

Review

Safer Conception Interventions for HIV-Affected Couples: Implications for Resource-Constrained Settings

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Developing and testing safer conception methods that reduce HIV transmission to HIV-seronegative partners in serodiscordant couples and reduce superinfection in HIV-seroconcordant couples is a crucial but often unaddressed component of HIV prevention programs. Most research has focused on developed-world settings, where “high-technology” assisted reproduction techniques are used for HIV-serodiscordant couples in which the male is HIV-infected. There is a dearth of research on safer conception methods for HIV-seropositive women and “low-technology” harm-reduction strategies for HIV-affected couples, including vaginal insemination for HIV-seropositive women and natural conception methods for HIV-seroconcordant and -serodiscordant couples. This review summarizes international studies of safer conception interventions for HIV-affected couples, with a focus on feasibility in public-sector health settings where assisted reproductive technology is not readily available. Given that such low-technology options are feasible in most settings, well-designed, prospective interventions offering low-technology safer conception methods need to be developed and tested.

With the majority of those living with HIV infection being of reproductive age, conception and reproductive options for this population are important issues for health care delivery and research.¹ Despite pronouncements from local and international guideline committees about whether and how those with HIV infection should have children, HIV-seropositive individuals deserve full reproductive rights. The need to develop and test safer conception interventions involving natural conception is underscored by findings that a substantial proportion of HIV-serodiscordant couples engage in unprotected sex, regardless of “safer sex” or “safer conception” messages.

International reproductive guidelines shifted a decade ago from recommending avoidance of pregnancy

to recognizing conception and parenting as realistic options for people with HIV infection and their partners.² Since 2001, the US Centers for Disease Control and Prevention (CDC) has encouraged information and support for HIV-affected couples who want to explore their reproductive options.³ HIV advocacy organizations, such as the ATHENA Network and others, have pioneered reproductive rights for people with HIV infection.

No conception methods are 100% risk-free of HIV transmission, other than the use of screened fresh sperm from HIV-seronegative donors (when a woman’s male partner is HIV-infected) and adoption. However, several risk-reduction methods for safer conception, in which the HIV-infected partner is on antiretroviral therapy, have been

used in the developed world. These include low-technology methods such as timed, unprotected sexual intercourse for HIV-seropositive concordant couples, and vaginal insemination (ie, fresh semen from a condom or sterile cup is inserted into the vagina via a disposable pipette or syringe) for HIV-seropositive women who have HIV-seronegative partners. High-technology methods include sperm washing and intrauterine insemination (IUI) and intracytoplasmic sperm injection (ICSI) for HIV-seropositive men with HIV-seronegative female partners. The use of antiretroviral drugs by the HIV-infected male partner to lower HIV in the seminal plasma to an undetectable level, and the potential use of preexposure prophylaxis (PrEP) by the HIV-seronegative partner, are other strategies for reducing the risk of HIV transmission in serodiscordant couples.

Aside from recommending expensive technologies to minimize transmission in HIV-affected couples planning to have children, best practices for counseling these couples are only recently being addressed. An increasingly crucial issue, given the high levels of HIV infection in resource-limited areas, is what harm-reduction, safer conception methods are feasible and acceptable. In a pronatal society such as South Africa, being HIV-infected is unlikely to stop people from desiring children.⁴⁻⁸ Accordingly, the South African HIV Clinicians Society has published safer conception guidelines.⁹ These issues are relevant

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not only in resource-limited countries, but in all settings where assisted reproduction is neither widely available nor affordable.

Several reviews on safer conception and HIV have been published,¹⁰⁻¹⁴ but they have tended to focus predominantly on options for HIV-seropositive male and HIV-seronegative female couples, the serodiscordance most common in developed countries.¹⁵ Furthermore, most reviews of safer conception interventions have been based on studies from industrialized-world contexts and do not focus on the feasibility of these interventions in resource-constrained settings. As a result, there are considerable data on the efficacy of sperm washing, but limited data on timed unprotected sex, and no available data on vaginal insemination.

Methods

This review draws on available English-language international studies of safer conception and HIV-affected couples published through October 2010. Relevant material was obtained primarily through a search of key electronic databases, including ScienceDirect, Academic Search Premier, PubMed, MEDLINE, Google Scholar, and TDNet. Key search terms included: safe conception and HIV; safer conception and HIV; HIV and assisted reproduction; and HIV and reproduction. Only articles that dealt specifically with safer conception interventions for HIV-affected couples and that reported on data from such interventions and studies were considered in this review. Commentary pieces and position papers were not included. Reference lists of all articles were also scanned for other relevant studies.

The search yielded 32 published studies that reported on data and findings from safer conception interventions. Given our focus on feasibility in the context of safer conception, in this article we concentrate primarily on reports of low-technology methods that are feasible in resource-constrained settings, including vaginal insemination for HIV-infected women and the use of natural conception methods.

Discussion

Our review of the 32 published safer conception interventions identified certain key themes and issues that recurred throughout. The discussion of these themes, as well as our general conclusions, are detailed below.

Safer Conception: Screening and Preliminary Considerations

Before any safer conception intervention, it is important, to the extent feasible with available resources, to determine that the HIV-infected person has a low viral load, a high CD4+ cell count, and no AIDS-defining symptoms. Both partners should have no sexually transmitted infections (STIs) or should be receiving treatment, and should preferably be in a stable relationship.¹² Where possible, fertility screening is also advisable—for example, semen analysis for HIV-infected men to detect asymptomatic epididymitis or azoospermia and the spinnbarkeit test of vaginal mucus in HIV-seropositive women to detect ovulation. Interventions should also be sensitive to the fact that HIV-infected women are a vulnerable group with unique psychosocial needs¹⁶ who may face considerable pressure from male partners to get pregnant, even if they do not wish to.¹⁷

Another key factor to bear in mind is the prevalence of infertility problems in people with HIV infection and their concomitant low success rates with assisted reproductive technologies. Tubal infertility, pelvic inflammatory disease, ovarian dysfunction, ovarian resistance to hormonal stimulation, low pregnancy rates, and high rates of fetal death have been reported among HIV-seropositive women,^{2,12,18-21} and low sperm counts among HIV-seropositive men.²² The diminished fertility profile of HIV-seropositive women and men is further complicated by the fact that antiretroviral drug use has been inconsistently linked to fertility problems in women and men.²³ Although HIV infection does not seem to affect the course of pregnancy per se, there is conflicting and thus incon-

clusive evidence regarding the effects of antiretroviral therapy on obstetrical outcomes such as preterm birth, low birth weight, gestational diabetes and low Apgar score.^{11,19}

Safer Conception for HIV-Seropositive Women

Relatively little research on safer conception has focused on HIV-serodiscordant couples in which the woman is HIV-infected. Ethical dilemmas in this context include the possibility of mother-to-child HIV transmission and the risk of HIV transmission to an uninfected partner.^{24,25} However, with the success and increasing availability of drug regimens that prevent mother-to-child HIV transmission (PMTCT) (concurrent with safer childbirth and breastfeeding practices), the risk of mother-to-child transmission has been lowered from more than 30% to less than 1% in industrialized countries^{12,14,26} and in a study conducted in South Africa was reduced to less than 3%.²⁷

Recent trials of combination antiretroviral therapy during pregnancy suggest similar reductions in mother-to-child transmission.²⁸ Consequently, national medical societies such as the American Society of Reproductive Medicine and the American College of Obstetricians/Gynecologists have argued that it is unethical to refuse to provide safer conception services to HIV-seropositive women and their partners.^{10,18} Protection of sexual and reproductive health of all people has been recognized as a fundamental human right and HIV-infected women and men have the right to choose to have children and to access nonjudgmental, high-quality sexual and reproductive health services.^{29,30}

Low-technology safer conception options for HIV-seropositive women include vaginal insemination with sperm from a seronegative partner or donated sperm; however, to date, no published studies are available on this method. There are limited data on the use of high-technology assisted reproductive technologies for HIV-seropositive women, including IUI, in vitro fertilization (IVF), and ICSI.^{12,20,31-34} Be-

cause of cost and potential problems in using hormone-stimulating drugs in HIV-seropositive women, it is difficult to envision these methods being widely used in any setting.¹²

There are no published studies involving vaginal insemination of HIV-infected women with an uninfected male partner's semen, and data are limited on safer conception methods for HIV-infected women more broadly. Only 6 interventions providing safer conception services for HIV-infected women have been reported to date. These studies focused solely on high-technology assisted reproduction methods and involved multidisciplinary approaches in which HIV-infected women were counseled, provided with comprehensive fertility and health screening, and assigned to high-technology IUI, IVF, or ICSI.^{12,20,31–34} The few studies that have been reported were based on small samples, with no studies reporting on a series of more than 50 couples.

Natural Conception for HIV-Affected Couples: Debates and Studies

Pregnancy via natural conception is increasingly accepted as a strategy for HIV-seroconcordant couples in developed countries. Some opposition still exists in resource-constrained settings, largely because of concerns about HIV superinfection. International literature, however, reports a very low absolute level of superinfection risk, particularly in the context of antiretroviral therapy.³⁵

Timed unprotected sex has thus far not been recommended by most practitioners and researchers for HIV-serodiscordant couples. A central concern is that compromising the “safer sex” message for the purpose of conception, even if only during a woman's fertile window, might have deleterious effects on condom use and public health more broadly.³⁶ Recently, however, there have been calls for more in-depth discussion about natural conception for HIV-serodiscordant couples.^{2,11,37} There is little research on the impact of natural conception programs on rates of transmission to the uninfected partner, especially in

sub-Saharan Africa where, given high HIV infection rates and high profertile norms, the need is great.

Sexual transmission rates of HIV in stable HIV-serodiscordant couples.

Closely related to the debate regarding natural conception and HIV-serodiscordant couples is the question of sexual transmission rates of HIV. It has recently been argued that the risk of sexual transmission of HIV is very low when the infected partner is receiving antiretroviral therapy, has an undetectable plasma viral load, and both partners are currently free of STIs.³⁸ In a meta-analytic review by Attia and colleagues of 11 cohorts involving 5021 stable, heterosexual, serodiscordant couples, no transmission to the uninfected partner occurred in couples in which the HIV-infected partner was receiving antiretroviral therapy and had a viral load below 400 copies/mL.³⁹ Although there was zero incidence in the studies reviewed, Attia and colleagues calculate that the data are compatible with 1 transmission per 79 person-years or 1 transmission per 7900 sex acts (taking the yearly average as 100 sexual contacts).

In a study by Castilla and colleagues in which 393 stable, heterosexual, serodiscordant couples in Spain were observed over a 12-year period (1991–2003), HIV prevalence in those with an HIV-infected partner *not* receiving antiretroviral therapy was 8.6%; no cases of HIV transmission occurred in couples in which the infected partner was on antiretroviral therapy.⁴⁰ Gray and colleagues observed 174 monogamous HIV-serodiscordant Ugandan couples over a 4-year period (1994–1998) and found a transmission rate of 0.0001 per coital act at viral load below 1700 copies/mL, 0.0023 per coital act at viral load above 38,500 copies/mL, and 0.041 in couples with genital ulceration.⁴¹ In this sample, 93% of couples reported never using condoms and cited a coital frequency of 8.9 acts per month.

A randomized placebo-controlled trial compared HIV transmission rates (over a 24-month follow-up) in heterosexual HIV-serodiscordant couples in

which the HIV-infected partner initiated antiretroviral therapy ($n = 349$) with those who did not ($n = 3032$) in 7 African countries (South Africa, Botswana, Kenya, Rwanda, Tanzania, Uganda, and Zambia). A transmission rate of 0.37 (95% confidence interval [CI], 0.09–2.04) per 100 person-years for couples in which the HIV-seropositive partner had initiated antiretroviral therapy (effectively 1 HIV transmission) and a transmission rate of 2.24 (95% CI, 1.84–2.72) per 100 person-years for those not on treatment (102 transmissions) were found.⁴² For couples in which the infected partner was receiving antiretroviral therapy, this was a 92% reduction in HIV transmission rate. These studies collectively point to a relatively low HIV sexual transmission rate under certain key conditions, namely stable partnerships, low plasma viral loads, the HIV-infected partner on antiretroviral therapy, and the absence of active STIs.

Studies of natural conception in HIV-serodiscordant couples.

Only 3 reports have been published outlining the outcome of natural conception in HIV-serodiscordant couples. The first, published by Mandelbrot and colleagues, reviewed natural pregnancies in HIV-serodiscordant couples (in which the male was HIV-infected) at a Paris hospital over a 10-year period in the pre-antiretroviral therapy era (1986–1996).⁴³ The study reported on 104 pregnancies in 92 couples. Most of the HIV-seropositive men were symptom-free (13% had HIV-related symptoms), and only 21 were on antiretroviral drugs. Couples received pre-conception counseling and education regarding best practices for timing of sex in the ovulatory window, and genital infections were diagnosed and treated, condom use was strongly advised after pregnancy attainment, and women were tested monthly for HIV antibodies and p24 antigen.

One-third of the couples reported inconsistent or no condom use. Of the 104 pregnancies, 68 occurred as a result of unprotected sex in the ovulation window and 17 resulted from only a single act of sexual intercourse dur-

ing ovulation. Although no seroconversions were reported in the first 6 months postconception, 2 women seroconverted at 7 months of pregnancy and another 2 women seroconverted in the postpartum period. All 4 seroconversions occurred in couples who reported inconsistent condom use after conception had been achieved. According to Mandelbrot and colleagues, these findings are compatible with a seroconversion rate of 1 per 1000 episodes of sexual contact.

Yee and colleagues reported on a small series of British HIV-seropositive men and their partners attaining natural pregnancy before the introduction of potent antiretroviral therapy.⁴⁴ In this series, 14 couples achieved 19 pregnancies. One woman seroconverted during her second pregnancy. Interestingly, this study found that the only man who transmitted HIV to his female partner had a high viral load (more than 38,700 copies/mL).

A more recent study conducted by Barreiro and colleagues during the era of potent antiretroviral therapy involved a review of all natural pregnancies attained by HIV-serodiscordant couples seen in 3 clinics in Spain over a 7-year period (1998-2005).⁴⁵ Only cases in which the infected partner was on antiretroviral therapy and had an undetectable plasma viral load were included in their review. They reported that 62 serodiscordant couples, of which 22 involved an HIV-seropositive woman and 40 involved an HIV-seropositive man, achieved 76 natural pregnancies—resulting in 68 children—over this time period. No horizontal seroconversions were reported, although 1 case of vertical transmission did occur.

The need to develop feasible safer conception interventions that involve natural conception is heightened by findings that a substantial number of HIV-serodiscordant couples prefer natural conception methods and engage in unprotected sex, regardless of safer conception guidelines. In a study conducted by van der Straten and colleagues, more than two-thirds of 104 American, heterosexual, HIV-serodiscordant couples reported un-

protected sex with their partner in the preceding 6 months.⁴⁶ Vandermaelen and Englert reported that 14.5% (32/221) of HIV-serodiscordant couples requesting assisted reproduction treatment in Belgium did not use condoms consistently.³⁷

Ryder and colleagues studied 178 married HIV-serodiscordant couples in the Democratic Republic of Congo over a 3-year period (1987-1990) in the pre-antiretroviral therapy era, observing pregnancy rates and HIV sero-incidence.⁴⁷ Couples wanting children frequently engaged in unprotected sex during the woman's perceived fertile time, which resulted in the birth of 24 children and 1 HIV seroconversion (4%; 95% CI, 0.0%-21.6%). Couples who wanted a child and practiced safer sex except during the woman's fertile period were successful in having a child.

A more recent cross-sectional study by Ezeanochie and colleagues involving 55 HIV-seropositive Nigerian women on antiretroviral therapy and married to HIV-seronegative men found that younger women (mean age, 29.8 ± 3.9 years) were statistically significantly more likely than older women (mean age, 33.6 ± 5.1 years) to choose natural conception over assisted reproduction technologies ($P = .02$).⁴⁸ Furthermore, 23 (48.9%) women reported inconsistent condom use, and 11 (23.4%) reported never using condoms after initiation of antiretroviral therapy. There was also a statistically significant difference in the consistency of condom use between those who preferred natural conception and those who preferred assisted reproduction technologies (56.8% vs. 20%, respectively; $P = .049$).

An American study reported by Van DeVanter and colleagues observed 71 heterosexual HIV-serodiscordant couples over 2 years (1990-1992) and found that women in serodiscordant relationships had a pregnancy rate (10.7 per 100 person-years) similar to women in the general population.⁴⁹ Over the 2-year period, 15 (21%) women achieved pregnancy: 9 HIV-seronegative women with an HIV-infected male partner and 6 HIV-seropositive

women with an uninfected male partner. One woman, whose partner was not on antiretroviral therapy and had a CD4+ cell count below 200 cells/μL, seroconverted during the study. Even couples who participated in safer conception programs have been found to engage in natural conception. According to Semprini and colleagues, 50% of couples in whom conception via assisted reproduction fails turn to natural conception methods.⁵⁰

Emphasizing safer sex practices after conception and throughout pregnancy should be underlined as an important component of safer conception programs. It is noteworthy that in Mandelbrot and colleagues' study of natural conception in HIV-serodiscordant couples, all 4 HIV horizontal seroconversions occurred in couples who reported unsafe sex practices during pregnancy.⁴³

Using Periconception PrEP to Reduce Sexual Transmission of HIV

An important development in the implementation of safer conception services for HIV-serodiscordant couples is the use of periconception PrEP to lower the risks of HIV transmission to the uninfected partner during conception attempts. The term "PrEP-ception" has recently been coined by American researchers and clinicians to refer to the possibilities of using PrEP for safer conception.⁵¹ Preliminary results from 2 studies reported at the 6th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in Rome in July 2011 provide compelling evidence about the efficacy of PrEP in the prevention of heterosexual HIV transmission.^{52,53} This adds to the results of the Preexposure Prophylaxis Initiative (IPrEx) trial that found combination tenofovir/emtricitabine to be safe and to reduce acquisition of HIV infection by 44% for HIV-seronegative men who have sex with men.⁵⁴

The Center for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial found that the use of 1% tenofovir topical gel reduced the rate of HIV acquisition by 39% in heterosexual HIV-

seronegative women.⁵⁵ The Partners PrEP trial of 4758 HIV-serodiscordant couples in Kenya and Uganda found 62% protective efficacy among HIV-seronegative partners who took a once-daily dose of tenofovir versus placebo, and 73% protective efficacy for those taking daily tenofovir/emtricitabine versus placebo.⁵² In the TDF2 PrEP trial of 1219 men and women in Botswana, once-daily tenofovir/emtricitabine had 62.6% protective efficacy compared with a placebo pill, consistent with the findings of the Partners PrEP trial.⁵³ Results from the HIV Prevention Trials Network (HPTN) 052 study in 9 countries provided proof-of-concept that early antiretroviral treatment of HIV-infected individuals suppressed viral replication and reduced heterosexual transmission to uninfected partners by 96% compared with delayed treatment.⁵⁶

It is thus not surprising that the use of PrEP is rapidly gaining ground as an important component of safer conception programs for HIV-serodiscordant couples.^{51,57} Although no formal results on the use of periconception PrEP were available during the period under review, preliminary (unpublished) data are available from an intervention study of periconception PrEP in HIV-serodiscordant couples (in which the male partner is HIV-seropositive), currently underway in Switzerland. These data indicate that 22 couples achieved 11 natural pregnancies (of which 50% occurred after only 3 timed intercourses) and no seroconversions occurred.^{23,58} In this series, all HIV-seropositive men were receiving antiretroviral therapy and female partners were provided with a short course of PrEP with 245 mg tenofovir at 36 hours and 12 hours before couples engaged in unprotected sex.²³

High-Technology Assisted Reproduction Techniques for HIV-Affected Couples

Most of the international research on safer conception for HIV-affected couples has concentrated on options for couples in which the man is HIV-seropositive and the woman is HIV-

seronegative. Although the use of screened and confirmed HIV-seronegative donor sperm and adoption remain the only options completely free of HIV transmission risk for these couples, a strong desire for biological children makes these options untenable for many. Risk-reduction strategies for these couples include sperm washing along with IUI or sperm washing along with IVF or ICSI.

Sperm washing with intrauterine insemination. Pioneered by Semprini, clinical application of sperm washing in conjunction with IUI has been offered to HIV-serodiscordant couples in Italy since 1989.⁵⁹ Numerous studies have reported on the efficacy of sperm washing in combination with IUI in terms of pregnancy rates, live birth rates, and HIV transmission incidence.^{12,22,23,31,60-68} However, evaluation of the efficacy of this safer conception strategy is limited by methodological issues, including small sample sizes, lack of standardized protocols, and nonrigorous study designs—for example, most studies reported only on retrospective data and very few used control groups.

Intracytoplasmic sperm injection. The use of ICSI—a high-technology *in vitro* fertilization procedure in which a single sperm is injected into an egg—is a popular assisted reproduction technique in the United States for HIV-seropositive men and their partners. Several studies reported that ICSI for HIV-serodiscordant couples in which the man is HIV-seropositive is relatively safe and efficacious.⁶⁸⁻⁷⁹ However, a number of problems are associated with its use.^{72,74} These include high cost, increased risk of multiple pregnancies,^{64,68,72,73,75} and the potential use of an HIV-infected gamete.

Summary

It is crucial to introduce harm-reduction methods and safer conception methods for people with HIV infection in settings where assisted reproductive technology cannot be easily obtained. This is particularly urgent

in countries like South Africa, which recently showed a decline in AIDS-related deaths from 257,000 in 2005 to 194,000 in 2010,⁸⁰ but that continues to have a high prevalence of HIV, largely because of increased longevity associated with antiretroviral therapy.⁸¹ Whereas some studies indicate that HIV-infected individuals on antiretroviral therapy are reluctant to have children,⁷ others show that use of antiretroviral therapy may increase fertility intentions and pregnancy rates,^{82,83} particularly among younger people who have no biological children.^{5,84,85}

Most international research on safer conception in the context of HIV infection has concentrated on options for couples in which the male partner is HIV-infected and the female partner is not, therefore focusing on high-technology methods such as sperm washing with IUI or ICSI in laboratory settings. However, these strategies are not feasible on a widespread basis in resource-constrained settings. Sperm washing with ICSI, in particular, has little, if any, justification for use even in most resource-rich conditions, let alone resource-constrained ones. Its high cost, the invasive nature of the procedure, the high number of cancelled cycles,^{72,75} increased risk of multiple pregnancies,^{68,72,73,75} and potential danger of using an HIV-infected gamete all mitigate the argument for use of ICSI. Furthermore, in sub-Saharan Africa, more women than men are HIV-seropositive.

The most feasible method in resource-constrained settings for HIV-serodiscordant couples in which the woman is HIV-seropositive (once the couple has been counseled and screened in line with the earlier recommendations regarding viral load, CD4+ cell count, and STIs) is vaginal insemination with an uninfected male partner's sperm during the fertile time of the woman's menstrual cycle. This involves the couple either having intercourse with a condom and then drawing out the semen into a needleless syringe and inserting it as high as possible into the vagina, or the male partner ejaculating into a sterile container and the semen being drawn up in a similar manner.

Given that neither IUI nor ICSI is feasible in resource-constrained settings and that vaginal insemination with the sperm of an HIV-seronegative male partner is highly feasible and has been found to be reasonably acceptable to both men and women,¹ this appears to be the most practical low-technology safer conception option to introduce in limited-resource settings. However, only anecdotal evidence on this method is available from resource-constrained settings, and systematic research is needed to establish pregnancy outcomes, HIV transmission risk to infants, and acceptability for couples and health care providers.

Timed, limited, unprotected sex for HIV-seroconcordant couples, and timed, unprotected sex accompanied by periconception PrEP for the HIV-seronegative female partner in serodiscordant couples, should form part of a harm-reduction strategy to reduce exposure to HIV when planning conception in resource-limited settings. Little is known, however, about the awareness, understanding, and acceptability of low-technology, safer conception strategies among people with HIV infection. Preliminary data from a South African study demonstrated acceptability of some of these methods among HIV-affected individuals, policy-makers, and providers.⁸⁶ More generally, antiretroviral therapy roll-out needs to be enhanced in resource-constrained settings, given the protective benefits of antiretrovirals not only for the HIV-infected person but for decreasing sexual transmission to uninfected partners in serodiscordant couples who want to conceive and do not use condoms.

Conclusion

Most research has looked at the efficacy and safety of sperm washing with IUI and ICSI as assisted reproductive treatments among HIV-serodiscordant couples in which the male partner is HIV-infected. Substantial evidence points to the relative safety of these procedures, although some methodological limitations impede the evaluation and comparison of these studies.

That is, most studies report on small sample sizes, use retrospective analysis, and do not include control groups. More rigorous and controlled prospective studies are therefore needed.

With the publication of safer conception guidelines in South Africa,⁹ discussion is urgently needed about piloting these guidelines to further assess acceptability, preparedness of public sector health services, and feasibility in implementation. In addition, studies to determine outcomes in terms of pregnancy success rates and HIV transmission would be valuable. Avoiding HIV transmission but enabling HIV-affected couples in resource-limited settings to embark on safer child-bearing is crucial in decreasing both mother-to-child HIV transmission and transmission to uninfected partners. Furthermore, failure of the health system to engage HIV-seropositive women and men in fertility management and denying safer conception services to those who want to conceive a child is unethical¹ and deprives them of a fundamental reproductive right. Most importantly, people with HIV infection require the support of health care providers in affirming their rights to make their own reproductive decisions.

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References

- Mantell JE, Smit JA, Stein ZA. The right to choose parenthood among HIV-infected women and men. *J Public Health Policy*. 2009;30:367-378.
- Fakoya A, Lamba H, Mackie N, et al. British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med*. 2008;9:681-720.
- Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. *MMWR Recomm Rep*. 2001;50(RR-19):1-57.
- Cooper D, Harries J, Myer L, Orner P, Bracken H, Zweigenthal V. "Life is still going on": reproductive intentions among HIV-positive women and men in South Africa. *Soc Sci Med*. 2007;65:274-285.
- Cooper D, Moodley J, Zweigenthal V, Bekker LG, Shah I, Myer L. Fertility intentions and reproductive health care needs of people living with HIV in Cape Town, South Africa: implications for integrating reproductive health and HIV care services. *AIDS Behav*. 2009;13:38-46.
- Kaida A, Bangsberg DR, Gray G, Hogg RS, King R, Miller CL. Editorial: Introduction to the supplement on HIV, HAART, and fertility in sub-Saharan Africa. *AIDS Behav*. 2009;13(Suppl 1):1-4.
- Kaida A, Laher F, Strathdee SA, et al. Contraceptive use and method preference among women in Soweto, South Africa: the influence of expanding access to HIV care and treatment services. *PLoS One*. 2010;5:e13868.
- Laher F, Todd CS, Stibich MA, et al. A qualitative assessment of decisions affecting contraceptive utilization and fertility intentions among HIV-positive women in Soweto, South Africa. *AIDS Behav*. 2009;13(Suppl 1):47-54.
- Bekker LG, Black V, Myer L, et al. Guideline on safer conception in fertile HIV-infected individuals and couples. *South Afr J HIV Med*. 2011;12:31-44.
- Kambin S, Batzer F. Assisted reproductive technology in HIV serodiscordant couples. *Sexuality, Reproduction & Menopause*. 2004;2:92-100.
- Barreiro P, Duerr A, Beckerman K, Soriano V. Reproductive options for HIV-serodiscordant couples. *AIDS Rev*. 2006;8:158-170.
- Gilling-Smith C, Nicopoulos JD, Semprini AE, Frodsham LC. HIV and reproductive care—a review of current practice. *BJOG*. 2006;113:869-878.
- Matthews LT, Mukherjee JS. Strategies for harm reduction among HIV-affected couples who want to conceive. *AIDS Behav*. 2009;13:5-11.
- Thornton AC, Romanelli F, Collins JD. Reproduction decision making for couples affected by HIV: a review of the literature. *Top HIV Med*. 2004;12:61-67.
- Gosselin JT, Sauer MV. Life after HIV: examination of HIV serodiscordant couples' desire to conceive through assisted repro-

- duction. *AIDS Behav.* 2011;15:469-478.
16. Delvaux T, Nostlinger C. Reproductive choice for women and men living with HIV: contraception, abortion and fertility. *Reprod Health Matters.* 2007;15:46-66.
 17. Homby J, Bunnell R, Moore D, et al. Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study. *PLoS One.* 2009;4:e4149.
 18. Englert Y, Lesage B, Van Vooren JP, et al. Medically assisted reproduction in the presence of chronic viral diseases. *Hum Reprod Update.* 2004;10:149-162.
 19. Coll O, Lopez M, Hernandez S. Fertility choices and management for HIV-positive women. *Curr Opin HIV AIDS.* 2008;3:186-192.
 20. Douglas NC, Wang JG, Yu B, Gaddipati S, Guarnaccia MM, Sauer MV. A systematic, multidisciplinary approach to address the reproductive needs of HIV-seropositive women. *Reprod Biomed Online.* 2009;19:257-263.
 21. Suy A, Martinez E, Coll O, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *AIDS.* 2006;20:59-66.
 22. Nicopoulos JD, Almeida PA, Ramsay JW, Gilling-Smith C. The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing. *Hum Reprod.* 2004;19:2289-2297.
 23. van Leeuwen E, Repping S, Prins JM, Reiss P, van der Veen F. Assisted reproductive technologies to establish pregnancies in couples with an HIV-1-infected man. *Neth J Med.* 2009;67:322-327.
 24. Nakhuda GS, Pena J, Sauer MV. Deaths of HIV-positive men in the context of assisted reproduction: five case studies from a single center. *AIDS Patient Care STDs.* 2005;19:712-718.
 25. Rhodes R. Moral deliberation about fertility treatment for HIV-1 serodiscordant couples. *Am J Bioeth.* 2003;3:50-53.
 26. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS.* 2008;22:289-299.
 27. Geddes R, Knight S, Reid S, Giddy J, Esterhuizen T, Roberts C. Prevention of mother-to-child transmission of HIV programme: low vertical transmission in KwaZulu-Natal, South Africa. *S Afr Med J.* 2008;98:458-462.
 28. Tonwe-Gold B, Ekouevi DK, Viho I, et al. Antiretroviral treatment and prevention of peripartum and postnatal HIV transmission in West Africa: evaluation of a two-tiered approach. *PLoS Med.* 2007;4:e257.
 29. World Health Organization. Sexual and reproductive health of women living with HIV/AIDS: guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. <http://www.who.int/hiv/pub/guidelines/sexualreproductivehealth.pdf>. Published 2006. Accessed November 16, 2011.
 30. Wilcher R, Cates W. Reproductive choices for women with HIV. *Bull World Health Organ.* 2009;87:833-839.
 31. Manigart Y, Rozenberg S, Barlow P, Gerard M, Bertrand E, Delvigne A. ART outcome in HIV-infected patients. *Hum Reprod.* 2006;21:2935-2940.
 32. Terriou P, Auquier P, Chabert-Orsini V, et al. Outcome of ICSI in HIV-1-infected women. *Hum Reprod.* 2005;20:2838-2843.
 33. Ohl J, Partisani M, Wittemer C, Lang JM, Viville S, Favre R. Encouraging results despite complexity of multidisciplinary care of HIV-infected women using assisted reproduction techniques. *Hum Reprod.* 2005;20:3136-3140.
 34. Tschudin S, Steimann S, Bitzer J, et al. Round-table multidisciplinary counselling of couples with HIV prior to assisted reproduction. *Reprod Biomed Online.* 2008;17:167-174.
 35. Gonzales MJ, Delwart E, Rhee SY, et al. Lack of detectable human immunodeficiency virus type 1 superinfection during 1072 person-years of observation. *J Infect Dis.* 2003;188:397-405.
 36. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet.* 2008;372:314-320.
 37. Vandermaelen A, Englert Y. Human immunodeficiency virus serodiscordant couples on highly active antiretroviral therapies with undetectable viral load: conception by unprotected sexual intercourse or by assisted reproduction techniques? *Hum Reprod.* 2010;25:374-379.
 38. Englert Y, Van Vooren JP, Place I, Liesnard C, Laruelle C, Delbaere A. ART in HIV-infected couples: has the time come for a change of attitude? *Hum Reprod.* 2001;16:1309-1315.
 39. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS.* 2009;23:1397-1404.
 40. Castilla J, del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *JAIDS.* 2005;40:96-101.
 41. Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet.* 2001;357:1149-1153.
 42. Donnell D, Baeten JM, Kiari J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet.* 2010;375:2092-2098.
 43. Mandelbrot L, Heard I, Henrion E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. *Lancet.* 1997;349:850-851.
 44. Yee TT, Goldman E, Devereux H, Sabin C, Lee CA. Family issues in HIV-infected haemophilic patients. *AIDS.* 1999;13:2314-2315.
 45. Barreiro P, del Romero J, Leal M, et al. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. *JAIDS.* 2006;43:324-326.
 46. van der Straten A, Gomez CA, Saul J, Quan J, Padian N. Sexual risk behaviors among heterosexual HIV serodiscordant couples in the era of post-exposure prevention and viral suppressive therapy. *AIDS.* 2000;14:F47-F54.
 47. Ryder RW, Kamenga C, Jingu M, Mbuyi N, Mbu L, Behets F. Pregnancy and HIV-1 incidence in 178 married couples with discordant HIV-1 serostatus: additional experience at an HIV-1 counselling centre in the Democratic Republic of the Congo. *Trop Med Int Health.* 2000;5:482-487.
 48. Ezeanochie M, Olagbuji B, Ande A, Oboro V. Fertility preferences, condom use, and concerns among HIV-positive women in serodiscordant relationships in the era of antiretroviral therapy. *Int J Gynaecol Obstet.* 2009;107:97-98.
 49. Van DeVanter N, Cleary PD, Moore J, Thacker AS, O'Brien TR. Reproductive behavior in HIV-discordant heterosexual couples: implications for counseling. *AIDS Patient Care STDs.* 1998;12:43-49.
 50. Semprini AE, Vucetich A, Hollander L. Sperm washing, use of HAART and role of elective Caesarean section. *Curr Opin Obstet Gynecol.* 2004;16:465-470.
 51. Lampe MA, Smith DK, Anderson GJ, Edwards AE, Nesheim SR. Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States. *Am J Obstet Gynecol.* 2011;204:488.
 52. Baeten J, Celum C, et al. The Partners PrEP Study Team. Antiretroviral pre-exposure prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. [Abstract MOAX01.] 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 17-20, 2011; Rome, Italy.
 53. Thigpen MC, Kebaabetswe PM, Smith DK, et al. Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study. [Abstract WELBC01.] 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 17-20, 2011; Rome, Italy.
 54. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med.* 2010;363:2587-2599.
 55. Abdoal Karim Q, Abdoal Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* 2010;329:1168-1174.
 56. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365:493-505.
 57. Matthews LT, Baeten JM, Celum C, Bangsberg DR. Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation. *AIDS.* 2010;24:1975-1982.
 58. Vernazza PL, Hollander L, Semprini AE, Anderson DJ, Duerr A. HIV-discordant couples and parenthood: how are we dealing with the risk of transmission? *AIDS.* 2006;20:635-636.
 59. Wilde JT. Conception in HIV-discordant couples. *Treatment of Hemophilia.* 2002;26.
 60. Marina S, Marina F, Alcolea R, et al. Human immunodeficiency virus type 1—serodiscordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril.* 1998;70:35-39.
 61. Semprini AE. Viral transmission in ART:

- risks for patients and healthcare providers. *Hum Reprod.* 2000;15:69.
62. Bujan L, Pasquier C, Labeyrie E, Lanassee-Crousse P, Morucci M, Daudin M. Insemination with isolated and virologically tested spermatozoa is a safe way for human immunodeficiency type 1 virus-serodiscordant couples with an infected male partner to have a child. *Fertil Steril.* 2004;82:857-862.
 63. Bujan L, Sergerie M, Kiffer N, et al. Good efficiency of intrauterine insemination programme for serodiscordant couples with HIV-1 infected male partner: a retrospective comparative study. *Eur J Obstet Gynecol Reprod Biol.* 2007;135:76-82.
 64. Bujan L, Hollander L, Coudert M, et al. Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network. *AIDS.* 2007;21:1909-1914.
 65. Nicopoulos JD, Almeida P, Vourliotis M, Goulding R, Gilling-Smith C. A decade of sperm washing: clinical correlates of successful insemination outcome. *Hum Reprod.* 2010;25:1869-1876.
 66. Papier S, Lipowicz R, Rawe V, Miasnik S, Espanol A, Nodar F. The use of low complexity assisted reproduction techniques in positive HIV (human immunodeficiency virus) male serodiscordant couples. *Fertil Steril.* 2005;84(Suppl 1):S351.
 67. Savasi V, Ferrazzi E, Lanzani C, Oneta M, Parrilla B, Persico T. Safety of sperm washing and ART outcome in 741 HIV-1-serodiscordant couples. *Hum Reprod.* 2007;22:772-777.
 68. Quintana R, Tiveron M, Garcia F, Kopcow L, Bisioli C, Young E. Intrauterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in human immunodeficiency virus (HIV) serodiscordant couples: results and perspectives. *Fertil Steril.* 2002;78(Suppl 1):S116.
 69. Chu MC, Pena JE, Thornton MH, Sauer MV. Assessing the treatment efficacy of IVF with intracytoplasmic sperm injection in human immunodeficiency virus-1 (HIV-1) serodiscordant couples. *Reprod Biomed Online.* 2005;10:130-134.
 70. Ohl J, Partisani M, Wittemer C, et al. Assisted reproduction techniques for HIV serodiscordant couples: 18 months of experience. *Hum Reprod.* 2003;18:1244-1249.
 71. Sauer MV, Chang PL. Establishing a clinical program for human immunodeficiency virus 1-seropositive men to father seronegative children by means of in vitro fertilization with intracytoplasmic sperm injection. *Am J Obstet Gynecol.* 2002;186:627-633.
 72. Sauer MV, Wang JG, Douglas NC, et al. Providing fertility care to men seropositive for human immunodeficiency virus: reviewing 10 years of experience and 420 consecutive cycles of in vitro fertilization and intracytoplasmic sperm injection. *Fertil Steril.* 2009;91:2455-2460.
 73. Guibert J, Merlet F, Le Du A, et al. ICSI for HIV-1 serodifferent couples: results of a preliminary study. *Hum Reprod.* 2001;16(Suppl 1):56-57.
 74. Pena JE, Thornton MH, Sauer MV. Assessing the clinical utility of in vitro fertilization with intracytoplasmic sperm injection in human immunodeficiency virus type 1 serodiscordant couples: report of 113 consecutive cycles. *Fertil Steril.* 2003;80:356-362.
 75. Kashima K, Takakuwa K, Suzuki M, et al. Studies of assisted reproduction techniques (ART) for HIV-1-discordant couples using washed sperm and the nested PCR method: a comparison of the pregnancy rates in HIV-1-discordant couples and control couples. *Jpn J Infect Dis.* 2009;62:173-176.
 76. Garrido N, Meseguer M, Bellver J, Remohi J, Simon C, Pellicer A. Report of the results of a 2 year programme of sperm wash and ICSI treatment for human immunodeficiency virus and hepatitis C virus serodiscordant couples. *Hum Reprod.* 2004;19:2581-2586.
 77. Chelo E, Livi C, Vichi F, Mazzotta F. ICSI for HIV serodiscordant couples: Our results with tested negative cryopreserved sperm samples. *Fertil Steril.* 2006;86(Suppl 1):S166.
 78. Morshedi M, Bocca S, Diaz J, et al. Assisted conception in serodiscordant couples in whom the man is HIV+ using a strict protocol for semen processing and testing. *Fertil Steril.* 2003;80(Suppl 3):S40.
 79. Pena J, Thornton M, Ruman J, Klein J, Kavic S, Sauer M. Assessing the clinical utility of in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) in human immunodeficiency virus-1 (HIV-1) serodiscordant couples: report of 103 consecutive cycles. *Fertil Steril.* 2002;78(Suppl 1):S122.
 80. Dorrington R. South Africa: ARV programme cuts AIDS deaths. <http://www.safaid.net/content/south-africa-arv-programme-cuts-aids-deaths>. Accessed August 2, 2011.
 81. Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med.* 2010;7:e1000229.
 82. Kaida A, Andia I, Maier M, et al. The potential impact of antiretroviral therapy on fertility in sub-Saharan Africa. *Curr HIV/AIDS Rep.* 2006;3:187-194.
 83. Myer L, Morroni C, Rebe K. Prevalence and determinants of fertility intentions of HIV-infected women and men receiving antiretroviral therapy in South Africa. *AIDS Patient Care STDs.* 2007;21:278-285.
 84. Agwu AL, Jang SS, Korthuis PT, Araneta MR, Gebo KA. Pregnancy incidence and outcomes in vertically and behaviorally HIV-infected youth. *JAMA.* 2011;305:468-470.
 85. Cooper D, Mantell J, Moodley J, et al. Parenthood and safer reproductive health choices for HIV-infected men and women in Cape Town, South Africa: desiring children in developing countries with generalized HIV epidemics. 11th World Congress of International Union against Sexually Transmitted Infections (IUSTI). November 9-12, 2009; Cape Town, South Africa.
 86. Matthews LT, Crankshaw T, Giddy J, Kaida A, Ware NC, Bangsberg DR. Reproductive decision-making and periconception practices among HIV-positive men and women accessing HIV care in Durban, South Africa. [Abstract TUPE325.] 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 17-20, 2011; Rome, Italy.

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