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Addressing the nexus of risk: Biobehavioral outcomes from a cluster randomized trial of the Women's Health CoOp *Plus* in Pretoria, South Africa

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ABSTRACT

Background: HIV prevalence has increased among South African women who use alcohol and other drugs (AOD). However, HIV prevention and treatment efforts have not focused on this population. This study presents the efficacy of the Women's Health CoOp Plus (WHC+) in a cluster-randomized trial to reduce AOD use, gender-based violence, and sexual risk and to increase linkage to HIV care among women who use AODs, compared with HIV counseling and testing alone.

Methods: Black African women (N = 641) were recruited from 14 geographic clusters in Pretoria, South Africa, and underwent either an evidence-based gender-focused HIV prevention intervention that included HIV counseling and testing (WHC+) or HIV counseling and testing alone. Participants were assessed at baseline, 6-months, and 12-months post enrollment.

Results: At 6-month follow-up, the WHC+ arm (vs. HCT) reported more condom use with a main partner and sexual negotiation, less physical and sexual abuse by a boyfriend, and less frequent heavy drinking (ps < 0.05). At 12-month follow-up, the WHC+ arm reported less emotional abuse ($p < 0.05$). Among a subsample of women, the WHC+ arm was significantly more likely to have a non-detectable viral load (measured by dried blood spots; $p = 0.01$).

Conclusion: The findings demonstrate the WHC+'s efficacy to reduce HIV risk among women who use AODs in South Africa. Substance abuse rehabilitation centers and health centers that serve women may be ideal settings to address issues of gender-based violence and sexual risk as women engage in substance use treatment, HIV testing, or HIV care.

1. Introduction

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the 90-90-90 targets (Joint United Nations Programme on HIV/AIDS, 2014a). The aim is that by 2020, 90% of people living with HIV will know their HIV status, 90% of those diagnosed with HIV will receive sustained antiretroviral therapy (ART), and 90% of those receiving ART will be virally suppressed. These targets addressed the progress along the HIV continuum of care. As we near 2020, significant progress has been made toward the 90-90-90 goals (Joint United Nations Programme on HIV/AIDS, 2017a). However, psychosocial factors such as alcohol and other drug (AOD) use, gender-based violence (GBV), and sexual risk create barriers to achieving these benchmarks, especially among women.

AOD use has been consistently linked to HIV risk for more than a decade (Kalichman et al., 2007; Parry and Pithey, 2006). Women who use substances are especially vulnerable to HIV risk (Pitpitan et al., 2013, 2012), as AOD use increases HIV risk through impaired

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judgment, increasing the likelihood of condomless sex (Fisher et al., 2007; Kalichman et al., 2007; Strathdee and Stockman, 2010; Wechsberg et al., 2012). Additionally, women who are dependent on AODs may rely on sex work to obtain drugs or money for drugs, and they may be less likely to negotiate condom use, which can increase their risk for HIV (Strathdee and Stockman, 2010). Alternatively, women may use AODs to cope with trading sex, which may lower their inhibitions to engage in condomless sex (Wechsberg et al., 2005, 2006). Consequently, it is troublesome that HIV prevention and treatment efforts such as seek, test, treat, and retain (STTR) and HIV treatment as prevention (TasP) have not focused on this population (Hull and Montaner, 2013; World Health Organization, 2012).

Further, AOD use is a barrier to health care access and ART adherence for women living with HIV (Azar et al., 2010; Luseno et al., 2010). Women who use AODs are less likely to initiate and adhere to HIV care and treatment (Medley et al., 2014; Mekuria et al., 2017; Ndirangu et al., 2014; Shoptaw et al., 2013). Some women may not take their ART medication on the weekends because they fear that mixing alcohol and ART medication may result in adverse side effects or reduce the effect of the medication (Kalichman et al., 2012, 2013; Pellowski et al., 2016). As a result of not being linked to care or not adhering to ART, some women who use AODs may have increased viral loads, suffer adverse health consequences, and transmit HIV (Cohen et al., 2011; Cohen and Gay, 2010). Unfortunately, AOD use is not addressed in standard HIV prevention and treatment efforts such as HIV testing and counseling (Republic of South Africa, 2015); many women are unaware of the effects of AOD use, especially alcohol (Hlomani, 2013); and there are multiple barriers to accessing substance abuse treatment (Myers et al., 2011). Consequently, to reduce HIV infection and prevent HIV transmission, substance use must be addressed among women in South Africa.

Moreover, women who use AODs are more likely to experience GBV (El-Bassel et al., 2011), which increases risk for HIV (Dunkle et al., 2004; El-Bassel et al., 2011; Jewkes et al., 2010) and decreases the ability to seek HIV care (Skovdal et al., 2011). GBV increases risk for HIV through coerced condomless sex, rape, and the inability of women to negotiate safer sex (Dunkle et al., 2004; Jewkes and Abrahams, 2002; Jewkes et al., 2010; Townsend et al., 2011; Wechsberg et al., 2013b). Among women living with HIV, GBV may impair their ability to seek HIV care (Lopez et al., 2010; Maman et al., 2002). Some South African men use violence to prevent their female partners from seeking HIV health services because they fear that their own HIV-positive status will be revealed (Skovdal et al., 2011). GBV poses a significant challenge to HIV prevention and care for South African women, especially those who use AODs.

In sum, the nexus of AOD use, GBV, and sexual risk contributes to HIV risk and decreased access to HIV care (Meyer et al., 2011). Consequently, interventions must address these risk factors to reduce HIV incidence (Meyer et al., 2011) and increase access to HIV healthcare (Luseno et al., 2010) among women who use AODs. Some interventions address AOD use, GBV, or sexual risk as HIV risk factors (Cain et al., 2012; Jewkes et al., 2006; Kalichman, 2010). However, few interventions address these factors to increase linkage to care or address the nexus of these factors (Wechsberg et al., 2010a).

The Women's Health CoOp (WHC) is an evidence-based, woman-focused, behavioral intervention that addresses AOD use, GBV, and sexual risk, with the primary goal of increasing skills and knowledge to reduce HIV risk among women who use AODs. The WHC is based on social cognitive theory (Bandura, 1994) and empowerment theory (Wechsberg, 1998), and it was originally developed for African American women who used crack cocaine in North Carolina (Wechsberg et al., 2004). The WHC has been adapted for multiple populations, named a best-evidence intervention by the Centers for Disease Control and Prevention, and included in the United States Agency for International Development's (USAID) compendium of prevention interventions that are recommended for use in Africa (Centers for Disease Control and Prevention, 2013; Lyles et al., 2007; USAID, 2009). Although the WHC has demonstrated efficacy in reducing behavioral HIV risk, it has not emphasized STTR; consequently, linkage to care and the promotion of ART initiation and adherence were added as an important biobehavioral advancement (Wechsberg et al., 2017c), given that TasP is key to accomplishing the UNAIDS goals (Joint United Nations Programme on HIV/AIDS, 2014b).

The current study evaluates the efficacy of the Women's Health CoOp *Plus* (WHC+), an evidence-based gender-focused HIV prevention intervention that includes HIV counseling and testing (HCT), to reduce AOD use, GBV and sexual risk, and to increase linkage to HIV care among women who use AODs, as compared with HCT alone. This cluster-randomized trial (CRT) was conducted in Pretoria, South Africa, where there is a high prevalence of HIV and AOD use among the study's target population (Wechsberg et al., 2011). A CRT design was used to prevent contamination across study arms. Our hypotheses, which focused on individual-level outcomes, were that women in the WHC+ arm would be less likely to report AOD use, GBV, and sexual risk behaviors at 6- and 12-month follow-up, as compared with women in the HCT arm. It is also expected that, among women who test positive for HIV, a greater proportion of women in the WHC+ arm will report attending a medical evaluation, as compared with women in the HCT arm.

2. Material and methods

2.1. Study design and procedure

Pretoria was divided into 14 mutually exclusive geographic clusters. Cluster creation was informed by the previous mapping of "hot spots" for AOD use and HIV risk among women across the city. Clusters were separated by barriers such as freeways, railroads, and rivers. Each cluster was matched with a similar cluster based on size, urbanicity, and previously known behaviors of AOD use, sex trading, and HIV risk. Within each pair, one cluster was randomized to either the WHC+ arm or the HCT arm. The randomization system was developed by the data manager and conducted using a computer-generated sequence. Consent at the cluster-level was not obtained. However, we consulted with a Community Collaborative Board and outreach workers familiar with Pretoria to determine the clusters and develop recruitment strategies.

The South African Medical Association Research Ethics Committee (SAMAREC), Tshwane Research Committee (TRC), and the RTI International Institutional Review Board for the Protection of Human Subjects approved the study procedures. Additionally, we established a Data and Safety Monitoring Board comprising experts and physicians in HIV and bioethics. The study results are reported in accordance with the CONSORT guidelines for CRTs (Campbell et al., 2012).

2.2. Participant recruitment and procedures

Recruitment was completed from May 2012 through September 2014 using a variety of community outreach methods (Wechsberg et al., 2006; Wechsberg et al., 2010b). Participants had to be Black African women aged 15 or older (if aged 15 to 17, with evidence of tacit emancipation[1]); use at least one substance (which could be alcohol) weekly for the past 3months; have had sex with a male partner without

[1] According to South African law, adolescents under 18, the age of majority, can provide consent unassisted if they can provide evidence of tacit emancipation. Tacit emancipation occurs when the capacity of a minor to act without parental consent is "enlarged" to encompass certain key areas that will enable him or her to be viewed by the law as a major. The prime consideration is the degree of financial independence that the minor has achieved. In this respect, ownership of a business or an occupation that brings in a salary is key. Residence outside the parental home is regarded as further proof of emancipation.(van Heerden et al., (1999). Boberg's Law of Persons and the Family).

a condom in the past 6months; speak English, Sesotho, Zulu/isiXhosa, or Setswana; provide informed consent; and provide verifiable locator information and plan to remain in Pretoria for the next 12months. Eligible women who wanted to participate in the study were scheduled for an intake appointment at the field site or in a private setting in the community. At the intake appointment, women were rescreened and asked to provide informed consent, complete a baseline interview using computer-assisted personal interviewing (CAPI), and participate in biological testing for drugs (i.e., panel drug urine screen), alcohol (i.e., breathalyzer), pregnancy (i.e., urine test), and HIV (i.e., rapid blood test). At a later stage of the study, dried blood spots were collected to measure the viral load concentration of participants who tested positive for HIV.

Women in the WHC+ arm were scheduled for two intervention sessions approximately one week apart. All participants were scheduled to return at 6 and 12 months to complete follow-up interviews and biological testing. Staff members who conducted the WHC+ intervention or baseline assessments did not conduct the follow-up interviews. Participants were provided with refreshments and vouchers valued at R70 (approximately US $7), R100 (approximately US $10), and R150 (approximately US $15) for their time during the baseline, 6-month, and 12-month appointments, respectively. Health kits were also provided at the 6- and 12-month appointments. Staff members also provided meals, coordinated childcare, and arranged transportation to the field site for all appointments. A total of 641 participants (between 16 and 58 women from each cluster) were enrolled (Fig. 1).

2.3. Interventions

2.3.1. Standard HIV counseling and testing

Participants in the HCT arm underwent the standard individual HCT protocol in accordance with South African treatment guidelines (Republic of South Africa, 2010). This protocol included pretesting, rapid HIV testing, post-counseling, and a brief syndromic tuberculosis screener. Participants who tested positive for HIV were first referred for further medical evaluation to determine eligibility for ART. To help alleviate the barrier to clinical staging, the study began conducting CD4 testing at the study site using a point of care PIMA™ analyzer. Participants received CD4 testing at 6- and 12-month follow-up. However, these data were not used for analysis. Women who were not eligible for ART at that time were referred to a wellness program conducted in local health facilities.

The study staff also provided passive referrals to substance abuse rehabilitation, GBV counseling, and skills development. If participants tested positive for pregnancy, they were provided active referrals for antenatal care.

On January 1, 2015, the South African HIV treatment guidelines changed and the CD4 count eligibility criterion for ART initiation changed from $\leq$350 cells/mm^2 to $\leq$500 cells/mm^2 (Department of Health, 2014). Consequently, some participants who tested positive for HIV who were ineligible for ART at enrollment later became eligible for ART. though this change was slow to take effect.

2.3.2. Women's Health CoOp Plus

Women in the WHC+ arm underwent HCT and participated in two individual intervention sessions approximately a week apart. Each session lasted about an hour. Sessions took place at the study site and were facilitated by an experienced, multilingual female interventionist from the community.

The sessions aimed to educate participants about the risks of AOD use and how AOD use and sexual risk are related to HIV for women and their gender power. Sessions also covered risk-reduction strategies—such as correct condom use, sexual negotiation, and violence prevention strategies—and included role-play and rehearsal. Participants created personalized action plans after their first session and completed this plan in their second session. The action plan included specific actions to reduce risk. Participants took home the plan at the end of the second session. A goal of the intervention was to provide case management via in-person visits or by mobile phone by study staff at least monthly to support the participant in her goals and risk-reduction behavior. Staff worked with substance abuse rehabilitation facilities to coordinate referrals to treatment for participants with AOD use problems.

2.4. Measures

Condom use was assessed as the number of vaginal sex episodes with a condom during the past month. Condom use at last sex was also assessed.

Alcohol use was measured by the number of days of heavy drinking (4 or more drinks) in the past 30 days. Given the high prevalence of heavy drinking in South Africa (Parry et al., 2005), participants who reported they had engaged in heavy drinking on 11 or more of the past 30 days were categorized as a frequent heavy drinker; participants who reported they did not, were categorized as not a frequent heavy drinker (Wechsberg et al., 2017b). We also assessed the number of days that participants engaged in alcohol use and the average number of alcoholic beverages that participants consumed when they were drinking in the past month.

Use of the most commonly used drugs—marijuana, cocaine, and opiates—was assessed using a urine drug screen. Test results were coded as positive or negative. Drug use was also measured using self-reported frequency of drug use in the past 30 days. Participants who reported using at least one drug every day during the past 30 days were categorized as a daily drug user; participants who did not were categorized as not a daily drug user.

GBV during the past 90 days was assessed using four individual items to measure emotional abuse, being attacked with a weapon, being beaten, or sexual abuse by a boyfriend. Each response was coded as 0 = No or 1 = Yes.

Among participants who had been diagnosed with HIV before their study appointment, self-reported linkage to care was assessed by the item "Have you been referred to a medical assessment?" Participants responded either 1 = Yes, went to medical assessment, 2 = Yes, but have not gone to medical assessment, or 3 = No. Responses were coded such that referral for a medical assessment (no or yes) and attendance at a medical assessment (no or yes) were separate variables.

To assess ART initiation, participants were asked, "Have you been prescribed any anti-HIV medications?" Participants responded either yes or no.

To assess ART adherence, whole blood spots (dried blood spot [DBS]) samples were taken from a subsample (n = 290) of participants living with HIV at the 6- and 12-month follow-up visits to test for viral load concentration. DBS samples were collected and prepared according to the recommended protocol from the World Health Organization (WHO) for the collection and handling of DBS (World Health Organization, 2005). Two assays were used to analyze the samples. The Abbott RealTime HIV-1 Assay using the 0.6 ml program was used to measure HIV-1 viral load in 103 samples, and the Panther® system Assay was used to measure HIV-1 viral load in an additional 187 samples (using one whole spot from each sample), accounting for the dilution factor of eluting the DBS, making the lower limit of quantification 1360 cp/ml for DBS on the Abbott assay and 600 cp/ml for DBS on the Hologic assay.

Samples that were below the lower limit of quantification of 1360 cp/ml were listed as "Non-detectable." Samples that were at or above the lower limit of quantification were considered "Detectable." A non-detectable viral load is associated with optimal ART adherence of 85% or higher (Kobin and Sheth, 2011). Consequently, we used viral load as a proxy for at least 85% ART adherence. Participants with a non-detectable viral load were considered adherent and participants

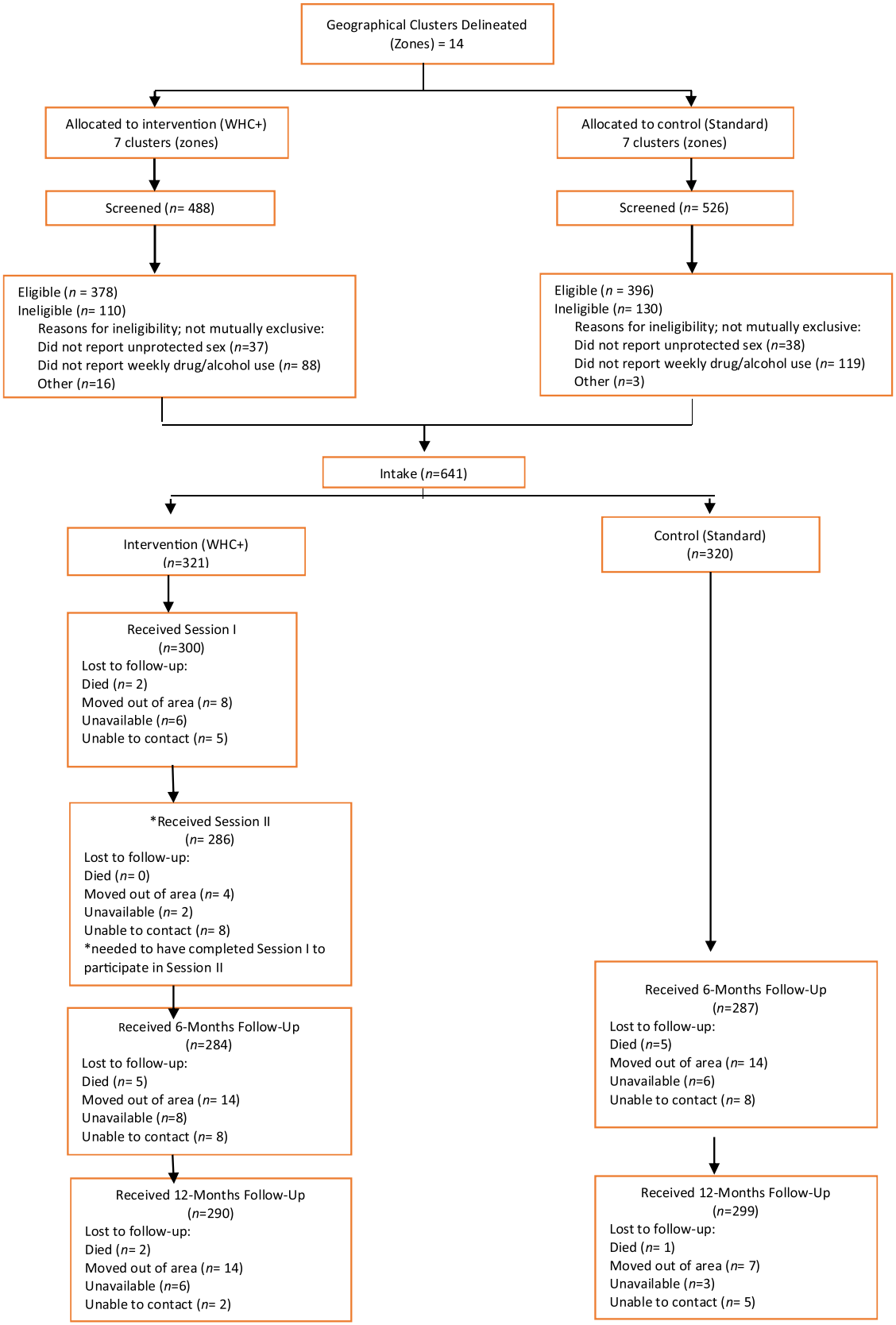

Fig. 1. CONSORT Diagram.

who had a detectable viral load were considered nonadherent.

Sexual negotiation with a boyfriend in the past 90 days also was assessed. Condom negotiation, condom use while high, and the refusal of sex without a condom were assessed using three separate items. Responses were given on a Likert scale, 1 = Not at all to 4 = All the time.

Sex worker status (i.e., engaging in sex work during the past 6 months) was entered as a covariate because 41% of the sample reported engaging in sex work, and sex work has been associated with sexual risk, AOD use, and engagement in HIV care (Centers for Disease Control and Prevention, 2016). HIV status at baseline also was included as a covariate because of its association with the outcomes of interest.

2.5. Analytic approach

We used Stata version 15 (StataCorp, College Station, TX) for all analyses and a p-value of 0.05 was used for significance testing.

The study arms were compared on baseline sociodemographic characteristics. Participants who tested positive for HIV at enrollment were compared in terms of HIV care. Comparisons were made using analysis of variance for continuous variables and logistic regression for binary variables, accounting for clustering. Participants lost to follow-up also were compared with participants who returned for their appointments across study arms and on key baseline sociodemographic variables.

The primary analyses sought to assess whether there were differences between the study arms in outcomes at 6-month follow-up and whether differences were sustained at 12-month follow-up. Treatment differences were estimated using multiple linear regression (for continuous outcomes), logistic regression (for binary outcomes), and negative binomial regression (for count outcomes because of overdispersion [Hilbe, 2011), with robust standard errors to account for geographical clustering. The intraclass correlation also was calculated for all outcomes, per the CONSORT guidelines (Campbell et al., 2004). All analyses controlled for baseline HIV status, sex worker status, and the baseline level of each outcome.

We performed outcome analyses using an intent-to-treat approach, with participants analyzed based on the study arm to which their cluster had been assigned, regardless of attendance or exposure. All clusters were included in each analysis.

3. Results

3.1. Demographics and baseline characteristics

Baseline characteristics of the sample by study arm are shown in Table 1. An average of 46 (SD = 18.7; median = 47) women were recruited in each cluster (not shown). At study enrollment, fewer women in the WHC+ arm reported trading sex in the past 6 months ($p = 0.01$) or engaging in frequent heavy drinking in the past 30 days ($p < 0.001$). More women in the WHC+ arm reported daily drug use and tested positive for cocaine, heroin, and marijuana (all $p < 0.001$).

3.2. Intervention dose and study retention

As shown in the CONSORT diagram in Fig. 1, of the participants who were in clusters randomized to the WHC+ arm, 93% completed the first session and 89% completed the second session. Approximately, 89% of participants completed their 6-month follow-up appointment and 92% of participants completed their 12-month follow-up appointment. There were no differences in 6- or 12-month attrition by study arm (all $p > 0.05$). There were 15 non-study-related deaths during the study. Other reasons for attrition were that participants had moved out of the area or the staff were unable to contact participants for their follow-up appointment. Differences were found in 6- and 12-month attrition across clusters (all $p < 0.04$).

There were differences in attrition by drug use. Participants who did not complete the 6-month follow-up were less likely to test positive for any drug ($p = 0.009$) and to report daily drug use in the past 30 days at baseline as compared with those who completed the follow-up visit (all $p < 0.05$). Participants who did not complete the 6-month follow-up also tested positive for a greater number of drugs at baseline than those who completed the appointment ($p = 0.02$). However, significant differences in drug use were only found in the WHC+ arm; there were no significant differences in drug use in the HCT only arm (all $p > 0.05$). Participants who did not complete the 6-month follow-up were also less likely to report being beaten by their boyfriend in the past 3 months at baseline ($p = 0.004$), and this difference was only significant in the WHC+ arm ($p = 0.03$). Lastly, participants who did not complete the 6-month follow-up appointment were younger than those who completed the appointment ($p = 0.004$). This difference was only significant in the WHC+ arm ($p = 0.007$).

There were also differences in 12-month attrition by drug use. Participants who did not complete the 12-month follow-up were less likely to test positive for any drug at baseline ($p < 0.001$). This difference was significant in both study arms (all $p < 0.05$). However, participants who did not complete the 12-month follow-up tested positive for a greater number of drugs at baseline ($p = 0.02$) than those who completed the appointment (WHC+: $p = 0.09$; HCT: $p = 0.22$). Participants who did not complete the 12-month follow-up appointment were less likely to report daily drug use in the past 30 days ($p = 0.001$), and this difference was only significant in the WHC+ arm ($p = 0.003$). Participants who did not complete the 12-month follow-up were also less likely to report at baseline that their boyfriend had attacked them in the past 3 months ($p = 0.05$), and this difference was only significant in the WHC+ arm ($p = 0.01$). Participants who did not complete the 12-month follow-up were also less likely to test positive for HIV at baseline ($p = 0.02$; WHC+: $p = 0.07$; HCT: $p = 0.06$). Lastly, participants who did not complete the 12-month follow-up were more likely to report engaging in condomless sex at their last sex act ($p = 0.005$), and this difference was only significant in the WHC+ arm ($p = 0.04$).

3.3. Primary outcomes

The effects of the WHC+ intervention on sexual risk, AOD use, and gender-based violence, controlling for reported sex work, HIV status, and baseline data are presented in Table 2.

3.3.1. Sexual risk

Women in the WHC+ arm were significantly more likely to report at 6-month follow-up that they used a condom during their last sex act with their boyfriend ($p = 0.05$), but not at 12-month follow-up ($p = 0.11$), as shown in Fig. 2. Women in the WHC+ arm also reported significantly more episodes of condom use during sex with their boyfriends in the past month at 6-month follow-up ($p = 0.03$), but not at 12-month follow-up ($p = 0.13$).

No statistically significant difference was found in condom use during the last sex act with participants' casual partner or client between the WHC+ arm and the HCT arm at 6- or 12-month follow-up (all $p > 0.05$). Episodes of condom use during sex with a casual partner or client in the past month did not differ between the WHC+ arm and the HCT arm at 6- or 12-month follow-up (all $p > 0.05$).

AOD use during the last sex act was not significantly different between the WHC+ arm and the HCT arm at 6- or 12-month follow-up (all $p > 0.05$).

3.3.2. Alcohol and other drug use

Participants in the WHC+ arm were significantly less likely to report frequent heavy drinking at 6-month follow-up ($p = 0.001$), but not at 12-month follow-up ($p = 0.19$; see Fig. 3). Participants in the WHC+ also reported fewer heavy drinking days at 6-month follow-up ($p = 0.01$), but not 12-month follow-up ($p = 0.36$). Participants in the WHC+ arm also reported fewer drinking days in the past month than participants in the HCT arm ($p = 0.03$) at 6-month follow-up, but not at 12-month follow-up ($p = 0.63$; not shown). However, there was no

Table 1
Characteristics of Sample for the Women's Health CoOp Plus by treatment (n = 641 at enrollment).

	Total		HCT		WHC+		p-value
	n = 641*		n = 320		n = 321		
	N/Mean	%/*SD*	N/Mean	%/*SD*	N/Mean	%/*SD*	
Age	29.86	7.80	29.90	7.61	29.82	7.99	0.90
Currently homeless	171	26.68	90	28.13	81	25.23	0.41
Currently unemployed	576	89.86	285	89.06	291	90.65	0.50
Traded sex in the past 6 months	262	40.87	148	46.25	114	35.51	**0.01**
HIV positive	354	55.23	196	61.25	158	49.22	< **0.001**
HIV Care-Related Factors							
Received a medical evaluation (n = 241)	121	50.21	72	54.14	49	45.37	0.18
Prescribed antiretrovirals (n = 236 who were diagnosed before enrollment)	80	33.90	47	35.34	33	32.04	0.60
Alcohol and Drug Use							
Frequent heavy drinking	205	31.98	124	38.75	81	25.23	< **0.001**
Days of binge drinking	8.67	8.18	9.93	8.28	7.41	7.89	< **0.001**
Daily drug use	205	31.98	86	26.88	119	37.07	**0.01**
Tested positive for cocaine	92	14.35	26	8.13	66	20.56	< **0.001**
Tested positive for opiates	115	17.94	30	9.38	85	26.48	< **0.001**
Tested positive for marijuana	201	31.36	79	24.69	122	38.01	< **0.001**
Abuse and Violence							
Lifetime physical or sexual abuse	226	35.26	114	35.63	112	34.89	0.85
Abuse by a Boyfriend in the Past 90 Days (n = 535)							
Emotional abuse	252	45.57	128	47.06	124	44.13	0.49
Attacked with a weapon	37	6.69	19	6.99	18	6.41	0.79
Beaten or struck	79	14.29	44	16.18	35	12.46	0.21
Sexual abuse	73	13.20	37	13.60	36	12.81	0.78
Sexual Risk							
Condomless last sex (n = 632)	400	63.29	199	62.78	201	63.81	0.79
Condom use with main partner at last sex (n = 553)	122	22.06	52	19.12	70	24.91	0.10
Condom use with casual partner or client at last sex (n = 352)	289	82.10	159	82.81	130	81.25	0.70
Alcohol or drugs before or during sex at last sex	359	56.01	173	54.06	186	57.94	0.32
Number of episodes of sex with a condom with main partner in the past 30 days (n = 535)	2.00	4.47	2.11	4.97	1.90	3.93	0.59
Number of episodes of sex with a condom with casual partner in the past 30 days (n = 179)	2.68	3.46	2.98	4.33	2.37	2.23	0.24

statistically significant difference in the average number of drinks that participants drank during a typical drinking day in the past month at 6- or 12-month follow-up (all $p > 0.05$; not shown).

No statistically significant difference was found in the proportion of participants who tested positive for opiates, cocaine, or marijuana at 6- or 12-month follow-up (all $p > 0.05$). Self-reported daily drug use did not differ between the WHC+ arm and the HCT arm at 6- or 12-month follow-up (all $p > 0.05$).

3.3.3. Gender-based violence

Participants in the WHC+ arm were significantly less likely to report being attacked with a weapon, beaten, or sexually abused by a boyfriend at 6-month follow-up (all $p < 0.05$), but not at 12-month follow-up (all $p > 0.05$). No significant difference was found in emotional abuse from a boyfriend between the WHC+ arm and the HCT arm at 6-month follow-up ($p = 0.09$; see Fig. 4). However, at 12-month follow-up, participants in the WHC + arm were significantly less likely to report emotional abuse from a boyfriend ($p = 0.002$).

3.3.4. HIV care

Among participants who tested positive for HIV, no statistically significant difference was found in the proportion of participants who attended an appointment for a medical evaluation since their HIV diagnosis between the WHC + arm and the HCT arm at 6- or 12-month follow-up (all $p > 0.05$). There was also no statistically significant difference at 6- or 12-month follow-up (all $p > 0.05$) in the proportion of participants who reported that they had been prescribed ART.

Chi-square tests of independence using the DBS samples indicated that there was no difference in the proportion of participants who had non-detectable viral loads at 6-month follow-up (n = 118; $p = 0.83$). However, there was a significant difference at 12-month follow-up (n = 172; $p = 0.01$). Approximately 53% of participants in the WHC+ arm (n = 50) had non-detectable viral loads compared with 47% of participants in the HCT arm (n = 45) at 12-month follow-up.

3.4. Secondary outcomes

3.4.1. Sexual negotiation

Participants in the WHC+ arm reported significantly more frequent condom negotiation, using a condom while high, and refusing sex without a condom with a boyfriend in the past 3 months at 6-month follow-up (all $p < 0.05$), but not at 12-month follow-up (all $p > 0.05$).

4. Discussion

Globally, gender inequality puts women at greater risk for HIV, and South Africa is a country where HIV is a gendered issue (Joint United Nations Programme on HIV/AIDS, 2017b). Furthermore, South Africa has one of the most hazardous patterns of alcohol use, and heavy alcohol use is prevalent among South African women. STTR and TasP hold the promise to eliminate the spread of HIV (World Health Organization, 2012); however, the nexus of AOD use, GBV, sexual risk, and lack of sexual agency may challenge the potential of these strategies. Consequently, these factors must be addressed in concert when trying to reduce the burden of HIV among South African women.

The current study is among the first to test the efficacy of a biobehavioral, gender-focused, empowerment-based HIV prevention intervention that aims to both prevent HIV and increase linkage to HIV care. Our findings suggest that the WHC+ intervention was efficacious in improving behavioral outcomes. Participants in the WHC+ arm reported significantly reduced frequent heavy drinking, a greater number of sex episodes with a condom with a boyfriend, and less physical and

Table 2
Adjusted Odds Ratios for Models with Treatment Condition Predicting Outcomes with HCT Only as the Reference Group.

6-month follow-up															
	Sexual Risk				Substance Use					Gender-based Violence				HIV Care	ARVs
	Condom Use at Last Sex (Y/N)		Number of Sex Acts with a Condom in the Past Month		Alcohol/ Drug Use at Last Sex (Y/N)	Frequent Heavy Drinking (Y/N)	Daily Drug Use (Y/N)	Pos. Opiates (Y/N)	Pos. Cocaine (Y/N)	Pos. Marijuana (Y/N)	Emotional Abuse (Y/N)	Attacked w/ Weapon (Y/N)	Beaten (Y/N)	Sexually Abused (Y/N)	Attended Appointment Since Diagnosis (Y/N)	Prescribed ARVs (Y/N)
	Main Partner/ Boyfriend	*Casual Partner or Client*	*Main Partner/ Boyfriend*	*Casual Partner or Client*	*Any Partner*											
AOR/β	1.63	1.03	0.43	0.07	1.18	0.45	1.21	1.79	1.34	1.13	0.63	0.33	0.41	0.40	0.86	0.98
CI	1.0099, 2.26156	0.3140, 3.3877	0.0488, 0.8085	−0.4494, 0.5992	0.5593, 2.4820	0.2792, 0.7345	0.4172, 3.5360	0.4272, 7.5312	0.3513, 5.1451	0.5033, 2.5502	0.3626, 1.0810	0.1180, 0.9224	0.2574, 0.6655	0.1860, 0.8630	0.4133, 1.8001	0.3888, 2.4810
p-value	0.05	0.96	0.03	0.78	0.67	0.001	0.72	0.43	0.67	0.76	0.09	0.04	< 0.001	0.02	0.69	0.97
12-month follow-up																
AOR/B	1.43	0.90	0.28	−0.02	0.97	0.71	0.64	1.77	1.78	0.89	0.73	0.57	1.27	1.09	1.21	1.00
CI	0.9187, 2.2137	0.3007, 2.6780	−0.0815, 0.6368	−0.5138, 0.4825	0.5181, 1.8057	0.4327, 1.1792	0.2518, 1.6144	0.8041, 3.8969	0.5424, 5.8310	0.4690, 1.7020	0.5988, 0.8861	0.2502, 1.3032	0.6639, 2.4172	0.4407, 2.6784	0.5512, 2.6505	0.4653, 2.1564
p-value	0.11	0.85	0.13	0.95	0.92	0.19	0.34	0.16	0.34	0.73	0.002	0.18	0.47	0.86	0.64	1.00

sexual abuse perpetrated by a boyfriend at 6-month follow-up, as compared with participants in the HCT arm. Similarly, participants in the WHC+ arm reported less emotional abuse by a boyfriend at 12-month follow-up, as compared with participants in the HCT arm. This study also provided some preliminary evidence that the WHC+ may have a positive effect on ART adherence. While most of the outcomes were not significantly different at 12-month follow-up, the data suggest that participants' risky behavior at follow-up remained lower than their risky behavior at baseline. Nonetheless, it may also be helpful to offer the WHC+ biannually, with a booster session 6 months after the initial intervention.

Overall, these results demonstrate the potential of a brief woman and focused intervention that addresses the nexus of AOD use, GBV, and sexual risk to reduce short-term HIV risk through primary and secondary prevention for wider scale up. The long-term effects of brief interventions should still be explored; however, deterioration should be expected.

The WHC+ offers an opportunity to reach both HIV-negative and women living with HIV who use AODs, as historically this group has been underserved. This study and previous research demonstrate the efficacy of woman-focused interventions to reduce the risks of HIV infection among women who use AODs (2004; Wechsberg et al., 2013a; Wechsberg et al., 2010b,). The WHC+ could provide a platform to address both HIV prevention and AOD use among women. This is particularly important because AOD use is a key driver of HIV risk in South Africa (Peltzer et al., 2009) and the current protocols for HCT do not include screening or linkage to care for AOD use disorders (Republic of South Africa, 2015). Therefore, the WHC+ may be a modality to help integrate HCT, AOD screening, and linkage to care as well as an intervention that can be used with other prevention tools such as pre-exposure prophylaxis (PrEP) among women in South Africa.

HIV prevention programs, HCT facilities, and substance abuse rehabilitation centers that work with HIV-negative clients and those living with HIV may consider incorporating the WHC+ and other related biological interventions into their activities. In fact, currently, the WHC+ is being incorporated into substance use and healthcare settings (Howard et al., 2017; Wechsberg et al., 2017a). Colocating services, like the WHC+, that address all these factors with treatment programs may increase access to services for clients as opposed to the current "silo" system of care and programs that is the norm in many healthcare settings. By linking the WHC+ within substance use or healthcare settings and other usual care settings, programs may also find that HIV-negative women and women living HIV may benefit from reduced AOD use, GBV and sexual risk, which may increase the likelihood of accessing HIV care or reduce their risk of HIV.

This study has important implications for the HIV prevention and treatment conti for South African women and demonstrates that a brief intervention that addresses multiple contextual factors can lead to behavioral change over a 6-month period. Although South Africa has invested in HIV prevention efforts for women who conduct sex work (The South African National AIDS Council, 2016) and plans are underway for other key populations, these initiatives primarily address sexual risk and health, violence, and economic empowerment to reduce HIV. Rarely has the focus been on AOD use among women, despite the fact that alcohol is the most prevalent substance of abuse and a major contributor to HIV acquisition in South Africa (Kalichman et al., 2007). Additionally, fetal alcohol effects remain a major public health problem (Roozen et al., 2016).

The current study highlights the severity of the HIV epidemic among women who use AODs, as more than 55% of the women in the sample were HIV-positive at enrollment. Furthermore, the findings illustrate that addressing AOD use, GBV, sexual risk, and HIV care simultaneously is feasible and effective. This is important because decreasing the occurrence of HIV risk and increasing engagement in the HIV continuum of care may ultimately lead to lower HIV incidence among women and their partners. Consequently, including women who use AODs in HIV

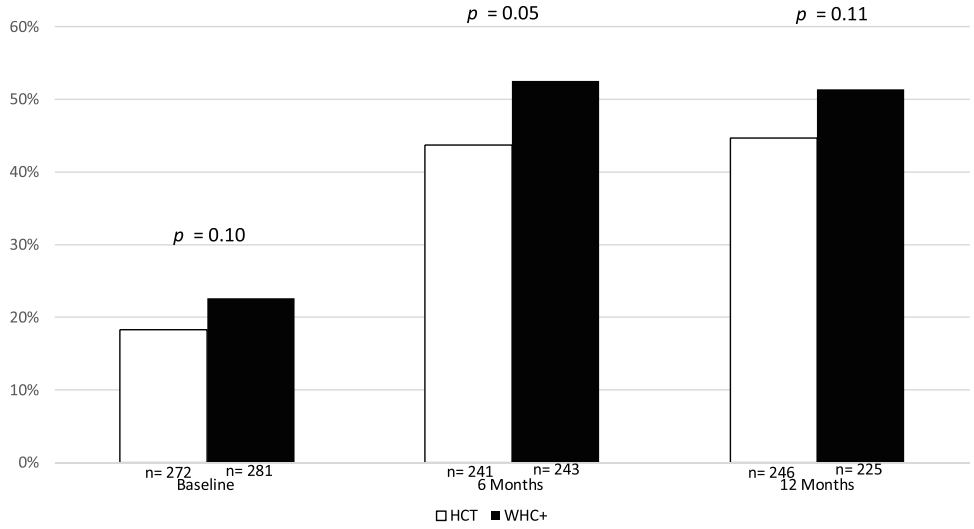

Fig. 2. Proportion of Women Reporting Condom Use during Last Sex with Boyfriend by Treatment and Time.
*Note: P-values represent the differences between groups at each time point based on chi-squared difference tests.

prevention programs is critical, as women represent an essential population in the fight against HIV.

Although these findings have important implications, some limitations should be noted. First, many of the measures were based on self-report. Consequently, there is the possibility of recall error or social desirability. Future studies may benefit from recent advances in ecological momentary assessments that allow for near-real-time data collection and reduce recall error.

Second, all women who tested positive underwent CD4 testing to facilitate clinical staging and were linked to HIV care, regardless of treatment condition. This procedure was aligned with the ethical principles of beneficence, justice, and respect. However, the effects of the WHC+ on linkage to care and prescription of ARVs may have been tempered by this protocol. Relatedly, this study was conducted during a period when the WHO and South African guidelines for the treatment of HIV were changing rapidly. The recent move toward universal treatment in South Africa will make ART more accessible to all persons living with HIV. Consequently, future studies should assess the impact of woman-focused interventions on HIV care and adherence within this new treatment context.

Third, ART adherence was assessed using viral load data from DBS samples from a subsample of women who were living with HIV. Although this method of viral load testing provides accurate information about viral load, this study did not assess the timing of ART initiation or re-initiation. Although viral load typically decreases rapidly after ARVs are initiated, it can take up to 6 months before viral loads become non-detectable in a person initiating an ART regimen, especially if they have trouble adhering (Cohen et al., 2011; National Institute of Allergy and Infectious Diseases, 2017). Consequently, it is possible that some participants who provided DBS samples had newly initiated ART, and therefore their viral loads may not accurately reflect their adherence levels. Relatedly, DBS collection capabilities were not available to the study team during the entire study. We were unable to collect DBS samples at baseline and were only able to collect data from a subsample of participants who completed their 6-month and 12-month follow-up, resulting in small sample sizes of 118 and 172 DBS samples at 6- and 12-month follow-up, respectively. This limits the inferences that can be made about the effectiveness of the WHC+ on adherence. However, it should be noted that even with this small

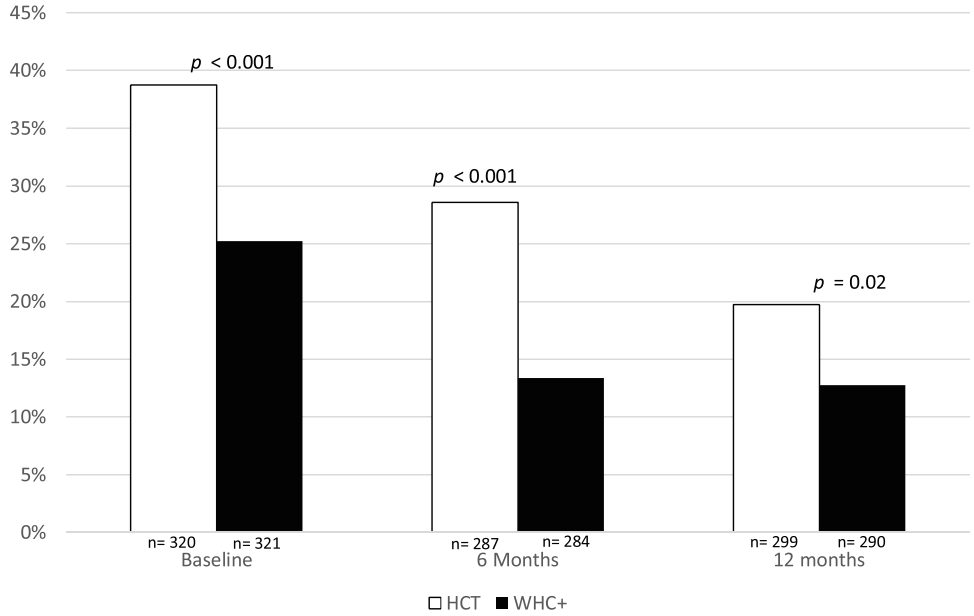

Fig. 3. Proportion of Women Who Reported Frequent Heavy Drinking by Treatment and Time.
*Note: P-values represent the differences between groups at each time point based on chi-squared difference tests.

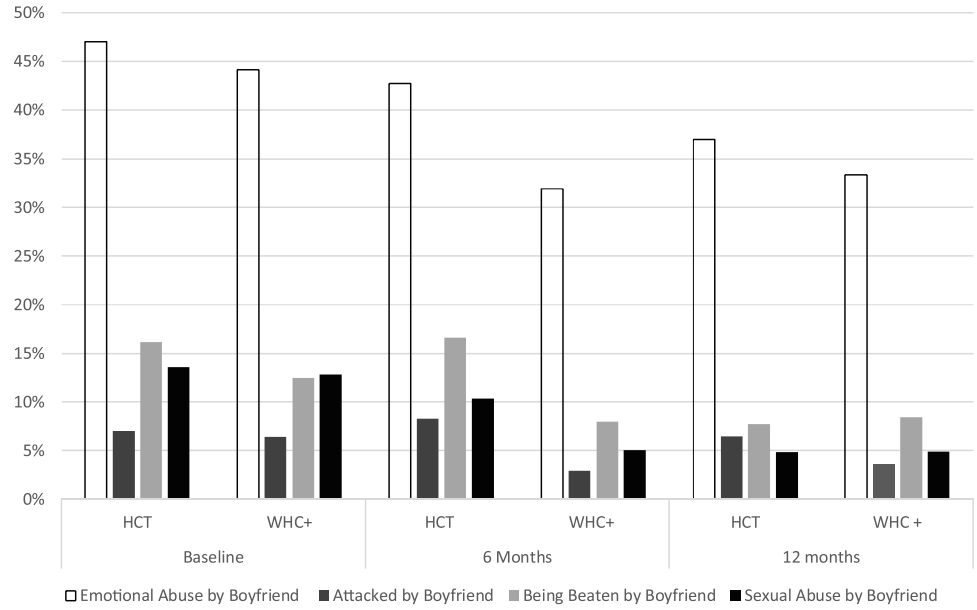

Fig. 4. Proportion of Women Who Reported Abuse Perpetrated by their Boyfriend by Treatment and Time.
*Note: P-values represent the differences between groups at each time point based on chi-squared difference tests.

sample size, participants in the WHC+ arm were more likely to have non-detectable viral loads than participants in the HCT arm. This is promising and should be explored in future studies.

Fourth, while women who use AODs are a population vulnerable to HIV in South Africa and globally, our sample is specific to the Pretoria area. Consequently, these findings may not necessarily be generalizable to other regions of South Africa or other African countries.

Fifth, the interventions in this trial were slightly unequal because of the provision of case management for the WHC + arm. The HCT arm was provided the standard of care, which usually does not include case management. Consequently, participants in the HCT arm were not provided case management.

Lastly, although the geographic zones were randomized to either the HCT arm or the WHC+ arm, differences still existed between the groups at baseline. Although each pair of clusters was matched based on similar characteristics, some of the zones were markedly different than other zones in terms of the severity of drug use and sex work. Consequently, there were still a few significant differences in conditions, even after randomization. We attempted to address these differences by controlling for baseline measures in the models; however, these differences may still threaten the internal validity of the inferences that can be made based on the results. However, the community-based and real-world nature of this study strengthens the external validity of the findings.

Despite these limitations, the study findings suggest that the WHC+ is an efficacious intervention with the potential to reduce HIV risk behaviors and increase protective behaviors among South African women who use AODs. Based on these findings, substance abuse rehabilitation centers that serve women may be ideal settings to address issues of GBV and sexual risk. Health centers also may be ideal settings to address these multiple risk factors as women test for or are treated for HIV. Given the outcomes at 6 months with this brief WHC+ intervention, future research should examine the effectiveness of the WHC+ in these real-world settings.

5. Conclusions

It is imperative to move forward in establishing the effectiveness and sustainability of this woman-focused intervention, which has the potential to reduce HIV risk among South African women. The WHC+ also could be a platform to introduce PrEP for women who report risk behaviors and test negative for HIV in public clinics. As more tools are added to the HIV prevention arsenal, all combinations of prevention need to be accessible and implementable.

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Contributors

All authors participated in the research and article preparation and approved of the final manuscript before submission to the journal. WMW conceived of the study, oversaw drafts, and finalized the manuscript; CPB conducted the analyses and contributed to drafting the manuscript; WAZ and CvdH contributed to writing and reviewing the manuscript; JN and FAB contributed to drafting the introductions, methods, and results of the manuscript; TLK and NFR contributed to data management, results, and methods; BNH, contributed to the writing and introduction of the manuscript. All authors approve the final manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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