Original research article

Contraception use and effectiveness among women in a trial of the diaphragm for HIV prevention☆,☆☆
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Abstract

Background: There is little data on contraceptive effectiveness or use patterns from sub-Saharan Africa.

Study Design: We analyzed data from women at risk of pregnancy (n=4905) in the Methods for Improving Reproductive Health in Africa trial of the diaphragm for HIV prevention. We described reported contraceptive method use and calculated rates of pregnancy by contraceptive method. We compared time to first pregnancy by study arm (condoms or condoms plus diaphragm), and estimated a Cox proportional hazards model to identify predictors of pregnancy.

Results: Condoms (25.8%), injectables (25.4%) and OC (21.6%) were the most commonly used methods; long-acting method use was rare. During the trial, 51.6% of women used the same method, 27.4% switched to a more effective method and 20.9% switched to a less effective method; 21.4% of women became pregnant. Pregnancy rates by contraceptive group mirrored published estimates; frequency of study product use was not associated with pregnancy.

Conclusion: Long-acting methods of contraception should be made available in HIV prevention trials and to women in Southern Africa.

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Keywords: Contraception; HIV prevention; South Africa; Zimbabwe; diaphragm

1. Introduction

Contraceptive methods, including hormonal methods, barrier methods and long-acting methods, have been shown to significantly reduce the risk of pregnancy among women participating in contraception clinical trials [1]. Women in these trials, though, are selected to be at significant risk of pregnancy, at low risk of sexually transmitted infections, and willing to exclusively use the method under study [2–4]. Although researchers traditionally estimate both perfect use and typical use efficacy rates to account for less than perfect adherence or incorrect method use, there are few prospective
The Methods for Improving Reproductive Health in Africa (MIRA) trial evaluated whether the diaphragm used with a lubricant gel could prevent HIV acquisition among women. The diaphragm, traditionally used with a spermicide, is one of the oldest contraceptive methods [5]. The diaphragm physically blocks passage of semen and sperm into the uterus preventing fertilization, and the spermicide provides added contraceptive protection. Although no longer popular, having been displaced by more effective hormonal methods, when used together, the diaphragm and spermicide have contraceptive efficacy rates similar to other barrier methods, like male or female condoms [6]. Researchers hypothesized that by preventing sperm and semen from reaching the cervix or the upper reproductive tract, which have high concentrations of HIV-susceptible cells and thinner epithelial linings than the vagina, the diaphragm could also potentially reduce the risk of HIV transmission [7–9]. In the MIRA trial the Ortho All-flex diaphragm was used with Replens®, a noncontraceptive lubricant gel. Nonoxynol-9 (N9), the spermicide generally used with the diaphragm for contraception, is contraindicated among women at risk of HIV infection [10]. The primary analysis of MIRA trial data showed that adding the diaphragm to a state of the art prevention package did not reduce HIV acquisition [11].

Using data from the MIRA trial, we evaluated the effectiveness of contraceptive methods used by women in the trial, including male and female condoms, progestin-only and combined oral contraceptives, injectables and long-acting methods [intrauterine devices (IUDs), implants and male and female sterilization]. We also evaluated whether provision of the diaphragm, a non-spermicidal gel and condoms reduced risk of pregnancy compared to provision of condoms only, among women using a range of other contraceptive methods, and attempted to assess the contraceptive effectiveness of the diaphragm used with a non-contraceptive lubricant gel. Finally, we identified predictors of pregnancy in this population of women at high risk of HIV infection.

2. Methods

The MIRA trial was an open-label, randomized controlled trial conducted among women recruited from family planning clinics, well-baby clinics, general health clinics and community venues in South Africa and Zimbabwe. Half of the 5045 women enrolled were randomly selected to receive an Ortho All-flex diaphragm, Replens® lubricant gel and male condoms (intervention arm). HIV incidence among women in the intervention arm was compared to incidence among women in the control arm, who received condoms only. Detailed study methods have been published elsewhere [11], but in brief, at enrollment, women who participated in the trial were: sexually active (reported sex at least 4 times a month), neither pregnant nor planning pregnancy for the next 2 years, HIV-negative and had a negative test or were treated for curable sexually transmitted infections (chlamydia, gonorrhea, trichomonas or syphilis). Women were ineligible if they had a full hysterectomy, had given birth or had an abortion in the previous 6 weeks. Women joining the trial were encouraged to use an effective contraceptive method as the diaphragm used with a lubricant gel had unknown contraceptive effectiveness. Midway through the trial, based on evolving standards for contraception provision in HIV prevention trials, the study clinics started offering hormonal contraceptives free of charge on site. Women returned to the study clinic two weeks after enrollment for a study products check-in and then for quarterly follow-up visits for up to two years. At each quarterly visit, staff performed a urine pregnancy test and the woman was asked whether she had been pregnant since her last visit. All women in the MIRA trial provided written informed consent prior to enrollment; study staff discussed the study procedures and key informed consent topics with each woman at each quarterly follow-up visit. The MIRA trial protocol was reviewed and approved by the institutional review boards or ethical review committees at each of the five collaborating organizations.

For this analysis, we included MIRA trial participants who were at risk of pregnancy (aged 18-49 years and did not report menopause or hysterectomy at study start, reported vaginal sexual intercourse during the trial) and provided data on sexual activity, contraceptive use and pregnancy at enrollment and at least one follow-up visit. Data from women who reported menopause (n=4) or hysterectomy (n=7) during the trial were censored at the time of report. The final sample of 4905 women contributed data from 28,463 study visits.

Data on contraceptive use were coded into seven mutually exclusive categories based on the woman’s most effective reported contraceptive method. For example, if a woman reported using a contraceptive injection and condoms she was coded as using injectables. The seven categories for contraceptive method included (in increasing order of effectiveness): no method, other method (including less effective methods like withdrawal and traditional methods), male or female condoms, progestin-only oral contraceptives (POPs), combined estrogen and progestin oral contraceptives (OCs), injectables and long-acting methods (including IUDs, implants, male and female sterilization). We calculated means for continuous measures and percentages for dichotomous and categorical demographic characteristics for the overall sample and for women in each of the contraceptive categories at enrollment.

For this analysis, pregnancy was defined as either a positive quarterly urine pregnancy test (laboratory-confirmed pregnancy) or a woman’s report that she had been pregnant since her last visit when asked by the clinician during a quarterly follow-up visit (self-reported pregnancy). Self-reported pregnancy was included because the three-
month window between study visits was long enough for a woman to have an identified pregnancy that was terminated (either by elective or spontaneous abortion) before her next visit. All analyses were conducted with lab-confirmed pregnancy alone, self-reported pregnancy alone and combined overall pregnancy rates. The results were similar across measures of pregnancy (data not shown) so only the combined measure is reported here. We calculated the percentage of women ever pregnant by study arm and in each contraceptive group using the most effective method reported at enrollment, and for women who reported consistent use of a method (defined as reported method used at more than 50% of study visits). We compared time to first pregnancy between study arms using Kaplan-Meier survival curves and log rank tests. We calculated contraceptive failure rates by estimating the rate of first pregnancy per 100 woman-years and the Kaplan-Meier 12-month cumulative probability of pregnancy in each study arm and for each contraceptive group at enrollment and among consistent users; we calculated failure both ways to compare effectiveness to published data from developed [12] and developing [13] countries. To identify predictors of pregnancy, we estimated a Cox proportional hazards model for time to first pregnancy including time-varying contraceptive use (reported at each quarterly visit), study arm and study product use (condom and/or diaphragm use at last sex in <50% of visits vs. ≥50% and use of the diaphragm always vs. less than always since last visit). Demographic characteristics known to be associated with pregnancy risk were also considered in the model, and backwards elimination was used to identify the final model.

3. Results

Among this sample of 4905 women at risk of pregnancy in the MIRA trial, the most commonly used contraceptive methods at study enrollment were condoms (25.8%), injectables (25.4%) and OC (21.6%) (Table 1). Women using these methods were on average 27–28 years of age; women who reported using long-acting methods (5.3%) and no method (5.3%) were older (mean 38 and 33 years, respectively). Women who reported long-acting method use and no method use also had fewer years of education.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None/no method</th>
<th>Other method</th>
<th>N</th>
<th>Condoms</th>
<th>N</th>
<th>POPs</th>
<th>N</th>
<th>OCs</th>
<th>N</th>
<th>Injectables</th>
<th>N</th>
<th>Long-acting methods</th>
<th>N</th>
<th>Total</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Most effective contraceptive method used (%)</td>
<td>5.3</td>
<td>260</td>
<td>2.3</td>
<td>112</td>
<td>25.8</td>
<td>1265</td>
<td>14.4</td>
<td>708</td>
<td>21.6</td>
<td>1058</td>
<td>25.4</td>
<td>1244</td>
<td>5.3</td>
<td>258</td>
<td>100.0</td>
</tr>
<tr>
<td>Age (mean)</td>
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<td>260</td>
<td>32.6</td>
<td>112</td>
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<td>1265</td>
<td>26.1</td>
<td>708</td>
<td>28.1</td>
<td>1058</td>
<td>27.0</td>
<td>1244</td>
<td>38.2</td>
<td>258</td>
<td>28.4</td>
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<tr>
<td>Years of education (mean)</td>
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<td>112</td>
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<td>708</td>
<td>9.7</td>
<td>1058</td>
<td>9.8</td>
<td>1242</td>
<td>7.8</td>
<td>257</td>
<td>9.6</td>
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<tr>
<td>Country (%)</td>
<td>9.2</td>
<td>225</td>
<td>1.5</td>
<td>37</td>
<td>34.2</td>
<td>839</td>
<td>1.8</td>
<td>44</td>
<td>7.1</td>
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<td>910</td>
<td>9.2</td>
<td>225</td>
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<td>75</td>
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<td>426</td>
<td>27.1</td>
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<td>36.1</td>
<td>885</td>
<td>13.6</td>
<td>334</td>
<td>1.4</td>
<td>33</td>
<td>50.0</td>
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<td>Zimbabwe</td>
<td>92.7</td>
<td>241</td>
<td>91.1</td>
<td>102</td>
<td>93.5</td>
<td>1183</td>
<td>94.9</td>
<td>671</td>
<td>93.6</td>
<td>990</td>
<td>93.6</td>
<td>1165</td>
<td>90.7</td>
<td>234</td>
<td>93.5</td>
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<td>Religion (%)</td>
<td>0.4</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>1.2</td>
<td>15</td>
<td>2.7</td>
<td>19</td>
<td>2.0</td>
<td>21</td>
<td>0.2</td>
<td>2</td>
<td>2.3</td>
<td>6</td>
<td>1.3</td>
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<tr>
<td>Christian</td>
<td>0.4</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>1.2</td>
<td>15</td>
<td>2.7</td>
<td>19</td>
<td>2.0</td>
<td>21</td>
<td>0.2</td>
<td>2</td>
<td>2.3</td>
<td>6</td>
<td>1.3</td>
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<tr>
<td>Hindu</td>
<td>0.8</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.7</td>
<td>9</td>
<td>0.1</td>
<td>1</td>
<td>0.4</td>
<td>4</td>
<td>0.5</td>
<td>6</td>
<td>1.9</td>
<td>5</td>
<td>0.6</td>
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<tr>
<td>Married (%)</td>
<td>39.9</td>
<td>103</td>
<td>76.8</td>
<td>86</td>
<td>40.7</td>
<td>515</td>
<td>95.6</td>
<td>677</td>
<td>87.8</td>
<td>929</td>
<td>36.9</td>
<td>459</td>
<td>62.4</td>
<td>161</td>
<td>59.8</td>
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<tr>
<td>Currently lives with partner (%)</td>
<td>59.3</td>
<td>153</td>
<td>82.1</td>
<td>92</td>
<td>49.5</td>
<td>626</td>
<td>97.3</td>
<td>689</td>
<td>89.9</td>
<td>951</td>
<td>53.7</td>
<td>668</td>
<td>76.4</td>
<td>197</td>
<td>68.9</td>
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<tr>
<td>Number of live births (mean)</td>
<td>2.2</td>
<td>260</td>
<td>3.0</td>
<td>112</td>
<td>1.7</td>
<td>1265</td>
<td>2.2</td>
<td>708</td>
<td>2.2</td>
<td>1058</td>
<td>2.0</td>
<td>1244</td>
<td>3.9</td>
<td>258</td>
<td>2.1</td>
</tr>
<tr>
<td>Age at first sex (mean)</td>
<td>17.4</td>
<td>260</td>
<td>18.2</td>
<td>112</td>
<td>18.0</td>
<td>1264</td>
<td>18.9</td>
<td>708</td>
<td>18.5</td>
<td>1058</td>
<td>17.7</td>
<td>1244</td>
<td>17.6</td>
<td>258</td>
<td>18.1</td>
</tr>
<tr>
<td>Number of lifetime male partners (mean)</td>
<td>2.9</td>
<td>258</td>
<td>1.6</td>
<td>112</td>
<td>2.9</td>
<td>1265</td>
<td>1.4</td>
<td>708</td>
<td>1.6</td>
<td>1058</td>
<td>2.5</td>
<td>1244</td>
<td>3.2</td>
<td>258</td>
<td>2.3</td>
</tr>
<tr>
<td>Ever had sex in exchange for money (%)</td>
<td>1.2</td>
<td>3</td>
<td>0.9</td>
<td>1</td>
<td>1.3</td>
<td>16</td>
<td>0.7</td>
<td>5</td>
<td>0.6</td>
<td>6</td>
<td>1.1</td>
<td>14</td>
<td>0.8</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever had vaginal sex with a male condom (%)</td>
<td>48.4</td>
<td>125</td>
<td>72.3</td>
<td>81</td>
<td>99.4</td>
<td>1258</td>
<td>88.4</td>
<td>626</td>
<td>90.6</td>
<td>959</td>
<td>85.1</td>
<td>1059</td>
<td>71.3</td>
<td>184</td>
<td>87.5</td>
</tr>
</tbody>
</table>

* Including less effective methods like withdrawal and traditional methods.
8 years) compared to women using condoms, injectables or OC (mean 10 years). There were some notable differences in the patterns of contraceptive use in the two study countries. More women in South Africa reported not using a method, using condoms as their most effective contraceptive method, using injectables and using long-acting methods; more women in Zimbabwe reported using POP and OC. Higher percentages of women who reported POP and OC use at enrollment were married compared to women who reported injectable, condom or no method use; this is likely due to differences in marriage patterns in Zimbabwe and South Africa. The vast majority of women who participated in the study in Zimbabwe reported being married while less than half of women in South Africa were married (data not shown). More than 90% of the women who reported POP use at their enrollment visit were from Zimbabwe where well-baby clinics were targeted for recruitment.

We compared women’s reported most effective contraceptive method used at enrollment with their reported most effective contraceptive method used at their last study visit. Overall, 51.6% of women reported using the same method at enrollment and their last visit. Among the women who changed methods, 27.4% reported using a more effective method at study end and 20.9% reported using a less effective method (Fig. 1); 86.8% of women using no method and 83.0% of women using an “other” method moved to a more effective method during the study. In contrast, only 10.4% of women who reported OC use at enrollment (a more effective method) switched to a method of higher effectiveness.

The rate of first pregnancy in this sample was 14.4 per 100 woman-years and 21.4% reported or had a laboratory-confirmed pregnancy during their study participation. Similar percentages of women in the intervention arm (21.6%) and in the control arm (21.2%) became pregnant and pregnancy rates were also similar between arms (14.5 per 100 woman-years and 14.2 per 100 woman-years, respectively); time to first pregnancy was not different between the two arms using a Kaplan-Meier analysis (p=.78) (Fig. 2).

Pregnancy rates by method reported at enrollment and among consistent users are presented in Table 2. Consistent users generally had lower failure rates except for POP users. Contraceptive failure rates were lowest for women using long-acting methods (between 0.5 and 1.1 per 100 woman-years) (Table 2). Pregnancy rates were highest for women consistently reporting use of no method (58.1 pregnancies...
Rates of first pregnancy among consistent injectable users were 6.5 per 100 woman-years, consistent condom users 14.7 per 100 woman-years and consistent OC users 7.3 per 100 woman-years. Among POP users the first pregnancy rate was 12.9 per 100 woman-years. Consistent POP users had lower Kaplan-Meier incidence of pregnancy than consistent injectable or OC users which is likely a result of breastfeeding post-partum women at lower risk of pregnancy being given POPs and then switching to other methods. No woman reported use of the diaphragm and gel for contraception at baseline and only four women reported consistent use of the diaphragm and lubricant gel as their most effective method of contraception during the trial, so we were unable to estimate contraceptive effectiveness for this method.

Although there was no difference in time to first pregnancy between the two study arms, we did find that women who consistently reported use of no method in the intervention arm had fewer pregnancies (59.4%) compared to the control arm (75.5%) (p=.07) (Table 2). However, there were small numbers of women and pregnancies in this group and the difference was not statistically significant. There were also fewer pregnancies among women who consistently reported using an “other” method in the intervention arm, but there were also very few women in this group. Among women who consistently reported using OC, significantly fewer women in the control arm had a pregnancy (9.7% compared to 14.1% in the intervention arm, p=.03).

In our Cox proportional hazards model, which included most effective self-reported contraceptive use at each visit as a time-varying covariate, all contraceptive methods were associated with significant reductions in pregnancy risk (compared to no method) and were included in the final model (Table 3). Mirroring the Kaplan-Meier results, study arm was not a significant predictor of pregnancy and dropped out of the model. Demographic and sexual behavior variables which were significantly associated with higher risk of pregnancy included younger age, living with one’s partner and reporting three or more lifetime sexual partners. Use of diaphragm and lubricant gel and use of condoms (either at last sex or frequency since the last visit) were not significant predictors of pregnancy in this analysis and were dropped from the model.

4. Discussion

Few prospective studies of contraceptive effectiveness are conducted in developing countries. Data from the MIRA trial may also more closely approximate “real-life” contraceptive effectiveness because women are not as highly selected as are women in contraceptive clinical trials. We found that rates of first pregnancy and the Kaplan-Meier cumulative incidence of first pregnancy among women in the MIRA trial who reported consistent method use followed the pattern of published data on typical-use contraceptive effectiveness (long-acting methods are more effective than injectables, which are more effective than OC and POP, which are more effective than condoms, other and no method); method-specific contraceptive effectiveness reported here largely

<table>
<thead>
<tr>
<th>Category</th>
<th>Reported use at enrollment</th>
<th>Consistent use during the study (≥50% of visits)</th>
<th>Study arm (among consistent users)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>N</td>
<td>Ratea</td>
</tr>
<tr>
<td>Contraceptive method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>24.2</td>
<td>63</td>
<td>17.7</td>
</tr>
<tr>
<td>Other</td>
<td>22.3</td>
<td>25</td>
<td>14.1</td>
</tr>
<tr>
<td>Male or female condoms</td>
<td>29.3</td>
<td>371</td>
<td>21.5</td>
</tr>
<tr>
<td>POP</td>
<td>17.5</td>
<td>124</td>
<td>10.7</td>
</tr>
<tr>
<td>OC</td>
<td>28.5</td>
<td>302</td>
<td>19.3</td>
</tr>
<tr>
<td>Injectables</td>
<td>13.1</td>
<td>163</td>
<td>8.5</td>
</tr>
<tr>
<td>Long-acting methods</td>
<td>0.8</td>
<td>2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

a Rate of first pregnancy per 100 women-years of follow-up; women censored at first pregnancy.

b Kaplan-Meier 12-month cumulative probability of first pregnancy.

c p values for the comparison of pregnancy among consistent users of each method.
mirrored published data from developed country contraceptive trials [12]. Pregnancy rates among women reporting consistent long-acting method and OC use in our study were somewhat higher than published data (i.e., published IUD typical use failure rate 0.8% in the first year compared to 1.1 pregnancies per 100 woman-years and cumulative pregnancy rate of 2.2% among women reporting consistent long-acting method use in our study; published OC/POP typical use failure rate 8.0% in the first year compared to 7.3 pregnancies per 100 woman-years and cumulative pregnancy rate of 9.4% among consistent OC users in our study) [12], which could be due to women receiving less intense contraceptive counseling than women in contraceptive trials or due to unmeasured non-compliance with method use. Pregnancy rates among condom users in our study were slightly lower [i.e., published condoms (male) typical use failure rate 15.0% in first year of use compared to 14.7 pregnancies per 100 woman-years and cumulative pregnancy rate of 9.0% in our study] [12].

Long-acting method users in the MIRA trial had fewer years of education, were older and reported having more children; this likely indicates a cohort effect and that long-acting methods in these settings are being offered mainly to older women who have completed their child-bearing, despite evidence that they are appropriate for younger women. Our quarterly collection of self-reported contraceptive use and measure of consistent method use may have overestimated adherence and is not precisely comparable to the detailed data collected in trials for typical use failure rate calculations. A recent analysis of contraceptive effectiveness among women enrolled in a study assessing the association between hormonal contraceptives and HIV by Steiner et al. [13] found lower 12-month cumulative pregnancy rates among injectable users (actual use 0.6%, intended use 2.0%) and similar 12-month cumulative pregnancy rates among OC users (actual use 9.5%, intended use 15.7%). Their measure of “actual” use is likely most similar to our consistent use measure, and intended use is most similar to our estimates of pregnancy based on most effective method reported at enrollment. The difference in injectable use effectiveness could be due to improved adherence—women in that study had to be willing to continue method use for 1 year—and since the focus of the study was on the impact of contraception on HIV acquisition, they may have received more intense contraceptive counseling in contrast to our study where contraceptive use was not a primary outcome or exposure. Although women in the MIRA trial were encouraged to use a family planning method, contraception was not the focus of the study and we did not precisely measure adherence (i.e., we did not assess whether women had follow-up injections on time). The fact that pregnancy rates among OC users were similar in both studies despite the differences in the study designs could reflect the fact that OC effectiveness is less forgiving of imperfect adherence and therefore more intense counseling or stronger intention to use a method among women in the Steiner et al. study did not translate into higher effectiveness.

We found no difference in pregnancy rates by study arm, despite the fact that women in the intervention arm were asked to use the diaphragm and lubricant gel in addition to condoms and their contraceptive method. Findings from the primary analysis did show that although there was lower condom use in the intervention arm, the percentage of protected acts (where either a condom or the diaphragm was used) was similar in both arms [11]; this could have led to similar pregnancy rates given similar rates of typical-use contraceptive effectiveness between the diaphragm and condoms. However, in the MIRA trial, the lubricant used with the diaphragm, Replens® gel, is not contraceptive, unlike N9 usually used with the diaphragm for contraception. N9 was not appropriate for use with the diaphragm for HIV prevention because N9 is contraindicated among women at high risk of HIV infection [10] and has been shown to potentially increase risk of HIV infection with frequent use [14]. We were unable to measure the contraceptive effectiveness of the diaphragm and Replens® gel because only four women consistently reported using them as their most effective contraceptive method during the trial; the little published data on the effectiveness of the diaphragm used alone for contraception is weak [15–17]. We did find some evidence to suggest that the diaphragm and Replens® gel may have had some effect on reducing risk of pregnancy among women who reported use of no contraceptive method or who used an “other” less effective method, but the number of women in these groups was small. Results from our multivariate model showed that study arm and frequency of diaphragm and gel or condom use were not significant predictors of pregnancy. Although the diaphragm and Replens® gel cannot be recommended for prevention of pregnancy based on these data, novel contraceptive gels like Buffergel that are not contraindicated for women at high HIV risk have been used with the diaphragm and have been shown to provide equivalent pregnancy protection to the diaphragm used with N9 [18]. Given that there are few
barrier contraceptive methods available, the diaphragm and a novel spermicide could provide an important contraception option for women in high-risk areas who do not want to or cannot use a hormonal method. Rigorous research on the contraceptive effectiveness of the diaphragm alone would provide valuable information on whether it can be used without a gel for contraception and would also be useful should current interest in the diaphragm or a diaphragm-like device as a vehicle for a microbicide translate into increased use of the method. Forthcoming data on a novel diaphragm-like device (SILCS, currently being evaluated in the US for contraceptive effectiveness) will also significantly advance our understanding of the potential for new barrier methods for contraception [19,20].

Nineteen percent of women in the MIRA trial became pregnant (rate of first pregnancy 13.1 per 100 woman-years) [11]; 21.4% of women in this sub-sample at higher risk of pregnancy became pregnant (rate of first pregnancy 14.4 per 100 woman-years). These are high rates of pregnancy especially considering that contraception use was promoted and women were counseled to use a contraceptive method in addition to using the study products, eligible women had to indicate they were not planning to become pregnant in the next two years, and hormonal methods were made available free of charge at the study clinics starting approximately midway through the trial. Of the 51.6% of women in this analysis who changed contraceptive methods during the trial, only slightly more than half moved to a more effective method and slightly less than half moved to a less effective method. Women who were originally using less effective methods were more likely to move to more effective methods, but few women chose to move from an effective but user-dependent method (like OC) to user-independent methods that have higher effectiveness (like injectables and long-acting methods including IUDs or implants). The high rates of failure among OC users in this analysis and other studies underscore the importance of increasing access to IUDs and implants to reduce unintended pregnancy.

Other HIV prevention trials have reported high rates of pregnancy: between 16 and 64 per 100 woman-years [21] and in some trials up to a quarter of participants became pregnant [22]. High pregnancy rates can seriously undermine the power of trials of investigational products if women must be removed from product use as soon as they become pregnant and for the duration of their pregnancy [23,24]. The products in the MIRA study were not investigational and women who became pregnant were counseled that they could continue to safely use the diaphragm and gel. The pregnancy rates in the MIRA trial fall at the lower end of the range for HIV prevention trials, which could be due to the emphasis on contraception use and offering hormonal methods at the study sites, as well as the contraceptive efficacy of the study products. Offering contraceptive methods at study clinics should be standard practice in HIV prevention trials, and researchers should consider offering long-acting methods both as a service to the women enrolled in the trial and to help reduce unintended pregnancy among their study population.

The main limitation of this analysis is that the study was not designed to measure contraceptive effectiveness and precise data on underlying fertility, method use and exposure to pregnancy were not collected. We also did not collect data on duration of contraceptive method use at study enrollment, so this analysis includes a mixture of continuing and new users, which could mean we are underestimating failure rates, although there is no reason to believe that the distribution of new and continuing users would differ by study arm and the comparisons across arm and method would still be valid. We relied on quarterly reports from women and urine pregnancy tests to measure pregnancy, and may have underestimated actual rates if pregnancies between visits were not reported and terminated before the next clinic visit. We did not collect prospective data on pregnancy intentions. In addition, the MIRA trial study products may have had some contraceptive effect, and coding women to their most effective contraceptive method may have obscured the effect of certain methods or the effect of the use of multiple methods or combinations of different methods. Contraceptive use was measured by self-report which may lead to bias in our measures of contraceptive use. The prospective design, long follow-up and large sample are strengths of the analysis, which adds to the limited published data on contraceptive effectiveness in developing countries.

Offering long-acting contraceptive methods to women participating in HIV prevention trials could significantly reduce unintended pregnancy, and increasing information about, access to and policy support for long-acting methods with higher effectiveness is a critical public health priority across the world. Our data show the dramatic differences in effectiveness between pills and injectables and long-acting methods, and highlight the need to increase investment in long-acting methods for women in Southern Africa.

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