Statistical Analysis Plan

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

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Table of Contents

Background and Rationale

The purpose of this study is to adapt and test the Friendship Bench for South African adolescent girls and young women (AGYW) attending PrEP services, using a hybrid effectiveness-implementation trial.

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. 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").

Study Objectives and Hypotheses

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

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 Youth Friendship Bench SA, Version 1.030August 202222receiving 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).

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.

Study Design

This is as 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,108standard-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 4and 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. This assessment is administered by a counselor or nurse or could be self-administered.

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. Group counseling sessions will last up to 120 minutes. 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. Throughout the study period (up to 2times 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.

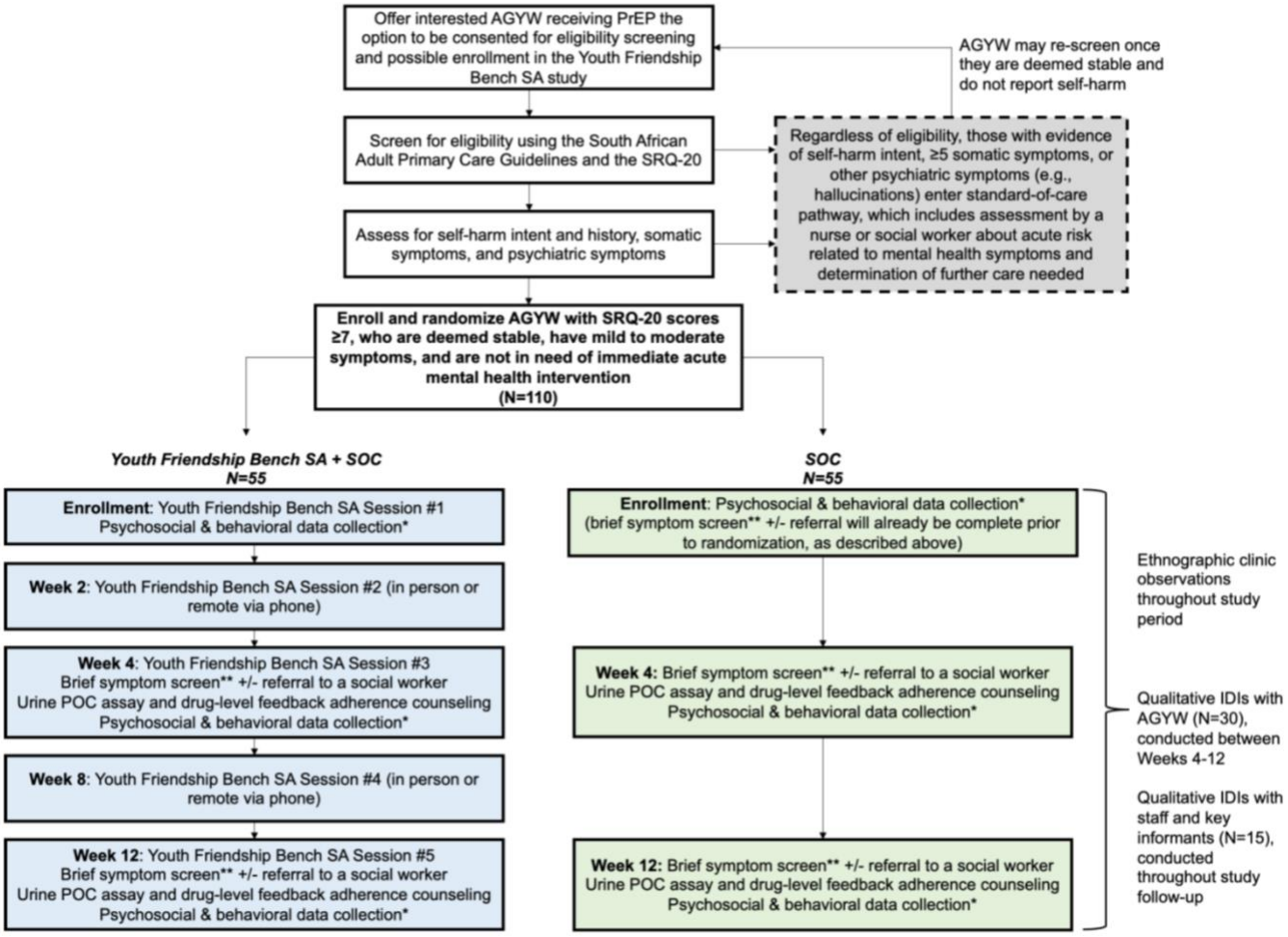
Schema

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 to30 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



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.

Power calculations

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.

Data Analysis

Co-Primary Analysis 1: 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

Analysis population: South African AGYW participants enrolled and randomized in a 1:1 ratio to either the Youth Friendship Bench SA plus SOC intervention or the SOC services alone arm.

- For an intent-to-treat analysis, we will include all randomized participants.
- For a per protocol analysis, we will include all randomized participants who received a full dose of the Youth Friendship Bench SA plus SOC intervention or SOC services alone, as specified below.

Outcome: proportion of AGYW with PrEP adherence at Week 12, defined as tenofovir (TFV) concentrations ≥1500 ng/mL in urine measured using a urine POC assay.

- We will utilize urine TFV levels to assess PrEP dosing in the prior 4-7 days.

Predictor(s) of interest: Randomized intervention arm, either the Youth Friendship Bench SA plus SOC or SOC services alone groups.

Covariate(s) of interest: For the per protocol analysis, the regression model will adjust for potential confounding from covariate characteristics assessed at baseline and follow-up, which may include:

- Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); symptoms of common mental disorders; self-esteem; and level of engagement with the intervention.

Measures of intervention use for per protocol analysis:

- Received the Youth Friendship Bench SA plus SOC intervention: 1 = received 4-5 sessions of the intervention (not including the group session). 0 = received less than 4 sessions of the intervention
- Received SOC services alone: 1 = received 4-5 sessions of SOC services alone. 0 = received less than 4 sessions of SOC services alone.

Statistical analyses:

1) We will compute descriptive statistics to describe the full study population of randomized individuals at baseline and to describe retention over time in both arms of the intervention. We will also summarize reasons for discontinuing PrEP.
2) We will compute descriptive statistics for missing data, including the pattern of missingness across visits for both arms of the intervention, and factors associated with missingness. All information from participants with missing data will be examined to determine if any pattern is evident that would account for the missingness.
3) Primary analysis: We will conduct an intent-to-treat analysis using a Poisson regression with robust standard errors to assess the effect of the Youth Friendship Bench SA plus SOC intervention compared to SOC services alone on TFV levels measured in urine (with PrEP adherence defined as TFV $\geq$1500 ng/mL) at 12 weeks after randomization. The main effect can be interpreted as the difference in PrEP adherence at 12 weeks between the SA plus SOC arm and SOC only arm of the intervention. The effect of the intervention will be estimated as a relative risk (RR) from the Poisson regression model, with treatment arm assigned at first randomization as the only predictor.

   Sensitivity analyses: In order to adjust for potential baseline imbalances between treatment arms, we will perform a multivariable analysis to adjust for hypothesized residual baseline imbalances to assess their impact on effect estimates. Poisson regression models will compare treatment effects with and without adjustment for important prognostic variables (including demographics, sexual behavior factors, and HIV risk factors) to account for treatment imbalances. We will select prognostic variables and assess baseline imbalances by conducting univariable chi-squared tests for each baseline factor by intervention arm. Based on this test, variables with a p-value greater than an alpha-level of 0.05 will be included in the sensitivity analysis.

   Per-protocol analyses: We will also conduct a per-protocol analysis using the same procedures described above but restricting to participants who received full doses of the Youth Friendship Bench SA plus SOC intervention compared to SOC services alone as described above in the *Measures of intervention use* section. Adjustment for covariates of interest will be performed as described above.

Missing data: Multiple imputation (MI) will be used to address missing data issues for covariates and outcomes. Complete case analysis may be used as the primary analysis if the proportions of missing data are below approximately 5%, or if only the dependent variable has missing values and variables not included in the regression analysis but correlated with a variable with missing values and/or related to its missingness are *not* identified. However, these scenarios are unlikely given our previous research in this patient population. Based on statistical convention that bias is likely in analyses with more than 10% missingness, we will use this threshold to determine whether to impute missing outcome data (Jakobsen et al., 2017). Based on these thresholds, our approach will use multiple imputations with chained equations (Nguyen et al., 2021; White et al., 2010). If the proportions of missing data are very large more than 40% on outcome variables, trial results may only be considered as hypothesis generating results. In the case of multiple imputation, we will use randomly imputed missing values generated from 100 imputations, under the assumption that the data are conditionally missing at random. Following multiple imputation, we will perform a confirmatory factor analysis such that any discrepancies in covariates introduced from imputing will be resolved for the final analysis.

Co-Primary Analysis 2: 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

Analysis population: South African AGYW participants enrolled and randomized in a 1:1 ratio to either the Youth Friendship Bench SA plus SOC intervention or the SOC services alone arm.

- For an intent-to-treat analysis, we will include all randomized participants.
- For a per protocol analysis, we will include all randomized participants who received a full dose of the Youth Friendship Bench SA plus SOC intervention or SOC services alone, as specified above in the *Measures of intervention use* section.

Outcome: proportion of AGYW with reduced symptoms of common mental health disorders, defined as SRQ-20 scores less than 7 at week 12.

Predictor(s) of interest: Randomized intervention arm, either the Youth Friendship Bench SA plus SOC or SOC services alone groups.

Covariate(s) of interest: For the per protocol analysis, the regression model will adjust for potential confounding from covariate characteristics assessed at baseline and follow-up, which may include:

- Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); symptoms of common mental disorders; self-esteem; and level of engagement with the intervention.

Statistical analyses:

1) We will compute descriptive statistics to describe the full study population of randomized individuals at baseline and to describe retention over time in both arms of the intervention. We will also summarize reasons for discontinuing PrEP.

2) We will compute descriptive statistics for missing data, including the pattern of missingness across visits for both arms of the intervention, and factors associated with missingness. All information from participants with missing data will be examined to determine if any pattern is evident that would account for the missingness.
3) Primary analysis: We will conduct an intent-to-treat analysis using a Poisson regression with robust standard errors to assess the effect of the Youth Friendship Bench SA plus SOC intervention compared to SOC services alone on SRQ-20 scores (with reduced symptoms of common mental health disorders defined as SRQ-20 scores < 7) at 12 weeks after randomization. The main effect can be interpreted as the difference in symptoms of common mental health disorders at 12 weeks between the SA plus SOC arm and SOC only arm of the intervention. The effect of the intervention will be estimated as a relative risk (RR) from the Poisson regression model, with treatment arm assigned at first randomization as the only predictor.

   Per-protocol analyses: We will also conduct a per-protocol analysis using the same procedures described above but restricting to participants who received full doses of the Youth Friendship Bench SA plus SOC intervention compared to SOC services alone as described above in the *Measures of intervention use* section. Adjustment for covariates of interest will be performed as described above.

   Missing data: Multiple imputation (MI) will be used to address missing data issues for covariates and outcomes. Complete case analysis may be used as the primary analysis if the proportions of missing data are below approximately 5%, or if only the dependent variable has missing values and variables not included in the regression analysis but correlated with a variable with missing values and/or related to its missingness are *not* identified. However, these scenarios are unlikely given our previous research in this patient population. Based on statistical convention that bias is likely in analyses with more than 10% missingness, we will use this threshold to determine whether to impute missing outcome data. If the proportions of missing data are very large more than 40% on outcome variables, trial results may only be considered as hypothesis generating results. In the case of multiple imputation, we will use randomly imputed missing values generated from 100 imputations, under the assumption that the data are conditionally missing at random. Following multiple imputation, we will perform a confirmatory factor analysis such that any discrepancies in covariates introduced from imputing will be resolved for the final analysis.

Secondary analysis: We will also assess the effect of the intervention separately on PTSD, depression, and anxiety symptoms. History of post-traumatic stress symptoms will specifically determined by the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) on the study Case Report Forms (CRFs), depressive symptoms by the Patient Health Questionnaire-9 (PHQ-9), and anxiety symptoms by the Generalized Anxiety Disorder questionnaire (GAD-7).

Secondary Analysis 1: 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.

Analysis population: South African AGYW participants enrolled and randomized in a 1:1 ratio to either the Youth Friendship Bench SA plus SOC intervention or the SOC services alone arm.

Outcome: proportion of AGYW with PrEP adherence at Week 4, defined as tenofovir (TFV) concentrations ≥1500 ng/mL in urine measured using a urine POC assay.

Predictor(s) of interest: Randomized intervention arm, either the Youth Friendship Bench SA plus SOC or SOC services alone groups.

Statistical analyses:

1) We will compute descriptive statistics to describe the full study population of randomized individuals at baseline and to describe retention over time in both arms of the intervention. We will also summarize reasons for discontinuing PrEP.
2) We will compute descriptive statistics for missing data, including the pattern of missingness across visits for both arms of the intervention, and factors associated with missingness. All information from participants with missing data will be examined to determine if any pattern is evident that would account for the missingness.
3) Primary analysis: We will conduct an intent-to-treat analysis using a Poisson regression with robust standard errors to assess the effect of the Youth Friendship Bench SA plus SOC intervention compared to SOC services alone on TFV levels measured in urine (with PrEP adherence defined as TFV $\geq$1500 ng/mL) at 4 weeks after randomization. The main effect can be interpreted as the difference in PrEP adherence at 4 weeks between the SA plus SOC arm and SOC only arm of the intervention. The effect of the intervention will be estimated as a relative risk (RR) from the Poisson regression model, with treatment arm assigned at first randomization as the only predictor.

Secondary Analysis 2: To assess the correlates of PrEP adherence, after adjusting for study arm, including sociodemographic factors and psychosocial and behavioral characteristics.

Analysis population: South African AGYW participants enrolled and randomized in a 1:1 ratio to either the Youth Friendship Bench SA plus SOC intervention or the SOC services alone arm.

Outcome: correlates of PrEP adherence at 12 weeks, adjusted for study arm

Predictor(s) of interest: Randomized intervention arm, either the Youth Friendship Bench SA plus SOC or SOC services alone groups; and covariates described below.

- 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.
- Other covariates will be selected via the processes described below.

Covariate selection process for multivariable models: We will use a combination of consulting previous research, univariate analyses, and forward stepwise selection to determine which sociodemographic factors and psychosocial and behavioral characteristics will be included in our multivariable models:

1) We will first determine which variables to include based on pre-existing research and theories. We will consult pre-existing research on variables associated with PrEP adherence to narrow down our list of variables to include in our secondary analysis. We will also create a rough theoretical “model” of the relationship between associated

variables and our outcome of PrEP adherence to ensure there are no temporality concerns and to help us understand which variables may be mediators/moderators of others.
2) Before building our model, we will conduct univariate chi-squared tests to assess the relationship between each covariate selected from the previously defined step and PrEP adherence. Based on this test, variables with a p-value greater than alpha-level of 0.05 will be included in our multivariable model.
3) After selecting our covariates, we will build our model using forward stepwise selection. Broadly, forward selection begins with a null model and adds one independent variable at a time, starting with the variable whose inclusion gives the most statistically significant improvement of the fit by looking at the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) model fit statistics. AIC penalizes the number of parameters to avoid overfitting. In a Poisson model, a lower AIC indicates a better model fit. BIC is similar to AIC but has greater penalties for more complex models. Similarly, a lower BIC indicates a better model fit. We will repeat this process until no additions significantly improve the model fit. The final model's AIC and BIC will be presented in the table.

Statistical analyses:

1) We will conduct an intent-to-treat analysis using a Poisson regression with robust standard errors to assess the association of selected covariates on TFV levels measured in urine (with PrEP adherence defined as TFV ³1500 ng/mL) at 12 weeks, adjusting for study arm. The effect of each covariate on PrEP adherence will be estimated as a relative risk (RR) from the Poisson regression model.
2) We will also conduct a per-protocol analysis using the same procedures described above, but only amongst participants who received full doses of the Youth Friendship Bench SA plus SOC intervention or SOC only.

Secondary Analysis 3: To assess the correlates of symptoms of common mental disorders, after adjusting for study arm, including sociodemographic factors and psychosocial and behavioral characteristics.

Analysis population: South African AGYW participants enrolled and randomized in a 1:1 ratio to either the Youth Friendship Bench SA plus SOC intervention or the SOC services alone arm.

Outcome: correlates of common mental disorder symptoms at 12 weeks, adjusted for study arm [categorical SRQ variable; categories: >7, <7]

Predictor(s) of interest: Randomized intervention arm, either the Youth Friendship Bench SA plus SOC or SOC services alone groups; and covariates described below.

- Covariate characteristics assessed at baseline and follow-up may include Sociodemographic characteristics; sexual behaviors; gender-based violence (GBV); self-esteem; and level of engagement with the intervention

Covariate selection process for multivariable models: We will use the same process described above using separate theoretical guidelines and univariable analyses for variable selection.

Statistical analyses:

1) We will conduct an intent-to-treat analysis using a Poisson regression with robust standard errors to assess the association of selected covariates on reduced symptoms of common mental disorders at 12 weeks, adjusting for study arm. The effect of each

covariate on symptoms of common mental disorders will be estimated as a relative risk (RR) from the Poisson regression model.
2) We will also conduct a per-protocol analysis using the same procedures described above, but only amongst participants who received full doses of the Youth Friendship Bench SA plus SOC intervention or SOC only.

Secondary Analysis 4: To qualitatively explore the acceptability, feasibility, and appropriateness of the Youth Friendship Bench SA intervention and the POC TFV urine assay.

- 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).
- 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.

Secondary Analysis 5: 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).

Statistical analyses:

1) We will compute descriptive statistics to describe the occurrence of serious adverse events and adverse events of special interest. For the full study population, we will compute means, standard deviations, medians, and inter-quartile ranges for each of the adverse events that may occur. Chi-squared tests will be used to assess differences in adverse study events across meaningful groupings, such as between study arms.

Exploratory Objective 1: To explore mediators and moderators of the Youth Friendship Bench SA intervention effect on PrEP adherence.

- 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.

Exploratory Objective 2: To explore mediators and moderators of the Youth Friendship Bench SA intervention effect on symptoms of common mental disorders.

- 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.

Appendix – Table shells for primary and secondary analyses

Table 1: Co-Primary Analysis 1

Associations between Youth Friendship Bench SA intervention and PrEP adherence at Week 12, assessed via univariate and multivariable Poisson regression models with robust standard errors

	Urine TFV ≥1500 ng/mL					
Exposure group	**ITT analysis (n = XX)**			**Per-protocol analysis (n = XX)**		
	n (%)	RR (95% CI)	*p*-value	n (%)	aRR (95% CI)	*p*-value
Intervention arm						
Standard-of-care						

Table 2: Co-Primary Analysis 2

Associations between Youth Friendship Bench SA intervention and symptoms of common mental health disorders at Week 12, assessed via univariate and multivariable Poisson regression models with robust standard errors

	SRQ-20 score < 7					
Exposure group	**ITT analysis (n = XX)**			**Per-protocol analysis (n = XX)**		
	n (%)	RR (95% CI)	*p*-value	n (%)	aRR (95% CI)	*p*-value
Intervention arm						
Standard-of-care						

Table 3: Secondary Analysis 1

Associations between Youth Friendship Bench SA intervention and PrEP adherence at Week 4, assessed via univariate and multivariable Poisson regression models with robust standard errors

	Urine TFV ≥1500 ng/mL					
Exposure group	**ITT analysis (n = XX)**			**Per-protocol analysis (n = XX)**		
	n (%)	RR (95% CI)	*p*-value	n (%)	aRR (95% CI)	*p*-value
Intervention arm						
Standard-of-care						

Table 4: Secondary Analysis 2

Correlates of PrEP adherence at Week 12 assessed via univariate and multivariable logistic regression models

Characteristic	**Unadjusted model**		**Adjusted for study arm**	
	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Sexual behaviors				
Gender-based violence				
Symptoms of common mental disorders				
Self-esteem				
Level of engagement with intervention				

Table 5: Secondary Analysis 3

Correlates of symptoms of common mental health disorders at Week 12 assessed via univariate and multivariable logistic regression models

Characteristic	**Unadjusted model**		**Adjusted for study arm**	
	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Sexual behaviors				
Gender-based violence				
Symptoms of common mental disorders				
Self-esteem				
Level of engagement with intervention				

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