The Influence of Hormonal Contraceptive Use on HIV-1 Transmission and Disease Progression

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Women account for nearly one-half of new human immunodeficiency virus type 1 (HIV-1) infections worldwide, including the majority of infections in Africa. Biological and epidemiological studies suggest that hormonal contraceptive use could influence susceptibility to HIV-1, as well as infectivity and disease progression for those who become infected. However, not all studies have shown this relationship, and many questions remain. Safe and effective contraceptive choices are essential for women with and at risk for HIV-1 infection. Thus, understanding the effect, if any, of hormonal contraception on HIV-1 disease among women is a public health priority.

Worldwide, 17.3 million women are infected with HIV-1 [1]. Heterosexual intercourse is responsible for most HIV-1 transmissions to women, and the majority of infected women are of reproductive age.

Hormonal forms of contraception, primarily oral contraceptive pills and the injectable depot medroxyprogesterone acetate (DMPA), are used by >100 million women [2]. Hormonal contraceptives have physiological actions beyond pregnancy prevention—both beneficial health effects and risks of adverse health consequences—some of which were unanticipated when these products were developed [3, 4].

During the past ∼15 years, a number of biological and epidemiological studies have suggested that the use of hormonal contraception may influence susceptibility to HIV-1, infectivity of HIV-1, and progression of HIV-1 disease, although this has not been consistently seen in all studies. A conclusive relationship between hormonal contraception and adverse HIV-1 outcomes would be of considerable public health importance, because effective family planning services are central to initiatives to slow population growth, promote economic development, and improve the health of women and children worldwide.

BIOLOGICAL STUDIES

Epidemiological and laboratory studies provide some insights into possible biological mechanisms by which hormonal contraception could influence HIV-1. In a series of studies, Marx and colleagues demonstrated that progesterone treatment of female macaques increased susceptibility to vaginal inoculation with simian immunodeficiency virus (SIV) [5], effects that could be reversed by pretreatment with estrogen [6, 7]. Indeed, progesterone has been used to increase susceptibility to SIV among macaques in studies of candidate HIV-1 vaccines and microbicides [8, 9]. The mechanism for these effects has not been determined, although the authors of the original study postulated that vaginal thinning may play a role. If altered vaginal epithelial structure is central to the effect of progesterone on increasing susceptibility to SIV in macaques, these findings may have less relevance to humans, because studies of the effect of DMPA among women have not shown thinning to the extent seen in the nonhuman primate studies [10–12].

Cervical ectopy, or extension of the endocervical columnar epithelium onto the exocervical face, has been associated with hormonal contraceptive use [13, 14] and with increased susceptibility to HIV-1 [15]. Ectopy is a common feature of the immature cervix, which may contribute to the disproportionate risk of HIV-1 faced by young African women [16].

Genital tract infections may also mediate a relationship between hormonal contraception and susceptibility to HIV-1. Epidemiological studies repeatedly have shown that users of hormonal contraceptives have increased risk of cervical chlamydial infection [14, 17–20], which agrees with animal studies showing
that estrogen and progesterone enhance growth of *Chlamydia trachomatis* [21]. Limited animal and human data suggest that use of hormonal contraceptives increases susceptibility to genital herpes [22, 23]. DMPA may decrease vaginal colonization by hydrogen peroxide–producing *Lactobacillus* species [12], which are protective against HIV-1 [24].

On a cellular level, hormonal contraceptives have been associated with cervical and vaginal inflammation [14, 25], increased genital tract expression of the HIV-1 coreceptor CCR5 [26, 27], and mucosal and systemic immune responses that could mediate susceptibility to HIV-1 [28–30]. Finally, hormones may directly enhance the replication of the virus itself [31], which could affect both early infection and the subsequent disease course.

Collectively, there are data to argue biological plausibility for hormonal contraception to influence HIV-1, especially initial susceptibility to the virus. Given the multiple mechanisms proposed, the effect may be multifactorial or indirect. However, it is important to recognize that most of these potential biological mechanisms are proposed on the basis of limited data, and it is difficult to discern which, if any, are actually relevant to the risk of HIV-1 transmission.

**Epidemiological Studies of HIV-1 Acquisition**

More than 50 studies have explored whether use of hormonal contraception is a risk factor for HIV-1 infection. Most were cross-sectional, whereas 15 were prospective studies (table 1) [16, 32–45]. A meta-analysis of 28 studies (7 prospective published in 1999 found that use of oral contraceptive pills was associated with a slightly elevated risk of HIV-1 acquisition (OR, 1.19; 95% CI, 0.99–1.42), with greater risk among 7 studies from Africa (OR, 1.65; 95% CI, 1.09–2.52) [46]. Five prospective studies published before 1999 examined the risk of HIV-1 acquisition associated with use of DMPA: 2 found statistically significantly increased risks [40, 41], 2 found non-statistically significantly increased risks [37, 42], and 1 demonstrated no association [16]. Nearly all of these studies were conducted in Africa, where heterosexual transmission of HIV-1 infection predominates.

Since 1999, 3 large prospective studies have been reported. The first included 5117 women in Rakai, Uganda; 202 acquired HIV-1 (incidence, 1.5 cases per 100 person-years) [43]. This cohort was followed from 1994 to 1999 for a community-randomized trial of sexually transmitted disease (STD) treatment for prevention of HIV-1 infection [47]. Follow-up, including measurement of current contraception and HIV-1 status, occurred at 10-month intervals. In unadjusted analysis, hormonal contraceptive use was associated with increased risk of acquisition of HIV-1 (risk ratio [RR], 1.56; 95% CI, 1.00–2.33). However, after controlling for demographic factors and measures of sexual behavior, no association remained (RR, 0.94). Similar results were found in separate analyses of oral contraceptive pill and DMPA use.

In 2004, we reported the results of a prospective study among 1272 female sex workers recruited into an open cohort in Mombasa, Kenya, between 1993 and 2003 [44]. A principal aim of this study was to describe risk factors for HIV-1 acquisition, including hormonal contraception [48]. At monthly follow-up, HIV-1 status and contraceptive method were measured. There were 248 seroconversions (incidence, 8.5 cases per 100 person-years). Both oral contraceptive pills (hazard ratio [HR], 1.5; 95% CI, 1.0–2.1) and DMPA (HR, 1.8; 95% CI, 1.4–2.4) were associated with greater risk of HIV-1, compared with nonuse of contraception, in multivariate analyses adjusted for demographic characteristics, sexual behavior, condom use, and incident STDs.

The largest study to measure the risk of HIV-1 infection associated with hormonal contraceptive use has recently been published [45]. The study recruited 4439 women from family planning clinics in Uganda and Zimbabwe specifically to address this question among a low-risk population. At 3-monthly intervals, contraceptive method was recorded and HIV-1 testing was performed. There were 213 HIV-1 seroconversions (incidence, 2.8 cases per 100 person-years). Overall, neither oral contraceptive pills (HR, 0.99; 95% CI, 0.69–1.42) nor DMPA (HR, 1.25; 95% CI, 0.89–1.78) was associated with HIV-1 acquisition. However, among women who were negative for herpes simplex virus type 2 (HSV-2) at study enrollment (48% of the study population), both methods increased risk of HIV-1 acquisition (for oral contraceptive pills: HR, 2.85; 95% CI, 1.39–5.82; for DMPA: HR, 3.97; 95% CI, 1.98–8.00), a finding that was robust in multiple sensitivity analyses.

**Methodological Considerations**

It is difficult to reconcile the divergent results of studies examining the effect of hormonal contraceptive use on risk of HIV-1 acquisition. Indeed, a 1998 review argued that substantial differences among studies made summarization of the data impossible [49].

Several methodological issues are important to consider. First, imprecision in measurement of the timing of hormonal contraceptive use relative to HIV-1 acquisition could have introduced bias [50]. This is most problematic for the cross-sectional studies, although several prospective studies measured contraceptive use only at study enrollment [38, 40] or infrequently during follow-up [37, 43]. Similarly, infrequent measurement of HIV-1 infection status limited the ability to know with precision which contraceptive method was used at the time of HIV-1 acquisition.

Second, differences in sexual behaviors between users and nonusers of hormonal contraception may have led to con-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>No. of HIV-1 seroconversions/ no. followed prospectively (incidence)*</th>
<th>Frequency of measurement of HIV-1 infection</th>
<th>Contraceptive method; analysis of exposure</th>
<th>Measure of association (95% CI)</th>
<th>Adjustments</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plummer et al. [32]</td>
<td>1991</td>
<td>Kenya</td>
<td>CSWs</td>
<td>83/124 (47)</td>
<td>Variable—monthly to 6-monthly</td>
<td>OCP vs. no OCP; use reviewed at follow-up visits, analyzed as use prior to seroconversion</td>
<td>OR, 3.1 (1.1–8.6); aOR, 4.5 (1.4–13.8)</td>
<td>For GUD, chlamydial infection, condom use</td>
<td>Very high HIV-1 incidence; OCP users had more sex partners, but similar STD rates and condom use; dose-response relationship between consistency of OCP use and risk of HIV-1 infection</td>
</tr>
<tr>
<td>Laga et al. [33]</td>
<td>1993</td>
<td>Former Zaire</td>
<td>CSWs</td>
<td>68/126° (9.8)</td>
<td>3-Monthly</td>
<td>OCP vs. no OCP; use during the interval 2–6 months prior to seroconversion</td>
<td>OR, 0.9 (0.1–13.5)</td>
<td>None</td>
<td>Few women (≤5) used hormonal contraception</td>
</tr>
<tr>
<td>Saracco et al. [34]</td>
<td>1993</td>
<td>Italy</td>
<td>Partners of HIV-1—seropositive men</td>
<td>19/343 (3.6)</td>
<td>6-Monthly</td>
<td>OCP vs. no OCP; use measured at each follow-up visit</td>
<td>No seroconversions occurred among 22 women who used oral contraceptives</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Plourde et al. [35]</td>
<td>1994</td>
<td>Kenya</td>
<td>STD clinic attendees with GUD</td>
<td>10/81 (48)</td>
<td>Monthly</td>
<td>OCP vs. no OCP; use during study period</td>
<td>Trend described, but risk estimate not reported; 4/10 seroconverters vs. 1/871 seropositive women used oral contraceptives at enrollment</td>
<td>None</td>
<td>11 of these 22 women also used condoms consistently</td>
</tr>
<tr>
<td>de Vincenzi [36]</td>
<td>1994</td>
<td>Western Europe</td>
<td>Partners of HIV-1—seropositive men</td>
<td>87 (≈5)</td>
<td>6-Monthly</td>
<td>OCP vs. none; use during study period</td>
<td>No association; OR, 0.5 (95% CI, 0.1–3.7) reported in later systematic review (49)</td>
<td>None</td>
<td>Analysis restricted to inconsistent condom users; no seroconversions among consistent condom users</td>
</tr>
<tr>
<td>Bulterys et al. [37]</td>
<td>1994</td>
<td>Rwanda</td>
<td>Prenatal clinic attendees</td>
<td>31/1150 (1.4)</td>
<td>Once, at 2-year follow-up</td>
<td>Any hormonal method vs. none; use at the 2-year follow-up visit</td>
<td>RR, 3.2 (1.6–6.5); aRR, 1.3 (0.9–4.6)</td>
<td>For demographic factors, history of STDs, sexual behavior, injections</td>
<td>HIV-1 infection and contraceptive exposure assessed only once; 74% DMPA, 18% OCP, 2% Norplant, 6% combination</td>
</tr>
<tr>
<td>Weir et al. [38]</td>
<td>1994</td>
<td>Cameroon</td>
<td>CSWs</td>
<td>17/196° (9%)</td>
<td>3-Monthly</td>
<td>OCP vs. no OCP; use at enrolment</td>
<td>No case-patients used OCPs vs. 5 controls</td>
<td>None</td>
<td>Few women used hormonal contraception</td>
</tr>
<tr>
<td>Sinei et al. [39]</td>
<td>1996</td>
<td>Kenya</td>
<td>Family planning clinic attendees</td>
<td>17/51° (2.1)</td>
<td>3-Monthly</td>
<td>OCP vs. non-OCP; use during last 6 months vs. no OCP use in last 6 months</td>
<td>OR, 3.5 (0.8–21.5)</td>
<td>For demographic factors, history of STD symptoms, sexual behavior, and condom use</td>
<td>Risk estimate for adjusted analysis not presented, but reported to be similar; no use of a comparison group unexposed to contraception (most used IUDs, fewer DMPA or Norplant)</td>
</tr>
<tr>
<td>Ungchusak et al. [40]</td>
<td>1996</td>
<td>Thailand</td>
<td>CSWs</td>
<td>15/240 (9.2)</td>
<td>3-Monthly</td>
<td>OCP vs. none; injectable vs. none; use at enrolment</td>
<td>OCP aIRR, 0.22 (0.03–1.87); injectable aIRR, 3.83 (1.02–14.43)</td>
<td>For demographic factors and syphilis seropositivity</td>
<td>...</td>
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<tr>
<td>Kapiga et al. [16]</td>
<td>1998</td>
<td>Tanzania</td>
<td>Family planning clinic attendees</td>
<td>75/1370 (3.4)</td>
<td>Variable, not defined</td>
<td>OCP vs. non-OCP; DMPA vs. non-DMPA; use analyzed as ever during the study period</td>
<td>OCP aIRR, 1.01 (0.45–2.28); DMPA aIRR, 0.30 (0.07–1.26)</td>
<td>For demographic factors, sexual behavior, gonorrhea, and candidiasis</td>
<td>All participants used contraception; 88% OCP, 12% IUD, 9% DMPA; thus, the OCP analysis compared OCP users with injectable and IUD users and the injectable analysis compared injectable users with OCP and IUD users</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Location</td>
<td>Type</td>
<td>Sample Size</td>
<td>Follow-up Period</td>
<td>Methodology</td>
<td>Adjusted OR (95% CI)</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Martin et al. [41]</td>
<td>1998</td>
<td>Kenya</td>
<td>CSWs</td>
<td>111/779 (12.6)</td>
<td>Monthly</td>
<td>OCP vs. none; DMPA vs. none; monthly measurement with time-dependent analysis</td>
<td>OCP HR, 1.5 (0.9–2.4); OCP aHR, 1.3 (0.8–2.2); DMPA HR, 2.2 (1.4–3.4); DMPA aHR, 2.0 (1.3–3.1)</td>
<td>For demographic factors, sexual behavior, condom use, and STDs (GUD, genital discharge, bacterial vaginosis, candidiasis, gonorrhea)</td>
<td></td>
</tr>
<tr>
<td>Kilmarx et al. [42]</td>
<td>1998</td>
<td>Thailand</td>
<td>CSWs</td>
<td>30/285 (4.3)</td>
<td>3-Monthly</td>
<td>OCP vs. non-OCP; DMPA vs. non-DMPA; 3-monthly, time-dependent analysis</td>
<td>OCP RR, 2.5 (1.1–5.3); OCP aRR, 1.8 (0.8–4.0); DMPA RR, 1.5 (0.6–4.0)</td>
<td>No association after adjustment for behavioral confounding; frequent measurement of contraceptive exposure and HIV-1 outcome</td>
<td></td>
</tr>
<tr>
<td>Kiddugavu et al. [43]</td>
<td>2003</td>
<td>Uganda</td>
<td>Rural community-based cohort</td>
<td>202/5117 (1.5)</td>
<td>10-Monthly</td>
<td>OCP vs. none; injectable vs. none; 10-monthly ascertainment; if contraceptive method changed between visits, the 10-month exposure interval was divided between the 2 methods</td>
<td>OCP IRR, 1.70 (0.85–3.04); injectable IRR, 1.12 (0.46–2.96); injectable aIRR 0.84 (0.41–1.72)</td>
<td>For demographic factors, number of sex partners, and condom use</td>
<td></td>
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<tr>
<td>Lavreys et al. [44]</td>
<td>2004</td>
<td>Kenya</td>
<td>CSWs</td>
<td>248/1272 (8.5)</td>
<td>Monthly</td>
<td>OCP vs. none; DMPA vs. none; Norplant vs. none; monthly ascertainment; time-dependent analysis, including accounting for changing contraceptive method</td>
<td>OCP aHR, 1.5 (1.0–2.1); DMPA aHR, 1.5 (1.0–2.1)</td>
<td>No association after adjustment for behavioral confounding; frequent measurement of contraceptive exposure and HIV-1 outcome</td>
<td></td>
</tr>
<tr>
<td>Morrison et al. [45]</td>
<td>2007</td>
<td>Uganda, Zimbabwe</td>
<td>Family planning clinic attendees</td>
<td>213/4439 (2.8)</td>
<td>3-Monthly</td>
<td>OCP vs. none; DMPA vs. none; 3-monthly ascertainment; time-dependent analysis, including accounting for changing contraceptive method</td>
<td>OCP aHR, 0.99 (0.69–1.42); DMPA aHR, 1.26 (0.89–1.76)</td>
<td>For study site, demographic characteristics, measures of participant and partner sexual behavioral risk, coital frequency, and condom use</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** aHR, adjusted hazard ratio; aIRR, adjusted incident rate ratio; aOR, adjusted OR; aRR, adjusted relative risk; CSWs, commercial sex workers; DMPA, depot medroxyprogesterone acetate; GUD, genital ulcer disease; HSV-2, herpes simplex virus type 2; IUD, intrauterine device; NR, not reported; OCP, oral contraceptive pills; STD, sexually transmitted disease.

* Per 100 person-years.

* Nested case-control design. For these studies, the no. of control participants is listed instead of the total no. of participants followed prospectively. HIV-1 incidence is for the entire study population.
found. Women using effective contraception may be less inclined to use condoms [51], because they feel protected from pregnancy, or they may have other behaviors that differ from those of women who choose not to use contraception. Some studies controlled for measures of sexual behavior and still found evidence for higher risk [32, 41, 44]. We have argued that behavioral confounding may be a lesser issue among high-risk women, who may use condoms for protection from HIV-1 infection independent of choices for prevention of pregnancy [44].

Along these lines, studies that have shown that elevated risk of HIV-1 acquisition associated with hormonal contraception has tended to be among higher-risk populations, such as sex workers [32, 41, 42, 44]. It is possible that contraceptive use increases risk of HIV-1 infection only in certain populations; there is evidence that probabilities of HIV-1 transmission differ for casual versus monogamous partnerships [52, 53]. However, this explanation is difficult to reconcile with the recent finding of elevated risk for HIV-1 infection only among HSV-2-seronegative users of hormonal contraceptives, who might be considered to be at lower risk [45]. Two prospective studies among HIV-1-serodiscordant couples (high HIV-1 exposure, from a single partner) did not find increased risk of HIV-1 infection among users of oral contraceptive pills [34, 36].

Several studies included contraceptive users in the comparison groups for analyses (e.g., users of oral contraceptive pills versus users of DMPA and/or intrauterine devices) [16, 39, 42], although these other methods may also increase risk of HIV-1 infection [54]. Other studies were limited by small numbers of HIV-1 seroconversions [35, 36] and few women using hormonal contraception [33, 38]. Few studies had sufficient statistical power to detect the 50%-80% increase in risk of HIV-1 infection suggested by the Mombasa study [44], and there are no analyses that are sufficiently powered to assess the relationship between other hormonal methods (e.g., implantable methods) and HIV-1 infection [44].

In 2002, a team of investigators from Family Health International reviewed 10 [16, 32–35, 37, 39–41, 43] prospective studies [55], of which 4 were judged to be of higher quality [32, 37, 39, 41]. To this list we would add the recent multicenter study [45] and our study from Mombasa [44] (a later analysis of [41]); both had large sample sizes, frequent measurements of contraception and HIV-1 infection, detailed adjustment for potential confounding factors, and appropriate comparison groups.

The fact that the main results of these 2 studies differ, in some ways as one found an overall effect of hormonal contraception on risk of HIV-1 acquisition and the other saw this effect only among HSV-2-seronegative participants, illustrates the limitations for summarizing the available data relating hormonal contraceptive use to susceptibility to HIV-1 infection. Despite careful study design and analysis, all studies of this question have been observational in nature and are therefore open to residual confounding by unmeasured and uncontrolled variables. The best available evidence suggests that risk of HIV-1 acquisition may be greater for higher-risk populations, such as sex workers, perhaps more so for users of DMPA than for users of oral contraceptive pills [40, 41, 44]. Among the general population, hormonal contraception appears not to increase the risk of HIV-1 infection overall, but women using hormonal methods who are seronegative for HSV-2 infection may be at elevated risk.

**NATURAL HISTORY OF HIV-1 INFECTION**

Many of the biological mechanisms proposed to increase risk of HIV-1 infection for women using hormonal contraception could also influence subsequent viral replication, at both early and chronic stages of infection. Among 161 women from the Mombasa cohort, we demonstrated that use of DMPA at the time of time of infection was associated with a higher plasma HIV-1 load set point (by 0.33 log\(_{10}\) copies/mL) [56]. Viral load set point reflects steady-state viral replication after immunologic containment of primary infection and predicts progression of HIV-1 disease [57–59]. Similarly, one primate study also found higher early SIV load among animals treated with progesterone [5].

Virological studies have demonstrated that women using hormonal contraception (both oral contraceptive pills and DMPA) at the time of HIV-1 infection are more likely to acquire multiple viral genotypes [60], which in turn has been associated with higher plasma viral load set point and faster decrease in CD4 cells [61, 62]. Thus, greater viral diversity during primary HIV-1 infection may mediate the effects of hormonal contraception on later HIV-1 replication and disease progression. Transmission of a more diverse virus population may reflect increased susceptibility to establishment of individual virus strains, either during initial infection or early virus dissemination.

Few studies have examined the effects of hormonal contraceptive use among HIV-1-seropositive women during chronic infection. In the US Women’s Interagency HIV Study [63], current use of any hormonal method was not related to plasma viral load and was associated with slightly higher CD4 cell counts. We found that use of either oral contraceptive pills or DMPA was associated with increased risk of cervical C. trachomatis infection and cervicitis in a longitudinal assessment of HIV-1–infected women in the Mombasa cohort [64]. Acute STDs may increase plasma HIV-1 load [65], which could mediate faster progression of HIV-1 disease among sex workers [66]. However, among Thai sex workers with prevalent HIV-
HIV/AIDS

Figure 1. Proposed links between hormonal contraceptive use and HIV-1. Solid arrows, studies in which hormonal contraception was specifically assessed. Notably, not all studies support these links, and many are based on limited data. Dashed arrows, studies done in other populations that reflect generally agreed-upon principles of HIV-1 infection. STD, sexually transmitted disease.

1 infection, use of hormonal contraception at any time during follow-up was not associated with survival [67]. No other longitudinal studies have assessed the effect of hormonal contraceptive use on progression of HIV-1 disease.

HIV-1 TRANSMISSION

The physiological changes that might increase risk of HIV-1 acquisition for uninfected users of hormonal contraception could also increase the infectiousness to sex partners of HIV-1–infected women. The only study to directly examine the effect of hormonal contraception on female-to-male HIV-1 transmission, among HIV–1-discordant European couples early in the epidemic, found no association [68]. Most studies have used detection of HIV-1 infection in genital tract secretions as a proxy measure of HIV-1 infectiousness [69, 70]. Two cross-sectional studies from Kenya [71, 72] demonstrated strong associations between hormonal contraceptive use and cervical shedding of HIV-1 DNA, but a US study [73] did not find any association with HIV-1 RNA. The only prospective study measured genital HIV-1 infection before and ∼2 months after initiation of hormonal contraception [74]. A modest increase in detection of HIV-1 DNA, but not quantity of HIV-1 RNA, was found. Studies of HIV-1 shedding during the menstrual cycle have demonstrated that HIV-1 RNA reaches its highest levels in genital secretions during the luteal phase, when progesterone predominates [75, 76], adding some biological plausibility to the hypothesis that hormonal contraception might increase HIV-1 infectiousness.

Indirect mechanisms by which hormonal contraceptive use may contribute to HIV-1 infectivity include increased risk of cervical STDs [64] and cervical inflammation [25], which may increase cervical HIV-1 shedding [77, 78]. Data concerning the effect of hormonal contraception on reactivation of genital herpes, which also increases genital HIV-1 levels [78–80], are inconsistent [81–83].

SUMMARY AND PRIORITIES

Epidemiological and biological studies suggest a possible—but by no means definitive—effect of hormonal contraceptive use on risk of HIV-1 acquisition among uninfected women and on HIV-1 disease progression and infectivity among those who become infected. A summary of the postulated links between hormonal contraception and HIV-1 disease is presented in figure 1. Inconsistent results across studies and incompletely answered questions mandate further research into this important public health issue. What are the priorities?

Interpreting the results of studies of hormonal contraception and HIV-1 acquisition. The most recent study of the risk of HIV-1 acquisition associated with hormonal contraceptive use illustrates the uncertainties surrounding this issue: no overall relationship between contraceptive use and susceptibility to HIV-1 infection was seen, but a strikingly elevated risk (∼3- to 4-fold) was found among HSV-2–seronegative women, a subgroup comprising nearly one-half of the study participants [45]. In that study, HSV-2 infection was strongly associated with HIV-1 acquisition, as it has been in many populations [84], and the authors hypothesized that HSV-2 infection may overwhelm any effect of hormonal contraception on risk of HIV-1 infection for HSV-2–infected women. Reanalysis of other cohort studies is needed to clarify the roles of hormonal contraception and HSV-2 infection in susceptibility to HIV-1 infection.

To date, clinical trials have not been conducted, because of arguments that randomizing women who desire hormonal contraception to methods that would necessitate cooperation of male partner(s) (e.g., condoms) could be unethical [55]. If new
observational analyses are initiated, careful study design must be the priority, with attention to precise measurement of contraception exposure, HIV-1 infection outcome, relevant confounders, and potential sources of bias (e.g., loss to follow-up, sexual behavior, and measures of risk of HIV-1 among sex partners). Studies of adolescents and HIV-1–serodiscordant couples would be particularly informative.

Finally, the interaction between biological and behavioral factors influencing risk of HIV-1 acquisition among women using hormonal methods should be a topic for greater investigation. Particularly needed are potential novel strategies for prevention of HIV-1 infection—both behavioral (e.g., promotion of barrier methods for contraceptive synergy and protection from HIV-1) and biomedical (e.g., topical estrogen to potentially reverse vaginal mucosal changes from DMPA use [7, 85]).

Defining the risk of hormonal contraception on progression of HIV-1 disease. Long-term assessment of the effect of contraceptive use on HIV-1 disease is lacking, particularly studies with clinical end points such as progression to AIDS or death. Longitudinal studies of hormonal contraception’s effect during chronic HIV-1 infection on viral load, CD4 cell count, and disease progression are needed, including effects of initiation/termination and total duration of contraceptive use. Finally, studies of the effect of hormonal contraception on disease progression up to and after initiation of antiretroviral therapy are warranted.

Measuring the effect of hormonal contraception on risk of HIV-1 transmission. The potential for hormonal contraception to increase infectiousness of HIV-1 remains unclear. Studies of HIV-1–discordant couples may help quantify this risk, if present, but may not fully reflect transmission dynamics in populations in which concurrent partnerships facilitate spread of HIV-1 infection. Thus, it is critical that long-term studies of surrogate markers of infectiousness be conducted, with measurement at multiple time points after initiation of contraception. These studies should include quantitative analyses of both cell-free and cell-associated HIV-1, because it is unclear which is the best marker for infectivity [70]. Also, studies of contraceptive use and genital detection of HIV-1 among women taking antiretroviral therapy should be a priority.

Assessing the biological effect of hormonal contraceptive use on genital viral replication. The biological mechanisms that have been postulated to underlie an effect of hormonal contraceptive use on HIV-1 acquisition are based on limited data. In situ analyses examining genital cell types and/or human tissue models using relevant HIV-1 strains, such as those from early infection, may shed light on whether hormones change the nature or number of target cells for HIV-1 replication. Similarly, biopsy samples from HIV-1–infected women may provide insight into whether use of hormones during chronic infection alters or increases the number of cell targets in the genital mucosa.

Translating the data into policy. It is essential that the results of the available studies on the influence of hormonal contraception on HIV-1 infection and their implications be communicated to women and their care providers so that informed contraceptive decisions can be made. The current data paint an inconsistent and incomplete picture, making effective communication difficult and all the more necessary.

For HIV-1–uninfected women, a recent World Health Organization (WHO) statement [86] concluded that, for most women, the benefits of hormonal contraception for preventing unintended pregnancy (and its attendant health risks) outweigh any potential increased risk of HIV-1 acquisition. For HIV-1–infected women, contraceptive options are equally desired and important [87], and effective contraception to prevent unintended pregnancies is a key component of efforts to reduce HIV-1 transmission to infants [88]. Current WHO guidelines [89] put no restrictions on the use of hormonal contraception by women with HIV-1 infection.

CONCLUSIONS

Safe and effective contraceptive choices are essential for women with and at risk for HIV-1 infection. Epidemiological and laboratory investigations suggest that hormonal contraception may have biologically plausible and clinically important effects on susceptibility to HIV-1, infectiousness of HIV-1, and progression of HIV-1 disease, but the data are inconsistent, and many questions remain. Still, it is clear that hormonal contraceptives are not protective against HIV-1 infection, and potentially the most important public health message is that dual protection with condoms should be the goal for women using hormonal contraception. This emphasizes the necessity for cooperation between those working in the fields of reproductive health and prevention of STDs, as well as the needs for increased involvement of men in reproductive health and for novel prevention interventions for women. Policymakers and clinicians must carefully consider how to translate the available data into public health messages that will reach the countries hardest hit by HIV-1 infection and women who are at risk for or who are living with this disease.

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