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# Contraception and HIV infection in women

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**BACKGROUND:** More than 15 million women, many of reproductive age, were infected with human immunodeficiency virus (HIV) at the end of 2007. As the HIV epidemic evolves, heterosexual intercourse is increasingly risky: the risk of infection in exposed young women is 4- to 7-fold higher than in young men and nearly half a million newborns annually have HIV. This review aims to show the effect of contraceptive choices on risk of HIV and on the course of disease in women with HIV.

**METHODS:** Relevant citations were selected by agreement between the authors after a search of MEDLINE using the terms HIV/AIDS and contraception.

**RESULTS:** Risk of transmission of HIV varies from 1 in 200 to 1 in 10 000 coital incidents, depending in part on the integrity of the vaginal epithelium. Consistent use of male condoms has been proven to reduce horizontal transmission of HIV by 80% among HIV-serodiscordant couples. Hormonal contraception may increase the risk of HIV acquisition in high-risk women such as commercial sex workers, but not in women at low risk of HIV. While hormonal contraception did not affect progression of disease in two cohort studies involving 370 women, in a randomized trial among women not receiving antiretroviral medication, clinical disease accelerated in the oral contraception group (13.2/100 woman-years) compared with the copper intrauterine devices group (8.6/100 woman-years; hazard ratio, 1.5; 95% confidence interval, 1.04–2.1). Hormonal contraception does not interfere with antiviral drug effectiveness.

**CONCLUSIONS:** All the available reversible contraceptive methods can generally be used by women at risk of HIV infection and by HIV-infected women. Further studies are needed to investigate the safety and efficiency of hormonal contraception in women living with HIV/AIDS.

**Key words:** HIV/AIDS / transmission / risk factors / hormonal contraception / intrauterine device

## Background

The global human immunodeficiency virus (HIV) pandemic is increasingly becoming a burden of the female population. At the end of 2007, an estimated 15.4 million women were infected with HIV, most of them being of fertile age (www.data.unaids.org). Importantly, young women aged 15–24 have a 4- to 7-fold increased risk of becoming infected with HIV, when compared with young men of the same age (Simon *et al.*, 2006). Moreover, an estimated 420 000 HIV-infected children are born annually (who.int), and most of these infections could and should be prevented.

The demographics and routes of infection vary according to the phase of the HIV epidemic (Beyrer, 2007). As the phase advances, heterosexual intercourse becomes an increasingly important route of transmission (Simon *et al.*, 2006). In sub-Saharan Africa, the vast majority of cases of HIV transmission (c. 90%) are estimated to occur via heterosexual intercourse (data.unaids.org).

In the light of vastly different cultures and contraceptive practices, several methods of providing protection from both unintended pregnancy and sexually transmitted disease (STD) should ideally be available. According to the current consensus of opinion, HIV-infected women and women at risk of HIV infection can use all available

contraceptive methods (www.who.int/reproductive-health). However, male condoms represent the only contraceptive method effective in prevention of horizontal transmission of HIV (Weller and Davis-Beaty, 2002). Given the expanding epidemic and the great number of HIV-infected children born, additional contraceptive methods are needed, preferably linked to methods reducing the risk of HIV transmission.

The aim of the present article is to review current knowledge on heterosexual transmission of HIV and the factors affecting the risk of transmission of HIV. We will focus particularly on the effect of contraceptive choices among women at risk of HIV infection and those living with HIV/AIDS. As a highly relevant public health issue, the topic has been reviewed previously (Howe *et al*., 1994; Stephenson, 1998; Mitchell and Stephens, 2004; Morrison *et al*., 2005; Baeten *et al*., 2007a).

# Materials and Methods

The citations for the present review were identified via MEDLINE and PubMed searches using the passwords of HIV, AIDS, transmission, risk factors and contraception. In addition, personal knowledge of the field and cross referencing was used. The citations were used only following agreement between the authors.

## HIV transmission during heterosexual intercourse

Transmission of HIV during heterosexual intercourse is inefficient, and has been estimated to occur at a rate of 1/200–10 000 (Shattock and Moore, 2003). The results of several prospective cohort studies performed among HIV-serodiscordant couples suggest that the risk of male-to-female transmission may be higher than that of female-to-male transmission (De Vincenzi, 1994; Padian *et al*., 1997). The estimates of increased risk have varied from 2- to 8-fold (Padian *et al*., 1997). However, there are also studies indicating a similar risk of HIV acquisition regardless of the gender of the HIV-seropositive partner (Deschamps *et al*., 1996; Quinn *et al*., 2000; Castilla *et al*., 2005). Explanations for the potentially increased susceptibility of women include female anatomy, longer exposure, as sperm remains in the vagina, and presence of another STD.

The molecular and cellular mechanisms of heterosexual transmission of HIV have been recently reviewed by Shattock and Moore (2003) and by Gupta and Klasse (2006). In brief, infectious HIV must cross the vaginal or cervical epithelium in order to reach its main cellular targets, CD4-expressing lymphocytes, and dendritic cells. If HIV can cross intact epithelium, and if so, then how, remains enigmatic—infection, transcytosis and transmigration via infected donor cells have been proposed (Shattock and Moore, 2003). In order for HIV to infect its cellular targets, both CD4 receptors and their co-receptors (either CCR-5 or CXCR4) are needed on the surface of the lymphocytes and dendritic cells.

Hence, healthy vaginal epithelium is vital in order to diminish the risk of HIV transmission, and all factors disrupting the epithelium—such as physical or infectious ulceration or inflammatory conditions, such as those associated with STDs—result in increased susceptibility to HIV. Tables I and II summarize various factors associated with an increased risk of heterosexual transmission of HIV.

## Risk factors of HIV acquisition in women

When discussing the risk of HIV transmission in heterosexual intercourse, two factors—infectiousness of the infected partner and susceptibility of the uninfected partner—need to be considered (Padian, 1998; Galvin and Cohen, 2004).

**Table I Factors associated with increased risk of HIV acquisition in women**

| |
|---|
| Partner/male-associated factors |
| Advanced stage of HIV infection (Saracco *et al*., 1993; DeVicenzi, 1994; Quinn *et al*., 2000) |
| High circulating HIV load (Quinn *et al*., 2000) |
| Uncircumcised partner (Kapiga *et al*., 1998) |
| Female-associated factors |
| Young age at coital debut (Pettifor *et al*., 2004) |
| Age <25 years (Laga *et al*., 1993; Morrison *et al*., 2007) |
| Age >45 years (De Vincenzi, 1994) |
| ≥4 sex partners (Kapiga *et al*., 1998) |
| Practice of anal sex (De Vincenzi, 1994) |
| Not living with partner (Morrison *et al*., 2007) |

*Factors affecting infectiousness*

The circulating HIV load of the infected partner is a major predictor of the risk of heterosexual transmission. In a prospective cohort study performed in Uganda (Quinn *et al*., 2000), the risk of HIV acquisition increased more than 10-fold as the circulating HIV-1 RNA load increased from <3500 to >50 000 copies/ml. No transmissions occurred during the follow-up period of 2.5 years if the circulating HIV-1 RNA load was below 1500 copies/ml (Quinn *et al*., 2000). The circulating HIV-1 RNA load is the most important predictor of HIV shedding into cervicovaginal secretions or seminal fluid (Gupta *et al*., 1997; Debiaggi *et al*., 2001). Thus, a high HIV load in the blood is likely to be reflected in increased levels of HIV in cervicovaginal secretions or seminal fluid. However, the genital pool of HIV is thought to be somewhat separate from the systemic one, and occasional genital shedding of HIV is seen even among subjects receiving highly active antiretroviral medication resulting in undetectable circulating HIV RNA levels (Debiaggi *et al*., 2001; Heikinheimo *et al*., 2006).

Along with the effect of the circulating HIV load, the stage of HIV infection has an effect of the risk of transmission. Thus, during the course of HIV/AIDS, infectiousness follows a U-shaped curve. The risk of HIV transmission is at its highest during early infection (at the time of viraemia) as well as during the final stages of infection (Wawer *et al*., 2005). In comparison with prevalent infections, the relative risk of HIV transmission during the acute phase of infection has been found to be increased more than 7-fold (Wawer *et al*., 2005). Analogously, the level of HIV RNA in serum and in seminal fluid is at its highest among antibody-negative men during the first month following infection (Pilcher *et al*., 2007). Accordingly, the risk of heterosexual transmission is strongly diminished (~80%) among serodiscordant couples when the HIV-infected partner is receiving highly active antiretroviral therapy (HAART) (Castilla *et al*., 2005).

Randomized controlled trials performed in Africa have shown that male circumcision lowers the risk of acquiring HIV infection among men (Auvert *et al*., 2005; Bailey *et al*., 2007; Gray *et al*., 2007; Newell and Bärnighausen, 2007). However, the impact of male circumcision on the risk of male-to-female transmission of HIV is less clear. Circumcision of the male partner has been associated with a lower risk of HIV transmission in some studies (Kapiga *et al*., 1998; Gray *et al*., 2000). However, in a recent prospective study involving evaluation of the safety of hormonal contraception in African women, the protective effect of male circumcision on the risk of HIV infection among women disappeared following

**Table II Inflammatory conditions associated with increased risk of HIV acquisition in women**

| Risk factor | Increase in the risk of HIV transmission | References |
|---|---|---|
| Cervical ectopy | 4.9 | Plourde *et al*. (1994) |
| Pelvic inflammatory disease | 6.3 | Plourde *et al*. (1994) |
| Ulcerative genital infection | 2.9–3.0 | DeVicenzi (1994), Martin *et al*. (1998), Kiddugavu *et al*. (2003) |
| Specific diagnosis of | | |
| Bacterial vaginosis | 1.4–2.8 | Martin *et al*. (1998), Kleinschmidt *et al*. (2007) |
| Vaginal candidiasis | 2–3.3 | Kapiga *et al*. (1998), Martin *et al*. (1998) |
| *Chlamydia trachomatis* | 1.3–3.6 | Laga *et al*. (1993), Martin *et al*. (1998) |
| *Neisseria gonorrhoea* | 1.8–5.2 | Laga *et al*. (1993), Kapiga *et al*. (1998), Martin *et al*. (1998), Kleinschmidt *et al*. (2007) |
| Herpes simplex virus-2 (seroprevalent) | 2.8–4.4 | Baeten *et al*. (2007b), Brown *et al*. (2007) |
| HSV-2 (seroincident) | 4.6–8.6 | Brown *et al*. (2007) |
| *Treponema pallidum* | 1.6–5.8 | Ungchusak *et al*. (1996), Martin *et al*. (1998) |
| *Trichomonas vaginalis* | 1.2–4.8 | Laga *et al*. (1993), Martin *et al*. (1998), Kleinschmidt *et al*. (2007) |

adjustment for other risk factors (Turner *et al*., 2007). Nevertheless, male circumcision is promoted as in important means of HIV prevention (http://whqlibdoc.who.int, 2007).

*Factors affecting susceptibility*

Concomitant infection with other STDs, especially those resulting in ulcerative genital lesions, has emerged as a highly significant risk factor of HIV transmission (Table II, Galvin and Cohen, 2004). Besides physical disruption of the epithelium, cervical infections increase the number of CD4-positive lymphocytes and dendritic cells in the cervix (Pudney *et al*., 2005), thereby increasing susceptibility to HIV. Thus, the prevalence of STDs has a major impact on the rapidity of spread and routes of HIV transmission in a given society.

Of the various STDs, co-infection with herpes simplex virus-2 seems to have the most pronounced effect on the risk of HIV transmission in heterosexual intercourse (Brown *et al*., 2007). Thus, suppression of HSV-2 with acyclovir prophylaxis might be effective in reducing the rate of HIV transmission. However, in a recent randomized study, prophylaxis with acyclovir had no effect on the incidence of HIV infection among HIV-1-seronegative and HSV-2-positive Tanzanian women (Watson-Jones *et al*., 2008).

In a recent meta-analysis of 68 epidemiological studies performed in sub-Saharan Africa, a history of multi-partner sex, paid sex and STDs were risk factors of HIV infection in women. The odds ratios (ORs) (with 95% confidence intervals) for various risk factors in women were 3.64 (2.87–4.62) for $\geq$3 versus 0–2 lifetime sex partners, 2.29 (1.45–3.62) for having ever been paid for sex and 2.39 (2.01–2.84) for a history of STD. The highest OR, of 4.6 (2.85–7.47), was associated with HSV-2 infection (Chen *et al*., 2007). The risk factors and the magnitude of risk persisted both in low- and high-risk populations, and in populations with early and advanced states of the HIV epidemic (Chen *et al*., 2007).

Thus, the optimal contraceptive strategy and service provision is aimed both at reducing the factors known to facilitate heterosexual transmission of HIV—particularly STDs—as well as minimizing unintended pregnancy. Promoting the use of dual contraception by concomitant use of condoms and additional contraception is likely to be demanding in many parts of the world.

## Barrier methods are effective in reducing the risk of HIV transmission

*Male condoms*

As of today, male condoms are the only means proven to significantly reduce the risk of HIV transmission in heterosexual intercourse (Cates, 2005). According to a recent Cochrane review, consistent use of male condoms results in 80% reduction in the risk of HIV transmission among HIV-serodiscordant couples (Weller and Davis-Beaty, 2002). Of the studies including only HIV-negative women and their HIV-infected men, the efficacy of consistent condom use in prevention of HIV transmission was remarkable, with a relative risk varying from 0.1 to 0.2 (Saracco *et al*., 1993; Musicco *et al*., 1994). Morover, during the follow-up period of nearly 2 years, De Vincenzi (1994) reported no seroconversions among the 124 couples consistently using condoms.

It is also noteworthy that a reduced risk of HIV transmission is associated only with consistent but not with occasional condom use. In fact, occasional condom use has been associated with an increased risk of HIV transmission in some studies (Saracco *et al*., 1993; Musicco *et al*., 1994). However, a major challenge in evaluation of condom use is that the data is self-reported and therefore, in many cases, its reliability may be questionable. This is related especially to consistency of use.

Many of the studies involving assessment of the efficacy of male condoms in prevention of HIV transmission were carried out before the era of effective antiretroviral medication. The use of zidovudine monotherapy by the HIV-infected male partner has been reported to halve the risk of HIV transmission (Musicco *et al*., 1994), and during the use of current combination therapy the rate of HIV transmission was even lower (Castilla *et al*., 2005). No HIV transmissions were reported among serodiscordant couples if the HIV-infected partner received HAART and a condom was used every time the couple had sex (Castilla *et al*., 2005).

Given the efficacy of consistent use of male condoms in the prevention of HIV transmission in heterosexual intercourse, it is disappointing to note the low prevalence of condom use reported in many studies. In addition, the rate of reported condom use varies greatly in studies performed in different continents. The lowest rate of condom use is reported in studies carried out in Africa. Only 10% or less of African women

participating in studies involving assessment of the safety of hormonal contraception among women at risk of HIV (Tables III and IV) reported the dual use of hormonal contraception and condoms (Kiddugavu *et al*., 2003; Morrison *et al*., 2007; Myer *et al*., 2007). Similarly, condom use at any time was reported by <10% of HIV-infected women participating in a study in which the use of a Cu-releasing intrauterine device (Cu-IUDs) was assessed (Richardson *et al*., 1999).

The rate of consistent condom use is also relatively low in studies performed in developed countries. In an early Italian study, only 48% of serodiscordant couples reported consistent condom use (De Vincenzi, 1994). Similarly, inconsistent condom use was common (45%) among HIV-serodiscordant Californian couples, and correlated with low socioeconomic status, African–American ethnicity and practice of anal sex (Buchaz *et al*., 2001).

**Table III Prospective cohort studies involving assessment of the effect of oral contraceptives on the risk of HIV acquisition among HIV-negative women**

| References | Nos | Study site | Population studied | Incidence of HIV/100 woman-years | Risk [95% CI] of HIV acquisition; OCs versus non-hormonal methods |
|---|---|---|---|---|---|
| Kapiga *et al*. (1998) | 1211 ever users of OCs versus 159 other methods | Tanzania | Family planning clinic attendees | 3.5 in ever users of OCs versus 2.6 in non-users | 1.01 (0.45–2.28) |
| Kiddugavu *et al*. (2003) | 421 OC users among 5117 women followed | Uganda | Community-based, women aged 15–49 | 2.5 users of OCs versus 1.5 in users of non-hormonal contraception | 1.12 [0.48–2.56] |
| Morrison *et al*. (2007) | 1583 COC users versus 1412 users of non-hormonal contraception | Uganda and Zimbabwe | Family planning clinic attendees | 2.59 in users of COCs versus 2.55 in users of non-hormonal contraception | 0.99 [0.69–1.42] |
| Myer *et al*. (2007) | 94 COC users versus 3304 non-hormonal method | South Africa | Women attending cervical screening trial | 1.80 in users of COCs versus 2.16 in users of non-hormonal contraception | 0.65 [0.16–2.66] |
| Baeten *et al*. (2007b)[a] | 269 OC users versus 568 users of non-hormonal methods | Kenya | Commercial sex workers | 11.88 in users of OCs versus 6.49 in users of non-hormonal contraception | 1.46 [1.00–2.13] |

[a]Of the on-going studies that have been reported in several publications (e.g. Martin *et al*., 1998 Lavreys *et al*., 2004a; Baeten *et al*., 2007b), only the latest results are included.

**Table IV Prospective cohort studies involving assessment of the effect of injectable contraceptives on the risk of HIV acquisition**

| References | Nos | Study site | Population studied | Incidence of HIV/100 woman-years | Risk [95% CI] of HIV acquisition versus non-hormonal method |
|---|---|---|---|---|---|
| Kapiga *et al*. (1998) | 129 DMPA users versus 1241 other methods | Tanzania | Family planning clinic attendees | 0.9 in DMPA users versus 4.1 in non-users | DMPA use 0.30 [0.07–1.26] |
| Kiddugavu *et al*. (2003) | 635 users of injectable contraception versus 4267 non-hormonal method | Uganda | Community-based, women aged 15–49 | 2.2 in sometime users of DMPA versus 1.5 in non-users | Injectable contraception use 0.84 [0.41–1.72] |
| Morrison *et al*. (2007) | 1536 users of DMPA versus 1412 users of non-hormonal contraception | Uganda and Zimbabwe | Family planning clinic attendees | 3.11 in users of DMPA versus 2.55 in users of non-hormonal contraception | DMPA use 1.25 [0.89–1.78] |
| Myer *et al*. (2007) | 603 DMPA users, 199 NET-EN users versus 3304 users of non-hormonal method | South Africa | Women attending cervical screening trial | 2.62 in users of DMPA, 2.16 in NET-EN users versus 2.16 in users of non-hormonal contraception | DMPA use 0.96 [0.58–1.59], NET-EN 0.79 [0.31–2.02] |
| Baeten *et al*., 2007b[a] | 369 DMPA users versus 568 users of non-hormonal method | Kenya | Commercial sex workers | 14.13 in users of DMPA versus 6.49 in users of non-hormonal contraception | DMPA use 1.73 [1.28–2.34] |
| Kleinschmidt *et al*., 2007 | 108 DMPA users, 192 NET-EN users versus 251 non-hormonal method | South Africa | Family planning clinic attendees | 1.1 in users of DMPA versus 7.5 in users of NET-EN versus 4.4 in users of non-hormonal contraception | DMPA use 0.46 [0.06–3.79], NET-EN 1.76 [0.64–4.84] |

[a]Of the on-going studies that have been reported in several publications (e.g. Martin *et al*., 1998, Lavreys *et al*., 2004a; Baeten *et al*., 2007b), only the latest results are included. DMPA, depot medroxyprogesterone acetate; NET-EN, norethindrone enanthate.

*Female condoms and diaphragms*

In addition to male condoms, female condoms have been developed. In a prospective study with one-third of the subjects being fully compliant with the method, the contraceptive efficacy of female condom was similar to that of other barrier methods (Farr *et al*., 1994). In an other prospective study, performed among women at high risk of STDs, <10% the women used female condom as their only barrier method and of those trying the method, one-third used it only once or twice (Macaluso *et al*., 2000). However, the use of female condoms may increase the use of condoms in general (Macaluso *et al*., 2000). So far, the efficacy of female condoms in reducing the risk of HIV transmission remains to be shown (Minnis and Padian, 2005).

Because the uterine cervix has a high number of dendritic cells and may constitute the main port of HIV entry in heterosexual transmission of HIV (Pudney *et al*., 2005), the use of diaphragms has been studied as regards the prevention of HIV transmission. However, the use of a diaphragm in addition to screening, counselling and provision of male condoms did not have an effect on the rate of HIV transmission among HIV-seronegative Southern African women recruited from community- and clinic-based organizations (Padian *et al*., 2007). However, the reported use of male condoms was significantly lower among the women randomized to use of a diaphragm (Padian *et al*., 2007).

*Spermicides*

Nonoxynol-9 is a detergent that functions as a spermicide and antimicrobial agent, and it has been used widely as a topical contraceptive. As nonoxynol-9 has anti-HIV activity *in vitro*, its use during sexual intercourse was expected to reduce the transmission of HIV. However, in large randomized, placebo-controlled trials performed among female sex workers in Africa and Asia, the use of nonoxynol-9 did not lower the risk of HIV acquisition (Roddy *et al*., 1998; Richardson *et al*., 2001; van Damme *et al*., 2002). Moreover, an increased incidence of HIV—most likely due to an increase in vaginal erosion—was seen among women using several daily applications of nonoxynol-9 (van Damme *et al*., 2002). Nonoxynol-9 is therefore no longer studied in HIV prevention programmes.

*Microbicides*

Microbicides are products in the form of a gel, tablet, film or sponge that need to be introduced into the vagina before sexual intercourse. Microbicides are being extensively studied in Africa and other regions as regards the development of female-controlled methods of HIV prevention (Stone and Jiang, 2006). Unfortunately, the results reported so far have been disappointing. In a recently published, prematurely terminated trial, the use of HIV-entry inhibitor cellulose sulphate did not prevent, but might have increased the risk of HIV transmission (van Damme *et al*., 2008). A phase 3 trial on the safety and efficacy of Carraguard, a seaweed-based candidate microbicide was completed (www.popcouncil.org). Although Carraguard proved to be safe, this trial did not demonstrate that it was superior to placebo in HIV prevention. The findings suggested that use of the products remained low throughout the trial. This may mean that adherence to methods that require coitus-dependent action will be less successful in HIV prevention. However, both basic and applied research on microbides continues and several microbicide trials are on-going (www.ipm-microbicides.org).

## Contraception in women at risk of HIV infection

*Oral contraceptives and the risk of HIV infection*

As more than 100 million women use hormonal contraception globally (www.un.org), the potential effects of hormonal contraception on susceptibility to HIV is of utmost importance. Whether the use of hormonal contraception has an effect on the risk of HIV acquisition has been a matter of debate. There are multiple mechanisms by which the use of hormonal contraceptives might increase a woman's susceptibility to HIV (Baeten *et al*., 2007a). Oral contraceptives (OCs) increase cervical ectopy (Critchlow *et al*., 1995), and cervical ectopy has been linked to increased susceptibility to STDs, including HIV in some (Louv *et al*., 1989; Plourde *et al*., 1994), but not in all studies (Morrison *et al*., 2004). However, results of prospective studies have revealed an increased incidence of STDs in women using hormonal contraception (Baeten *et al*., 2001; Morrison *et al*., 2004). In addition, sex steroids have been reported to increase expression of the HIV-1 co-receptor CCR5 in cervical CD4+ lymphocytes (Prakash *et al*., 2002) and up-regulate HIV-1 gene expression (Furth *et al*., 1990).

The fear of increased susceptibility to HIV during the use of hormonal contraception was further fuelled by results published by Marx *et al*. (1996). In the primate model of HIV infection, i.e. simian immunodeficiency virus (SIV) infection, vaginal transmission of SIV was markedly enhanced during the use of progesterone-releasing implants (Marx *et al*., 1996). The increased transmission of SIV was associated with marked thinning of the vaginal epithelium in progesterone-treated primates (Marx *et al*., 1996), most likely due to suppression of ovarian function and resultant hypoestrogenism. Thus, vaginal estrogen application normalized the epithelium and inhibited the transmission of SIV in a primate model (Li and Short, 2002; Smith *et al*., 2004). In addition, progestin-only contraceptives—levonorgestrel-releasing implants and depot medroxyprogesterone acetate (DMPA)—designed for women, result in progestin levels, which exceed those measured in women, and thinning of the vaginal epithelium in primates (Hild-Petito *et al*., 1998). However, no thinning of the vaginal epithelium has been reported in women during the use of DMPA (Mauck *et al*., 1999; Bahamondes *et al*., 2000).

The potential effect of OCs on the risk of HIV acquisition has been evaluated in both cross-sectional and prospective clinical studies. The number of studies that have involved assessment of contraception among the risk factors of HIV acquisition exceed 50 (Baeten *et al*., 2007a, Bulterys *et al*., 2007). These studies have been performed among different populations, mainly in developing countries. In addition, most of the studies were carried out before the era of antiretroviral medication. Thus, many of the early studies and their conclusions have been criticized for reasons such as low number of hormonal contraception users, poor comparability of different study groups, insufficient follow-up and poor generalizability of results (Morrison *et al*., 2005).

The first prospective studies involving assessment of the risk of HIV infection in women in relation to sexual behaviour, including the use of OCs, were published in the early 1990s. In the early studies performed in Africa, the risk factors of HIV acquisition began to surface—young age, genital ulceration, cervical ectopy, STDs and inconsistent use of condoms—and these were later confirmed in large studies (Plummer *et al*., 1991; Laga *et al*., 1993; Bulterys *et al*., 1994; Plourde *et al*., 1994). Use of OCs was a risk factor of HIV acquisition among high-risk women (Plummer *et al*., 1991), but not among women at low risk (Bulterys *et al*., 1994).

In the only prospective study performed in Europe, no HIV infections occurred during the follow-up period of 14 months among the 22 seronegative women who used OCs and were in monogamous relationships with HIV-infected men (Saracco *et al*., 1993). In the study, performed during the era of zidovudine monotherapy, the overall incidence of HIV infection was 3.6/100 woman-years (Saracco *et al*., 1993).

The largest prospective cohort studies involving assessment of the effects of OCs on the risk of HIV acquisition, all performed in Africa, are summarized in Table III. All these studies were specifically designed to assess the effects of hormonal contraception on the risk of HIV acquisition, with adequate numbers of women and follow-up procedures.

The incidence of HIV infection has varied markedly in different studies, the highest incidence being noted among Kenyan sex workers (Baeten *et al*., 2007b). Similarly, considerable variation between different study sites and countries has been reported. For example, in the study by Morrison *et al*. (2007), the incidence of HIV infection was 1.6/100 woman-years in Uganda, whereas it was 4.1 in Zimbabwe. Thus, the risk of HIV acquisition varies greatly among different populations and locations.

Based on the results of the studies summarized (Table III) it may be concluded that the use of OCs seems to be associated with an increased risk of HIV acquisition among women at high risk (such as sex workers). Moreover, in a continuing study performed among sex workers in Mombasa (Martin *et al*., 1998; Lavreys *et al*., 2004b; Baeten *et al*., 2007b), women acquiring HIV were infected with multiple variants of the virus (Long *et al*., 2000). In a subsequent prospective study, genital tract infections and the use of hormonal contraception specifically increased the risk of acquiring multiple variants of HIV among Kenyan sex workers (Sagar *et al*., 2004). However, among other African women, no increased risk of HIV has been observed during the use of OCs. Thus, the background risks, and not the potential effect of OCs, seem to be the major determinants of the risk of HIV acquisition.

*Injectable contraceptives and the risk of HIV infection*

The first studies concerned with assessment of the use of injectable contraceptives, performed among female prostitutes in Thailand, revealed an increased risk of HIV acquisition. The risk of HIV associated with the use of injectable contraceptives was as high as 3.4/100 woman-years (95% CI 1.2–13.2). The incidence of HIV was also high—9.2/100 woman-years (Rehle *et al*., 1992; Ungchusak *et al*., 1996). Similary, a recent analysis performed among young (15–24 years old) women in four African countries concluded that the use of DMPA, but not that of OCs, increased significantly the risk of HIV seropositivity (Leclerc *et al*., 2008). Yet, the overall risk associated with the use of DMPA was small, i.e. 1.34 (95% CI 1.1–1.6) (Leclerc *et al*., 2008).

However, cohort studies assessing the safety of injectable contraceptives, carried out in Africa among family planning clinic attendees, or community-based cohorts, have not confirmed the elevated risk (Table IV). As with OCs, the risk of HIV acquisition seems to be increased during the use of injectable contraception only among women at high risk (Ungchusak *et al*., 1996; Baeten *et al*., 2007b).

Thus an increased risk of HIV acquisition associated with the use of hormonal contraceptives has been demonstrated only among commercial sex workers, and potentially among young women. As the various confounding factors (such as demographic, exposure or biologic) have been controlled for (Martin *et al*., 1998; Baeten *et al*., 2007b) this suggests the existence of still an uncontrollable factor, explaining the increased risk of HIV-infection among these high-risk women. However, among African women in general the use of hormonal contraception does not seem to convey an increased risk of HIV acquisition.

When comparing different studies, considerable variation in the rates of lost to follow-up as well as in the prevalence of STDs has been noted. In the studies summarized in Tables III and IV, the number of women lost to follow-up has varied from 8% (Kleinschmidt *et al*., 2007; Morrison *et al*., 2007) to 45% (Kapiga *et al*., 1998). The prevalence of STDs at baseline was also highly variable. For example, the prevalence of *Trichomonas vaginalis* varied from 3% (Morrison *et al*., 2007) to 13% (Kapiga *et al*., 1998), whereas that of *Neisseria gonorrhoea* was reported among 2–7% of the women followed (Kapiga *et al*., 1998; Martin *et al*., 1998; Kleinschmidt *et al*., 2007; Morrison *et al*., 2007).

*Do concomitant STDs modify the risk of HIV acquisition?*

As STDs significantly increase women's susceptibility to HIV, evaluation of the potential additive effects of STDs and hormonal contraception on the risk of HIV infection is important. In one of the largest studies (Morrison *et al*., 2007), the presence of chlamydia, gonorrhoea, trichomoniasis, bacterial vaginosis or yeast infection did not have an effect on the risk of HIV acquisition among women using hormonal contraception.

However, a significantly increased risk of HIV acquisition was seen among women using hormonal contraception (both OCs and DMPA) and who were HSV-2-negative at baseline (Morrison *et al*., 2007). The risk was not associated with HSV-2 seroconversion, and no such increase was noted among HSV-2-seropositive women (Morrison *et al*., 2007). Given the highly increased susceptibility of HSV-2-positive women to HIV (Table II), the increased incidence of HIV among HSV-2-negative women is puzzling. In contrast to the above-mentioned results obtained among women attending family planning clinics, HSV-2 serostatus did not modify the risk of HIV acquisition among commercial sex workers who used hormonal contraception (Baeten *et al*., 2007b). However, relationships between hormonal contraception, HSV-2 status and the risk of HIV infection merit further studies.

*The use of IUDs in women at risk of HIV infection*

Traditionally, the use of IUDs among women at risk of HIV infection has been viewed cautiously (WHO, 2000). As the number of women using IUDs globally exceeds 130 million (www.un.org), with twice as high a prevalence of IUD use in less-developed countries, the issue of IUD safety is of vital importance.

The two prospective studies evaluating the risk of HIV acquisition during use of an IUD are summarized in Table V. No increased risk of HIV has been reported. Given the high rate of global IUD use, the small number of studies is surprising. This may partly be a result of the fact that only a small proportion of women use IUDs in sub-Saharan Africa, whereas Asian countries (such as China) constitute the most important areas of global IUD use (d'Arcangues, 2007). Until recently, women were considered to be at a relatively low risk of HIV infection in most parts of China (data.unaids.org).

Thus, the available data suggest that use of a Cu-IUD does not increase the risk of HIV acquisition (Table V). Therefore, in 2004, the WHO

**Table V Prospective cohort studies involving assessment of the effect of intrauterine devices on the risk of HIV acquisition**

| References | Nos | Study site | Population studied | Incidence of HIV/100 woman-years | Risk [95% CI] of HIV acquisition versus other methods |
|---|---|---|---|---|---|
| Martin *et al*. (1998) | 23 IUD users, 756 other methods | Kenya | Commercial sex workers | Data not available | Cu-IUD use 1.2 [0.4–3.9] |
| Kapiga *et al*. (1998) | 162 IUD users, 1208 other methods | Tanzania | Family planning clinic attendees | 2.7 in IUD users versus 3.4 in non-users | Cu-IUD use 0.80 [0.38–1.69] |

reclassified the use of both Cu-IUDs and the levonorgestrel-releasing intrauterine system (LNG-IUS) to category 2 ('generally use the method') for women at increased risk of HIV infection, and HIV-infected women (http://www.who.int/reproductive-health/publications/mec/mec.pdf).

## Contraception in women living with HIV/AIDS

*Safety and efficacy of hormonal contraception*

The safety of hormonal contraception among HIV-1-infected women has been assessed in two prospective cohort studies (Cejtin *et al*., 2003; Richardson *et al*., 2007). In the study by Richardson *et al*. (2007), a cohort of 193 postpartum Kenyan women, of whom 44% used hormonal contraception (either DMPA or OCs), were followed-up for 2 years. No differences in HIV RNA load, absolute levels or decline of CD4 lymphocyte levels were noted (Richardson *et al*., 2007). Similarly, in the Women's Interagency HIV Study, performed in the USA, the use of hormonal contraception was not associated with changes in circulating HIV RNA levels, whereas minor increases in the levels of CD4 lymphocytes were seen (Cejtin *et al*., 2003).

Only in one randomized study has the efficacy and safety of OCs versus IUDs among HIV-infected women been assessed (Stringer *et al*., 2007). Nearly 600 HIV-infected Zairean women were randomized to hormonal contraception (DMPA or OCs) versus Cu-IUD arms following delivery. The women did not receive antiretroviral medication (Stringer *et al*., 2007). During the minimum follow-up period of 2 years the women randomized to hormonal contraception were 2.4-fold (95% CI 1.3–4.7) more likely to become pregnant again (Stringer *et al*., 2007). Thus similarly as in healthy women (Heikinheimo *et al*., 2008), intrauterine contraception was more effective in preventing unintended pregnancy also in HIV-infected women. Surprisingly, progression of HIV was more pronounced among women randomized to hormonal contraception, and the risk of severe immunodeficiency or death was increased 1.5-fold (95% CI 1.04–2.1) (Stringer *et al*., 2007). The reasons for this are unclear, and confirmatory results are urgently needed.

Nevertheless, the use of hormonal contraception in HIV-infected women is classified by the WHO as category 1 ('use the method in any circumstances'). As a result of potential pharmacokinetic interactions, use of systemic hormonal contraceptives in women receiving antiretroviral medication is listed in category 2 (http://www.who.int/reproductive-health/publications/mec/mec.pdf).

*Drug interactions*

Use of antiretroviral medication may alter the metabolism of contraceptive steroids (Mitchell and Stephens, 2004). However, evidence supporting pharmacokinetic interactions is somewhat sporadic. Continuous use of the antiretroviral drug nevirapine was associated with a lower area under the concentration curve of ethinylestradiol and norethisterone following singe dose administration (Mildvan *et al*., 2002). Thus, when used together with various antiretroviral drugs, administration of contraceptive steroids might be susceptible to enhanced, unaltered or inhibited metabolism (El-Ibiary and Cocohoba, 2008). Similarly, contraceptive steroids may have an effect on the metabolism of various antiretroviral drugs (Fröhlich *et al*., 2004; Cohn *et al*., 2007). However, the clinical significance of these interactions is unclear and the interactions have not been studied during the use of various combinations of antiretroviral medication (such as HAART) currently in clinical use. Thus, concern over pharmacokinetic interactions should not keep service providers from prescribing hormonal contraceptives to women undergoing antiretroviral therapy.

Non-oral administration of contraceptive steroids to women using antiretroviral medication might be an efficient means to minimize the risk of pharmacokinetic interactions. However, this has been assessed only in case of progestin-only contraceptives. In an open-label study, Cohn *et al*. (2007) showed that serum levels of medroxyprogesterone acetate (MPA) following DMPA injections were similar in women using and not using antiretroviral medication. Ovulation is effectively suppressed following DMPA use in women using antiretroviral medication (Cohn *et al*., 2007; Watts *et al*., 2008), and unaltered levels of circulating HIV RNA load and CD4 lymphocytes have been reported (Watts *et al*., 2008). Changes, albeit clinically insignificant, have been seen in the levels of nelfinavir and nevirapine following the use of DMPA (Cohn *et al*., 2007).

Similarly, the effects of the LNG-IUS among HIV-infected women have been reported to be similar to those seen in healthy women. The circulating levels of LNG were in the same range among women using and not using antiretroviral therapy (Heikinheimo *et al*., 2006). Thus, non-oral administration of progestin-only contraceptives is an important strategy among women using antiretroviral medication. However, use of antiretroviral medication in combination with parenteral administration of combined contraceptives, such as contraceptive vaginal ring or patch remain to be studied.

*Intrauterine devices*

The safety of the Cu-IUD among women living with HIV/AIDS was first assessed in a prospective study performed in Kenya (Sinei *et al*., 1998; Morrison *et al*., 2001). During the follow-up period of 2 years, no differences in overall complications or infectious morbidity emerged between women infected and not infected with HIV. In addition, the status of the HIV infection (as judged by CD4 lymphocyte levels) did not have an effect on the risk of complications (Morrison *et al*., 2001). However, the number of women lost to follow-up was high.

Similarly, in a recent randomized study performed in Zambia among HIV-infected women, insertion of a Cu-IUD postpartum was effective and safe (Stringer *et al*., 2007). In contrast to hormonal contraception, the course of HIV infection was unaffected among women randomized to the Cu-IUD group. Only one case of pelvic inflammatory disease, resulting in a rate of 0.2/100 woman-years, was reported (Stringer *et al*., 2007).

Use of the LNG-IUS in HIV-infected women has been assessed in one case report (Cooling, 1999), a case series (Lehtovirta *et al*., 2007) and in one clinical trial performed in Northern Europe (Heikinheimo *et al*., 2006). In a prospective study the effects of the LNG-IUS were similar to those observed in healthy women (Luukkainen and Toivonen, 1995)—menstrual bleeding was reduced, ovarian activity maintained and the continuation rate was high (Heikinheimo *et al*., 2006). Moreover, the LNG-IUS had no effect on cervicovaginal shedding of HIV RNA (Heikinheimo *et al*., 2006).

Thus, IUDs seem to be safe contraceptive options for HIV-infected women with continuous access to medical care, and they are thus classified as category 2 by the WHO. Due to suspected risk of pelvic infections, initiation of intrauterine contraception in cases of AIDS remains in category 3 ('use of method not usually recommended unless other more appropriate methods are not available or not acceptable') (http://www.who.int/reproductive-health/publications/mec/mec.pdf). However, we speculate that this recommendation may be overly cautious and should be a subject to reconsideration.

*Effects of various contraceptives on cervicovaginal shedding of HIV*

The circulating HIV load is the most important determinant of cervicovaginal shedding of HIV RNA, even among women using antiretroviral medication (Kovacs *et al*., 2001; Benki *et al*., 2004). However, in various studies occasional cervicovaginal shedding of HIV has been detected in as many as 25–40% of subjects using HAART. As increased genital shedding of HIV

might result in increased infectiousness, the impact of various contraceptive methods on cervicovaginal shedding of HIV is of great interest.

Use of hormonal contraception has been associated with modest increases in genital shedding of HIV in some (Mostad *et al*., 1997; Wang *et al*., 2004), but not all (Kovacs *et al*., 2001) studies. However, the clinical importance, if any, of the slight alterations in cervicovaginal levels of HIV remains enigmatic.

Besides systemically administered hormonal contraception, the effects of Cu-IUDs and the LNG-IUS on shedding of HIV has been studied in prospective studies (Richardson *et al*., 1999; Heikinheimo *et al*., 2006). Reassuringly, use of either a Cu-IUD or the LNG-IUS did not increase cervical shedding of HIV.

*Prevalence of contraceptive use among HIV-infected women*

Recent studies have been addressed to the issue of use of contraception among HIV-infected women in France (Heard *et al*., 2004), in the USA (Massad *et al*., 2007) and among postpartum Kenyan women (Balkus *et al*., 2007). The use of effective contraception (sterilization, hormonal or intrauterine contraception) was low (<30%) both in France and the USA, whereas high uptake of hormonal contraception (up to 70%) was reported during the first few months after delivery in Kenya.

A quarter of the American women reported the use of sterilization, whereas hormonal contraception was used by <10% (Massad *et al*., 2007). In the French study, the prevalence of effective contraceptive use was <20% (Massad *et al*., 2007). Serostatus of the partner had a significant effect on the contraceptive practices—consistent condom use was reported during 84% of the visits when the partner was HIV-negative but only in 57% if the partner was HIV-seropositive (Heard *et al*., 2004). However, the prevalence of effective contraceptive use was higher (31 versus 4%) among seroconcordant couples (Heard *et al*., 2004). Thus among serodiscordant couples, minimizing the risk of HIV transmission by means of condom use was highlighted, whereas in seroconcordant couples prevention of pregnancy had became more important.

The effect of use of antiretroviral medication on contraceptive practices has also been assessed. In France, HIV-infected women using HAART were less likely to use effective contraception (Heard *et al*., 2004). The prevalence of effective contraceptive use decreased significantly among serodiscordant couples after the introduction of HAART (Heard *et al*., 2004). However, in the USA, use of HAART did not have an effect on contraceptive practices (Massad *et al*., 2007). Dual contraception was used by only a small minority in both studies (Heard *et al*., 2004; Massad *et al*., 2007). Thus, effective contraception remains underused among HIV-infected women, even those living in developed countries.

*Does knowledge of HIV infection alter sexual and contraceptive practices?*

As heterosexual intercourse has become the main route of HIV transmission in several parts of the world, lowering the risk via intervention aimed at reducing risky sexual behaviour has emerged as an important issue in HIV prevention. In several prospective trials, performed in the developed world, such interventions have proven successful in promoting condom use and safe sex (Crepaz *et al*., 2006). In the only study performed among HIV-infected women, a significantly decreased incidence of STDs and non-use of condoms was seen in the intervention group (Wingood *et al*., 2004). Thus behavioural interventions aimed at reducing risky behaviour can be effective.

## How should reproductive health care services be arranged?

It is clear that contraception, and screening for STDs and pre-malignant cervical abnormalities are all connected in women living with HIV/AIDS. Therefore, establishment of services in a manner such that all these aspects of female reproductive health are covered is important. Guidelines for organization of such clinics were recently published by the British Association for Sexual Health and HIV (www.bashh.org). Evaluation of one such clinic showed that all aspects of sexual health services were improved following integration of these different aspects of female health (Coyne *et al*., 2007).

There will be no single model for arranging reproductive health services in different areas and countries. In some countries the best way would be to integrate family planning into public health services; somewhere else a vertical programme may work more efficiently. It will be important to make both contraception and voluntary HIV counselling and testing easily accessible and affordable, and preferably free of charge in most developing countries.

The stigma related to HIV is so strong that it will be an important potential hindrance to the services unless carefully thought-out. It would make sense that voluntary counselling and testing for HIV would be provided together with contraceptive services. However, once HIV infection has been diagnosed and the treatment provided elsewhere, the staff in the care unit should also be trained to provide contraceptive services. For example, it still too often happens that injectables are discontinued because the services are somewhere else or the day of injection is overdue.

## Future prospects

To provide effective, safe, user-friendly and preferably female-controlled contraceptive methods, which offer protection from both HIV and unintended pregnancy, is a major biomedical challenge. On that note, one has to realize that currently, the spread of HIV is both a behavioural and cultural issue. While condoms provide an effective means of preventing the spread of HIV, their use remains low in areas where the disease is most prevalent. Therefore, at a time when new means of HIV prevention are being developed, a major effort is needed to change attitudes towards HIV prevention and more stringent adherence to the methods already available.

Hormonal contraception and HIV infection has been a topic of a major international meeting in 2005 in Nairobi, Kenya (http://who.int/reproductive-health/stis/hc_hiv/nairobi_statement.pdf). Besides the above mentioned WHO endorsed recommendations concerning the use of contraceptives in women living at the risk of HIV, or with HIV/AIDS, several recommendations for future research were made. These included assessment of the effects of hormonal contraception in specific subgroups, especially in young women, evaluation of novel contraceptives (such as vaginal rings and contraceptive patches), further studies on the effects of contraceptives on the HIV-infection and means to optimize the use of dual protection.

Contraceptives releasing both antimicrobial and contraceptive molecules may be one avenue towards a contraceptive microbicide that potentially could also improve compliance and product adherence (www.ipm-microbicides.org). Vaginal rings releasing both zidovudine (AZT) and non-hormonal contraceptive molecules (such as ferrous sulphate and ascorbic acid) have been found to be effective *in vitro* in inhibiting sperm mobility and they released sufficient amounts of AZT to inhibit HIV proliferation (Han *et al*., 2007). Similarly, vaginal transmission of HIV was inhibited by pre-exposure prophylaxis of antiretroviral medication in a mouse humanized with CD4 lymphocytes (Denton *et al*., 2008).

## Summary

Development and provision of safe, effective, affordable and acceptable contraception for women at risk of HIV and those living with HIV/AIDS is one of the major challenges of reproductive medicine. Currently, consistent use of male condoms is the only proven means to reduce the

risk of HIV transmission in heterosexual intercourse. All the available reversible contraceptive methods—OCs, contraceptive injections and IUDs—can generally be used both by women at risk of HIV infection and by HIV-infected women. Thus, the current optimal contraceptive strategy includes dual use of condoms combined with a more effective contraceptive method. Unfortunately, the reported use of dual contraception has been very low even in research settings. An ideal contraceptive strategy for women at risk of HIV infection would provide simultaneous protection against both unintended pregnancy and HIV acquisition. Appropriate products are currently being developed.

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