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Alignment of PrEP adherence with periods of HIV risk among adolescent girls and young women in South Africa and Zimbabwe: A secondary analysis from the HPTN 082 randomized controlled trial

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AUTHOR CONTRIBUTIONS

CC, SDM, DD, SH, LGB, NM, and MC designed the parent study. JV conducted all data analyses, verified the data, and wrote the manuscript. DD had access to and verified the underlying data, providing a secondary review for this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All reviewed and approved the final version of the manuscript.

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MAM: study design, laboratory oversite results interpretation, edited manuscript
LGB: study design, results interpretation, edited manuscript
SDM: funding, study design, results interpretation, edited manuscript
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DATA SHARING STATEMENT

Deidentified data, and additional relevant documentation including the study protocol and analysis plan, will be made available upon request after the time of publication. Data will be shared via email after receiving proposal of any data analysis concepts and investigator support.

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STRUCTURED SUMMARY

Background: African adolescent girls and young women (AGYW) have adherence challenges with daily oral HIV pre-exposure prophylaxis (PrEP). However, the most important aspect of PrEP use is high adherence during periods of risk ("prevention-effective adherence"). An understanding of temporal patterns of HIV risk and PrEP use is needed among African AGYW.

Methods: HPTN 082 was an open-label PrEP study among AGYW (ages 16-24) in South Africa and Zimbabwe from 2016-2018. At Weeks 13, 26, and 52, we measured cumulative PrEP adherence with tenofovir (TFV)-diphosphate (DP) concentrations in dried blood spots and PrEP use in the prior week using TFV in plasma. Behavioral and STI data were collected quarterly. We categorized visits into a binary "any HIV risk" variable based on condomless sex, ≥1 partner, partner's HIV status and antiretroviral use, transactional sex, drug or alcohol use around sexual activity, and laboratory-diagnosed STIs. In this protocol-defined secondary analysis, we used generalized estimating equations to evaluate associations between HIV risk (reflecting behavior during three prior months) and cumulative and recent PrEP adherence (dichotomized as TFV-DP </≥700 fmol/punch, TFV </≥40 ng/mL) and any PrEP use (quantifiable drug concentrations) in intervals between Weeks 13, 26, and 52.

Findings: Among 427 AGYW, 364 (85%), 226 (60%), 243 (65%), and 224 (61%) reported ≥1 risk factor at enrollment and weeks 13, 26, and 52, respectively. Any HIV risk at the visit was associated with greater likelihood of TFV-DP ≥700 fmol/punch (adjusted relative risk [RR]:1.57; 95% confidence interval [CI]: 1.09-2.25) and plasma TFV ≥40 ng/mL (aRR:1.36; 95% CI: 1.11-1.65). Any risk was also associated with quantifiable TFV-DP (aRR:1.15; 95% CI: 1.03-1.29) and plasma TFV (aRR:1.27; 95% CI: 1.09-1.49). We observed significant dose-response relationships between number of risk factors and drug concentrations.

Interpretation: The association between HIV risk and PrEP adherence indicates that African AGYW were able to use PrEP during periods of risk, an indicator of prevention-effective PrEP adherence. Our findings support a shift in the PrEP paradigm to acknowledge "prevention-effective adherence" practices, which may improve PrEP delivery and adherence support for AGYW in HIV endemic settings.

Funding: US NIH

Keywords

HIV; Pre-exposure prophylaxis; Prevention-effective adherence; Africa; Adolescent girls and young women

INTRODUCTION

Adolescent girls and young women (AGYW) in sub-Saharan Africa have high HIV incidence rates of 4-7 per 100 person-years in HIV prevention trials.[1,2] Daily oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy being scaled up for AGYW ages 18-25 in HIV endemic settings.[3] Recent oral PrEP demonstration projects with adolescents conducted in South Africa, Kenya, Uganda, Thailand, United States, and Brazil have found high initial PrEP uptake but declines in PrEP adherence with time.[4–7] Barriers to daily oral PrEP adherence include psychosocial factors, intimate partner violence (IPV), lack of social support, stigma, and underestimation of HIV risk.[8–11] PrEP studies report that partnership dynamics and accurate perception of HIV risk may facilitate consistent PrEP use among women in South Africa, Zimbabwe, Kenya, and Tanzania.[12–14] Key unanswered questions remain about how AGYW align PrEP with HIV risk and optimal approaches to inform HIV risk perceptions and promote PrEP use.

The HIV Prevention Trials Network (HPTN) 082 study explored daily oral PrEP adherence support approaches for sexually-active AGYW in South Africa and Zimbabwe, and found PrEP adherence declined over one year of follow-up.[15] HIV incidence in the HPTN 082 cohort was 1%, which was lower than the modeled counterfactual HIV incidence of 3.7% and contemporary HIV incidence estimates among AGYW ages 15-24 in South Africa (between 4.9-7.8%) and Zimbabwe (1.6-1.9%).[15,16] Current analyses of oral PrEP adherence are limited in part due to simplistic approaches for classifying AGYW as adherent or non-adherent and our lack of understanding about how AGYW time their PrEP use with HIV risk.[17] While PrEP effectiveness depends on continued adherence, PrEP use is not lifelong and should align with periods of HIV risk (a concept called “prevention-effective adherence”).[18] Oral PrEP programs for African AGYW have faced challenges interpreting the impact of PrEP on HIV incidence, with limited information on adherence during periods of risk.[17–19] Qualitative data suggests that PrEP users practice intermittent use aligned to periods of risk (e.g., discontinuations around partner break-ups),[13,20–23] but there is little quantitative data assessing whether and how often AGYW use oral PrEP intermittently and the effectiveness of this approach for AGYW. We used data from the HPTN 082 study to: 1) describe HIV risk behavior and daily oral PrEP adherence and 2) understand how well AGYW adhered to PrEP during risk periods.

METHODS

Study design

HPTN 082 was a demonstration project among African AGYW initiating daily oral PrEP from October 2016 – October 2018.[16] Eligible AGYW were: 16-25 years of age; HIV-negative; residing in Johannesburg or Cape Town, South Africa or Harare, Zimbabwe; and sexually active as defined by vaginal or anal intercourse in the month prior to screening.

Eligible and consenting participants were offered PrEP at enrollment. Full details on study procedures and PrEP adherence interventions are provided elsewhere.[16] Briefly, AGYW who accepted PrEP were randomized (1:1) to the control arm (standard PrEP adherence support with counseling sessions) or the intervention arm (standard PrEP adherence

support package plus counseling based on PrEP drug levels, called “drug-level feedback counseling”). Participants were followed for 52 weeks, with follow-up visits at Weeks 4, 8, 13, 26, 39, and 52 for PrEP adherence support, HIV testing, counseling, and PrEP refills.

Data collection

Sociodemographic and psychosocial variables—Sociodemographic data were collected at enrollment. At baseline and follow-up visits, participants completed computer-assisted self-interviewing (CASI) surveys assessing sexual behavior, HIV and PrEP stigma, social support, depressive symptoms, IPV, and post-traumatic stress. Stigma was measured with 10 items from prior HIV and PrEP studies. Items were summed, with a higher continuous score indicating greater stigma (possible range: 0-40). Social support was measured with two items assessing support from adults and close friends, adapted from prior work with African AGYW. Likert responses were summed, with higher scored indicating higher support (possible range: 0-4). Depressive symptoms were measured using the 10-item Center for Epidemiologic Studies (CES-D) scale. Sum scores were calculated (possible range: 0-30) and a score ≥10 was indicative of elevated depressive symptoms. IPV was assessed with four items \ from the World Health Organization’s IPV definitions. Participants were considered to have experienced IPV if they answered “yes” to at least one item. Post-traumatic stress was assessed with the 4-item posttraumatic stress disorder (PTSD) Checklist for the DSM-5 (PCL-5). An answer of “yes” to any item was indicative of post-traumatic stress symptoms.

HIV risk variables—Sexual behavior data included questions on number of sex acts, frequency of condom use, number of sexual partners, and any transactional sex since the prior visit. Participants were also asked whether they had a primary sexual partner and those who endorsed this item were subsequently asked about their primary partner’s HIV status (living with HIV, HIV-uninfected, or unknown status) and antiretroviral therapy (ART) use. Two questions assessed whether recreational drugs or alcohol were used before and/or during sexual activity.

Participants were tested for sexually transmitted infections (STIs) at enrollment and Weeks 26 and 52. *N. gonorrhoeae* (GC) and *C. trachomatis* (CT) were assessed by nucleic acid amplification (Cepheid GeneXpert, Sunnyvale CA). *T. vaginalis* (TV) was assessed by rapid test (OSOM® Trichomonas Test, Seikusui Diagnostics, Burlington MA). Syphilis was assessed by rapid plasma regain (RPR) followed by a treponemal-specific confirmatory assay, TPHA/TPPA.

Outcome variables—The primary outcome for this analysis was high PrEP adherence among AGYW who ever accepted PrEP during the study. PrEP adherence was measured in two ways, using: 1) intraerythrocytic tenofovir-diphosphate concentrations (TFV-DP) from dried blood spots (DBS) collected at Weeks 13, 26, and 52 to provide a measure of average PrEP use in the prior 4-6 weeks; and 2) tenofovir concentrations (TFV) from plasma samples collected at Weeks 4, 8, 13, 26, and 52 to measure PrEP use in the prior 7-10 days. DBS testing was performed at the University of Colorado Pharmacology laboratory and plasma testing was performed at the Clinical Pharmacology Analytical Laboratory at

Johns Hopkins. Our outcome of high PrEP adherence was defined as intracellular TFV-DP concentrations ≥700 fmol/punch, which represents consistent dosing (an average of ≥4 PrEP doses per week) in the prior 1-2 months, and was associated with 100% PrEP effectiveness in men who have sex with men (MSM).[24] For plasma analyses, high PrEP adherence was defined as TFV concentrations ≥40 ng/mL, which is highly predictive of PrEP efficacy among African women and men in the Partners PrEP Study.[25]

Secondarily, we also considered quantifiable versus unquantifiable PrEP drug concentrations; quantifiable TFV-DP levels indicate any PrEP use in about the prior 1-2 months.[24] Quantifiable TFV concentrations in plasma represent a more narrow window of exposure, indicating any PrEP use in the prior week.[25]

Statistical analyses

We categorized all participant-visits into a binary variable indicating “any HIV risk” in the three-month period prior to the visit, as defined by South African and Zimbabwean PrEP eligibility guidelines.[26] According to these guidelines, any AGYW who reports condomless sex, a sexual partner living with HIV but not known to be taking ART, a sexual partner with unknown HIV status, ≥1 sexual partner, incident STIs, transactional sex, and/or recreational drug or alcohol use around sexual activity is considered to be eligible for HIV risk reduction counseling and PrEP.[26] AGYW in HPTN 082 who reported at least one of these behaviors were considered to be at risk of HIV during that period. Although all participants reported recent sexual activity as an eligibility criteria, those who reported always using a condom and had no other HIV risk factors were considered to not be at risk of HIV during enrollment. We also calculated a total score for participant-visits based on the number of risk factors reported (range: 0-7).

We used generalized estimating equations in a longitudinal analysis of repeated measures of any HIV risk to estimate the relative rates of high PrEP adherence measured via DBS (TFV-DP ≥700 fmol/punch) and plasma (TFV ≥40 ng/mL) at the corresponding visit. For example, “any HIV risk” at the Week 13 visit included data from questions about sexual behavior in the prior three months, which corresponds with the DBS sample collected at Week 13 reflecting PrEP dosing in the 1-2 months prior to the visit. Models were fit with a log link, Poisson distribution, and robust standard errors to estimate relative risk. All models adjusted for site and randomized arm (either the control arm with standard PrEP adherence support or the intervention arm with drug-level feedback counseling) to understand the magnitude of the association between HIV risk and PrEP use after accounting for study-specific factors.

We conducted several exploratory analyses. First, we explored the association between any HIV risk and quantifiable TFV-DP and TFV concentrations, to understand whether HIV risk factors influenced any PrEP use. Second, we considered number of HIV risk factors as our exposure and continuous TFV-DP and TFV concentrations as outcome variables in linear regression models to investigate dose-response relationships between the number of factors and PrEP use. While the possible range of HIV risk factors was 0-7, for this analysis we created a four-category HIV risk variable (0, 1, 2, or ≥3 risk factors) to ensure adequate sample size in each exposure level. Third, given potential associations between age, HIV risk, and PrEP use, we explored changes in model estimates after including age

as a covariate. Finally, we stratified our analyses by HPTN 082 arm to explore whether the association between HIV risk and PrEP use was modified by the intervention.

We also conducted a series of sensitivity analyses. Our primary analyses included only visits where data were available and participants were on PrEP, but we explored whether being lost to follow-up or discontinuing PrEP was associated with HIV risk or demographic factors at enrollment. Because STI testing was done at enrollment, Week 26, and Week 52, we assessed whether imputing STI data at Week 13 (by carrying forward and backward STI results) changed our findings. We also considered whether our findings were robust to different definitions of any HIV risk by running models with: 1) drug and alcohol use around sexual activity excluded; 2) condomless sex defined as report of condom use "never" versus "rarely", "sometimes", "often", or "always"; 3) condomless sex defined as report of condom use "never" or "rarely" versus "sometimes", "often", or "always"; and 4) inclusion of condom use, ≥1 sexual partner, partner with an unknown HIV status, and incident STIs in our HIV risk score.

All analyses were conducted using SAS 9.4 (Cary, North Carolina, USA).

Ethical statement

This study protocol was approved by ethics committees at each site. Participants provided written informed consent (or assent with consent from a parent or legal guardian if <18 years old) in their preferred language prior to participation. The protocol was registered at ClinicalTrials.gov (identifier NCT02732730).

Role of the funding source

The funder reviewed and approved the protocol and revisions. The funder had no role in study design, data collection, analysis, or interpretation, or writing of the report. The corresponding author had full access to study data and had final responsibility for the decision to submit for publication.

RESULTS

A total of 427 AGYW initiated PrEP in the HPTN 082 study (Table 1). The median age was 21 years (interquartile range [IQR] 19-22) and 98% had completed secondary school or university. Retention was 85% at the Week 52 visit and being lost to follow-up was not associated with HIV risk factors or demographics at enrollment. At enrollment, 364 (85%) participants reported at least one HIV risk factor. There were no statistically significant differences in arm, site, age, education, and psychosocial and behavioral factors between those with and without any HIV risk factors at enrollment (Table 1).

The proportion of participants reporting at least one HIV risk factor declined significantly over follow-up, with the greatest drop occurring between the enrollment and Week 13 (Z statistic from Cochran-Armitage trend test: 5.3; p-value for trend <0.0001; Table 2). The largest decline in HIV risk behavior was observed for condomless sex (p-value <0.0001). Condomless sex decreased similarly among AGYW with detectable PrEP drug levels through follow-up (from 59% at enrollment to 19% at Week 52) and without detectable

levels (from 65% to 15%). We did not observe statistically significant changes in report of drug or alcohol use around sexual activity between enrollment and Week 52 (Table 2).

PrEP use also declined during follow-up. Approximately 25%, 21%, and 9% of participants had high PrEP adherence based on TFV-DP concentrations ≥700 fmol/punch from DBS samples at Week 13, 26, and 52, respectively (Z statistic from Cochran-Armitage trend test: 5.7; p-value for trend <0.0001; Table 3). In addition, 48%, 38%, and 18% had high adherence based on TFV concentrations ≥40 ng/mL in plasma samples at Weeks 13, 26, and 52, respectively (Z statistic from Cochran-Armitage trend test: 9.7; p-value for trend <0.0001). Similar decreasing patterns were observed for quantifiable TFV-DP and TFV concentrations (Table 3). By Week 52, 55% of AGYW had not had a PrEP discontinuation and a total of 114 PrEP drug holds occurred among 110 AGYW (of which 40 were temporary). A total of 53 discontinuations were participant-initiated and there were no statistically significant differences in HIV risk factors between participants who resumed PrEP and those who permanently discontinued in this subset. We also did not detect significant differences in HIV risk factors among participants who had a provider-initiated PrEP product hold (65% had at least one HIV risk factor at the visit closest to discontinuation) compared to those who self-initiated a hold (55% had at least one HIV risk factor at the closest visit).

A total of 1081 participant visits were included in the longitudinal analysis of associations between any HIV risk factors and PrEP adherence measured via TFV-DP (Table 4). High PrEP adherence (TFV-DP ≥700 fmol/punch) was observed at 21% of study visits with any HIV risk factors and 14% of visits with no HIV risk factors (adjusted relative risk [aRR]: 1.57; 95% Confidence Interval [95% CI]: 1.09-2.25; p-value: 0.014). Participant-visits with any HIV risk were 1.15 times more likely to have quantifiable TFV-DP concentrations through follow-up than those with no HIV risk factors reported (aRR: 1.15; 95% CI: 1.03-1.29; p-value: 0.013). Similar results were found when including age in models of high PrEP adherence (aRR: 1.59; 95% CI: 1.11-2.28; p-value: 0.017) and quantifiable TFV-DP concentrations (aRR: 1.16; 95% CI: 1.04-1.30; p-value:0.011). The association between HIV risk and PrEP outcomes was modified by study arm (p-value for interaction terms <0.0001). Specifically, we found that HIV risk was not statistically significantly associated with high adherence or quantifiable TFV-DP among participants in the control arm. Among those in the intervention arm with drug level feedback counseling, HIV risk was significantly associated with high adherence (aRR: 1.83; 95% CI: 1.12-3.00; p-value: 0.022) and detectable TFV-DP (aRR: 1.20; 95% CI: 1.02-1.41; p-value: 0.028). Compared to visits when no risk factors were reported, those with 1 risk factor had TFV-DP 54.0 fmol/punch higher, those with 2 risk factors had TFV-DP 94.5 fmol/punch higher, and those with ≥3 risk factors had TFV-DP 223 fmol/punch higher (p-value <0.0001). These findings illustrate a dose-response relationship between number of risk factors and TFV-DP levels (Table 5).

A total of 1114 participant visits were included in the longitudinal analysis of associations between any HIV risk factors and PrEP adherence measured by plasma drug concentrations (Table 4). High recent PrEP adherence (TFV ≥40 ng/mL) was observed at 38% of study visits with any HIV risk factors and 29% of visits with no HIV risk factors (aRR: 1.36;

95% CI: 1.11-1.65; p-value: 0.0025). Similar results were observed for associations between any HIV risk and quantifiable TFV concentratons (aRR: 1.27; 95% CI: 1.09-1.49; p-value: 0.0022). Again, findings were robust to including age in models of high PrEP adherence (aRR: 1.38; 95% CI: 1.13-1.68; p-value: 0.014) and quantifiable TFV (aRR: 1.30; 95% CI: 1.11-1.51; p-value: 0.011). As was seen with analyses of TFV-DP concentrations, the association between HIV risk and PrEP outcomes was modified by arm (p-value for interaction terms <0.0001), with no associations between HIV risk and plasma outcomes among AGYW in the control arm and associations with high PrEP adherence (aRR: 1.53; 95% CI: 1.15-2.04; p-value: 0.014) and detectable TFV concentrations (aRR: 1.39; 95% CI: 1.10-1.74; p-value: 0.012) for those in the intervention arm. Compared to visits when no risk factors were reported, those with 1 risk factor had TFV levels which were 12.6 ng/mL higher, those with 2 risk factors had TFV concentrations 9.6 ng/mL higher, and those with ≥3 risk factors had TFV concentrations 28.6 ng/mL higher (p-value <0.0001; Table 5).

DISCUSSION

Among AGYW using PrEP in an open label study in South Africa and Zimbabwe, we observed modest statistically significant associations between HIV risk and PrEP adherence. More than three-quarters of participants reported at least one HIV risk factor at enrollment and self-reported HIV risk and tenofovir drug concentrations declined over follow-up. These declines could have been the result of reporting biases or participant fatigue with the study and PrEP. Alternatively, they may suggest that HPTN 082's package of HIV prevention and counseling services could have encouraged AGYW to modify their HIV risk where possible and use PrEP during periods with higher risk of HIV. This interpretation is supported by our findings showing that the relationship between HIV risk and PrEP adherence was modified by study arm: HIV risk was associated with PrEP adherence only for participants receiving the HPTN 082 intervention. Drug or alcohol use around sex did not change over follow-up, but were not explicitly addressed in our PrEP counseling and the HPTN 082 intervention. The observed 1% HIV incidence in this HPTN 082 cohort was almost four-fold lower than modeled counterfactual estimates and, combined with our findings, supports that some AGYW were able to assess their HIV risk accurately enough to use PrEP effectively during periods of risk.[16,27]

Our findings are consistent with the alignment between HIV risk behaviors and PrEP use observed among adult women in HIV serodiscordant couples.[18,20] However, our findings should be interpreted with caution. While a proportion of young women in our cohort did assess their risk and align their PrEP use with their to sexual behavior, relative risk estimates ranged from 1.15-1.57 and PrEP adherence was only observed in 20% of visits where risk was reported, indicating that PrEP use may still be imperfect among AGYW if they are not able to gauge their HIV risk or if other factors influence PrEP use (e.g., depression, stigma, IPV).[13] Approximately half of participants experienced depressive symptoms, IPV, and post-traumatic stress, which could negatively effect AGYW's ability to take oral PrEP regularly.[10] While these factors did not confound our associations (they were not associated with HIV risk), AGYW experiencing depression, IPV, and/or post-traumatic stress may be less likely to adhere to PrEP regardless of their HIV risk.

A first step in successful prevention-effective PrEP use is accurate risk assessment.[28] Recent analyses among AGYW in South Africa, Zimbabwe, and Malawi have found that young women consider themselves at risk of HIV largely based on condom use and number of partners.[12,13,21] These factors were included in our analyses of any HIV risk and were associated with PrEP use in this cohort. Conversations around risk assessment and counseling in HPTN 082 did not specifically discuss the concept of prevention-effective PrEP use; risk for HIV acquisition was discussed following PrEP eligibility guidelines for South Africa and Zimbabwe. Our counseling focused primarily on guidance around consistent PrEP dosing to maximize HIV protection, although study counselors were experienced in providing messages around stopping and re-starting PrEP during periods of HIV vulnerability. AGYW may have used this to develop a prevention-effective dosing strategy that fit their circumstances.

Our findings are encouraging as HIV prevention programs are beginning to move from focusing on consistently high PrEP adherence to a prevention-effective PrEP adherence paradigm defining success as PrEP use during periods of risk. This will require a particularly nuanced discussion during PrEP counseling, given that we do not have enough evidence currently to support event-driven PrEP dosing regimens among women. Existing measures of HIV risk perception may not align with ways that AGYW consider their own HIV risk.[29] PrEP counseling messages could be more specifically focused on: 1) helping AGYW accurately assess their HIV risk at PrEP initiation and refills to make decisions about ongoing PrEP need; 2) contextualizing HIV risk with targeted discussions about higher susceptibility from factors like STI acquisition, partner(s) of unknown HIV or ART use status, and drug or alcohol use around the time of sexual activity; and 3) provide guidance on stopping and re-starting PrEP.[30] However, as described previously, high PrEP adherence was only detected in one-fifth of visits where HIV risk was reported, indicating individual-level gaps in young women's understanding of their HIV risk or their ability to take PrEP well during periods of risk.[8,9,11] PrEP providers may be able to foster women's risk assessment by asking supportive, open-ended questions about recent behaviors and perceptions about their relationships. They can also support prevention-effective PrEP use by acknowledging and identifying strategies to address social and structural barriers faced by young women.[13] Future research is needed to develop adherence counseling and provider training interventions that address risk assessment and prevention-effective adherence and to determine whether such approaches do improve PrEP adherence as we hypothesize.

New metrics of programmatic success for oral PrEP use among AGYW are also needed. Real-time adherence assays and diaries or narrative sexual histories may help quantify PrEP use around periods of risk. Ideally, programmatic metrics should define PrEP uptake, persistence, and adherence by assessing the proportion of AGYW initiating and sustaining PrEP use during periods of sexual activity.[17,28] Future efforts should explore how to operationalize prevention-effective PrEP adherence among AGYW in different contexts and qualitative work is also needed to assess AGYW's understanding of the prevention-effective adherence concept.

Strengths of this study include a cohort with high retention and biomarker data on PrEP adherence collected at three points during follow-up. Our primary analysis utilized

previously established TFV-DP and plasma TFV cut-offs for high PrEP adherence, which enhanced interpretability of our findings. Although the drop-off in high PrEP adherence during follow-up could have reduced statistical power, we detected significant associations between HIV risk and PrEP adherence and our results remained consistent for different thresholds of drug measurements. We regularly assessed HIV risk factors and used computer-assisted self-interviewing rather than interviewer-administered questionnaires to reduce social desirability bias. STIs were measured by etiologic testing for curable STIs, which provides a sensitive and specific marker of recent sexual behavior and potential HIV exposure.

Limitations include that our conclusions may be biased by issues of reverse temporality if PrEP adherence at an earlier visit influenced subsequent HIV risk behaviors. We measured sexual behavior during visits but quarterly surveys may not have captured dynamic changes in sexual activity. We classified HIV risk using PrEP eligibility guidelines for the study locations to specifically align our work with PrEP readiness assessments and counseling messages provided by local clinics, but the eight items included in our assessment were not validated as a risk score and may not accurately capture relevant aspects of HIV risk for AGYW. Other analyses have considered different risk factors (e.g., the VOICE risk score), limiting comparability of our analysis. However, four sensitivity analyses modifying our definition of HIV risk did not significantly alter our findings. We focused on behavioral and biologic factors most closely linked with acquiring HIV during a sexual encounter (e.g., use of condoms, having an STI), but other more distal variables such as depression, IPV, alcohol and substance use, social support, and food insecurity are also linked with HIV risk and may play a role in AGYW's decision-making around oral PrEP use. Future research is needed to develop, validate, and test an adolescent HIV risk score tool that incorporates more distal psychosocial and behavioral factors. We restricted our analysis to visits with complete data on HIV risk factors and PrEP use and to visits where participants were not on a documented PrEP stop, which could have biased our findings. However, overall retention was high in the cohort and we did not detect statistically significant differences in HIV risk and demographic characteristics by retention or PrEP discontinuation. Finally, given that AGYW were participants in a PrEP demonstration project and over 90% had completed at least secondary school education, our results may not be generalizable to AGYW accessing PrEP through programmatic PrEP delivery.

In conclusion, we found that 85% of AGYW from South Africa and Zimbabwe initiating PrEP had at least one HIV risk factor and HIV risk was significantly associated with PrEP adherence using biomarkers assessing recent and longer-term dosing over a 12-month period. While our results about associations between HIV risk factors and PrEP adherence were statistically significant on a relative scale, the absolute numbers of AGYW who were able to align their PrEP use with periods of HIV risk were quite small and our findings may have limited clinical importance at a population level. Despite this, our study presents a novel examination of PrEP use among AGYW by showing differences in adherence by sexual behavior, in contrast to typical adherence measures that provide information on average pill-taking without information about HIV risk. The low HIV incidence observed in HPTN 082 and our findings about the statistically significant, albeit modest, temporal association of HIV risk and PrEP adherence suggest that some AGYW may be able to

adhere to PrEP sufficiently and align PrEP dosing with periods of HIV risk while they are receiving a comprehensive HIV prevention package. This is supported by our finding that the association between HIV risk and PrEP adherence was statistically significant for participants receiving a PrEP adherence support intervention with drug level feedback counseling. Our work highlights the need to expand PrEP delivery with counseling that acknowledges "prevention-effective adherence" practices among AGYW and supports them to accurately assess and anticipate periods of risk, while acknowledging that evidence for event-driven oral PrEP in women is limited. In addition, our findings support the need for long-acting HIV prevention products, such as the dapivirine ring and cabotegravir injections, to provide HIV protection options for AGYW who are unable to take daily oral PrEP during periods of HIV risk. Future trials of long-acting prevention options could also incorporate counseling around product use during periods of HIV risk (e.g., advice to return for an injection during a multi-month period when one is at higher risk of HIV). Finally, high proportions of our sample experienced depressive symptoms, IPV, and post-traumatic stress, and social and economic issues may cause or exacerbate both these psychosocial issues and difficulties with prevention-effective PrEP use. Integrated services that link vulnerable AGYW to care for mental health, IPV, and economic issues may help to address more intractable barriers to prevention-effective PrEP use in this population. By shifting the paradigm to a meaningful consideration of prevention-effective PrEP adherence, PrEP programs may improve PrEP delivery and adherence support for AGYW in HIV endemic settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DECLARATION OF INTERESTS

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PANEL: RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed from database inception up to September 2021, with the search terms “HIV” AND “pre-exposure” AND “prophylaxis” and “PrEP” (alone and combined with “adherence” OR “prevention-effective adherence” OR “HIV risk”). We also searched relevant conference abstracts from the past five years with similar keywords. HIV incidence remains high in young African women. Pre-exposure prophylaxis (PrEP) is an effective HIV prevention intervention when used consistently during periods of HIV risk. However, recently PrEP demonstration projects and trials have found low adherence and continuation of oral PrEP among young African women. Our current understanding of PrEP adherence is limited, due in part to simplistic approaches to classifying adolescent girls and young women (AGYW) as adherent or non-adherent, without considering changes in their HIV risk behavior over time. PrEP use should align with periods of HIV risk (called “prevention-effective adherence”), but PrEP programs with African AGYW have faced challenges with interpreting the impact of PrEP on HIV incidence in the absence of considerations about how PrEP use aligns with HIV risk behavior. While qualitative studies have explored PrEP use aligned to periods of HIV risk, there is little quantitative data on the effectiveness of this approach for AGYW.

Added value of this study

This study presents a novel examination of PrEP use among AGYW by showing meaningful differences in PrEP use by sexual behavior to provide a more nuanced understanding of PrEP dosing, in contrast to typical adherence measures that provide information on average pill-taking without information about HIV risk. Among AGYW using PrEP in an open label study in South Africa and Zimbabwe, we observed strong associations between HIV risk and high PrEP adherence. More than three-quarters of participants reported at least one HIV risk factor at enrollment and, notably, both self-reported HIV risk and tenofovir drug concentrations declined over the 52-week follow-up period. These declines suggest that the comprehensive package of HIV prevention and counseling services provided through HPTN 082 may have encouraged AGYW to modify their HIV risk where possible and use PrEP for HIV prevention during periods when they had higher risk of HIV exposure. The observed 1% HIV incidence in the cohort was almost four-fold lower than modeled counterfactual estimates and, combined with our findings on significantly higher PrEP adherence during periods when AGYW had at least one HIV risk factor, supports that some AGYW were able to assess their HIV risk accurately enough to use PrEP effectively during periods of risk.

Implications of all the available evidence

Our findings are consistent with the alignment between HIV risk behaviors and PrEP use observed among adult women in HIV serodiscordant couples. The low HIV incidence observed in HPTN 082 and our results about the temporal association of HIV risk and PrEP adherence suggest that some AGYW can adhere to PrEP sufficiently and align PrEP dosing with periods of HIV risk while they are receiving a comprehensive HIV prevention package. This supports expanding PrEP delivery with counseling that

acknowledges “prevention-effective adherence” practices among AGYW and helps them to more accurately assess or anticipate periods of risk.

Table 1.

HPTN 082 participant characteristics at baseline (N=427, unless otherwise indicated)[1]

Baseline characteristics	Overall	By HIV Risk Group[2]		
		Any HIV Risk (N=364; 85%)	No HIV Risk (N=63; 15%)	p-value[3]
Arm				
Standard package	212 (50%)	180 (50%)	32 (51%)	0.84
Standard package plus drug-level feedback counseling	215 (50%)	184 (51%)	31 (49%)	
Study site				
Johannesburg, South Africa	142 (33%)	124 (34%)	18 (29%)	0.094
Cape Town, South Africa	140 (33%)	124 (34%)	16 (25%)	
Harare, Zimbabwe	145 (34%)	116 (32%)	29 (46%)	
Age, years	21.0 (19.0-22.0)	21.0 (19.0-22.0)	22.0 (20.0-23.0)	0.13
Education				
Primary school	9 (2%)	8 (2%)	1 (2%)	0.86
Secondary school	371 (87%)	317 (87%)	54 (86%)	
College or university	47 (11%)	39 (11%)	8 (13%)	
Likely depression (N=418)[4]	259 (62%)	221 (61%)	38 (60%)	0.72
Social support (N=423)[5]	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-3.0)	0.21
Stigma (N=422)[6]	6.0 (1.0-7.0)	6.0 (1.0-7.0)	6.0 (3.0-8.0)	0.63
Any intimate partner violence (N=424)[7]	209 (49%)	183 (50%)	26 (43%)	0.26
Any posttraumatic stress disorder symptoms (N=418)[8]	194 (46%)	165 (46%)	29 (50%)	0.55

[1] Data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables

[2] Any HIV risk was defined as reporting at least one of the following at a given study visit: condomless vaginal or anal sex with condoms; reporting a primary partner living with HIV who was not known to be taking antiretrovirals; reporting a primary partner with unknown HIV status; more than one sexual partner; any STI diagnosis; reporting transactional sex; reporting drug and/or alcohol use before or during sex

[3] p-values are based on Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables

[4] A sum CESD-10 score ≥10 was indicative of "likely depression"

[5] Social support was measured as the sum score across two items assessing social support from adults and close friends (range: 0-4)

[6] Stigma was measured as the sum score across ten items assessing stigma related to HIV and PrEP use (range: 0-40)

[7] Participants were considered to have experienced any intimate partner violence if they endorsed at least one of four items asking about recent physical, emotional, or sexual violence from a sexual partner

[8] A response of "yes" to any of four items from the Posttraumatic Stress Disorder (PTSD) Checklist for the DSM-5 (PCL-5) was indicative of PTSD symptoms

Table 2.

Distribution of HIV risk characteristics in HPTN 082 cohort over follow-up[1]

	Enrollment (N=427)	Week 13 (N=380)	Week 26 (N=373)	Week 52 (N=369)	p-value[2]
Any HIV risk in the prior three months[3]	364 (85%)	226 (60%)	243 (65%)	224 (61%)	<0.0001
Any condomless vaginal or anal sex[4]	271 (63$)	129 (34%)	109 (29%)	106 (29%)	<0.0001
Report a primary partner living with HIV, who was not taking ARVs or has unknown ARV use	1 (0%)	4 (1%)	2 (1%)	2 (1%)	0.96
Report a primary partner with unknown HIV status	69 (16%)	49 (13%)	50 (13%)	44 (12%)	0.24
>1 sexual partner	130 (30%)	72 (19%)	64 (17%)	58 (16%)	<0.0001
Any STI diagnosis[5]	162 (38%)	---	82 (22%)	82 (22%)	<0.0001
Report of transactional sex	97 (23%)	58 (15%)	67 (18%)	54 (15%)	0.022
Report of drug use before or during sex	22 (5%)	13 (3%)	14 (4%)	16 (4%)	0.81
Report of alcohol use before or during sex	109 (26%)	80 (21%)	87 (23%)	80 (22%)	0.89
Levels of HIV risk					
0 HIV risk factors	63 (15%)	153 (40%)	130 (35%)	135 (37%)	
1 HIV risk factors	94 (22%)	115 (30%)	108 (29%)	108 (29%)	<0.0001
2 HIV risk factors	126 (30%)	61 (16%)	74 (20%)	70 (19%)	
≥3 HIV risk factors	144 (34%)	50 (13%)	61 (16%)	56 (15%)	

ARV=antiretroviral medication; STI=sexually transmitted infection; TFV-DP=tenofovir diphosphate; TFV=tenofovir

[1]Data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables

[2]p-value for trend based on regression model assessing whether frequencies significantly differed by visit

[3]Any HIV risk was defined as reporting at least one of the following at a given study visit: condomless vaginal or anal sex; reporting a primary partner living with HIV who was not known to be taking antiretrovirals; reporting a primary partner with unknown HIV status; more than one sexual partner; any STI diagnosis; reporting transactional sex; reporting drug and/or alcohol use before or during sex

[4]A participant was considered to engage in condomless sex if they endorsed the responses of “never”, “rarely”, “sometimes”, or “often” (versus “always”) when asked about vaginal and anal sex acts since in the prior three months.

[5] STI testing was not done at Week 13

Table 3.

Distribution of PrEP adherence outcomes in HPTN 082 cohort over follow-up[1]

	Week 13 (N=380)	Week 26 (N=373)	Week 52 (N=369)	p-value[2]
TFV-DP ≥ 700 fmol/punch[3]	91/370 (25%)	76/364 (21%)	30/347 (9%)	<0.0001
TFV ≥ 40 ng/mL[4]	183/379 (48%)	142/372 (38%)	63/361 (18%)	<0.0001
Quantifiable TFV-DP concentration[3]	309/370 (84%)	205/364 (56%)	109/347 (31%)	<0.0001
Quantifiable TFV concentration[4]	245/379 (65%)	173/372 (47%)	92/361 (26%)	<0.0001

ARV=antiretroviral medication; STI=sexually transmitted infection; TFV-DP=tenofovir diphosphate; TFV=tenofovir

[1]Data are presented as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables

[2]p-value for trend based on regression model assessing whether frequencies significantly differed by visit

[3]Denominantors are shown in each column to reflect the total number of DBS samples that were tested for TFV-DP concentration at each visit

[4]Denominantors are shown in each column to reflect the total number of plasma samples that were tested for TFV concentration at each visit

Table 4.

Associations between any HIV risk and high PrEP adherence in the HPTN 082 cohort, as indicated by TFV-DP and TFV

	DBS TFV-DP (N=371)			Plasma TFV (N=413)		
Primary outcome: High PrEP Adherence						
	Visits with TFV-DP 700fmol/punch (N=197/1081 visits)[1,2]	**aRR (95% CI)[4]**	**p-value**	**Visits with TFV ≥40 ng/mL (N=389/1114 visits)[1,3]**	**aRR (95% CI)[4]**	**p-value**
No HIV risk	55 (13.8)	REF	---	120 (29.1)	REF	---
Any HIV risk	142 (20.8)	1.57 (1.09-2.25)	0.014	269 (38.4)	1.36 (1.11-1.65)	0.0025
Secondary outcome: Any PrEP Use						
	Visits with quantifiable TFV-DP (N=623/1081 visits)[1,5]	**aRR (95% CI)[2]**	**p-value**	**Visits with quantifiable TFV (N=512/1114 visits)[1,6]**	**aRR (95% CI)[2]**	**p-value**
No HIV risk	213 (53.5)	REF	---	166 (40.2)	REF	---
Any HIV risk	410 (60.0)	1.15 (1.03-1.29)	0.013	346 (49.4)	1.27 (1.09-1.49)	0.0022

DBS=dried blood spot; TFV-DP=tenofovir diphosphate; TFV=tenofovir; PrEP=pre-exposure prophylaxis; aRR=adjusted relative risk; 95% CI=95% confidence interval

[1] Data are presented as frequency (percentage)

[2] 700 fmol/punch represents consistent dosing (≥4 PrEP doses per week) and was associated with 100% PrEP effectiveness among men who have sex with men.

[3] 40 ng/mL represents consistent stead-state dosing (≥4 PrEP doses per week) and was highly predictive of PrEP efficacy among African women and men in the Partners PrEP Study.

[4] Multivariable models adjusted for study site and randomized arm

[5] The limit of detection for TFV-DP was 15.6 fmol/punch

[6] The limit of detection for plasma TFV was 0.15 ng/mL

Table 5.

Dose-response relationship between HIV risk level and continuous TFV-DP and TFV concentrations in the HPTN 082 cohort

	DBS TFV-DP (N=371)				Plasma TFV (N=413)			
	Mean (SD) TFV-DP Concentration, fmol/punch	**β (95% CI)[2]**	**p-value**	**Global p-value**	**Mean (SD) TFV Concentration, ng/mL**	**β (95% CI)[2]**	**p-value**	**Global p-value**
0 HIV risk factors[1]	247.8 (369.5)	REF	---	<0.0001	32.4 (66.0)	REF	---	<0.0001
1 HIV risk factor	291.0 (415.9)	54.0 (−7.3-115.2)	0.081		46.0 (81.1)	12.6 (2.2-22.9)	0.017	
2 HIV risk factors	322.9 (441.4)	94.5 (16.7-172.4)	0.017		46.8 (83.7)	9.6 (−4.5-21.7)	0.199	
≥3 HIV risk factors	447.1 (530.3)	223 (125.0-321.8)	<0.0001		65.6 (99.3)	28.6 (12.6-44.7)	<0.0001	

DBS=dried blood spot; TFV-DP=tenofovir diphosphate; TFV=tenofovir; SD=standard deviation; 95% CI=95% confidence interval

[1]HIV risk factors included report of condomless sex, ≥1 sexual partner, partner HIV status and antiretroviral therapy use, transactional sex, drug and alcohol use around sex, and laboratory confirmed sexually transmitted infections in the prior three months.

[2]Multivariable models adjusted for study site and randomized arm