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Review Article

HIV and Women: A Review Paper

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Abstract: Studies have been published in the area of HIV in women but much is not known in the area of HIV in women and its natural history. There are limited data on the natural history of AIDS in women independent of these social and economic conditions. A recent study showed that, increasing numbers of women with AIDS are from rural and smaller metropolitan areas rather than large urban centers, communities that often face additional barriers to access and retention. In Conclusion, Overall, this review has expanded our understanding of the HIV in women and its natural history, risk factors and clinical manifestations. This review will help to improve clinical practices in diagnosis and treatment of HIV in women.

Keywords: HIV, Immunity, Women, Pregnancy

INTRODUCTION

Hiv and Women

Women represent one of the fastest growing populations infected with the human immunodeficiency virus (HIV) in the United States. While many of the clinical manifestations of HIV/AIDS in women are similar to men, there remain significant gender-based differences in the disease. These include:

- Differences in viral load early in infection
- Differences in selected opportunistic infections
- Difference in selected ARV-related toxicities and side effects
- A number of female-specific complications
- Issues related to HIV and pregnancy
- The psychosocial impact and the environment in which HIV/AIDS occurs in women
- Access to and receipt of quality care

EPIDEMIOLOGY

Prevalence of HIV in women

Since the early 1980s, the percent of AIDS cases accounted for by women in the United States has grown annually according to reports from the Centers for Disease Control and Prevention (CDC) (CDCP.2007). In 1985, 7 percent of AIDS cases were in adult women compared to 27 percent in 2007. As of December 2007, 198,544 AIDS cases had been reported in girls and women. Since the initial reports of AIDS in women, women from minority populations have been disproportionately represented. In 1997, rates in African American and Latina women were 20 and 7 times higher than in Caucasians (58.8 and 21.5, respectively, versus 3.0 per 100,000) with persistence of over-representation of minorities through 2007 (CDCP.2007; Diagnoses of HIV/AIDS--32 States, 2000-2003). In 2007, 83 percent of women diagnosed with AIDS were from communities of color, with 65 percent in non-Hispanic Blacks (CDCP.2007).

Many of the women with AIDS come from communities with a history of poor access to health care and with high rates of poverty, unstable housing, domestic violence, and substance abuse (Hader, S. L. *et al.*, 2001). In one study in which 291 women with AIDS were interviewed between 1990 and 1992, 90 percent were unemployed, 83 percent had an annual income under $10,000, and approximately half had at least one child under the age of 15 (Chu, SY, & Diaz, T. 1993). HIV in women is still disproportionately represented in poor disadvantaged communities. There are limited data on the natural history of AIDS in women independent of these social and economic conditions (Zierler, S., & Krieger, N. 1997). In addition, increasing numbers of women with AIDS are from rural and smaller metropolitan areas rather than large urban centers, communities that often face additional barriers to access and retention (CDCP.2007).

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Risk factors for HIV acquisition

Other aspects of the epidemiology of HIV are also changing for women. Heterosexual contact is the most common reported risk factor for women, overtaking injection drug use (CDCP.2007). A number of risk factors for acquisition are shared between men and women, including presence of ulcerative sexually transmitted infections, higher viral loads, and unprotected sexual intercourse (Chersich, M. F., & Rees, H. V. (2008). It has been proposed that during the normal menstrual cycle, there is a period lasting approximately 7 to 10 days when innate, humoral, and cell-mediated immunity are suppressed by estradiol and/or progesterone, enhancing the potential for acquisition of HIV by women; this hypothesis requires further exploration (Wira, C. R., & Fahey, J. V. 2008). However, even if this may represent a period of higher risk, primary prevention efforts for women should continue to emphasize the need for consistent adherence to safer sex practices regardless of timing in the menstrual cycle.

NATURAL HISTORY

Morbidity and mortality

The understanding of the presence and extent of differences between the sexes in the natural history of HIV and the progression to AIDS continues to evolve. Early in the epidemic, a number of studies reported higher mortality and increased progression of HIV/AIDS in women compared with men. However, more careful analyses incorporating other potential factors such as HIV risk, age, and the AIDS-defining condition showed that these differences were largely explained by decreased access to quality care and treatment rather than representing a more aggressive disease progression in women on biological grounds (Ellerbrock, T. V. *et al.,* 1991; Lepri, A. C.*et al.,* 1994). Women who receive care in more experienced clinics survive longer than women cared for by less experienced clinics (Laine, C. *et al.,* 1998). However, even among established HIV clinics and adjusting for insurance rates, race and transmission, women were still less likely to be on HAART (Gebo, K. A. et a 2005). Delay in diagnosis is also common, with one-third of women either presenting with AIDS at the time of their HIV diagnosis or progressing to AIDS within the first 12 months (CDCP.2007).

In 1996, declines in AIDS-related mortality began to be noted, attributed to improved HIV treatment with highly active antiretroviral therapy (HAART) and improved prevention of opportunistic infections (OIs). However, the decline in AIDS-related mortality for women was less dramatic and lagged behind that of men (10 versus 25 percent) (CDC. 1997), although the rates of survival three years after diagnosis are now similar for men and women overall (CDCP.2007). This delay in benefit has not been fully explained but, based upon the experiences earlier in the epidemic, is probably in part related to decreased access to or use of quality care (Cunningham, W. E. *et al.,* 2000), although ongoing work to understand the potential impact of biological differences continues. Regardless, AIDS remains a leading cause of death in women from minority populations (CDCP.2007).

Depression and HIV Disease Progression

Depression may be a contributory factor for HIV progression in women. In a prospective longitudinal cohort study of 765 HIV seropositive women in the United States, those with chronic depressive symptoms were twice as likely to die as those with mild or no depressive symptoms, after controlling for clinical features and treatment (Ickovics, J. R. *et al.,* 2001).

ACCESS TO QUALITY OF CARE

A large number of barriers to care exist for women, ranging from concrete needs (childcare, transportation, lack of insurance) to psychological and social barriers (fear of disclosure, denial, and cultural mistrust of the healthcare system). In addition, a large percentage of women with HIV/AIDS provide primary care for family members who may include children or other patients with HIV/AIDS. Thus, it is not uncommon for women to compromise their own care to provide care for others. Despite efforts to increase access and utilization of care, HIV-infected women continue to receive lower quality of care, even after adjusting for potential confounders, including race and HIV transmission risk (Clark, R.A. *et al.,* 1993).

GENDER-RELATED BIOLOGICAL DIFFERENCES

Viral load differences

While gender-based differences in access and receipt of care exist, biological differences also exist. A natural cohort study of 812 specimens from 650 injection drug users (IDU) identified differences in viral load measurements between men and women; women had lower viral copies compared to men after controlling for CD4 counts (3365 copies/mL versus 8907 by branched DNA assay and 45,416 copies/mL versus 93,130 by reverse transcriptase polymerase chain reaction assay) (Farzadegan, H. *et al.,* 1998). The time to the development of AIDS was not different between the sexes. Another way to look at this is that women had a 1.6-fold increased risk of progressing to AIDS compared with men with the same viral load and CD4 cell count. Many other studies have also found this gender-based difference in viral loads, with no difference in overall mortality; the difference appears to be occurring primarily in the years following seroconversion. One group found significantly lower viral loads at seroconversion in women compared with men (15,103 versus 50,766 copies/mL, respectively) without differences in CD4 cell count. Initial viral load was a predictor of HIV progression for men but not for women, with women rapid progressors having a median initial viral load of 17,149 compared with 77,822 for

male progressors. A review of 9 cross-sectional and 4 longitudinal studies, which included viral load measurements in males and females, women had greater than twofold lower levels of HIV RNA than men, despite controlling for CD4 counts and time from seroconversion (Gandhi, M. *et al.,* 2002). Although the initial level of HIV RNA was lower in women than in men, the rates of disease progression appear similar (Sterling, T. R. *et al.,* 2001).

Primary HIV Infection

The clinical manifestations of primary HIV infection are similar in women and men. However, a study looking at sex-based differences at the time of seroconversion from Kenya found that women were more likely to be infected with diverse variants of HIV, even at the time of initial infection in comparison to men (Long, E. M. *et al.,* 2000). Viral isolates were obtained during primary HIV infection and prior to seroconversion in both men and women. Both groups had similar frequency of sexual intercourse and sexually transmitted diseases. The difference was quite striking; 20 of 32 women had multiple variants of the virus compared to 0 of 10 for the men, although the clinical significance of this finding and impact on viral load at seroconversion remains unknown at this time.

CLINICAL MANIFESTATIONS IN WOMEN

Pneumocystis jirovecii pneumonia is the most common AIDS-defining infection in women and men, and advanced immunosuppression (CD4 cell count <200/mm3) is the most common AIDS-defining condition in both populations. Rates of other OIs do not differ with a few exceptions (Fleming, P. L. *et al.,* 1993). Kaposi's sarcoma (KS) remains more common in men in the United States, probably related to a higher prevalence of coinfection with the etiologic agent, human herpesvirus type 8. In one study of 107 patients with KS in a large municipal hospital, 11 percent were women; birth outside of the United States was a significant risk factor (Cooley, T.P. *et al.,* 1996). Women with KS tended to present with more advanced and extensive disease, possibly related to delay in diagnosis.

A number of cohort studies have reported a higher incidence of Candida esophagitis in HIV-infected women. Some studies have also found increased rates of bacterial infections and herpes simplex virus (HSV) infections in these women (Lepri, A. C. *et al.,* 1994; Clark, R.A. *et al.,* 1993).

For many women, gynecologic complaints are the initial manifestation of HIV/AIDS. These conditions, which also exist in uninfected women, can occur with higher frequency and severity in women with HIV.

- Candida vaginitis
- Abnormal cervical cytology
- Pelvic inflammatory disease
- Genital ulcer disease (eg, HSV, chancroid, syphilis, idiopathic)
- Menstrual disorders

A number of these conditions, including Candida vaginitis and abnormal cervical cytology, occur at increased rates; others, including HSV and other genital ulcer diseases, may be more difficult to treat. Women with HIV should receive a pelvic examination with appropriate studies including KOH and normal saline examination of any vaginal discharge, testing for chlamydia and gonococcal infections, regular Papanicolaou smears, and other studies as indicated by the complaints and clinical findings.

Candida Vaginitis

Recurrent Candida vaginitis (at least four episodes in one year) may be the initial complaint of women with HIV and is the most common HIV-related gynecological symptom in women. It is also a common condition in women without HIV infection. One prospective study found a higher incidence and persistence but not severity of Candida vaginitis among HIV-infected women compared to women at risk for HIV who did not have the virus (Duerr, A. *et al.,* 2003).

Treatment is generally topical unless the infection does not respond or recurs frequently. Systemic treatment and suppression with imidazoles are effective, although long-term use can lead to colonization with resistant Candida species (Maenza, J. R. *et al.,* 1996). One study in 323 HIV-infected women with CD4 counts <300/mm3 found that intermittent suppression with fluconazole (200 mg PO once weekly) was effective as suppressive therapy without a high risk of resistance (under 5 percent in both the treatment group and control patients not receiving therapy) (Schuman, P. *et al.,* 1997). Weekly fluconazole prevented both vaginal and oropharyngeal candidiasis but not esophageal candidiasis. However, the need for preventive therapy has declined with the advent of more potent and durable ART regimens.

Bacterial vaginosis, genital ulcers, and pelvic inflammatory disease

Other gynecologic infections also occur in women with HIV. Bacterial vaginosis may result in recurrent vaginal discharge. A prospective cohort study conducted over a five-year period found that bacterial vaginosis was both more prevalent and more persistent among HIV-infected women compared to those without HIV (Jamieson, D. J. *et al.,* 2001). HIV-infected women with CD4 cell counts <200/microL were more likely to have both persistent and severe bacterial vaginosis than those with CD4 counts >500/microL. Standard treatment regimens for HIV-infected patients with bacterial vaginosis are recommended (Workowski, K. A., & Berman, S. M. 2006). Bacterial vaginosis may

also be a risk factor for HIV acquisition (Myer, L. *et al.*, 2005).

In comparison, genital HSV infections are increased in frequency and severity in women with HIV. Treatment with oral acyclovir or famciclovir and suppressive therapy for women with frequent recurrences is recommended. Valacyclovir is also active against genital HSV; however, reports of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in patients with advanced AIDS suggest caution in its use. Genital ulcers can be caused by infectious agents other than HSV or may be idiopathic (LaGuardia, K. D. *et al.*, 1995; Risbud, A. *et al.*, 1999). Chancroid (Haemophilus ducreyi infection) is especially common in women from developing countries.

Some studies of pelvic inflammatory disease (PID) in women with HIV have found increased risk of complications while others have not. Early in the epidemic, one study reported that HIV-positive women with pelvic inflammatory disease (PID) presented with fewer signs of acute infection, were more likely to have a delayed response to treatment, and more frequently required surgical intervention (Korn, A. P. *et al.*, 1993). A second survey did not show any increased risk for complications but did document more disease severity on presentation and longer hospital stays for HIV-infected women (Barbosa, C. *et al.*, 1997). However, a third prospective study of 207 women with PID (44 with HIV infection and 163 without) found no differences between HIV-infected and uninfected women in severity of symptoms or response to therapy, regardless of CD4 counts (Irwin, K.L. *et al.*, 2000). Current recommendations are to hospitalize HIV-infected women with PID and to use standard therapy.

Failure to respond, especially in patients with advanced HIV, should prompt a change in treatment, ultrasonographic evaluation for tuboovarian abscess (TOA), and consideration of surgical intervention. As an example, in one study of 133 Kenyan women with PID verified by laparoscopy, the incidence of TOA was significantly higher in HIV-positive women (odds ratio 2.8) and was twice as frequent among HIV-positive women in whom the CD4 cell count was <14 percent (55 versus 14 percent) (Cohen, C. R. *et al.*, 1998).

ABNORMAL CERVICAL CYTOLOGY

Increased risk for low and high-grade squamous intraepithelial lesions (LSIL and HSIL), atypia (ASCUS), and carcinoma in women with HIV infection was first described early in the epidemic. As in women without HIV infection, high-risk types HPV-16 and HPV-18 are highly associated with abnormal cervical smears.

Risk Factors

The increase in risk is related to the degree of immunosuppression (CD4 cell count), coinfection with moderate and high-risk human papilloma virus (HPV) genotypes (Duerr, A. *et al.*, 2001; Jamieson, D. J.*et al.*, 2002), age (Wright Jr, T. C. *et al.*, 1994; Mandelblatt, J. S. *et al.*, 1999), and cutaneous anergy (Harris, T. G. *et al.*, 2007). A study prospectively evaluated a cohort of 328 HIV-infected women and 325 epidemiologically similar HIV-negative women without evidence of SIL by PAP smear or colposcopy for the development of SIL over a three-year period (Ellerbrock, T. V. *et al.*, 2000). The HIV-infected patients were significantly more likely to develop SIL compared to the uninfected women (8.3 versus 1.8 cases per 100 person-years); 91 percent of these lesions were LSIL. None of the patients in either group developed cervical cancer during the follow-up period. Persistent HPV DNA, evidence of infection with multiple HPV types, and younger age were also associated with the appearance of SIL in a multivariate analysis.

The strong association between HIV infection and human papillomavirus (HPV) infection increases with progressive immunosuppression and higher plasma viral loads (Vernon, S. D. *et al.*, 1995; Ahdieh, L. *et al.*, 2000). In one report, HIV-positive women with a CD4 count less than 200/microL were at the highest risk of HPV infection, followed by women with a CD4 count greater than 200/microL and an HIV RNA load greater than 20,000 copies/mL; women with a CD4 count greater than 200/microL and an HIV RNA load less than 20,000 copies/mL were at lowest risk (Palefsky, J. M. *et al.*, 1999). The association between advancing immunosuppression and risk for cervical disease may be related to decreased rates of HPV clearance (Rowhani-Rahbar, A. *et al.*, 2007). In contrast, there is a low risk of cytologic abnormalities in HIV-infected women with relatively preserved CD4 counts who test negative for HPV. Participants in the Women's Interagency HIV Study (WIHS) included 855 HIV-infected patients (mean age, 36 years) and 343 HIV-seronegative patients (mean age, 34 years) who had normal cervical cytology at baseline (Harris, T. G. *et al.*, 2005). The authors concluded that if these results are confirmed by other studies, screening procedures used for HIV-seronegative women who are 30 years or older and have normal cytology and negative HPV screening tests at baseline, may be applicable to HIV-infected patients with CD4+ T lymphocyte counts greater than 500 cells and have no history of abnormal cytology, HPV coinfection, or other risk factors for cervical cancer.

Cervical Neoplasia

Women with HIV are also more likely to present with multifocal disease and to progress more rapidly to cervical cancer. In addition, neoplasia is more likely to recur after treatment in these women, particularly as their CD4 cell counts decline (Maiman, M. *et al.*, 1993). One study found that cervical neoplasia was the leading indication for hysterectomy in HIV-infected women (Massad, L. S. *et al.*, 2007).A

prevalence study in HIV-infected patients also found that high-risk HPV types, other than HPV-16 and HPV-18, are often found in this patient population and are frequently associated with abnormal cervical cytology (Luque, A. E. *et al.,* 2006). Types most commonly associated with high-grade lesions were HPV-52 and HPV-58.

Effect of HAART

There are conflicting study results as to whether HAART has any impact on the risk and natural history of ASCUS, LSIL, and HSIL, and carcinoma in women with HIV. However, some studies are beginning to show decreased risk of progression of these abnormalities in women responding to HAART, although longer follow-up is clearly needed (Taylor, G. *et al.,* 2004; Xi, L. F., & Kiviat, N. B. 2004). In a retrospective analysis of all incident malignancies occurring in 1996 to 2005 among 2566 patients in an urban clinic in Maryland, cervical cancer incidence remained statistically unchanged at 1 to 2 per 1000 person-years (Long, J. L. *et al.*, 2008).

Screening

Since HIV-infected women have a much higher risk of HPV infection and cervical cancer than do HIV uninfected women, cervical screening is of paramount importance worldwide. The scale-up of ART programs in resource-poor countries may also provide an opportunity to develop cervical cancer screening programs for women with HIV as well as for uninfected women in areas that previously did not have the needed infrastructure (Franceschi, S., & Jaffe, H. 2007).

The performance of Papanicolaou smears as a screening tool for cervical disease in women with HIV is now generally considered to be adequate for most women. Although early studies reported a low sensitivity to detect cervical lesions, subsequent data have shown similar performance as in HIV-negative women:

- One multicenter, prospective cohort study evaluated the accuracy of Pap smears versus colposcopy and biopsy in 284 women, 189 of whom were HIV-infected (Anderson, J. R. *et al.*, 2006). Overall, the correlation of cytologic findings with colposcopic and/or histologic findings was high. Nineteen HIV-infected patients with a normal Pap smear had abnormal histology; however, 95 percent of those with discordant results had an abnormal Pap smear within one year of follow-up, supporting the accuracy of cytologic examinations in HIV-infected women.

However, even mildly abnormal cytology is a potential sign of cervical neoplasia and an indication for colposcopy (Wright Jr, T. C. *et al.*, 1996).

- In a study of 774 HIV-infected patients and 480 HIV-uninfected women in the United States, detection of atypical squamous cells of undetermined significance (ASCUS) was more common in HIV-infected women (odds ratio 1.6; 95% CI 1.3-2.0) after adjustment for human papillomavirus (HPV) infection (Duerr, A. *et al.,* 2006). Among women with ASCUS, 60 percent of HIV-infected and 25 percent of HIV-uninfected women developed squamous intraepithelial lesions (SIL). The risk of developing SIL among HIV-infected women with ASCUS was higher in those with a CD4 count <200 cells/microL.

Although HPV DNA testing is available, there are no formal recommendations that exist for use of this test in HIV-seropositive women (Kaplan, J. *et al.,* 2010). A study of 101 HIV-infected women with CD4 counts <500/mm3 found that HPV DNA assays did not add to Papanicolaou smear in the detection of cervical intraepithelial neoplasia (Cohn, J. A. *et al.*, 2001). The sensitivity, specificity, and positive predictive values were 85, 42, and 35 percent, respectively, for HPV DNA assays compared to 63, 74, and 47 percent of Papanicolaou smear. However, a cost-effectiveness analysis found that adding HPV DNA screening to two cervical cytology smears during the first year after an HIV diagnosis was found to be more cost-effective than annual screening alone.

Cervical cytology screening every six months for women with detectable HPV DNA and annual screening for all others who have not had a previously abnormal Pap smear was the recommended approach based upon this analysis. These conflicting data suggest that further evaluation of this test as a routine clinical tool is needed (Goldie, S. J. *et al.*, 2001; Keiser, O. *et al.,* 2006).

Colposcopy should be reserved for women with abnormal cytology, including ASCUS (Conley, L.J. *et al.,* 1994). The appropriate management of abnormal cervical cytology and neoplasia, including optimal ablative therapy, role of postablative treatment with topical agents, and timing and method of follow-up, is still largely unknown. However, close follow-up by a provider with experience in HIV-related cervical disease is essential. The potential role of HPV vaccines in preventing cervical neoplasia in HIV-positive women is an area of active investigation.

VULVAR AND PERIANAL PATHOLOGY

A prospective study of a cohort of 925 women found that vulvar and perianal lesions with the potential to progress to atypia also arose more commonly in HIV-positive compared to HIV-negative women (Conley, L. J. *et al.*, 2002). Intraepithelial neoplasia of the vulva and/or perianal region occurred in five (1 percent) of HIV-infected patients compared to none in

the HIV-negative group. As with cervical pathology, HIV infection, HPV infection, and decreased CD4 counts were all associated with vulvovaginal and perianal lesions. Frequent injection drug use was also a risk factor for these lesions.

Another prospective cohort study of 1562 HIV-infected and 469 women without HIV also found an increased incidence of genital warts and vulvar intraepithelial neoplasia among those with HIV infection (Massad, L. S. *et al.*, 2004). The administration of HAART decreased the risk of developing these conditions. Therefore, a pelvic examination should include careful inspection of the vulvar and perianal area as well as the Pap smear and cultures.

MENSTRUAL ABNORMALITIES AND MENOPAUSE

Menstrual abnormalities, including early menopause, have been described in a number of women with HIV infection, but the rates and patterns are not well studied (Schoenbaum, E. E. *et al.*, 2005). One cohort study found no difference in menstrual patterns between 197 HIV-infected women and 189 HIV-negative controls (Ellerbrock, T. V. *et al.*, 1996).

As the population with HIV infection ages, the number of women approaching and experiencing menopause is growing. The risk-benefit ratio of hormonal replacement for these women remains to be described, as well as potential pharmacologic interactions between protease inhibitors and estrogen replacement. At this time, the decision about hormonal replacement should be made individually after education and counseling of the woman and determination of risk factors for cardiac disease, osteoporosis, cancer, and other conditions.

GENITAL TRACT SHEDDING OF HIV

Several studies have detected HIV-1 proviral DNA, cell-free RNA, and/or cell-associated RNA in the female genital tract with variable rates of detection (Quinn, T. C.*et al.*, 2000; Cu-Uvin, S. *et al.*, 2000). In one study of 97 women, paired plasma and cervical lavage specimens were collected to determine the patterns and predictors of genital tract HIV RNA during a 36 month period (Cu-Uvin, S. *et al.*, 2006). The strongest predictor of HIV RNA detection in cervicolavage fluid was a plasma viral load of more than 2.6 log (10) copies/mL.

The effect of antiretroviral therapy on genital tract shedding of HIV has been an active area of investigation. In a study of 20 treatment-naive women, ART was associated with significant decreases in the quantity of HIV RNA in cervical and vaginal secretions within two to four days of treatment initiation (Graham, S. M. *et al.*, 2007). However, in another study of 290 women, despite the fact that all enrolled participants had an HIV RNA level of <500 copies/mL, 15 percent still had detectable HIV RNA in their cervical specimens (Neely, M. N. *et al.*, 2007). Potential risk factors in other studies for shedding of HIV in the genital tract may include HSV infection. The impact of these findings on HIV transmission from mother to child or to sex partners is yet unknown.

PRIMARY CARE

Primary care for HIV-infected women raises some special issues.

HIV therapy

The efficacy of antiretroviral therapy in women appears comparable, or with certain antiretrovirals, even superior, to the response in men (Prins, M. *et al.*, 2005; Sterling, T. R.2001):

- After controlling for potential confounders, there were no significant sex differences in virologic, immunologic, or clinical outcomes after starting HAART in a large multicenter study (Moore, A. L. *et al.*, 2003).
- In a prospective, observational, multicenter study from Spain, 1885 men and 735 women were evaluated over a 12-month period after initiating ART with a nelfinavir-containing regimen (Collazos, J. *et al.*, 2007). In a multivariate analysis, women had a better overall immunologic and virologic response to ART than men.

However, there are some differences in medication tolerability (Collazos, J. *et al.*, 2007). Data from a large urban clinic found that women were more likely to have side effects related to HIV therapy and so discontinue their medications (Lucas, G. M. *et al.*, 1999). In clinical trials, women were less likely than men to tolerate ddI, and had more nausea, vomiting, and fatigue with ritonavir (Currier, J. S. *et al.*, 2001; Currier, J. S.*et al.*, 1997) . HIV-infected women also have a higher incidence of rash in association with nevirapine or efavirenz administration compared to men (Bersoff-Matcha, S. *et al.*, 2001; Mazhude, C. *et al.*, 2002). Higher rates of severe hepatotoxicity have also been described in pregnant women with CD4 counts >250 cells/mL who were taking nevirapine. These gender-based differences may reflect differences in pharmacokinetics due to body weight or drug metabolism, hormonal differences, or other factors.

There is no clearly established gender difference in the frequency of lipodystrophy or diabetes as a consequence of antiretroviral therapy. However, some studies have found increased risk of fat accumulation versus lipoatrophy in women and decreased risk of hyperlipidemia compared with men (Gervasoni, C. *et al.*, 1993). Women may also be at an increased risk of developing lactic acidosis (Boxwell, D. E., & Styrt, B. A. 1999, September).

Adherence is a major barrier to success with HAART for women and men. Most studies to date have not found a gender-based difference in adherence, but women may have higher rates of other factors that present barriers to successfully taking these regimens. These may include competing needs of other family members with HIV and other infections, fear of disclosure in their own household, side effects, and body changes related to the lipodystrophy syndrome. Adherence support programs should be designed to address the multiple challenges for women on HIV therapy.

In recent guidelines for the treatment of HIV/AIDS by the International AIDS Society-USA and DHHS, there are no gender-specific differences in recommendations for the treatment of women with HIV/AIDS, although consideration of changes in treatment guidelines based upon viral load in women early in disease is discussed (DHHS. 2008; USPHS/IDSA. 2002). Exceptions are women of childbearing potential who require careful follow-up when given hydroxyurea and efavirenz, due to their suspected teratogenicity, liquid amprenavir, or thalidomide because of congenital malformations.There are no gender-based differences in recommendations for monitoring CD4 cell counts and plasma viral load or for the prevention and treatment of opportunistic infections (Williams, A., & Friedland, G. 1997). When initiating HAART in women of childbearing age, a baseline pregnancy test should be performed, particularly if any category D medications are being prescribed (such as efavirenz).

Health Maintenance

The care of women with HIV infection must incorporate primary care into their state-of-the-art HIV care. As women survive longer with HIV, other comorbid conditions will increase with age, including cardiac disease, diabetes, and breast cancer. Medical care must include routine medical screening (mammograms, breast self-examination, nutritional counseling for osteoporosis, smoking cessation, etc) and a recognition that not all complaints are necessarily HIV-related. The complex psychosocial needs of many women with HIV often requires a multidisciplinary team to address issues such as housing, substance abuse, and mental illness, either on-site or by linkage with other institutions or community-based organizations. One group found that case management significantly improved care and use of HIV therapies for individuals with HIV (Katz, M. H., Cunningham, *et al.*, 2001).

CHOICE OF CONTRACEPTION

The choice of contraception for a woman with HIV is often complicated and must incorporate issues related to:

- Specific contraceptives and their efficacy in preventing pregnancy
- Prevention of transmission of HIV and other sexually transmitted diseases
- Drug interactions between certain antiretroviral agents and hormonal contraceptives

Women should be counseled that HIV can be transmitted even when the HIV-infected person has a very low HIV viral load. Due to the risk of HIV and other STD transmission, a form of barrier contraception is always recommended. Other factors may also influence a woman's choice of contraception, including whether she has been able to disclose her HIV status, fear of domestic violence, and other medical conditions. The best practice is dual contraception with a hormonal agent to prevent pregnancy and condoms to reduce the transmission of the virus.

Hormonal Contraceptives

Hormonal contraceptives (eg, oral, injectable) are effective reversible agents for the prevention of pregnancy in women.

Drug Interactions

While reliability does not appear to be reduced by HIV infection, efficacy can be compromised by drug interactions between estrogen and certain antiretroviral agents and other medications commonly used in individuals with HIV including:

- Non-nucleoside reverse transcriptase inhibitors (specifically efavirenz and nevirapine)
- Protease inhibitors
- Other medications which may be needed to treat HIV-related complications
- Rifampin

Zidovudine pharmacokinetics were not affected by either oral norethindrone/ethinyl estradiol (Ortho Novum) or intramuscular depot medroxyprogesterone acetate (Depo-Provera) in a study of 20 HIV-infected women (Aweeka, F. T. *et al.*, 2006). Although no known interactions with progesterone-based contraceptives have been described, providers are cautioned to check for new information as research continues. A number of online resources are available which provide up-to-date information on drug interactions.

Effect on HIV Disease Progression

Conflicting results have been published on the effects of hormonal contraception on HIV disease progression (Stringer, E., & Antonsen, E. 2008). In two large studies, hormonal contraception was associated with more rapid CD4 T-cell depletion (Stringer, E. M. *et al.*, 2007; Lavreys, L. 2006); however, other smaller studies did not support these findings (Richardson, B. A. *et al.*, 2007; Cejtin, H. E. *et al.*, 2003). All of these trials were performed in women who were not taking ART.

Susceptibility to HIV

Over the past decade, there have been conflicting data on whether or not hormonal contraception may influence susceptibility to HIV acquisition. Several concerns regarding methodological issues have been raised regarding these observational data (Baeten, J. M. *et al.,* 1995). Study of this area is also difficult due to differences in sexual behaviors between users and non-users of hormonal contraception. In one study, hormonal contraceptive use was not associated with susceptibility to HIV infection. However, in the subgroup of women who were HSV seronegative, acquisition of HSV infection was associated with increased risk of HIV transmission. This finding has been seen in other cohorts and may represent a marker for unsafe sexual practices rather than an impact of hormonal contraception. This study highlights the need to examine HSV serostatus, and other potential confounders, in any further studies of contraceptive use.

Intrauterine contraceptive Device

The intrauterine contraceptive device also provides effective contraception, but is not widely used in HIV-infected women because of concerns about pelvic infection and increased blood loss (Sinei, S. K. *et al.,* 1998).

CONDOMS

Use of male condoms, although less efficacious for the prevention of pregnancy, has been proven to reduce transmission of HIV and other STDs (De Vincenzi, I. 1994; Weller, S. C. 1993). Acceptance of male condom use may be limited by fear of disclosure, refusal by the partner and many other issues. Although the data are limited, it is likely that the female condom, when used properly, has similar efficacy as the male condom and is attractive as a woman-controlled method (Fontanet, A. L. *et al.,* 1998). While cost, convenience and esthetics have limited widespread use of the female condom; however effective interventions to increase the use of barrier methods in women and men are increasingly available. The diaphragm and cervical cap are associated with a decreased risk of gonorrhea, Chlamydia and trichomonas infections, and PID (Cates Jr, W., & Stone, K. M. 1992; Kelaghan, J. *et al.,* 1982). Much of the protective effect is probably due to the concomitant use of spermicides, and no impact on HIV transmission has been consistently shown.

Microbicides

Vaginal microbicides, which are also spermicidal, are an area of ongoing research.

HIV AND PREGNANCY

Since many women with HIV are diagnosed during pregnancy and women with HIV may choose to become pregnant, primary care providers should have a basic understanding of the current state of knowledge regarding HIV and pregnancy (Minkoff, H. 2003). In addition, a frank discussion about pregnancy plans is important when determining optimal ART management, as some drugs, such as efavirenz are teratogenic and therefore should not be used in women who are considering pregnancy or not willing to use effective contraception. Attainment of a stable, maximally suppressed viral load prior to conception is recommended for HIV-infected women who are on ART and considering pregnancy (Public Health Service April 29, 2009).

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