Contraception and HIV-1 prevention among women in Africa: informing choices amid expanding options

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Abstract

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Introduction

Options for both contraception and HIV-1 prevention are expanding in sub-Saharan Africa, offering important opportunities to provide women with products they need to achieve their prevention goals. Decision-making in the face of many options is complex, and we aimed to generate evidence to inform women's selection of contraception and HIV-1 prevention with the following specific aims: (1) evaluate the association between the increasingly-available copper intrauterine device (Cu-IUD) and a potential side effect, bacterial vaginosis (BV), and assess whether the association varies over time; (2.1) determine the association between reporting any receptive anal intercourse and HIV-1 risk and efficacy of a dapivirine intravaginal ring for HIV-1 prevention; (2.2) estimate the average per-exposure ring effect among women engaged in both vaginal and anal intercourse; and (3) develop and evaluate the predictive performance of age-specific HIV-1 risk scoring tools to optimize provision of HIV-1 prevention options to women at risk of HIV-1.

Methods

We used data from two large clinical trials conducted among women in sub-Saharan Africa, the ASPIRE trial of a dapivirine-containing intravaginal ring for HIV-1 prevention and the ECHO trial, which evaluated HIV-1 risk and contraceptive efficacy of three contraceptive methods. Primary statistical methods were proportional hazards models and a microsimulation mathematical model.

Results and conclusions

Risk of BV among Cu-IUD users: BV risk was 28% (95% CI: 12, 46) higher among Cu-IUD users than among women using no contraception or another non-hormonal method. Elevated BV risk persisted throughout Cu-IUD use and declined to pre-initiation levels within seven months to one year following discontinuation. Women and their providers may wish to consider BV risk when selecting contraception. Association between receptive anal intercourse (RAI) and HIV-1 risk and ring efficacy: RAI was not associated with HIV-1 acquisition (aHR: 0.93, 95% CI: 0.57, 1.54). The ring reduced HIV-1 risk by 25% (95% CI: -3, 55) among all women, by 27% (95% CI: -5, 49) among women reporting only vaginal intercourse, and by 18% (95% CI: -57, 57) among women reporting any RAI (interaction *p*-value=0.77), suggesting that RAI had a minimal impact on estimates of ring efficacy. Per-exposure ring effect among women engaged in both vaginal and anal intercourse: Among women with high adherence engaged in RAI for 6.3% of their acts (the median proportion among women engaged in both vaginal and anal intercourse), the per-exposure ring effect was 56% (IQR: 40, 63) and declined to 25% (IQR: 11, 37) among women for whom 30% of acts were RAI. The ring provides substantial overall risk reduction to the vast majority of women, supporting ring use for most women. HIV-1 predictive performance of age-specific risk scores: Both age-specific and non-age-specific risk scores had moderate HIV-1 predictive performance among women enrolled in a clinical trial in South Africa. Precision public health approaches for targeted PrEP provision in South Africa may require additional data to improve prediction.

Availability of both the Cu-IUD and an intravaginal ring are important additions to help women achieve their contraception and HIV-1 prevention goals, as both have important advantages compared to

currently available options. Counseling approaches to help women select the prevention methods that will best suit their values and preferences are needed as options expand, as well as complementary risk reduction strategies to mitigate the disadvantages of each method.

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Chapter 1. Introduction

Despite declining HIV-1 incidence, there were approximately 1.1 million new infections in sub-Saharan Africa in 2018, with women aged fifteen and above accounting for a disproportionate number of incident infections [1]. Among this same population of reproductive-aged women in sub-Saharan Africa, there is a large unmet need for contraception, with no contraceptive use among as many as one in five women who express a desire to delay future childbearing or to not have further children [2]. To address the dual needs for contraception and HIV-1 prevention among this population, expanded options and availability of prevention products are needed. To this end, oral pre-exposure prophylaxis (PrEP), a biomedical HIV-1 prevention method with greater than 90% efficacy when used with high adherence [3], was introduced widely in 2017 in Kenya [4] and South Africa [5] and an intravaginal dapivirine-containing ring shown to be safe and effective [6, 7] is under regulatory review for potential future availability [8]. Additionally, the contraceptive method mix in sub-Saharan Africa is expanding, with increases of up to 400% in use of the copper intrauterine device (Cu-IUD) and the recently available hormonal implant [9]. In the cases of prevention of both HIV-1 and pregnancy, women's prevention preferences reflect a complex set of considerations, including efficacy and side effects, among others [10-16]. To contribute to the knowledge base underpinning these considerations and thereby inform decision-making among women and their providers in light of expanding options, this dissertation aims to (1) estimate the association between the increasingly-available Cu-IUD and a potential side effect of Cu-IUD use, bacterial vaginosis (BV), (2) evaluate the potential role of receptive anal intercourse (RAI) in efficacy dilution of a dapivirine-containing intravaginal ring for HIV-1 prevention, as well as overall ring effectiveness among women engaged in both receptive vaginal and anal intercourse, and (3) optimize identification of women who could most benefit from HIV-1 prevention through development and evaluation of age-specific HIV-1 risk scoring tools.

In recent research in the United States, approximately half to three-quarters of women cited side effects as a top-three consideration in their selection of a contraceptive method [15, 16], and approximately one in four women with unmet contraception need in low- and middle-income countries choose not to use contraception due to side effect concerns [17]. The copper IUD (Cu-IUD), a highly-effective and widely-

used method, has several well-documented side effects, including increased menstrual cramping and increased volume and duration of menses [18], yet its association with incident reproductive tract infections is less clear. Research to evaluate the association between Cu-IUD use and BV has been mixed, and generally of poor quality, consisting primarily of cross-sectional studies [19-21]. To date, a single longitudinal study of high quality has demonstrated an increased risk of BV among Cu-IUD users [22]. BV is common among the target population of prospective Cu-IUD users, affecting about one in four women of reproductive age [23]. Understanding the relationship of Cu-IUD and BV is particularly important in sub-Saharan Africa, given the high burden of HIV-1 and sexually transmitted infections (STI) in this region, and the potentially causal association between BV and incident HIV-1 and STIs [24-27]. In Chapter 2, we therefore aimed to add to information women and their providers have regarding potential side effects of the Cu-IUD by further investigating the relationship between Cu-IUD and BV.

Aim 1: Estimate the association between Cu-IUD use and risk of BV, and evaluate if this association varies over time.

Hypotheses: Cu-IUD use will be associated with a higher risk of BV. BV risk will decline with increasing duration of Cu-IUD use.

Approach: We conducted a prospective cohort analysis to (1) compare the hazard of BV among women using Cu-IUD, relative to women using no contraception or an alternative contraceptive method, and (2) test changes in BV frequency prior to, while using, and following discontinuation of Cu-IUD.

Oral PrEP is the first female-initiated HIV-1 prevention product, offering an important prevention tool to women in the context of limited ability to negotiate condom use [28, 29]. However, women continue to face challenges in accessing and using PrEP due to concerns such as a high pill burden, community acceptability, and prevailing relationship and gender norms [29, 30]. Intravaginal prevention products are private, discreet, and do not require daily action, providing a potential alternative to women for whom oral PrEP is not a good fit. While these products offer discretion and convenience, intravaginal products tested

to-date have minimal cross-compartmental dissemination of drug to the rectum [31, 32], thereby offering suboptimal protection to the approximately 5-17% of women who engage in receptive anal intercourse (RAI) in Eastern and Southern Africa [33-35]. The MTN-020/ASPIRE and Ring trials evaluated the efficacy of a dapivirine-containing intravaginal ring for HIV prevention, finding efficacy of 27% [6] and 31% [7], respectively, considerably lower than intent-to-treat estimates of oral PrEP efficacy [36]. Prior analyses of ASPIRE data established non-adherence as a behavioral factor that limited efficacy estimates obtained in the primary modified intent-to-treat analysis [37], and theoretical modeling suggests the potential for RAI to undermine the effectiveness of such products [38, 39]. There is a need to understand if RAI contributed to reduced estimates of ring efficacy, as well as ring effectiveness among women who engage in any RAI, to aid women and their providers in their selection of the prevention product that best meets a woman's preferences, context, and sexual lifestyle. In Chapters 3 and 4, we therefore investigated the following aims:

Aim 2.1: Describe demographic and behavioral correlates of women who report engaging in RAI and evaluate the association between RAI and (1) HIV-1 risk and (2) dapivirine ring efficacy.

Hypothesis: RAI will be significantly associated with both increased HIV-1 risk and reduced dapivirine ring efficacy.

Approach: Women reported any RAI by audio computer-assisted self-interview at enrollment and month three of follow-up in the ASPIRE trial. We used Cox proportional hazards models to evaluate the association between engaging in any RAI and (1) HIV-1 risk and (2) dapivirine ring efficacy.

Aim 2.2: Estimate the average per-exposure ring effect among women engaged in any RAI.

Hypotheses: Average per-exposure ring effectiveness among women engaged in any RAI will be lower than among women engaged in exclusively vaginal intercourse.

Approach: We developed a microsimulation model replicating the participants, procedures, and outcomes of the ASPIRE trial to estimate the average per-exposure ring effect among women engaged in both vaginal and anal intercourse.

Finally, as availability of biomedical HIV-1 prevention expands in sub-Saharan Africa, approaches that target PrEP provision to those at highest risk will ensure maximal impact in the context of limited resources. The PrEP implementation frameworks of both Kenya and South Africa target PrEP provision to geographic areas with the highest HIV-1 incidence and to key populations [4, 5]. Risk scoring tools offer an additional approach to refine PrEP targeting by identifying a discrete set of factors that characterize those at highest risk. The VOICE risk scoring tool for women aged 18-45 was developed and externally validated in three cohorts of women in sub-Saharan Africa with moderate predictive performance [40, 41]. However, recent research suggests that this tool may not perform well among adolescent girls and young women [42], a population that experiences particularly high HIV-1 incidence [1], suggesting that a different set of risk factors may best predict HIV-1 acquisition in this population. In Chapter 5, we evaluated the added benefit of age-specific risk scoring tools, compared to the existing non-age-specific VOICE risk scoring tool for women.

Aim 3: Develop and evaluate the predictive performance of age-specific HIV-1 risk scoring tools among women aged 18-24 and 25-35, compared to a non-age-specific HIV-1 risk scoring tool for women aged 18-45.

Hypotheses: The components of age-specific risk scoring tools will vary by age, and age-specific risk scoring tools will improve HIV-1 prediction among women.

Approach: Using data from a large prospective clinical trial among women seeking effective contraception, we used standard methods for development of clinical decision rules to develop and internally validate risk scoring tools for women aged 18-24 and 25-35. We compared the predictive performance, characterized by calibration and discrimination, of these tools to a risk scoring tool for women aged 18-45.

Thus, with these three aims, we intended to generate evidence to inform women's selection of contraception and HIV-1 prevention methods, contributing to an overarching public health objective of supporting women to achieve their prevention goals.

Chapter 2. The association between copper intrauterine device use and bacterial vaginosis

Elevated Risk of Bacterial Vaginosis among Users of the Copper Intrauterine Device: A Prospective Longitudinal Cohort Study

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Summary: In this prospective cohort analysis, women using copper intrauterine device (Cu-IUD) contraception experienced 1.28-fold ($p<0.001$) elevated risk of BV. This elevated risk persisted through eighteen months of use ($p<0.05$), and declined to pre-initiation risk levels following Cu-IUD discontinuation.

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Abstract

BACKGROUND. Limited evidence suggests that copper intrauterine device (Cu-IUD) use may increase BV risk, possibly due to increased volume and duration of menses, a common side effect of Cu-IUD use. While increases in bleeding typically resolve within 6-12 months following initiation, evaluations of the association between Cu-IUD and BV have not included more than six months of follow-up.

METHODS. This secondary analysis of the MTN-020/ASPIRE trial included 2,585 HIV-1-negative African women ages 18-45 followed for up to 33 months. Women reported contraceptive use at monthly visits. BV was evaluated by Nugent score in six-monthly intervals and, if clinically indicated, by Amsel's criteria. Andersen-Gill proportional hazards models were used to (1) evaluate BV risk among Cu-IUD users relative to women using no/another non-hormonal contraceptive and (2) test changes in BV frequency before, while using, and following Cu-IUD discontinuation.

RESULTS. BV frequency was highest among Cu-IUD users at 153.6 episodes per 100 person-years (95% CI: 145.2, 162.4). In adjusted models, Cu-IUD users experienced 1.28-fold (95% CI: 1.12, 1.46) higher BV risk relative to women using no/another non-hormonal contraception. Compared to the six months prior to initiation, BV risk was 1.52-fold (95% CI: 1.16, 2.00) higher in the first six months of Cu-IUD use and remained elevated over eighteen months of use ($p<0.05$). Among women who discontinued Cu-IUD, BV frequency was similar to pre-initiation rates within one year.

CONCLUSIONS. Cu-IUD users experienced elevated BV risk that persisted throughout use. Women and their providers may wish to consider BV risk when discussing contraceptive options.

Introduction

Bacterial vaginosis (BV) is the most common vaginal infection among women of reproductive age [43] and is associated with multiple adverse outcomes, including pelvic inflammatory disease [44], preterm birth [45], and increased risk of acquisition and transmission of HIV-1 [26, 46] and other sexually transmitted infections [27]. Among this same population of reproductive-aged women, use of long-acting reversible contraception (LARC) is increasing, particularly in sub-Saharan Africa, where use of progestin-only implants and copper intrauterine devices (Cu-IUD) has increased four-fold over the previous decade [9].

Previous research has established a reduced risk of BV among women using either combined hormonal contraception containing both estrogen and progestins or progestin-only contraception [47, 48]. However, there are limited data on the effect of the non-hormonal Cu-IUD on BV risk. Cross-sectional studies of the association between Cu-IUD use and BV prevalence have reported mixed results [19, 20], as have two prior longitudinal studies. One prior longitudinal study did not find a statistically significant association between BV incidence and use of either Cu-IUD or a levonorgestrel intrauterine system, although an underpowered exploratory analysis suggested an increased risk of BV among women who reported irregular bleeding while using either method [21]. An additional study specifically designed to evaluate changes in prevalence of BV across contraceptive methods identified a nearly two-fold increase in prevalence of BV at six months following initiation of Cu-IUD (p=0.005) [22].

Two mechanisms of action have been proposed through which Cu-IUD may increase risk of BV. First, the presence of a foreign body in the uterus and vagina may facilitate the overgrowth of the mixed facultative and anaerobic bacteria associated with BV [21]. Second, the relative abundance of *Gardnerella vaginalis* and *Lactobacillus* species morphotypes fluctuates throughout the normal menstrual cycle, with an increase in *Gardnerella vaginalis* and decrease in *Lactobacillus* species during menses [49]. Cu-IUD initiation is typically accompanied by an increased volume and duration of menses [50, 51], potentially allowing preferential shedding of *Lactobacillus* species and heme-stimulated growth of *Gardnerella vaginalis* during this time [49] to persist to the point of dysbiosis.

Prior longitudinal investigations of the association between Cu-IUD use and BV risk have included up to six months of follow-up time [21, 22], while bleeding patterns following Cu-IUD insertion show that initial increases in volume and duration of menses decline over six months to one year after Cu-IUD initiation [50, 51]. Should changes in bleeding patterns form a part of the biological mechanism through which Cu-IUD use increases BV risk, longer periods of follow-up time are needed to evaluate a potential time-varying effect of Cu-IUD on BV risk.

We therefore conducted a secondary analysis of data collected as part of a phase III biomedical HIV prevention trial. Within the trial, a Contraceptive Action Team (CAT) was formed to scale up access to LARC methods [52]. These efforts to expand the contraceptive method mix provided a unique opportunity to (1) evaluate the association between current Cu-IUD use and BV frequency relative to women using no contraception or a non-hormonal method other than Cu-IUD, and (2) among new Cu-IUD users, assess changes in BV frequency prior to Cu-IUD initiation, during up to 18 months of use, and following discontinuation.

Methods

We conducted a secondary analysis of data from the MTN-020/ASPIRE trial, a placebo-controlled, double-blind, randomized clinical trial of the HIV-1 prevention efficacy of a dapivirine-containing intravaginal ring; detailed trial methods have been published previously [6]. Briefly, 2,629 HIV-1-negative, healthy, sexually active women aged 18-45 were enrolled from 2012 to 2015 from Malawi, South Africa, Uganda, and Zimbabwe. Institutional review boards at each study site approved the study protocol and all participants provided written informed consent. Analyses here include 2,585 (98.3%) women confirmed to be HIV-1-negative at enrollment and with complete baseline data.

At study enrollment, participants were required to use an effective contraceptive method, including LARC methods (progestin-only implants, Cu-IUD), short-acting reversible contraceptives (SARC), including oral contraceptive pills (OCP) and the injectables intramuscular depot medroxyprogesterone acetate (DMPA-IM) and norethisterone enanthate (NET-EN), or tubal ligation. Throughout follow-up,

women could choose a new contraceptive method or discontinue contraception at any time. Contraceptive method use was determined by either onsite provision of contraception, review of participant's family planning records, and/or ascertained per participant self-report at monthly study visits.

Vaginal swabs for BV evaluation by Nugent score [53] were collected at enrollment and every six months thereafter. Additionally, clinical evaluation of BV by Amsel's criteria [54] was performed at any visit if clinically indicated, with treatment provided for clinical BV per the local standard of care. At enrollment, demographic data were collected and women were evaluated for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and syphilis. Women reported intravaginal practices (insertion of soap or water; paper, cloth, tissue, rags, or cotton wool; products to make the vagina dry or tight) in the prior three months by audio computer-assisted self-interview at enrollment and the three-month follow-up visit. Circumcision status of primary partners and sexual behavior data over the prior three months were collected in standardized surveys at enrollment and quarterly thereafter. Urine pregnancy tests and HIV-1 serologic tests were performed monthly. Participants reported unexpected heavy menstrual bleeding and/or intermenstrual bleeding as part of clinical trial adverse event reporting requirements.

We compared participant characteristics at enrollment across contraceptive methods with Cochran-Maentel-Haenzel chi-square tests stratified by site for categorical variables and from analysis of variance adjusted for site for continuous variables. We used Andersen-Gill proportional hazards models with robust standard errors to evaluate the association between Cu-IUD use and BV frequency (including recurrent episodes), relative to women using no contraceptive or a non-hormonal contraceptive method other than Cu-IUD. Andersen-Gill models assume each BV episode is independent, with robust standard errors accounting for intra-individual correlation in events over time. Women were censored at HIV-1 seroconversion or first pregnancy. In our primary analysis, a time-varying, single contraceptive method exposure is defined as the method most recently initiated and BV end points include both regularly-scheduled BV evaluations as well as interim BV evaluations diagnosed by either Nugent score or Amsel's criteria. We additionally report results for a model including only regularly-scheduled BV evaluations. We conducted two sensitivity analyses to account for simultaneous exposure to additional exogenous

hormones. First, we included an interaction term between current contraceptive method and recent exposure to an alternative hormonal contraceptive to account for overlap in contraceptive exposures following a method switch. Recent exposure was defined as within the prior 17 weeks for DMPA-IM and the prior 10 weeks for NET-EN. Second, some women reporting heavy and intermenstrual bleeding were prescribed additional estrogen and/or progestins to reduce excess bleeding. The second sensitivity analysis includes an interaction term between current contraceptive method and concomitant use or use within the prior 30 days of additional exogenous hormones. Finally, there may be residual confounding when using a reference group of women using no contraception or a non-hormonal contraceptive method other than Cu-IUD. We therefore conducted additional analyses using hormonal implant, OCP, and DMPA-IM users as referents. We used Andersen-Gill proportional hazards models with robust standard errors to evaluate changes in BV frequency prior to Cu-IUD initiation, while using, and following discontinuation. For all Andersen-Gill models, we evaluated the appropriateness of the proportional hazards assumption with tests of independence between time and Schoenfeld residuals. All models are stratified by study site and adjusted for variables hypothesized *a priori* to be confounders or expected to increase the precision of our analysis, including a new primary sex partner, number of sex partners, condom use at last vaginal sex, circumcision status of the primary partner, and any intravaginal practices reported at baseline and/or month three. Quarterly values of retrospective data were carried backward. All analyses were performed in R 3.5.0 [55].

Results

At study enrollment, injectable contraceptive methods were used by over half of women (1,412, 54.6%), followed by hormonal implants (492, 19.0%), Cu-IUD (323, 12.5%), OCP (280, 10.8%), and women with a tubal ligation (78, 3.0%). Compared to women using a SARC, women using a LARC or with tubal ligation were somewhat older, more likely to be married, less likely to have completed secondary education, and less likely to test positive for *C. trachomatis* at enrollment (Table 1). Enrollment contraceptive use additionally varied by country, with relatively low prevalence of Cu-IUD (5.5%) and

hormonal implant use (1.4%) at enrollment in South Africa, reflecting low background use of these methods and delayed access to LARC methods in South Africa within the trial.

Contraceptive method switching was common, with 1,003 (38.8%) women switching from their enrollment method at some point during trial participation. Among women who switched from their baseline method, 298 (29.7%) switched to Cu-IUD (Supplement Figure 1). Continuation rates for Cu-IUD were high, with only 22% of women using Cu-IUD at baseline switching to a different method (Table 2). Throughout study follow-up, 619 (23.9%) women ever used Cu-IUD, 803 (31.1%) ever used a hormonal implant, 520 (20.1%) ever used OCP, 1,185 (45.8%) ever used DMPA-IM, 477 (18.5%) ever used NET-EN, and 262 (10.1%) ever used another non-hormonal method (including tubal ligation, male and female condoms, and spermicide) or no contraception.

Women contributed 9,552 BV evaluations, of which 93.9% were regularly-scheduled evaluations and 3.9% were interim evaluations prompted by reported BV symptoms and conducted by Amsel's criteria (the remainder were interim Nugent score evaluations). BV was common among trial participants at 101.6 episodes (95% CI: 98.5, 104.7) per 100 person-years, ranging from 69.1 (95% CI: 64.9, 73.6) per 100-person years among DMPA-IM users to 153.6 (95% CI: 145.2, 162.4) per 100 person-years among Cu-IUD users (Supplement Table I). In adjusted models, BV risk among Cu-IUD users was 1.28-fold (95% CI: 1.12, 1.46) higher than among women using no contraception or another non-hormonal contraceptive method (Figure I). In contrast, DMPA-IM and NET-EN users had lower risk of BV (HR: 0.65, 95% CI: 0.56, 0.74; HR: 0.74, 95% CI: 0.63, 0.86, respectively), while hormonal implant and OCP users did not have significantly different BV risk compared to women using no contraception or another non-hormonal contraceptive method (HR: 0.94, 95% CI: 0.82, 1.07; HR: 0.95, 95% CI: 0.81, 1.12, respectively) (Figure I). Results were similar in sensitivity analyses in which models included only regularly-scheduled BV evaluations, accounted for recent exposure to an alternative hormonal contraceptive, or accounted for concomitant use of additional exogenous hormones to treat excess bleeding (Figure I). The pattern of hazard ratios was also consistent across analyses with reference groups of women using implant, OCP, and DMPA-IM (Supplement Table II).

Among 298 women who initiated Cu-IUD during ASPIRE, use of DMPA-IM was most common in the six months prior to Cu-IUD initiation (147, 49.3%), followed by NET-EN (69, 23.2%), OCP (63, 21.1%), progestin-only implant (35, 11.7%), or no/another non-hormonal contraceptive method (5; 1.7%). BV frequency in the six months prior to Cu-IUD initiation was 89.7 episodes (95% CI: 70.1, 113.1) per 100 person-years, and increased to 136.6 episodes (95% CI: 117.3, 158.2) per 100 person-years in the first six months following Cu-IUD initiation and remained elevated for up to 18 months of use (Figure IIA). In adjusted models, the hazard of BV was significantly higher following Cu-IUD initiation over 18 months of use (all $p<0.05$; Figure IIA). When including only regularly-scheduled BV evaluations, the number of BV episodes at all time points was somewhat lower and hazard ratios of BV following initiation relative to the six months prior to Cu-IUD initiation were attenuated (Figure IIA).

Seventy-four new Cu-IUD users subsequently discontinued Cu-IUD during ASPIRE participation. In the six months following discontinuation, women used OCP (28; 37.8%), implant (26; 35.1%), DMPA-IM (18; 24.3%), NET-EN (16, 21.6%) or no/another non-hormonal method (15; 20.3%). Among 70 women who reported a reason for Cu-IUD discontinuation, the primary side effect-related reasons were excessive bleeding (25, 35.7%) and increased menstrual pain (12, 17.1%), while only one woman (1.4%) reported recurrent genital symptoms as a reason for Cu-IUD discontinuation. Following discontinuation, BV frequency declined from 155.6 episodes (95% CI: 143.0, 169.0) per 100 person-years during use to 143.9 episodes (95% CI: 104.0, 193.2) per 100 person-years in the six months following discontinuation and 100.4 episodes (95% CI: 64.5, 150.3) per 100 person-years in the seven to 12 months following discontinuation. In adjusted models, frequency of BV following Cu-IUD discontinuation was not significantly different from frequency in the six months prior to initiation (Figure IIB). Results were similar in a model including only regularly-scheduled BV evaluations (Figure IIB).

In adverse event reporting, incidence of unexpected heavy menstrual bleeding was similar in the six months prior to Cu-IUD initiation as in the six months following Cu-IUD initiation, with declining incidence over the subsequent year (Figure III). Incidence of unexpected intermenstrual bleeding declined

from the six months prior to initiation relative to the first six months following initiation, and continued to decline over the following twelve months (Figure III).

Discussion

In this large prospective analysis, Cu-IUD users experienced a 28% increased risk of bacterial vaginosis, relative to women using either no contraception or an alternative non-hormonal method. This finding was robust to multiple sensitivity analyses and adds to a growing body of literature demonstrating an elevated risk of BV among Cu-IUD users [22, 56]. These analyses additionally suggest that BV risk remains elevated through up to eighteen months of Cu-IUD use and demonstrate that BV risk returns to pre-initiation levels following Cu-IUD discontinuation. Given this elevated risk, women and their contraceptive providers may wish to consider BV risk when discussing contraception options.

The Contraceptive Action Team within ASPIRE scaled up access to long-acting reversible contraceptives for study participants, with high initiation and continuation rates of these methods [57]. Similarly, there is a need to increase the contraceptive method mix to meet the diverse needs and preferences of women in sub-Saharan Africa, with provision of Cu-IUD included as part of this expansion. However, BV is associated with multiple adverse outcomes, regardless of symptomatology [26, 27, 43-46]. In particular, in regions of high HIV-1 prevalence, where BV may account for 15% of new HIV-1 infections [58], BV risk may be an especially important consideration when selecting contraceptives. The levonorgestrel intrauterine system (LNG-IUS) may be a preferable alternative for some women, as several longitudinal studies have shown either no significant changes in the composition of the vaginal microbiota among LNG-IUS users [59, 60], or a short-term increase in BV risk immediately following initiation, with a return to pre-initiation risk within one year [61]. However, as the LNG-IUS remains largely unavailable in sub-Saharan Africa, there were no users of the LNG-IUS in the present study, and so we were unable to evaluate the association between LNG-IUS and BV in this population.

Women using Cu-IUD experienced consistently elevated BV risk over eighteen months of use, relative to the six months prior to Cu-IUD initiation. Over the same time period following Cu-IUD

initiation, adverse event reports of unexpected heavy and intermenstrual bleeding declined, consistent with prior literature showing declining incidence of bleeding side effects in the six to twelve months following Cu-IUD insertion [50, 51]. Taken together, this suggests that heavy and intermenstrual bleeding secondary to Cu-IUD use may not mediate the association between Cu-IUD and increased BV incidence. However, adverse events of heavy and intermenstrual bleeding in ASPIRE were reported only when the change in bleeding was unexpected; systematic evaluation of bleeding patterns across methods can provide the data needed to formally evaluate a potentially mediating role of bleeding-related side effects in the relationship between Cu-IUD and BV incidence. Furthermore, while prior literature has established adhesion of *Candida* species to Cu-IUD [62], research is limited demonstrating increasing diversity and quantity of adhered microbes to Cu-IUD *in situ* with increasing duration of use [63]. Additional research is needed to investigate the biological mechanism that underlies the association between Cu-IUD use and BV risk.

Our estimates of the effect of DMPA-IM and NET-EN are consistent with prior literature [47, 48], and our analyses additionally replicate findings [22] showing no association between the progestin-only implant and BV frequency, consistent with the relatively small quantity of hormone released by this method [64, 65]. Analyses of the effect of oral contraceptives showed no association with BV risk in this cohort, in contrast to prior literature [47, 48]. Pregnancy incidence among women who reported OCP use was 30.2 per 100 woman-years [66], several times higher than typical use failure rates [14], indicating that exogenous hormonal exposure was lower in our group of oral contraceptive users than in other studies, perhaps resulting in a null association.

There are several limitations to the analyses presented here. Our comparison of BV frequency prior to initiation and while using Cu-IUD is limited by the presence of exogenous hormones prior to initiation, as women typically used a hormonal contraceptive method prior to Cu-IUD use. Estimates of the hazard of BV while using Cu-IUD relative to pre-initiation are likely higher than would be observed in the absence of additional exogenous hormones. Furthermore, the contraceptive method mix following Cu-IUD discontinuation was more likely to include methods not associated with BV frequency in this cohort, while the method mix in the six months prior to initiation was predominantly made up of methods associated with

lower BV frequency. As a result, our estimate of the hazard of BV following Cu-IUD discontinuation relative to the six months prior to initiation may be higher than would be observed with a more comparable contraceptive method mix in both pre-initiation and following discontinuation. Finally, BV was evaluated infrequently, precluding a test-of-cure to define incident BV. However, 60% of asymptomatic BV cases resolve within six months [67], suggesting that the majority of recurrent episodes are incident cases. More frequent evaluation of BV would allow for more precise description of the pathogenesis of BV in relation to Cu-IUD use.

In conclusion, Cu-IUD users experienced a 1.28-fold increase in the risk of BV, relative to women using no contraception or another non-hormonal method. The elevated risk of BV persisted through up to eighteen months of Cu-IUD use, with BV frequency declining to pre-initiation rates within one year of discontinuation. Women and their providers may wish to consider BV risk when discussing contraceptive options.

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Table I. Baseline participant characteristics by contraceptive method used at study enrollment.

	Cu-IUD *n* = 323 (12.4%)	**Implant** *n* = 492 (19.0%)	**OCP** *n* = 280 (10.8%)	**DMPA-IM** *n* = 1,044 (40.4%)	**NET-EN** *n* = 368 (14.2%)	**Tubal ligation** *n* = 78 (3.0%)	*p*[a]
Age, median (IQR)	28 (24, 33)	28 (24, 32)	25 (21, 31)	26 (22, 30)	24 (21, 28)	36 (33, 39)	< 0.001
Currently married, *n* (%)	184 (57.0)	396 (80.5)	52 (18.6)	368 (35.2)	19 (5.2)	47 (60.3)	< 0.001
Secondary school education or higher, *n* (%)	261 (80.8)	376 (76.4)	259 (92.5)	881 (84.4)	359 (97.6)	49 (62.8)	0.028
Current smoking, *n* (%)	7 (2.2)	5 (1.0)	16 (5.7)	58 (5.6)	25 (6.8)	4 (5.1)	0.531
Number of prior pregnancies, median (IQR)	2 (1, 3)	3 (2, 3)	1 (1, 2)	2 (1, 3)	1 (1, 2)	4 (3, 4)	< 0.001
Number of live births, median (IQR)	2 (1, 3)	2 (2, 3)	1 (0, 2)	2 (1, 2)	1 (0, 2)	4 (3, 4)	< 0.001
Sexually transmitted infection, *n* (%)							
Chlamydia trachomatis	25 (7.7)	42 (8.5)	34 (12.1)	140 (13.4)	62 (16.8)	3 (3.8)	0.037
Neisseria gonorrhoeae	13 (4.0)	26 (5.3)	12 (4.3)	41 (3.9)	12 (3.3)	5 (6.4)	0.614
Trichomonas vaginalis	26 (8.0)	41 (8.3)	23 (8.2)	57 (5.5)	25 (6.8)	6 (7.7)	0.336
Syphilis	4 (1.2)	13 (2.6)	5 (1.8)	17 (1.6)	0 (0.0)	0 (0.0)	0.164
Two or more sexual partners, *n* (%)	71 (22.0)	66 (13.4)	57 (20.4)	170 (16.3)	55 (14.9)	12 (15.4)	0.332
Condom used at last sex, *n* (%)	177 (54.8)	231 (47.0)	193 (68.9)	589 (56.4)	247 (67.1)	35 (44.9)	0.060
Primary sex partner circumcised, *n* (%)	123 (38.1)	126 (25.6)	125 (44.6)	459 (44.0)	215 (58.4)	32 (41.0)	0.029

[a] *p*-values are obtained from Cochran-Maentel-Haenzel chi-square tests stratified by site for categorical variables and from analysis of variance adjusted for site for continuous variables.

Cu-IUD = copper intrauterine device; DMPA-IM = intramuscular depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; OCP = oral contraceptive

Table II. Contraceptive method discontinuation and duration of use during trial participation.

	Cu-IUD *n* = 323 (12.5%)	**Implant** *n* = 492 (19.0%)	**OCP** *n* = 280 (10.8%)	**DMPA-IM** *n* = 1,044 (40.4%)	**NET-EN** *n* = 368 (14.2%)	**None/other non-hormonal**[a] *n* = 78 (3.0%)
Switched from baseline method, *n* (%)	71 (22.0)	97 (19.7)	169 (60.4)	441 (42.2)	225 (61.1)	0 (0.0)
Time to method switch (months), median (IQR)[b]	9.2 (5.2, 14.8)	8.2 (5.5, 12.9)	4.0 (2.0, 7.2)	7.4 (3.6, 14.7)	7.8 (3.9, 13.7)	--
Duration of method use (months), median (IQR)[c]	16.4 (9.9, 22.0)	11.0 (7.4, 18.2)	5.6 (2.8, 10.4)	13.6 (6.5, 21.2)	11.4 (5.2, 19.2)	5.5 (1.3, 16.6)

[a] At baseline, includes only women with tubal ligation. At follow-up, includes all women using no contraceptive method or another non-hormonal contraceptive method.

[b] Estimated from among women who switched their baseline contraceptive method.

[c] Estimated from among women who used the method at any time during ASPIRE participation.

Cu-IUD = copper intrauterine device; DMPA-IM = intramuscular depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; OCP = oral contraceptive

Figure I. Hazard ratio of bacterial vaginosis (BV) by contraceptive method, relative to women using no contraception or a non-hormonal contraceptive method other than copper intrauterine device (Cu-IUD). Analyses were conducted including (1) all BV evaluations, (2) only regularly-scheduled BV evaluations, (3) estimated hazard ratio for those without recent exposure to an alternative hormonal contraceptive, and (4) estimated hazard ratio for those without current or recent concomitant additional hormonal medication use to treat heavy and/or intermenstrual bleeding. The proportional hazards assumption was appropriate for all models.
Cu-IUD = copper intrauterine device; DMPA-IM = intramuscular depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; OCP = oral contraceptive

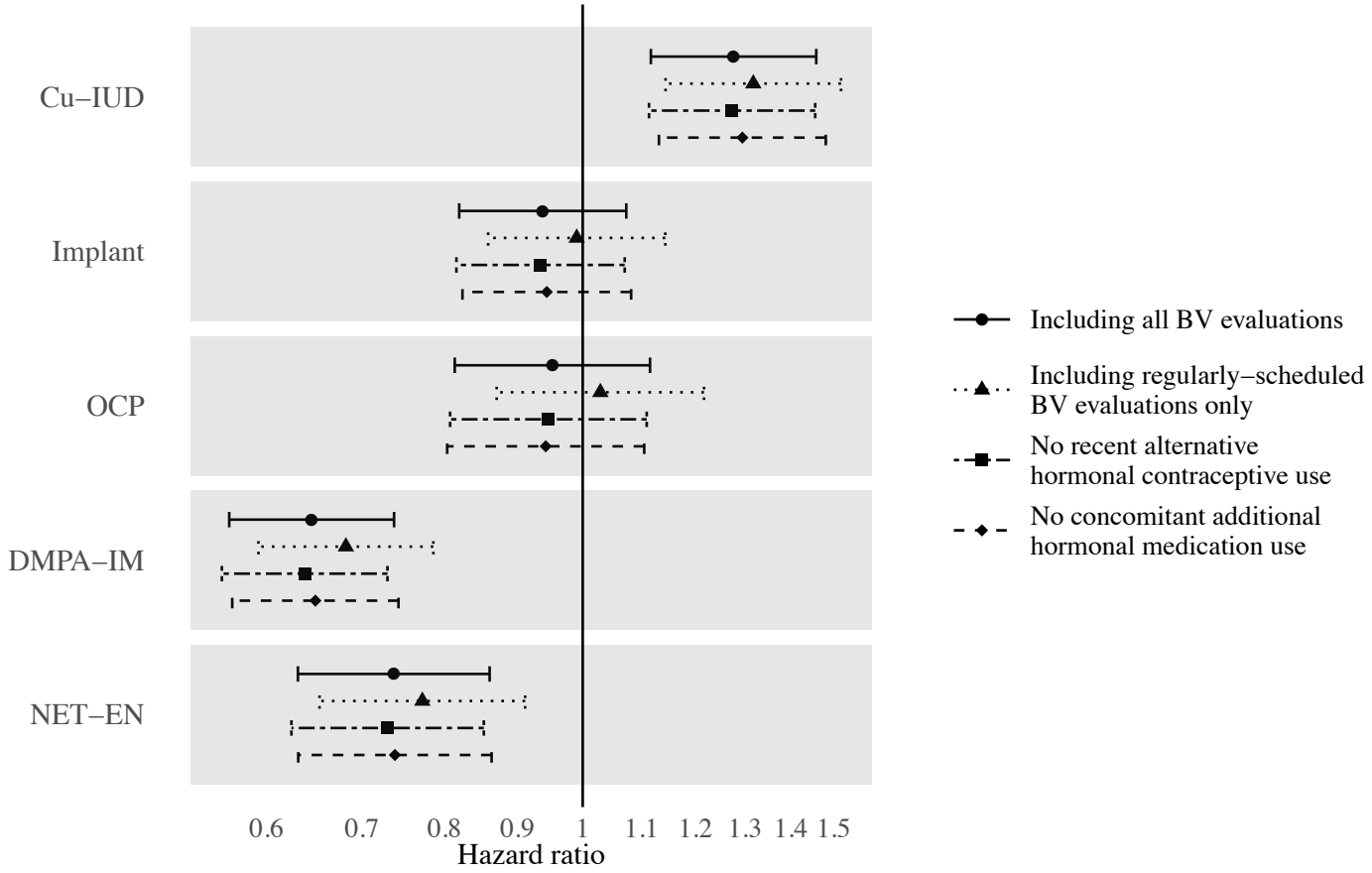
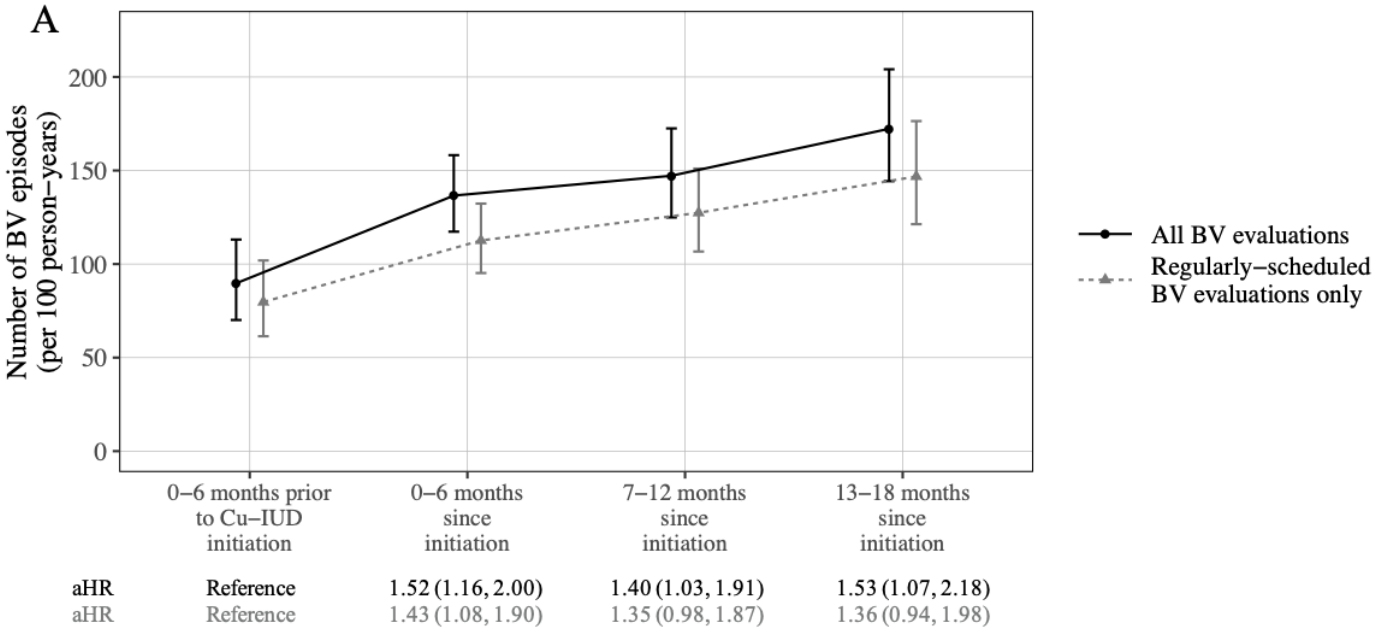
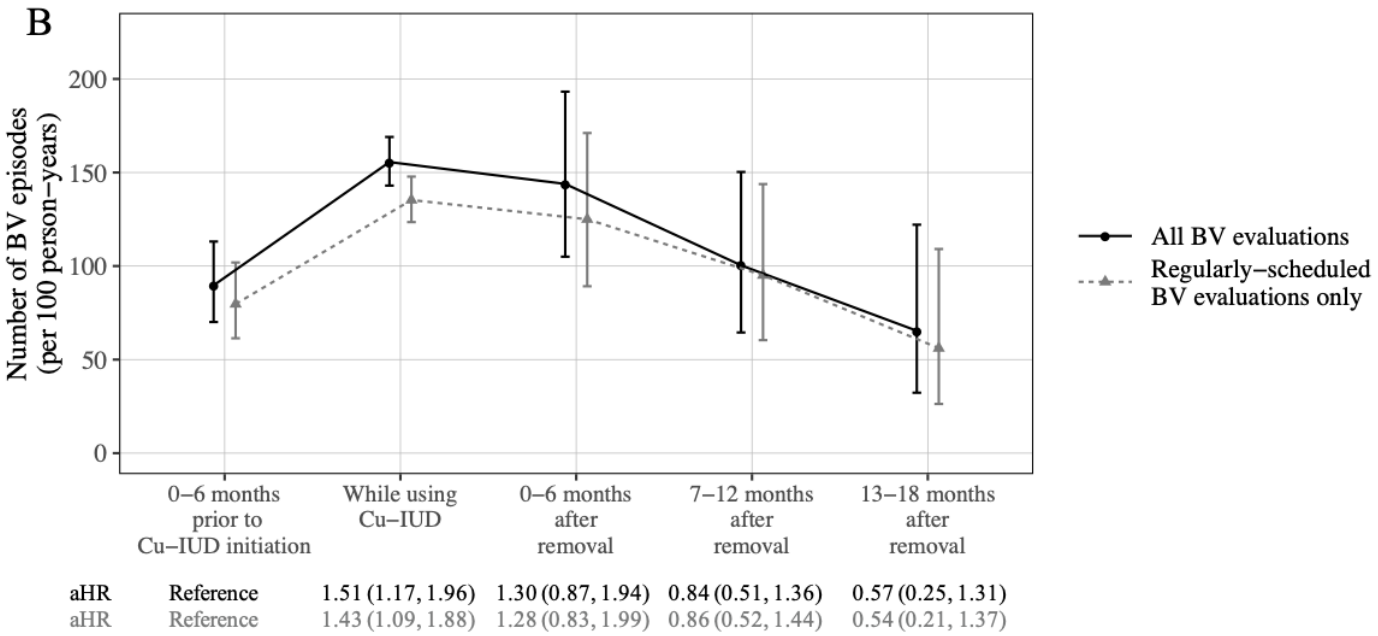


Figure II. Frequency of bacterial vaginosis (BV) in (A) the time period prior to copper intrauterine device (Cu-IUD) initiation and while using Cu-IUD and (B) in the time period prior to Cu-IUD initiation, while using Cu-IUD, and following Cu-IUD discontinuation. Adjusted hazard ratios and 95% confidence intervals from Andersen-Gill proportional hazards models are shown below each figure.

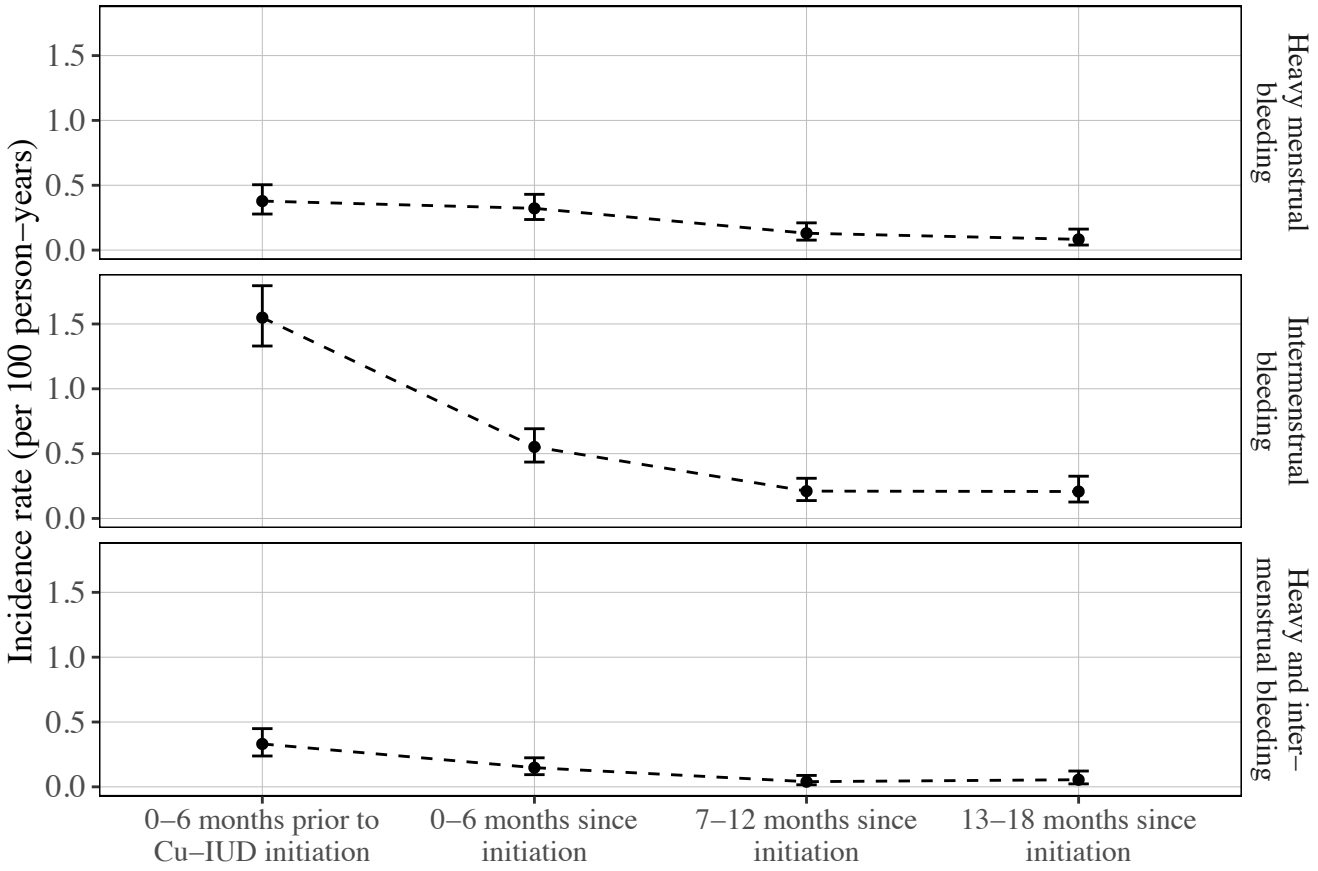


aHR	Reference	1.52 (1.16, 2.00)	1.40 (1.03, 1.91)	1.53 (1.07, 2.18)
aHR	Reference	1.43 (1.08, 1.90)	1.35 (0.98, 1.87)	1.36 (0.94, 1.98)

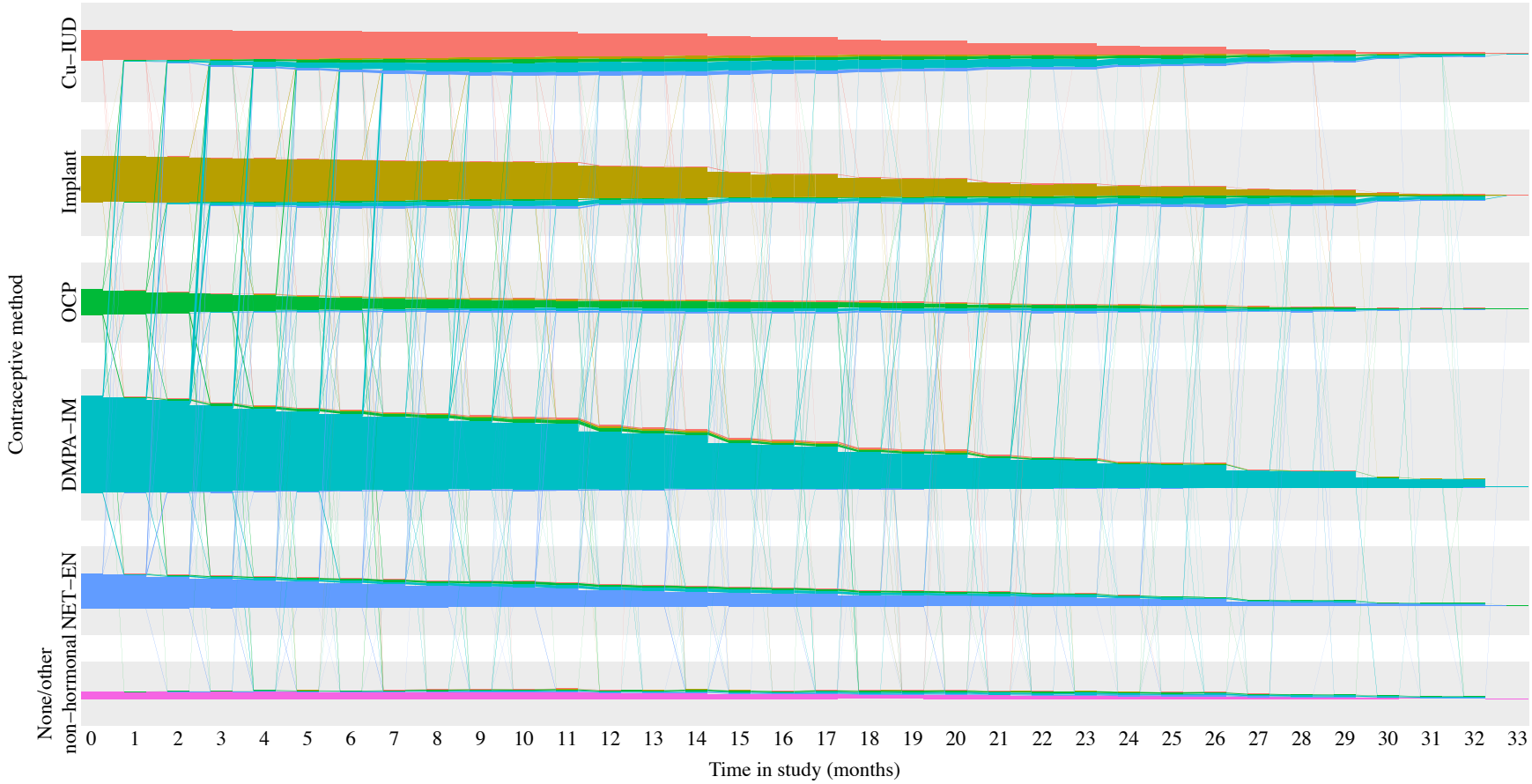


aHR	Reference	1.51 (1.17, 1.96)	1.30 (0.87, 1.94)	0.84 (0.51, 1.36)	0.57 (0.25, 1.31)
aHR	Reference	1.43 (1.09, 1.88)	1.28 (0.83, 1.99)	0.86 (0.52, 1.44)	0.54 (0.21, 1.37)

Figure III. Incidence rate of reported heavy menstrual bleeding, intermenstrual bleeding, and both heavy and intermenstrual bleeding in the six months prior to copper intrauterine device (Cu-IUD) initiation and in the eighteen months following initiation.



Supplement Figure I. Contraceptive method use over time. The width of each line at a given time point is proportional to the number of women using each given contraceptive method at that time point. Colors correspond to the contraceptive method in use at study enrollment.
Cu-IUD = copper intrauterine device; DMPA-IM = intramuscular depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; OCP = oral contraceptive



N =	2585	2567	2541	2501	2467	2431	2397	2366	2338	2315	2297	2275	2055	2000	1974	1730	1661	1648	1467	1423	1408	1232	1187	1177	1007	956	947	702	650	641	381	292	290	28
Cu–IUD	12%	13%	14%	16%	16%	17%	18%	19%	20%	20%	20%	21%	22%	22%	22%	24%	24%	24%	24%	23%	23%	23%	23%	23%	22%	22%	21%	21%	20%	19%	19%	17%	16%	32%
Implant	19%	19%	20%	21%	21%	21%	22%	22%	22%	22%	22%	22%	21%	21%	21%	19%	19%	19%	19%	19%	20%	20%	21%	22%	22%	23%	24%	26%	26%	27%	26%	25%	26%	36%
OCP	11%	10%	9%	8%	8%	8%	7%	7%	7%	7%	7%	7%	7%	7%	8%	8%	8%	8%	9%	9%	8%	8%	8%	8%	9%	8%	9%	8%	9%	8%	7%	6%	5%	7%
DMPA–IM	40%	40%	40%	38%	37%	37%	36%	36%	35%	35%	34%	35%	34%	33%	33%	32%	32%	31%	30%	30%	30%	30%	29%	28%	28%	29%	28%	28%	29%	29%	29%	32%	32%	14%
NET–EN	14%	14%	14%	14%	13%	13%	13%	13%	12%	12%	12%	12%	12%	12%	11%	12%	12%	12%	12%	12%	11%	12%	12%	11%	11%	11%	10%	9%	9%	10%	10%	10%	10%	7%
None/other non–hormonal	3%	3%	3%	3%	4%	4%	4%	4%	4%	5%	5%	5%	5%	5%	5%	5%	5%	6%	6%	7%	7%	7%	7%	7%	8%	8%	8%	8%	8%	7%	9%	10%	11%	4%

Supplement Table I. Frequency of bacterial vaginosis by contraceptive method. Contraceptive method is defined as a single exposure according to the method most recently initiated. Recurrent cases are included in the count of events.

Contraceptive method	All BV evaluations			Regularly-scheduled BV evaluations only		
	Episodes[1]	Person-years	BV episodes per 100 person-years (95% CI)	Episodes[2]	Person-years	BV episodes per 100 person-years (95% CI)
Cu-IUD	1,216	791.5	153.6 (145.2, 162.4)	1,069	791.5	135.1 (127.2, 143.3)
Implant	987	853.2	115.7 (108.7, 123.0)	906	853.2	106.2 (99.5, 113.2)
OCP	327	322.1	101.5 (91.1, 112.8)	285	322.1	88.5 (78.8, 99.0)
DMPA-IM	961	1,390.1	69.1 (64.9, 73.6)	869	1,390.1	62.5 (58.5, 66.7)
NET-EN	381	498.5	76.4 (69.1, 84.3)	318	498.5	63.8 (57.2, 71.0)
None/other non-hormonal	252	203.9	123.6 (109.3, 139.3)	217	203.9	106.4 (93.2, 121.0)

[1] Includes all regularly-scheduled BV evaluations, as well as an additional 210 evaluations by Nugent score and 376 evaluations by Amsel's criteria

[2] Bacterial vaginosis (BV) was evaluated every six months by Nugent score

Cu-IUD = copper intrauterine device; DMPA-IM = intramuscular depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; OCP = oral contraceptive

Supplement Table II. Association between contraceptive method use and incident bacterial vaginosis, using reference groups of women using progestin-only implant, oral contraceptive pills, or depot medroxyprogesterone acetate. Contraceptive method is defined as a single exposure according to the method most recently initiated. All BV evaluations are included. The proportional hazards assumption was appropriate for all models.

	Adjusted hazard ratio (95% CI)	*p*	Adjusted hazard ratio (95% CI)	*p*	Adjusted hazard ratio (95% CI)	*p*
Contraceptive method						
Cu-IUD	1.36 (1.26, 1.48)	< 0.001	1.34 (1.19, 1.51)	< 0.001	1.98 (1.82, 2.15)	< 0.001
Implant	Reference	--	0.98 (0.87, 1.11)	0.805	1.45 (1.33, 1.59)	< 0.001
OCP	1.02 (0.90, 1.15)	0.805	Reference	--	1.48 (1.31, 1.67)	< 0.001
DMPA-IM	0.69 (0.63, 0.75)	< 0.001	0.68 (0.60, 0.76)	< 0.001	Reference	--
NET-EN	0.79 (0.69, 0.89)	< 0.001	0.77 (0.67, 0.89)	< 0.001	1.14 (1.02, 1.38)	0.026
None/other non-hormonal	1.07 (0.93, 1.22)	0.348	1.05 (0.90, 1.23)	0.543	1.55 (1.36, 1.77)	< 0.001

Cu-IUD = copper intrauterine device; DMPA-IM = intramuscular depot medroxyprogesterone acetate; NET-EN = norethisterone enanthate; OCP = oral contraceptive

Chapter 3. Receptive anal intercourse and its potential association with HIV-1 risk and dapivirine ring prevention efficacy

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Anal intercourse, HIV-1 risk, and efficacy in a trial of a dapivirine vaginal ring for HIV-1 prevention

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Abstract

Objectives. To describe receptive anal intercourse (RAI) behaviors and correlates in a cohort of sub-Saharan African women, evaluate the association of RAI with HIV-1 risk, and evaluate whether the HIV-1 prevention efficacy of a dapivirine vaginal ring differs among women who reported RAI.

Design. Secondary analysis of the MTN-020/ASPIRE trial, a randomized, double-blind, placebo-controlled trial evaluating a dapivirine vaginal ring for HIV-1 prevention.

Methods. At enrollment and month three, women reported RAI in the prior three months in audio computer-assisted self-interviews. We evaluated associations between RAI and participant characteristics with chi-square and t-tests adjusted for study site. Cox proportional hazards models stratified by study site tested the association of RAI with HIV-1 acquisition and effect modification by RAI.

Results. Eighteen percent of women reported any RAI at enrollment and/or month 3, with a median of 2 (IQR: 1, 4) RAI acts in the prior three months, accounting for 1.5% of total sex acts. RAI prevalence was higher among women with lower educational attainment and those reporting transactional sex. In adjusted models, RAI was not associated with HIV-1 acquisition (aHR: 0.93, 95% CI: 0.57, 1.54). The ring reduced HIV-1 risk by 27% (95% CI: -5, 49) among women reporting no RAI and by 18% (95% CI: -57, 57) among women reporting any RAI (interaction *p*-value=0.77).

Conclusions. RAI was modestly infrequent and was not associated with reduced HIV-1 protection from the ring, suggesting that, in populations with rates of RAI similar to this cohort, RAI may not appreciably reduce the population-level impact of the dapivirine vaginal ring.

Key words: dapivirine vaginal ring, HIV-1 prevention, anal intercourse

Introduction

Women in sub-Saharan Africa face disproportionately high HIV-1 risk, with particularly elevated risk among young women and adolescents [68]. Receptive anal intercourse (RAI) has long been recognized as a potentially important HIV-1 transmission route among women [69]. Approximately 5-17% of women of the general-risk population report engaging in RAI in the prior three months in Eastern and Southern Africa [33-35], with each act conferring risk estimated to be 4 to 16-fold higher than an act of receptive vaginal intercourse (RVI) [70-72]. However, while RAI confers greater per-act risk, the product of site-specific per-act risk and relative proportion of RAI and RVI acts determines their respective contribution to the likelihood of HIV-1 acquisition.

Vaginal microbicides in development provide higher levels of drug to the lower genital tract than oral dosing of licensed products, with limited cross-compartmental transfer of drug to the rectum [31, 32]. Thus, RAI could hypothetically undermine the impact of vaginal microbicides [38, 39], since vaginal products would not offer protection against HIV-1 transmission in acts of RAI. Two clinical trials of a dapivirine vaginal ring estimated HIV-1 risk reduction of 27% [6] and 31% [7] in intent-to-treat analyses, with evidence that product non-adherence contributed to a diluted estimate of efficacy [6, 37]; however, it is unknown whether RAI also contributed to dilution of trial efficacy estimates.

An understanding of RAI practices and their potential impact on ring effectiveness is needed to inform ring implementation and HIV-1 risk among prospective ring users. We describe RAI behavior and correlates among the MTN-020/ASPIRE trial participants and investigate the association between RAI and HIV-1 risk and whether RAI may have contributed to efficacy dilution of the ring.

Methods

We conducted a secondary analysis of data from the ASPIRE clinical trial of a dapivirine vaginal ring for HIV-1 prevention; detailed trial methods have been published previously [6]. Briefly, 2,629 healthy, sexually active, HIV-1-negative women living in Malawi, South Africa, Uganda, and Zimbabwe

enrolled in the trial from 2012-2014. Enrolled women were randomized 1:1 to receive either an intravaginal ring containing 25 mg of dapivirine or a placebo intravaginal ring that was changed each month. Women were instructed to use the ring continuously over a 28-day period, with monthly follow-up visits for HIV-1 serologic testing and dispensation of new rings.

At enrollment, participants reported vaginal and anal sex act frequency over the prior three months and condom use at their most recent sex act in standardized face-to-face interviews. RAI was assessed with the question, "In the past 3 months, how many times have you had anal sex? By anal sex, we mean when a man puts his penis inside your anus." This item was translated and back-translated to ensure that its meaning was well-understood by participants, following lessons learned in the VOICE trial in which some participants interpreted RAI items as referring to vaginal sex from behind [73]. To encourage accurate reporting of sensitive behaviors, all women also completed audio computer-assisted self-interviews (ACASI) at baseline and the month 3 follow-up visit, which included items that assessed RAI frequency and condom use, alcohol consumption in the prior three months, and transactional sex in the prior year. Both baseline demographic data and follow-up RVI frequency (over the prior seven days) were collected in face-to-face surveys only. At baseline, women were evaluated for syphilis, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and bacterial vaginosis (defined as Nugent score > 6[53]).

Analyses here include 2,562 (98.0%) participants who responded to RAI survey items at baseline and/or month 3. RAI exposure was classified according to ACASI-reported behavior in all analyses. We assessed the association between baseline participant characteristics and reporting any RAI in the previous three months using Cochran-Mantel-Haenzel chi-squared tests stratified by study site for categorical variables and a t-test from linear models adjusted for site for continuous variables. We estimated the proportion of all sex acts that were RAI using enrollment reports of the number of RAI and RVI acts over the prior three months. We used a Cox proportional hazards model stratified by study site and with an interaction term for RAI and study arm to estimate the association between any RAI and HIV-1 acquisition and to evaluate potential ring effect measure modification associated with RAI. We additionally estimated the association of any RAI and HIV-1 risk within study arm, as well as ring efficacy within groups of

women defined by reporting any versus no RAI. Models were adjusted for variables identified as potential confounders (baseline report of transactional sex, education level, and use of hormonal injectable contraception). In the primary analysis, we defined RAI exposure as self-reported RAI at baseline and/or month three. In sensitivity analyses, we characterized RAI exposure as a continuous variable of the total number of RAI acts reported at baseline and month 3. Additionally, we conducted sensitivity analyses excluding subpopulations with enrollment characteristics predictive of low adherence (two study sites and women younger than 25) [6] in order to increase the sensitivity of the analysis to detect an interaction effect between RAI and ring efficacy. All analyses were conducted in R 3.5.0 [55].

Institutional review boards from each study site approved the study protocol. All participants provided written informed consent.

Results

In interviewer-administered surveys at study enrollment, 54 (2.1%) women reported engaging in receptive anal intercourse in the previous three months, whereas 334 (13.1%) women reported RAI in the previous three months via ACASI. A total of 468 (18.3%) women reported RAI at baseline and/or month 3, with 136 (5.3%) women reporting RAI at both time points. Among women reporting RAI at baseline, 14.3% of their total sex acts over three months were RAI; among all participants, 1.5% of all sex acts reported at baseline were RAI (Table S1, Supplemental Digital Content 1). Combining baseline and month three, approximately three-quarters of women who engaged in RAI reported three or fewer RAI acts in the previous three months. Self-reported condom use was lower for vaginal than anal sex acts (57.4% and 62.9% condom use at the most recent vaginal and anal sex act at baseline, respectively, $p<0.001$). Baseline RAI prevalence was highest among women who reported engaging in transactional sex (22.6%; Table 1). RAI was also more common among women with less than secondary education and women who used hormonal injection contraceptive methods (Table 1). RAI was not associated with baseline vaginal STI infection nor baseline bacterial vaginosis (Table 1).

In models adjusted for randomization arm, RAI at baseline and/or month 3 was not associated with HIV-1 risk (aHR: 0.93, 95% CI: 0.57, 1.54; p=0.71); this association did not differ by study arm (p-value for interaction=0.83). Within the placebo arm, HIV-1 incidence among women who did not engage in RAI was lower, at 4.3 per 100 woman-years (95% CI: 3.4, 5.3; 70 events/1,642 woman-years), relative to 5.2 per 100 woman-years (95% CI: 3.4, 7.7; 21 events/401 woman-years) among women who reported any acts of RAI. Differences in incidence rates were primarily driven by confounding by study site; after stratification on site and adjustment for potential confounders, incidence was not significantly different between groups (aHR: 0.97, 95% CI: 0.58, 1.62, p=0.87) (Figure 1a). Similarly, in the dapivirine arm, incidence was 3.1 per 100 woman-years (95% CI: 2.4, 4.0; 52 events/1,663 woman-years) among those who engaged in only vaginal sex and 4.2 (95% CI: 2.6, 6.5; 16 events/381 woman-years) among those who also engaged in any acts of RAI (aHR: 0.94, 95% CI: 0.52, 1.68, p=0.80) (Figure 1b). In a sensitivity analysis in which RAI exposure was modeled continuously as the number of total RAI acts reported at baseline and month 3, adjusted hazard ratios were similar to those in the primary analysis, and did not differ by study arm (p-value for interaction=0.15).

Among all women, the dapivirine ring reduced the risk of HIV-1 acquisition by 25% (95% CI: -3, 55). In comparison, among women reporting exclusively RVI at baseline and month 3, risk reduction was 27% (95% CI: -5, 49; Figure 1d) after stratification for study site, whereas among women who reported any RAI, the reduction in risk of HIV-1 acquisition was attenuated at 18% (95% CI: -57, 57; Figure 1c) (p-value for interaction=0.77). In sensitivity analyses in which groups with low adherence were excluded, the interaction effect between RAI and the dapivirine ring remained statistically non-significant (analysis excluding two study sites: p=0.63; analysis excluding women younger than 25 years of age: p=0.74; Table S2, Supplemental Digital Content 1).

Discussion

In the ASPIRE trial of a dapivirine vaginal ring for HIV-1 prevention, RAI was not associated with HIV-1 acquisition, nor was the protective effect of the ring significantly reduced among women who

reported any RAI. Approximately one in five women reported RAI at baseline and/or month 3, though notably, a much smaller proportion (approximately one in twenty) reported RAI at both time points, suggesting that RAI is an occasional rather than consistent sexual practice among this cohort of African women. Nearly three-quarters of the women reporting any RAI reported an average of one RAI act per month or less. Because the vast majority of sex acts among trial participants were reported to be RVI, the total risk contributed by RAI may have been sufficiently small as to not result in a sizeable nor statistically significant association with HIV-1 risk, nor significant effect modification of ring efficacy. While our primary analysis assessed effect modification by randomization arm, results were robust to sensitivity analyses in which we excluded groups of women with relatively lower adherence. Our study also collected RAI data at two time points only, limiting the precision of our estimates of the association of RAI with HIV-1 risk and ring efficacy. Nonetheless, among women reporting only vaginal sex at baseline and month 3, we estimated that ring efficacy was 27%, only modestly higher than the overall efficacy of 25% estimated among all women included in these analyses. This suggests that any efficacy dilution in the ASPIRE trial due to RAI may be minimal, supporting the hypothesis that the majority of efficacy dilution is attributable to ring non-adherence [37].

Mathematical modeling might provide greater clarity about the relative contribution of RAI to reduced ring efficacy, and the impact that such efficacy dilution would have on HIV-1 prevention. The frequency of RAI in the ASPIRE cohort was lower than has been reported in other cohorts [33]; the potential for RAI to undermine the effectiveness of the ring at the population level may be higher in other settings where RAI is more common. Additionally, despite use of ACASI to collect RAI behaviors, RAI remains a taboo behavior [74] and may be underreported in our cohort. Should the ring become widely available in the future, geographically-specific representative estimates of RAI prevalence and frequency among women at risk of HIV-1 acquisition are needed to inform ring implementation strategies, including the need for counselling on prevention options, and to evaluate the potential for RAI to reduce the population-level impact of the ring.

Our study adds to a limited body of research on RAI in sub-Saharan African settings. A single study in South African community and clinic settings observed higher RAI prevalence among younger and unmarried individuals and those with a history of sexually transmitted infections or transactional sex [75]. Similarly, RAI was associated with several risk factors for HIV-1 acquisition in this cohort, including transactional sex, suggesting potential populations for targeted communication regarding RAI-associated risk and, among prospective ring users, the lack of protective effect of the ring against RAI. For such women, the availability of alternative methods that protect against HIV-1 acquisition in all compartments, such as oral PrEP or condoms, will be particularly important. While previous research in South Africa reported similar condom use rates for both vaginal and anal sex acts [33], ASPIRE participants reported higher rates of condom use during acts of RAI than acts of RVI, potentially mitigating RAI-associated risk in this population and contributing to the observed lack of association between RAI and HIV-1 acquisition. These higher rates of condom use also suggest that women are appropriately evaluating the higher risk associated with RAI, in contrast to previous qualitative research in which women reported lower perceived HIV-1 risk from RAI relative to RVI [76]. Similar to previous research, we observed strikingly different self-reports of RAI behaviors in face-to-face interviews, in which only about 1 in 50 women reported any RAI, relative to ACASI [33], emphasizing the need to offer confidential data collection methods to ensure more accurate reporting of sensitive behaviors in future research in this area.

In summary, RAI was not a prominent risk factor for HIV-1 nor was the protective effect of the ring significantly lower among women who engaged in RAI. These findings suggest that, in populations with similar prevalence and frequency of RAI as in this cohort, RAI may not appreciably reduce the population-level impact of the ring, thus supporting use of the ring for HIV-1 prevention in women.

Table 1. Association of baseline participant characteristics and engaging in any anal intercourse in the previous three months. Values are *n* (%) except where noted.

	Receptive anal intercourse		
	No (*n* = 2,225)	Yes (*n* = 334)	*p*[*]
Arm			
Placebo ring	1,105 (86.3)	176 (13.7)	0.297
Dapivirine ring	1,120 (87.6)	158 (12.4)	
Country			
Malawi	225 (85.9)	37 (14.1)	< 0.001
South Africa	1,118 (81.0)	262 (19.0)	
Uganda	227 (93.4)	16 (6.6)	
Zimbabwe	655 (97.2)	19 (2.8)	
Plasma dapivirine > 95 pg/mL			
Yes	857 (88.8)	108 (11.2)	0.240
No	983 (85.0)	173 (15.0)	
Age			
18-21	421 (83.4)	84 (16.6)	0.518
22-26	699 (85.3)	120 (14.7)	
27-45	1,105 (89.5)	130 (10.5)	
Education level			
Less than secondary	337 (86.0)	55 (14.0)	0.002
Secondary or above	1,888 (87.1)	279 (12.9)	
Marital status			
Unmarried	1,249 (82.8)	259 (17.2)	0.757
Married	976 (92.9)	75 (7.1)	
Any alcohol consumption in prior three months			
Yes	264 (85.2)	46 (14.8)	0.138
No	1,961 (87.2)	288 (12.8)	
Vaginal intercourse frequency, median (IQR)	20 (8, 36)	12 (6, 25)	0.515
Condom use at last vaginal intercourse			
Yes	1,257 (85.5)	214 (14.5)	0.463
No	968 (89.0)	120 (11.0)	
Contraceptive method			
Intrauterine device	300 (94.3)	18 (5.7)	0.042
Hormonal implant	472 (95.4)	23 (4.6)	
Hormonal injection [a]	1,158 (83.0)	238 (17.0)	
Oral contraceptive pills	228 (83.8)	44 (16.2)	
None	67 (85.9)	11 (14.1)	
Any STI infection			
Yes	460 (85.5)	78 (14.5)	0.839
No	1,765 (87.3)	256 (12.7)	
Bacterial vaginosis			
Yes	922 (86.7)	142 (13.3)	0.934
No	1,303 (87.2)	192 (12.8)	
Engaged in transactional sex in the past year			
Yes	123 (77.4)	36 (22.6)	0.002
No	2,100 (87.6)	297 (12.4)	

[*] *p*-value obtained from Cochran-Mantel-Haenzel chi-squared tests stratified by site for categorical variables (with the exception of "Country", which is not stratified by site) and t-tests from linear models adjusted for site for continuous variables.
[a] Depot medroxyprogesterone acetate (DMPA) or noretheristerone enanthate (NET-EN)

Supplement Table 1. Summary of receptive anal intercourse and receptive vaginal intercourse frequency and condom use, as reported in face-to-face interviews and by audio computer-assisted self-interview at enrollment and three-month follow-up.

	Enrollment, face-to-face interviews	**Enrollment, ACASI**	**Three-month follow-up, face-to-face interviews**	**Three-month follow-up, ACASI**
Number of RAI acts, median (IQR)[1]	1.5 (1.0, 3.0)	1.5 (1.0, 4.0)	--	2.0 (1.0, 4.0)
Number of RAI acts, total	130[3]	1,086[3]	--	948[3]
Last RAI act condom-protected, *n* (%)	35 (64.8)	210 (62.9)	--	168 (62.2)
Number of RVI acts, median (IQR)[2]	20.0 (7.0, 36.0)[3]	--	3.0 (2.0, 4.0)[4]	--
Number of RVI acts, total	69,337[3]	--	7,036[4]	--
Last RVI act condom-protected, *n* (%)	1,499 (57.4)	--	1,058 (54.8)	--

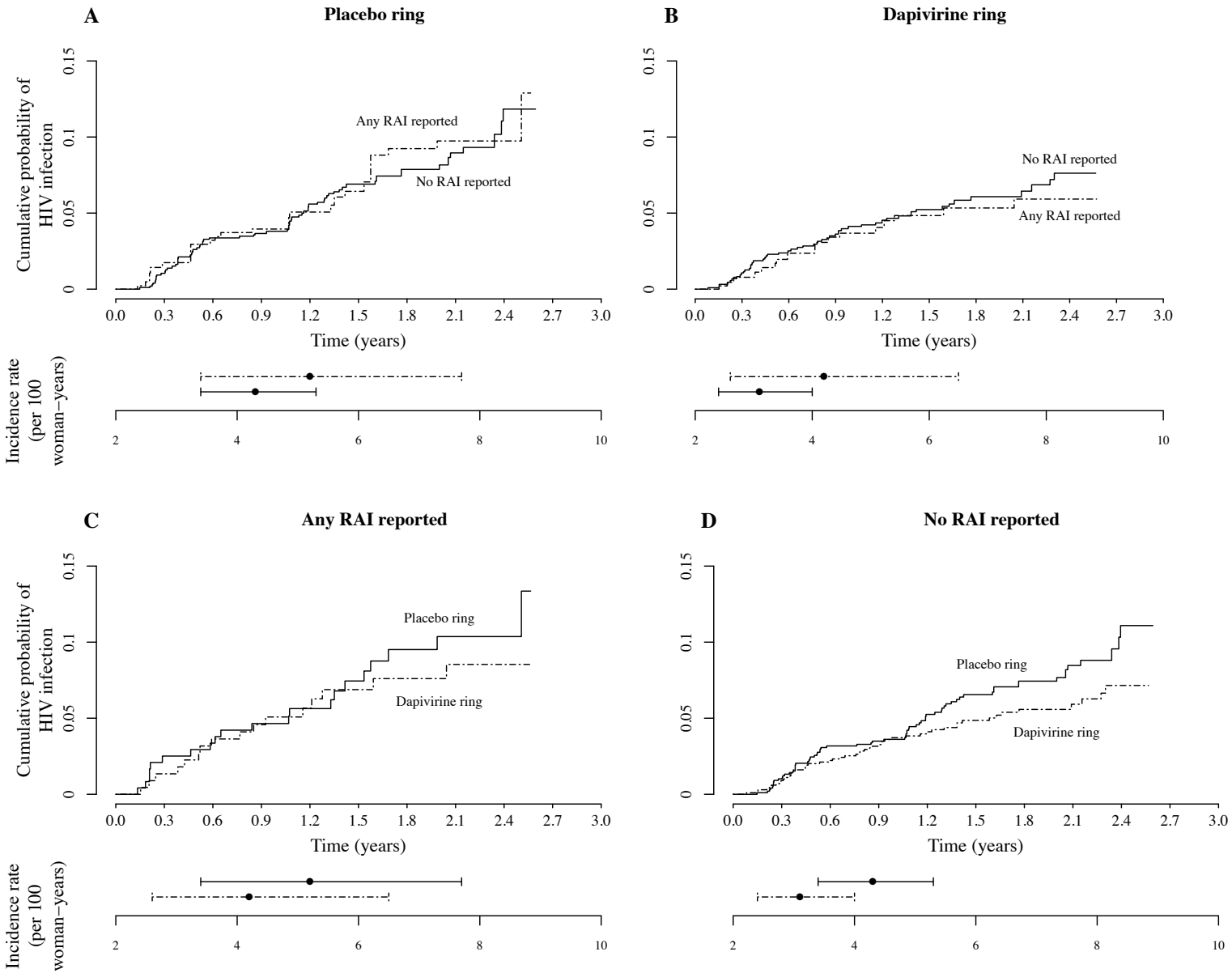
[1] Calculated from among women reporting any RAI acts
[2] Calculated from among women reporting any RVI acts
[3] Acts were reported for the prior three months
[4] Acts were reported for the prior seven days
RAI = receptive anal intercourse; RVI = receptive vaginal intercourse; ACASI = audio computer-assisted self-interview

Supplement Table 2. Efficacy of the dapivirine-containing vaginal ring and RAI interaction effect in primary and sensitivity analyses.

Analysis	**Hazard ratio of DPV ring (95% CI)[1]**	***p***	**Interaction effect of RAI and DPV ring, Hazard ratio (95% CI)[1]**	***p***
Any RAI at baseline or month three, *n* = 2,478[2]	0.73 (0.51, 1.05)	0.089	1.12 (0.53, 2.35)	0.770
Excluding Isipingo and Tongaat sites, *n* = 2,277[2]	0.62 (0.42, 0.91)	0.016	1.23 (0.53, 2.85)	0.625
Excluding women < 25 years, *n* = 1,528[2]	0.51 (0.30, 0.88)	0.015	0.78 (0.18, 3.35)	0.739
Total number of RAI acts at baseline and month three, *n* = 2,416[3]	0.68 (0.49, 0.96)	0.026	1.09 (0.97, 1.23)	0.137

[1] Estimates and *p*-values are obtained from Cox proportional hazards models stratified by site and adjusted for baseline report of transactional sex, education level, and use of hormonal injectable contraception.
[2] Women missing responses to RAI items at both baseline and month three, or reporting no RAI at one time point and missing a response at the other, are excluded.
[3] Women missing responses to RAI items at either baseline or month three are excluded.
RAI = receptive anal intercourse; DPV = dapivirine

Figure 1. HIV-1 incidence rates and Kaplan-Meier curves of cumulative HIV-1 incidence, stratified by A) Any AI reported at baseline or month 3 among those assigned to placebo ring; B) Any AI reported at baseline or month 3 among those assigned to dapivirine ring; C) Treatment assignment among those who reported any AI at baseline or month 3; and D) Treatment assignment among those who reported no AI at baseline nor month 3. Kaplan-Meier curves in (A) and (B) are adjusted for site.



Chapter 4. Dapivirine ring HIV-1 prevention effectiveness among women engaged in receptive anal intercourse

Dapivirine ring HIV-1 prevention effectiveness among women engaged in receptive anal intercourse: insights from mathematical modeling

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Abstract

Objective(s): The dapivirine vaginal ring reduces risk of HIV-1 acquisition through vaginal intercourse, and though it does not offer HIV-1 protection in acts of receptive anal intercourse (RAI), it may provide some overall risk reduction if any sex acts are vaginal. We estimated the average per-exposure effect of the ring among women with high adherence engaged in both vaginal intercourse and RAI.

Design: We developed a microsimulation model using data from the MTN-020/ASPIRE trial.

Methods: Among women who reported any RAI, we estimated the proportion of all acts that were RAI. Model scenarios varied this proportion among women engaged in both vaginal and anal intercourse from 5-30%, including the trial-observed median proportion of 6.3% of acts being RAI. Primary analyses assumed dapivirine ring efficacy of 70% for vaginal exposures.

Results: Among highly-adherent women for whom 6.3% of their acts were RAI, the median per-exposure ring effect was 56% (IQR: 40, 63) and declined to 25% (IQR: 11, 37) among women for whom 30% of acts were RAI. The average per-exposure effect was less than 40% for women for whom RAI accounted for greater than 16% of all sex acts, although this represented approximately 5% of all women in the ASPIRE trial.

Conclusions: The dapivirine vaginal ring can provide important HIV-1 protection for the vast majority of women, including those who engage in RAI.

Key words: women; HIV-1 prevention; dapivirine ring; receptive anal intercourse; sub-Saharan Africa

Introduction

Women in sub-Saharan Africa are at high risk of HIV-1 infection, with 550,000 new infections annually [1]. Prevention products that are both discreet and female-controlled are needed to address the unique challenges that women face in accessing and using biomedical HIV-1 prevention products [29, 30].

The MTN-020/ASPIRE trial of a dapivirine vaginal ring for HIV-1 prevention estimated 27% HIV-1 risk reduction in modified intent-to-treat analyses [6]. This estimate provides a population-level estimate of efficacy among both adherent and non-adherent women, whereas the causal parameter of interest to prospective ring users and their providers is product efficacy when used, with analyses conditioned on high adherence estimating ring efficacy in the range of 65%-75% [37]. The ring does not provide protection in acts of receptive anal intercourse (RAI) due to minimal dissemination of drug to the rectum [31, 32], though it may still provide some overall risk reduction if any acts are vaginal intercourse. Prior analyses suggested that any RAI in the trial would have a minimal impact on overall estimates of efficacy, yet estimated that the ring reduced HIV-1 risk among women reporting any RAI by only 18% (95% CI: -57, 57) [77]. However, like the primary modified intent-to-treat analysis, this estimate was an average of ring effectiveness among a population of both adherent and non-adherent women. Estimates of overall risk reduction with high adherence are needed for individual women and their providers to inform HIV-1 prevention method selection for women who engage in any RAI [33-35]. We therefore developed a microsimulation model of the ASPIRE trial to estimate the average per-exposure effect of the ring among women engaging in both vaginal and anal intercourse.

Methods

We developed a microsimulation model to reproduce the population, procedures, and outcomes of the ASPIRE trial, including 2,614 women confirmed HIV-1-negative at enrollment [6]. Full model details are included in the technical appendix in Supplemental Digital Content 1. In summary, a probabilistic model generates adherence, HIV-1 infection, and relationship formation, persistence, and dissolution in monthly timesteps, according to parameters determined from observed trial data conditional on age, sexual behaviors

(number of partners and frequency of sex acts), baseline sexually transmitted infections and bacterial vaginosis, and study enrollment and exit times. HIV-1 status of male partners was largely unknown in the trial. The model assigns prevalent and incident male partner HIV-1 status proportional to male age- and country-specific prevalence and incidence, respectively, with the probability of positive HIV-1 status modified by select factors observed in ASPIRE to be associated with HIV-1 acquisition, including participant age and reported condom use in the prior week. We used a sequential Monte Carlo approximate Bayesian computation calibration procedure [78] to fit uncertainty parameters (including the per-act risk of receptive anal relative to receptive vaginal intercourse, among others) to trial-observed age-specific placebo arm incidence throughout the trial and overall placebo arm incidence in the final half of the trial.

Women reported their number of vaginal and anal sex acts at enrollment and month three in ASPIRE [77]. From these reports, we estimated the proportion of total acts that were RAI among women who reported engaging in both receptive vaginal intercourse (RVI) and RAI, and used the median proportion in primary analyses. We defined the average per-exposure ring effect as the ratio of the number of HIV-1 infections occurring out of the number of HIV-1-exposed acts in the dapivirine arm relative to the placebo arm. This quantity can be considered a weighted average of the per-vaginal exposure ring efficacy and the per-anal exposure ring efficacy (0%), weighted by the relative number of vaginal and anal sex acts and the HIV-1 risk for each act type. Among women who engage in only RVI, the average per-exposure ring effect and per-vaginal exposure efficacy are equivalent. We evaluated the average per-exposure effect of the ring among women with high adherence across variation in the proportion of acts that are RAI, ranging from 5 to 30% in 5% increments. Furthermore, small imbalances in randomization arm at enrollment in ASPIRE [6] may bias the estimated average per-exposure effect of the ring. Our primary analyses of the average per-exposure effect of the ring therefore re-randomize participants stratified on site, enrollment bacterial vaginosis, and average monthly number of sex acts.

Each model scenario was evaluated with per-vaginal exposure ring efficacy of 65%, 70%, and 75% as model inputs, consistent with efficacy estimates among women with high ring adherence [37]. To evaluate if our model was consistent with these values, we conducted the primary modified intent-to-treat

analysis to estimate the hazard ratio in model scenarios with the trial-observed small imbalances in randomization arm at enrollment and observed levels of non-adherence and RAI. Additionally, because existing metrics for ring adherence may not correctly classify women's use of the ring at the time of infection and RAI may be both under- or overreported due to stigma or misinterpretation of survey items [73], we varied prevalence of non-adherence and RAI in 5% increments from 0% to 50% and 0% to 30%, respectively. The model distributes non-adherence and RAI proportional to site-specific prevalence of each to reflect geographic differences observed within the trial [6, 77]. We estimated the geometric mean hazard ratio across 300 simulations and used locally weighted regression with a quadratic polynomial to fit a smooth surface to these modeled scenarios to identify scenarios within 1% of the primary modified intent-to-treat hazard ratio of 0.73 [6].

Primary analyses used the best-fitting parameters obtained in model calibration. We additionally evaluated the sensitivity of results to uncertainty in the per-act risk of RAI relative to RVI by repeating analyses with the top-fitting ten parameter sets that represented the range of per-act relative risk values (from 5.1 to 15.8) included in the model calibration prior distribution, compared to the per-act relative risk of 6.6 used in primary analyses. We simulated each model scenario 300 times and report the median and interquartile range of the average per-exposure effect of the ring. All analyses were completed in R [55].

All trial participants provided written, informed consent, and ethical review boards at each site approved the study protocol.

Results

Among 2,562 (98.0%) women responding to RAI items at enrollment and/or month three, 468 (18.3%) women reported engaging in any RAI, with a median of 6.3% of their acts being RAI (IQR: 2.7, 16.7). RAI accounted for more than 30% of all acts for 12.6% of women reported any RAI and for less than 5% of all acts among 42.1% of women. In simulations with 70% per-vaginal exposure efficacy and stratified re-randomization, the average per-exposure effect of the ring among women engaged in RAI for 6.3% of total acts was 56% (IQR: 40, 63), a 19% reduction in effectiveness relative to women with high adherence

engaging in only RVI (Figure 1). The average per-exposure effect of the ring declined as the proportion of acts that were RAI increased, from 70% among women with only vaginal exposures, to 57% (IQR: 48, 64) among women for whom 5% of acts were RAI, to 25% average per-exposure effect (IQR: 11, 37) among women for whom 30% of acts were RAI (Figure 1). In a sensitivity analysis in which the per-act relative risk of RAI was 15.8-fold higher than RVI, the average per-exposure effect of the ring was somewhat lower than in our primary analysis, at 50% (IQR: 38, 57) among women for whom 6.3% of acts were RAI, and declined to 15% (IQR: 6, 31) among women engaged in RAI for 30% of her acts (Supplement Figure 1 in Supplemental Digital Content 2). Across all scenarios, stratified re-randomization increased the estimated average per-exposure ring effect by an absolute difference of 10% (IQR: 10, 12) (Figure 1).

Translating these results to RAI behaviors reported by the full cohort of women in ASPIRE, the average per-exposure ring effect was greater than 50% for more than 90% of all women (Figure 2). Among the approximately 5% of women for whom RAI accounts for greater than 16.7% of all sex acts, the average per-exposure ring effect was less than 40% (Figure 2), compared to 70% per-vaginal exposure. Results were similar with per-vaginal exposure efficacy of 65% and 75% (Supplement Table 1 in Supplemental Digital Content 2).

In simulations including the observed slight imbalance in arms and variation in the prevalence of non-adherence and RAI, per-vaginal exposure efficacy values of 65-75% were consistent with modified intent-to-treat trial estimates of 27% efficacy (Supplement Figure 2 in Supplemental Digital Content 2).

Discussion

In a mathematical model replicating the participants, procedures, and outcomes of the ASPIRE trial, simulations demonstrate that the dapivirine vaginal ring, when used, confers substantial overall risk reduction to most women who engage in any RAI, despite not providing HIV-1 risk reduction in acts of RAI. Approximately four in five women in ASPIRE reported no RAI. Among the remaining 18% of women, at the median frequency of RAI of one in every 16 acts, the ring reduced overall HIV-1 risk by more than 50% among women with high adherence. While this risk reduction diminished to 25% among

women for whom one in every three acts is RAI, that population of women was relatively small: 12.6% of women engaging in both RVI and RAI, translating to approximately 2.5% of the full cohort of participants in the ASPIRE trial. This supports the utility of the ring for the vast majority of women, but nevertheless emphasizes the need for counselling approaches that help women identify the prevention option best-aligned with their context and sexual lifestyle, as well as for discreet methods that offer protection in both vaginal and rectal HIV-1 exposures [79, 80]. Furthermore, in our model analyses, per-vaginal exposure efficacy values of 65% to 75% were consistent with the modified intent-to-treat estimate of 27% efficacy obtained in the primary ASPIRE analysis [6]. These results support prior analyses conditioning on high adherence, and highlight that the ring offers high levels of HIV-1 risk reduction to women who may prefer an alternative prevention method to condoms and oral pre-exposure prophylaxis.

There is substantial uncertainty in the per-act risk of RAI relative to RVI, with a range of 5 to 16 based on per-act estimates of RAI and RVI obtained from different populations, time periods, settings, and study designs [70, 71, 81]. Our analysis benefited from use of a calibration approach that fit this value to observed data, yielding a per-act relative risk of RAI of 6.6. However, model calibration was relatively insensitive to this parameter, perhaps due to competing risks for infection among this cohort of women at high risk of HIV-1 infection, and the resulting posterior credible interval is wide (90% CrI: 5.5, 15.4). Nonetheless, in sensitivity analyses assuming a per-act relative risk of RAI of 5.1 to 15.8, results were qualitatively similar to the primary analysis.

In conclusion, among the majority of women who engaged in RAI, the ring provides substantial overall HIV-1 protection, supporting use of the ring for most women.

Figure 1. Average per-exposure ring effect among women engaged in both receptive vaginal and anal intercourse estimated from simulations varying per-vaginal exposure efficacy and the proportion of a woman's acts that are anal from among her total acts. The horizontal dashed line indicates the per-vaginal exposure efficacy. The median and interquartile range of the average per-exposure effect are shown.

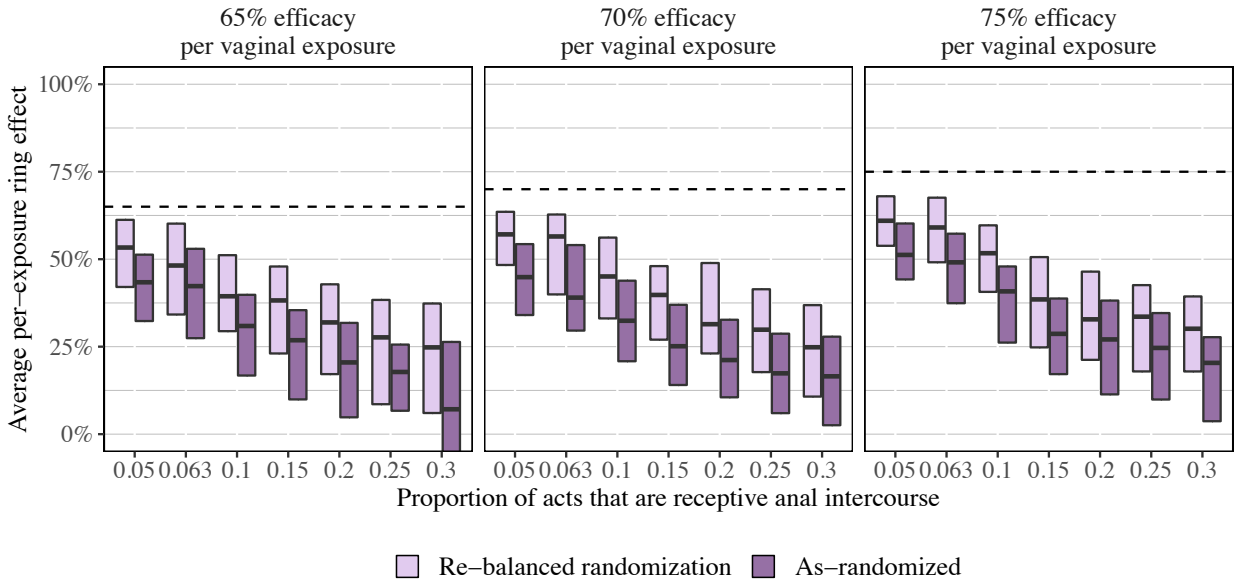
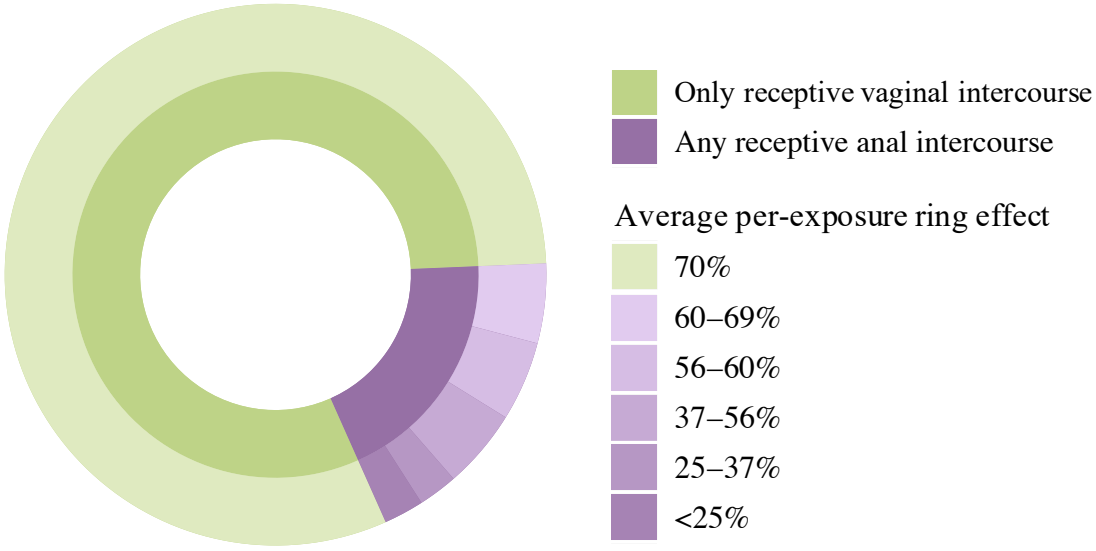
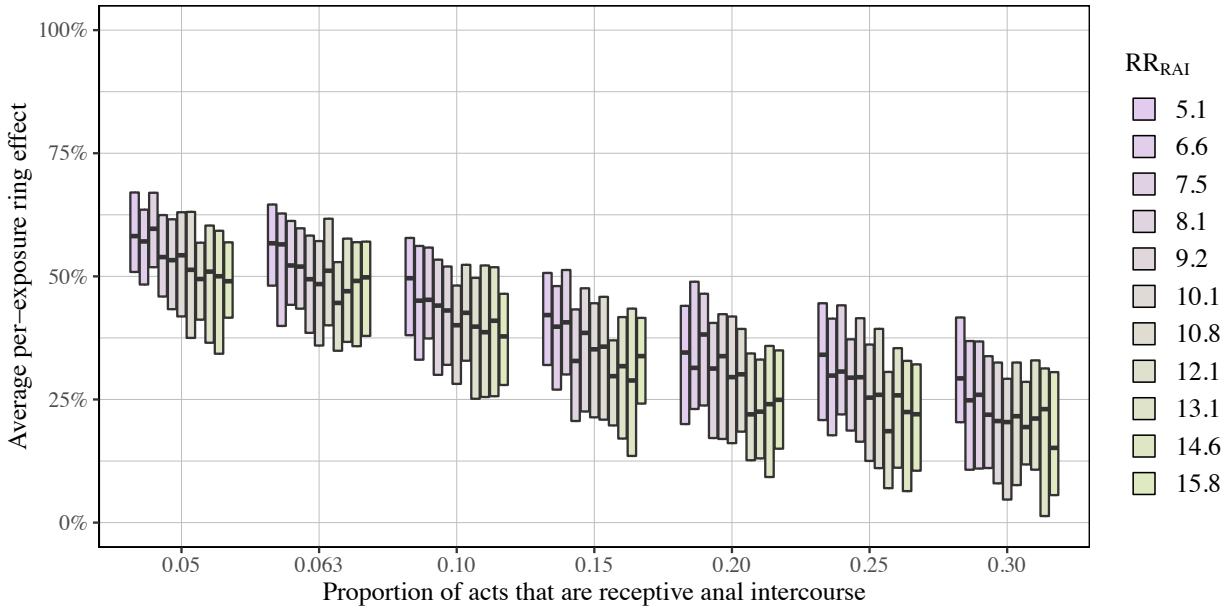


Figure 2. Among all women in the ASPIRE trial, the distribution of (1) engaging in only receptive vaginal intercourse or any receptive anal intercourse (inner circle) and (2) the average per-exposure ring effect given the reported proportion of all acts that were receptive anal intercourse (outer circle).



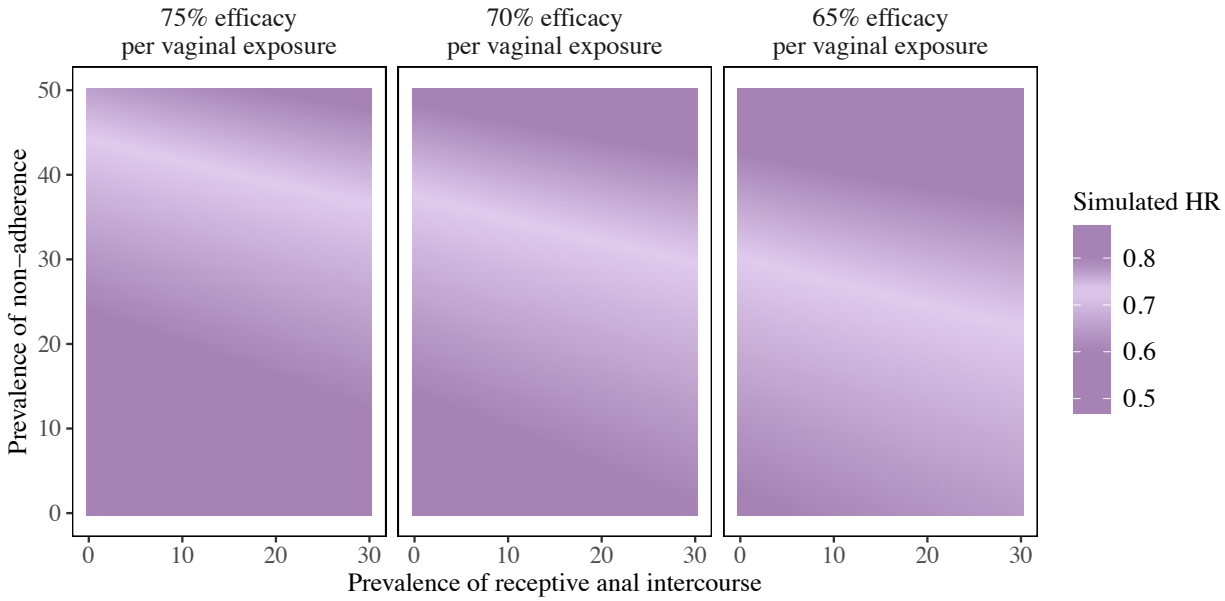
Supplement Figure 1. Average per-exposure ring effect among women engaged in both receptive vaginal and anal intercourse estimated from simulations varying per-vaginal exposure efficacy and the proportion of a woman's acts that are anal from among her total acts. The per-act risk of receptive anal relative to receptive vaginal intercourse (RR_{RAI}) is varied in sensitivity analyses. Per-vaginal exposure ring efficacy is 70% in all model scenarios.



Supplement Table 1. Average per-exposure ring effect conditional on per-vaginal exposure efficacy and the proportion of acts that are receptive anal intercourse (RAI).

Percent of acts that are RAI	Percent of ASPIRE cohort	Average per-exposure ring effect		
		65% per-vaginal exposure efficacy	70% per-vaginal exposure efficacy	75% per-vaginal exposure efficacy
0%	82.0%	65%	70%	75%
1.0% - 2.7%	4.5%	55-63%	60-69%	68-73%
2.7% - 6.3%	4.5%	48-55%	56-60%	59-68%
6.3% - 16.7%	4.5%	31-48%	37-56%	41-59%
16.7% - 30.0%	2.25%	25-31%	25-37%	30-41%
> 30.0%	2.25%	<25%	<25%	<30%

Supplement Figure 2. Geometric mean hazard ratio (HR) across 300 simulations varying per-vaginal exposure ring efficacy and prevalence of non-adherence and receptive anal intercourse. The trial-observed small imbalance in arms is included in all scenarios. Parameter combinations consistent with the trial-observed HR of 0.73 are shown in light purple.



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We are deeply grateful to the many women whose dedicated study participation in the ASPIRE trial made this work possible. This work was facilitated through the use of advanced computational, storage, and networking infrastructure provided by the Hyak supercomputer system at the University of Washington. The International Partnership for Microbicides developed the dapivirine ring and supplied rings for this trial.

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Supplemental technical appendix

This document describes specifications and assumptions underlying the microsimulation model used in "Dapivirine ring HIV-1 prevention effectiveness among women engaged in receptive anal intercourse: insights from mathematical modeling". Each component of the model is described in detail below. Briefly, the model is initialized with a longitudinal dataset comprised of baseline and time-varying characteristics of women participating in the MTN-020/ASPIRE clinical trial of a dapivirine-containing vaginal ring for HIV-1 prevention [6]. In monthly timesteps, the model assigns adherence, assesses HIV-1 transmission, and evaluates relationship formation, persistence, and dissolution. All model code is publicly available at https://github.com/ICRC-Models/aspire.

1. Study participant characteristics

The model simulates 2,614 women participating in the ASPIRE trial confirmed to be HIV-1-negative at enrollment and with at least one follow-up visit, and utilizes observed characteristics as the basis for primary functions of the model, including tracking the number and type of sexual acts, predicting adherence, and evaluating HIV-1 transmission. Observed characteristics include alcohol consumption, marital status, baseline number of sexual partners, baseline sexually transmitted infections (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*), baseline bacterial vaginosis, reported male partner HIV-1 status and antiretroviral use, any unprotected sex in the previous week, dates of study enrollment and exit, and reason for study termination.

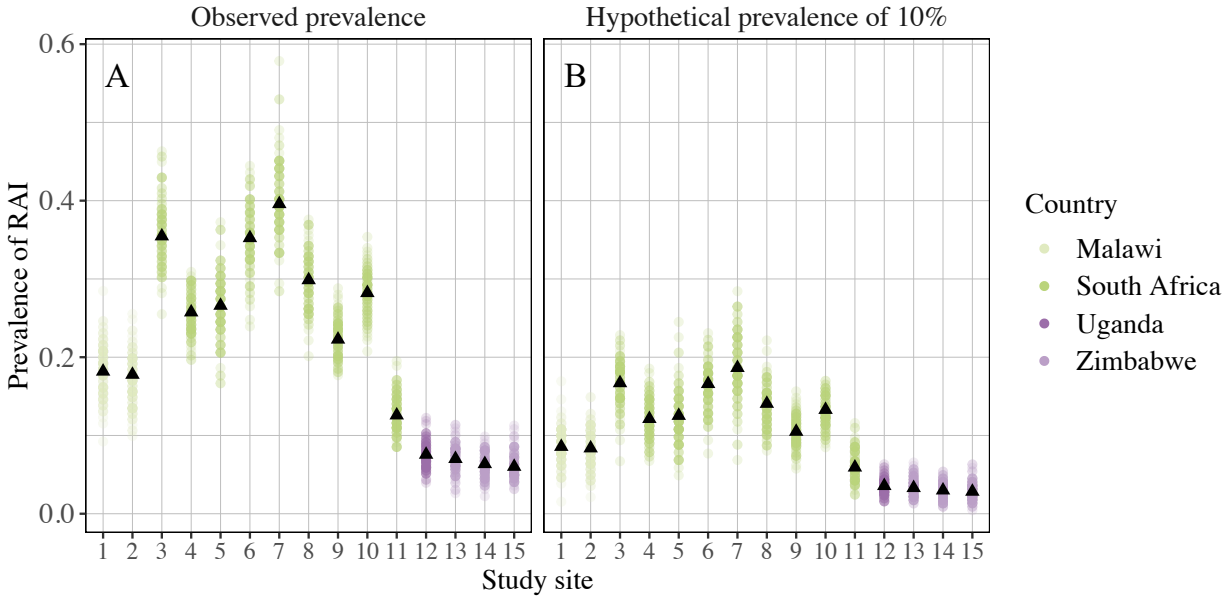
1.1 Prevalence and frequency of receptive vaginal intercourse and receptive anal intercourse

Women reported their total number of vaginal sex acts over the previous three months at baseline and over the prior seven days at quarterly follow-up visits. Women reported their total number of anal sex acts over the prior three months via audio computer-assisted self-interview at enrollment and month three of follow-up. We assume that baseline vaginal sex act reports represent an average number of sex acts, and therefore assign an average number of monthly acts around which there is random variation in each simulation. We assume a minimum of one vaginal sex act per quarter and assume no minimum number of anal sex acts. We convert the average total number of monthly acts to a per-partner average by dividing the total number of baseline monthly acts by the number of baseline sexual partners.

We estimated the site-specific proportion of women reporting any receptive anal intercourse (RAI) over the six-month reporting period in the trial. Simulations that systematically vary the prevalence of RAI distribute RAI in proportion to site-specific prevalence (Figure 1.1.1).

Among women who reported any RAI at enrollment or month three of follow-up, we estimated the proportion of all acts that were RAI over the six-month reporting period. The number of vaginal sex acts over this reporting period was estimated from baseline reports covering the prior three months and month-three reports covering the prior seven days, standardized to a three-month period. Among women engaging in any RAI in simulations, the proportion of acts that are RAI is assigned from a beta distribution with mean equal to the observed total proportion of acts that were RAI (7.8%) and variance of 0.005. Her total number of monthly vaginal acts is then redistributed among vaginal and anal sex acts, maintaining the same total reported number of sex acts. The number of sexual acts of each type per woman at a given month is then assigned from a Poisson distribution with mean equal to the per-partner monthly average number of acts of each type, multiplied by the number of active partners.

Figure 1.1.1. Prevalence of receptive anal intercourse by site in (A) 100 simulations with the observed distribution of RAI in ASPIRE and (B) 100 simulations with hypothetical prevalence of RAI of 10%. In scenarios that use a hypothetical prevalence of RAI, model prevalence of RAI is distributed proportional to site-specific observed prevalence.



1.2 Missing data and imputed values

Reported condom use in the previous week is missing for 13 (0.5%) women at baseline. In each simulation, missing values for condom use in the previous week are imputed using logistic prediction models (Table 1.2.1).

Table 1.2.1. Coefficients of prediction model for condom use in the previous week

	Coefficient
Intercept	-1.473
Age[†]	0.003
Married[†]	1.545
No alcohol in prior 3 months[†]	-0.325
Any sexually transmitted infection[†]	-0.285
Partner HIV-1 status[†]	
Positive	-2.289
Negative	0.623
Undisclosed	0.752

[†] At baseline

1.3 Condom use

We assign individual-specific per-act probability of condom use according to the country-specific proportion of women reporting condom use in the prior week at the quarter-one follow-up visit (Table 1.3.1).

Table 1.3.1. Country-specific baseline proportion of women reporting condom use at last sex act

Country	Proportion
Malawi	0.41
South Africa	0.52
Uganda	0.29
Zimbabwe	0.45

1.4 Stratified re-randomization

In the ASPIRE trial, there were slight imbalances by arm in the prevalence of bacterial vaginosis at enrollment and the average monthly number of vaginal sex acts. To correct for this imbalance in simulations, we conducted stratified re-randomization by site, bacterial vaginosis status, and the cohort median number of average monthly sex acts.

2. Male partner characteristics

2.1 Male partner age

Male partner age is assigned according to the age distribution of male partners observed in the VOICE trial (Table 2.1.1) [35].

Table 2.1.1. Distribution of male partner age by female partner age

		Female age						
		15-19	20-24	25-29	30-34	35-39	40-44	45-49
Male age	15-19	0.09	0.01	0.00	0.00	0.00	0.00	0.00
	20-24	0.63	0.34	0.02	0.00	0.00	0.00	0.00
	25-29	0.23	0.51	0.37	0.04	0.01	0.00	0.00
	30-34	0.04	0.12	0.41	0.33	0.07	0.11	0.11
	35-39	0.01	0.02	0.15	0.41	0.32	0.002	0.00
	40-44	0.00	0.00	0.03	0.15	0.40	0.33	0.33
	45-49	0.00	0.00	0.01	0.05	0.14	0.33	0.33
	50+	0.00	0.00	0.00	0.02	0.06	0.22	0.22

2.2 HIV-1 status

We assign male partner HIV-1 status according to age- and country-specific distributions of male HIV-1 prevalence [82-85] (Table 2.2.1), modified in the following ways to account for the population selected to participate in the ASPIRE trial.

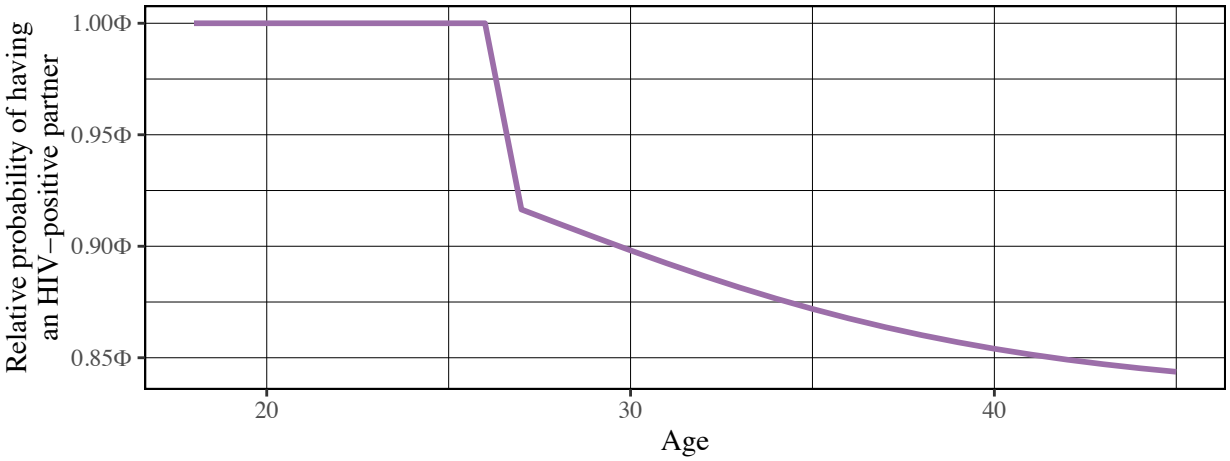
Table 2.2.1. Country- and age-specific distribution of HIV-1 prevalence among males.

	Male age							
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50+
Malawi	0.010	0.011	0.064	0.092	0.118	0.140	0.192	0.205
South Africa	0.007	0.051	0.173	0.256	0.288	0.158	0.134	0.074
Uganda	0.017	0.028	0.040	0.091	0.110	0.113	0.102	0.062
Zimbabwe	0.034	0.038	0.103	0.173	0.252	0.262	0.299	0.195

First, we use the male partner HIV-1 status reported by women at baseline in select cases. If a woman reported that her male partner is HIV-positive, her male partner is assigned HIV-positive status. Additionally, we assign HIV-negative status to male partners reported to be HIV-negative if a woman is married and greater than 27 years of age, under the assumption that HIV-1 status disclosure increases with age, such that reported male partner HIV-1 status is accurate among those greater than 27 years of age, while reported male partner HIV-1 status may be less reliable among younger women.

Second, we assume that women with greater time of HIV-free survival at enrollment were less likely to be HIV-exposed by their partners. We therefore assign a reduction in the probability of having an HIV-positive male partner, relative to male age- and country-specific HIV-1 prevalence distributions, with increasing female age (Figure 2.2.1). The reduction in probability follows a piecewise function in which the probability of having an HIV-positive partner is unchanged in women younger than 27, and the reduction in probability of having an HIV-positive partner follows an inverse logistic function for women ages 27 and greater, with the carrying capacity and scale parameters determined in model calibration (Section 9).

Figure 2.2.1. Piecewise function showing the age-dependent probability of having an HIV-positive male partner relative to male age- and country-specific HIV-1 prevalence distributions (Φ).



Finally, reported condom use is treated as an indicator of a woman's perceived risk, such that women reporting any condom use within the last seven days at baseline are more likely to have an HIV-positive male partner. The relative increase in probability of an HIV-positive partner associated with condom use is determined in model calibration (Section 9).

2.3 Viral load

Women reporting an HIV-positive partner at baseline in ASPIRE also reported the treatment status of her partner. HIV-positive male partners reported to be on antiretroviral therapy (ART) are assigned a viral load value of 50 copies/mL, while HIV-positive male partners reported to not be on ART are assigned a viral load value greater than or equal to 1,000 copies/mL from an age-specific distribution of viral loads collected in a 2013 population-based survey in KwaZulu-Natal, South Africa (Table 2.3.1) [86]. HIV-positive male partners with unknown treatment status are assigned a viral load value from the full age-specific distribution (Table 2.3.1).

Table 2.3.1. Male age-specific distribution of viral load among HIV-positive male partners

Viral load (copies/mL)	Male age 15-24	25-34	35-44	45+
1-99	0.22	0.34	0.55	0.59
100-999	0.06	0.07	0.05	0.04
1,000-9,999	0.18	0.14	0.10	0.09
10,000-99,999	0.31	0.24	0.17	0.13
100,000-999,999	0.23	0.21	0.13	0.14

2.4. HIV-1 incidence among male partners

HIV-1 incidence among male partners of ASPIRE trial participants occurs in proportion to country-specific annual HIV-1 incidence. However, because the population of male partners in ASPIRE may not be represented by the general male population, we calibrated a reference male partner HIV-1 incidence value, modeled as incidence among male partners in South Africa, and applied incidence rate ratios to the reference incidence rate to represent relatively lower incidence in Malawi, Uganda, and Zimbabwe (Table 2.4.1). Similarly to modifiers of prevalent HIV-1 status described above, incidence among male partners is modified by female participant age, such that incident infections are less likely among partners of women aged greater than 26, and by reported condom use, such that incident infections are more likely among partners of women who reported condom use in the prior week at enrollment. Additional details on calibration of the reference HIV-1 incidence rate are included in section 9.

Table 2.4.1. Country-specific HIV-1 incidence rates among males ages 15-49

Country	Incidence rate	Source	Incidence rate ratio[1]
Malawi	0.22%	Malawi Population-based HIV Impact Assessment [87]	0.18
South Africa	1.21%	Rehle, et al., 2015 [88]	1.00
Uganda	0.31%	Uganda Population-based HIV Impact Assessment [89]	0.26
Zimbabwe	0.28%	Zimbabwe Population-based HIV Impact Assessment [90]	0.23

[1] Incidence rate ratios are relative to incidence in South Africa

3. Relationship formation, persistence, and dissolution

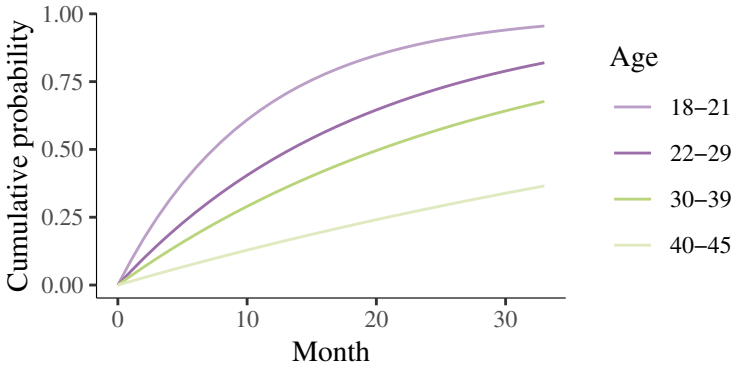
At each monthly time step, partnerships may persist or dissolve and new partnerships may be formed, each with age-specific probability. Partnership formation and dissolution rates are taken from a cohort of people living with HIV-1 in KwaZulu-Natal followed from 2009 to 2012 [91]. As women in this cohort may differ from the cohort of women enrolled in ASPIRE with respect to partnership change rates, we calibrated a multiplier parameter that would modify partnership formation and dissolution rates while maintaining relative rates by age. Annual rates are converted to monthly probabilities (Table 3.3.1; Figure 3.3.1). Among unmarried women, the model allows a maximum number of simultaneous relationships calculated as one plus the number of partners reported at baseline by each woman. We assume that marital relationships prevalent at baseline are stable and therefore are not subject to dissolution, nor do women in marital relationships at baseline acquire additional partners during the simulation.

Table 3.3.1. Age-specific monthly probability of partnership acquisition and dissolution

Female age	Probability among cohort of PLWHIV	Calibrated probability among ASPIRE participants
18-21	0.023	0.089
22-29	0.013	0.050
30-39	0.009	0.035
40-45	0.004	0.016

PLWHIV = People living with HIV-1

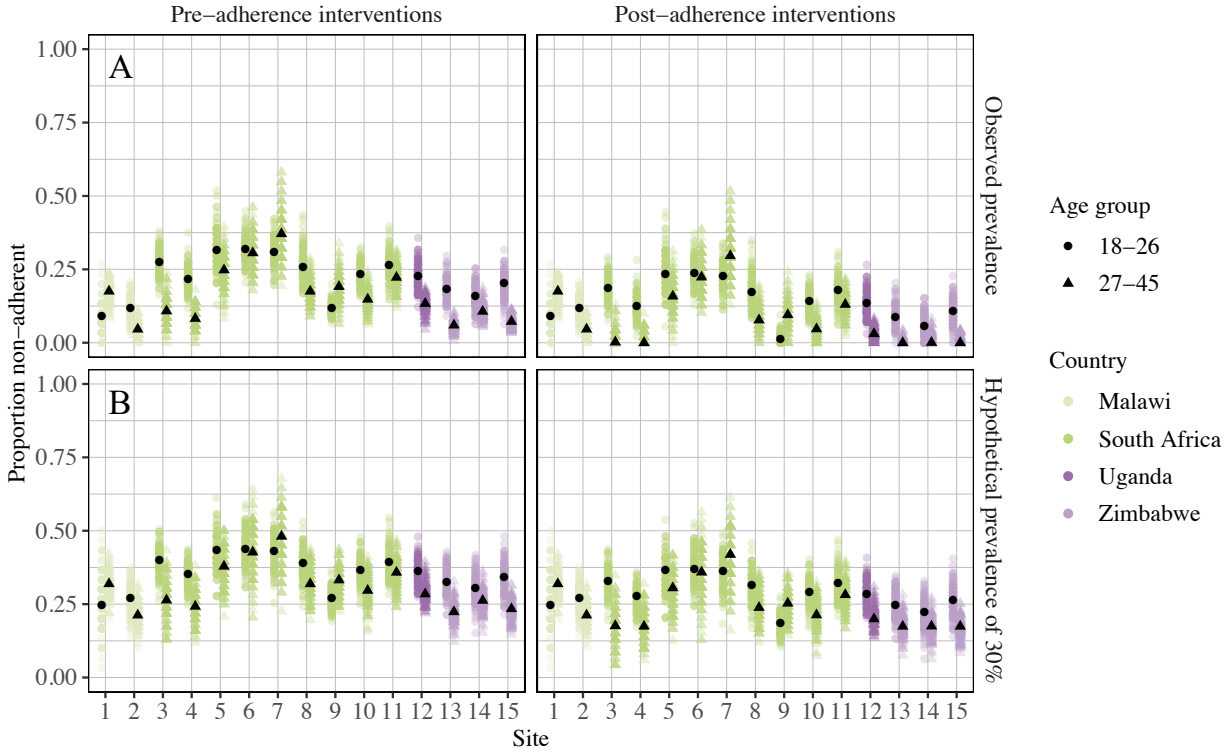
Figure 3.3.1. Age-specific cumulative probability of acquiring at least one new partner among unmarried women.



4. Non-adherence

Non-adherence is modeled in monthly timesteps and distributed proportional to observed prevalence of non-adherence by site and age group, both of which were identified as important predictors of non-adherence in the ASPIRE trial [6]. Non-adherence was defined by plasma concentrations of dapivirine, with a threshold of <95 pg/mL, as plasma measures were available throughout the trial (non-adherence was additionally evaluated by residual dapivirine levels in returned rings in years two and three of the trial only). Interventions to improve adherence were implemented in August, 2013. We therefore estimated the relative increase in the proportion of the cohort with plasma dapivirine concentrations >95 pg/mL in visits after August, 2013 with generalized estimating equations with an exchangeable correlation matrix and robust standard errors in a model adjusted for site and age group. Figure 4.1.1 shows the prevalence of non-adherence by site and age before and after the implementation of adherence interventions.

Figure 4.1.1. Prevalence of non-adherence by site, age group, and time period as observed in ASPIRE and in (A) 100 simulations with the observed distribution of non-adherence (18% overall) in ASPIRE and (B) in 100 simulations with hypothetical prevalence of non-adherence of 30%. In scenarios that use a hypothetical prevalence of non-adherence, model prevalence of non-adherence is distributed proportional to site-, age-, and time period-specific observed prevalence.



5. HIV-1 transmission

HIV-1 transmission is evaluated at each act, with risk of infection at each act calculated as:

$$1 - (1 - \lambda)^{e^{X\beta}}$$

where $X\beta$ is a vector of covariates and relative risks specific to each act (Table 5.0.1) [92]. The risk per act with an HIV-positive partner is dependent on partner viral load, infection stage of the HIV-positive partner (acute or other), baseline female age, trial arm and time-varying adherence, condom use, act type (vaginal or anal), baseline number of sexually transmitted infections, and baseline bacterial vaginosis status. HIV-1 transmission is assigned as a random binomial draw with probability equal to the per-act risk of transmission.

Table 5.0.1. Parameters used in evaluation of HIV-1 transmission

Parameter	Value	Source
λ	0.002[a]	Boily, 2009 [71]
Relative risk per $1\log_{10}$ increase in viral load	2.89	Hughes, 2012 [92]
Relative risk during acute infection	5.30	Bellan, 2015 [93]
Duration of acute infection	2.0[b]	Bellan, 2015 [93]
Relative risk per year of age	0.96	Hughes, 2012 [92]
Relative risk of dapivirine ring	Varied in simulations	
Relative risk of condom use	0.22	Hughes, 2012 [92]

Relative risk of anal intercourse	6.60[a]	Baggaley, 2010 [94] Patel, 2014 [70] Boily, 2009 [71] Powers, 2008 [81]
Relative risk of sexually transmitted infection	2.50	Hughes, 2012 [92]
Relative risk of bacterial vaginosis	3.63	Hughes, 2012 [92]

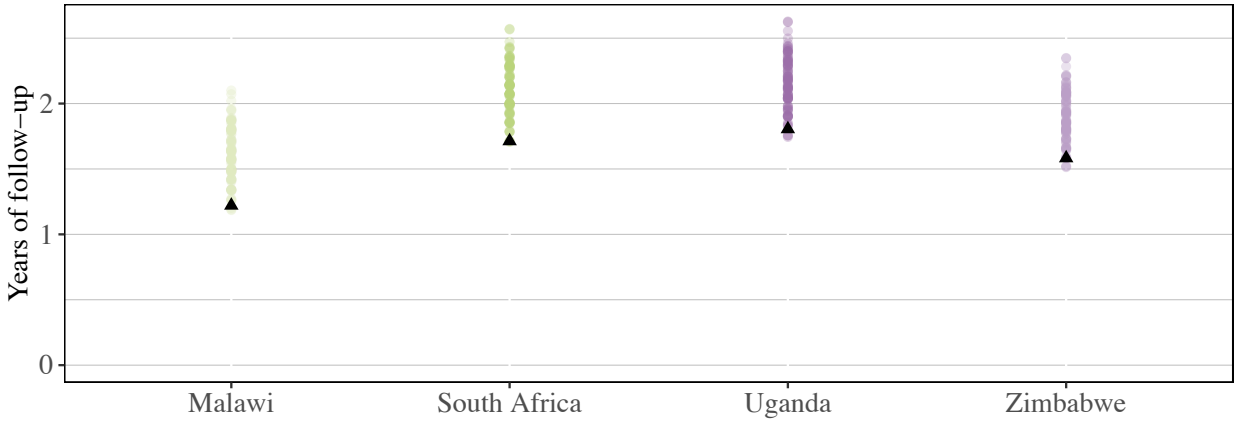
[a] Parameter value inferred in approximate Bayesian computation (ABC) model-fitting process (Section 9). Source column in these cases refers to published estimates that informed selection of the prior distribution used in the ABC model-fitting process.

[b] Value is modified from estimated 1.7 months in Bellan, 2015 to accommodate model monthly time intervals.

7. Simulation duration and participant follow-up time

Simulations are endpoint-driven, with each simulation completing monthly timesteps until 168 HIV-1 infections have occurred among trial participants [6]. Calendar time is tracked throughout simulations, with women at-risk for HIV-1 infection from her observed study enrollment date. Women who terminated the study early are censored from model simulations at their observed censor date, whereas women who completed their scheduled study follow-up may contribute more than their observed follow-up time if a model simulation continues beyond her observed final study visit. Figure 7.1 shows observed and simulated follow-up time per person by country.

Figure 7.1. Follow-up time per person by country as observed in ASPIRE and in 100 example simulations.



8. Estimation of ring efficacy

8.1 Estimation of ring effectiveness at the population level

To identify the combinations of non-adherence, receptive anal intercourse, and ring efficacy consistent with ASPIRE trial results, we estimated ring efficacy with a site-stratified intent-to-treat analysis, equivalent to the model used to estimate ring efficacy in the ASPIRE trial [6].

8.2 Estimation of per-exposure ring efficacy

We estimated the per-exposure risk of infection as the number of infections out of the number of sex acts with an HIV-positive partner. Per-exposure ring efficacy is then calculated as the ratio of per-exposure risk among adherent women in the dapivirine arm to per-exposure risk among women in the placebo arm.

9. Model calibration

We used sequential Monte Carlo approximate Bayesian computation (ABC) [78] a simulation-based iterative sampling approach, to infer values for model parameters about which there was substantial

uncertainty: (1) the baseline per-act probability of HIV-1 transmission, (2) the carrying capacity and (3) scale terms of an inverse logistic distribution of age-dependent relative risk of having an HIV-positive partner, (4) the relative risk of having an HIV-positive partner given reported condom use at last sex, (5) the per-act relative risk of anal intercourse, (6) the relative increase in the partner change rate among women in ASPIRE compared to a cohort of individuals living with HIV-1 [91], and (7) reference HIV-1 incidence among male partners. This section describes the selection of prior distributions, the algorithm used to infer parameter values, and results of the model-fitting procedure.

9.1 Prior distributions

The prior distribution for baseline probability of HIV-1 transmission was obtained from Boily, et al., 2009 [71], which reports a pooled per-act risk of HIV-1 transmission from males to females in low- and middle-income country settings of 0.0300 (95% CI: 0.0014, 0.0063). We used a beta distribution as the prior for baseline probability of HIV-1 transmission, with parameters estimated such that the mean of the beta distribution is equal to the point estimate of 0.0300 and 95% of the area of the beta distribution falls within the bounds of the 95% confidence interval of the point estimate (alpha = 6, beta = 1,664).

We used uniform prior distributions for all remaining parameters. Both the carrying capacity and scale terms of the inverse logistic distribution of the age-dependent relative risk of having an HIV-positive partner were bounded in [0, 1]. The relative risk of having an HIV-positive partner given reported condom use at last sex was bounded in [1, 3]; prior analyses indicated that reported condom use was positively associated with HIV-1 risk, and we therefore used a prior that would not allow a protective effect of reporting condom use at last sex.

The prior distribution for the per-act relative risk of anal intercourse was obtained from four meta-analyses that reported the per-act HIV-1 risk of anal intercourse (0.014, 95% CI: 0.002, 0.025 [94]; 0.014, 95% CI: 0.01, 0.019 [70]) and vaginal intercourse (0.0009, 95% CI: 0.0006, 0.0012 [81]; 0.0030, 95% CI: 0.0014, 0.0063 [71]). These point estimates correspond to a range of per-act relative risk of anal intercourse bounded within [5, 16]; these bounds form the minimum and maximum values of the uniform prior distribution used in the ABC model-fitting procedure.

We used a wide prior distribution for a reference HIV-1 incidence rate among male partners to reflect uncertainty about the extent to which male partners of ASPIRE participants are reflective of the general population of men in Malawi, South Africa, Uganda, and Zimbabwe. The lower bound of the prior of 0.97% annual incidence is obtained from nationally representative incidence estimates among men ages 15-49 in South Africa[88] and the upper bound of 9.88% annual incidence is twice the estimated 2018 annual HIV-1 incidence among individuals of all ages and genders in South Africa [95].

Previous research has shown a decline in sexual risk behaviors following HIV-1 diagnosis [96]. We therefore assumed that partner change rates among people living with HIV-1 may be lower than among women enrolled in ASPIRE, and therefore used a uniform prior in [1, 20] to identify the relative increase in partner change rates among women enrolled in the ASPIRE trial, compared to individuals living with HIV-1 from whom we obtain baseline age-specific partner change rates [91].

9.2 Approximate Bayesian computation algorithm

Calibration uses a sequential Monte Carlo approximate Bayesian computation algorithm, an approach designed to efficiently sample from the full parameter space while ensuring high coverage of the highest likelihood areas of the parameter space [78]. The calibration algorithm first samples 100,000 particles (i.e., parameter sets) from the specified prior distributions and runs a single model simulation for each particle. The likelihood of each particle given observed age-specific and time-specific incidence in the placebo arm is then calculated, and the 60,000 particles with the highest corresponding likelihoods are retained as the intermediate distribution of iteration 0. For each subsequent iteration, 40,000 particles are selected with

weighted probability, and a new particle is derived from each of the sampled particles by selecting new parameter values from a multivariate Gaussian perturbation kernel with a mean of the sampled particle and empirically estimated variance from the previous set of accepted particles. Each of the new particles is then simulated and weighted according to the inverse of the multivariate Gaussian kernel from which it was selected. At each iteration, the 60,000 particles with the highest likelihood are retained, and the algorithm completes subsequent iterations until the proportion of newly accepted particles from the current iteration is less than 10%.

Our approximate Bayesian computation algorithm is as follows:

Set $t = 0$
For $t = 0$, do
Sample 100,000 particles $\theta^{(0)} \sim \pi(\theta)$
For i = 1 to 100,000, do

1. Simulate $x_i^{(0)} \sim f(x_i^{(0)} | \theta_i^{(0)})$
2. Set $w_i^{(0)} = 1$
3. Calculate $\rho_i^{(0)}\left(S\left(x_i^{(0)}\right), S(y)\right) = \prod_{k=1}^{3} \frac{e^{-S\left(x_{ik}^{(0)}\right)} \left(S\left(x_{ik}^{(0)}\right)\right)^{S(y_k)}}{S(y_k)!} \prod_{n=1}^{2} \frac{e^{-S\left(x_{in}^{(0)}\right)} \left(S\left(x_{in}^{(0)}\right)\right)^{S(y_n)}}{S(y_n)!}$, where k indexes ages 18-21, 22-26, and 27-45 and n indexes two time period, months 15-23 and 24-31.

Set $\epsilon_0 = Q_{\rho^{(0)}}(0.6)$ and $p_{acc} = 1$
Let $\left(\theta^{(0)}, w^{(0)}\right) = \left(\theta_i^{(0)}, w_i^{(0)} \middle| \rho_i^{(0)} \leq \epsilon_0\right)$
Calculate $\sigma_{(0)}^2$ as twice the weighted empirical variance of $\left(\theta^{(0)}, w^{(0)}\right)$
Set $t = t + 1$
While $p_{acc} < 0.1$, do
For i = 1 to 40,000, do

1. Sample particle θ_i^* from $\theta_j^{(t-1)}$ with probability $\frac{w_j^{(t-1)}}{\sum w_j^{(t-1)}}$
2. Perturb particle θ_i^* with a multivariate Gaussian perturbation kernel with mean θ_i^* and variance $\sigma_{(t-1)}^2$
3. Simulate $x_i^{(t)} \sim f(x_i^{(t)} | \theta_i^{(t)})$
4. Calculate $w_i^{(t)} = \frac{\pi(\theta_i^{(t)})}{\sum_{j=1}^{60,000} (w_j^{(t-1)} K(\theta_i^t | \theta_j^{(t-1)}))}$, where $K(\theta_i^t | \theta_j^{(t-1)})$ is a multivariate Gaussian kernel $\sim(\theta_j^{(t-1)}, \sigma_{(t-1)}^2)$
5. Calculate $\rho_i^{(t)}\left(S\left(x_i^{(t)}\right), S(y)\right) = \prod_{k=1}^{3} \frac{e^{-S\left(x_{ik}^{(t)}\right)} \left(S\left(x_{ik}^{(ts)}\right)\right)^{S(y_k)}}{S(y_k)!}$

Set $\epsilon_t = Q_{\rho^{(t)}}(0.6)$
Calculate $p_{acc} = \frac{\sum \mathbf{1}(\rho_i^{(t)} \leq \epsilon_t)}{40,000}$
Let $\left(\theta^{(t)}, w^{(t)}\right) = \left(\theta_i^{(t)}, w_i^{(t)} \middle| \rho_i^{(t)} \leq \epsilon_t\right)$
Calculate $\sigma_{(t)}^2$ as twice the weighted empirical variance of $\left(\theta^{(t)}, w^{(t)}\right)$
Set $t = t + 1$

9.3 Calibration results

The algorithm achieved approximate convergence following twelve resampling and simulating steps. The model was relatively insensitive to both the relative risk of anal intercourse and the scale term of an inverse logistic distribution of the age-dependent relative risk of having an HIV-positive partner (Figure 9.3.1). Furthermore, a bivariate plot of the weighted density of the relative increase in partner change rates and the reference male HIV-1 incidence rate demonstrated correlation (Figure 9.3.2) in these parameters that prevented a more precise estimation of their best-fit values in this cohort. Parameter values with the highest weighted density are shown in Table 9.3.1, and a plot of 100 simulations using the best-fit parameter values is shown in Figure 9.3.3.

Table 9.3.1. Parameter values inferred in approximate Bayesian computation model-fitting procedure.

Parameter	Value
Baseline HIV-1 infectivity (λ)	0.002
Inverse logistic distribution of age-dependent relative risk of an HIV-positive partner	
Carrying capacity term	0.167
Scale term	0.149
Relative risk of an HIV-positive partner given condom use at last sex	1.133
Relative risk of anal intercourse	6.601
Relative increase in partnership change rates	3.889
Reference male HIV-1 incidence rate	0.078

Figure 9.3.1. Prior and intermediate distributions of five parameters fitted in approximate Bayesian computation model-fitting procedure. Dashed lines show the 90% credible interval of the posterior distribution.

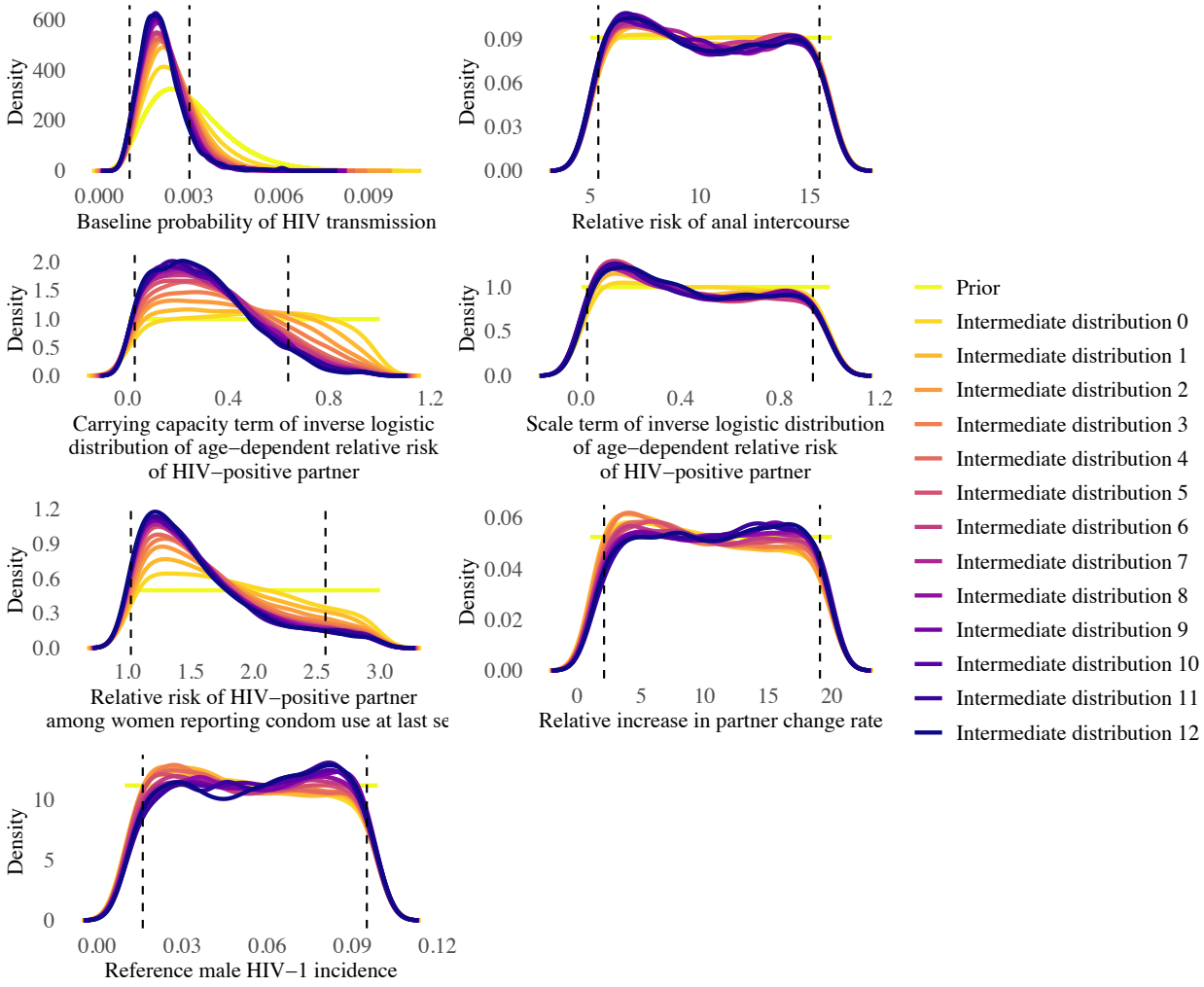


Figure 9.3.2. Bivariate plot of posterior distribution of the relative increase in partner change rate and reference male HIV-1 incidence, with the point of highest density in black.

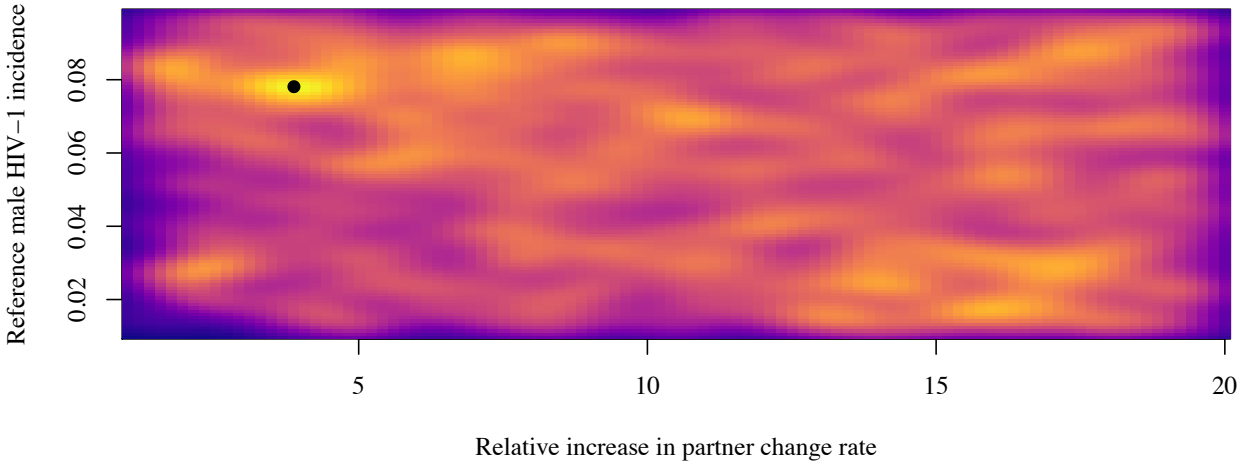
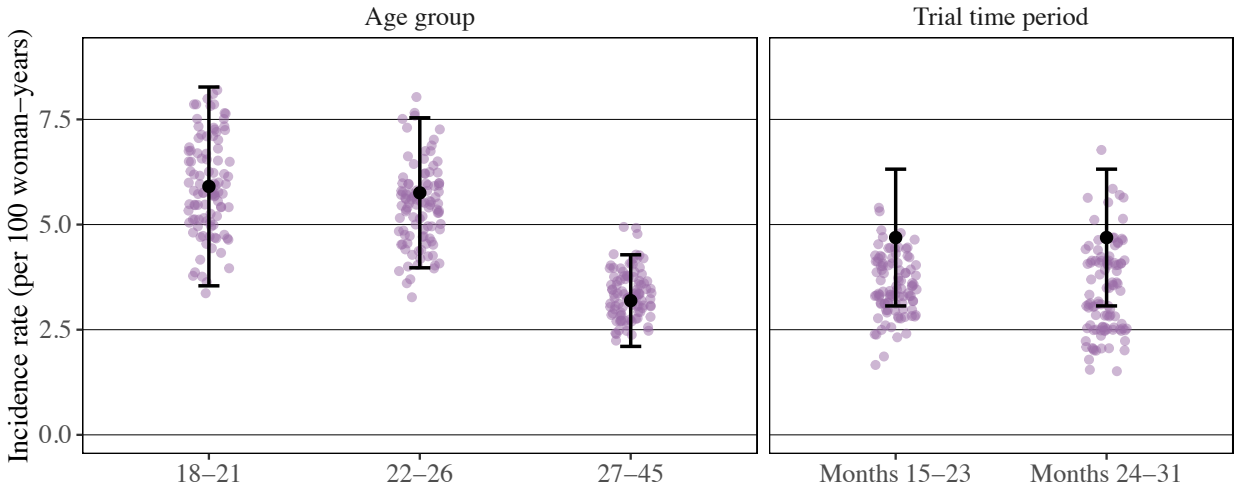


Figure 9.3.3. Simulated age- and time-specific incidence in the placebo arm from 100 model simulations using the best-fit parameters identified in the ABC model-fitting procedure. Observed incidence in the ASPIRE trial is overlaid in black.



Chapter 5. Predictors of HIV-1 risk among women aged 18-35 seeking effective contraception

Age-specific risk scores do not improve HIV-1 prediction among women in South Africa

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Keywords: sub-Saharan Africa; South Africa; empiric risk scoring tool; HIV-1; women

Abstract

Introduction: HIV-1 risk scoring tools could help target uptake of prevention modalities such as pre-exposure prophylaxis (PrEP). Recent research suggests that risk scores for women aged 18-45 may not perform well among young women aged 18-24. We evaluated the predictive performance of age-specific risk scores compared to an existing risk score for women aged 18-45 and investigated risk factors for HIV-1 acquisition by age.

Methods: We conducted a secondary analysis of the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, using standard methods to develop and internally validate risk scores predictive of HIV-1 acquisition within one year for women aged 18-24 and 25-35 in South Africa. Candidate predictors included baseline demographic, clinical, behavioral, and contextual characteristics readily available in clinical settings. The VOICE risk score was applied to women aged 18-35 in South Africa. We evaluated predictive performance of each risk score by area under the receiver operating characteristic curve (AUC).

Results: A combination of behavioral, clinical, and contextual factors were predictive of HIV-1 acquisition among women aged 18-24. Among women aged 25-35, a different combination of factors that included demographic, rather than behavioral, characteristics, along with clinical and contextual factors were predictive of HIV-1 acquisition. Predictive performance was moderate, with AUC of 0.64 (95% CI: 0.60, 0.68) among women aged 18-24, 0.68 (95% CI: 0.62, 0.74) among those aged 25-35, and 0.61 (95% CI: 0.57, 0.64) for the VOICE risk score applied to women aged 18-35. Predictive performance was poorer for modified risk scores excluding laboratory-based variables. Among women aged 18-24, HIV-1 incidence was high even at low risk scores, at 3.9 per 100 person-years (95% CI: 3.2, 4.7) among women with four or fewer risk score points.

Conclusions: All risk scores were moderately predictive of HIV-1 acquisition in these settings. While we identified important differences in the composite factors that best predict risk by age, age-specific risk scores performed only marginally better than an existing non-age-specific risk score. Precision public health approaches for targeted PrEP provision in South Africa may require more extensive data than are currently available to improve prediction.

Clinical Trial Number: NCT02550067

Introduction

Women account for more than half of the 1.1 million new HIV-1 infections occurring annually in sub-Saharan Africa, with an even more marked disparity in risk among adolescent girls and young women, who account for 70% of new infections among those aged 15-24 [1]. Pre-exposure prophylaxis (PrEP) is a highly effective HIV-1 prevention method, reducing risk by more than 90% when used with high adherence [3]. With increasing availability in sub-Saharan Africa, PrEP has the potential to contribute significantly to HIV-1 prevention goals in the region [97]. However, strategies to efficiently promote and allocate PrEP to those at highest risk are needed to ensure maximal impact within resource constraints.

Clinical decision rules, or empirically-derived risk scoring tools, are one potential strategy to help identify those who might most benefit from PrEP. Risk scoring tools to identify those at greatest risk for HIV-1 have been developed for a number of settings and populations including for men who have sex with men (MSM) in the United States [98-100] and for sero-discordant couples [101], pregnant and postpartum women [102], and women aged 18-45 in sub-Saharan Africa [40]. In prior research, these risk scores have been associated with self-perceived HIV-1 risk [103], which is in turn associated with higher PrEP uptake [104, 105]. Nonetheless, in both the United States and in sub-Saharan Africa, only approximately one-third of those identified via risk score evaluation to be at high risk of HIV-1 acquisition had self-perceived high risk [106, 107]. Qualitative research and pilot studies suggest that high risk scores may provide an opportunity to re-assess self-perceived low risk and prompt engagement in protective behaviors [108, 109]. Use of risk scores to inform prioritization of PrEP provision could thus serve to increase both efficiency and overall uptake of PrEP.

Risk scores are population- and setting-specific, often performing well only among groups comparable to the population in which the risk score was initially developed [110, 111]. The VOICE risk score was previously developed and externally validated in three cohorts of women aged 18-45 in sub-Saharan Africa [40, 41]. However, recent research showed that the VOICE risk score performed poorly among adolescent

girls and young women [42], suggesting that a different set of risk factors may be more predictive of HIV-1 acquisition among younger age groups. Given the high HIV-1 incidence experienced by this group of women [1], risk scores tailored to their unique risk profile are needed.

We conducted a secondary analysis of the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial [112]. This study enrolled more than 3,500 young women aged 18-24 in diverse geographic settings in South Africa, providing a unique opportunity to (1) develop and evaluate the predictive performance of age-specific risk scores, compared to the predictive performance of the non-age specific VOICE risk score, and (2) investigate whether the components of age-specific risk scores differed among women aged 18-24 and women aged 25-35.

Methods

The ECHO Trial was a randomized trial enrolling and following 7,829 HIV-1-negative women seeking effective contraception in Eswatini, Kenya, South Africa, and Zambia from 2015-2018; detailed trial methods and results have been published previously [112]. As the majority of study participants were from South Africa, we limited development of the risk score to women enrolled in the nine sites in South Africa, representing a geographically diverse range of settings across five provinces (Western Cape, Eastern Cape, Gauteng, KwaZulu-Natal, and North West provinces). The primary endpoint of analyses was incident HIV-1 seroconversion; we therefore limited the analysis to women who were confirmed HIV-1-negative at enrollment and with at least one follow-up HIV-1 test. Institutional review boards at each site approved the study protocol and women provided written informed consent.

We used Cochran-Mantel-Haenszel chi-squared tests stratified by study site to evaluate differences in the distribution of participant characteristics among women aged 18-24 and 25-35. We used standard methods [113] to develop and internally validate risk scores for women aged 18-24 and 25-35. Follow-up time was censored at one year (within a window of two weeks prior to the scheduled annual visit and up to eleven

weeks after), as shorter-term outcomes are most relevant for decision-making regarding short-acting prevention methods, such as oral PrEP. We aimed to develop risk scores that could be applied in clinical settings in sub-Saharan Africa, and therefore considered as candidate predictors 25 baseline demographic, clinical, behavioral, and contextual (defined as HIV-1 prevalence of the surrounding area or province) characteristics that would be readily available in clinical settings. Given that laboratory evaluation of sexually transmitted infections (STI) in these settings is not common, we additionally developed a modified risk score excluding laboratory-based variables for each age group. We used a categorical parameterization for continuous variables if the predictive performance with such a parameterization, defined by area under the receiver operating characteristic curve (AUC), was comparable to the continuous parameterization or if the continuous parameterization would be infeasible in practice (for example, continuous number of partners may result in a risk score with too many points to be easily computed). We estimated study site-specific HIV-1 prevalence in 5% increments from 10% to 30% from publicly available prevalence microdata [114]. We evaluated the association between each candidate predictor and incident HIV-1 with Cox proportional hazards models, excluding women with incomplete baseline data. Variables associated with incident HIV-1 with statistical significance $p<0.10$ were included in a fully stepwise multivariable Cox proportional hazards model. We selected the model with the lowest Akaike Information Criterion [115] as the final risk score model and assigned points to individual variables by dividing each coefficient by the smallest coefficient among all variables in the model and rounding to the nearest integer.

We evaluated model calibration by calculating HIV-1 incidence by risk score value. We calculated AUC to evaluate overall predictive performance of the risk score [116] and identified the optimal risk score threshold value as the value that maximized AUC, indicating the threshold value that best discriminates between those most and least likely to acquire HIV-1 within the subsequent year. If HIV-1 incidence among those not meeting the optimal threshold value exceeded the World Health Organization (WHO)-recommended threshold for PrEP use of 3% [117], we also identified an alternative threshold below which incidence was less than 3%. We additionally compared the predictive performance of the full risk score to

the predictive performance of each individual predictor. For each risk score, we calculated the sensitivity, specificity, and positive and negative predictive values. Due to a limited number of HIV-1 endpoints when stratifying by age groups and in order to use all available data to inform development of the risk scores, we performed internal validation by repeating the full risk score development process in 100 bootstrapped datasets. Use of this approach minimizes the risk of model over-fitting [113].

We performed external validation of the VOICE risk score [40] by evaluating its predictive performance among women aged 18-35 in South Africa. The VOICE risk score was developed from a cohort of women in South Africa, Uganda, and Zimbabwe, and includes as predictors age less than 25, marital and co-habitation status, alcohol use in the prior three months, receipt of financial or material support from a partner, whether a partner has other sex partners, any curable STI, and herpes simplex virus type 2 (HSV-2) [40]. While the VOICE risk score includes an item on alcohol consumption in the prior three months, alcohol use in ECHO was collected as the number of weekly drinks. We therefore used an indicator of any weekly alcohol consumption in place of alcohol consumption in the prior three months in applications of the VOICE risk score to these cohorts. All analyses were conducted in R [55] version 3.5.0.

Results

Study population

Analyses include 5,573 women aged 18-35 from South Africa. Women aged 25-35 were more likely than those aged 18-24 to be married or living with a partner, earning an income, and receiving financial and/or material support from a partner (all $p<0.001$; Table 1). Infection with *C. trachomatis* at enrollment was more common among women aged 18-24, while women aged 25-35 were nearly two-fold more likely to test positive for HSV-2 (both $p<0.001$; Table 1). Median follow-up time with censoring at the twelve-month visit was 364 days (IQR: 364, 368).

Risk scores among women aged 18-24

In the first year of ECHO follow-up in South Africa, 188 women aged 18-24 acquired HIV-1, at an incidence rate of 5.4 cases per 100 person-years (95% CI: 4.6, 6.2). Factors associated with HIV-1 at significance level $p<0.10$ in univariate analyses were reported condom use frequency, marital and co-habitation status, number of sex partners in the prior three months, whether a primary partner has other sex partners, alcohol consumption, HIV-1 prevalence, *N. gonorrhoeae*, *C. trachomatis*, and HSV-2. Of these, all but marital and co-habitation status and *C. trachomatis* were retained in the final stepwise model and risk score (Table 2). *N. gonorrhoeae* was weighted most heavily in the final risk score, with three points, followed by receiving services in an area with HIV-1 prevalence greater than 15% and having more than one sex partner in the prior three months (two points each). Nonetheless, the full risk score performed better than each of the individual predictors (Supplementary Figure 1). AUC for the full risk score was 0.64 (95% CI: 0.60, 0.67), indicating modest predictive ability (Figure 1). In internal validation, AUC was 0.62 (95% CI: 0.58, 0.64) across 100 bootstrapped resamples in which the full model selection procedure was repeated

Across all risk scores, there was a dose-response relationship in HIV-1 incidence with increasing risk score points (Figure 2A; Table 4). Among women aged 18-24, incidence ranged from zero cases among women with zero points in the full risk score including laboratory-based variables to 25.0 (95% CI: 7.7, 69.6) cases per 100 person-years among women with 10 or more points. Women meeting the optimal threshold value of ≥5 points experienced HIV-1 incidence of 8.8 (95% CI: 7.1, 10.7) cases per 100 person-years, whereas incidence among women with <5 points was approximately halved at 3.9 (95% CI: 3.2, 4.7) per 100 person-years (Supplementary Figure 2). At an alternative threshold of ≥4 points, HIV-1 incidence was 6.7 (95% CI: 5.7, 7.9) among those screening positive and 2.9 (95% CI: 2.1, 4.0) per 100 person-years among those with a risk score of fewer than 4 points. Thirty percent of women aged 18-24 met the optimal threshold value of ≥5 points, accounting for 48.9% of infections among all women aged 18-24 (Table 3). Sensitivity was higher at the alternative threshold of ≥4 points, with a concomitant decline in specificity (Table 3).

A modified risk score for women aged 18-24 excluding laboratory-based variables was similar to the full risk score (Table 2), but had somewhat poorer predictive performance, with an AUC of 0.60 (95% CI: 0.56, 0.63) (Figure 1). In internal validation, AUC across 100 bootstrapped resamples was 0.59 (95% CI: 0.56, 0.61). HIV-1 incidence ranged from 0 cases among women with 0 risk score points to 11.8 cases (95% CI: 7.5, 17.9) per 100 person-years among those with 6 or more risk score points (Figure 2B; Table 4). At the optimal threshold value of ≥4 points, incidence was 6.6 cases (95% CI: 5.5, 7.8) per 100 person-years, compared to 3.7 cases (95% CI: 2.9, 4.8) among women with fewer than 4 risk score points (Supplementary Figure 2). Among women meeting an alternative threshold of ≥3 points, HIV-1 incidence was 6.0 (95% CI: 5.1, 6.9) per 100 person-years, compared to 2.3 (95% CI: 1.4, 3.6) per 100 person-years among those with fewer than 3 risk score points. Approximately half of all women aged 18-24 met the optimal threshold value, accounting for 67.9% of incident infections (Table 3). Four-fifths of women met the alternative threshold of ≥3 points, accounting for 91.9% of infections (Table 3).

Risk scores among women aged 25-35

HIV-1 incidence in the first year of follow-up among women aged 25-35 was 3.4 cases per 100 person-years (95% CI: 2.7, 4.0). A combination of demographic (age and marital and co-habitation status), contextual (province), and clinical (*N. gonorrhoeae*, *C. trachomatis*, and HSV-2) factors were associated with HIV-1 incidence at significance $p<0.10$ (Table 2). With the exception of *C. trachomatis*, all variables were retained in the final stepwise prediction model. Of these, province was weighted most heavily in risk score points, with three points assigned to those living in Eastern Cape, Gauteng, KwaZulu-Natal, and North West provinces. All other components of the risk score were assigned one point each. Similar to the full risk score developed for women aged 18-24, the full risk score for women aged 25-35 performed better than each of its component risk factors (Supplementary Figure 1). Predictive performance for the full risk score was moderate, with an AUC of 0.68 (95% CI: 0.62, 0.74) and mean AUC in internal validation of

0.64 (95% CI: 0.59, 0.69). HIV-1 incidence by risk score points ranged from zero among women with zero risk score points to 12.0 (95% CI: 3.7, 33.6) cases per 100 person-years among women with the maximum risk score points of seven. At the optimal threshold value of six or more points, incidence was 8.6 cases (95% CI: 6.1, 12.0), approximately four-fold higher than incidence among women with fewer than six risk score points (2.3, 95% CI: 1.7, 3.0) (Supplementary Figure 2). Women with ≥6 risk score points accounted for 42.9% of incident infections, yet accounted for only 16.7% of all women aged 25-35 (Table 3).

A modified risk score excluding laboratory-based variables was similar, with all included risk factors retaining the same risk score points as in the full risk score. Predictive performance was slightly lower, with an AUC of 0.64 (95% CI: 0.59, 0.70) in the full derivation dataset and a mean AUC of 0.62 (95% CI: 0.58, 0.67) across 100 bootstrapped resamples in internal validation. HIV-1 incidence was highest among women with the optimal threshold value of ≥5 points at 6.0 cases (95% CI: 4.3, 8.3) per 100 person-years, relative to incidence of 2.5 (95% CI: 1.8, 3.3) cases per 100 person-years among women with fewer than five risk score points (Supplementary Figure 2). Approximately one-quarter of women aged 25-35 had five risk score points, accounting for 44.4% of incident infections (Table 3).

Validation of VOICE risk scores among women aged 18-35

The VOICE risk score including laboratory-based variables had moderate predictive performance among South African women aged 18-35, with an AUC of 0.61 (95% CI: 0.58, 0.65), similar to predictive performance of age-specific risk scores (Figure 1). Performance of the modified VOICE risk score excluding laboratory variables was slightly lower in South Africa, with AUC of 0.59 (95% CI: 0.56, 0.62) (Figure 1).

Discussion

We developed and internally validated age-specific HIV-1 risk scores for women in South Africa, identifying both differences and similarities in risk factors by age. Among women aged 18-24, a combination of baseline behavioral, clinical, and contextual factors best predicted subsequent HIV-1 acquisition, while among women aged 25-35, demographic, rather than behavioral, risk factors combined with clinical and contextual factors to form the optimal risk score. Across all ages, HIV-1 prevalence of the surrounding area was an important predictor of risk, though the full risk score performed better than prevalence alone, emphasizing the importance of both individual and contextual factors in HIV-1 risk. These findings support the multi-pronged approach to PrEP implementation taken by governments such as Kenya's, where targeting of PrEP provision is guided by both regional prevalence and consideration of key populations, and is further refined with use of a rapid screening tool [4]. Such approaches are predicted to both achieve high coverage [118] and maximize the impact of HIV-1 prevention across regions with heterogeneous HIV-1 prevalence [119]. In uniformly high-prevalence settings, on the other hand, additional modeling research is needed to evaluate the incremental impact of PrEP provision targeted by individual risk factors.

In both age groups and in the application of the VOICE risk score, the predictive performance of the full risk score was reduced in a modified risk score excluding laboratory-based evaluations of STI. In particular, among young women aged 18-24, *N. gonorrhoeae* was the most heavily weighted risk factor component. In prior research, a history of STIs was associated with PrEP uptake [106, 111], suggesting that STI diagnoses may be a particularly salient marker of HIV-1 risk for individuals. Inclusion of such objective measures of risk may help potential PrEP users recognize their HIV-1 risk and motivate uptake. However, STI testing in routine clinical care is uncommon in sub-Saharan Africa, posing an important barrier to application of the most useful version of these risk scores, as well as missing opportunities to treat infections associated with increased HIV-1 risk [92]. Efforts to scale up point-of-care STI tests would increase the

feasibility of including such variables in risk scores, and thereby optimize their performance and subsequent efficiency of PrEP allocation, particularly for young women.

Age-specific full risk scores developed from the ECHO trial had moderate predictive performance, with AUC ranging from 0.64 to 0.68. However, HIV-1 incidence among women who did not meet the optimal threshold was still as high as 2.3 cases per 100 person-years among women aged 25-35, and even higher, at 3.9 cases per 100 person-years, among women aged 18-24. Elevated HIV-1 incidence among those who would screen negative by risk score emphasizes that these tools are not suitable as eligibility criteria. In the absence of improved predictive performance, a lower risk score threshold of ≥4 points, identifying a group of women with incidence exceeding the WHO-recommended threshold for PrEP use of 3%, is preferable. While this alternative threshold increased the sensitivity of the risk score to identify women most likely to benefit from PrEP, it also had a higher proportion of false positives, indicating that neither approach is likely to capture the full context of an individual's risk, yet may be important means through which to open dialogue around risk [120] and set the stage for shared decision-making to select a prevention option [108]. Additionally, while risk scores may prompt re-evaluation of self-perceived risk [108, 109], self-perceived risk does not necessarily translate to PrEP uptake [107]. Overall efforts to increase uptake for PrEP should also focus on barriers such as cost, accessibility, and stigma, as well as expansion of prevention options to meet women's needs [121].

Our validation of the VOICE risk score showed similar predictive performance in this cohort as in other cohorts of women of similar age enrolled in clinical trials in sub-Saharan Africa [40, 41]. Although age-specific risk scores had moderate predictive performance, they performed only slightly better than the VOICE risk score applied to the full cohort of women aged 18-35, suggesting that, despite differences in risk factors across age groups, the added value of these age-specific risk scores to the existing VOICE risk score may be limited. Furthermore, data contributing to the development of both these risk scores and the VOICE risk score were collected in the context of clinical trials, and so may be limited by the necessarily

small amount of behavioral and clinical history data collected in such studies. Recent research in the United States demonstrated the added benefit of leveraging machine learning methods and the large amount of data available from electronic health records (EHR) by developing an HIV-1 risk score that outperformed simpler risk scores used to-date [122]. The SEARCH study applied machine learning approaches to a limited number of demographic variables, with modest improvements over model-based risk scores developed from the same set of candidate predictors (AUC of 0.73 vs. 0.70), suggesting that richer data, like that from EHR, are needed improve risk score predictive performance [123]. As use of EHR grows in the future in sub-Saharan Africa [124], their extensive data may inform development of more precise risk scores, as well as potentially leverage non-sensitive health information to minimize discomfort in patient-provider interactions in discussing potentially sensitive sexual behaviors. Automated approaches for calculating risk scores may also limit confusion by making counter-intuitive risk factors hidden from the risk score calculation. For example, among women aged 18-24, use of condoms was positively associated with HIV-1 acquisition. While this association may be explained by condom use as an indicator of self-perceived risk or less stable partnerships, its inclusion in the risk score may be confusing to providers given that it runs counter to standard HIV-1 prevention advice. EHR data may also provide an opportunity to externally validate these simplified risk scores in non-clinical trial settings, a critical next step to understanding their practical utility [100, 125].

All women participating in the ECHO trial were sexually active at enrollment, limiting the generalizability of these risk scores to sexually active women. However, sexually active women are those at highest risk for HIV-1 acquisition [42]. Risk scores developed for this population may be well-suited for family planning clinics and other points of care where women seek contraception. Indeed, contraceptive initiation is an indicator of being sexually active, and may represent a particularly opportune time to screen for HIV-1 risk and initiate conversations about prevention options [126].

In conclusion, we identified important differences in the composite factors that best predict HIV-1 seroconversion among young women aged 18-24 and women aged 25-35 and highlighted the role of contextual factors in combination with individual-level factors in predicting HIV-1 risk. Nonetheless, the developed risk scores showed only modest improvement over existing non-age-specific risk scoring tools. Overall risk of HIV-1 acquisition is high even among those with a low risk score, supporting high coverage of combination HIV prevention including PrEP for all but the lowest risk women. Precision public health approaches for targeted PrEP provision in South Africa may require more extensive data systems than are currently available.

Table 1. Baseline characteristics among women enrolled in ECHO in South Africa, $n = 5{,}573$[1]. All values are *n* (%).

Characteristic	Ages 18-24, $n = 3{,}461$	Ages 25-35, $n = 2{,}112$	p[2]
Married or living with partner	294 (8.5)	607 (28.7)	< 0.001
Educational attainment			
None or any primary	6 (0.2)	17 (0.8)	
Any secondary	2,825 (81.6)	1,777 (84.1)	< 0.001
Post-secondary	630 (18.2)	318 (15.1)	
Earns own income	488 (14.1)	587 (27.8)	< 0.001
Receives material and/or financial support from partner	1,671 (48.3)	1,324 (62.7)	< 0.001
Any weekly alcohol consumption	745 (21.5)	475 (22.5)	0.319
More than one sex partner in the prior three months	284 (8.2)	178 (8.4)	0.981
Partner has sex with others			
No	1,119 (32.3)	617 (29.4)	
Don't know	618 (17.9)	344 (16.4)	< 0.001
Yes	1,724 (49.8)	1,141 (54.3)	
Condom use frequency			
Never or rarely	807 (23.3)	643 (30.6)	< 0.001
Sometimes, often, or always	2,654 (76.7)	1,458 (69.4)	
Neisseria gonorrhoeae	202 (5.8)	88 (4.2)	0.017
Chlamydia trachomatis	888 (25.7)	303 (14.3)	< 0.001
HSV-2 status[3]	1,363 (39.4)	1,412 (66.9)	< 0.001

[1] Among 5,670 enrolled in South Africa, 97 (1.7%) are excluded from analyses due to missingness in variables included in multivariable prediction models.
[2] Obtained from Cochran-Mantel-Haenszel chi-squared test stratified by study site.
[3] Defined as a HSV-2 enzyme immunoassay index value of greater than or equal to 0.90.
HSV-2 = Herpes Simplex Virus Type 2

Table 2. Association between select baseline predictors and HIV-1 incidence from multivariable and stepwise models and resulting risk score points

	Ages 18-24					Ages 25-35				
Characteristic	Hazard ratio (95% CI)[1]	Coefficient[2]	Risk score points[2]	Coefficient[3]	Risk score points[3]	Hazard ratio (95% CI)[1]	Coefficient[2]	Risk score points[2]	Coefficient[3]	Risk score points[3]
Age less than 27	--	--	--	--	--	2.12 (1.31, 3.41)	0.776	1	0.668	1
Not married nor living with partner	1.57 (0.80, 3.09)	--	--	--	--	1.85 (1.07, 3.31)	0.64	1	0.728	1
One or more weekly drinks	1.45 (1.03, 2.05)	0.375	1	0.430	1	--	--	--	--	--
HIV-1 prevalence 16-20%	1.64 (1.08, 2.48)	0.485	2	0.449	2	--	--	--	--	--
HIV-1 prevalence 21-25%	1.71 (0.99, 2.96)	0.565	2	0.538	2	--	--	--	--	--
HIV-1 prevalence 26-30%	1.81 (1.03, 3.19)	0.602	2	0.610	2	--	--	--	--	--
Eastern Cape province[4]						9.05 (1.18, 69.2)	2.203	3	2.169	3
KwaZulu-Natal province[4]	--	--	--	--	--	6.37 (0.87, 46.84)	1.792	3	1.791	3
Gauteng province[4]	--	--	--	--	--	5.81 (0.78, 43.31)	2.047	3	1.995	3
North West province[4]	--	--	--	--	--	7.94 (0.99, 63.56)	2.163	3	2.159	3
More than one sex partner in prior three months	1.61 (1.06, 2.44)	0.491	2	0.565	2	--	--	--	--	--
Partner has sex with others[5]	1.31 (0.93, 1.85)	0.291	1	0.346	1	--	--	--	--	--
Condom use sometimes, often, or always	1.34 (0.92, 1.95)	0.316	1	0.291	1	--	--	--	--	--
N. gonorrhoeae	2.07 (1.33, 3.24)	0.788	3	--	--	2.22 (0.99, 5.00)	0.913	1	--	--
C. Trachomatis	1.22 (0.89, 1.67)	--	--	--	--	1.42 (0.79, 2.54)	--	--	--	--
HSV-2 positive[6]	1.51 (1.13, 2.02)	0.411	1	--	--	1.88 (1.07, 3.31)	0.631	1	--	--

[1] Hazard ratio from a multivariable Cox proportional hazards model

[2] Coefficients and risk score points from the final model of a fully stepwise model selection procedure

[3] Coefficients and risk score points from a modified fully stepwise model excluding laboratory-based variables

[4] Referent group is Western Cape province

[5] Responses of "yes" or "don't know" are included.

[6] Defined as a HSV-2 enzyme immunoassay index value of greater than or equal to 0.90.

HSV-2 = Herpes Simplex Virus Type 2

Table 3. Predictive performance characteristics of age-specific risk scores including and excluding laboratory-based variables

Risk score points	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Ages 18-24								
	Including laboratory-based variables				**Excluding laboratory-based variables**			
1	1.000	0.006	0.053	1.000	1.000	0.011	0.054	1.000
2	0.989	0.054	0.056	0.989	0.984	0.073	0.056	0.988
3	0.941	0.159	0.060	0.979	0.919	0.190	0.060	0.977
4	0.798	0.373	0.067	0.970	0.679	0.459	0.066	0.962
5	0.486	0.708	0.086	0.960	0.265	0.831	0.081	0.953
6	0.236	0.890	0.108	0.954	0.205	0.895	0.099	0.952
7	0.138	0.946	0.126	0.951	0.027	0.989	0.121	0.948
8	0.067	0.974	0.130	0.948	0.017	0.992	0.110	0.947
9	0.024	0.992	0.151	0.947	--	--	--	--
10	0.007	0.998	0.153	0.947	--	--	--	--
11	0.000	1.000	0.000	0.946	--	--	--	--
Ages 25-35								
	Including laboratory-based variables				**Excluding laboratory-based variables**			
1	1.000	0.002	0.034	1.000	1.000	0.011	0.035	1.000
2	1.000	0.017	0.034	1.000	1.000	0.060	0.036	1.000
3	0.986	0.063	0.035	0.992	0.986	0.085	0.037	0.994
4	0.972	0.153	0.038	0.994	0.890	0.294	0.044	0.987
5	0.786	0.427	0.046	0.983	0.445	0.756	0.061	0.975
6	0.427	0.842	0.086	0.977	--	--	--	--
7	0.028	0.993	0.118	0.967	--	--	--	--

Table 4. HIV-1 incidence by risk score points and threshold values among women aged 18-24 and 25-35 in risk scores including or excluding laboratory-based sexually transmitted infection variables.

Risk score points	Ages 18-24		Ages 25-35	
	Including lab-based variables	Excluding lab-based variables	Including lab-based variables	Excluding lab-based variables
0	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
1	1.3 (0.4, 3.5)	1.4 (0.5, 3.4)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
2	2.5 (1.4, 4.5)	3.0 (1.7, 4.9)	1.1 (0.3, 3.9)	1.9 (0.5, 6.9)
3	3.6 (2.5, 5.1)	4.7 (3.5, 6.2)	0.5 (0.1, 2)	1.6 (0.8, 3.0)
4	4.9 (3.8, 6.3)	5.8 (4.7, 7.2)	2.3 (1.3, 3.7)	3.3 (2.3, 4.5)
5	7.2 (5.4, 9.5)	5.0 (2.8, 8.4)	2.9 (1.9, 4.1)	6.0 (4.3, 8.3)
6	9.2 (5.8, 13.9)	9.8 (7.0, 13.4)	8.5 (5.9, 11.9)	--
7	12.5 (7.3, 20.1)	14.9 (4.6, 41.6)	12.0 (3.7, 33.6)	--
8	12.4 (6.4, 22.3)	10.7 (3.9, 25.8)	--	--
9	15.5 (5.6, 37.2)	--	--	--
10	28.6 (8.8, 79.6)	--	--	--
11	0.0 (0.0, 0.0)	--	--	--
< optimal threshold	3.9 (3.2, 4.7)	3.7 (2.9, 4.8)	2.3 (1.7, 3.0)	2.5 (1.8, 3.3)
≥ optimal threshold	8.8 (7.1, 10.7)	6.6 (5.5, 7.8)	8.6 (6.1, 12.0)	6.0 (4.3, 8.3)
< alternative threshold	2.9 (2.1, 4.0)	2.3 (1.4, 3.6)	--	--
≥ alternative threshold	6.7 (5.7, 7.9)	6.0 (5.1, 6.9)	--	--

Figure 1. Receiver operating characteristic curves for age-specific and VOICE risk scores including and excluding laboratory-based variables. The grey line indicates a risk score with area under the curve of 0.50, indicating no predictive ability.

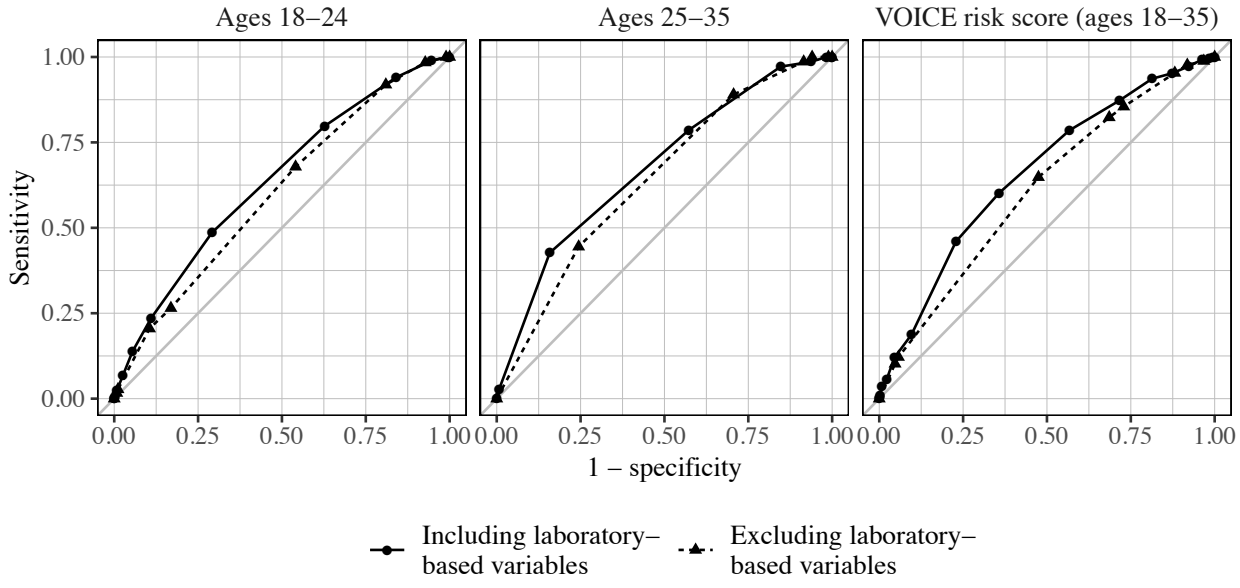
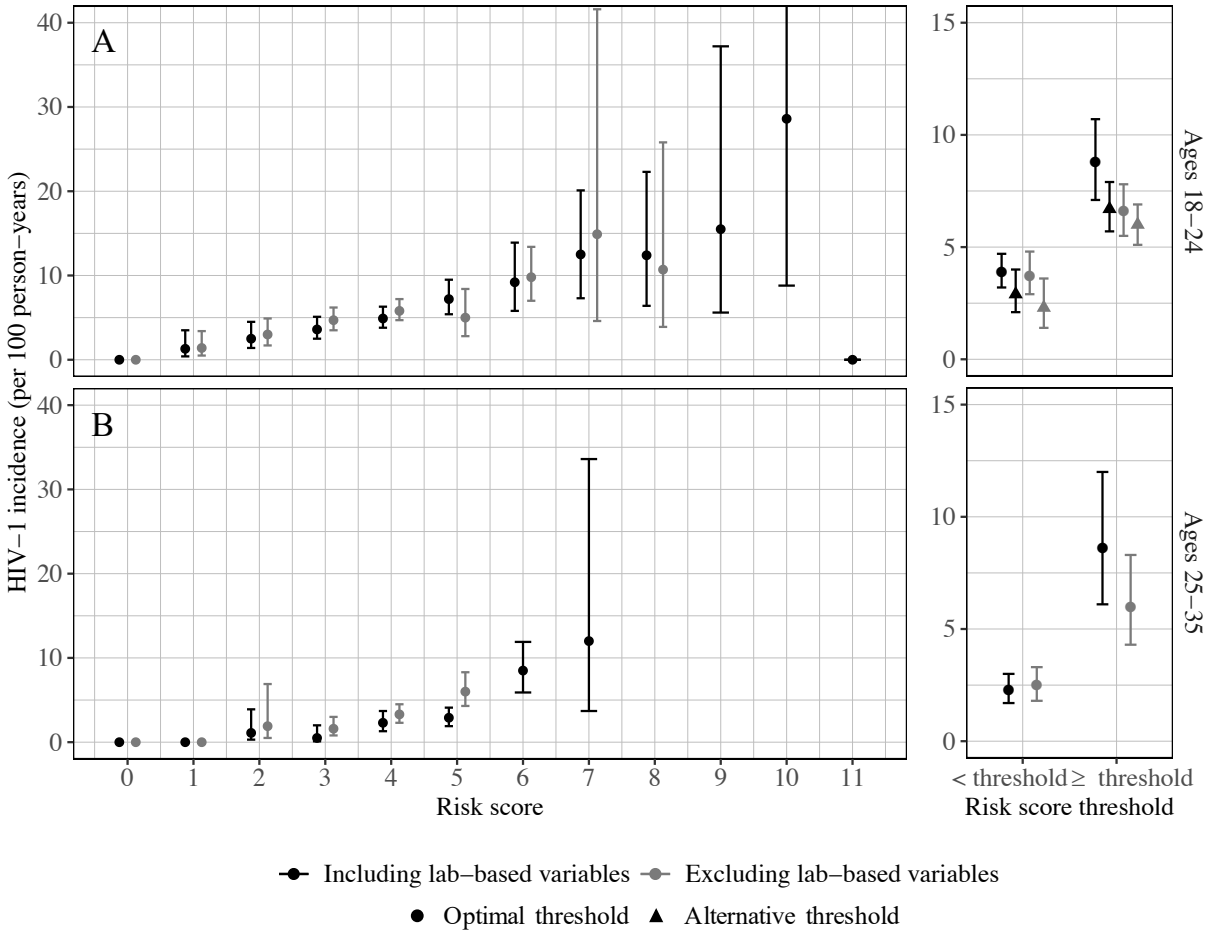
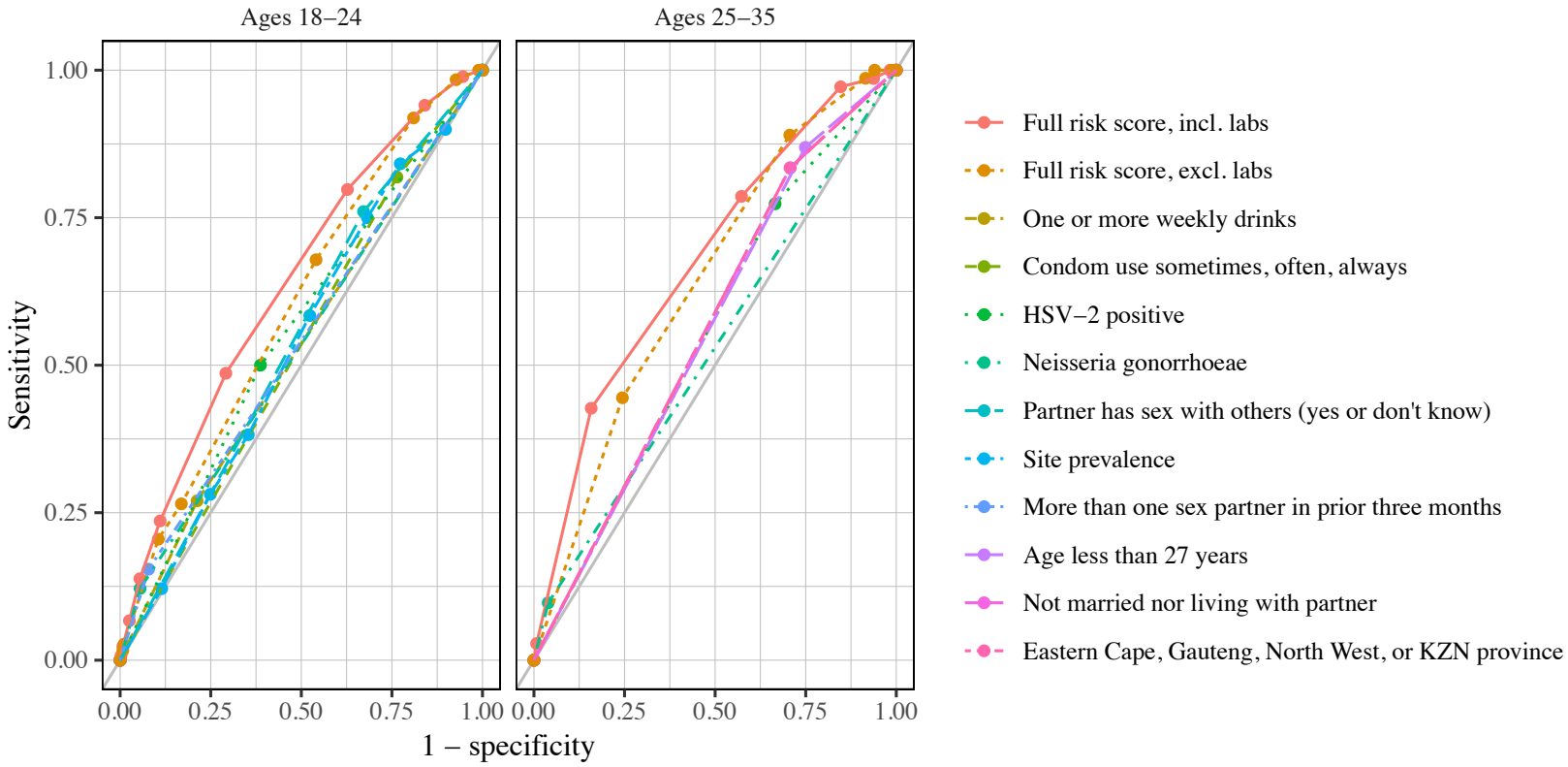


Figure 2. HIV-1 incidence by risk score points and threshold values in risk scores including or excluding laboratory-based sexually transmitted infection variables among (A) women aged 18-24 and (B) women aged 25-35.

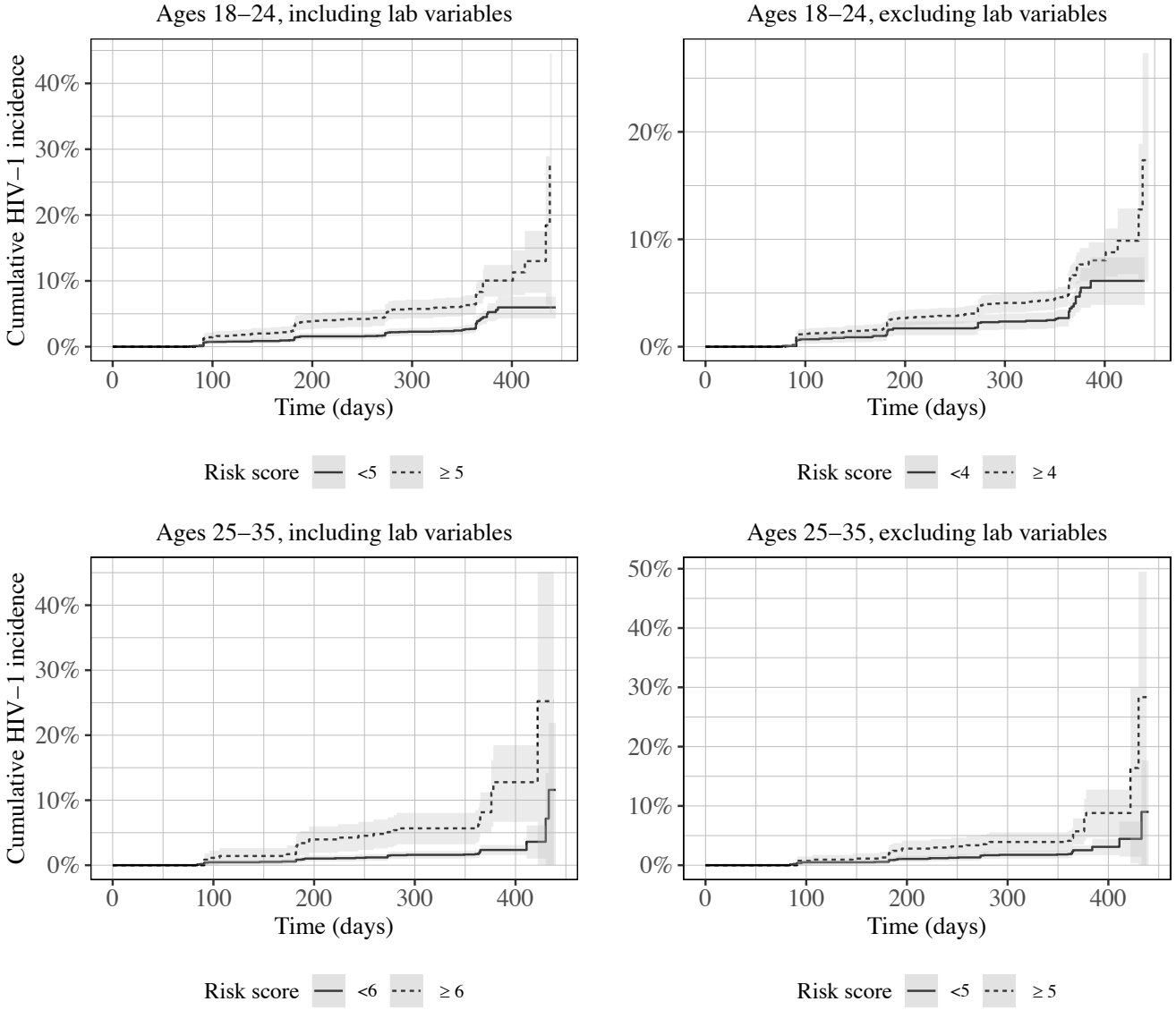


Among women aged 18-24 with 10 points on the full risk score, the confidence interval extends to 69.6 cases per 100 person-years; y axes are restricted to a maximum incidence of 40 cases per 100 person-years to allow interpretability of all plotted points.

Supplementary Figure 1. Receiver operating characteristic curves for the HIV-1 predictive performance of full risk scores and individual predictors among women aged 18-24 and 25-35.



Supplementary Figure 2. Cumulative HIV-1 incidence among women meeting the optimal discriminatory threshold value by age-specific risk score.



Chapter 6. Discussion

As contraception and HIV-1 prevention options expand, the complexity of decision-making for women and their providers will grow. This dissertation highlighted several of the trade-offs in selecting prevention options, including consideration of side effects, product effectiveness, and simplicity of decision-making in allocation of prevention. In aim 1, we showed that Cu-IUD users had an elevated risk of bacterial vaginosis that persisted throughout use and declined to baseline risk levels within one year of discontinuation. In aims 2.1 and 2.2, we demonstrated that estimates of dapivirine ring efficacy were minimally affected by receptive anal intercourse among women in the ASPIRE trial, and furthermore, that the ring provides substantial protection to the majority of women who engage in any RAI. In aim 3, our analyses showed that simplified HIV-1 prevention decision-making was not improved by age stratification, and indeed, that none of the simplified risk scoring tools performed exceptionally well among women in this context. These findings point to a number of clinical and implementation implications, as well as future research directions, summarized in Table 1 below.

Taken together, these results highlight a potential role for a shared decision-making model for selection of both contraception and HIV-1 prevention methods. In this model, the clinician's role is to engage in an interactive discussion with the patient with the goal of integrating the patient's values and needs with knowledge of acceptable options to create an informed preference, thus framing the advantages and drawbacks of each method explicitly within the unique context of each woman [127]. Components of shared decision-making are often cited by patients as desired characteristics of provider interactions and service provision [128, 129]. Limited evidence additionally suggests that use of the shared decision-making model in contraceptive decision-making increases use of effective contraception [130] and that components of shared decision-making are associated with higher rates of contraceptive continuation [131]. While this is a promising approach, use of the shared decision-making model rather than other counselling approaches adds approximately three minutes to each counselling session [132]. Given limited resources within many healthcare systems in sub-Saharan Africa, the feasibility of the shared decision-making model, as well as its outcomes (including patient satisfaction with both counselling and method selection, incremental

duration of the clinic visit, and method continuation), for contraception and HIV-1 prevention services should be evaluated in future research. The integration of family-planning and HIV-1 prevention into a comprehensive prevention platform for women, as has been done successfully in a recent PrEP implementation study [126], may facilitate the introduction of the shared decision-making approach and consolidate training and tasks, thereby reducing the additional burden to the healthcare system and its workers.

Once a prevention option is selected, minimizing its side effects is critical to ensure method continuation [133-135]. The results of these analyses point to potential changes in clinical treatment guidelines to prevent BV among Cu-IUD users. As contraception options expanded in the United States, so, too, did the proportion of women using a highly effective contraceptive [136]. We might expect the same reduction in unmet family planning needs with an expansion of contraception options in sub-Saharan Africa, and Cu-IUD should form a part of this expansion. Despite growing evidence that BV is an additional potential side effect of Cu-IUD use, Cu-IUD will still be the preferred contraceptive option for many women, just as the levonorgestrel intrauterine system (LNG-IUS) is selected by many women despite its association with a 21% increased risk of breast cancer [137]. The question, then, is how to mitigate BV risk among women who opt to use the Cu-IUD? More than 90% of BV cases are asymptomatic in sub-Saharan Africa [23], but BV has adverse effects even among asymptomatic persons, including preterm birth and an approximately 1.5- to 2-fold increase in the risk of HIV-1, herpes simplex virus type 2, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* [24-27, 44, 138]. The increased risk of BV among Cu-IUD users may put them at higher risk for these sequelae of BV. While the high pregnancy prevention efficacy of the Cu-IUD [139] makes reproductive and obstetric consequences associated with BV of lesser immediate concern, the prevalence of HIV-1 and other sexually transmitted infections is high in many areas of sub-Saharan Africa [114, 140]. Higher rates of BV screening for Cu-IUD users to increase appropriate treatment may reduce incidence of these sequelae. Diagnosis of BV by Nugent score [53], the gold standard diagnostic, requires microscopy, which is largely lacking in routine clinical settings in sub-Saharan Africa. Amsel's criteria is widely used to diagnose BV clinically, yet its sensitivity is only 70% compared to Nugent

score [141]. Wider availability of point-of-care BV screening tools with high sensitivity and specificity relative to Nugent score, such as the BVBlue test [142, 143], would facilitate targeted BV screening among asymptomatic Cu-IUD users, ensuring that those women at highest risk are treated promptly. At a market price of approximately $10 per test [144, 145], however, the cost of higher rates of screening among Cu-IUD users may be prohibitive. Advocacy to reduce costs for limited-resource settings and research to develop low-cost BV screening tests are needed. Alternatively, periodic presumptive treatment aims to reduce BV episodes through provision of monthly or quarterly treatment regardless of diagnosis and symptomatology [146] and has been shown to reduce incidence of sexually transmitted infections [147]. The cost for metronidazole, a recommended first-line BV treatment, is estimated to cost between 0.03 and 0.57 US dollars in sub-Saharan Africa [148, 149], considerably more affordable than current prices for point-of-care screening tests, indicating that periodic presumptive treatment may be a viable BV treatment and prevention approach for Cu-IUD users in resource-limited settings.

The mechanism underlying the association between Cu-IUD use and BV is unknown. Two principal hypotheses of the mediating factor of this relationship have been proposed. First, a common side effect of Cu-IUD is initial increases in the volume and duration of menses. These increases may facilitate overgrowth of *Gardnerella vaginalis* and preferential shedding of *Lactobacillus* species, leading to bacterial vaginosis [150]. Prior evaluations of bleeding increases subsequent to Cu-IUD initiation showed that volume and duration of menses return to baseline levels within six to twelve months [50, 51], while our analyses showed that the elevated risk of BV persists over up to eighteen months of Cu-IUD use. This suggests that the relationship between Cu-IUD and BV is not mediated by the common Cu-IUD side effect of increased volume and duration of menses. The second causal mechanism hypothesis posits that Cu-IUD strings in the vagina offer a surface for adhesion of anaerobic bacteria, leading to BV. In support of this hypothesis, prior literature has established adhesion of *Candida* species to Cu-IUD [62] and limited research has shown increasing diversity and quantity of adhered microbes to Cu-IUD *in situ* with increasing duration of use [63]. Identification of the causal mechanism that underlies the association between Cu-IUD use and increased BV risk will help inform the most effective BV treatment for Cu-IUD users and requires further

research. For example, should the presence of a foreign body in the vagina and consequent increased adhesion of bacteria to Cu-IUD strings facilitate the formation of a BV biofilm, biofilm disruptors [151] may perform better than standard treatments among this population to prevent or delay recurrence.

Oral PrEP is available currently as an HIV-1 prevention option for women, with the dapivirine ring in the product approval pipeline [8]. Should the ring become widely available in the future, women selecting a prevention option will have to balance preferences for discretion, privacy, product use attributes, and effectiveness, and specifically, efficacy in different sex act types. Receptive anal intercourse forms part of a healthy sexual life for a not insignificant portion of the population, and it's important that this group of women have access to effective prevention methods, but also that concerns about the appropriateness of a method for *all* women not undermine access to the method for *most* women. In aim 2.1, we found that efficacy among all women of 25% was nearly equal to efficacy of 27% among women engaged in only vaginal intercourse, suggesting that any RAI had only a minimal impact on estimates of ring efficacy. The conclusion that RAI played a minimal role in efficacy dilution stands in contrast to previous modeling work that concluded that RAI may substantially undermine the effectiveness of intravaginal HIV-1 prevention products [39]. Our conclusions differ for two principal reasons. First, in the absence of representative estimates of the prevalence and frequency of RAI, this hypothetical modeling assumed that between 1-5% of all acts in a cohort of women were RAI, whereas in ASPIRE, approximately 1.5% of all acts were RAI, at the lower end of the assumed range. Additionally, the per-act risk of RAI relative to receptive vaginal intercourse was modeled as a 1-, 10-, 20-, or 30-fold increase. In contrast, our calibration inferred a relative risk of 6.6 among women in the ASPIRE trial. Taken together, 16 of 20 modeled scenarios in prior work used more extreme assumptions than those observed in ASPIRE, leading to a dramatically different conclusion about the utility of intravaginal HIV-1 prevention products for women. Similarly, modeling work estimating that 17-40% of heterosexual HIV-1 transmissions are attributable to RAI relied on a wide range of estimates of prevalence, frequency, and per-act relative risk of RAI, the lower bounds of which were higher than point estimates obtained from ASPIRE data and our model calibration [152]. Population-based estimates of the prevalence and frequency of RAI in sub-Saharan Africa are needed to inform future

modeling work in this area. Previous HIV-1-related surveys have included questionnaire items regarding sensitive sexual behaviors [83, 153], indicating that an addition of RAI items is feasible. These questionnaire items should be asked via audio computer-assisted self-interview, as prior research [34] and the results of analyses included in this dissertation demonstrate considerable under-reporting of RAI in face-to-face interviews. Availability of representative estimates will end reliance on hypothetical values that produce alarming findings at their extremes, potentially contributing to a lack of availability of products that could benefit the majority of women who engage only in vaginal intercourse, as well as the many women who engage only occasionally in anal intercourse.

Results of our model simulations are consistent with per-vaginal exposure efficacy of the ring ranging from 65-75%. Women have cited product effectiveness as a key consideration in selecting prevention options [15, 16, 154], and while this range of efficacy is considerably lower than that of oral PrEP, it is still a substantial level of protection for women who are unable or prefer not to use oral PrEP. Indeed, per-vaginal exposure efficacy of 65-75% is above the 50% target efficacy of ongoing HIV-1 vaccine trials [155]. Additionally, while recent research identified product efficacy as the primary motivator in hypothetical selection of an HIV-1 prevention product, women were willing to trade some level of efficacy for other desirable product attributes [154], highlighting that somewhat lower efficacy may be an acceptable tradeoff for a longer-acting and discreet method. Prior research of contraceptive decision-making has similarly identified a complex set of considerations in contraception selection, including multiple product attributes (for example, efficacy, side effect profiles, and user burden) as well as contextual factors (including family and partner approval and social network opinions) [156]. As HIV-1 prevention options expand, similar research should be conducted to understand how women choose from among diverse HIV-1 prevention methods in implementation settings.

Among women in the ASPIRE trial who engaged in any RAI, approximately three-quarters reported that acts of RAI accounted for up to 16.7% of their total acts. In model analyses, ring effectiveness for this group of women ranged from 40-50% if highly adherent, providing substantial risk reduction. Ring effectiveness declined for women for whom a higher proportion of acts were RAI, representing

approximately 25% of women who reported any RAI and 5% of the total ASPIRE cohort. Among this relatively smaller group of women, protection offered by the ring is limited, and women's prevention needs may be best-met by alternative methods, including oral PrEP alone or used in combination with the dapivirine ring. Among men who have sex with men, on-demand, or event-driven, oral PrEP for episodes of receptive anal intercourse reduces risk of HIV-1 acquisition by 97% [157]. A similar PrEP regimen may complement ring protection of vaginal acts among women who engage in both vaginal and anal intercourse. Pharmacokinetic data from men and women show similar drug concentrations in colorectal tissues, suggesting that oral PrEP would be similarly efficacious in preventing HIV-1 acquisition via RAI in both sexes [158, 159]. The feasibility of on-demand PrEP for acts of RAI among women should be explored in formative qualitative research.

In our analyses of RAI behaviors, we observed considerable geographic heterogeneity in the prevalence of RAI, ranging from 3% in Zimbabwe to 19% in South Africa. Despite this heterogeneity, ring implementation considerations with respect to RAI should not vary by location. Mass media communication regarding oral PrEP has focused on HIV-1 prevention generally [160], often without explicit mentions of sexual transmission of HIV-1. Similarly, explicit reference to the sex acts protected – and not protected – by the ring in mass media promotion are likely not socially acceptable in regions with both low and relatively high prevalence of RAI. Furthermore, our estimates that RAI accounted for a small proportion of total acts among women who engage in RAI apply to high-prevalence areas, as well, indicating that the ring offers substantial protection to the vast majority of women across geographical regions. Discussions to determine which method will best fit into an individual woman's sexual lifestyle should take place within clinical consultations.

Finally, as HIV-1 prevention options for women expand, there remains a need to ensure that those options make it into the hands of women most in need of prevention. While shared-decision making may optimize women's ability to access prevention services that will work best for them, the feasibility of this approach in resource-limited settings is unknown. Indeed, HIV-1 treatment programs in sub-Saharan Africa have taken a public health approach, with standardized protocols and simplified treatment regimens, to

ensure that healthcare worker burden is minimized [161]. In this context, clinical decision rules, such as a risk score for HIV-1 prevention, can streamline provision of prevention services. However, in our evaluations of risk scores for women in this setting, risk scores had only moderate predictive performance in this population. At the optimal threshold, defined by predictive accuracy assessed by area under the receiver operating curve, a risk score for women ages 18-24 would identify approximately 49% of women who would subsequently acquire HIV-1, while also incorrectly identifying 29% of women with a lower risk of HIV-1. While this threshold may optimize the trade-off between sensitivity and specificity, incidence among women screening negative at this threshold was 3.9 (95% CI: 3.2, 4.7) per 100 person-years. The World Health Organization recommends PrEP for all populations with HIV-1 incidence greater than 3% [117], so despite decreasing the probability of a false positive, this threshold misses opportunities to offer PrEP to women with substantial HIV-1 risk. An alternative threshold designed to offer prevention to women with a greater than 3% risk of seroconversion within one year resulted in capturing a higher proportion (80%) of those with highest risk, while also incorrectly classifying a higher proportion (63%) of those with less than 3% risk as being at highest risk. In the case of PrEP, where sustained side effects are minimal, lower screening thresholds may be preferred to increase availability to those who want to use PrEP. A higher threshold identifying those at the highest risk could alternatively be used to identify women who, should they discontinue PrEP, merit intensified re-engagement efforts, such as follow-up phone calls, home visits, or home delivery of PrEP. The decision at the health systems level as to which threshold to use may depend on resource constraints: if commodities are limited, prioritizing them for individuals with the highest likelihood of HIV-1 acquisition, despite missing a high proportion of seroconverters, may still maximize impact of available prevention resources. Context-specific modeling of the cost-effectiveness, budget impact, and epidemic impact can inform selection of the risk scoring tool threshold that best meets the needs, resource availability, and priorities of each country.

In generalized epidemic settings, the identification of a succinct set of discrete factors to predict HIV-1 acquisition may be particularly challenging, in contrast to the superior predictive performance of risk scoring tools for concentrated epidemics [100, 122]. Development of future risk scores may benefit

from the implementation of electronic health records [124] and machine learning approaches [107]. Furthermore, in PrEP implementation thus far, individuals may enroll for PrEP by self-identifying as being at high-risk of HIV-1 acquisition, and it is unknown if self-identified risk or empirically-estimated risk is a better predictor of subsequent seroconversion. In the absence of the ability to better identify those who will most benefit from HIV-1 prevention methods, these risk scores may ideally be used as opportunities to discuss risk and evaluate prevention options, rather than as strict eligibility criteria. Prior research in the United States has suggested that risk score evaluations may serve as opportunities for prospective PrEP users to re-assess their own risk, opening opportunities to consider the role that PrEP may play in achieving HIV-1 prevention goals [108, 109]. Future research should evaluate if application of risk screening tools in sub-Saharan Africa have a similar effect of aligning objective and perceived risk.

In conclusion, the results of this dissertation emphasize that there is no ideal method for either contraception or HIV-1 prevention for all women, but rather that women's choices reflect a broad consideration of the advantages and drawbacks of each method. Availability of diverse options is a critical first step to ensure that women have access to the method that will best suit their values and preferences. Once such diversity of options is achieved, the shared decision-making model may help women evaluate their risks and balance the benefits and disadvantages of each option to optimize family planning and HIV-1 prevention. Additionally, upon selecting a prevention method, strategies to maximize the prevention benefits and minimize side effects of the selected option are needed. Together, this combination of expanded options, informed decision-making, and complementary prevention tools can contribute to women's achievement of their pregnancy and HIV-1 prevention goals.

Table 1. Dissertation findings, their implementation and policy implications, and future research directions

Finding	Implementation and policy implications	Future research
Cu-IUD use is associated with an increased risk of BV	The shared decision-making approach to counseling can better help women weigh the pros and cons of each contraceptive method available.	The feasibility and outcomes of the shared decision-making model should be evaluated in low-resource settings.
	Users of the Cu-IUD may particularly benefit from periodic presumptive treatment to reduce episodes of BV and sequelae, including HIV-1 and STIs.	--
The elevated risk of BV among Cu-IUD users persists through up to eighteen months of use, suggesting that the relationship is not mediated by Cu-IUD-induced changes in menstrual bleeding.	--	The biological mechanism underlying this association should be investigated.
RAI played a minimal role in efficacy dilution of ASPIRE trial estimates.	The dapivirine ring is a suitable HIV-1 prevention method for the vast majority of women.	Representative estimates of the prevalence and frequency of RAI among women to inform future modeling should be obtained in representative surveys.
The average per-exposure ring effect ranged from 40-55% among women engaged in RAI for 5-15% of their total acts, and was lower among women for whom a larger proportion of acts were RAI.	The dapivirine ring is a suitable HIV-1 prevention method for the vast majority of women, yet a small proportion of women may benefit from dual HIV-1 prevention to provide additional protection in acts of RAI.	The feasibility of on-demand PrEP for acts of RAI among women should be explored in qualitative research.
	The shared decision-making approach to counseling can better help women weigh the pros and cons of each HIV-1 prevention method available.	The feasibility and outcomes of the shared decision-making model should be evaluated in low-resource settings.
Age-specific HIV-1 risk scoring tools did not improve predictive performance of a non-age-specific risk scoring tool.	The use of risk scoring tools to inform PrEP use among women should not be further complicated by age-stratified tools.	--
	Additional data may be needed to improve the predictive performance of risk scoring tools in this context.	Application of machine learning methods to more extensive data may yield improved predictive accuracy as electronic health records are implemented.

Risk scores excluding STI variables performed more poorly than risk scores including STI variables.	Low-cost point-of-care STI tests should be available to ensure availability of the most useful version of these tests.	--
For groups of women ages 18-24 and 25-35, HIV-1 prevalence of the surrounding area was heavily weighted in risk scores, though did not predict HIV-1 acquisition better alone than the full risk score.	--	The incremental impact, in terms of HIV-1 infections averted, of risk score-based PrEP targeting to geography-targeted PrEP provision alone should be evaluated.

Cu-IUD = copper intrauterine device; BV = bacterial vaginosis; STI = sexually transmitted infection; RAI = receptive anal intercourse

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References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDSinfo. Available at: http://aidsinfo.unaids.org. Accessed 28 October 2019.
2. United Nations. World Family Planning Highlights. In: Affairs DoEaS. New York: United Nations, **2017**.
3. Murnane PM, Brown ER, Donnell D, et al. Estimating efficacy in a randomized trial with product nonadherence: application of multiple methods to a trial of preexposure prophylaxis for HIV prevention. Am J Epidemiol **2015**; 182(10): 848-56.
4. National AIDS & STI Control Programme (NASCOP) Ministry of Health. Framework for the Implementation of Pre-Exposure Prohpylaxis of HIV in Kenya. Nairobi, Kenya: NASCOP, **2017**.
5. South Africa National Department of Health. PrEP Implementation Pack: South Africa 2016-2017. Available at: https://www.prepwatch.org/wp-content/uploads/2017/07/SA_ImplementationPack.pdf. Accessed 15 November 2019.
6. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. The New England journal of medicine **2016**; 375(22): 2121-32.
7. Nel A, van Niekerk N, Kapiga S, et al. Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women. The New England journal of medicine **2016**; 375(22): 2133-43.
8. International Partnership for Microbicides. IPM's Application for Dapivirine Vaginal Ring for Reducing HIV Risk in Women Now Under Review by European Medicines Agency. **2017**.
9. Jacobstein R. Liftoff: The Blossoming of Contraceptive Implant Use in Africa. Global health, science and practice **2018**; 6(1): 17-39.
10. Mensch BS, van der Straten A, Katzen LL. Acceptability in microbicide and PrEP trials: current status and a reconceptualization. Current opinion in HIV and AIDS **2012**; 7(6): 534-41.
11. van der Straten A, Shapley-Quinn MK, Reddy K, et al. Favoring "Peace of Mind": A Qualitative Study of African Women's HIV Prevention Product Formulation Preferences from the MTN-020/ASPIRE Trial. Aids Patient Care STDS **2017**; 31(7): 305-14.
12. Luecke EH, Cheng H, Woeber K, Nakyanzi T, Mudekunye-Mahaka IC, van der Straten A. Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study. Journal of the International AIDS Society **2016**; 19(1): 20875.
13. Mack N, Evens EM, Tolley EE, et al. The importance of choice in the rollout of ARV-based prevention to user groups in Kenya and South Africa: a qualitative study. Journal of the International AIDS Society **2014**; 17(3 Suppl 2): 19157.
14. Rodriguez J, Abutouk M, Roque K, Sridhar A. Personalized contraceptive counseling: helping women make the right choice. Open access journal of contraception **2016**; 7: 89-96.
15. Lessard LN, Karasek D, Ma S, et al. Contraceptive features preferred by women at high risk of unintended pregnancy. Perspect Sex Reprod Health **2012**; 44(3): 194-200.
16. Madden T, Secura GM, Nease RF, Politi MC, Peipert JF. The role of contraceptive attributes in women's contraceptive decision making. Am J Obstet Gynecol **2015**; 213(1): 46.e1-6.
17. Sedgh G, Ashford LS, Hussain R. Unmet Need for Contraception in Developing Countries: Examining Women's Reasons for Not Using a Method. Available at: https://www.guttmacher.org/sites/default/files/report_pdf/unmet-need-for-contraception-in-developing-countries-report.pdf. Accessed 18 November 2019.
18. Kaiser Family Foundation. Intrauterine Devices (IUDs): Access for Women in the U.S. Available at: https://www.kff.org/womens-health-policy/fact-sheet/intrauterine-devices-iuds-access-for-women-in-the-u-s/#footnote-202538-1. Accessed 16 November 2019.
19. Kancheva Landolt N, Chaithongwongwatthana S, Nilgate S, et al. Use of copper intrauterine device is not associated with higher bacterial vaginosis prevalence in Thai HIV-positive women. AIDS care **2018**: 1-5.
20. Donders G, Bellen G, Janssens D, Van Bulck B, Hinoul P, Verguts J. Influence of contraceptive choice on vaginal bacterial and fungal microflora. European journal of clinical microbiology &

infectious diseases : official publication of the European Society of Clinical Microbiology **2017**; 36(1): 43-8.
21. Madden T, Grentzer JM, Secura GM, Allsworth JE, Peipert JF. Risk of bacterial vaginosis in users of the intrauterine device: a longitudinal study. Sex Transm Dis **2012**; 39(3): 217-22.
22. Achilles SL, Austin MN, Meyn LA, Mhlanga F, Chirenje ZM, Hillier SL. Impact of contraceptive initiation on vaginal microbiota. Am J Obstet Gynecol **2018**; 218(6): 622.e1-.e10.
23. Peebles K, Velloza J, Balkus JE, McClelland RS, Barnabas RV. High Global Burden and Costs of Bacterial Vaginosis: A Systematic Review and Meta-Analysis. Sex Transm Dis **2019**; 46(5): 304-11.
24. Cherpes TL, Meyn LA, Krohn MA, Lurie JG, Hillier SL. Association between acquisition of herpes simplex virus type 2 in women and bacterial vaginosis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2003**; 37(3): 319-25.
25. Atashili J, Poole C, Ndumbe PM, Adimora AA, Smith JS. Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. AIDS (London, England) **2008**; 22(12): 1493-501.
26. Cohen CR, Lingappa JR, Baeten JM, et al. Bacterial vaginosis associated with increased risk of female-to-male HIV-1 transmission: a prospective cohort analysis among African couples. PLoS medicine **2012**; 9(6): e1001251.
27. Bautista CT, Wurapa E, Sateren WB, Morris S, Hollingsworth B, Sanchez JL. Bacterial vaginosis: a synthesis of the literature on etiology, prevalence, risk factors, and relationship with chlamydia and gonorrhea infections. Military Medical Research **2016**; 3: 4.
28. Langen TT. Gender power imbalance on women's capacity to negotiate self-protection against HIV/AIDS in Botswana and South Africa. Afr Health Sci **2005**; 5(3): 188-97.
29. Celum CL, Delany-Moretlwe S, McConnell M, et al. Rethinking HIV prevention to prepare for oral PrEP implementation for young African women. Journal of the International AIDS Society **2015**; 18(4 Suppl 3): 20227.
30. Montgomery ET, van der Straten A, Stadler J, et al. Male Partner Influence on Women's HIV Prevention Trial Participation and Use of Pre-exposure Prophylaxis: the Importance of "Understanding". AIDS and behavior **2015**; 19(5): 784-93.
31. Murphy DJ, Desjardins D, Dereuddre-Bosquet N, et al. Pre-clinical development of a combination microbicide vaginal ring containing dapivirine and darunavir. The Journal of antimicrobial chemotherapy **2014**; 69(9): 2477-88.
32. Justman JE, Nair GL, Hendrix CW, et al. Pharmacokinetics and Pharmacodynamics of Tenofovir Reduced-Glycerin 1% Gel in the Rectal and Vaginal Compartments in Women: A Cross-Compartmental Study With Directly Observed Dosing. Journal of acquired immune deficiency syndromes (1999) **2018**; 78(2): 175-82.
33. Owen BN, Elmes J, Silhol R, et al. How common and frequent is heterosexual anal intercourse among South Africans? A systematic review and meta-analysis. Journal of the International AIDS Society **2017**; 20: 21162.
34. Gorbach PMM, B. S.; Husnik, M.; Coly, A.; Masse, B.; Makanani, B.; Nkhoma, C.; Chinula, L.; Tembo, T.; Mierzwa, S.; Reynolds, K.; Hurst, S.; Coletti, A.; Forsyth, A. Effect of Computer-Assisted Interviewing on Self-Reported Sexual Behavior Data in a Microbicide Clinical Trial. AIDS and behavior **2013**; 17(2): 790-800.
35. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine **2015**; 372(6): 509-18.
36. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. The New England journal of medicine **2012**; 367(5): 399-410.
37. Brown E, Palanee-Phillips T, Marzinke M, et al. Residual dapivirine ring levels indicate higher adherence to vaginal ring is associated with HIV-1 prevention. In: AIDS 2016. Durban, South Africa, 2016.
38. Masse BR, Boily MC, Dimitrov D, Desai K. Efficacy dilution in randomized placebo-controlled vaginal microbicide trials. Emerging themes in epidemiology **2009**; 6: 5.

39. McGowan I, Taylor DJ. Heterosexual Anal Intercourse Has the Potential to Cause a Significant Loss of Power in Vaginal Microbicide Effectiveness Studies. Sex Transm Dis **2010**; 37(6): 361-4.
40. Balkus JE, Brown E, Palanee T, et al. An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African Women. Journal of acquired immune deficiency syndromes (1999) **2016**; 72(3): 333-43.
41. Balkus JE, Brown ER, Palanee-Phillips T, et al. Performance of a Validated Risk Score to Predict HIV-1 Acquisition Among African Women Participating in a Trial of the Dapivirine Vaginal Ring. Journal of acquired immune deficiency syndromes (1999) **2018**; 77(1): e8-e10.
42. Giovenco D, Pettifor A, MacPhail C, et al. Assessing risk for HIV infection among adolescent girls in South Africa: an evaluation of the VOICE risk score (HPTN 068). Journal of the International AIDS Society **2019**; 22(7): e25359.
43. Bradshaw CS, Brotman RM. Making inroads into improving treatment of bacterial vaginosis - striving for long-term cure. BMC Infect Dis **2015**; 15: 292.
44. Taylor BD, Darville T, Haggerty CL. Does bacterial vaginosis cause pelvic inflammatory disease? Sex Transm Dis **2013**; 40(2): 117-22.
45. Hillier SL, Nugent RP, Eschenbach DA, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. The New England journal of medicine **1995**; 333(26): 1737-42.
46. Low N, Chersich MF, Schmidlin K, et al. Intravaginal practices, bacterial vaginosis, and HIV infection in women: individual participant data meta-analysis. PLoS medicine **2011**; 8(2): e1000416.
47. Riggs M, Klebanoff M, Nansel T, Zhang J, Schwebke J, Andrews W. Longitudinal association between hormonal contraceptives and bacterial vaginosis in women of reproductive age. Sex Transm Dis **2007**; 34(12): 954-9.
48. Vodstrcil LA, Hocking JS, Law M, et al. Hormonal contraception is associated with a reduced risk of bacterial vaginosis: a systematic review and meta-analysis. PLoS One **2013**; 8(9): e73055.
49. Srinivasan S, Liu C, Mitchell CM, et al. Temporal variability of human vaginal bacteria and relationship with bacterial vaginosis. PLoS One **2010**; 5(4): e10197.
50. Hubacher D, Chen PL, Park S. Side effects from the copper IUD: do they decrease over time? Contraception **2009**; 79(5): 356-62.
51. Sanders JN, Adkins DE, Kaur S, Storck K, Gawron LM, Turok DK. Bleeding, cramping, and satisfaction among new copper IUD users: A prospective study. PLoS One **2018**; 13(11).
52. Bunge K, Baeten J, Chappell C, et al. Expanding the mix of contraceptive methods in an HIV prevention trial. In: IAS Conference. Durban, South Africa, 2016.
53. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol **1991**; 29(2): 297-301.
54. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. The American journal of medicine **1983**; 74(1): 14-22.
55. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, **2008**.
56. Jaspan H, Bunjun R, Brown B, et al. Contraceptive-induced changes in genital tract HIV-1 cellular targets and microbiota among women enrolled in the ECHO trial. In: 10th IAS Conference on HIV Science. Mexico City, Mexico, 2019.
57. Chappell CA, Harkoo I, Szydlo DW, et al. Contraceptive method switching among women living in sub-Saharan Africa participating in an HIV-1 prevention trial: a prospective cohort study. Contraception **2019**.
58. Masese L, Baeten JM, Richardson BA, et al. Changes in the contribution of genital tract infections to HIV acquisition among Kenyan high-risk women from 1993 to 2012. AIDS (London, England) **2015**; 29(9): 1077-85.

59. Jacobson JC, Turok DK, Dermish AI, Nygaard IE, Settles ML. Vaginal microbiome changes with levonorgestrel intrauterine system placement. Contraception **2014**; 90(2): 130-5.
60. Brooks JP, Edwards DJ, Blithe DL, et al. Effects of combined oral contraceptives, depot medroxyprogesterone acetate and the levonorgestrel-releasing intrauterine system on the vaginal microbiome. Contraception **2017**; 95(4): 405-13.
61. Donders GGG, Bellen G, Ruban K, Van Bulck B. Short- and long-term influence of the levonorgestrel-releasing intrauterine system (Mirena(R)) on vaginal microbiota and Candida. Journal of medical microbiology **2018**; 67(3): 308-13.
62. Chassot F, Negri MF, Svidzinski AE, et al. Can intrauterine contraceptive devices be a Candida albicans reservoir? Contraception **2008**; 77(5): 355-9.
63. Pal Z, Urban E, Dosa E, Pal A, Nagy E. Biofilm formation on intrauterine devices in relation to duration of use. Journal of medical microbiology **2005**; 54(Pt 12): 1199-203.
64. Bayer AG. Jadelle: Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020544s010lbl.pdf. Accessed August 13 2019.
65. Merck. Nexplanon: Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021529s011lbl.pdf. Accessed August 13 2019.
66. Balkus JE, Palanee-Phillips T, Reddy K, et al. Brief Report: Dapivirine Vaginal Ring Use Does Not Diminish the Effectiveness of Hormonal Contraception. Journal of acquired immune deficiency syndromes (1999) **2017**; 76(2): e47-e51.
67. Pyra M, Abdala A, Mwinyikai K, et al. Natural History of Asymptomatic Bacterial Vaginosis among Kenyan Women at High Risk for HIV Infection. In: Annual Meeting of the Infectious Diseases Society for Obstetrics and Gynecology. Big Sky, Montana, 2019.
68. Joint United Nations Programme on HIV/AIDS (UNAIDS). The Gap Report. Geneva, Switzerland: UNAIDS, **2016**.
69. Voeller B. AIDS and Heterosexual Anal Intercourse. Arch Sex Behav **1991**; 20(3): 233-76.
70. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS (London, England) **2014**; 28(10): 1509-19.
71. Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis **2009**; 9(2): 118-29.
72. Baggaley RF, Owen BN, Silhol R, et al. Does per-act HIV-1 transmission risk through anal sex vary by gender? An updated systematic review and meta-analysis. American journal of reproductive immunology (New York, NY : 1989) **2018**; 80(5): e13039.
73. Duby Z, Hartmann M, Mahaka I, et al. Lost in Translation: Language, Terminology, and Understanding of Penile-Anal Intercourse in an HIV Prevention Trial in South Africa, Uganda, and Zimbabwe. J Sex Res **2016**; 53(9): 1096-106.
74. Duby Z, Colvin C. Conceptualizations of Heterosexual Anal Sex and HIV Risk in Five East African Communities. J Sex Res **2014**; 51(8): 863-73.
75. Kalichman SCS, L. C.; Cain, D.; Jooste, S. Heterosexual anal intercourse among community and clinical settings in Cape Town, South Africa. Sex Transm Infect **2009**; 85(6): 411-5.
76. Duby Z, Hartmann M, Montgomery ET, Colvin CJ, Mensch B, van der Straten A. Condoms, Lubricants and Rectal Cleansing: Practices Associated with Heterosexual Penile-Anal Intercourse Amongst Participants in an HIV Prevention Trial in South Africa, Uganda and Zimbabwe. AIDS and behavior **2016**; 20(4): 754-62.
77. Peebles K, Van der Straten A, Palanee-Phillips T, et al. Anal intercourse, HIV-1 risk, and efficacy in a trial of a dapivirine-containing vaginal ring for HIV-1 prevention. J Acquir Immune Defic Syndr **2019**.
78. Lenormand M, Jabot F, Deffuant G. Adaptive approximate Bayesian computation for complex models. Computational Statistics **2013**; 28: 2777-96.

79. Vincent KL, Moss JA, Marzinke MA, et al. Phase I trial of pod-intravaginal rings delivering antiretroviral agents for HIV-1 prevention: Rectal drug exposure from vaginal dosing with tenofovir disoproxil fumarate, emtricitabine, and maraviroc. PLoS One **2018**; 13(8): e0201952.
80. Landovitz RJ. Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex With Men. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02720094. Accessed 4 November 2019.
81. Powers KAP, C.; Pettifor, A. E.; Cohen, M. S. Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. Lancet Infect Dis **2008**; 8(9): 553-63.
82. National Statistical Office (NSO) Malawi, ICF. Malawi Demographic and Health Survey 2015-2016. Zomba, Malawi and Rockville, Maryland, USA: NSO and ICF, **2017**.
83. Shisana O, Rehle T, Simbayi LC, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town: HSRC Press, **2014**.
84. Ministry of Health U, International I. Uganda AIDS Indicator Survey, 2011. Calverton, Maryland, USA and Kampala, Uganda: Ministry of Health, Uganda and ICF International Inc., **2012**.
85. Zimbabwe National Statistics Agency (ZIMSTAT), ICF International. Zimbabwe Demographic and Health Survey, 2010-2011. Calverton, Maryland: ZIMSTAT and ICF International Inc., **2012**.
86. Huerga H, Van Cutsem G, Ben Farhat J, et al. Who Needs to Be Targeted for HIV Testing and Treatment in KwaZulu-Natal? Results From a Population-Based Survey. Journal of acquired immune deficiency syndromes (1999) **2016**; 73(4): 411-8.
87. Malawi Population-based HIV Impact Assessment. MPHIA 2015-2016. Available at: https://phia.icap.columbia.edu/wp-content/uploads/2018/10/MPHIA-SS_2018_FINAL.pdf. Accessed 22 October 2019.
88. Rehle T, Johnson L, Hallett T, et al. A Comparison of South African National HIV Incidence Estimates: A Critical Appraisal of Different Methods. PLoS One **2015**; 10(7): e0133255.
89. Uganda Population-based HIV Impact Assessment. UPHIA 2016-2017. Available at: https://phia.icap.columbia.edu/wp-content/uploads/2018/07/3430•PHIA-Uganda-SS_NEW.v14.pdf. Accessed 22 October 2019.
90. Zimbabwe Population-based HIV Impact Assessment. ZIMPHIA 2015-2016. Available at: https://phia.icap.columbia.edu/wp-content/uploads/2016/11/ZIMBABWE-Factsheet.FIN_.pdf. Accessed 22 October 2019.
91. McGrath N, Grapsa E. Does antiretroviral therapy change partnership dynamics and HIV risk behaviours among HIV-infected adults. AIDS (London, England) **2017**; 31(10): 1451-60.
92. Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. The Journal of infectious diseases **2012**; 205(3): 358-65.
93. Bellan SE, Dushoff J, Galvani AP, Meyers LA. Reassessment of HIV-1 acute phase infectivity: accounting for heterogeneity and study design with simulated cohorts. PLoS medicine **2015**; 12(3): e1001801.
94. Baggaley RFW, R. G.; Boily, M. C. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. Int J Epidemiol **2010**; 39(4): 1048-63.
95. Joint United Nations Programme on HIV/AIDS (UNAIDS). South Africa Overview. Available at: https://www.unaids.org/en/regionscountries/countries/southafrica. Accessed 22 October 2019.
96. Rucinski KB, Rutstein SE, Powers KA, et al. Sustained Sexual Behavior Change After Acute HIV Diagnosis in Malawi. Sex Transm Dis **2018**; 45(11): 741-6.
97. Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS: Progress Towards the 90-90-90 Targets. Geneva, Switzerland: UNAIDS, **2017**.
98. Hoenigl M, Weibel N, Mehta SR, et al. Development and validation of the San Diego Early Test Score to predict acute and early HIV infection risk in men who have sex with men. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2015**; 61(3): 468-75.

99. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a clinical screening index predictive of incident HIV infection among men who have sex with men in the United States. Journal of acquired immune deficiency syndromes (1999) **2012**; 60(4): 421-7.
100. Haukoos JS, Lyons MS, Lindsell CJ, et al. Derivation and validation of the Denver Human Immunodeficiency Virus (HIV) risk score for targeted HIV screening. Am J Epidemiol **2012**; 175(8): 838-46.
101. Kahle EM, Hughes JP, Lingappa JR, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. Journal of acquired immune deficiency syndromes (1999) **2013**; 62(3): 339-47.
102. Pintye J, Drake AL, Kinuthia J, et al. A Risk Assessment Tool for Identifying Pregnant and Postpartum Women Who May Benefit From Preexposure Prophylaxis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2017**; 64(6): 751-8.
103. Wilton J, Kain T, Fowler S, et al. Use of an HIV-risk screening tool to identify optimal candidates for PrEP scale-up among men who have sex with men in Toronto, Canada: disconnect between objective and subjective HIV risk. Journal of the International AIDS Society **2016**; 19(1): 20777.
104. Plotzker R, Seekaew P, Jantarapakde J, et al. Importance of Risk Perception: Predictors of PrEP Acceptance Among Thai MSM and TG Women at a Community-Based Health Service. Journal of acquired immune deficiency syndromes (1999) **2017**; 76(5): 473-81.
105. Hoagland B, Moreira RI, De Boni RB, et al. High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV Infection: the PrEP Brasil demonstration project. Journal of the International AIDS Society **2017**; 20(1): 21472.
106. Oostrom L, Rosentel K, Motley D, Hill BJ. Discordance in Objective and Self-perceived HIV Risk: A Potential Barrier to Pre-exposure Prophylaxis in Young Gay and Bisexual Men. The Journal of the Association of Nurses in AIDS Care : JANAC **2019**.
107. Koss CA, Ayieko J, Mwangwa F, et al. Early Adopters of HIV Preexposure Prophylaxis in a Population-based Combination Prevention Study in Rural Kenya and Uganda. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2018**.
108. Gilkey MB, Marcus JL, Garrell JM, Powell VE, Maloney KM, Krakower DS. Using HIV Risk Prediction Tools to Identify Candidates for Pre-Exposure Prophylaxis: Perspectives from Patients and Primary Care Providers. Aids Patient Care STDS **2019**; 33(8): 372-8.
109. Sullivan PS, Driggers R, Stekler JD, et al. Usability and Acceptability of a Mobile Comprehensive HIV Prevention App for Men Who Have Sex With Men: A Pilot Study. JMIR mHealth and uHealth **2017**; 5(3): e26.
110. Jones J, Hoenigl M, Siegler AJ, Sullivan PS, Little S, Rosenberg E. Assessing the Performance of 3 Human Immunodeficiency Virus Incidence Risk Scores in a Cohort of Black and White Men Who Have Sex With Men in the South. Sex Transm Dis **2017**; 44(5): 297-302.
111. Lancki N, Almirol E, Alon L, McNulty M, Schneider JA. Preexposure prophylaxis guidelines have low sensitivity for identifying seroconverters in a sample of young Black MSM in Chicago. AIDS (London, England) **2018**; 32(3): 383-92.
112. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet **2019**; 394(10195): 303-13.
113. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart **2012**; 98(9): 683-90.
114. Dwyer-Lindgren L, Cork MA, Sligar A, et al. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature **2019**; 570(7760): 189-93.
115. Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control **1974**; 19(6).

116. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics **2000**; 56(2): 337-44.
117. World Health Organization. Policy Brief: WHO expands recommendation of oral pre-exposure prophylaxis of HIV infection (PrEP). Geneva, Switzerland, **2015**.
118. Pintye J, Singa B, Wanyonyi K, et al. Pre-exposure prophylaxis (PrEP) for HIV prevention among HIV-uninfected pregnant women: estimated coverage using risk-based versus regional prevalence approaches. Sex Transm Dis **2018**.
119. Anderson SJ, Ghys PD, Ombam R, Hallett TB. HIV prevention where it is needed most: comparison of strategies for the geographical allocation of interventions. Journal of the International AIDS Society **2017**; 20(4).
120. Ortblad KF, Baeten JM. Electronic health record tools to catalyse PrEP conversations. Lancet HIV **2019**; 6(10): e644-e5.
121. Palanee-Phillips T, Baeten JM. Topical delivery of long-acting antiretrovirals to prevent HIV acquisition. Current opinion in HIV and AIDS **2019**.
122. Marcus JL, Hurley LB, Krakower DS, Alexeeff S, Silverberg MJ, Volk JE. Use of electronic health record data and machine learning to identify candidates for HIV pre-exposure prophylaxis: a modelling study. Lancet HIV **2019**; 6(10): e688-e95.
123. Balzer LB, Havlir DV, Kamya MR, et al. Machine learning to identify persons at high-risk of HIV acquisition in rural Kenya and Uganda. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2019**.
124. Katurura MC, Cilliers L. Electronic health record system in the public health care sector of South Africa: A systematic literature review. African journal of primary health care & family medicine **2018**; 10(1): e1-e8.
125. Dijkstra M, Lin TC, de Bree GJ, Hoenigl M, Schim van der Loeff MF. Validation of the San Diego Early Test Score for early HIV infection among Amsterdam men who have sex with men. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2019**.
126. Mugwanya KK, Pintye J, Kinuthia J, et al. Integrating preexposure prophylaxis delivery in routine family planning clinics: A feasibility programmatic evaluation in Kenya. PLoS medicine **2019**; 16(9): e1002885.
127. Elwyn G, Dehlendorf C, Epstein RM, Marrin K, White J, Frosch DL. Shared decision making and motivational interviewing: achieving patient-centered care across the spectrum of health care problems. Annals of family medicine **2014**; 12(3): 270-5.
128. Dehlendorf C, Krajewski C, Borrero S. Contraceptive counseling: best practices to ensure quality communication and enable effective contraceptive use. Clin Obstet Gynecol **2014**; 57(4): 659-73.
129. Dehlendorf C, Levy K, Kelley A, Grumbach K, Steinauer J. Women's preferences for contraceptive counseling and decision making. Contraception **2013**; 88(2): 250-6.
130. Nobili MP, Piergrossi S, Brusati V, Moja EA. The effect of patient-centered contraceptive counseling in women who undergo a voluntary termination of pregnancy. Patient Educ Couns **2007**; 65(3): 361-8.
131. Dehlendorf C, Henderson JT, Vittinghoff E, et al. Association of the quality of interpersonal care during family planning counseling with contraceptive use. Am J Obstet Gynecol **2016**; 215(1): 78.e1-9.
132. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. The Cochrane database of systematic reviews **2017**; 4: Cd001431.
133. Barden-O'Fallon J, Speizer I. What differentiates method stoppers from switchers? Contraceptive discontinuation and switching among Honduran women. Int Perspect Sex Reprod Health **2011**; 37(1): 16-23.
134. Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. Am J Obstet Gynecol **1998**; 179(3 Pt 1): 577-82.

135. Sanders SA, Graham CA, Bass JL, Bancroft J. A prospective study of the effects of oral contraceptives on sexuality and well-being and their relationship to discontinuation. Contraception **2001**; 64(1): 51-8.
136. Daniels K, Mosher WD. Contraceptive methods women have ever used: United States, 1982-2010. National health statistics reports **2013**; (62): 1-15.
137. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. The New England journal of medicine **2017**; 377(23): 2228-39.
138. Manns-James L. Bacterial vaginosis and preterm birth. Journal of midwifery & women's health **2011**; 56(6): 575-83.
139. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports **2016**; 65(4): 1-66.
140. Unemo M, Bradshaw CS, Hocking JS, et al. Sexually transmitted infections: challenges ahead. The Lancet Infectious diseases **2017**; 17(8): e235-e79.
141. Schwebke JR, Hillier SL, Sobel JD, McGregor JA, Sweet RL. Validity of the vaginal gram stain for the diagnosis of bacterial vaginosis. Obstet Gynecol **1996**; 88(4 Pt 1): 573-6.
142. Myziuk L, Romanowski B, Johnson SC. BVBlue test for diagnosis of bacterial vaginosis. J Clin Microbiol **2003**; 41(5): 1925-8.
143. Bradshaw CS, Morton AN, Garland SM, Horvath LB, Kuzevska I, Fairley CK. Evaluation of a point-of-care test, BVBlue, and clinical and laboratory criteria for diagnosis of bacterial vaginosis. J Clin Microbiol **2005**; 43(3): 1304-8.
144. Tiger Medical I. Sekisui Diagnostics 183 Osom® Bvblue® Rapid Test - 25/kit. Available at: https://www.tigermedical.com/Products/Osom-Bvblue-Rapid-Test---25kit__SEK183.aspx?invsrc=adwords_tm&gclid=CjwKCAiA_MPuBRB5EiwAHTTvMeAHLFKB1X9LU8_3ld6_8UawlJLOOGNcmkAqAzjrWn8KOqTERWTjqBoCEKAQAvD_BwE. Accessed 17 November 2019.
145. Medex Supply. Genzyme Osom BVBLUE Test Kit, 25/bx. Available at: https://www.medexsupply.com/diagnostic-tests-urine-tests-genzyme-osom-bvblue-test-kit-25-bx-x_pid-48578.html?pid=48578&gclid=CjwKCAiA_MPuBRB5EiwAHTTvMWp1MAryXLnKBfv2cYM1L3PSWelChv1ADnBveV3acfYLO4eCTVj6gxoCegYQAvD_BwE. Accessed 17 November 2019.
146. Balkus JE, Carter KA, McClelland RS. Lessons from Suppressive Therapy and Periodic Presumptive Treatment for Bacterial Vaginosis. Curr Infect Dis Rep **2019**; 21(10): 34.
147. Balkus JE, Manhart LE, Lee J, et al. Periodic Presumptive Treatment for Vaginal Infections May Reduce the Incidence of Sexually Transmitted Bacterial Infections. The Journal of infectious diseases **2016**; 213(12): 1932-7.
148. Kacker S, Frick KD, Quinn TC, Gray RH, Tobian AA. Financial implications of male circumcision scale-up for the prevention of HIV and other sexually transmitted infections in a sub-Saharan African community. Sex Transm Dis **2013**; 40(7): 559-68.
149. Pepin J, Mabey D. Sexually transmitted infections in Africa: single dose treatment is now affordable. Sex Transm Infect **2003**; 79(6): 432-4.
150. Schwebke JR, Muzny CA, Josey WE. Role of Gardnerella vaginalis in the pathogenesis of bacterial vaginosis: a conceptual model. The Journal of infectious diseases **2014**; 210(3): 338-43.
151. Marrazzo JM, Dombrowski JC, Wierzbicki MR, et al. Safety and Efficacy of a Novel Vaginal Anti-infective, TOL-463, in the Treatment of Bacterial Vaginosis and Vulvovaginal Candidiasis: A Randomized, Single-blind, Phase 2, Controlled Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2019**; 68(5): 803-9.
152. Boily MC. The relative contribution of anal intercourse and primary infection to mature heterosexual HIV epidemics. Sex Transm Infect **2011**; 87: A38-A.

153. National AIDS & STI Control Programme (NASCOP) Ministry of Health. Kenya AIDS Indicator Survey 2012: Final Report. Nairobi, Kenya: NASCOP, **2014**.
154. Browne EN, Montgomery ET, Mansfield C, et al. Efficacy is Not Everything: Eliciting Women's Preferences for a Vaginal HIV Prevention Product Using a Discrete-Choice Experiment. AIDS and behavior **2019**.
155. National Institutes of Health. Pivotal Phase 2b/3 ALVAC/Bivalent gp120/MF59 HIV Vaccine Prevention Safety and Efficacy Study in South Africa (HVTN702). Available at: https://clinicaltrials.gov/ct2/show/NCT02968849. Accessed 21 July 2018.
156. World Health Organization. Contraceptive eligibility for women at high risk of HIV. Guidance statement: recommendations on contraceptive methods used by women at high risk of HIV. Geneva, Switzerland: World Health Organization, **2019**.
157. Molina JM, Charreau I, Spire B, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV **2017**; 4(9): e402-e10.
158. Cottrell ML, Yang KH, Prince HM, et al. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. The Journal of infectious diseases **2016**; 214(1): 55-64.
159. Patterson KB, Prince HA, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Science translational medicine **2011**; 3(112): 112re4.
160. Masyuko S, Mukui I, Njathi O, et al. Pre-exposure prophylaxis rollout in a national public sector program: the Kenyan case study. Sex Health **2018**; 15(6): 578-86.
161. World Health Organization. A public health approach to antiretroviral treatment : overcoming constraints. Geneva, Switzerland: World Health Organization, **2003**.