GYNECOLOGY

Subfertility among HIV-affected couples in a safer conception cohort in South Africa

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BACKGROUND: Subfertility among couples affected by HIV has an impact on the well-being of couples who desire to have children and may prolong HIV exposure. Subfertility in the antiretroviral therapy era and its determinants have not yet been well characterized.

OBJECTIVE: The objective of the study was to investigate the burden and determinants of subfertility among HIV-affected couples seeking safer conception services in South Africa.

STUDY DESIGN: Nonpregnant women and male partners in HIV seroconcordant or HIV discordant relationships desiring a child were enrolled in the Sakh'umndeni safer conception cohort at Witkoppen Clinic in Johannesburg between July 2013 and April 2017. Clients were followed up prospectively through pregnancy (if they conceived) or until 6 months of attempted conception, after which they were referred for infertility services. Subfertility was defined as not having conceived within 6 months of attempted conception. Robust Poisson regression was used to assess the association between baseline characteristics and subfertility outcomes; inverse probability weighting was used to account for missing data from women lost to safer conception care before 6 months of attempted conception.

RESULTS: Among 334 couples enrolled, 65% experienced subfertility (inverse probability weighting weighted, 95% confidence interval, 0.59–0.73), of which 33% were primary subfertility and 67% secondary subfertility. Compared with HIV-negative women, HIV-positive women not on antiretroviral therapy had a 2-fold increased risk of subfertility (weighted and adjusted risk ratio, 2.00; 95% confidence interval, 1.19–3.34). Infertility risk was attenuated in women on antiretroviral therapy but remained elevated, even after ≥2 years on antiretroviral therapy (weighted and adjusted risk ratio, 1.63; 95% confidence interval, 0.98–2.69). Other factors associated with subfertility were female age (weighted and adjusted risk ratio, 1.03, 95% confidence interval, 1.01–1.05 per year), male HIV-positive status (weighted and adjusted risk ratio, 1.31; 95% confidence interval, 1.02–1.68), male smoking (weighted and adjusted risk ratio, 1.29; 95% confidence interval, 1.05–1.60), and trying to conceive for ≥1 year (weighted and adjusted risk ratio, 1.38; 95% confidence interval, 1.13–1.68).

CONCLUSION: Two in 3 HIV-affected couples experienced subfertility. HIV-positive women were at increased risk of subfertility, even when on antiretroviral therapy. Both male and female HIV status were associated with subfertility. Subfertility is an underrecognized reproductive health problem in resource-limited settings and may contribute to prolonged HIV exposure and transmission within couples. Low-cost approaches for screening and treating subfertility in this population are needed.

Key words: fertility, HIV, safer conception, subfertility, sub-Saharan Africa

With increased access to highly active antiretroviral therapy (HAART), HIV-positive individuals across sub-Saharan Africa are living longer, healthier lives.[1–3] This improved outlook is altering the context of childbearing among HIV-affected couples, and many people affected by HIV now desire to have children.[4] While public health efforts to eliminate mother-to-child transmission have made great progress, attention only recently focused on prevention of horizontal transmission among serodiscordant couples trying to conceive.[5–8]

Reduced fertility may alter horizontal transmission risks and is influenced by behavioral, environmental, and biological factors. One of the strongest determinants is age, with an inverse relationship with fecundity in women and to a lesser extent for men.[2] Behavioral factors such as use of cigarettes, alcohol, caffeine, diet, and stress levels also influence fertility along with occupational and environmental exposures.[2]

The degree to which biological and behavioral factors influence fertility in the context of HIV is not fully understood.[3,9-11] Data from the pre-HAART and early HAART-era suggested reduced fertility in the context of HIV[12–16] caused by immune suppression, coinfection with sexually transmitted infections (STIs), reduced sperm motility and volume in men, and anovulation/menstrual cycle irregularities in women.[2,12,17–22]

The relationship between subfertility and HIV may be bidirectional in sub-Saharan Africa because subfertility may precede HIV infection when personal desires alongside cultural and social pressures to bear children contribute to repeated condomless sex and multiple partnerships, thus increasing STI and HIV acquisition risks among women trying to conceive.[14,19] Among HIV serodiscordant couples, which account for 30% of stable heterosexual couples in South Africa,[23] 20–50% indeed report pregnancy desires as a reason for engaging in condomless sex.[24]

In the HAART era, an undetectable viral load prevents HIV transmission, which is particularly important in the periconception period when horizontal and vertical transmission risks are elevated.[5,25,26] Viral suppression can,

AJOG at a Glance

Why was this study conducted?
Safer conception care for couples with at least 1 HIV-positive partner promotes optimal pregnancy health and prevents onward HIV transmission to HIV-negative partners while trying to conceive and to potential infants but may be negatively impacted by underlying subfertility.

Key findings
Among couples engaged in safer conception services in South Africa, two thirds did not conceive by 6 months of trying; subfertility was twice as high among HIV-positive women not on antiretroviral therapy and was also independently associated with male-partner HIV status.

What does this add to what is known?
HIV had a negative impact on fertility in the preantiretroviral therapy era; however, more recent data have been limited; these findings suggest that even with growing antiretroviral therapy coverage, HIV-affected couples commonly experience subfertility, which may play a role in sustained HIV transmission risks among HIV serodiscordant couples trying to conceive.

however, not be assumed among individuals on HAART.

Understanding the prevalence and determinants of subfertility among HIV-affected couples is thus essential for decreasing HIV transmission resulting from prolonged periods of HIV exposure and to maximize the effectiveness of safer conception services.[1,27] The objective of this analysis was to determine the burden and predictors of subfertility among HIV-affected couples seeking safer conception care.

Materials and Methods
Study population and design
Study participants were clients enrolled into the Sakh'umndeni Safer Conception Cohort between July 2013 and April 2017. Sakh'umndeni was a nurse-run primary care safer conception service located at Witkoppen Clinic in northern Johannesburg, South Africa.[5]

Participants were recruited through posters, flyers, media outreach, and clinician referrals at Witkoppen Clinic, surrounding primary health clinics, and within-community gathering places (eg, malls and taxi ranks). Nonpregnant women of reproductive age (18–49 years) and men were eligible to participate if they were in a relationship in which 1 or both partners were HIV positive, planned to become pregnant in the next 6 months, and had not

previously received an untreated infertility diagnosis.

Participants were provided a comprehensive package of preconception care and safer conception strategies (eg, STI screening and treatment, HAART initiation/management, viral load monitoring, preexposure prophylaxis (PrEP), male medical circumcision, condomless sex timed to the periovulatory period, and home-based self-insemination for partnerships in which the male partner was HIV negative) and were followed up monthly. Once the couple was virally suppressed (<50 copies/mL) or stable on PrEP and clinically ready for conception (eg, STIs screened and treated), providers gave clients a greenlight to attempt conception.

Following enrollment, clients were prospectively followed up until delivery (if they conceived), until completion of 6 months of attempted conception at which time they were referred to outside fertility services, or until they voluntarily exited the service.

Clinic procedures and data collection
At enrollment into the safer conception clinic, participants underwent a medical examination, Papanicolau smear, syphilis testing, syndromic screening for STIs, a medical history assessment, including a full reproductive history,

HIV counseling and testing (if HIV negative or unknown status), HAART initiation (if HIV positive and not on treatment), and viral load monitoring (if HIV positive). PrEP was offered to HIV-negative partners after discussing risks and benefits. In all cases, patients with syndromic screening indicative of an STI or diagnostic diagnoses (syphilis, abnormal histology on cervical Papanicolau smears) were treated and advice was provided to delay conception until completion of STI management.

STI and reproductive histories, current symptoms, time spent previously trying to conceive and prior infertility procedures, consultations, and diagnoses were considered by the attending clinician at enrollment. Participants with known untreated infertility were not eligible for the service and those with a strong underlying suspicion of infertility were referred immediately to gynecological and/or infertility services. However, the closest public fertility service was 50 kilometers away and, even at reduced prices, cost prohibitive to most couples in this cohort. As such, we were conservative in our baseline referrals, understanding that infertility was not established, and in the absence of safer conception services, most patients would fall out of preconception care.

Information was collected for all female (n = 334) and male participants (n = 192). Women unaccompanied by their male partners (n = 142) provided information about her male partner's age, behaviors (eg, smoking, drinking), health, and reproductive history.

Measures
The primary outcome for this analysis was subfertility, defined as failure to conceive within 6 months from the first reported condomless vaginal intercourse during safer conception follow-up.

Subfertility is generally defined as any form of reduced fertility with prolonged time of unwanted nonconception.[28] We chose 6 months because most pregnancies (85%) occur within the first 6 months of condomless sex during the fertile phase,[28] because the safer conception service aims to reduce

TABLE 1
Characteristics of Sakh'umndeni Safer Conception Service female clients at Witkoppen Health and Welfare Centre, Johannesburg, South Africa (n = 334)

Variables	Early exit from study (n = 152)	Completed 6 months of follow-up (n = 182)	Total (n = 334)	P value
Individual-level characteristics				
Age, median (IQR)	34.0 (30.0—38.5)	33.0 (30.0—37.0)	34.0 (30.0—38.0)	.341
Partner age, median (IQR)	38.0 (33.0—43.0)	37.9 (34.0—41.0)	38.0 (34.0—42.0)	.331
Employed, n (%)	91 (59.9%)	125 (68.7%)	216 (64.7%)	.093
Median monthly income, US dollars (IQR)	344.0 (172.0—516.0)	344.0 (215.0—516.0)	344.0 (215.0—516.0)	.732
Completed education, n (%)				.216
Grade school or less	94 (61.8%)	127 (69.8%)	221 (66.2%)	
Completed secondary school	39 (25.7%)	41 (22.5%)	80 (24.0%)	
Tertiary	19 (12.5%)	14 (7.7%)	33 (9.9%)	
Residence, n (%)				.877
Northern Johannesburg	132 (86.8%)	157 (86.3%)	289 (86.5%)	
Outside northern Johannesburg	20 (13.2%)	25 (13.7%)	45 (13.5%)	
Partnership-level characteristics				
HIV status within the partnership, n (%)				.024
F (negative), M (positive)	20 (13.2%)	23 (12.6%)	43 (12.9%)	
F (positive), M (positive)	56 (36.8%)	93 (51.1%)	149 (44.6%)	
F (positive), M (negative) (unknown)	76 (50.0%)	66 (36.3%)	142 (42.5%)	
Male partner HIV status, n (%)				.039
HIV negative	63 (41.4%)	56 (30.8%)	119 (35.6%)	
HIV positive	76 (50.0%)	116 (63.7%)	192 (57.5%)	
Unknown	13 (8.6%)	10 (5.5%)	23 (6.9%)	
Age difference between partners, y				.357
≤5	87 (57.2%)	95 (52.2%)	182 (54.5%)	
>5	65 (42.8%)	87 (47.8%)	152 (45.5%)	
Relationship duration with current partner, median (IQR)	6.0 (2.0—10.0)	4.0 (3.00—10.0)	5.0 (2.0—10.0)	.507

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prolonged HIV exposure to partners, and because women who fail to conceive within a 6 month trial period were routinely referred to fertility services. The subfertility outcome includes both primary subfertility (among women who have never become pregnant) and secondary subfertility (among women who have been pregnant before).

Exposures of interest included sociodemographic and partnership characteristics, behavioral factors, and clinical and reproductive characteristics that were supported by the literature or

hypothesized to be associated with fertility outcomes. All variables used were collected at baseline, with the exception of average number of sex acts and whether the male partner ever attended, which were summarized across study visits.

Sociodemographic characteristics included female age and employment status. Partnership-level characteristics included HIV status within the partnership, age difference between partners, and relationship duration with the current partner. Clinical characteristics

examined included female and male partner HIV status (confirmed through clinical records/testing for enrolled participants and self-report for male partners not in attendance), HAART use, female weight, self-reported and baseline-measured STI history, history of tuberculosis and male partner erectile dysfunction.

Behavioral characteristics included male partner cigarette smoking (current vs nonsmoker), alcohol and drug use (yes/no), average condomless sex acts per month, and whether the couple ever

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TABLE 1
Characteristics of Sakh'umndeni Safer Conception Service female clients at Witkoppen Health and Welfare Centre, Johannesburg, South Africa (n = 334) (continued)

Variables	Early exit from study (n = 152)	Completed 6 months of follow-up (n = 182)	Total (n = 334)	P value
Clinical and behavioral characteristics				
On antiretroviral therapy, n (%)[a]				.656
No	20 (15.2%)	27 (17.1%)	47 (16.2%)	
Yes	112 (84.8%)	131 (82.9%)	243 (83.8%)	
Female HIV status and HAART use				.905
HIV negative	20 (13.2%)	23 (12.6%)	43 (12.9%)	
HIV positive, no HAART	20 (13.2%)	28 (15.4%)	48 (14.4%)	
HIV positive, HAART 0—2 y	53 (34.9%)	58 (31.9%)	111 (33.2%)	
HIV positive, HAART 2 or more y	59 (38.8%)	73 (40.1%)	132 (39.5%)	
Female baseline viral load[a,b]				.528
Undetectable, n (%)	81 (63.3%)	93 (59.6%)	174 (61.3%)	
Female CD4, n (mm^3) (%)[a,c]				.405
$\leq$200	13 (10.2%)	11 (7.0%)	24 (8.4%)	
201—349	31 (24.2%)	30 (19.1%)	61 (21.4%)	
350—499	31 (24.2%)	37 (23.6%)	68 (23.9%)	
500 or more	53 (41.4%)	79 (50.3%)	132 (46.3%)	
Weight, kg, median (IQR)	70.9 (59.5-79.8)	66.6 (58.6—79.3)	69.0 (59.0—79.5)	.766
Current or history of STI, n (%)	9 (5.9%)	9 (4.9%)	18 (5.4%)	.694
Smoker	11 (7.2%)	8 (4.4%)	19 (5.7%)	.264
Partner smoker	49 (32.2%)	43 (23.6%)	92 (27.5%)	.080
Any alcohol consumption by partner	66 (43.4%)	55 (30.2%)	121 (36.2%)	.010
Alcoholic drinks per week, median (IQR)[d]	0 (0—2)	0 (0—1)	0 (0—1)	< .01
History of TB, n (%)	19 (12.5%)	28 (15.4%)	47 (14.1%)	.450
Reported erectile dysfunction	8 (5.3%)	22 (12.1%)	30 (9.0%)	.030
Condomless sex acts per month, median (IQR)	1.6 (0.0—3.4)	2.9 (1.5—4.3)	2.3 (1.0—4.3)	.182
Accompanied by partner in clinic	73 (48.0%)	119 (65.4%)	192 (57.5%)	< .01

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attended safer conception services together. Female reproductive history variables included the number of previous live births, previous pregnancies with current partner (yes/no), age at menarche, history of abortion or miscarriage, irregular and missed menstrual periods, average reported number of flow days per menstrual cycle, and history of inability to conceive over at least 12 months of trying.[13,29,30]

Statistical analysis

Characteristics of study participants were described and the prevalence of subfertility assessed. Univariate and multivariable robust Poisson regression models were used to estimate associations with subfertility. Inclusion of variables in the multivariable model was determined by the univariate model results ($P < .10$) as well as predictors hypothesized a priori. Variance inflation factors were used to assess multicollinearity between variables of interest, and collinear variables (variance inflation factor>10) were excluded from the model.

Many women discontinued services prior to 6 months of attempted conception because they were no longer trying to conceive, because of partnership dissolution or in cases of loss to follow-up. Inverse probability weighting (IPW) was used to account for underrepresentation of those missing the full 6 months of attempted conception time.[31] For IPW, multivariable robust Poisson regression was used to identify variables associated with having completed 6 months of follow-up.[32] A multivariable logistic regression model was then used to estimate the IPWs.

Each participant was assigned a weight equal to the inverse probability of having 6 months of attempted

TABLE 1
Characteristics of Sakh'umndeni Safer Conception Service female clients at Witkoppen Health and Welfare Centre, Johannesburg, South Africa (n = 334) (continued)

Variables	Early exit from study (n = 152)	Completed 6 months of follow-up (n = 182)	Total (n = 334)	P value
Reproductive history				
History of previous pregnancy	111 (73.0%)	145 (79.7%)	256 (76.6%)	.153
Previously been pregnant with current partner, n (%)	46 (30.3%)	70 (38.5%)	116 (34.7%)	.117
Number of live births				.016
Zero	62 (40.8%)	50 (27.5%)	112 (33.5%)	
One	59 (38.8%)	75 (41.2%)	134 (40.1%)	
Two or more	31 (20.4%)	57 (31.3%)	88 (26.3%)	
Reported history of abortion[e]	6 (5.4%)	16 (11.0%)	22 (8.6%)	.111
Reported history of miscarriage[e]	37 (33.3%)	44 (30.3%)	81 (31.6%)	.610
Age at menarche, y, median (range)	15 (14—16)	15 (14—16)	15 (14—16)	.408
Flow days in menstrual cycle, median (range)	4 (3—5)	4 (3—5)	4 (3—5)	.972
Missed or irregular period in the past 3 mo	27 (17.8%)	36 (19.8%)	63 (18.9%)	.639
Tried to conceive for at least 1 y and failed	64 (42.1%)	65 (35.7%)	129 (38.6%)	.232

F, female; *HAART*, highly active antiretroviral therapy; *IQR*, interquartile range; *M*, male; *STI*, sexually transmitted infection; *TB*, turberculosis, undetectable viral load (<50 copies/mL).

[a] Among HIV-positive female clients (n = 291); [b] Baseline viral loads available for 284 HIV-positive women; [c] CD4 counts available for 285 HIV-positive women; [d] Among partners with any reported alcohol (n = 121); [e] Among clients who have history of previous pregnancy (n = 256).

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conception based on observed associated covariates for this outcome. Weights from the multivariable model were estimated, creating a new pseudopopulation in which clients missing 6 months of attempted conception are replaced by up-weighting those with complete attempted conception time, who have the same exposure covariates.[31]

A final IPW-weighted multivariable predictive model of subfertility was estimated using robust Poisson regression.

We conducted several sensitive analyses to assess the overall robustness of our findings. Sensitivity analyses were completed to account for potential selection bias, given that many women attending the service reported unsuccessfully trying to conceive for 12 months or more at enrollment. To explore whether this may have had an impact on our inferences, we reran our primary analyses in the restricted subset of women who did not report trying to conceive for 12 or more months at enrollment.

Additionally, given that CD4 cell counts were available only among HIV-positive women, to assess the potential unaccounted-for impact of CD4 cell count, following our primary analysis approach, we conducted a sensitivity analysis among HIV-positive women, which included baseline CD4 count as a categorical variable in the model ($\leq$200 cells/mm^3, 201—349 cells/mm^3, 350—499 cell/mm^3, $\geq$500 cell/mm^3).

Finally, because of collinearity, HAART use and duration could not be assessed simultaneously with partner serodynamics in any of the models. We thus conducted a sensitivity analysis to assess the joint effect of partner serodynamics (seroconcordant vs serodiscordant) on subfertility.

IPW-weighted, univariate risk differences were estimated to assess the absolute risk of subfertility across predictors because risk differences consider the population prevalence of exposures and provide a potentially clinically meaningful guide to subfertility screening. Predictors included in this analysis were those that were significant by univariate relative risk comparisons.

Data were entered into a REDCap database (Vanderbilt, TN), and all analyses were conducted using Stata 14.1 (Stata Corp, College Station, TX).

Ethics
This study was approved by the Human Research Ethics Committee (Medical) at the University of Witwatersrand, Johannesburg, and the University of North Carolina (Chapel Hill). Participants completed written, informed consent.

Results
Client characteristics
Overall, 334 women were enrolled into care and followed up for pregnancy in the Sakh'umndeni Safer Conception Cohort from July 2013 to December 2017. Characteristics of individuals utilizing services are presented in Table 1.

The median age of women and male partners at enrollment was 34 years (interquartile range [IQR], 30—38 years) and 38 years (IQR, 34—42 years), respectively. The majority of couples (74%, n = 246) reported having been together for

TABLE 2
Correlates of subfertility among women attending the safer conception cohort (n = 182)

Variables	Univariate		Multivariable		Weight-adjusted multivariable	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Individual and partnership characteristics						
Female age	1.03 (1.01—1.05)	< .01	1.03 (1.01—1.05)	< .01	1.03 (1.01—1.05)	< .01
Employment status						
Unemployed	Reference					
Employed	0.95 (0.75—1.19)	.646				
Age difference between partners, y						
≤5	Reference		Reference		Reference	
>5	0.81 (0.65—1.02)	.072	0.86 (0.70—1.05)	.149	0.87 (0.71—1.07)	.177
Length of relationship with current partner, y						
0—2	Reference					
≥2	1.06 (0.82—1.39)	.652				
Clinical and behavioral characteristics						
Female HIV status and HAART use						
HIV negative	Reference		Reference		Reference	
HIV positive, no HAART	2.01 (1.16—3.47)	.012	2.00 (1.21—3.28)	< .01	2.00 (1.19—3.34)	< .01
HIV positive, HAART 0—2 y	1.63 (0.94—2.82)	.080	1.76 (1.08—2.87)	.024	1.89 (1.14—3.10)	.013
HIV positive, HAART ≥2	1.72 (1.00—2.93)	.048	1.62 (0.99—2.65)	.056	1.63 (0.98—2.69)	.058
Male partner HIV status						
HIV negative	Reference		Reference		Reference	
HIV positive	1.11 (0.86—1.44)	.417	1.33 (1.04—1.71)	.025	1.31 (1.02—1.68)	.035
Unknown	1.36 (0.93—1.99)	.115	1.32 (0.87—2.00)	.189	1.34 (0.91—1.98)	.134
Weight, kg	1.00 (0.99—1.01)	.903				
Current or history of STI						
No	Reference					
Yes	1.04 (0.65—1.67)	.875				
Partner smoker						
No	Reference		Reference		Reference	
Yes	1.27 (1.03—1.57)	.028	1.31 (1.05—.63)	.015	1.29 (1.05—1.60)	.017
Any alcohol consumption by partner						
No	Reference					
Yes	1.03 (0.81—1.30)	.827				
History of TB						
No	Reference					
Yes	1.07 (0.80—1.41)	.656				
Partner reported erectile dysfunction						
No	Reference					
Yes	0.68 (0.42—1.09)	.109				
Condomless sex acts per month	1.01 (0.97—1.06)	.542				

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TABLE 2
Correlates of subfertility among women attending the safer conception cohort (n = 182) (continued)

Variables	Univariate		Multivariable		Weight-adjusted multivariable	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Accompanied by partner in clinic						
Unaccompanied	Reference					
Accompanied	0.95 (0.76–1.18)	.621				
Reproductive history						
Number of live births						
Zero	Reference		Reference		Reference	
One	0.82 (0.65–1.03)	.085	0.96 (0.77–1.21)	.736	0.98 (0.77–1.24)	.861
Two or more	0.67 (0.51–0.90)	< .01	0.80 (0.60–1.07)	.133	0.77 (0.57–1.03)	.079
Previously been pregnant with current partner						
No	Reference		Reference		Reference	
Yes	0.80 (0.63–1.02)	.072	0.92 (0.72–1.16)	.472	0.91 (0.72–1.15)	.431
Reported history of abortion[a]						
No	Reference					
Yes	1.14 (0.79-1.63)	.484				
History of miscarriage[a]						
No	Reference					
Yes	1.11 (0.85–1.45)	.447				
Age at menarche	0.97 (0.92–1.03)	.356				
Flow days in menstrual cycle	1.02 (0.97–1.07)	.448				
Missed or irregular period in the past 3 months						
No	Reference		Reference		Reference	
Yes	1.10 (0.86–1.42)	.447	1.20 (0.92–1.56)	0.182	1.17 (0.90–1.51)	.240
Tried to conceive for at least 1 year and failed						
No	Reference		Reference		Reference	
Yes	1.49 (1.22–1.82)	< .001	1.42 (1.17–1.73)	<0.01	1.38 (1.13–1.68)	< .01

Models were estimated using robust Poisson regression. Weight-adjusted multivariable models apply inverse probability weighting.

CI, confidence interval; *HAART*, highly active antiretroviral therapy; *RR*, risk ratio; *STI*, sexually transmitted infection; *TB*, turberculosis.

[a] Among clients who have a history of a previous pregnancy (n = 145).

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more than 2 years, with a median relationship duration of 5 years (IQR, 2–10 years). Most women (n = 291 of 334, 87%) and 58% of male partners (n = 192 of 334) were HIV-positive; the status of 7% of men (n = 23 of 334) was unknown.

In terms of couples' serostatus, 45% of couples were seroconcordant HIV positive, 43% were serodiscordant or sero-unknown, with an HIV-positive female partner, and 13% were serodiscordant with an HIV-positive male partner. Of the HIV-positive women, 84% were on

HAART at cohort enrollment, 61% had undetectable viral loads (<50 copies/ mL), and 46% had a CD4 count of 500 or greater.

Reported STI history, baseline and syndromic diagnosis through follow-up for women was 3% (n = 9 of 334), 3% (n = 11 of 334), and 12% (n = 21 of 182) among women retained through 6 months of follow-up. Most women had previously been pregnant (77%, n = 256 of 334) and 19% (n = 63 of 334) reported a missed or irregular period within the past 3 months.

Nine percent of male partners (n = 30 of 334) reported erectile dysfunction. During follow-up, the median number of reported condomless sex acts per month was 2.3 (IQR, 1.0–4.3), which did not differ by couple partner serodynamics (*P* = .99).

Retention throughout conception trial period
Overall, 152 women (46%) did not complete the 6 month conception trial period and thus could not be classified with respect to subfertility. Reasons

FIGURE
Weighted univariate risk difference estimates for the predictors of subfertility
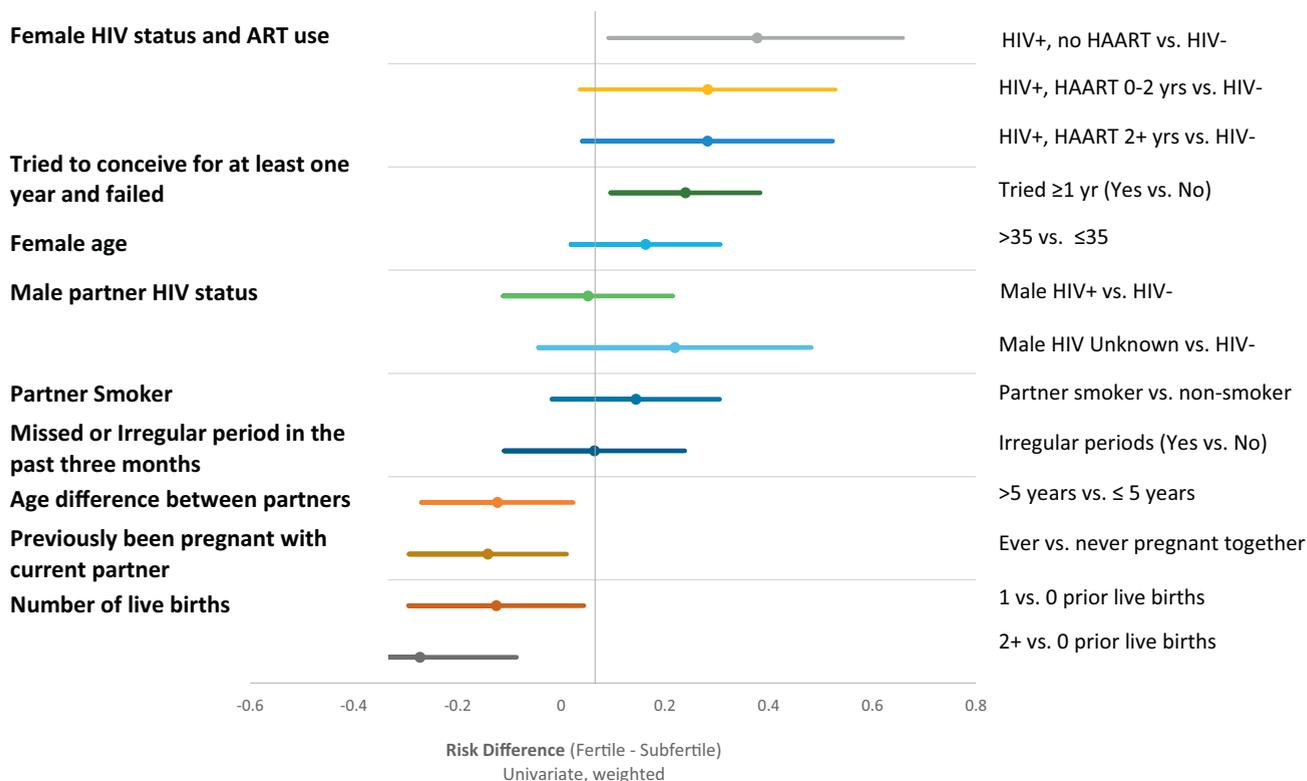
Weighted univariate risk difference estimates for the predictors of subfertility in the safer conception cohort are shown.

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included loss to follow-up (n = 70 of 152, 46%), referral for fertility work-up prior to 6 months based on clinician judgment (n = 25 of 152, 16%), termination of relationship with partner (n = 13 of 152, 9%), and combined other infrequently reported reasons (n = 26 of 152, 17%). Study retention was associated with partner accompaniment to the clinic, erectile dysfunction, male HIV status, history of 2 or more live births, history of abortion, and male partner cigarette and alcohol use. These factors and a priori determined variables of importance (female partner HIV status and duration of HAART use) were included in the multivariable IPW model (Supplemental Table 1), generating weights ranging from 1.09 to 6.20, with a median value of 1.83.

Subfertility
Two thirds of women were classified as subfertile (crude proportion of 64%,

IPW-weighted estimate 65% (95% confidence interval [CI], 0.59−0.73) with primary and secondary subfertility contributing to 33% (n = 39 of 117) and 67% (n = 78 of 117) of cases, respectively.

In a univariate analysis, female age, HIV positivity of the female partner (regardless of HAART use), having a male partner who is a smoker, and a history of unsuccessfully trying to conceive for at least 1 year prior to participation in safer conception services were all associated with greater subfertility, while having 2 or more children was associated with a decreased risk for subfertility (Table 2).

In multivariable and IPW-multivariable−adjusted models, female age, HIV positivity of the female partner, male partner smoking, history of unsuccessfully trying to conceive for at least 1 year, and parity remained associated with subfertility, as was male-partner

HIV positivity (Table 2). The relationship between a woman's HIV status and subfertility was present among both women who were HAART experienced and HAART naive at enrollment. Compared with HIV-negative women, the risk of subfertility was increased 2-fold among HIV-positive women on HAART for less than 2 years at enrollment and by 63% among women on HAART for ≥2 years.

Subfertility was 31% higher among women with HIV-positive male partners (a-wRR: 1.31, 95% CI: 1.02-1.68). For every one-year increase in women's age there was a three percent increased risk of subfertility (a-wRR: 1.03, 95% CI: 1.01-1.05, p-value <0.01). Other factors associated with increased subfertility were male partner smoking (weighted and adjusted risk ratio [w-aRR], 1.29; 95% CI, 1.05−1.60) and a history of trying to conceive for ≥1 year prior to enrollment (w-aRR, 1.38; 95% CI, 1.13−1.68).

The overall findings, including relationships between HIV status and HAART use, were robust in a sensitivity analysis restricted to women who did not report unsuccessfully trying to conceive for 12 months or more at enrollment (Supplemental Table 2). Similarly, in a sensitivity analysis restricted to HIV-positive women, HAART use and duration remained unprotective after adjusting for CD4 count (table not shown).

In a further sensitivity analysis assessing the joint effect of couples' HIV status on subfertility (rather than the independent effects of the woman's HIV status and the man's HIV status), being in a seroconcordant-positive relationship increased the risk of subfertility by 78% as compared with serodiscordant couples with HIV-negative female partners (w-aRR, 1.78, 95% CI, 1.10−2.90) (Supplemental Table 3). Subfertility was elevated, but not statistically significantly higher, in partnerships in which only the female partner was living with HIV, as compared with serodiscordant relationships with an HIV-negative woman (w-aRR, 1.42, 95% CI, 0.85−2.38).

Risk differences were calculated to assess the factors most strongly associated with absolute risk for subfertility (Figure). The predictors attributable to the largest fraction of subfertility were female HIV status and HAART duration, followed by failure to conceive after at least 1 year of trying at some point prior to safer conception care, female partner age, and male partner HIV status.

Comment

We found a very high burden of subfertility among HIV-affected couples trying to conceive, with 2 of every 3 women accessing safer conception services failing to conceive within 6 months. HIV infection, in both women and men, had a negative effect on fertility, even among women on HAART. HIV-positive seroconcordant couples had a 78% increased risk of subfertility compared with serodiscordant couples in which only the male partner was HIV positive. These data suggest that even in the HAART era, HIV can have an important impact on fertility and potentially prolong attempted conception, which could in turn increase HIV transmission risks between partners.

In terms of predictors of subfertility, older female age was significantly associated with subfertility, which is well established in the literature.[33] HIV infection among women was associated with subfertility, even when accounting for HAART use and duration. Compared with HIV-negative women, HIV-positive women not on HAART at enrollment or starting HAART in the past 2 years had a 2-fold increased risk of subfertility. Women on HAART for more than 2 years still had a 63% increased risk of subfertility compared with HIV-negative women.

These findings support previous research that suggests that HAART use does not fully restore fertility among HIV-positive women to the level of HIV-negative women.[34,35] Explanations for subfertility despite HAART use may include a sustained relative immune-compromised state or HAART drug-related toxicities. Data on these issues are limited and inconclusive.[13]

Prior work has shown that in 20−26% of couples, a male factor is the cause of subfertility.[36] Few studies, however, have investigated the association of HIV infection on male fertility, and of these the evidence is mixed. Some studies report unimpaired semen parameters among men with asymptomatic HIV infection, while others report reduced sperm motility and semen volume.[2,18]

Although our study did not include a semen analysis, our findings add epidemiological evidence of the impact of HIV on male subfertility, independent of their female partner's HIV status. Women with partners who smoke were also at higher risk for subfertility, which is in line with prior evidence.[37,38] Overall, our findings support the need to screen for male biological and behavioral characteristics when assessing potential risk for subfertility among HIV-affected couples instead of just assessing female factors.

We also found that more than 1 in 3 couples had already failed to conceive for more than 1 year, and these couples had a 34% increased risk of subfertility after 6 months of attempted conception. Timely referrals for couples with suspected fertility challenges to gynecologists or fertility specialists while simultaneously ensuring optimal clinical management of HIV within safer conception care is thus essential to reduce prolonged HIV transmission risks. However, specialized fertility services are frequently not accessible or affordable in the public sector in many resource-constrained settings, and anecdotal data from our service suggest that very few women referred out successfully received infertility-related workups and care.

These findings suggest the importance of providing low-cost fertility services in resource-constrained settings to support reproductive health and reduce transmission among HIV-affected couples who may have prolonged HIV transmission risks when desired conception outcomes are not achieved.

Strengths and limitations of this study should be considered while interpreting results. Although patients receiving safer conception services are advised to stop condomless sex until risk of transmission is minimized, clients often started attempting conception prior to being given the greenlight from their health care providers. To account for this, our study began the 6 month period of attempted conception at the start of reported condomless sex. This approach more accurately captures the time at risk for pregnancy but does not capture heterogeneity in the frequency of condomless sex, which may increase after the greenlight was given and may underestimate time at risk for subfertility among women not reporting condomless sex prior to the greenlight period for social desirability purposes.

Additionally, to account for insufficient follow-up time for individuals

missing the full 6 months of attempted conception, IPWs were applied to address biases resulting from potential differences between clients with and without 6 months of attempted conception. Because women were referred to outside care after 6 months of attempted conception, we limited our assessment to subfertility and were unable to prospectively assess infertility, which is defined as attempted conception for 12 months. Our approach importantly accounts for characteristics of both the female and male partners; however, for the subset of women who reported information on their male partner because he was not in attendance, misclassification of male characteristics is possible.

Our study relied on many self-reported measures, which may introduce bias; for example, alcohol and smoking reports may underestimate usage. Additionally, biological measures including hormone levels, semen analysis, and diagnostic screening for gonorrhea and chlamydia were not available. These findings highlight the importance of research to examine these underlying markers that may be having an impact on fertility. Furthermore, safer conception services may attract a population at higher risk of subfertility than the general population of HIV-affected couples, further emphasizing the need for providers to take detailed medical histories at HIV care entry to screen for potential infertility and adequately counsel HIV couples about the risks and benefits of trying to conceive.

We assessed the robustness of our findings among women who did not report previously trying to conceive for 12 months or more at enrollment and found our inferences to be unchanged. Even so, our results may not be generalizable to other settings if women choosing to use this service differ from those who may take up services in different contexts.

Our findings raise awareness of the burden of subfertility among HIV-affected couples and advocate for the development of subfertility screening.

HIV serodynamics, including both the woman's and man's HIV status, and women's treatment status are important determinants of absolute risk of subfertility in this population along with prior failed conception attempts, female age, and male partner smoking status. Screening for preexisting fertility concerns, smoking-cessation counseling, and low-cost ovulation predictor kits should be incorporated into HIV care and safer conception interventions to reduce the risk of HIV transmission within couples and to ensure opportunities for creating a family for all couples, independent of their HIV status. ∎

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SUPPLEMENTAL TABLE 1
Unadjusted and adjusted predictors of women being retained in the study for 6 months or more following attempted conception (n = 334)

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*value	OR (95% CI)	*P*value
Demographics				
Female age	0.99 (0.97—1.01)	.343		
Employment				
Unemployed	Reference			
Employed	1.20 (0.96—1.49)	.106		
Monthly income, US dollars	1.00 (1.00—1.00)	.741		
Education				
Grade school or less	Reference			
Completed matric	0.89 (0.70—1.14)	.354		
Tertiary	0.74 (0.49—1.12)	.151		
Residence in North Johannesburg				
North Johannesburg	Reference			
Outside North Johannesburg	1.02 (0.77—1.36)	.876		
Partnership-level characteristics				
HIV status within the partnership				
F (negative), M (positive)	Reference			
F (positive), M (positive)	1.17 (0.86—1.58)	.322		
F (positive), M (negative) (unknown)	.87 (0.62—1.21)	.405		
Male partner HIV status				
HIV negative	Reference			
HIV positive	1.28 (1.03—1.60)	.028		
Unknown	0.92 (0.56—1.53)	.758		
Length of relationship with current partner, y				
0—2	Reference			
≥2	1.12 (0.89—1.42)	.341		
Age difference between partners, y				
≤5	Reference			
>5	1.10 (0.90—1.33)	.365		
Clinical and behavioral characteristics	0.91 (0.57—1.47)	.710		
Female HIV status and HAART use				
HIV negative	Reference		Reference	
HIV positive, no HAART	1.09 (0.75—1.58)	.644	2.59 (1.01—6.67)	.048
HIV positive, HAART 0—2 y	0.98 (0.70—1.36)	.890	2.01 (0.89—4.53)	.091
HIV positive, HAART ≥2	1.03 (0.75—1.42)	.837	2.16 (0.96—4.82)	.061
Female CD4[a,b]				
≤200	Reference			
201—349	1.07 (0.65—1.78)	.784		
350—499	1.19 (0.73—1.93)	.490		
≥500	1.31 (0.83—2.06)	.253		

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SUPPLEMENTAL TABLE 1
Unadjusted and adjusted predictors of women being retained in the study for 6 months or more following attempted conception (n = 334) (continued)

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Male partner HIV status				
HIV negative	Reference		Reference	
HIV positive	1.28 (1.03—1.60)	.028	1.70 (1.01—2.86)	.047
Unknown	0.92 (0.56—1.53)	.758	1.30 (0.49—3.48)	.603
Weight, kg	1.00 (0.99—1.01)	.770		
Current or history of STI				
No	Reference			
Yes	0.91 (0.57—1.47)	.707		
Partner smoker				
No	Reference		Reference	
Yes	0.81 (0.64—1.04)	.098	0.74 (0.42—1.29)	.285
Any alcohol consumption by partner				
No	Reference		Reference	
Yes	0.80 (0.64—1.00)	.054	0.73 (0.44—1.23)	.242
History of TB				
No	Reference			
Yes	1.11 (0.86—1.44)	.429		
Partner reported erectile dysfunction				
No	Reference		Reference	
Yes	1.39 (1.09—1.77)	< .01	2.28 (0.92—5.66)	.074
Unprotected sex acts per month	1.02 (0.99—1.04)	.201		
Accompanied by partner in clinic				
Unaccompanied	Reference		Reference	
Accompanied	1.40 (1.13—1.73)	< .01	2.00 (1.20—3.32)	< .01
Reproductive history				
Number of live births				
0	Reference		Reference	
1	1.25 (0.97—1.62)	.083	2.05 (0.93—4.49)	.074
≥2	1.45 (1.12—1.88)	.005	3.03 (1.31—7.02)	.010
Previously been pregnant with current partner				
No	Reference			
Yes	1.17 (0.97—1.43)	.108		
History of abortion[c]				
No	Reference		Reference	
Yes	1.32 (1.00—1.75)	.053	2.14 (0.77—5.99)	.146
History of miscarriage[c]				
No	Reference			
Yes	0.94 (0.74—1.19)	.616		

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SUPPLEMENTAL TABLE 1

Unadjusted and adjusted predictors of women being retained in the study for 6 months or more following attempted conception (n = 334) (continued)

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*value	OR (95% CI)	*P*value
Age at menarche	0.98 (0.93—1.03)	.406		
Flow days in menstrual cycle	1.00 (0.93—1.07)	.971		
Missed or irregular period in the past three months				
No	Reference			
Yes	1.06 (0.83—1.35)	.632		
Tried to conceive for at least 1 year and failed				
No	Reference			
Yes	0.88 (0.72—1.09)	.242		

CI, confidence interval; *HAART*, highly active antiretroviral therapy; *OR*, odds ratio; *STI*, sexually transmitted infection; *TB*, tuberculosis.

[a] Among HIV-positive female clients (n = 291); [b] CD4 counts were available for 285 HIV-positive women; [c] Among clients who have a history of previous pregnancy (n = 256).

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SUPPLEMENTAL TABLE 2

Correlates of subfertility among women with 6 months of attempted conception, excluding couples who reported attempting to conceive unsuccessfully for 12 months prior to enrollment (n = 117)

Variables	RR (95% CI)	*P*value	RR (95% CI)	*P*value	RR (95% CI)	*P*value
Individual and partnership characteristics						
Female age	1.03 (1.00—1.06)	.052	1.04 (1.01—1.07)	< .001	1.04 (1.01—1.07)	.010
Employment status						
Unemployed	Reference					
Employed	1.00 (0.69—1.45)	.983				
Age difference between partners, y						
≤5	Reference					
>5	0.79 (0.57—1.12)	.186				
Length of relationship with current partner, y						
0—2	Reference					
≥2	0.98 (0.69—1.40)	.901				
Clinical and behavioral characteristics						
Female HIV status and HAART use						
HIV negative	Reference		Reference		Reference	
HIV positive, no HAART	3.57 (1.23—10.41)	.020	3.44 (1.28—9.27)	.015	2.82 (1.13—7.08)	.027
HIV positive, HAART 0—2 y	3.10 (1.09—8.79)	.034	2.80 (1.05—7.48)	.040	2.34 (0.94—5.85)	.068
HIV positive, HAART ≥2 y	2.72 (0.95—7.77)	.062	2.76 (1.03—7.38)	.044	2.10 (0.83—5.28)	.115

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SUPPLEMENTAL TABLE 2
Correlates of subfertility among women with 6 months of attempted conception, excluding couples who reported attempting to conceive unsuccessfully for 12 months prior to enrollment (n = 117) (continued)

Variables	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Male partner HIV status						
HIV negative/unknown	Reference		Reference		Reference	
HIV positive	1.05 (0.72—1.52)	.810	1.23 (0.86—1.76)	.263	1.32 (0.91—1.90)	.140
Weight, kg	1.00 (0.99—1.02)	.416				
Current or history of STI						
No	Reference					
Yes	1.05 (0.54—2.04)	.891				
Partner smoker						
No	Reference		Reference		Reference	
Yes	1.40 (1.01—1.94)	.043	1.29 (0.92—1.82)	.142	1.32 (0.91—1.93)	.149
Any alcohol consumption by partner						
No	Reference					
Yes	1.12 (0.79—1.59)	.522				
History of TB						
No	Reference					
Yes	1.14 (0.75—1.73)	.530				
Partner reported erectile dysfunction						
No	Reference					
Yes	0.65 (0.34—1.26)	.204				
Unprotected sex acts per month	1.05 (1.01—1.10)	.022	1.06 (1.01—1.11)	.029	1.06 (1.00—1.11)	.036
Accompanied by partner in clinic						
Unaccompanied	Reference					
Accompanied	0.82 (0.59—1.14)	.230				
Reproductive history						
Number of live births						
0	Reference		Reference		Reference	
1	0.93 (0.64—1.33)	.682	1.00 (0.72—1.40)	.987	0.95 (0.66—1.36)	.775
≥2	0.67 (0.43—1.04)	.075	0.56 (0.37—0.84)	< .001	0.55 (0.36—0.86)	< .01
Previously been pregnant with current partner						
No	Reference					
Yes	0.94 (0.67—1.32)	.739				
Reported history of abortion[a]						
No	Reference					
Yes	1.27 (0.81—2.00)	.295				

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SUPPLEMENTAL TABLE 2
Correlates of subfertility among women with 6 months of attempted conception, excluding couples who reported attempting to conceive unsuccessfully for 12 months prior to enrollment (n = 117) (continued)

Variables	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
History of miscarriage[a]						
No	Reference					
Yes	1.29 (0.89—1.85)	.178				
Age at menarche	0.96 (0.88—1.05)	.391				
Flow days in menstrual cycle	1.04 (0.89—1.21)	.657				
Missed or irregular period in the past 3 mo						
No	Reference		Reference		Reference	
Yes	1.21 (0.85—1.71)	.297	1.22 (0.85—1.74)	.273	1.16 (0.79—1.70)	.454

Models were estimated using robust Poisson regression. Weight-adjusted multivariable models apply inverse probability weighting.

CI, confidence interval; HAART, highly active antiretroviral therapy; OR, odds ratio; STI, sexually transmitted infection; TB, tuberculosis.

[a] Among clients who have a history of previous pregnancy (n = 145).

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SUPPLEMENTAL TABLE 3
Univariate, multivariate and weight adjusted multivariate correlates of subfertility among women with completed 6 months of attempted conception (n = 182), including couple HIV serostatus

Variables	Univariate RR (95% CI)	P value	Multivariate RR (95% CI)	P value	Weight-adjusted multivariate RR (95% CI)	P value
Individual and partnership characteristics						
Female age	1.03 (1.01—1.05)	< .01	1.03 (1.01—1.04)	.010	1.03 (1.01—1.05)	< .01
Employment status						
Unemployed	Reference					
Employed	0.95 (0.75—1.19)	.65				
HIV status within the partnership						
F (negative), M (positive)	Reference		Reference		Reference	
F (positive), M (positive)	1.84 (1.09—3.12)	.023	1.74 (1.08—2.79)	.022	1.78 (1.10—2.90)	.019
F (positive), M (negative) (unknown)	1.59 (0.92—2.74)	.096	1.36 (0.82—2.24)	.23	1.42 (0.85—2.38)	.18
Age difference between partners, y						
≤5	Reference		Reference		Reference	
>5	0.81 (0.65—1.02)	.072	0.87 (0.71—1.06)	.17	0.87 (0.70—1.06)	.17
Relationship duration with current partner, y						
0—2	Reference					
≥2	1.06 (0.82—1.39)	.65				
Clinical and behavioral characteristics						
Weight, kg	1.00 (0.99—1.01)	.90				
Current or history of STI						
No	Reference					
Yes	1.04 (0.65—1.67)	.88				
Partner smoker						
No	Reference		Reference		Reference	
Yes	1.27 (1.03—1.57)	.028	1.27 (1.02—1.57)	.030	1.26 (1.02—1.55)	.030
Any alcohol consumption by partner						
No	Reference					
Yes	1.03 (0.81-1.30)	.83				
History of TB						
No	Reference					
Yes	1.07 (0.80—1.41)	.66				
Partner reported erectile dysfunction						
No	Reference					
Yes	0.68 (0.42—1.09)	.11				
Unprotected sex acts per month	1.01 (0.97—1.06)	.54				
Accompanied by partner in clinic						
Unaccompanied	Reference					
Accompanied	0.95 (0.76—1.18)	.62				

Iyer et al. Subfertility among HIV-affected couples. Am J Obstet Gynecol 2019.   *(continued)*

SUPPLEMENTAL TABLE 3
Univariate, multivariate and weight adjusted multivariate correlates of subfertility among women with completed 6 months of attempted conception (n = 182), including couple HIV serostatus *(continued)*

Variables	Univariate RR (95% CI)	*P*value	Multivariate RR (95% CI)	*P*value	Weight-adjusted multivariate RR (95% CI)	*P*value
Reproductive history						
Number of live births						
0	Reference		Reference		Reference	
1	0.82 (0.65—1.03)	.085	0.95 (0.76—1.18)	.63	0.97 (0.77—1.23)	.83
≥2	0.67 (0.51—0.90)	< .01	0.78 (0.59—1.04)	.090	0.75 (0.56—1.01)	.062
Previously been pregnant with current partner						
No	Reference		Reference		Reference	
Yes	0.80 (0.63—1.02)	.072	0.93 (0.73—1.19)	.55	0.92 (0.72—1.17)	.48
History of abortion[a]						
No	Reference					
Yes	1.14 (0.79—1.63)	.48				
History of miscarriage[a]						
No	Reference					
Yes	1.11 (0.85—1.45)	.45				
Age at menarche	0.97 (0.92—1.03)	.36				
Flow days in menstrual cycle	1.02 (0.97—1.07)	.45				
Missed or irregular period in the past 3 months						
No	Reference		Reference		Reference	
Yes	1.10 (0.86—1.42)	.45	1.21 (0.92—1.57)	.17	1.18 (0.91—1.53)	.21
Tried to conceive for at least 1 year and failed						
No	Reference		Reference		Reference	
Yes	1.49 (1.22—1.82)	< .001	1.44 (1.19—1.75)	< .001	1.38 (1.13—.70)	< .01

Models were estimated using robust Poisson regression. Weight-adjusted multivariable models apply inverse probability weighting.

CI, confidence interval; *HAART*, highly active antiretroviral therapy; *OR*, odds ratio; *STI*, sexually transmitted infection; *TB*, tuberculosis.

[a] Among clients who have a history of previous pregnancy (n = 145).

Iyer et al. Subfertility among HIV-affected couples. Am J Obstet Gynecol 2019.