Title: Friendship Bench Mental Health Intervention for Adolescent Girls and Young Women in South African PrEP Delivery Settings

NCT05664490

December 27, 2022

Funded by:
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)

Youth Friendship Bench SA
Optimization of the Friendship Bench mental health intervention for adolescent girls and young women in South African PrEP delivery settings

TABLE OF CONTENTS

Youth Friendship Bench SA
Optimization of the Friendship Bench mental health intervention for adolescent girls and young women in South African PrEP delivery settings

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AESI	adverse event of special interest
AGYW	adolescent girls and young women
AIDS	acquired immunodeficiency syndrome
AIM	acceptability of intervention measure
ART	antiretroviral therapy
CAB	community advisory board
CBT	cognitive behavioral therapy
CFIR	consolidated framework for implementation research
CRF	case report form
DBS	dried blood spots
DOH	Department of Health
DSMB	Data Safety Monitoring Board
EC	ethics committee
FB	Friendship Bench
FDA	Food and Drug Administration
FGD	focus group discussion
FIM	feasibility of intervention measure
FTC/TDF	emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF); Truvada®
GBV	gender based violence
GCP	Good Clinical Practice
HCD	human centered design
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IAM	intervention appropriateness measure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMB	information-motivation-behavioral skills model
INSC	integrated next step counseling
IRB	Institutional Review Board
MPI	multiple principal investigators
MSM	men who have sex with men
NIH	National Institutes of Health

PI	principal investigator
PK	Pharmacokinetics
POC	Point-of-care
PrEP	pre-exposure prophylaxis
PST	problem-solving therapy
SAE	serious adverse experience
SMS	short message service
SOC	standard of care
SOP	standard operating procedure
SRQ-20	Self reporting questionnaire 20-item
TFV-DP	tenofovir disoproxil fumarate diphosphate
TFV	tenofovir
UCSF	University of California San Francisco
US	United States
WHO	World Health Organization
WRHI	Wits Reproductive Health and HIV Institute
YCAB	youth community advisory board

Youth Friendship Bench SA
Optimization of the Friendship Bench mental health intervention for adolescent girls and young women in South African PrEP delivery settings

PROTOCOL TEAM ROSTER

Co-Chair: Sinead Delany-Moretlwe, MBChB, PhD Professor and Director: Research, Wits RHI University of Witwatersrand, 22 Esselen Street Hillbrow Johannesburg, Gauteng 2001, South Africa Phone: 27 (0) 11 358 5414 Email: sdelany@wrhi.ac.za	**Co-Chair:** Jennifer Velloza, PhD, MPH Assistant Professor Department of Epidemiology & Biostatistics University of California San Francisco 550 16th Street, 2nd Floor San Francisco, CA, 94158, USA Phone: 415 476 2300 Email: Jennifer.velloza@ucsf.edu
Connie Celum, MD, MPH Professor, Global Health & Medicine Director International Clinical Research Center University of Washington 325 Ninth Avenue Box 359927 Seattle, WA 98104, USA Phone: 206 520 3824 Fax: 206 520 3831 Email: ccelum@uw.edu	Nomhle Ndimande-Khoza, PhD, MA Social scientist Wits RHI 22 Esselen Street Hillbrow Johannesburg 2001 South Africa Phone +27 11 358 5659 Email: nkhoza@wrhi.ac.za
Sybil Hosek, PhD Clinical Psychologist / Director of Research Department of Psychiatry Stroger Hospital of Cook County 1900 W. Polk Street #854 Chicago, IL 60612, USA Phone: 312 864 8030 Fax: 312 864 9203 Email: shosek@cookcountyhhs.org	Nicole Poovan, MBBCh Research Clinician Wits RHI 22 Esselen Street Hillbrow Johannesburg 2001 South Africa Phone: +27 11 358 5100 Email: npoovan@wrhi.ac.za
Danielle Travill, MBBCh, MSc Research Clinician Wits RHI 22 Esselen Street Hillbrow Johannesburg 2001 South Africa Phone +27 11 358 5100 Email: dtravill@wrhi.ac.za	Ruth Verhey, PhD Assistant CEO & Director of Programs, Friendship Bench 4 Weale Road Milton Park, Harare, Zimbabwe Phone: +263 77 385 7376 Email: ruth.verhey@friendshipbench.io

Lisa Mills, MA Study Coordinator Wits RHI 22 Esselen Street Hillbrow Johannesburg 2001 South Africa Phone +27 11 358 5100 Email: lmills@wrhi.ac.za	

Youth Friendship Bench SA
Optimization of the Friendship Bench mental health intervention for adolescent girls and young women in South African PrEP delivery settings

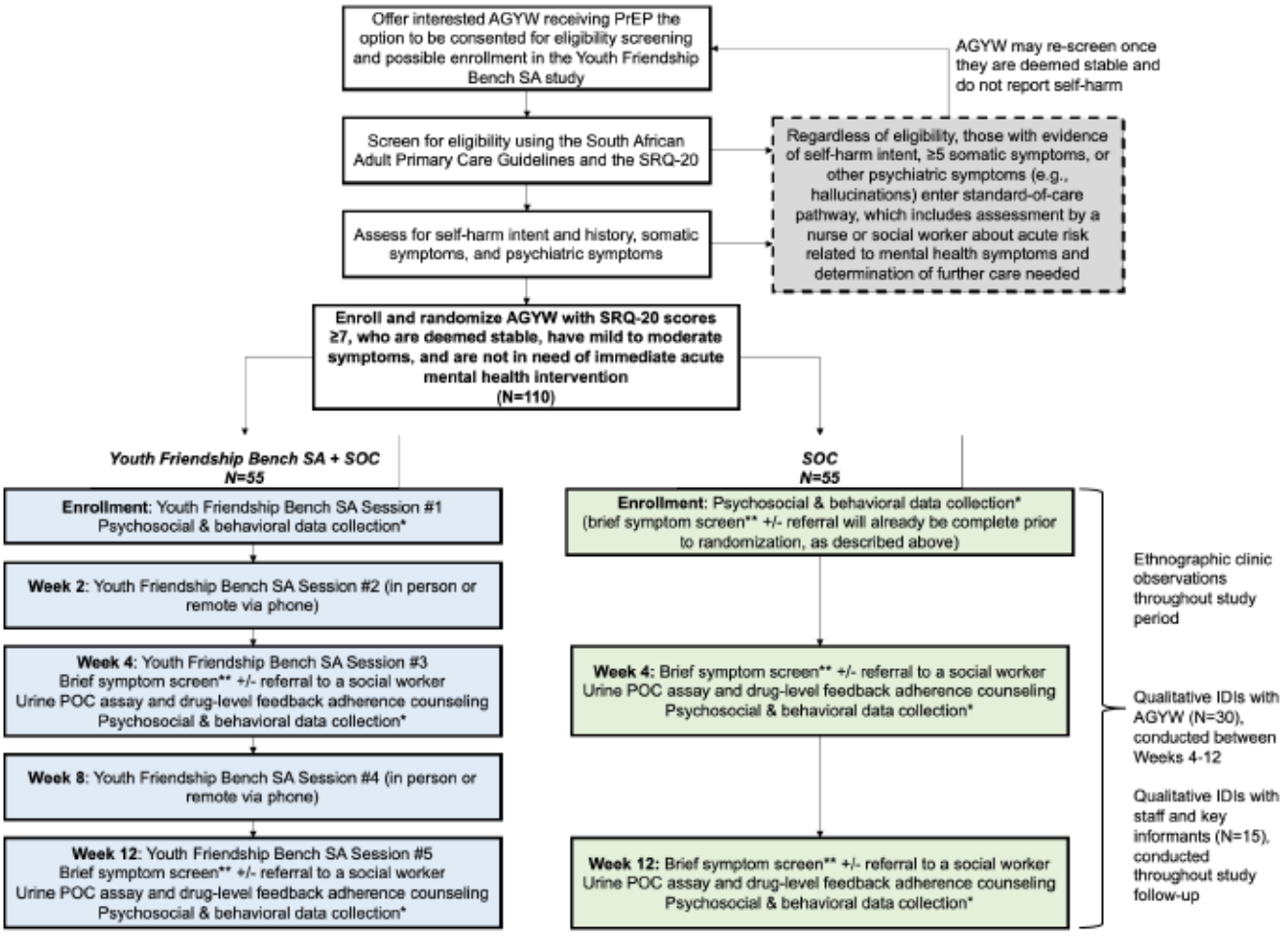
SCHEMA

Rationale:	Adolescent girls and young women (AGYW) at risk of HIV in sub-Saharan Africa, frequently (20-50%) have symptoms of common mental disorders, including depression, anxiety, and stress. These symptoms are associated with suboptimal adherence to HIV pre-exposure prophylaxis (PrEP), a highly effective HIV prevention approach. In this project, the team seeks to address poor mental health and consequent impacts on PrEP adherence and among AGYW at risk of HIV by testing an evidence-based mental health intervention (the Youth Friendship Bench SA) adapted for PrEP delivery programs.
Co-Primary Objectives:	To compare the proportion of young South African women who adhere well to PrEP (based on tenofovir levels detected in a point-of-care [POC] urine assay) between those receiving the Youth Friendship Bench SA plus standard-of-care mental health services versus receipt of standard-of-care mental health services alone, after 3 months. To compare the proportion of young South African women with reduced symptoms of common mental disorders (based on SRQ-20 score) between those receiving the Youth Friendship Bench SA plus standard-of-care mental health services versus receiving standard-of-care services alone, after 3 months
Design:	This is a randomized hybrid implementation-effectiveness trial which will be conducted in a real-world healthcare setting. Eligible women who accept open-label daily oral PrEP (n=110) will be enrolled and randomized to either the Youth Friendship Bench SA intervention (plus standard-of-care mental health services as needed) or standard-of-care mental health services alone. Randomization will be conducted in a 1:1 ratio with randomly-sized blocks of ≤10. Participants randomized to the Youth Friendship Bench SA will be offered up to 5 60-minute counseling sessions conducted at enrollment, Week 2, Week 4, Week 8, and Week 12 and 1 optional group counseling session between their Week 8 and 12 visits. All counseling will be conducted by peer lay counselors, who are young women between the ages of 24-30 years. Lay counselors will receive a one-week training course prior to study activation and will be supervised weekly by a trained research psychologist. Participants will have the option to complete counseling sessions remotely via phone and to receive SMS reminders about upcoming clinic visits. Standard-of-care (SOC) mental health services will be provided in accordance with the South African Adult Primary Care Guidelines, and include a brief depression symptom assessment at all visits administered by a counselor or nurse. All clients who screen positive will be referred for further assessment by a clinic social worker, who may refer the client for psychotherapy or pharmacotherapy as needed. All participants irrespective of study arm will receive further assessment by clinic staff (social worker, nurse, etc.) if they report self harm, somatic symptoms of mental health distress, or other psychiatric symptoms. Eligible participants in the

	Youth Friendship Bench SA arm may receive the intervention in addition to any recommended SOC services if they are eligible. All participants will be offered PrEP in accordance with national PrEP guidelines as part of routine care. We will also provide all participants with brief PrEP adherence counseling based on their urine POC assay results at the Week 4 and Week 12 visits. This adherence counseling will be in addition to their Youth Friendship Bench SA or standard-of-care mental health service delivery All participants will be followed for three months. We will conduct qualitative data collection with a purposive sample of up to 30 AGYW in the trial (between Week 4 and Week 12) and 15 health care providers and key informants to characterize themes around acceptability, appropriateness, and feasibility of Youth Friendship Bench SA and the urine POC TFV assay. We will also conduct ethnographic clinic observations throughout the study period (to 2 times per month).
Study Population:	HIV-uninfected women ages 18-25 in Johannesburg, South Africa, who have symptoms of common mental disorders as evidenced by a score greater than or equal to 7 on the SRQ-20.
Study Size:	Up to 110 women who accept PrEP will be consented and randomized
Outcome measures	We have co-primary outcomes: PrEP adherence and common mental disorder symptoms. The PrEP adherence primary outcome is the proportion with PrEP adherence at Month 3, defined as tenofovir (TFV) concentrations ≥1500 ng/mL in urine measured using a urine POC assay. We will also assess the short-term effect of the Youth Friendship Bench SA intervention on PrEP adherence using the urine POC assay at the Week 4 visit. The mental health related primary outcome is the proportion with reduced symptoms of common mental disorders (SRQ-20 scores <7) at Month 3, measured using the SRQ-20.
Study Duration:	Approximately 36 months, including submissions to Institutional Review Boards (IRBs) and study start up activities (6 months), recruitment and enrollment (12 months), participant follow up (3 months following the last enrolled participant), and data analysis (remaining time through 36 months).
Study Site:	Ward 21 public clinic in Johannesburg, South Africa.

OVERVIEW OF STUDY DESIGN

Figure 1. Study schema for the evaluation of the Youth Friendship Bench SA counseling intervention



AGYW=adolescent girls and young women; SRQ-20=self reporting questionnaire 20-item; SOC=standard of care; IDIs=in-depth interviews; POC=point-of-care

* Psychosocial and behavioral data collection includes assessment of common mental disorder symptoms using the SRQ-20.

**At enrollment, "Brief screening" in the standard-of-care arm includes the two questions about depressive symptoms outlined in the Adult Primary Care Guidelines. "Brief screening" described in Weeks 4 and 12 will consist of asking the participants whether anything has changed in their mental health symptoms and how they have been feeling, since their last visit.

5.0 INTRODUCTION

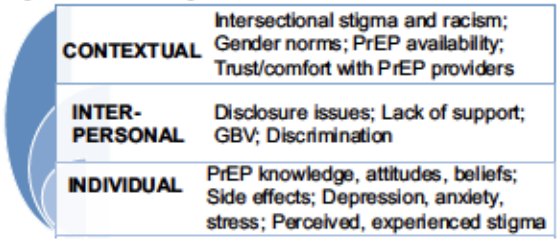
5.1. Background and Prior Research

HIV prevention among adolescent girls and young women (AGYW) is a global priority. African AGYW ages 18-25 face alarmingly high rates of HIV with recent trials reporting HIV incidence as high as 7 per 100 person-years in this group.[1–3] South Africa has the world's highest HIV incidence among AGYW and the South African Department of Health (DoH) has listed AGYW as a priority population for HIV prevention services.[4,5]

Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy being rapidly scaled up for African AGYW. The World Health Organization recommends oral PrEP for AGYW and PrEP is approved as HIV prevention in 40 countries.[6] It is now being scaled up to >1000 clinics in South Africa.[7–9] Trials have found that oral PrEP is >90% effective at preventing HIV when taken with high adherence during periods of risk.[10–13] Demonstration projects with AGYW report high initial uptake of PrEP in real-world settings.[14–19]

However, AGYW have difficulty adhering to PrEP in real-world delivery, limiting its impact. PrEP programs with AGYW consistently report declining adherence over time,[16,20–22] due to individual, interpersonal, and contextual factors, including symptoms of common mental disorders (depression, anxiety, stress), lack of support, gender-based violence (GBV), and stigma and discrimination **(Fig 2).**[21,23–27] This points to a need for layered service delivery to provide PrEP alongside interventions to address multilevel adherence barriers among AGYW.[28] The South African DoH "She Conquers" program and DREAMS partnership are integrating PrEP with social support interventions, GBV services, stigma-reduction campaigns, and empowerment clubs in youth-friendly clinics to address interpersonal and contextual drivers of HIV.[29] However, absent from both programs is an inclusion of mental health interventions integrated with these multilevel HIV prevention services for AGYW.

Fig 2. Socio-ecological barriers to PrEP use



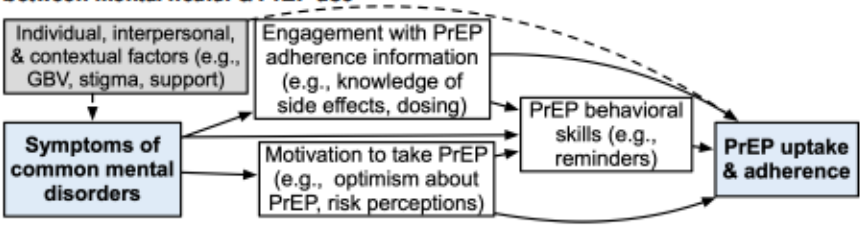
More recent PrEP demonstration projects of open label FTC/TDF among young African women have indicated that PrEP uptake is high (>90%) but that young women have challenges with PrEP adherence and persistence by 1-3 months after PrEP initiation. In the POWER prospective PrEP implementation study conducted in South Africa and Kenya, of 2550 AGYW enrolled, 94% initiated PrEP but only 31% had a refill at 1 month. By the six month visit, 20% of 646 AGYW reached for a follow-up visit persisted on PrEP.[30] Other studies offering PrEP to AGYW alongside adherence support interventions found slightly higher rates of PrEP adherence and persistence through the first 3-6 months of PrEP use. For example, in HPTN 082, 25% of young women in Zimbabwe and South Africa had high adherence to oral PrEP at month 3 based on intracellular tenofovir diphosphate levels (TFV-DP) $\geq$700 fmol/punch.[31] In the 3P study in Cape Town, approximately half of women (48%) had TFV-DP levels $\geq$700 fmol/punch at month 3.[100] The PrEP delivery field is now moving toward considering differentiated models of PrEP adherence support to focus resources on AGYW with difficulty adhering to PrEP early on.[33] The PrEP SMART study evaluated a differentiated PrEP adherence support model for young women in Johannesburg and initiated 360 young on PrEP, of whom 94% (N=264) were retained by Month 3. Approximately 62% of participants had TFV-DP levels $\geq$700 fmol/punch by month 3 and 27% had TFV-DP levels $\geq$700 fmol/punch at month 9, representing a large drop-off in PrEP adherence over time despite encouraging month 3 adherence results compared with the HPTN 082 and 3P studies.[34]

These demonstration projects indicate that persons at risk are motivated to use PrEP when counseled about efficacy in an open-label context and a subset are able to use daily oral PrEP with high adherence, achieving higher effectiveness than was observed in placebo-controlled trials. POWER and other demonstration projects of oral FTC/TDF have also demonstrated challenges with PrEP adherence and persistence among young African women, with large drop offs in PrEP adherence in just 1-3 months after initiation. There remains a need for additional interventions that can be delivered near the time of PrEP initiation (within the first 1-3 months of PrEP use) and that are targeted to those with greatest need for additional adherence support.

Differentiated and timely individual-level behavioral interventions may be insufficient to address the adherence and persistence challenges of all oral PrEP users. Longer-acting PrEP formulations may also offer greater flexibility and higher coverage than daily oral PrEP for AGYW with adherence challenges to daily pill taking. However, long-acting PrEP formulations will still require PrEP clients to be engaged in care and return to the clinic for regular assessment and resupply.[35] Integrated, holistic, and person-centered health services that are responsive to both the physical and mental health needs of AGYW will be critical to ensure engagement and retention in long-acting biomedical HIV prevention products delivery.[28]

Symptoms of common mental disorders are prevalent among AGYW in HIV endemic settings and are associated with multilevel drivers of HIV risk. Our newly published work shows that 20-50% of AGYW initiating PrEP have moderate-to-severe symptoms of common mental disorders.[24,25,27,36] Determinants of common mental disorders include proximal (e.g., racial discrimination, food insecurity, GBV,) and distal (e.g., gender inequality) factors, often acting together to cause elevated risk of depression, anxiety, and stress among AGYW.[37,38] Our recent PrEP studies with South African AGYW found that depression and stress symptoms are associated with low support, stigma, food insecurity, and GBV, and these symptoms persist over one year among 50% of AGYW initiating PrEP.[27,39] Other studies with African AGYW also report associations between symptoms of common mental disorders, structural drivers of HIV risk (GBV, financial insecurity, stigma), and increased HIV incidence.[40–44] The COVID-19 pandemic has exacerbated mental health issues, food and financial insecurity, and ability to access HIV prevention and treatment services globally and in South Africa, underscoring the critical need to intervene on these drivers of HIV risk.[45–47]

Fig 3. Modified Information-Motivation-Behavioral Skills (IMB) model of relationship between mental health & PrEP use



Common mental disorders negatively impact PrEP adherence, despite regular PrEP counseling and access to a multilevel, DoH package of PrEP services. Mental health symptoms may mediate the relationship between individual, interpersonal, and contextual factors and PrEP adherence, or they may reduce engagement with PrEP information, motivations, and behavioral skills (**Fig 3**).[21,48–53] Our published work with young women in Southern and Eastern Africa show that those with depressive symptoms have 25% lower PrEP adherence after accounting for GBV, stigma, social support, and receipt of a PrEP adherence support intervention.[25,27] Negative relationships between symptoms of common mental disorders and PrEP adherence have been reported among young men who have sex with men and transgender women, suggesting that findings are generalizable across at-risk adolescents groups.[54,55] The HIV treatment and oral contraceptive fields also consistently report negative associations between depression, anxiety, and stress symptoms and medication adherence among young women in the US and Africa.[52,56–63] Qualitative work has provided insights into narratives around distress and PrEP use which point to reasons for quantitative associations seen between these constructs (**Table 1**).[24,64]

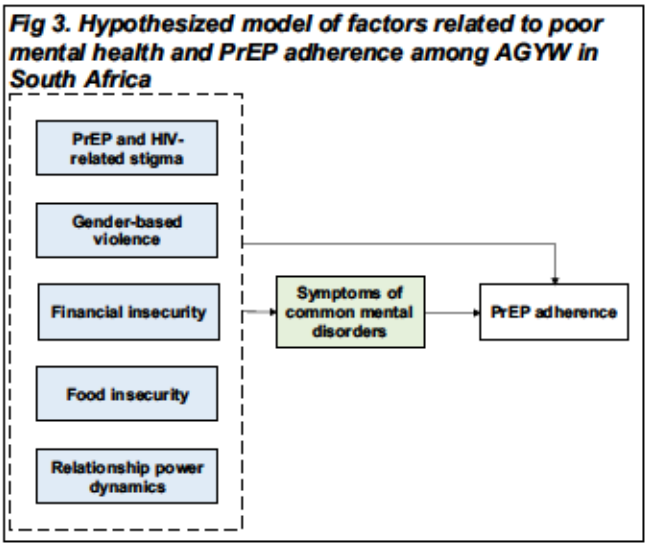
Currently, South African AGYW receive PrEP in the context of comprehensive services including demand creation, support groups, and access to GBV services, although implementation is variable. Despite this, data from our HPTN 082 study which delivered PrEP as part of a comprehensive package of care in Johannesburg show that 49% of AGYW initiating PrEP had depression, anxiety, and/or stress symptoms that persisted over one year even as GBV and stigma experiences declined and social support improved. Persistent symptoms in particular were associated with GBV, transactional sex and financial insecurity, and lower odds of PrEP adherence (aOR=0.73; 95% CI:0.56-0.96) compared with no or declining symptoms.[65] This work highlights the need for a "problem-solving" based approach (using talk therapy and cognitive behavioral principles to help a client cope with stressful life experiences and empower them to develop an action plan to reduce or modify stressors in their lives), integrated into comprehensive adolescent PrEP services, to empower AGYW to address modifiable issues related to mental health and PrEP use and improve coping and pill-taking.

Table 1. Qualitative perspectives on mental health and PrEP use

Quotations from South African and Kenyan AGYW in PrEP studies
"I get depressed because of fears of HIV. Once I went to get poison to take. Luckily my partner came home but I think about it still." (Velloza et al., *BMC Psych, 2020*)
"Guys take it you are a whore, that is why you want to protect yourself. My boyfriend was saying I am a whore, why am I taking PrEP? It made me feel quite low and bad about myself…I stopped PrEP." (Velloza et al., *JIAS, 2020)*
"Sometimes you are quarreling with your husband. Or the children are chased from school for no fees, there is no food. You feel so stressed…there is no mood to eat, talk to people, or take your PrEP." (Velloza et al., *BMC Psych, 2020)*

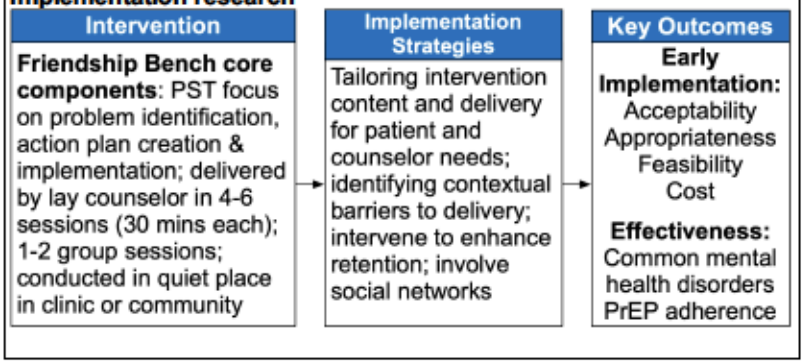
Problem-solving psychotherapy interventions, integrated with HIV service delivery, have the potential to improve mental health and PrEP adherence among AGYW. Evidence suggests that structural programs targeting contextual drivers of mental health and HIV outcomes (e.g., stigma reduction campaigns) may be most effective when layered with individual-level interventions.[66–69] Based on our prior research, we hypothesize that PrEP and HIV-related stigma, GBV, financial insecurity, food insecurity, and relationship power dynamics are all associated with poor mental health and PrEP adherence among AGYW (**Figure 3**). In addition, as previously described, symptoms of common mental disorders are associated with poor PrEP adherence, even in the context of PrEP adherence and social support interventions. Psychotherapy, delivered alone or in a package of comprehensive services, has been shown to improve mental health, self-esteem, GBV, and stigma, and HIV outcomes among young African women.[70–76] Moreover, psychotherapy integrated in HIV care can reduce further GBV and victimization.[77] Problem-solving therapy (PST), cognitive behavioral therapy (CBT), and interpersonal therapy (IPT) are all effective therapies for adolescents and women.[78–80] PST is recommended by the WHO for treating common mental disorders in resource-limited settings given its flexibility, low cost, and lay counselor delivery models.[81–83] Core components include problem identification, generation of alternative solutions, decision-making, and solution implementation.[84] By teaching clients to identify problems and enact solutions, PST empowers them to solve modifiable issues and improve positive coping around less modifiable social and societal concerns.[80,85,86] PST can also improve antiretroviral (ART) adherence among young women when delivered in HIV clinics.[37,70,74,78,87–89] As a result, PST components are regularly included in PrEP counseling and the South African DoH is increasing availability of PST in HIV care settings.[90–93]

Fig 3. Hypothesized model of factors related to poor mental health and PrEP adherence among AGYW in South Africa



The Friendship Bench is an effective PST intervention uniquely poised for delivery among AGYW in PrEP settings. The Friendship Bench is a package of PST components developed specifically for lay counselor delivery in low-resource African settings.[94–96] Core components include 4-6 sessions on problem identification and action planning incorporating problem-solving around individual, interpersonal, and contextual issues as directed by the client, plus an optional group support session focused on economic empowerment (**Fig 4**).[94] In comparison with other PST approaches with lay counselors,[96–101] only the Friendship Bench has demonstrated efficacy to improve symptoms of common mental disorders when conducted in primary and HIV care clinics.[96,102] In the initial trial in Zimbabwe, grandmother figures (mean age: 53) were trained to provide therapy on clinic benches.[94,96] The trial also used SMS messages, home visits, and counselor supervision as implementation strategies to improve retention and fidelity.[96] In a cluster randomized controlled trial, conducted with 573 patients in 24 primary care clinics in Harare, Zimbabwe, the intervention participants had significantly fewer depressive symptoms than those in the control group.[96] The intervention has since been adapted for younger counselors and is now being delivered to young women in Malawi and South African HIV clinics (R34MH116806, PI: Pence). In addition, pilot data from a Friendship Bench adaptation for adults living with HIV in Zimbabwe found improved mental health and ART adherence outcomes.[74,103]

Fig 4. Model of Friendship Bench, adapted from Proctor's model for implementation research



The Friendship Bench is an ideal psychotherapy intervention to integrate with PrEP delivery in South Africa for a variety of reasons. First, it was designed for and tested in a similar African setting and would therefore need less adaptation for public clinics in South Africa than an intervention developed in a very different context. Second, it was recently adapted to improve medication adherence among PLWH in Southern and Eastern Africa and to improve symptoms of common mental disorders for adolescents and young adults. While these adaptation studies are underway, initial data suggests that the intervention is feasible and acceptable for delivery with HIV medication and among young people.[74,104–107] Third, our prior quantitative and qualitative work confirms that common mental disorders are prevalent among AGYW attending PrEP services and this population would likely benefit from a PST approach that could help them address and cope with underlying causes of poor mental health (HIV and PrEP stigma, GBV, food and financial insecurity, relationship power dynamics; **Figure 3**). A PST intervention would also have likely benefits beyond improved mental health and PrEP adherence, by empowering young women in their lives and relationships and reducing risk of HIV and negative sexual and reproductive health outcomes more broadly. Fourth, our prior PrEP studies (PrEP SMART, HPTN 082, EMPOWER), demonstrated that young women in Johannesburg are willing to open up to young female counselors and discuss mental health challenges with them and they find this type of problem-focused counseling appealing and acceptable when delivered alongside PrEP services. The Friendship Bench approach also has the potential to be scalable in the South African PrEP delivery context because it is meant to be delivered by lay counselors (rather than already over-burdened clinic staff), can be administered in only 4-6 sessions, and, if effective, would provide a useful referral option for young women who screen positive for symptoms of common mental disorders at their PrEP visits according to South African standard-of-care guidelines for adults in primary and HIV care.[108] This approach would also be consistent with WHO guidelines on integrating PrEP within a package of adolescent-friendly and differentiated health services that tailor support to those at greatest need.[6,33]

Research is needed to adapt and test the Friendship Bench for South African AGYW in PrEP settings. We propose a novel application of the Friendship Bench in South African AGYW attending

PrEP services (the "Youth Friendship Bench SA") and will be the first to test the Youth Friendship Bench SA's impact on PrEP adherence. We will test an intervention package that is appropriate for AGYW at risk of HIV in a South African Department of Health (DOH) clinic where PrEP is delivered as part of primary health care. We will conduct a hybrid effectiveness-implementation trial, which has a dual focus on testing a clinical intervention and implementation strategies.[109] We hypothesize that our PST intervention will improve mental health which will in turn lead to improved PrEP adherence for AGYW.

5.2. Rationale

African adolescent girls and young women (AGYW) are at high risk for HIV and are a priority population for pre-exposure prophylaxis (PrEP). South African AGYW ages 18-25 years have HIV incidence rates of 4-7 per 100 person-years and PrEP is being scaled-up for AGYW in >1000 clinics in an ambitious Department of Health (DoH) program that includes HIV testing, sexual and reproductive health care, and gender-based violence (GBV) services.[1–3]

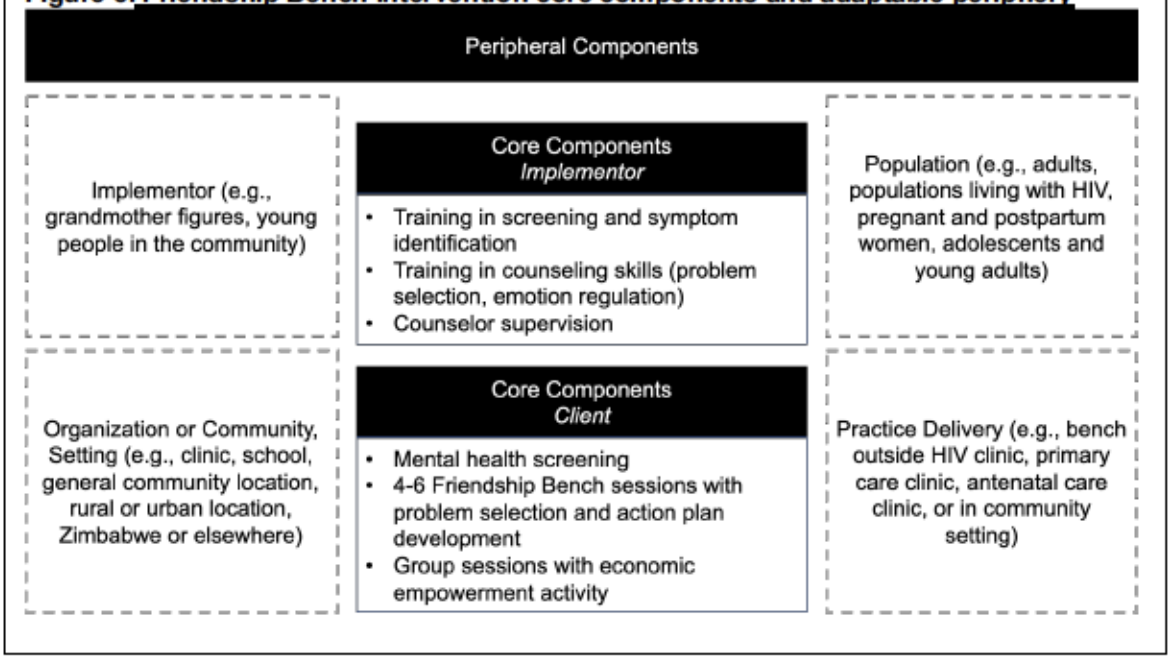
A major gap in South African PrEP delivery is a strategy for addressing complex mental health factors that reduce PrEP adherence for some AGYW. Symptoms of common mental disorders (e.g., depression, post-traumatic stress disorder, anxiety) are prevalent among 20-50% of African AGYW initiating PrEP and are linked to individual, interpersonal, and contextual barriers to PrEP use (e.g., GBV, stigma, discrimination).[24,25,27,36] Published work shows that AGYW with symptoms of common mental disorders are 25% less likely to adhere to PrEP and this association remains after accounting for multilevel barriers to PrEP use. Moreover, symptoms are likely to persist even with PrEP adherence counseling, referrals for medical services, and other DoH-provided PrEP services.[27,39] In a recent study (HPTN 082), 50% of South African AGYW initiating PrEP had persistent symptoms of common mental disorders over one year, resulting in poor PrEP adherence in this group although GBV and stigma experiences declined.[65] However, while prior studies found high prevalence and persistence of common mental disorders among AGYW seeking PrEP, they did not conduct systematic mental health screening, only referred AGYW with the greatest need to additional services, and offered PrEP adherence rather than mental health focused counseling. This highlights an existing gap in reaching a broader population of AGYW with routine mental health screening, counseling, and referrals within current PrEP service delivery.

Integrating mental health interventions into PrEP programs has the potential to improve mental health and PrEP adherence for AGYW. Problem-solving therapy (PST) is an appealing approach for AGYW facing an array of psychological and behavioral challenges because it aims to develop actionable solutions and improve coping for mental health and adherence issues.[80,85,86] It can empower AGYW to address modifiable drivers of mental health and PrEP use, particularly when delivered alongside existing PrEP programs, and is a recommended approach included in South African DoH guidelines for mental health and PrEP counseling. The Friendship Bench is an effective PST intervention with promise for South African PrEP settings given that it was developed for busy HIV clinics in Zimbabwe, can improve mental health and ART use in just 4-6 sessions, and is now being delivered in South African HIV clinics.[96] The proposed study will test and optimize the Friendship Bench for AGYW with mental health needs in South African/ PrEP programs ("Youth Friendship Bench SA").

Rationale for the Friendship Bench as the evidence-based intervention and further description of intervention core components

The Friendship Bench is an ideal starting point for treating mild-to-moderate symptoms of common mental disorders among AGYW in PrEP delivery settings, given that it was designed for and tested in a similar African context. It can also be adapted to improve mental health and medication adherence among young women when delivered by lay counselors in busy HIV clinic settings.[74,103,104] The Friendship Bench has a number of implementer-facing and client-facing core components, which were integral parts of the evidence-based intervention and cannot be modified in adaptations seeking to remain fidelity-consistent with the Friendship Bench model (**Figure 5**).

Figure 5. Friendship Bench intervention core components and adaptable periphery



Implementer-facing core components include: training in the administration and use of screening tools for common mental disorders; training in counseling skills including problem solving approaches (e.g., problem selection, action plan development), emotion regulation, and motivational interviewing; and regular counselor supervision and check-ins. Client-facing core components include: some form of symptom screening for common mental disorders conducted on a routine basis; 4-6 individual counseling sessions conducted either weekly or monthly; and 1 optional group session with an economic empowerment activity (e.g., basket weaving, assistance with writing job or school applications). The first counseling session includes the following problem solving steps:

- "Opening up the mind": identify the problem, define a selected problem, define and select a goal
- "Empowerment": brainstorm for solutions and decide on a solution to reach your selected goal
- "Strengthening": Devise a SMART (specific, measurable, achievable, realistic, and timely) action plan to conduct your solution

Subsequent counseling sessions start by evaluating the client's progress with their SMART action plan and discussing other possible problems or solutions as directed by the client.

There are a number of other components of the Friendship Bench intervention and its implementation that are across what is termed the "adaptable periphery": these are components that can be modified and tailored to suit a particular study population and setting (**Figure 5**). First, we can modify *who is implementing* the Friendship Bench intervention. In the initial randomized controlled trial, "grandmother figures" conducted Friendship Bench settings with adults in the community but subsequent versions of the Friendship Bench have included young people, peer mothers, and other lay counselor figures, provided they are people with whom the target population feels comfortable and willing to trust and talk with. Second, we can modify *who receives* the Friendship Bench, moving from the study population of the first Friendship Bench trial (adults in primary care settings) to other populations including AGYW and pregnant and postpartum women. Third and fourth, we can modify *the setting and practice delivery space where* the Friendship Bench is conducted. Studies have varied in conducting the Friendship Bench in urban or rural settings and clinics or community spaces. In addition, while some have delivered Friendship Bench sessions on actual benches outside clinic spaces, others have preferred to conduct sessions inside of clinic rooms where participants have felt more privacy. The group session activity can also be modified as long as it includes a tangible activity to empower clients to earn some

independent financial support (e.g., through learning a craft, receiving assistance with school or loan applications).

The Youth Friendship Bench SA intervention package: rationale for adaptations to the Friendship Bench intervention and delivery components

In our prior study, K99MH123369, we sought to understand preferences and views on these adaptable components from AGYW, clinic staff, PrEP policy-makers and funders, mental health service providers, and other key stakeholders, which informed the development of our Youth Friendship Bench SA intervention package. We first conducted in-depth interviews with 48 AGYW and 22 clinic staff and other key informants to understand needs around a mental health intervention integrated into PrEP delivery settings and possible facilitators and barriers to Friendship Bench implementation in this setting. This work was guided by the Consolidated Framework for Implementation Research (CFIR) which groups implementation facilitators and barriers into five domains: characteristics of the intervention, the outer community setting, the inner clinic setting, characteristics of individuals involved, and the implementation process. Interview participants also described potential implementation strategies that could overcome barriers to Friendship Bench implementation in this setting. The themes from the AGYW, clinic staff, and key informant interviews are summarized in **Table 2**:

Table 2. Summary of determinants of mental health intervention implementation and potential implementation strategies for South African PrEP clinics

CFIR Domain	Implementation determinants identified by interviewees	Potential implementation strategies suggested by interviewees
Characteristics of the intervention – *psychosocial counselling*	**Facilitators:** building capacity for psychosocial counseling is more appealing than medication and standard-of-care referrals **Barriers:** unethical to screen for a counseling intervention if no specialists are available for referral; could result in long clinic wait times; AGYW may be reluctant to open up	• Refined screening practices to triage AGYW • Person-centered, stepped care models tailored to AGYW needs • Warm hand-offs (ensuring connection) for all referral services • Adapt intervention to incorporate local perspectives and content relevant for AGYW • Adapt clinic flow to maximize time efficiency for AGYW
Outer setting – *urban Johannesburg, South Africa*	**Facilitators:** Clear need for psychotherapy related to depression and other mental health issues (gender-based violence, relationship issues, PrEP stigma); mental health service integration aligns with South African Department of Health goals **Barriers:** Community stigma around mental health awareness and care seeking; lack of clarity on referral options, care pathways for screening and referral, and lack of existing services	• Community outreach activities for demand-creation, PrEP, and mental health stigma reduction • Conduct group sessions with AGYW to normalize mental health issues • Inventory referral services and engage key stakeholders to identify a broad range of referral options to address mental health issues and gender-based violence; define care pathways and criteria for escalation
Inner setting – *Ward 21 adolescent-friendly PrEP clinic*	**Facilitators:** Strong network to support within-clinic referrals; some mental health services already provided (referrals, some screening) although without formal procedures or monitoring **Barriers:** Perceived provider judgment and discrimination among staff; tension between wanting to provide psychotherapy but also not adding more staff work or clinic inefficiencies; lack of time, space, and funding for counselors	• Create a non-judgmental and friendly atmosphere for AGYW • Incorporate mental health screening and counseling with other youth-friendly services (e.g., PrEP counseling) to maximize efficiency • Create a rewards system for counselors with recognition for outcomes • Training, supervision, and peer support to empower counselors • Engage clinic leadership to "own" the intervention
Characteristics of individuals involved – *lay counsellors*	**Facilitators:** None described **Barriers:** Lack of counselor training on mental health and psychotherapy approaches, judgmental attitudes among providers	• Train counselors in adolescent-friendly communication skills and psychotherapy counseling approaches • Provide a space for counselors to process difficult cases (e.g., during supervision meetings) • Conduct training on patient-counselor confidentiality

		• Regular supervision with audit and feedback to promote counselor self-efficacy for intervention delivery
Process	**Facilitators:** External change agents (celebrities, social media influencers) have spoken out about mental health during COVID **Barriers**: None	• Engage AGYW as peer champions and social influencers, to conduct demand creation

We then conducted a series of 6 workshops with 13 AGYW and 15 staff and key informants to prioritize barriers to Friendship Bench implementation by importance and relevance and to specify strategies for delivering the Friendship Bench to AGYW in PrEP clinic spaces. AGYW prioritized five key implementation barriers: perceptions of poor service in clinic spaces offering PrEP (this barrier was described in relation to generic PrEP delivery points, not a specific clinic or adolescent-friendly service delivery points); fear of judgment around PrEP taking or mental health care engagement; length of time spent at the clinic; trust issues with parents and partners; and challenges with consistent participation. Staff and key informants also prioritized five key implementation barriers: accessibility of reaching the clinic for mental health and PrEP services; staff knowledge and ability to deliver a mental health intervention; community stigma around mental health and PrEP; lack of resources; and competing health needs for AGYW. These are summarized in **Table 3.**

Table 3. Summary of workshop findings on implementation barriers and implementation strategies

Implementation barrier domain	Theme	Representative quotation	Description of specified implementation strategy
Themes stated by AGYW			
Perceptions of poor service at the clinic	AGYW feel they are mistreated, ignored, or disrespected and are concerned about confidentiality	*"Providers of PrEP at any institution have to be more friendly and respectful."*	Counselor monitoring to help hold them accountable and improve their skills
Judgment taking PrEP or seeking mental health care	There is judgment and stigma around PrEP and mental health service seeking	*"My suggestion would be that we have a community dialogue especially with [AGYW] so that we break the stigma that lies in our community of not talking about issues that affect us mentally that way."*	Community education via social media and television advertisements to share with the community benefits of taking PrEP and participating in a mental health intervention
Time spent at clinic	AGYW do not want to spend a lot of time at the clinic or travel a large distance to get there	*"We had a discussion around or rather looking at people back in the villages, some clinics are far, they have to travel, and they understand that it's always full when you get there, you would be there for the whole day, so it could be a barrier, because people will not respond positively to constantly go to the clinic"*	Increase staffing capacity
Trust issues	Parents and partners will be concerned about PrEP use and mental health issues	*"Another barrier is trust issues with parents, who will now begin to think that you are no longer trustworthy and you're not taking care of yourself or you need attention…you are seeking [mental health care] basically for attention."*	Hold community meetings at schools to talk about PrEP and mental health issues
Consistency of participation	AGYW may start sessions but will not continue with sessions regularly	*"It could be that people will respond, but the consistency will not be as expected, as we've seen with people taking medication and dropping before it finishes, so consistency would be a concern here."*	Empowering SMS reminder messages to encourage AGYW to keep coming to the clinic and engaging with PrEP and mental health care
Themes stated by staff and other key stakeholders			
Accessibility	It is important to ensure appropriate location for the bench itself and to help make the clinic	*"Oh, the accessibility of the clinic is important, so if it's not a safe space…the bench needs to be easily accessible. Like do adolescents need to take a taxi, a train-- you know what is the affordability of getting*	Create an option for a virtual Friendship Bench to make the service tailored to AGYW needs, if they would prefer a phone call

	more accessible for AGYW; will need to ensure confidentiality and safety on the bench	*to the clinic and to access this sort of service, and how would that work?"*	
Staff knowledge and ability	Counselors may not know where to refer patients and will not know about mental health counseling or the Friendship Bench	*"I think there are [training gaps] for both the counselors who would be involved in the actual delivery of the intervention, of their training, but more broadly, for the facility teams recognizing what this is all about and when they should be referring a patient who could potentially benefit from the intervention."*	Set up WhatsApp groups for supervision and debriefing
Stigma	There is a large amount of community, family, and facility-level stigma related to PrEP, HIV, and mental health issues	*"Mental health stigma is quite intense compared to other stigma. People would rather be HIV positive, COVID positive than to have poor mental health. So, I think that may prevent people to sometimes seek out mental health support, or even healthcare providers refer."*	Engage community stakeholders (e.g., key celebrities, gatekeepers, school administrators) in creating a dialogue around mental health awareness
Resources	Clinics are lacking staff (including counselors, social workers), referral points outside the clinic, and screening tools	*"We felt there was lack of resources—a lack of staff, like social workers, psychologists and also referrals. When referring, the time and the availability of these professionals are not always in line with adolescents' availability. Adolescents are in school and they might not be available when [referrals are] available so even if they get a referral the way the waiting list is really long for them."*	Use a self-screening tool so AGYW can screen themselves, which may reduce stigma and could also help streamline clinic flow if providers are able to then view results in a timely fashion
AGYW needs	AGYW may not want to talk about mental health issues, they likely have other more pressing concerns (e.g., food insecurity), and do not want to spend a lot of time at the facility	*"There is the lack of basic needs of those seeking out clinic services. They wouldn't want to talk about mental health issues if they might focus on what am I going to eat tonight, or you know how am I going to get food on the table for the next day."*	Reframe mental health needs from a positive lens (e.g., use words like "wellbeing" instead of "problems") Provide referrals to organizations that can assist with concrete concerns that may be contributing to poor mental health Ground work from a PST approach to empower AGYW

For each barrier listed, at least one implementation strategy was discussed, which served as the basis for our Friendship Bench adaptation. Based on findings from the qualitative in-depth interviews and workshops, the Youth Friendship Bench SA intervention package includes the following adaptations:

- Addr

In the final phase of our adaptation study, we trained two counselors and piloted our Youth Friendship Bench SA intervention with three AGYW who were PrEP experienced and had symptoms of common mental disorders. Both AGYW and counselors found the sessions acceptable and feasible for delivery in PrEP settings. The current study will build on this by evaluating our Youth Friendship Bench SA intervention package (the individual counseling sessions and optional group session, along with the adaptations previously described such as the optional remote phone counseling sessions, optional one-way SMS reminders, etc.) among 110 AGYW randomized to intervention or SOC control and receiving PrEP in a public HIV clinic in Johannesburg.

Rationale for the use of a urine point-of-care (POC) tenofovir (TFV) assay for our primary outcome and as a tool in PrEP adherence counseling

Urine POC assay for our primary outcome assessment: Prior PrEP studies with South African AGYW used tenofovir diphosphate (TFV-DP) levels detected in dried blood spots (DBS) as a primary outcome to assess intervention effects on PrEP adherence at 3-12 months.[16,30–32,34] TFV-DP levels from DBS samples provides a measure of cumulative adherence behavior over the prior 4-6 weeks.[110] However, while prior DBS studies have generally used a threshold of 700 fmol/punch to represent dosing at least 4 times per week, our prior work with women in sub-Saharan Africa has shown that this threshold may misclassify approximately 40% of women as non-adherent to PrEP when they are actually taking at least 4 doses per week (sensitivity of DBS with a threshold of 700 fmol/punch compared to electronic pill contained data indicating at least 4 doses per week=60%; 95% confidence interval: 42-78%).[111] In addition, DBS samples are costly to collect, process, and store and have to be batch-shipped to one of just two laboratories worldwide where processing of TFV-DP concentrations can be done.

A point-of-care (POC) tenofovir (TFV) assay was developed to measure TFV levels in urine and could overcome the cost and logistical barriers of using DBS for PrEP adherence measurement.[112] The POC lateral flow assay has a threshold of 1500 ng/mL consistent with dosing in the last 4-7 days based on a directly observed therapy study.[112] It was developed in collaboration with Alere Diagnostics and costs approximately $3. The urine POC TFV assay measures more recent PrEP use than the DBS drug levels, and could therefore be subject to misclassification of PrEP adherence due to white coat effects (PrEP dosing just around the time of a clinic visit). However, we recently piloted the urine POC TFV assay in a PrEP adherence study with South African AGYW and found that it was highly acceptable and feasible to both AGYW and clinic staff (98% of AGYW would choose the urine POC test over DBS testing for future PrEP adherence assessment) and the test was able to discriminate between consistent and inconsistent PrEP adherence in comparison with DBS drug levels.[113] Of 61 AGYW with a negative urine POC assay result indicating no recent PrEP dosing, 100% also had a TFV-DP concentration <700 fmol/punch indicating low PrEP adherence.[113] Of 54 AGYW with a positive urine POC assay indicating some PrEP use in the prior 4-7 days, 48% had TFV-DP concentrations ≥700 fmol/punch and 22% had TFV-DP concentrations between 350-699 fmol/punch (70% total had DBS levels indicating moderate to high PrEP adherence).[113] The urine POC assay will also allow us to capture shorter-term changes in PrEP use as a result of our Youth Friendship Bench SA counseling sessions in the 4-12 week period.

Urine POC assay for drug-level feedback counseling at Weeks 4 and 12: The basis for the use of PrEP adherence counseling based on the level of PrEP detected in a pharmacologic sample is that women in VOICE qualitative interviews reported a desire for feedback about their adherence with directed counseling.[23] HPTN 082 randomized Zimbabwean and South African young women to standard adherence support (counseling, two-way SMS, and adherence clubs) with or without drug level feedback based on TFV-DP levels in DBS. There was no difference in adherence levels at six months by arm and, the cost and logistics of the DBS TFV-DP levels do not warrant use for PrEP adherence counseling. Notably, almost 40% of women in the drug-level feedback arm either did not receive counseling because DBS had to be batch-shipped and performed and the results were not back at the next monthly visit, or did not receive the appropriate counseling message due to transcript errors in coding the laboratory results.[31] Although retrospective drug-level feedback in addition to standard adherence counseling did not increase adherence at six months in HPTN 082, compared to standard adherence support,[31] same day counseling using a POC TFV assay offers a new potential improved strategy to support PrEP adherence. POC assays are much simpler and less costly to implement than DBS assays which only two laboratories can perform.

A POC assay could support real-time adherence monitoring to provide drug-level feedback about recent PrEP dosing in the week prior to the clinic appointment.[112] The UCSF Hair Analytical Laboratory (HAL) developed a collaboration with Abbott Rapid Diagnostics, a company with vast expertise in POC immunoassays, to develop an immunoassay that quantitates TFV levels in urine. The test is sensitive (96%), specific (100%), precise (coefficient of variation <15%), and can quantitate TFV levels in urine as accurately as liquid chromatography-mass spectrometry (LC-MS/MS) which is the gold standard (correlation between TFV levels by both assays=0.96), based on a study with HIV-negative individuals

taking PrEP as coformulated tenofovir disoproxil fumarate and emtricitabine (TDF/FTC).[112,114–116] The urine POC assay may have lower sensitivity and specificity with clients using tenofovir alafenamide (TAF) rather than TDF/FTC,[117] but South African clinics offer PrEP as TDF/FTC and TAF is not currently available in the country. Therefore, the urine POC assay is an appropriate choice for our study context and population. The assay is currently available for research purposes only and is not a tool to guide clinical decision making in routine care settings.

Approximately 2-3 minutes after 3-4 drops of urine are placed on the urine test strip, a "control" line should appear. An additional "tenofovir test line" will appear only if a participant has TFV levels <1500 ng/mL indicative of no recent PrEP dosing. This threshold will be used to provide drug-level feedback counseling to all participants at the Week 4 and Week 12 visits. The counseling messages were developed in consultation with Dr. Monica Gandhi (the POC test developer) and Dr. Sybil Hosek and were previously used in a PrEP study with AGYW in South Africa.[34,113] This study found urine POC TFV testing and counseling to be acceptable and feasible (94% of 155 South African AGYW liked receiving counseling based on urine TFV levels and 97% felt it would motivate higher PrEP adherence),[113] leading to our use in this protocol. While the urine POC assay is 100% specific, it is 96% sensitive and a small number of number of individuals who are truly taking their PrEP will have a negative urine test result. It is also possible that participants will take PrEP pills around their study visit only, but not consistently between visits, which could results in a positive urine test for those with difficulty adhering to PrEP. The urine results and our counseling messages are not intended to be interpreted as an accurate picture of an AGYW's PrEP use, but rather as a counseling tool to begin a conversation about PrEP pill-taking with the urine test results as an anchor for the discussion. The messages include words like, "it looks like" to imply some level of uncertainty about how well the urine POC assay results correspond with pill-taking and end with questions to elicit conversation about either how we can help the client take PrEP well or whether PrEP still feels like a good fit for them:

Control line only (one line appears on test)
Key message: It looks like you took a PrEP pill recently--you are doing great! Remember that taking one PrEP pill every day is needed for strong protection against HIV. How can we help you keep up the good

Control and tenofovir test line (two lines appear on test)
Key message: It looks like you haven't been able to take the PrEP medication in the past few days. Is PrEP something that you are still interested in? If yes, how can we help you?

6.0 STUDY OBJECTIVES

6.1. Primary Objective(s)

The co-primary objectives of this study are:

- To compare the proportion of young South African women who adhere well to PrEP (based on tenofovir [TFV] levels from a urine point-of-care [POC] assay) between those receiving the Youth Friendship Bench SA plus standard-of-care (SOC) mental health services versus receipt of standard-of-care services alone, after 3 months
- To compare the proportion of young South African women with reduced symptoms of common mental disorders (based on SRQ-20 score) between those receiving the Youth Friendship Bench SA plus standard-of-care mental health services versus receiving standard-of-care services alone, after 3 months

6.2. Secondary Objectives

The secondary objectives of this study are:

- To compare the proportion of young South African women who adhere well to PrEP (based on tenofovir [TFV] levels from a urine point-of-care [POC] assay) between those receiving the Youth Friendship Bench SA plus standard-of-care mental health services versus receipt of standard-of-care services alone, after 4 weeks.
- To assess the correlates of PrEP adherence, after adjusting for study arm, including sociodemographic factors and psychosocial and behavioral characteristics.
- To assess the correlates of symptoms of common mental disorders, after adjusting for study arm, including sociodemographic factors and psychosocial and behavioral characteristics.
- To qualitatively explore the acceptability, feasibility, and appropriateness of the Youth Friendship Bench SA intervention and the POC TFV urine assay.
- To monitor and describe the occurrence of serious adverse events over the study (defined as those events that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity) plus adverse events of special interest (reports of self-harm or self-injury).

6.3. Exploratory Objectives

The exploratory objectives of this study are:

- To explore mediators and moderators of the Youth Friendship Bench SA intervention effect on PrEP adherence.
- To explore mediators and moderators of the Youth Friendship Bench SA intervention effect on symptoms of common mental disorders.

7.0 STUDY DESIGN

7.1. Design

This is a single-site effectiveness-implementation randomized controlled trial. 110 participants are planned and will be consented to have 12 weeks of follow-up. All participants will be offered PrEP by clinic personnel as part of standard PrEP prescribing practices, and PrEP delivery (including PrEP readiness assessment, HIV testing, PrEP adherence counseling that is not part of the urine point-of-care drug-level feedback, and PrEP prescribing) is not considered a research procedure.

Each participant will be randomized in a 1:1 ratio to receive ***either*** **standard-of-care plus our Youth Friendship Bench SA mental health intervention package or standard-of-care alone**. Our co-primary endpoints are PrEP adherence assessed using tenofovir detected in a urine POC assay performed at the Week 12 study visit and symptoms of common mental disorders assessed using the SRQ-20 at the Week 12 visit. All participants will also receive PrEP adherence counseling based on results of their urine POC TFV assay at the Week 4 and 12 visits ("drug-level feedback counseling"), in addition to their standard-of-care or Youth Friendship Bench SA services.

Standard-of-care mental health services: As specified in the Adult Primary Care Guidelines,[108] standard-of-care services include a 2-item symptom assessment at enrollment and a brief screen about whether their mental health symptoms have changed at Week 4 and Week 12, to align with PrEP refill schedule. Symptom assessment is to be followed by escalation and referral for mental health care assessment by a trained health care professional (e.g. social worker, psychologist, or medical doctor) as needed. The initial symptom assessment includes two questions asking if one has felt down, depressed, or hopeless or has little interest or pleasure in doing things (**Appendix 1**). This assessment is administered by a counselor or nurse, or could be self-administered. The Adult Primary Care Guidelines specify that clients who screen positive on these initial questions are then asked about

somatic symptoms (if the client has five or more somatic symptoms and these symptoms impair their ability to engage in daily tasks, it is likely that they have a common mental disorder and will need further referral and care). The social worker may then refer the client for acute hospitalization, psychotherapy, or pharmacotherapy as needed.

Youth Friendship Bench SA + Standard-of-Care: The Youth Friendship Bench SA intervention includes: five individual counseling sessions conducted at Enrollment, Week 2, Week 4, Week 8, and Week 12; one optional in-person or WhatsApp-based group counseling session between Week 8 and Week 12; optional remote counseling sessions; and optional one-way SMS messages to provide reminders about upcoming visits. Individual counseling sessions will last up to 60 minutes. Participants will meet with a lay counselor to complete common mental disorder screening via an interviewer-administered SRQ-20 form (**Appendix 2**) during their visits at screening/enrollment, Week 4, and Week 12. During the initial Youth Friendship Bench SA session, participants will meet with the trained counselor to discuss mental health challenges, identify problems in their life that affect their mental health and PrEP use, generate alternative solutions, make decisions about the alternatives, and collaboratively decide on a plan to implement the solutions. The counselor will review the participant's SRQ-20 form prior to session start to identify salient mental health concerns and symptoms and will use that to guide the initial discussion with the participant. During follow-up counseling sessions, participants will discuss progress in implementing solutions to address the problems they identified in prior sessions with the lay counselor. They will also discuss any other mental health challenges and problems in their life that affect their mental health and PrEP use which they would like to address. During the Week 4 and 12 visits, counselors will also reference the completed SRQ-20 tool for key areas to probe around symptoms of common mental disorders and any symptom changes since the last visit. Group counseling sessions will last up to 120 minutes. Participants in the Youth Friendship Bench SA arm will be offered the choice of completing remote counseling sessions at Weeks 2 and 8 and receiving one-way SMS appointment reminder messages to plan for upcoming clinic visits. See **Section 4.2** below for additional information on lay counselor training and supervision.

A subset of up to 30 AGYW will also be recruited to participate in qualitative in-depth interviews to be conducted between Weeks 4 and 12 of study participation. These interviews will explore their perceptions of the acceptability, feasibility, and appropriateness of the Youth Friendship Bench SA and standard-of-care services. We will also ask about perceptions around the use of a urine POC assay for PrEP adherence assessment and drug-level feedback counseling. We will conduct interviews with study staff and key informants involved in PrEP and mental health service delivery for AGYW throughout the study period. In addition to this qualitative interview data, we will also collect ethnographic non-participant observation data. Throughout the study period (up to 2 times per month), trained social scientist interviewers will observe participants' waiting room discussions and comfort in the clinic, clinic flow, and the clinic environment for AGYW. They will record field notes during these observations to capture key information and inform future Youth Friendship Bench SA and standard-of-care mental health service delivery.

Screening data will be reviewed to determine participant eligibility. Participants who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. The total duration of participant participation will be three months. We will escalate any participants who report self-harm, worsening symptoms of common mental disorders or psychiatric distress, and/or new presentation of somatic symptoms for referral and linkage to additional psychotherapy or pharmacotherapy as needed. The total duration of the study is expected to be three years.

7.2. Study Population

Sexually active young women ages 18-25 who are seeking PrEP at the Ward 21 Department of Health Clinic, in Johannesburg, South Africa, and who have mild-to-moderate symptoms of common mental disorder as defined below.

7.3. Eligibility

7.3.2. Inclusion Criteria

Young women who meet all of the following criteria are eligible for enrolling in this study:

- Female 18-25 years of age at screening
- Documentation of symptoms of a common mental disorder, as evidenced by a score greater than or equal to 7 on the Self Reporting Questionnaire 20-item (SRQ-20)
- Willingness to enroll and be randomized to either the Youth Friendship Bench SA or standard-of-care mental health services
- Written informed consent (obtained from participant or participant's legal representative and ability for participant to comply with the requirements of the study.
- Able to verbally communicate in one or more study languages to ensure participation in the counseling sessions (English, isiZulu)
- Taking PrEP at the Ward 21 clinic, as determined by clinic records. PrEP provision will be conducted by the clinic following National PrEP Guidelines and will not be part of study-specific procedures.

7.3.3. Exclusion Criteria

Young women who meet any of the following criteria will be excluded from enrolling in this study:

- Not on PrEP and/or not intending to use PrEP for the duration of the study
- Planning to relocate in the next three months
- Report of suicidal intent or self harm
- Active, unmanaged mental health disorders, including untreated or severe somatic symptoms and active psychiatric symptoms (e.g., hallucinations)
- Reactive or positive HIV test at enrollment (based on clinic records only; we will not perform HIV testing under this protocol)

7.4. Co-Enrollment Guidelines

We will ask all potential participants to disclose their involvement in any other HIV or mental health (psychotherapy or pharmacotherapy) interventions at screening. The investigator team will make decisions about enrollment eligibility for those in other HIV or mental health studies on a case-by-case basis, depending on the type and level of service received and the likelihood of it interfering with Youth Friendship Bench SA delivery or primary outcome assessment.

8.0 STUDY PROCEDURES AND INTERVENTIONS

8.1. Recruitment and Screening Process

Recruitment and demand-creation activities will frame mental health issues from an empowerment-based lens. All recruitment materials will be approved by IRBs/ECs at the University of the Witwatersrand and the University of California at San Francisco prior to the start of enrollment. Recruitment will take place at the GDOH Ward 21 Adolescent Clinic. We will display posters and pamphlets about our study in the clinic. Potential participants will be identified through referral by clinic personnel (nurses, PrEP adherence counselors, receptionists). Clinic personnel will identify AGYW seeking PrEP either at initiation or follow up

and will approach these AGYW during their clinic visits to offer screening for Youth Friendship Bench SA intervention (which will subsequently be conducted by the Youth Friendship Bench SA lay counselor). All AGYW will be informed that participation in the Youth Friendship Bench SA intervention will not prevent them from receiving standard-of-care mental health treatment or from having their case elevated to a social worker or psychologist as needed, in addition to their possible receipt of the Youth Friendship Bench SA counseling intervention.

8.2. Lay Counselor Training and Supervision

Training: All Youth Friendship Bench SA counseling sessions will be conducted by one of two lay counselors, young women between approximately 24-30 years of age. These lay counselors will be trained by the protocol team during a one-week intensive training and will receive weekly in-person supervision by the study's research psychologist (**Appendix 3**). The training materials were developed and tested by the Friendship Bench team in Zimbabwe and have been used in a number of Friendship Bench adaptations globally.[95,96,105] They include didactic sessions on common mental health conditions, symptom identification including screening tools like the SRQ-20, person-centered counseling skills, active listening, and problem-solving therapy techniques. The training is also designed to include time for practicing counseling skills throughout the week and to provide space for counselors to process their own feelings and stressors during the training. We will adapt the training materials as needed to ensure they are appropriate for young lay counselors in our population.

Supervision: Counselors will keep a progress note for the session. Sessions may be audio-recorded to ensure fidelity to the counseling messages and these audio-recordings will be reviewed with study team members in the US for remote supervision meetings with the counselors and the study team on a monthly basis. Participants will be asked whether they consent to having their counseling sessions audio-recorded as part of the enrollment consent process and will be informed that they can withdraw their consent for recording at any time. The study research psychologist will also conduct in-person supervision meetings with the counselors on a weekly basis, to discuss counseling progress, troubleshoot any difficult cases, and process any feelings of their own that are brought up during the counseling sessions.

8.3. Study Procedures

An overview of the study visit and procedures schedule is presented in **Appendix 4** (below) and **Figure 1** (page 12). The text below is additional information on visit-specific study procedures.

8.3.2. Screening and Enrollment Visit

The screening and enrollment visit may be conducted as a split visit as needed. Young women who are eligible and agree to study participation will be consented for 3 months of follow-up. The following procedures will take place:

1. Review and obtain written informed consent.
2. Confirm/Record locator information and phone number and contact preferences.
3. Assign a unique study identification number
4. Assess eligibility (e.g., age 18-25 years, newly initiating PrEP at the clinic, symptoms of common mental disorders), including Adult Primary Care Guidelines screening questions and the SRQ-20
    a. If participants report suicidal ideation or intent, have untreated or severe somatic symptoms or have other active psychiatric symptoms (e.g., hallucinations) the participant will be referred for assessment by a trained health professional (see Section 4.2).

Participants that are already on treatment with stable symptoms may continue to randomization.

5. Offer enrolment to eligible participants and refer ineligible for additional services if needed.
6. Collect additional data on past mental history, participation in other mental health or HIV interventions, and other psychosocial and behavioral data (see Section 6).
7. Randomize participant to either Youth Friendship Bench SA intervention or the standard-of-care condition.
    a. Participants randomized to the Youth Friendship Bench SA intervention will complete their first counseling session at this visit.
        i. Collect preferences for SMS appointment reminders (see Section 4.3)
        ii. Schedule participant for their Week 2 visit in 14 days. They will be offered the option to complete the Week 2 visit in-person or remotely (over the phone).
    b. Standard-of-care participants will be scheduled for their next clinic visit at Week 4 in 30 days. They will not receive appointment reminders or remote services.

8.3.3. Week 2 Visit – Youth Friendship Bench SA participants only

1. Only participants randomized to the Youth Friendship Bench SA intervention will complete this visit, which will be their 2nd counseling session. This session may be conducted via phone.
2. Schedule participant for their Week 4 visit in 14 days. The Week 4 visit will be scheduled as an in-person session for a time when they are able to return to the clinic.

8.3.4. Week 4 Visit

1. Confirm consent
2. Confirm locator information and update as needed
3. Collect psychosocial and behavioral data additional data (see Section 6).
4. Assess symptoms of common mental disorders
    a. All participants will receive assessments per APC guidelines and referrals as needed. They will also complete the SRQ-20 with the lay counselor.
    b. Participants Youth Friendship Bench SA arm will complete their 3rd counseling session.
5. Schedule participant's next visit
    a. Standard-of-care participants will be scheduled for their Week 12 visit in 60 days.
    b. Youth Friendship Bench SA participants will be scheduled for their Week 8 visit in 30 days. They will be offered the option to complete the Week 8 visit in-person or remotely (over the phone).
6. All participants will be asked to provide a urine sample for the tenofovir (TFV) point-of-care (POC) assay. Urine POC assay testing and drug-level feedback counseling based on assay results will be conducted by the lay Youth Friendship Bench SA for participants in both arms and proceed as described in Section 5.1.2. The urine assay results will be used for research purposes only and will not be included in the clinic record.
7. Schedule in-depth interviews for AGYW between the Week 4 and Week 12 study visit.

8.3.5. Week 8 Visit – Youth Friendship Bench SA participants only

1. Participants randomized to the Youth Friendship Bench SA intervention will complete their 4th counseling session at this visit. This session may be conducted via phone
2. Schedule participant for their Week 12 visit in 30 days.
3. Schedule participants for optional group session (either in person or via WhatsApp as they prefer, for between the Week 8 and 12 visits with the exact timing depending on availability of participants and enrollment accrual rates).

8.3.6. Week 12/Exit Visit

1. Collect psychosocial and behavioral data (see Section 6)
2. Assess symptoms of common mental disorders
    a. All participants will receive assessments per APC guidelines and referrals as needed. They will also complete the SRQ-20 with the lay counselor.
    b. Participants Youth Friendship Bench SA arm will complete their 5th counseling session.
3. All participants will be asked to provide a urine sample for the tenofovir (TFV) point-of-care (POC) assay. Urine POC assay testing and drug-level feedback counseling based on assay results will proceed as described in Section 5.1.2. The urine assay results will be used for research purposes only and will not be included in the clinic record.
4. Complete termination procedures: exit participants, record any serious adverse events, ensure that participant is linked to and returns to the clinic for any routine services, and remove participants from any SMS communication as needed.

8.3.7. Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the clinic staff. We will ask participants about whether they attended the clinic for an interim visit at each study vist and will inquire about interim visit reason and outcome.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically, record the event on the CRF, and provide or refer the participant to appropriate medical care.

8.3.8. Early Exit/Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The site investigator also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or site IRBs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete final evaluations for participants who terminate from the study prior to the last study assessment or visit; study staff will record the reason(s) for all withdrawals from the study in participants' study records. Participant non-adherence to the intervention(s) or PrEP is not a reason for participant withdrawal from the study and we will continue to follow participants even if they decline the interventions (e.g., reply "STOP" to the SMS messages) prior to the completion of follow-up.

8.4. Participant Retention and SMS Reminders for Intervention Arm

Participants will be in the study for 3 months of follow-up and retention procedures may include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Collection of detailed locator information at the Enrollment visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Rapid and multi-faceted follow-up for missed visits (for participants in the Youth Friendship Bench SA arm only).
- Regular communication with the study community at large to increase awareness about HIV/AIDS and common mental disorders and explain the purpose of this research and the importance of completing research study visits.
- Use of appropriate and timely visit-reminder mechanisms via SMS (for participants in the Youth Friendship Bench SA arm only). Participants in the intervention arm will receive one-way SMS messages that remind them about their upcoming clinic visits and provide them with the appointment date and time.
- Use of the urine POC assay and corresponding drug-level feedback in both arms to support AGYW in returning to clinic for their PrEP refills and our accompanying mental health services and PrEP adherence assessment.

9.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

9.1. Management of health outcomes

5.1.1. Mental health symptoms

This section provides details on the management of symptoms of common mental disorders including self-harm, other psychiatric symptoms, and report of worsening symptoms throughout the study follow-up period.

Participants with a high SRQ-20 score at screening/enrollment visit: If the SRQ-20 score is greater than or equal to 7, the individual would be eligible for enrollment in this study but we will ensure that they have first completed standard-of-care procedures prior to study enrollment. As part of standard-of-care procedures, they will be offered a referral to talk with a social worker if they answered five or more questions on the SRQ-20 indicating that they have felt little pleasure in regular activities, have felt down or unhappy, and have experienced several items linked to common mental disorders (poor appetite, difficulty sleeping, etc.). The social worker will then meet with the young woman and make a further determination about referral for additional psychotherapy or pharmacotherapy as needed. AGYW who meet the SRQ-20 threshold for participation but require active management and care for untreated mental health symptoms, including psychiatric symptoms like hallucinations or severe somatic symptoms, will not be eligible for participation. However, they will be invited to return to the clinic and re-screen for eligibility in the study when their symptoms have stabilized (Figure 1).

Participants with a low SRQ-20 score at screening/enrollment: If the SRQ-20 score is less than 7, the individual would not be eligible for enrollment in this study but we will ensure that she is offered a referral to talk with a social worker as appropriate based on South African Department of Health Adult Primary Care Guidelines. Referrals will be provided to those who endorse at least one of the standard-of-care assessment items indicating that they have felt down or little pleasure in regular activities (**Appendix 1**) and five or more questions on the SRQ-20 indicating experience of somatic items linked to common mental disorders (poor appetite, difficulty sleeping, etc.; **Appendix 2**), regardless of SRQ-20 score. The social worker will then meet with the young woman and make a further determination about referral for additional

psychotherapy or pharmacotherapy as needed. We will also inform these AGYW that they can continue to receive PrEP at the study clinic.

Suicidal ideation, regardless of SRQ-20 score: The SRQ-20 includes one question on suicidal ideation ("Has the thought of ending your life been on your mind"), and anyone who endorses this item (regardless of their total SRQ-20 score) will be asked a series of three additional questions to determine suicidal intent ("Do you ever have thoughts of hurting or killing yourself?", "Are you currently thinking of killing yourself?", "Have you ever tried to kill yourself?"). They will also be provided referral to a social worker for further support as needed. Anyone who expresses suicidal intent or is deemed a risk to themselves or others will be ineligible for participation and immediately linked to inpatient care. They will only be able to re-screen into the study if and when their symptoms have stabilized and they not longer report self-harm or suicidal intent.

Worsening symptoms of common mental disorders throughout study follow-up: All participants will be asked whether their symptoms of common mental disorders have changed during the Week 4 and 12 visits and they will also complete the SRQ-20 at these time points. We will follow similar procedures as described for items a-c above, to ensure that individuals are linked with standard-of-care services regardless of SRQ-20 score. Those with symptoms of severe mental health distress or psychosis (e.g., unmanaged somatic symptoms, suicidal intent) will be linked to care and the study team will consider early termination from the study on a case-by-case basis.

9.1.2. PrEP provision and adherence counseling

The clinic will dispense PrEP and women will be counseled per South African national guidelines including about the importance of high PrEP adherence to achieve high levels of HIV protection, frequency, type and timing of side effects with oral FTC/TDF, and strategies for confidential storage and anticipating barriers to adherence. The clinic will also conduct HIV testing as needed. This is not a study-specific procedure***: the clinic will conduct PrEP prescribing, and HIV testing procedures separately from these study-specific procedures.*** Generally, at PrEP initiation visits, the clinic will dispense PrEP and counsel women per South African national guidelines, including about the importance of high PrEP adherence to achieve high levels of HIV protection, frequency, type and timing of side effects with oral FTC/TDF, and strategies for confidential storage and anticipated barriers to adherence.

With respect to urine POC and drug level feedback adherence counseling, all participants will be asked to provide a urine sample for the tenofovir (TFV) point-of-care (POC) assay as part of study specific procedures. Approximately 2-3 minutes after 3-4 drops of urine are placed on a urine test strip, a "control" line should appear. An additional "tenofovir test line" will appear only if a participant has TFV levels <1500 ng/mL indicative of no recent PrEP dosing. This threshold will be recorded on a study case report form (CRF) and will be used to provide drug-level feedback counseling at the Week 4 visit. Participants will be counselled on their results by a lay counsellor. Youth Friendship Bench SA counselors will provide participants with a counseling message corresponding with their TFV POC assay results as follows. These counseling messages were used in prior PrEP studies with AGYW[31,34,113]:

Control line only (one line appears on test)
Key message: It looks like you took a PrEP pill recently--you are doing great! Remember that taking one PrEP pill every day is needed for strong protection against HIV. How can we help you keep up the good

Control and tenofovir test line (two lines appear on test)
Key message: It looks like you haven't been able to take the PrEP medication in the past few days. Is PrEP something that you are still interested in? If yes, how can we help you?

We are including the POC assay and drug-level feedback counseling in the SOC arm (as well as in the Youth Friendship Bench arm) so that we can isolate the effect of our Youth Friendship Bench SA above and beyond this assay. Also, we hypothesize that this drug-level feedback approach will help to ensure retention in the SOC arm.

9.1.3. Other sexual and reproductive health outcomes

AGYW in South Africa are eligible for PrEP during pregnancy and postpartum and face a high burden of common mental disorders during these periods.[118,119] In addition, the Friendship Bench has been used to provide mental health services for pregnant and postpartum women in other African contexts.[120] We will enroll AGYW regardless of pregnancy or postpartum status and will continue providing study procedures to AGYW who become pregnant during follow-up. AGYW mental health service delivery will continue to be managed according to South African Adult Primary Care Guidelines.

We may learn of participant concerns about GBV and immediate risk of harm due to a violent partner. In accordance with this guidance, clinic staff will provide first line support using the LIVES model (Listen, Inquire about needs and concerns, Validate, Ensure safety, and Support) for all AGYW who report gender-based violence or fears about gender-based violence during a clinic visit, counseling session, qualitative interview, or data collection. Clinic staff will ask about violence in a private, confidential setting and provide processes for referring participants to other services (e.g., medical services, additional counseling or social work services, police and law enforcement). We will continue to follow and offer standard-of-care and Youth Friendship Bench SA services to all participants reporting GBV in this study.

9.2. Safety Monitoring

Close cooperation between the Protocol co-Chairs and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of SAEs in a timely manner. The study investigators are responsible for continuous close monitoring and management of SAEs.

9.3. Adverse Event Definition and Reporting

For the purposes of this study, only serious adverse events (SAEs) and adverse events of special interest (AESIs) will be recorded. These will be summarized by arm, as a secondary outcome of our study. SAEs are defined as those events that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity. AESIs are considered reports of self-harm or self-injury.

With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to SAEs will be obtained and required data elements will be recorded

on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Site staff will also report information regarding SAEs to their IRB or other local regulatory agencies in accordance with all applicable regulations and local IRB requirements.

9.4. Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as having a stigmatizing mental health condition, being HIV-infected, or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. These are social harm events. Social harm events are those negative events that a participant reports as affecting them as a result of being involved in a research study. A social harm that is reported by the participant and judged by the study staff to be serious or unexpected will be reported to the site's IRBs at least annually, or according to local requirements.

In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. While maintaining participant confidentiality, the site may engage the Youth Community Advisory Board (YCAB) in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

9.5. Study Oversight

The study will establish a Data Safety Monitoring Board (DSMB) to review data relating to safety and to ensure the continued scientific validity and merit of the study, according to the National Institute for Mental Health Data Safety Monitoring Board Operations Manual and a DSMB Charter to be established for this protocol. We will hold one DSMB meeting prior to study activation and enrollment to review study procedures and the statistical analysis plan and one after we enroll at least 50% of study participants to review preliminary data on enrollment characteristics including information on referrals for additional mental health services, retention, and social impact or SAE reporting. Other meetings will be held on an ad hoc basis.

10.0 DATA COLLECTION

10.1. Quantitative data collection

Demographic and behavioral data will be collected, including information on symptoms of common mental disorders, drug and alcohol use, GBV, post-traumatic stress symptoms, coping behavior, self-esteem, sexual relationship power, and sexual behavior (e.g., number of partners, vaginal sex with partners).

We will access the participant's clinic record to obtain information on age, HIV status, and PrEP status at screening. We will also abstract information on PrEP refills (bottle dispensed, dates of dispensation, and PrEP terminations) from the clinic records during the participant's three-month follow-up period.

Symptoms of common mental disorders will be assessed using the SRQ-20, which will be interviewer-administered by the lay counselors at enrollment, Week 4, and Week 12. Data on depressive symptoms (using the Patient Health Questionnaire-9 [PHQ-9]), anxiety (the Generalized Anxiety Disorder questionnaire [GAD-7]), history of mental health conditions and

services received, drug and alcohol use, GBV, and post-traumatic stress symptoms will also be interviewer-administered on study Case Report Forms (CRFs). All other demographic and behavioral data will be self-collected by participants using a tablet application. Research staff will be available in the clinic to provide guidance and assistance in completing the questionnaire as needed. De-identified data will be collected using REDCap and stored on a secure server.

10.2. Qualitative data collection

The use of qualitative methods that give young women, staff, and key informants the opportunity to discuss their opinions on the acceptability, appropriateness, and feasibility of Youth Friendship Bench SA in their own words will result in a more culturally-sensitive and potentially scalable approach to integrated mental health and PrEP adherence support among young women in Africa. Interviews will be conducted with a purposive sample of up to 30 young women and 15 clinic staff and key informants (with sampling until we reach saturation of themes), and will include:

1. Young women in both the Youth Friendship Bench SA and standard-of-care arms, with varying levels of PrEP adherence (based on Week 4 urine POC assay results) and common mental disorder symptom severity (based on Enrollment and Week 4 SRQ-20 scores)
2. Clinic staff involved in the delivery of the Youth Friendship Bench SA and standard-of-care mental health and PrEP services including the lay counselors providing the Youth Friendship Bench SA intervention.
3. Key informants involved in mental health and/or PrEP service provision, programs, funding, and/or policy-making.

In-depth qualitative interviews will occur sometime between the Week 4 and Week 12 study visits (for young women) and throughout the study period (for staff and key informants). The interviews with young women will explore the decision to take PrEP, barriers and facilitators to PrEP adherence, experiences with symptoms of common mental disorders and any links between these symptoms, HIV risk, and PrEP use, perceptions of standard-of-care service delivery, perceptions of Youth Friendship Bench SA service delivery (including satisfaction with the intervention, perceived benefits, challenges with the intervention, recommended changes, and perceived acceptability, appropriateness, and feasibility for delivery in PrEP clinics), and suggestions for future integrated mental health and PrEP adherence interventions. Interviews with clinic staff and key informants will focus on perceptions of standard-of-care service delivery, perceptions of Youth Friendship Bench SA service delivery (including satisfaction with the intervention, perceived benefits, challenges with the intervention, recommended changes, and perceived acceptability, appropriateness, and feasibility for delivery in PrEP clinics), and suggestions for future integrated mental health and PrEP adherence interventions. All interviews will be up to 60 minutes. We will also ask participants in both arms about the acceptability of the urine POC assay for PrEP adherence assessment and their receipt of counseling based on their urine assay results. All qualitative participants will be asked to provide written informed consent to participation and to having their interviews audio-recorded so that data can be used for subsequent analysis and publication. All interviews discussions will be conducted in the participant's preferred language.

Interview guides will be developed using reviews of local literature and youth community advisory board (YCAB) feedback. The semi-structured qualitative interview guide will provide a general structure for discussion but will allow interviewers and respondents to explore unique themes for a given interview. Local researchers/ethnographers will conduct all qualitative interviews with oversight from the protocol team and approximately one social scientist. All interviews will be audio-recorded and transcribed and translated into English by trained site staff.

When conducting a qualitative exploration, the sampling method should be designed to include a range of possible perspectives on the phenomenon under study, thus ideal qualitative samples are purposive in nature. The proposed study will utilize a stratified purposive sample, which will allow for consideration of the concepts of range, saturation/redundancy, and stratification in the sampling frame. We also took into account feasibility when creating our sample sizes, a factor that is especially relevant in qualitative research with "hard-to-reach" populations such as youth. We will stratify the sample based on PrEP adherence, intervention arm, and symptoms of common mental disorder as described above. Stratification on these factors will allow for a diverse purposive sample that will include a range of types of young women who may have various experiences with mental health issues, PrEP adherence, and the Youth Friendship Bench SA intervention. We will also conduct debriefs with the qualitative interviewers and the counseling staff to explore their views on participant's experiences with the in-depth interviews and the interventions.

All qualitative interview recordings and transcripts will be de-identified and will be stored on a secure server for at least two years at the University of the Witwatersrand. De-identified transcripts will be provided to the University of California San Francisco where they will be stored for three years after completion of the study.

In addition to data collection using in-depth interviews, we will also conduct ethnographic non-participant observations of clinic activities. A trained social scientist interviewer will observe participant waiting room discussions and comfort in the clinic, clinic flow, and the clinic environment for AGYW. Non-participant observations will allow the research team to observe interactions and clinic activities as a "fly on the wall" but otherwise remain as an identified outsider.[121,122] One weakness of overt non-participant observation is the potential that participants may change their behavior because they are aware of being observed. However, this effect on participants' behavior has been shown to wane over time, even as observations continue.[123] We will conduct up to 2 clinic observations per month during the duration of the study and the social scientist will complete field notes describing key learnings from the observation (without any specific identifiers). Prior to beginning an observation session, the social scientist will announce himself or herself in the waiting room. Observation data will be considered process notes to inform study activities, rather than research data to advance generalizable knowledge. Data will be stored on a secure server and reviewed periodically through the study.

11.0 STATISTICAL CONSIDERATIONS

11.1. Review of Study Design

At enrollment, women will be randomized 1:1 to either the standard-of-care mental health services (screening, referral, etc.) plus the Youth Friendship Bench SA intervention or standard-of-care services alone. Participants receiving the Youth Friendship Bench SA will complete individual counseling sessions at Enrollment, Week 2 (option to be conducted remotely), Week 4, Week 8 (option to be conducted remotely), and Week 12. They will also be invited to participate in an in-person or virtual group-based session (between their Week 8 and 12 visits, with the exact timing depending on participant availability and participant accrual rate) focused on an economic empowerment activity like job and school applications. Participants in the standard-of-care arm will complete visits at Enrollment, Week 4, and Week 12. The co-primary outcomes are: 1) the proportion with PrEP adherence measured by TFV levels detected in urine using a POC assay at Week 12 and 2) the proportion with reduced symptoms of common mental disorders measured by the SRQ-20 at Week 12. For the PrEP adherence measure, we will utilize urine TFV levels to assess PrEP dosing in the prior 4-7 days. The assay uses a threshold

of 1500 ng/mL to categorize participants as adherent as this was associated with daily dosing over 4-7 days in directly observed therapy.[112]

We will conduct all randomizations using a SAS-based computer-generated randomization scheme developed by the study data manager. The site sub-investigator will conduct the randomizations and fill out a randomization log which will be reviewed by the study data manager during visits to the study site. The identity of participants in each of the arms will not be known to investigators and access to the randomization code will be strictly controlled. The study blind will be broken only on completion of the clinical study and after the database has been locked. The study investigators will receive the unblended results only after that point.

11.2. Endpoints

11.2.2. Primary Endpoint

The primary outcomes are: 1) urine TFV levels above 1500 ng/mL at 12 weeks and 2) SRQ-20 scores less than 7 at 12 weeks

11.2.3. Secondary Endpoints

- Urine TFV levels above 1500 ng/mL at 4 Weeks
- Correlates of PrEP adherence at 12 weeks, adjusted for study arm.
    - Covariate characteristics assessed at baseline and follow-up may include: Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); symptoms of common mental disorders; self-esteem; and level of engagement with the intervention.
- Correlates of common mental disorder symptoms at 12 weeks, adjusted for study arm.
    - Covariate characteristics assessed at baseline and follow-up may include: Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); symptoms of common mental disorders; self-esteem; and level of engagement with the intervention.
- Qualitative factors that influence acceptability, feasibility, and appropriateness of the Youth Friendship Bench SA intervention
- SAEs (including events that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, and/or result in persistent or significant disability/incapacity) and adverse events of special interest (reports of self-harm or self-injury).

11.2.4. Exploratory endpoints

- Mediators and moderators of the Youth Friendship Bench SA intervention effect on PrEP adherence at 12 weeks
    - Covariate characteristics assessed at baseline and follow-up may include: Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); symptoms of common mental disorders; self-esteem; intervention acceptability, feasibility, and appropriateness; and level of engagement with the intervention.
- Mediators and moderators of the Youth Friendship Bench SA intervention effect on symptoms of common mental disorders at 12 weeks
    - Covariate characteristics assessed at baseline and follow-up may include: Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); symptoms of common mental disorders; self-esteem; self-reported PrEP

adherence; intervention acceptability, feasibility, and appropriateness; and level of engagement with the intervention.

11.3. Accrual, Follow-up, and Sample Size

We will randomize 110 AGYW in a 1:1 ratio to either our adapted intervention or standard-of-care mental health services over a 12-month study period (approximately 9-10 AGYW enrolled per month). Based on current levels of AGYW receiving PrEP at the public health clinic in Johannesburg, and reporting symptoms of common mental disorders and receiving referral services, we will likely need to screen approximately 18-20 AGYW per month to meet our enrollment targets. Based on prior PrEP studies with AGYW in this setting (HPTN 082, PrEP SMART, POWER), we expect to retain 85-90% of AGYW through three months of follow-up.

For our primary outcome of PrEP adherence, if we assume 40% PrEP adherence in the standard-of-care arm (as was seen in the HPTN 082 trial with AGYW in this setting) and an alpha of 0.05, we will have 80% power to detect at least a 20% difference in the proportion with adherence between arms.

For our primary outcome of common mental disorder symptoms, if we assume 50% prevalence of symptoms of common mental disorders (again, as was seen in the HPTN 082 and PrEP SMART trials) and an alpha of 0.05, we will have 80% power to detect at least a 25% difference in the proportion with symptoms of common mental disorders between arms.

11.4. Data Analysis

11.4.2. Primary Analyses

We will use Poisson regression with robust standard errors to assess the effect of standard-of-care services compared with our adapted mental health intervention on TFV levels measured in urine (with adherence defined as TFV ≥1500 ng/mL) at 12 weeks after randomization. We will also use Poisson regression with robust standard errors to assess the effect of standard-of-care services compared with our adapted mental health intervention on symptoms of common mental disorders at 12 weeks after randomization, using an SRQ-20 score of 7 as our threshold.

11.4.3. Secondary Analyses

We will use Poisson regression with robust standard errors to assess the effect of standard-of-care services compared with our adapted mental health intervention on TFV levels measured in urine (with adherence defined as TFV ≥1500 ng/mL) at 4 weeks after randomization.

The correlates of response (PrEP adherence based on TFV levels, symptoms of common mental disorders based on the SRQ-20) at 12 weeks will be assessed using logistic regression modelling, evaluating the covariates described in the endpoints section above.

Survival analysis will be used assess the effect of the adherence strategies as well as individual characteristics (demographics, etc.) on time to PrEP discontinuation for those who choose to stop PrEP before 12 months.

We will analyze qualitative data (in-depth interviews, clinic observation field notes) using an inductive and deductive coding approach and will use descriptive statistics to summarize quantitative data on intervention acceptability, feasibility, and appropriateness and SAEs and AESIs.

12.0 HUMAN SUBJECTS CONSIDERATIONS

12.1.2. Ethical Review

The protocol, ICF, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site. Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually.

12.1.3. Informed Consent

Written informed consent for screening and enrollment will be obtained from each study participant. Participants who are not literate will be read the informed consent document by a research staff member, in the presence of a literate, impartial witness (who will not be part of the study team). They will provider verbal consent and use a mark or thumbprint to indicate their consent. The consent will also be counter-signed by their witness. The ICFs describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The ICFs will be translated into a local language (isiZulu) and the accuracy of the translation will be verified by performing an independent back-translation. Participants will be provided with a copy of their ICFs if they are willing to receive them.

12.1.4. Risks

Sensitive Questions

Participants will be asked questions about their mental health and sexual behavior that may make them feel uneasy. Participants do not have to answer any question that they do not want to and can stop answering the questions at any time. Steps will be taken to minimize any psychological discomfort by providing ongoing counseling during study visits and as needed in between monthly sessions. We will also establish group norms prior to group counseling sessions to ensure that all participants feel comfortable during these group sessions.

Worsening symptoms of common mental disorders

Study participants may experience or more intense psychological discomfort during interviews or psychosocial counseling sessions due to disclosure about severe mental health symptoms or suicidal thoughts. The clinic has an on-site social worker and psychologist, who will be able to see more complicated participants either during their study visit or at a subsequent time. AGYW who report mental health distress related to gender-based violence or fears of violence will be provided referrals to meet with the on-site social worker and psychologist as needed. We will also provide participants with phone numbers to contact study staff after hours and information on how to report an issue to local police and law enforcement. We will follow Ward 21 standard operating procedures and South African Adult Primary Care Guidelines for responding to issues of acute mental distress among AGYW. AGYW who report a history of suicide attempt and/or current suicidal ideation or intent during the study (assessed via three questions routinely used for screening and linkage to care in this study setting) will immediately be linked to further care as needed.

Confidentiality

Although the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (e.g., because participants could become known as at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and communities. We will establish group

norms prior to group counseling sessions to ensure that all participants are aware of the need to protect one another's confidentiality. Participants who are concerned about confidentiality may choose to use a pseudonym when participating in group counseling sessions and all group session attendees will be encouraged to refrain from discussing other participants with friends and families. We will remind participants prior to individual and group sessions that they can leave the session or decline to participate at any time. Lists of referrals are in place to address recent psychological problems needing intervention and the study site has a social worker and clinical psychologist available on site to address any pressing participant needs. All research staff are rigorously trained and all intervention activities and data collection will take place in private rooms with closed doors.

Confidentiality and data storage concerns for SMS reminder messages

Participants will be offered optional SMS appointment reminders. The SMS platform used for participant text messaging is end-to-end encrypted, meaning only members of the study team can access it. The SMS platform will be accessed by study staff through a password-protected laptop, stored in a locked office. All data records will be identified by study ID only. The link between identifiable participant information and study IDs will be locked in a secure location and destroyed following study completion. There is some potential risk of confidentiality loss associated with having sensitive SMS messages with appointment reminders or communication with healthcare staff stored on participants' personal phones. We will ensure all prospective participants review example SMS messages so that they are aware of the content of SMS they will receive as part of informed consent procedures. All participants will be informed that their participation is voluntary and can stop receiving the SMS messages at any time by texting "STOP" which will cease on SMS communication between study staff and the participant. All study staff will be trained in protection of human subjects and the clinical and emotional needs of AGYW with symptoms of common mental disorders on PrEP.

Confidentiality and data storage concerns for remote visits

Participants will be offered optional remote counseling sessions (via telephone). The lay counselor will confirm readiness for remote visits by phone to ensure the participant safety and confidentiality. Remote visit procedures will be detailed in a standard operating procedure. Remote sessions will not be recorded and no identifiable data about the session will be stored. All participants will be informed that their participation is voluntary and they can stop the remote session at any time. All study staff will be trained in protection of human subjects and the clinical and emotional needs of AGYW with symptoms of common mental disorders on PrEP.

12.1.5. Benefits

There may be no direct benefits to participants in this study beyond the provision of counseling and referrals; however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to prevent common mental disorders, HIV, and other infections.

12.1.6. Compensation

Pending IRB/EC approval, participants will be compensated for their time and effort in this study (beyond standard-of-care service delivery) at enrolment, week 4 and week 12 study visits. Reimbursement amounts will be specified in the study informed consent forms (ICFs). Participants in the Youth Friendship Bench SA arm who complete a virtual group session between their Week 8 and 12 visits will be provided 2GB data prior to the start of the session.

12.1.7. Study Records

All study-related records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner at the study site.

12.1.8. Confidentiality

The study site will establish a standard operating procedure for confidentiality protection. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All DBS cards, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PTID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Staff will use a code word prior to each text message (similar to Weltel)[124] to prevent inadvertent disclosure of study participation in the case of shared mobile phones. Staff will not be able to access any information on participants' mobile phones.

Participants' study information will not be released without their written permission, except as necessary for oversight by:

- The Protocol Chair or designees
- Study funders
- Site IRB/ECs
- University of California San Francisco
- Any additional study sponsors

13.0 REFERENCES

1. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet Lond. Engl.* **394**, 303–313 (2019).
2. Baeten, J. M. *et al*. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. *N. Engl. J. Med.* (2016) doi:10.1056/NEJMoa1506110.
3. UNAIDS. *Trend in new infections: Eastern, Southern, Western, Central Africa by Sex.* aidsinfo.unaids.org (2018).
4. South African National AIDS Council (SANAC). *National Strategic Plan 2017-2022.* https://sanac.org.za/wp-content/uploads/2019/03/2017_18_SANAC_31_01_2019.pdf (2017).
5. UNAIDS. *HIV prevention among adolescent girls and youth women: Putting HIV prevention among adolescent girls and young women on the Fast-Track and engaging men and boys.* https://www.unaids.org/sites/default/files/media_asset/UNAIDS_HIV_prevention_among_adolescent_girls_and_young_women.pdf (2016).
6. *WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 12: Adolescents and young adults*. (2018).
7. World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. (2014).
8. Baggaley, R., Armstrong, A., Dodd, Z., Ngoksin, E. & Krug, A. Young key populations and HIV: a special emphasis and consideration in the new WHO Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. *J. Int. AIDS Soc.* **18**, 19438 (2015).
9. Low, M. Government plans massive PrEP foll out. *Spotlight* (2020).
10. Grant, R. M. *et al.* Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.* **363**, 2587–2599 (2010).

11. Baeten, J. M. *et al*. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N. Engl. J. Med*. **367**, 399–410 (2012).
12. Choopanya, K. *et al*. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Lond. Engl.* **381**, 2083–2090 (2013).
13. Thigpen, M. C. *et al.* Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N. Engl. J. Med*. **367**, 423–434 (2012).
14. Baeten, J. M. *et al*. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1-Serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. *PLoS Med.* **13**, e1002099 (2016).
15. Heffron, R. *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 Res.* **1**, (2017).
16. Bekker, L.-G. *et al*. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *Lancet HIV* (2017) doi:10.1016/S2352-3018(17)30156-X.
17. Grant, R. M. *et al.* Daily and Nondaily Oral Preexposure Prophylaxis in Men and Transgender Women Who Have Sex With Men: The Human Immunodeficiency Virus Prevention Trials Network 067/ADAPT Study. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* (2018) doi:10.1093/cid/cix1086.
18. Hosek, S. G. *et al.* An HIV Preexposure Prophylaxis Demonstration Project and Safety Study for Young MSM. *J. Acquir. Immune Defic. Syndr. 1999* **74**, 21–29 (2017).
19. Grinsztejn, B. *et al.* Retention, engagement, and adherence to pre-exposure prophylaxis for men who have sex with men and transgender women in PrEP Brasil: 48 week results of a demonstration study. *Lancet HIV* **5**, e136–e145 (2018).
20. Gill, K. *et al*. Pluspills: an open label, safety and feasibility study of oral pre-exposure prophylaxis (PrEP) in 15-19 year old adolescents in two sites in South Africa. (2017).

21. Amico, K. R. *et al.* Experiences with HPTN 067/ADAPT Study-Provided Open-Label PrEP Among Women in Cape Town: Facilitators and Barriers Within a Mutuality Framework. *AIDS Behav.* (2016) doi:10.1007/s10461-016-1458-y.

22. Hosek, S. *et al.* Preventing HIV among adolescents with oral PrEP: observations and challenges in the United States and South Africa. *J. Int. AIDS Soc.* **19**, (2016).

23. van der Straten, A. *et al.* Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: the VOICE-C qualitative study in Johannesburg, South Africa. *J. Int. AIDS Soc.* **17**, (2014).

24. Velloza, J. *et al.* The influence of HIV-related stigma on PrEP disclosure and adherence among adolescent girls and young women in HPTN 082: a qualitative study. *J. Int. AIDS Soc.* **23**, e25463 (2020).

25. Velloza, J. *et al.* Effect of Depression on Adherence to Oral PrEP Among Men and Women in East Africa. *J. Acquir. Immune Defic. Syndr. 1999* **79**, 330–338 (2018).

26. Cabral, A. *et al.* Intimate Partner Violence and Self-Reported Pre-exposure Prophylaxis Interruptions Among HIV-Negative Partners in HIV Serodiscordant Couples in Kenya and Uganda. *J. Acquir. Immune Defic. Syndr. 1999* **77**, 154–159 (2018).

27. Velloza, J. *et al.* The Effect of Depression on Adherence to HIV Pre-exposure Prophylaxis Among High-Risk South African Women in HPTN 067/ADAPT. *AIDS Behav.* (2020) doi:10.1007/s10461-020-02783-8.

28. Velloza, J., Delany-Moretlwe, S. & Baeten, J. M. Comprehensive HIV risk reduction interventions for 2020 and beyond: product choices and effective service-delivery platforms for individual needs and population-level impact. *Curr. Opin. HIV AIDS* (2019) doi:10.1097/COH.0000000000000567.

29. Saul, J. *et al.* The DREAMS core package of interventions: A comprehensive approach to preventing HIV among adolescent girls and young women. *PloS One* **13**, e0208167 (2018).

30. Celum, C. L. *et al.* PrEP use and HIV seroconversion rates in adolescent girls and young women from Kenya and South Africa: the POWER demonstration project. *J. Int. AIDS Soc.* **25**, e25962 (2022).
31. Celum, C. *et al.* PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence among young women in southern Africa: Results from HPTN 082, a randomized controlled trial. *PLoS Med.* **18**, e1003670 (2021).
32. Celum, C. L. *et al.* Incentives conditioned on tenofovir levels to support PrEP adherence among young South African women: a randomized trial. *J. Int. AIDS Soc.* **23**, e25636 (2020).
33. *Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance*. (2022).
34. Velloza, J. *et al.* Evaluating adaptive HIV pre-exposure prophylaxis adherence interventions for young South African women: results from a sequential multiple assignment randomized trial. (2022).
35. Landovitz, R. J., Kofron, R. & McCauley, M. The promise and pitfalls of long-acting injectable agents for HIV prevention. *Curr. Opin. HIV AIDS* **11**, 122–128 (2016).
36. Celum, C. L. *et al.* Risk behavior, perception, and reasons for PrEP among young African women in HPTN 082. (2018).
37. Patel, V. *et al.* The Lancet Commission on global mental health and sustainable development. *The Lancet* (2018) doi:10.1016/S0140-6736(18)31612-X.
38. Lund, C. *et al.* Social determinants of mental disorders and the Sustainable Development Goals: a systematic review of reviews. *Lancet Psychiatry* **5**, 357–369 (2018).
39. Velloza, J. *et al.* Assessing longitudinal patterns of depressive symptom and the influence of sumptom trajectories on PrEP persistence among adolescent girls in HPTN 082. in (2020).
40. Goin, D. E. *et al.* Depression and incident HIV in adolescent girls and young women in HPTN 068: Targets for prevention and mediating factors. *Am. J. Epidemiol.* doi:10.1093/aje/kwz238.

41. Cluver, L. D., Orkin, F. M., Meinck, F., Boyes, M. E. & Sherr, L. Structural drivers and social protection: mechanisms of HIV risk and HIV prevention for South African adolescents. *J. Int. AIDS Soc.* **19**, (2016).

42. Kuringe, E. *et al.* Prevalence and correlates of depression and anxiety symptoms among out-of-school adolescent girls and young women in Tanzania: A cross-sectional study. *PloS One* **14**, e0221053 (2019).

43. Nyato, D. *et al.* Prevalence and correlates of partner violence among adolescent girls and young women: Evidence from baseline data of a cluster randomised trial in Tanzania. *PloS One* **14**, e0222950 (2019).

44. Mathur, S. *et al.* High rates of sexual violence by both intimate and non-intimate partners experienced by adolescent girls and young women in Kenya and Zambia: Findings around violence and other negative health outcomes. *PloS One* **13**, e0203929 (2018).

45. Jarolimova, J. *et al.* Experiences of participants in a decentralized antiretroviral therapy program in South Africa during the COVID-19 pandemic. *AIDS Care* 1–7 (2022) doi:10.1080/09540121.2022.2095333.

46. Dorward, J. *et al.* The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. *Lancet HIV* **8**, e158–e165 (2021).

47. Pollard, R. *et al.* HIV service delivery in the time of COVID-19: focus group discussions with key populations in India. *J. Int. AIDS Soc.* **24 Suppl 6**, e25800 (2021).

48. Remien, R. H. *et al.* Mental health and HIV/AIDS: the need for an integrated response. *AIDS Lond. Engl.* **33**, 1411–1420 (2019).

49. van der Straten, A. *et al.* Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. *PloS One* **9**, e89118 (2014).

50. Gore-Felton, C. & Koopman, C. Behavioral mediation of the relationship between psychosocial factors and HIV disease progression. *Psychosom. Med.* **70**, 569–574 (2008).

51. Turan, B. *et al.* Mechanisms for the Negative Effects of Internalized HIV-Related Stigma on Antiretroviral Therapy Adherence in Women: The Mediating Roles of Social Isolation and Depression. *J. Acquir. Immune Defic. Syndr. 1999* **72**, 198–205 (2016).

52. Rao, D. *et al.* A Structural Equation Model of HIV-Related Stigma, Depressive Symptoms, and Medication Adherence. *AIDS Behav.* **16**, 711–716 (2012).

53. Ferrer, R. A., Morrow, K. M., Fisher, W. A. & Fisher, J. D. Toward an information–motivation–behavioral skills model of microbicide adherence in clinical trials. *AIDS Care* **22**, 997–1005 (2010).

54. Mehrotra, M. L. *et al.* The Effect of Depressive Symptoms on Adherence to Daily Oral PrEP in Men who have Sex with Men and Transgender Women: A Marginal Structural Model Analysis of The iPrEx OLE Study. *AIDS Behav.* **20**, 1527–1534 (2016).

55. Pasipanodya, E. C. *et al.* Trajectories and Predictors of Longitudinal Preexposure Prophylaxis Adherence Among Men Who Have Sex With Men. *J. Infect. Dis.* **218**, 1551–1559 (2018).

56. Hall, K. S., White, K. O., Rickert, V. I., Reame, N. & Westhoff, C. Influence of depressed mood and psychological stress symptoms on perceived oral contraceptive side effects and discontinuation in young minority women. *Contraception* **86**, 518–525 (2012).

57. Garbers, S., Correa, N., Tobier, N., Blust, S. & Chiasson, M. A. Association Between Symptoms of Depression and Contraceptive Method Choices Among Low-Income Women at Urban Reproductive Health Centers. *Matern. Child Health J.* **14**, 102–109 (2010).

58. Hall, K. S., Kusunoki, Y., Gatny, H. & Barber, J. The risk of unintended pregnancy among young women with mental health symptoms. *Soc. Sci. Med. 1982* **100**, 62–71 (2014).

59. Lennon, C. A., Huedo-Medina, T. B., Gerwien, D. P. & Johnson, B. T. A role for depression in sexual risk reduction for women? A meta-analysis of HIV prevention trials with depression outcomes. *Soc. Sci. Med. 1982* **75**, 688–698 (2012).

60. Nakimuli-Mpungu, E. *et al.* Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. *AIDS Behav.* **16**, 2101–2118 (2012).

61. Sheth, S. S. *et al.* Association between depression and nonadherence to antiretroviral therapy in pregnant women with perinatally acquired HIV. *AIDS Care* **27**, 350–354 (2015).

62. Smith Fawzi, M. C. *et al.* Mental Health and Antiretroviral Adherence Among Youth Living With HIV in Rwanda. *Pediatrics* **138**, (2016).

63. Nabukeera-Barungi, N. *et al.* Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from 10 districts in Uganda. *BMC Infect. Dis.* **15**, 520 (2015).

64. Velloza, J. *et al.* Cognitive testing of the PHQ-9 for depression screening among pregnant and postpartum women in Kenya. *BMC Psychiatry* **20**, 31 (2020).

65. Velloza, J. *et al.* Assessing longitudinal patterns of depressive symptoms and the influence of symptom trajectories on HIV pre-exposure prophylaxis adherence among adolescent girls in the HPTN 082 randomized controlled trial. *J. Int. AIDS Soc.* **24 Suppl 2**, e25731 (2021).

66. Meinck, F. *et al.* Interventions to reduce gender-based violence among young people living with or affected by HIV/AIDS in low-income and middle-income countries. *AIDS Lond. Engl.* **33**, 2219–2236 (2019).

67. Andersson, G. Z. *et al.* Stigma reduction interventions in people living with HIV to improve health-related quality of life. *Lancet HIV* **7**, e129–e140 (2020).

68. Yount, K. M., Krause, K. H. & Miedema, S. S. Preventing gender-based violence victimization in adolescent girls in lower-income countries: Systematic review of reviews. *Soc. Sci. Med. 1982* **192**, 1–13 (2017).

69. Gourlay, A. *et al.* Awareness and uptake of layered HIV prevention programming for young women: analysis of population-based surveys in three DREAMS settings in Kenya and South Africa. *BMC Public Health* **19**, 1417 (2019).

70. Sikkema, K. J. *et al.* Improving mental health among people living with HIV: a review of intervention trials in low- and middle-income countries. *Glob. Ment. Health Camb. Engl.* **2**, (2015).

71. Andersen, L. S. *et al.* A pilot study of a nurse-delivered cognitive behavioral therapy intervention (Ziphamandla) for adherence and depression in HIV in South Africa. *J. Health Psychol.* 135910531664337 (2016) doi:10.1177/1359105316643375.

72. Petersen, I., Hanass Hancock, J., Bhana, A. & Govender, K. A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: A randomized controlled pilot study. *J. Affect. Disord.* **158**, 78–84 (2014).

73. Bolton, P. *et al.* Group Interpersonal Psychotherapy for Depression in Rural Uganda: A Randomized Controlled Trial. *JAMA* **289**, 3117 (2003).

74. Abas, M. *et al.* Feasibility and Acceptability of a Task-Shifted Intervention to Enhance Adherence to HIV Medication and Improve Depression in People Living with HIV in Zimbabwe, a Low Income Country in Sub-Saharan Africa. *AIDS Behav.* (2017) doi:10.1007/s10461-016-1659-4.

75. Sikkema, K. J. *et al.* Improving AIDS Care After Trauma (ImpACT): Pilot Outcomes of a Coping intervention Among HIV-Infected Women with Sexual Trauma in South Africa. *AIDS Behav.* **22**, 1039–1052 (2018).

76. Sin, N. L. & DiMatteo, M. R. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Ann. Behav. Med. Publ. Soc. Behav. Med.* **47**, 259–269 (2014).

77. Tol, W. A. *et al.* Can mental health treatments help prevent or reduce intimate partner violence in low- and middle-income countries? A systematic review. *BMC Womens Health* **19**, 34 (2019).

78. Keynejad, R. C., Hanlon, C. & Howard, L. M. Psychological interventions for common mental disorders in women experiencing intimate partner violence in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Psychiatry* **7**, 173–190 (2020).

79. Cox, G. R. *et al.* Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst. Rev.* **11**, CD008324 (2012).

80. Ebmeier, K. P., Donaghey, C. & Steele, J. D. Recent developments and current controversies in depression. *The Lancet* **367**, 153–167 (2006).

81. Clarke, K., King, M. & Prost, A. Psychosocial Interventions for Perinatal Common Mental Disorders Delivered by Providers Who Are Not Mental Health Specialists in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *PLoS Med.* **10**, (2013).

82. Singla, D. R. *et al*. Psychological Treatments for the World: Lessons from Low- and Middle-Income Countries. *Annu. Rev. Clin. Psychol.* **13**, 149–181 (2017).

83. World Health Organization (WHO). *mhGAP implementation guide for mental, neurological and substance use disorders in non-specialized health settings*. (2010).

84. Bell, A. C. & D'Zurilla, T. J. Problem-solving therapy for depression: A meta-analysis. *Clin. Psychol. Rev.* **29**, 348–353 (2009).

85. Nezu, A. M. & Perri, M. G. Social problem-solving therapy for unipolar depression: an initial dismantling investigation. *J. Consult. Clin. Psychol.* **57**, 408–413 (1989).

86. Malouff, J. M., Thorsteinsson, E. B. & Schutte, N. S. The efficacy of problem solving therapy in reducing mental and physical health problems: a meta-analysis. *Clin. Psychol. Rev.* **27**, 46–57 (2007).

87. Prince, M. *et al.* No health without mental health. *The Lancet* **370**, 859–877 (2007).

88. Gross, R. *et al.* Managed problem solving for antiretroviral therapy adherence: a randomized trial. *JAMA Intern. Med.* **173**, 300–306 (2013).

89. Chaiyachati, K. H. *et al.* Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. *AIDS Lond. Engl.* **28 Suppl 2**, S187-204 (2014).

90. Amico, K. R. *et al*. Integrated Next Step Counseling (iNSC) for Sexual Health and PrEP Use Among Young Men Who Have Sex with Men: Implementation and Observations from ATN110/113. *Aids Behav.* **23**, 1812–1823 (2019).

91. Fairall, L. *et al*. Collaborative care for the detection and management of depression among adults receiving antiretroviral therapy in South Africa: study protocol for the CobALT randomised controlled trial. *Trials* **19**, 193 (2018).

92. Petersen, I. *et al.* Collaborative care for the detection and management of depression among adults with hypertension in South Africa: study protocol for the PRIME-SA randomised controlled trial. *Trials* **19**, 192 (2018).

93. Amico, K. R., Mansoor, L. E., Corneli, A., Torjesen, K. & van der Straten, A. Adherence Support Approaches in Biomedical HIV Prevention Trials: Experiences, Insights and Future Directions from Four Multisite Prevention Trials. *AIDS Behav.* **17**, 2143–2155 (2013).

94. Chibanda, D. *et al.* The Friendship Bench programme: a cluster randomised controlled trial of a brief psychological intervention for common mental disorders delivered by lay health workers in Zimbabwe. *Int. J. Ment. Health Syst.* **9**, 21 (2015).

95. Chibanda, D. *et al.* Problem-solving therapy for depression and common mental disorders in Zimbabwe: piloting a task-shifting primary mental health care intervention in a population with a high prevalence of people living with HIV. *BMC Public Health* **11**, 828 (2011).

96. Chibanda, D. *et al.* Effect of a Primary Care-Based Psychological Intervention on Symptoms of Common Mental Disorders in Zimbabwe: A Randomized Clinical Trial. *JAMA* **316**, 2618–2626 (2016).

97. Nyatsanza, M., Schneider, M., Davies, T. & Lund, C. Filling the treatment gap: developing a task sharing counselling intervention for perinatal depression in Khayelitsha, South Africa. *BMC Psychiatry* **16**, 164 (2016).

98. van't Hof, E., Stein, D. J., Marks, I., Tomlinson, M. & Cuijpers, P. The effectiveness of problem solving therapy in deprived South African communities: results from a pilot study. *BMC Psychiatry* **11**, 156 (2011).

99. Oladeji, B. D. *et al.* A pilot randomized controlled trial of a stepped care intervention package for depression in primary care in Nigeria. *BMC Psychiatry* **15**, (2015).

100. Smith Fawzi, M. C. *et al.* Healthy Options: study protocol and baseline characteristics for a cluster randomized controlled trial of group psychotherapy for perinatal women living with HIV and depression in Tanzania. *BMC Public Health* **20**, (2020).

101. Udedi, M. *et al.* Integrating depression management into HIV primary care in central Malawi: the implementation of a pilot capacity building program. *BMC Health Serv. Res.* **18**, 593 (2018).

102. Chibanda, D. Reducing the treatment gap for mental, neurological and substance use disorders in Africa: lessons from the Friendship Bench in Zimbabwe. *Epidemiol. Psychiatr. Sci.* **26**, 342–347 (2017).

103. Verhey, R. *et al.* Perceptions of HIV-related trauma in people living with HIV in Zimbabwe's Friendship Bench Program: A qualitative analysis of counselors' and clients' experiences. *Transcult. Psychiatry* 1363461519850337 (2019) doi:10.1177/1363461519850337.

104. Wallén, A., Eberhard, S. & Landgren, K. The Experiences of Counsellors Offering Problem-Solving Therapy for Common Mental Health Issues at the Youth Friendship Bench in Zimbabwe. *Issues Ment. Health Nurs.* **0**, 1–18 (2021).

105. Brooks, M. J. *et al.* Principles for delivery of youth lay counsellor programs: Lessons from field experiences. *J. Glob. Health* **12**, 03047 (2022).

106. Brooks, M. J. *et al.* Building a Community Based Mental Health Program for Adolescents in Botswana: Stakeholder Feedback. *Community Ment. Health J.* **58**, 1068–1075 (2022).

107. Simms, V. *et al.* Peer-led counselling with problem discussion therapy for adolescents living with HIV in Zimbabwe: A cluster-randomised trial. *PLoS Med.* **19**, e1003887 (2022).

108. South African National Department of Health. *Adult Primary Care: Symptom-based integrated approach to the adult in primary care.* 1–152 (2019).

109. Curran, G. M., Bauer, M., Mittman, B., Pyne, J. M. & Stetler, C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med. Care* **50**, 217–226 (2012).

110. Anderson, P. L. *et al.* Intracellular Tenofovir-Diphosphate and Emtricitabine-Triphosphate in Dried Blood Spots following Directly Observed Therapy. *Antimicrob. Agents Chemother.* **62**, (2018).

111. Pyra, M. *et al.* Tenofovir-Diphosphate as a Marker of HIV Pre-exposure Prophylaxis Use Among East African Men and Women. *Front. Pharmacol.* **10**, (2019).

112. Gandhi, M. *et al*. Validation of a Urine Tenofovir Immunoassay for Adherence Monitoring to PrEP and ART and Establishing the Cutoff for a Point-of-Care Test. *Jaids-J. Acquir. Immune Defic. Syndr.* **81**, 72–77 (2019).

113. Poovan, N. *et al.* Performance and acceptability of a urine point-of-care test for drug-level feedback counseling on PrEP use among young women in South Africa. (2022).

114. Gandhi, M. *et al*. Development and validation of the first point-of-care assay to objectively monitor adherence to HIV treatment and prevention in real-time in routine settings. *AIDS Lond. Engl.* **34**, 255–260 (2020).

115. Gandhi, M. *et al*. Development and Validation of an Immunoassay for Tenofovir in Urine as a Real-Time Metric of Antiretroviral Adherence. *EClinicalMedicine* **2–3**, 22–28 (2018).

116. Spinelli, M. A. *et al.* Brief Report: High Accuracy of a Real-Time Urine Antibody-Based Tenofovir Point-of-Care Test Compared With Laboratory-Based ELISA in Diverse Populations. *J. Acquir. Immune Defic. Syndr. 1999* **84**, 149–152 (2020).

117. Johnson, K. A. *et al.* Lower Urine Tenofovir Concentrations Among Individuals Taking Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate: Implications for Point-of-Care Testing. *Open Forum Infect. Dis.* **8**, ofab200 (2021).

118. Bekker, L.-G. *et al*. Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection. *South. Afr. J. Hiv Med.* **17**, (2016).

119. Stringer, E. M. *et al.* Depression, pregnancy, and HIV: the case to strengthen mental health services for pregnant and post-partum women in sub-Saharan Africa. *Lancet Psychiatry* **1**, 159–162 (2014).

120. Stockton, M. A. *et al.* The impact of an integrated depression and HIV treatment program on mental health and HIV care outcomes among people newly initiating antiretroviral therapy in Malawi. *PloS One* **15**, e0231872 (2020).

121. O'Cathain, A. *et al*. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot Feasibility Stud.* **1**, 32 (2015).

122. Fitzpatrick, R. & Boulton, M. Qualitative methods for assessing health care. *Qual. Health Care QHC* **3**, 107–113 (1994).

123. Leonard, K. & Masatu, M. C. Outpatient process quality evaluation and the Hawthorne Effect. *Soc. Sci. Med. 1982* **63**, 2330–2340 (2006).

124. Lester, R. T. *et al*. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet Lond. Engl.* **376**, 1838–1845 (2010).

125. Cherian, V. I., Peltzer, K. & Cherian, L. The factor-structure of the Self Reporting Questionnaire (SRQ-20) in South Africa. *East Afr. Med. J.* **75**, 654–656 (1998).

126. van der Westhuizen, C., Wyatt, G., Williams, J. K., Stein, D. J. & Sorsdahl, K. Validation of the Self Reporting Questionnaire 20-Item (SRQ-20) for Use in a Low- and Middle-Income Country Emergency Centre Setting. *Int. J. Ment. Health Addict.* **14**, 37–48 (2016).

Appendix 1: Standard-of-care assessment of common mental disorders for patients seeking primary or HIV care, according to the South African Adult Primary Care Guidelines[108]

1. **In the past month, has the patient felt down, depressed, or hopeless?** (Yes, No)
2. **In the past month, has the patient felt little interest or pleasure in doing things?** (Yes, No)

If yes to either, then assess whether patient has had 5 or more of the following features for the last 2 weeks:

- Depressed mood most of the day, nearly every day
- Loss of interest or pleasure in activities that are usually pleasurable
- Fatigue or loss of energy
- Disturbed sleep or sleeping too much
- Change in appetite or weight
- Feeling guilty or worthless
- Reduced concentration or indecisiveness
- Visible agitation or restlessness, or talking or moving more slowly than usual
- Ideas or acts of self-harm or suicide

Appendix 2: Self-reporting questionnaire, 9-item (SRQ-20) for screening common mental disorders[125,126]

1. Do you often have headaches?
2. Is your appetite poor?[1]
3. Do you sleep badly?[1]
4. Are you easily frightened?
5. Do your hands shake?[1]
6. Do you feel nervous, tense, or worried?
7. Is your digestion poor?[1]
8. Do you have trouble thinking clearly?[1]
9. Do you feel unhappy?[1]
10. Do you cry more than usual?
11. Do you find it difficult to enjoy your daily activities?[1]
12. Do you find it difficult to make decisions?[1]
13. Is your daily work suffering?[1]
14. Are you unable to play a useful part in life?[1]
15. Have you lost interest in things?[1]
16. Do you feel that you are a worthless person?[1]
17. Has the thought of ending your life been on your mind?[1,2]
18. Do you feel tired all the time?[1]
19. Do you have uncomfortable feelings in your stomach?
20. Are you easily tired?[1]

[1]Item corresponds with factors to be assessed in the Adult Primary Care guidelines for standard-of-care mental health assessment and will be used to determine somatic symptoms that require additional care and possible referral by a social worker.

[2]Participants who endorse this item will be asked three additional questions to determine suicide intent and self-harm: 1) Do you ever have thoughts of hurting or killing yourself?; 2) Are you currently thinking of killing yourself?; 3) Have you ever tried to kill yourself?. Endorsement of any of these items will result in linkage to care and the AGYW will not be eligible for participation in the study until acute self-harm issues are resolved.

Appendix 3: Overview of Friendship Bench lay counselor training sessions[1]

Session[2]	Overview of content to be covered
Session 1 (9 AM – 5PM)	• Background information on common mental disorders including symptom profiles and how to recognize them • Psychoeducation on mental health • Screening using the SRQ-20 • Practice with the SRQ-20 • Overview of counseling skills and problem-solving therapy • Referral procedures • Overview of supervision plans • Collecting and reporting client data for study purposes • Creating awareness of mental health and understanding community stigma and stigma reduction approaches • Practicing skills from the day
Session 2 (9 AM – 5PM)	• Overview and practice of first session with Youth Friendship Bench SA client • Continued discussion of problem-solving therapy, including how to work with a client to select and define a problem • Emotion regulation approaches for client management • Prioritizing one problem for Youth Friendship Bench SA sessions • Approaches to brainstorm solutions for the problem with clients • Practicing skills from the day
Session 3 (9 AM – 5PM)	• Creating a "safe space" for Youth Friendship Bench SA clients • Approaches to select appropriate and actionable solutions with clients • S.M.A.R.T. goals and developing an action plan • Recording information in the research records • Practice skills from the day • Practice receiving feedback from supervisors and study team members
Session 4 (9 AM – 5PM)	• Review of problem-solving therapy practice session • Mental health literacy for working with adolescent girls and young women • Psychoeducation: depression • Psychoeducation: grief • Psychoeducation: anxiety • Psychoeducation: panic disorders • Psychoeducation: post-traumatic stress disorder • Psychoeducation: alcohol and drug use • Psychoeducation: suicide and self-harm • Approaches for linking patients to care for issues of self-harm, suicidal ideation, or suicidal intent

	• Self-care strategies for counselors
Session 5 (9 AM – 5PM)	• Review of prior sessions • Healthy and unhealthy relationships • Working with clients who have experienced gender-based violence or fear violence from a partner • Discussing sexual behavior and PrEP use • Urine point-of-care assay training • Summary and questions

SRQ-20=Self Reporting Questionnaire – 20 item; PrEP=pre-exposure prophylaxis
[1]Training session outline and content will be informed by the materials used in the primary Friendship Bench intervention study in Zimbabwe and other Friendship Bench implementation studies in sub-Saharan Africa
[2]Each session will last one day and will be conducted consecutively during a 1-week period

Appendix 4: Schedule of Study Visits and Procedures

	Enrollment	Week 2	Week 4	Week 8	Week 12
Administrative and Behavioral Evaluations/Procedures					
Informed Consent	X				
Collect/update locator information	X		X		
Apply inclusion/exclusion criteria, including the SRQ-20	X				
Randomization	X				
Collect demographics, behavioral, and psychosocial data, including the SRQ-20	X		X		X
PrEP adherence assessment via self-report			X		X
Youth Friendship Bench SA counseling	X	X[1]	X	X[1]	X
Standard-of-care mental health service delivery	X		X		X
Assess any SAEs		X	X	X	X
Laboratory Evaluation/Procedures					
Urine sample collection for TFV testing using a point-of-care assay			X		X
PrEP counseling based on urine TFV drug levels			X		X

TFV=tenofovir; PrEP=pre-exposure prophylaxis; SAE=serious adverse event; SRQ-20=self-reporting questionnaire 20-item
[1]Youth Friendship Bench SA sessions could be conducted remotely via phone