arms. Second, we did not include a run-in period to identify African young women who were newly initiating PrEP but quickly decided to stop using it. Therefore, our participants who were re-randomised approximated a real-word population including those who were interested in PrEP but had adherence challenges and

those who had decided they were no longer interested in PrEP. However, in a true real-world scenario, we probably would not continue to intervene on a subset of young women with PrEP-adherence challenges who decided they were no longer interested in or able to use PrEP. Third, only trial investigators were masked to intervention assignments. However, we believe the lack of masking did not affect participant engagement (all participants were receiving an active intervention), clinic-based procedures, or outcome ascertainment (both interventions were received primarily outside of the clinic setting). Fourth, we did not compare the interventions to standard-of-care PrEP delivery, to allow for efficient use of resources. Fifth, sequential multiple-assignment randomised trials necessitate the choice of a re-randomisation definition and timepoint; we chose tenofovir diphosphate at month 2 because of large drop-offs in PrEP adherence and persistence during months 1–3 after PrEP initiation.[2–4,25] However, our chosen timepoint and threshold might have failed to identify young women who could have benefited from adherence support earlier in the trial or could have resulted in the misclassification of girls and young women as not needing additional adherence support when they were struggling to take PrEP. Sixth, our analyses were primarily powered on the basis of the effectiveness of our first-line interventions compared with one another because of challenges with accurately estimating power for second-line interventions, which require assumptions about rate of response to the first-line interventions and effectiveness of second-line interventions only among people who did not respond to the intervention. This approach is typical for sequential multiple-assignment randomised trials, but could have compromised our ability to detect a statistically significant difference between drug-level feedback and monthly counselling. Seventh, we did not incorporate information on sexual behaviour or periods of risk to measure prevention-effective PrEP use, which could have resulted in additional misclassification. We expect that any misclassification was similar across arms, so could have weakened our ability to detect statistically significant differences. Eighth, our per-protocol and modified ITT analyses could have been biased if analysis subgroups differed on key covariates associated with PrEP adherence. Finally, this trial was conducted in a single research clinic in Johannesburg, so our results are not generalisable to public PrEP delivery programmes or areas where young women have different access to mobile telephones.

There are several lessons from this trial to inform future PrEP-adherence intervention efforts. First, we might have identified people who did not respond to the intervention too late (eg, at month 3 based on a missed visit and refill or low tenofovir diphosphate at month 2). Other stepped adherence-support approaches could consider identifying participants who are motivated to use PrEP earlier (eg, after 1 month), which would provide additional opportunities to provide interventions to those who were motivated to use PrEP and to change their adherence behaviours. Second, declining adherence between months 2 and 9 and similar response rates across the four embedded dynamic intervention approaches could indicate that motivations and perceived needs for PrEP declined over time in all arms, or that the combinations of interventions did not provide the type of support that participants needed to use PrEP consistently. Our individual-focused and interpersonal-focused interventions might have failed to address broad social factors (eg, experiencing stigma due to a pill bottle for PrEP that looks like bottles dispensed for antiretroviral therapy) and structural constraints to PrEP adherence. Third, although our two-way SMS and WhatsApp interventions were intended to provide different behaviour-change approaches (eg, from providers with two-way SMS and from peers with WhatsApp), the similarities between them could have prevented us from establishing whether one was more effective than the other. Future studies could further distinguish the two with different doses (eg, monthly SMS but weekly WhatsApp) or could include a standard-of-care arm for comparisons with routine PrEP delivery. Fourth, we had difficulties retaining participants, particularly during the COVID-19 pandemic; there is a need for retention approaches friendly to young women. Fifth, drug-level feedback counselling was challenging because of laboratory turnaround time and costs of sample processing, which restricted how frequently we could perform these tests. Use of point-of-care PrEP adherence assessments could enable real-time detection of tenofovir diphosphate and more timely drug-level feedback counselling in the future to provide an improved understanding of the effectiveness of this approach. Future research is needed on how, whether, and when to scale-up oral PrEP-adherence support and to whom to inform cost-effective and efficient PrEP delivery in resource-constrained settings and to improve the public health effects of PrEP among young women in sub-Saharan Africa.

Contributors

CC, SD-M, DD, SH, JMB, JV, NP, and NN-K designed this trial. CG, AM, and JV conducted all analyses. CG led all statistical analyses. AM and JV directly accessed and verified the underlying data, with help from DD. JV wrote the manuscript. NN, NP, and NN-K led study operations. PZ facilitated WhatsApp groups. SM and MM conducted all counselling procedures. All authors reviewed and approved the final version of the manuscript, had full access to all data in the trial, and had final responsibility for the decision to submit for publication.

Declaration of interests

The US National Institutes of Health (NIH) provides research grants to the institutions of JV, NP, AM, DD, PZ, and CC. JMB is an employee of Gilead Sciences who holds stock and options, and receives research grants from the US NIH. AM receives a research grant, paid to her institution, from the Bill & Melinda Gates Foundation and participates in a data safety monitoring board for a NCT04982250. CC receives a research grant, paid to her institution, from the Gates Foundation; receives research grants from Gilead Sciences, Merck, and GSK; and has received payment from Gilead Sciences for expert testimony. All other authors declare no competing interests.

Data sharing

De-identified, individual-level participant data with a data dictionary, as well as the study protocol, will be available with publication on request to the corresponding author. The statistical analysis plan will also be available. Data sharing is dependent on investigator support and approval of a proposal with a signed data access agreement.

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