2007-2010 WIHS Findings: Lay Language Summaries for the Community
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Cancers/Gynecology
**Title:** Clinical reactivations of herpes simplex virus type 2 infection and human immunodeficiency virus disease progression markers

**Lay Language Summary:** Individuals with HIV infection are often found to be co-infected with herpes simplex virus type 2 (HSV-2) - a cause of genital herpes. Genital herpes has a highly variable clinical course. Some individuals have severe forms of HSV-2 infection and frequently develop painful genital lesions while others experience less severe or mild forms that can easily go unnoticed. In rare situations, the herpes virus can spread to other parts of the body and cause devastating complications in many internal organs. The effect of such variability in the course of HSV-2 infection on the course of HIV is not clear. This study looked at the association between the type (symptomatic vs. asymptomatic) and severity (frequency of symptomatic reactivations) of HSV-2 infection with HIV disease progression markers (plasma HIV RNA and CD4+ T cell count) among HAART naïve HIV/HSV-2 coinfected participants. This study may help enhance our understanding and improve management of HSV-2 infections in HIV infected and at risk for HIV infection in women.


**Title:** Marijuana use is not associated with cervical human papillomavirus natural history or cervical neoplasia in HIV-seropositive or HIV-seronegative women

**Lay Language Summary:** Marijuana use is associated with higher risk of head and neck cancers caused by human papillomavirus. It is unclear whether marijuana could directly cause these cancers or could increase human papillomavirus persistence and thus increase cancer risk. We looked at the effect of marijuana use on cervical HPV infection and cervical pre-cancer. Current marijuana use was not associated with any increase in cervical HPV infection or cervical pre-cancer risk. The results were similar among HIV-seropositive and HIV-seronegative women, and in tobacco smokers and non-smokers. These data suggest that marijuana use does not increase the risk of cervical HPV persistence or cervical disease.

Title: HIV as a risk factor for lung cancer in women: data from the Women's Interagency HIV Study

Lay Language Summary: Lung cancer, which is also known to be caused by smoking. We looked at all lung cancer cases in the WIHS, over the first 9 years of follow-up, and compared the risk of lung cancer among HIV infected women, versus HIV negative women in the WIHS. A total of 11 cases of lung cancer were diagnosed, including 9 cases in HIV positive women, and 2 in HIV negative. We then compared the risk of lung cancer in the WIHS with the expected lung cancer rates in the population as a whole. There was a clear increase in lung cancer among the HIV + women, but there was also a similar increase among the HIV-negative WIHS women, suggesting that the increase was NOT due to HIV, per se, but due to some other factor(s). All lung cancer patients in the WIHS had history of smoking, with an average of 22 pack years of smoking prior to developing lung cancer. WIHS women, in general, had a greater likelihood of smoking than other women in the United States, in general. We conclude that the increase in lung cancer in HIV infected women is not due to the HIV, but rather, is due to the strong smoking history in the group. Smoking cessation programs are likely to be associated with improved survival among HIV infected women in the future.


Title: Knowledge of cervical cancer prevention and human papillomavirus among women with HIV

Lay Language Summary: In 2006, we asked 1,588 WIHS women what they knew about cervical cancer prevention, including Pap testing, colposcopy, the human papillomavirus (HPV, the virus that causes cervical cancer), and the HPV vaccine, which can prevent cervical cancer. Most women in WIHS were uninformed about many aspects of cervical cancer prevention. Of those who had heard of HPV vaccination, most would recommend it to relatives and friends. Most had heard of the HPV vaccine through news and advertising, not through clinicians. Only completing high school distinguished women who knew about cervical cancer prevention from those who did not. Women with and without HIV had similar knowledge. Clinicians should develop effective strategies to educate patients about cervical cancer prevention.

**Title:** Histologic Correlates of Glandular Abnormalities in Cervical Cytology Among Women With Human Immunodeficiency Virus

**Lay Language Summary:** Sometimes cervical cancers can grow from cells in the cervical lining, the glands. These cancers can be picked up by Pap tests. Glandular abnormalities on Pap are serious but rare, and for that reason they haven't been studied much in HIV+ women. We looked at these glandular changes. They occurred in less than 1% of HIV+ women, at a rate similar to HIV- women. However, HIV+ women with lower CD4 counts were more likely to have glandular abnormalities on Pap. Since 2001 there have been national guidelines that recommend colposcopy and biopsy for women with glandular abnormalities on Pap, and many WIHS women did not have that done (though many were diagnosed with glandular abnormalities on Pap before 2001). There is room for improvement in how to handle these uncommon but serious Pap problems. As a result of this study, WIHS has reviewed its colposcopy protocol and is developing mechanisms to improve biopsy rates for women with glandular abnormalities on Pap.


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**Title:** Marginal and mixed-effects models in the analysis of human papillomavirus natural history data

**Lay Language Summary:** This paper provides an overview of current mathematical (statistical) methods that can be used to better study human papillomavirus (HPV), the cause of abnormal Pap smears.

Title: Long-term incidence of cervical cancer in women with human immunodeficiency virus

Lay Language Summary: Women with HIV often are infected with HPV, the virus that causes cervical cancer, and they often have abnormal Paps, a test for cervical precancer. These facts have led many to become concerned that women with HIV will develop cervical cancer at high rates. In fact, cervical cancer is an AIDS-defining illness. WIHS has shown that after 5 years of follow-up, women with HIV don't develop cervical cancer at higher rates than HIV-negative women, but whether longer observation shows a higher cervical cancer risk isn't known. In fact, this paper shows that risk remains low. We only found 3 women with cervical cancer in the first 10 years of WIHS. We believe this is because WIHS women are screened and treated for precancerous changes effectively. However, cervical cancer can be lethal even when diagnosed in WIHS. It is important for women to continue to participate in Pap testing and colposcopy.

Incidence and risk factors for verrucae in women

The WIHS HIV-positive women were more likely to develop oral and anogenital warts over 8 years of study follow-up than HIV-negative women. HIV-positive women were at increased risk for skin warts if they were White race. HIV-positive women were at increased risk for anogenital warts if they were enrolled in the WIHS in the years 1994 or 1995, were HPV seropositive at their baseline WIHS visit, were younger, smoked cigarettes, had lower CD4 cell counts, and higher viral load. Use of highly active antiretroviral therapy (HAART) did not alter the risk of developing skin or anogenital warts.


Insulin-like growth factor axis and oncogenic human papillomavirus natural history

This study looks at the association between a hormone that stimulates cells to replicate, called insulin-like growth factor (IGF)-I, and the risk of developing an infection with human papillomavirus (HPV), the virus that can cause cervical cancer if abnormal Pap smears go untreated. We found that high IGF-I levels and low levels of the protein that binds IGF-I, called IGF binding protein (IGFBP)-3 were associated with higher risk of HPV infection, greater persistence of HPV infection, as well as higher rates of abnormal Pap smears.

Title: High-grade cervical disease in adolescents with HIV

Lay Language Summary: Young women often contract human papillomavirus (HPV) infections through sexual intercourse. HPV is the virus that causes cervical cancer and abnormal Pap results. Most young women clear HPV through activation of the immune system, but young women with HIV may have immune problems that limit their ability to get rid of HPV. A prior study (REACH) suggested that many young women with HIV have HPV infections that rapidly progress to advanced precancerous changes. We set out to verify this, but we found that most young women (<21 years old) in WIHS have a low risk for developing serious precancerous changes. This suggests that women with borderline Paps and early cervical dysplasia can be observed without treatment.


Title: Squamous cervical lesions in women with HIV: Long-term follow-up in the Women's Interagency HIV Study

Lay Language Summary: We reviewed Pap results collected from WIHS women over 10 years. Abnormal results were common, but high grade results-the ones that suggest a significant risk for developing cancer-were found in only 4 of every 1000 women every year. The risk for having an abnormal Pap actually went down over time.

Title: The relationship between cocaine use and human papillomavirus infections in HIV-seropositive and HIV-seronegative women

Lay Language Summary: Many HIV-infected women have infections within human Papilloma virus (HPV), the virus that can cause cervical diseases, including cancer. Many HIV infected women have also used cocaine or crack. In animals, cocaine has been shown to affect the ability to combat infections. It is not known whether humans who use cocaine may have more infections with HPV or whether they have more trouble clearing HPV. Therefore we compared cocaine-using women in the WIHS with women who did not use cocaine to see if they differed in the course of HPV infections. We found that women who used cocaine had more HPV infections. They also took longer to clear (get rid of) those infections. There was also some suggestion that the more cocaine a woman used, the worse the problem was.


Title: Six-month natural history of oral versus cervical human papillomavirus infection

Lay Language Summary: Human papillomavirus (HPV) infection causes some oral cancers but what happens between oral HPV infection and oral cancer development is not known. Samples from the mouth and cervix were collected at 2 visits 6 months apart in 138 HIV-positive and 63 HIV-negative women. We measured HPV DNA for 37 types of HPV in oral and cervical samples. Oral HPV infection was less common than cervical HPV infection. Twenty seven percent of subjects had an oral HPV infection at one or both visits compared to cervical HPV infection in 68% of subjects. HIV positive women were more likely than HIV-negative women to have an oral or cervical HPV infection detected during the study. Oral HPV infections at the first visit were equally likely as cervical HPV infections to still be detected at the second visit six months later. Current smokers, older age, severe HIV related immunosuppression and HAART therapy made oral (but not cervical) HPV infections more likely to remain six months later. This study shows we can study oral HPV infection at serial visits. This study suggests the natural history of oral and cervical HPV may differ.

**Title:** Association of cutaneous anergy with human papillomavirus and cervical neoplasia in HIV-seropositive and seronegative women

Lay Language Summary:
Anergy testing evaluates the ability of the immune system to respond to particles of microorganisms that it should recognize because it has encountered them before. If there is no response then this indicates the immune system is not working properly. The relationship between the ability of the immune system to respond to these particles and human papillomavirus (HPV), the virus that causes cervical cancer, is unknown. We evaluated this association in women in the WIHS cohort (1029 HIV-seropositive and 272 HIV-seronegative women) that had anergy test results available. Women whose test showed a poor immune response were more likely to have cervical lesions at that same visit and they were more likely to have a new HPV infection detected at a later visit. These results suggest that anergy testing may measure aspects of immune function that are important to the control of HPV. Future studies should evaluate whether a test using pieces of the HPV virus might be able to identify HIV seropositive and other women at high risk of HPV-associated cervical lesions.


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**Title:** Hysterectomy among women with HIV: indications and incidence

Lay Language Summary:
Hysterectomy is the second most common major surgical procedure among U.S. women, but little is known about how often and why it is done for women with HIV. We reviewed cases of hysterectomy in WIHS. Operative notes were obtained when possible. We found 106 hysterectomies in HIV+ women and 24 in HIV- women. We found that HIV+ women have hysterectomy at a rate of 7.7/1000 person-years, compared to 5.3/1000 person-years in HIV women, with a trend toward more hysterectomies in HIV+ women. Most hysterectomies in HIV+ women were done for cervical disease. Women with HIV were more likely to have had an abnormal Pap before surgery and less likely to have the cervix left in at the time of hysterectomy than HIV- women.

Title: **Outcomes After Treatment of Cervical Intraepithelial Neoplasia Among Women With HIV**

Lay Language Summary:

We evaluated the results of treatment for precancerous cervical disease in 185 women from WIHS and HERS (170 HIV+, 15 HIV-). Six months after treatment, cervical disease was back in 45%. Successful treatment was less likely in women with lower CD4 counts and those with DNA from HPV, the virus that causes warts and cervical cancer. Among women who were disease-free at 6 months, only 34% were disease-free after 5 years. Recurrences in these women were more likely in HIV+ women, those with high-grade cervical precancer, and those with HPV at their posttreatment visit. Most six-month failures and later recurrences were low grade, but one woman developed cancer 4.2 years after treatment. We conclude that treatment failure and recurrence are common in women with HIV but are usually low grade. Cancer is much less common but can occur despite treatment, and careful observation is needed.


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Title: **Biologic markers of ovarian reserve and reproductive aging: application in a cohort study of HIV infection in women**

Lay Language Summary:

At present a variety of methods are used to assess the functioning of the ovaries, but they require that women either have an ultrasound or have their blood drawn at a particular time in their menstrual cycle. Recent studies indicate that Müllerian inhibiting substance (MIS) (also known as Anti-Müllerian hormone-AMH), may be the most accurate, simple and noninvasive method for determining ovarian reserve (the number of eggs remaining in the ovary). This cross-sectional study tested serum samples obtained from HIV infected and uninfected WIHS participants who were not in menopause or taking female hormones. The study results showed that MIS was an accurate marker of ovarian reserve, regardless of the timing of the blood sample. Also the researchers did not find that HIV infection was associated with early decreases in ovarian function.

There are 3 common types of infections that affect the vagina. These are bacterial vaginosis (caused by an imbalance in the normal bacteria in the vagina), Candida vaginitis (yeast infection), and trichomoniasis (caused by a protozoa that is sexually transmitted). These infections can cause local discomfort, but more importantly bacterial vaginosis can increase the risk of early labor in pregnant women and these three types of infection might increase the likelihood of a woman becoming HIV infected or potentially of a HIV-infected woman transmitting it to her partner. We used the WIHS cohort to compare the methods of diagnosing these 3 infections in the HIV-infected women in the WIHS to the HIV-uninfected women. We did not find any major differences in how the tests behaved. We did find that for diagnosing a yeast infection examining a smear of vaginal fluid under a microscope was more likely to agree with the results of a Pap smear finding yeast in HIV-infected women compared to HIV-uninfected women. In addition this relationship was stronger in women with a CD4 cell count of <200/m3. We also found that the tests that required a health care provider to interpret performed less well at the beginning of the study. We believe this was due to provider inexperience at the beginning of the study.

Co-Morbidities

Cardiovascular.................19-25
Metabolic.............................26-28
Neurocognition.....................29
Other..................................30-31
Our bodies constantly react with oxygen that we breathe in as our cells produce energy. As a result of this activity, special chemicals (molecules) are made in the body called free radicals. Free radicals can bump into other molecules inside of cells and cause damage to the cells. This type of damage is called oxidative stress. Oxidative stress may lead to aging and be part of the cause of many diseases such as cancer and heart disease. We measured a substance in the blood called F2-isoprostanes, which is one way of measuring oxidative stress. We found that HIV+ women at the Bronx site of the WIHS who had hepatitis C infection, larger waist sizes, and abnormal levels of a liver blood test had higher amounts of F2-isoprostanes in the blood. Women with higher amounts of F2-isoprostanes also tended to have higher amounts of a substance in the blood called homocysteine, which may increase their chances of having heart disease. However, when we looked at the thickness of the carotid artery in the necks of these women, which is a way of measuring the risk of heart disease, women with higher amounts of either F2-isoprostanes or homocysteine did not have thicker carotid arteries. Based on this study, we think that some women with HIV have higher amounts of oxidative stress (F2-isoprostanes) in their bodies, which could lead to future health problems. More research is needed to see if it is useful to measure the amount of F2-isoprostanes in the blood of women with HIV.

Title: The association of HIV infection with left ventricular mass/hypertrophy

Lay Language Summary: Increased size of the left side of the heart (the side that pumps blood to the body) is called LV Hypertrophy (LVH) or abnormally increased left ventricular mass (LV Mass). LVH or increased LV Mass is associated with increased cardiovascular health problems including heart attack, congestive failure of the heart and stroke. Previous studies have found increased and decreased LV mass among HIV infected patients. None of these studies specifically address minority women and none have determined how common LVH (increased left heart size) is. The present study compared LV mass among a group of HIV-infected and un-infected women in the WIHS cohort and determined the prevalence of LVH in this group. Results of this study are that HIV-infection is associated with increase in LV mass but not significant increase in the prevalence of LV hypertrophy. The study also found that among HIV infected women, higher LV mass was not associated with severity of immunosuppression during the infection as measured by a history of AIDS-defining illness (ADI) or a history of nadir CD4+ count <200cells/μl or with the use/duration of highly active retroviral therapy (HAART).


Title: Plasma Homocysteine Is Not Associated With HIV Serostatus or Antiretroviral Therapy in Women

Lay Language Summary: Women living with HIV infection may have a greater chance of developing heart disease than women without HIV infection. There may be a number of different reasons for heart disease developing in HIV+ women, including things related to HIV itself and the drugs used to treat HIV. We measured a substance in the blood called homocysteine. In general, people without HIV who have high levels of homocysteine appear to have a greater chance of developing heart disease. We found that HIV+ women at the Bronx site of the WIHS had similar amounts of homocysteine in their blood compared to HIV- women. We also found that among the HIV+ women, being on medicines to treat HIV did not seem to affect the amount of homocysteine. HIV+ women with lower blood levels of two vitamins, vitamin B12 and folate, had higher homocysteine levels. Also, women with lower percents of (CD4) T- cells in their blood and those with reduced kidney function had higher homocysteine levels. Based on this study, we think that women with more advanced HIV infection and women who do not have enough folate in their diets tend to have higher homocysteine levels. However, we could not tell from the study whether HIV+ women with higher homocysteine levels they have a greater chance of developing heart disease.

Recent studies suggest that some people with HIV infection may have an increased chance of developing cardiovascular diseases, which are diseases affecting the heart and blood vessels. In this study, we made measurements of the thickness of arteries in the neck using ultrasound, which is a test that allows us to detect early-stage cardiovascular disease before it causes symptoms or becomes life-threatening. The study included HIV-infected and HIV-uninfected men and women participating in the WIHS and MACS studies. We found that compared to HIV-uninfected women, some subgroups of HIV-infected women tended to have more early-stage cardiovascular disease in their neck arteries, and other subgroups of HIV-infected women tended to have less early-stage cardiovascular disease in their neck arteries. Regardless of whether they were HIV-infected or HIV-uninfected, we found more early-stage cardiovascular disease in older people, African-Americans, overweight persons, those with high blood pressure and abnormal lipids (blood fats), smokers, and diabetics. These factors were at least as important as HIV status, antiretroviral medications, or other HIV-related variables in determining which men and women had increased risk of cardiovascular disease. The conclusions of this study were that it remains unclear whether HIV-infected persons as a whole may have more cardiovascular disease than HIV-uninfected persons.

Title: Interarm blood pressure differences in the women's interagency HIV study

Summary:
Rates of high blood pressure ranging from 8%-32% have been reported in people with HIV. Large inter-arm blood pressure differences (IABPD) are associated with increased risk for cardiovascular problems in non-HIV infected individuals. In order to study this further, we measured blood pressures twice in both arms of a total of 335 participants at the Brooklyn WIHS site (238 HIV+; 97 HIV -). Twenty-six percent of subjects had systolic IABPD >10 mmHg and 6% had systolic IABPD >20mmHg. Fifteen percent of subjects had diastolic IABPD >10mmHg. Differences in inter-arm BP were not associated with HIV serostatus, CD4+ cell count, and use of highly active antiretroviral therapy. Systolic IABPD>20mmHg was associated with obesity, hypertension, and LDL cholesterol above 160. Bilateral arm BP measurement increased the classification of high/uncontrolled BP from 10% (right arm only) to 15%. We conclude that: 1) systolic and diastolic IABPD are common; 2) systolic IABPD are related to cardiovascular risk factors but not to HIV related factors; and 3) taking BPs in both arms is important for the detection and management of hypertension as well as for accurate cardiovascular risk assessment.

Citation: Lazar J, Holman S, Minkoff HL, DeHovitz JA and Sharma A. Interarm blood pressure differences in the Women's Interagency HIV Study. AIDS Res Hum Retroviruses 2008;24:695-700.
Title: Ten-year predicted coronary heart disease risk in HIV-infected men and women

Recent studies suggest that some people with HIV infection may have an increased chance of developing cardiovascular diseases, which are diseases affecting the heart and blood vessels. We examined information on "risk factors" such as smoking, diagnoses of high blood pressure, diabetes, and levels of fats ("good" and "bad" cholesterol) in the blood that may affect risk of cardiovascular disease. Compared with HIV-uninfected men, HIV-infected men tended to have more of these cardiovascular risk factors. However, HIV-infected women did not have increased cardiovascular risk factors overall compared with HIV-uninfected women. HIV-infected individuals who had low income and who used protease inhibitor-based medication regimens tended to have more cardiovascular disease risk factors. Relatively few HIV-infected men and women in the MACS and WIHS studies had what doctors consider high risk for cardiovascular disease, based on their information about smoking, diagnoses of high blood pressure, diabetes, and levels of fats ("good" and "bad" cholesterol). However, it is important to address the high rate of smoking and obesity found in this study; improving these factors may not only decrease cardiovascular risk, but may also have good effects on HIV disease progression.

High blood pressure (hypertension) has been associated with development of heart disease, stroke, kidney failure and other serious consequences. Hypertension has been studied in HIV infected persons, but the results have not been consistent, with some studies showing an increase in hypertension in HIV infected people, while other studies have shown no such increase. Aside from the role of HIV, per se, highly active anti-retroviral therapy (HAART) has also been shown to be associated with high blood pressure in some studies. In order to determine the risk of hypertension among our WIHS participants, we studied the blood pressure results among our HIV positive and negative women, from visit 13 to visit 16, after the time when a standardized blood pressure protocol was begun in the WIHS. We found no difference in the occurrence of hypertension among our HIV positive women, when compared with the HIV negatives. Also, we found that CD4 count or HIV viral load had no influence on the presence of hypertension. We also found no relationship between use of HAART itself, or any component of HAART medicines, on the presence of high blood pressure. We conclude that hypertension is not associated with HIV itself, nor with the antiretroviral medications used to treat HIV. In contrast, the factors associated with hypertension in the WIHS cohort were "traditional" factors, such as older age, African American race, or higher body weight.

Peripheral arterial disease in HIV-infected and uninfected women

HIV infection and antiretroviral therapy have been associated with cardiovascular disease including atherosclerosis (narrowing of the arteries). Peripheral arterial disease (PAD) occurs when the arteries of the arms and legs get narrow. PAD can lead to disability and limb loss and is linked to an increased risk of heart attacks. The purpose of this study was to determine how common PAD is among the WIHS women and risk factors that are associated with it. We assessed PAD using ankle-brachial index (ABI) measurement in HIV-infected and uninfected women. ABI measurement involved taking blood pressure readings in both arms and both legs. A total of 335 subjects enrolled in the Women's Interagency HIV Study at the Brooklyn site were included. The prevalence of low ABI (<0.9) was 0.9% (n=3) and the prevalence of high ABI (>1.40) was 6.9% (n=23). The remainder of the subjects, 92.2% (n=309), had normal ABIs on both sides of their bodies. The prevalence of low ABI was too low to allow for risk factor analysis. We found that low and high body mass index (BMI) as well as current cigarette smoking were associated with high ABI. HIV serostatus, age, race, HIV exposure risk category, high blood pressure, diabetes, and elevated blood fat levels were not associated with high ABI. Although, the prevalence of PAD (defined as ABI <0.9) was low in this cohort of HIV infected and uninfected women, the prevalence of abnormally high ABI was unexpectedly high, and was associated with cigarette smoking, low BMI, and high BMI, but not HIV status. Further studies will help determine what high ABI means for women's health and whether it is related to increased risk of heart attacks in HIV-infected and uninfected women.

Title: **Hormonal contraception and metabolic outcomes in women with or at risk for HIV infection**

Lay Language Summary: This study looked at whether or not the use of progestin-only contraception (Depo-Provera or Norplant), combined with being HIV-positive, caused a drop in good cholesterol (HDL) in women from the WIHS. We found that, in fact, good cholesterol outcomes were worse in HIV-positive women than in HIV-negative women, and that HDL levels dropped even further if HIV-positive women (as well as HIV-negative women) also used Depo-Provera or Norplant. This is an initial study that points to a potential problem. More research is needed to further explore long-term outcomes, to see what happens to good cholesterol when women stop using Depo-Provera or Norplant, and to see if Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI), an anti-retroviral medication used to treat HIV, use in women who use Depo-Provera or Norplant helps increase levels of good cholesterol. This study does not mean that HIV-positive women should not use Depo-Provera or Norplant, rather it means that women need to be aware of the risks, and that providers should particularly follow HDL levels in HIV-positive women who use Depo-Provera or Norplant.


Title: **Short-term bone loss in HIV-infected premenopausal women**

Lay Language Summary: Low bone density is a recognized complication of HIV infection and antiretroviral therapy. HIV infected men and women have lower bone density than HIV uninfected men and women with similar age and race/ethnicity. It is uncertain whether bone loss persists with stable antiretroviral therapy and whether this will lead to increased fractures in HIV+ individuals. In this study, we examined how bone density changed in HIV+ and HIV- premenopausal women from the WIHS cohort over 2.5 years. There was a yearly decrease of less than 1% in both the HIV+ and HIV- women, and the rate of change was not different between groups. In our study, traditional factors such as vitamin D deficiency and opiate use were associated with increased bone loss, but use and class of antiretroviral therapy was not.

Prevalence and predictors of metabolic syndrome among HIV-infected and HIV-uninfected women in the Women's Interagency HIV Study

Lay Language Summary: The metabolic syndrome is a constellation of abnormalities consisting of at least 3 of the following: impaired fasting glucose, increased waist circumference, elevated triglycerides, low HDL cholesterol, and hypertension. Among HIV negative individuals these abnormalities are associated with long-term cardiovascular complications. We looked at the prevalence of this metabolic syndrome among women in the WIHS cohort and have found it to be considerably more common among HIV positive women than HIV negative women: one third of the HIV infected women had it. HIV infected women who were older, smoked, had higher weight and higher Body Mass Index, and were taking certain HIV medications, such as stavudine, were more likely to have this metabolic syndrome. This has important implications for participants who may benefit from early interventions and modification of risk factors such as abnormal lipids to minimize their risk of cardiovascular complications.


Correlates of CD4+ and CD8+ lymphocyte counts in high-risk immunodeficiency virus (HIV)-seronegative women enrolled in the Women's Interagency HIV Study (WIHS)

Lay Language Summary: Measurements of CD4 and CD8 cells are commonly used to monitor a variety of immunodeficiency disorders including HIV. Studies of HIV infection often compare values from HIV-uninfected controls, including CD4 and CD8 lymphocyte counts. Nonetheless, little is known regarding factors associated with CD4 and CD8 cell numbers in HIV-uninfected individuals. To ascertain potential factors associated with differences in CD4 and CD8 cells among HIV negative women, we studied these cells in a group of 953 women, enrolled as HIV-negative comparators in the Women's Interagency HIV Study. To our knowledge, this study represents the largest such investigation yet conducted.

Obesity and immune cell counts in women

Obesity has been associated with a number of serious illnesses including heart disease, hypertension, diabetes, cancer, and infectious diseases. Given the increasing population of obese individuals in the U.S., particularly women, and the importance of nutrition and weight management in many serious illnesses, a better understanding of the impact of obesity on cells of the immune system involved in these disease processes is necessary. T lymphocytes play an important role in protecting against infection and have been the focus of many studies evaluating the obesity-immune function relationship. The objective of this study was to evaluate the relationship between various measures of obesity and T cell distribution in a cohort of women. We found strong evidence of an association between obesity and increased T cell numbers. The increased number of immune cells associated with higher weight may be the result of a chronic inflammatory state.

Title:  Impairments in memory and hippocampal function in HIV-positive vs HIV-negative women: a preliminary study

Lay Language Summary: This study investigates the impact of HIV on a woman's ability to learn and remember words. This ability is called "verbal memory." The study was done exclusively at the Chicago site of WIHS. We compared women with and without HIV on a test of verbal memory that they completed at the CORE visit. We also invited some WIHS participants to complete a test of verbal memory in a brain scanner. The brain scanner allows us to examine what parts of the brain are involved in learning and remembering words. We can compare this brain activity in women with and without HIV to determine what areas of the brain might be impacted by HIV. Our findings indicated that women with HIV show a reduced capacity to learn and remember words on a memory test. Recent drug use, depressive symptoms, and low quality of education also were associated with lower scores. On brain scans, women with HIV showed differences in brain activity in a brain structure called the hippocampus. The hippocampus is needed to learn and remember words and other kinds of information. These findings are similar to recent findings in men with HIV and suggest that HIV impacts the ability to learn and remember new verbal information.

**Title:** Predictors of reported influenza vaccination in HIV-infected women in the United States, 2006-2007 and 2007-2008 seasons

**Lay Language Summary:** Individuals with HIV are recommended to receive the influenza vaccine each year. Many HIV-infected individuals, however, do not receive the vaccine. In this study we were able to determine how many HIV-infected women in the WIHS reported receiving the influenza vaccination and find factors that make someone more or less likely to receive the influenza vaccination. Only 45% of HIV-infected women reported receiving the influenza vaccine. Individuals that reported having a discussion with their health care provider or reported believing the vaccine protects them from the flu were more likely to be vaccinated. We were also able to identify women who were not likely to receive the vaccine. They had higher viral loads, lower CD4 count, and overall less access to health care. They were also less likely to think the vaccine protected them from influenza illness or have a discussion about it with their health care provider. We can use these characteristics of women who are less likely to receive the vaccine to create or modify programs that help HIV-infected individuals get vaccinated against influenza.


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**Title:** Variations in serum mullerian inhibiting substance between white, black, and Hispanic women

**Lay Language Summary:** This study was designed to compare serum mullerian inhibiting substance (MIS) (a protein in the blood that decreases as a woman's ovaries age) between women of different racial groups. MIS levels of white, black and Hispanic women were assessed in the same women at two different time points at median ages of 37 « and 43.3 years. Analysis showed no significant effect of race on the mean decrease in MIS over time.

Title: Effect of tuberculosis on the survival of women infected with human immunodeficiency virus

Lay Language Summary: Tuberculosis (TB) disease is the most common infectious illness among HIV positive people worldwide. We used new statistical methods to explore the effect of TB disease on the mortality in 1,412 women followed in the Women's Interagency HIV Study from April 1995 to September 2002. Twenty nine women suffered incident TB disease and 355 women died, of whom 222 died of AIDS-related causes. We found TB disease augments almost four times the chances of death due to AIDS, whether or not women receive highly active antiretroviral therapy. The findings of this research stress the importance of promptly identifying latent TB infection and providing preventive treatment to avoid TB disease in HIV infected persons, as it could help delay HIV disease progression.

Keywords: Acquired Immunodeficiency Syndrome; AIDS; CD4; CD4 cell count; epidemiology; HAART; Income; mortality; RNA; serum albumin; survival; therapy

HIV Clinical Disease
Progression and Mortality
Title: Using marginal structural measurement-error models to estimate the long-term effect of antiretroviral therapy on incident AIDS or death

Lay Language Summary: The present study will estimate the long-term effect of highly active antiretroviral therapy (HAART) on time to AIDS or death. In addition, the present study will account for actual therapy reported rather than assuming that once initiated individuals remain on therapy. Further, the present work will account for imperfections in reported HAART use rather than assume reports are completely accurate.

Citation: Cole SR, Jacobson LP, Tien PC, Kingsley L, Chmiel JS, and Anastos K. Using marginal structural measurement-error models to estimate the long-term effect of antiretroviral therapy on incident AIDS or death. Am J Epidemiol 2010;171(1):113-122.

Title: Trends in mortality and causes of death among women with HIV in the United States: a 10-year study

Lay Language Summary: We examined trends in mortality for HIV-infected women in the WIHS. We found that the mortality rate decreased dramatically when active anti-HIV drugs came into wide use but that mortality rates have not continued to fall over time but have stabilized at a rate about 3 times higher than HIV uninfected women in the WIHS and about 10 times higher than age-matched US women as a whole. We found that non-AIDS deaths have increased over time and now make up about half of the deaths among HIV-infected women. The most common causes of non-AIDS death are liver disease, cardiovascular disease, non-AIDS cancers and overdose or trauma. Active hepatitis B and C and depressive symptoms over the course of follow-up were associated with higher mortality in this study.

We evaluated pain in 339 women enrolled in the Women's Interagency HIV Study (WIHS), a study of disease progression in women living with HIV/AIDS. Patients were asked to report how often they were in pain and how severe the pain was during past six months. Forty percent of the women experienced pain six or more days in the past six months and 50% of the women said the pain severity was 4 or 5 with 5 meaning extreme pain. Pain frequency and pain severity were not associated with age, education, ethnicity or location of the WIHS site. Lower CD4 and increased viral load were related to increased pain frequency and severity. Pain was not related to current therapy. Pain was related to depression. Pain was associated with smoking tobacco and marijuana. Those with more severe pain were more likely to have a history of injection drug use but this was not significantly related to pain frequency. Pain severity but not frequency was associated with having ever used crack/cocaine or heroin. This study shows that pain is a significant problem among women with HIV disease and is associated with disease progression, depression and substance use history. The long term effects of tobacco use may be to increase pain experience but women may also smoke tobacco to give mild pain relief. The issue of pain experience among women with HIV is a serious issue requiring medical management.

Title: Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm

Lay Language Summary: Development of an HIV vaccine is of critical importance in reducing new HIV infections. HIV presents a unique challenge because there are many different types of the virus present in different regions of the world. This variability represents one of the greatest obstacles in the development of a safe and effective vaccine. Most antibodies produced in patients with HIV infection do not prevent HIV infection or control the infection once it is established. However even though there is a great deal of virus variability there are a small number of antibodies which appear to have some impact on the multiplication of the virus. Thus it's important to develop a rapid and efficient system to identify individuals with effective HIV antibodies. This study will screen samples from HIV-infected patients to identify those individuals who have these antibodies. Blood specimens from those individuals will then be used to isolate the antibodies, analyze the antibodies in more detail, analyze the HIV virus they are infected with, and analyze other aspects of their immune response to HIV. This information will be used in the design of new HIV vaccine candidates.

Title: Multiple-infection and recombination in HIV-1 within a longitudinal cohort of women

Lay Language Summary: Using a recently developed, novel analytic technology, this study examines the frequency with which HIV-1 infected individuals develop new infections with different HIV-1 viruses and how often they are infected with two different viruses at the same time. The study then examines how these different HIV-1 viruses interact: Does the new virus or the old virus become the most common virus during the course of the disease? How often do these new or second viruses combine with the other virus to form yet a new virus strain within the infected individual? The study found that in most cases any pre-existing viruses remain the dominant virus, but that new virus strains formed by a combination of the two pre-existing viruses are very common. Furthermore, establishment of these new virus strains occurs much more frequently in individuals with a history of injection drug use. This ability to form new viruses represents a powerful tool that the virus can employ to ensure its persistence.

Citation: Templeton AR, Kramer MG, Jarvis J, Kowalski J, Gange SJ, Schneider MF, Shao Q, Zhang GW, Yeh MF, Tsai HL, Zhang H, and Markham RB. Multiple-infection and Recombination in HIV-1 Within a Longitudinal Cohort of Women. Retrovirology 2009;6(1):54.
HIV Pathogenesis
Title: Elevated caspase-3 expression and T-cell activation in elite suppressors

Lay Language Summary: We have evaluated the immune characteristics of a unique population of HIV+ women called Elite Controllers. These women can control their viral replication without antiretroviral therapy. We found that the immune cells in these women are activated and prone to dying from cells from HIV negative subjects. The results of the study have important implication in determining what characteristics of immune cells contribute to HIV control.


Title: CD8(+) T cell activation in women coinfected with Human Immunodeficiency Virus Type 1 and hepatitis C virus

Lay Language Summary: Studies have shown that activation of T cells is associated with HIV disease progression. We performed a study where we looked at a population of T cells that perform an important function in controlling viral replication. Using a laboratory method called flow cytometry, we assessed a subpopulation of CD4 and CD8 T cell for the percent of T cells that appeared activated. T cells must become activated to perform their function. We evaluated 68 HIV+/HCV+, 101 HIV+/HCV- 17 HIV-/HCV+, and 34 HIV-/HCV- women. We found an increased percentage of activated CD8, but not CD4 T cells among HIV+HCV+ co-infected women compared to women only infected with HIV, prior to HAART initiation and early in HIV disease. Since activation of CD8 T cells is related to HIV disease progression, these data may have implications for the medical management of co-infected patients.

**Title:** Associations of insulin-like growth factor (IGF)-I and IGF-binding protein-3 with HIV disease progression in women

**Lay Language Summary:** The risk of developing AIDS is not the same for all HIV-infected patients. The reason for this is not entirely known. Recent studies suggest that a protein called insulin-like growth factor-I (IGF-I) and its binding protein (IGFBP-3) might affect the risk of HIV disease progression. The current study for the first time shows that HIV-infected women with low IGFBP-3 levels have reduced risk of AIDS. We conclude that further studies are warranted to better understand this association.


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**Title:** Vaginal IL-8 levels are positively associated with Candida albicans and inversely with lactobacilli in HIV-infected women

**Lay Language Summary:** We evaluated 406 cervicovaginal lavage (CVL) samples from HIV-infected women in the WIHS and measured the level of an immune protein called interleukin-8 (IL-8). This protein recruits white blood cells that fight infection to an area of inflammation. The 406 CVL samples came from 65 women who had yeast forms seen on their vaginal KOH smears at the time of collection of the CVL indicative of a vaginal yeast infection. Another 324 vaginal smears did not show yeast forms and 17 were missing evaluations. The level of IL-8 in the CVL of women who had yeast vaginitis was much higher than in the CVL of women who did not. We also measured levels of 3 other immune proteins (TNF-a, IL-10, and IL-12) but only found measurable levels of these proteins in less than 10 samples. This is the first study to show an association between Candida albicans in the female genital tract and presence of IL-8.

**Citation:** Spear GT, Zariffard MR, Cohen MH, and Sha BE. Vaginal IL-8 levels are positively associated with Candida albicans and inversely with lactobacilli in HIV-infected women. *J Reprod Immunol* 2008;78(1):76-79.
Liver Disease/Hepatitis
Title: Hepatitis C virus infection and biological false-positive syphilis tests

Lay Language Summary: We found that patients with hepatitis C virus infection more commonly have falsely positive tests for syphilis. This seems to be unrelated to other factors such as HIV infection or intravenous drug use history both have which have also been associated with this false blood test.


Title: Activation of CD8 T cells predicts progression of HIV infection in women coinfected with hepatitis C virus

Lay Language Summary: There have been conflicting publications as it relates to the impact of hepatitis C on HIV disease progression. New information is also available in regards to immune activation which means that the T cells are overly active and as a result become less effective in fighting HIV. In this study we evaluated whether hepatitis C virus had any effects on HIV disease and if immune activation is worse in women who are infected with both HIV and HCV. Our study demonstrates that compared with HIV mono-infected women, HIV+ patients with HCV viremia (presence of HCV viral load) had higher levels of activated CD8 T cells (immune activation) and during a median of 5.6 years of follow-up they also had a higher incidence of AIDS/AIDS-deaths (47% vs 38%). We also found that the risk of AIDS was significantly greater among HIV+HCV+ viremic women who had very high levels of activated CD8 T cells compared to women with lower levels. This was not found in HIV only infected women. We also found that having a higher percentage of a subset of activated T cells or having less activation was associated with less progression to AIDS. These findings suggest that HIV+HCV+ viremic women may need earlier, more aggressive anti-retroviral treatment and perhaps treatment of HCV viremia might be beneficial.

**Title:** Specific human leukocyte antigen class I and II alleles associated with hepatitis C virus viremia

**Lay Language Summary:** This study analyzed the effect of WIHS women's genes on the progression of their hepatitis C virus (HCV) disease. We found that a small number of specific genes are consistently associated with susceptibility or resistance to HCV disease. The public health implications of this work are two-fold. Firstly, this study represents an important step toward personalization of HCV prevention and treatment. This means, for example, that in the future a woman's HCV treatment could be made better by incorporating information about her genes. Secondly, understanding about the genetic basis for susceptibility or resistance to HCV disease may be useful in the effort to create an effective HCV vaccine.


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**Title:** Factors associated with prevalent hepatitis C infection among HIV-infected women with no reported history of injection drug use: the Women's Interagency HIV Study (WIHS)

**Lay Language Summary:** Although the primary mode of transmission for hepatitis C virus (HCV) is through exposure to blood or from intravenous drug use (IDU), recent information suggests that sexual transmission may also be an important way to become infected with HCV infection like HIV. We looked at women who had not injected drugs or received a transfusion to find out how they may have become infected. We found that older age, HIV positivity, unemployment, being born in the U.S., having a history of hepatitis B virus (HBV) infection and a history of sexual contact with an IDU male partner and for HIV-infected women, a CD4 count <200 cells/mm3 were all associated with HCV infection. This information suggests that sexual transmission may be an important mode of HCV transmission for these high risk women.

**Citation:** Frederick T, Burian P, Terrault N, Cohen M, Augenbraun M, Young M, Seaberg E, Justman J, Levine AM, Mack W, and Kovacs A. Factors associated with prevalent Hepatitis C infection among HIV-infected women with no reported history of injection drug use: The Women's Interagency HIV Study (WIHS). *AIDS Patient Care and STDS* 2009;23(11):915-923.
Title: Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure

Lay Language Summary: In several small studies, pregnant women using nevirapine had a high rate of liver toxicity. We compared the rate of liver toxicity among non-pregnant women in the WIHS taking nevirapine with pregnant women from 2 other studies taking the drug. We found no higher rate of liver toxicity associated with nevirapine in pregnancy; however, HIV-infected women who were pregnant had a higher rate of liver toxicity overall than women who were not pregnant.

Keywords: Adolescent; Clinical Trials; Nevirapine; Risk; therapy; transmission


Title: Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the women’s interagency HIV study

Lay Language Summary: There is concern that HIV-positive persons may be at higher risk of cardiovascular disease. Infection with hepatitis C might worsen and speed up the process. Few studies have looked at the association of HIV/HCV coinfection with cardiovascular disease. Studies comparing persons with HCV infection only to those without HCV infection show that those with HCV infection are at increased risk for cardiovascular disease. We sought to determine the relation of HIV infection and HCV infection with measurements of the thickness of the carotid artery wall (which is a marker of atherosclerosis) in WIHS women who underwent carotid ultrasound as part of the carotid ultrasound substudy. Contrary to prior reports, we did not find an association of HCV infection with thickness of the common carotid artery wall after taking into account age, race, and traditional cardiovascular risk factors such as smoking, diabetes, high cholesterol, and high blood pressure. However, HIV/HCV coinfection may be associated with a greater risk of carotid lesions. Lesions are determined by measuring a certain amount of thickness in any of three different sections of the carotid artery (common carotid, internal carotid, and carotid bulb). Further study is needed to see if HCV infection might lead to thickness of the carotid artery wall in certain segments of the carotid artery and how this might affect risk for cardiovascular disease.

Title: Hepatitis C seropositivity and kidney function decline among women with HIV: data from the Women's Interagency HIV Study

Lay Language Summary: This study looked at the effect of having a positive hepatitis C test on risk for developing worsening kidney function. It used data that was previously collected in WIHS participants and required no additional testing of samples, questionnaires or visits.


Title: Factors associated with hepatitis C viremia in a large cohort of HIV-infected and -uninfected women

Lay Language Summary: Hepatitis C virus (HCV) infection is common among HIV-infected women. The infection clears in 20-50% of HCV-infected women, but in fewer women if they also have HIV infection. We investigated characteristics associated with presence and level of HCV virus in the blood (viremia) of 898 HIV-infected and 169 HIV-uninfected who had current or past HCV infection. Of 1,067 women in WIHS, 852 (80%) had HCV viremia. We found that women who were Black, had large amounts of HIV in their blood, or reported smoking or crack/freebase cocaine use, were more likely to have HCV viremia, and women who had current infection with hepatitis B were less likely to have HCV viremia. Women who were older, HIV-infected, or reported marijuana/hash use had higher levels of HCV in their blood; women who reported heroin use had lower levels. These results suggest that age, race, lifestyle, virologic, and immunologic characteristics affect presence and level of HCV viremia, but these characteristics differ in their impact on presence and level.

Title: The insulin-like growth factor axis and risk of liver disease in hepatitis C virus/HIV-co-infected women

Lay Language Summary: This study examined the association between the risk of liver disease in HIV/HCV co-infected and a growth factor, called insulin-like growth factor I (IGF-I). IGF-I has been shown to stimulate the replication of cells in the liver that play a major role in the development of liver fibrosis. Our results indicate that high IGF-I levels and low levels of a protein that binds IGF-I (called IGF binding protein-3; IGFBP-3) were associated with increased risk of liver disease in these women. If correct, the IGF-axis could be a target for new treatments to slow progress of HCV related liver disease.


Title: Defective response to Toll-like receptor 3 and 4 ligands by activated monocytes in chronic hepatitis C virus infection

Lay Language Summary: White cells circulating in peripheral blood are important for protection against infection. We studied the function of cells called monocytes in the blood of women with HCV infection. Monocytes of HCV-positive women were in an activated and over-working state in fresh blood and responded poorly when stimulated with drugs that look like bacteria or viruses. Both patients with single HCV infection and patients coinfected with HIV had similar poor response in monocytes. On the contrary, women with single HIV infection (negative for HCV) had monocytes that responded like control subjects that were HIV-negative and HCV-negative. For women with HIV coinfection, the poor function of monocytes indicates another layer of compromised immunity in addition to the low function of CD4 cells.

**Title:** Estimating past hepatitis C infection risk from reported risk factor histories: implications for imputing age of infection and modeling fibrosis progression

**Lay Language Summary:**
Hepatitis C virus (HCV) can cause liver damage called fibrosis, which can lead to liver failure or cancer. Because many people are infected with HCV, especially those who are HIV-infected, it is important to understand what makes some people get more fibrosis faster than others. This is very hard to study because we usually don't know exactly when people first got infected with HCV, so we don't know how fast they got to their current amount of fibrosis. To solve this problem, studies usually assume that people got infected with HCV when they say they first injected drugs (if they did). This paper analyzed WIHS and another large study to see how accurate or inaccurate this assumption may be. We found that there is often a good chance that people were not infected with HCV within a year of when they say they first started injection drug use. Also, the assumption appears likely to be wrong in a systematic way, with infection more likely to actually be later than first injection if first injection was at a young age and infection likely to be earlier if first injection was at an older age. This suggests that previous studies might have been wrong when they concluded that people who were infected at older ages developed fibrosis much faster than those infected at younger ages.

**Title:** Awareness of hepatitis C infection among women with and at risk for HIV

In the U.S. a large number of women with HIV are also infected with Hepatitis C. Although it is recommended that people with both HIV and Hepatitis C be evaluated for treatment for hepatitis C, that doesn't always happen. In the WIHS, almost one of three women tested positive for antibody to Hepatitis C. We asked questions to those still in the WIHS in 2004 about what they knew about their own Hepatitis status and about hepatitis C treatment in general. About one in four women didn't know they had Hepatitis C. About half of those who knew they had Hepatitis C had been referred for a liver biopsy and about one third had been referred for treatment. We also found that women who were African American, Hispanic/Latina, or were poor, or were using crack/cocaine/heroin were less likely to be referred for treatment. Those who went for treatment were likely to get treated if their liver tests were abnormal. So this study shows that health providers should be educated about the guidelines and should not discriminate and patients should be better educated about hepatitis C.


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**Title:** Isolated hepatitis B core antibody is associated with HIV and ongoing but not resolved hepatitis C virus infection in a cohort of US women

Isolated hepatitis B core antibody is a common laboratory finding in women with HIV and hepatitis C but the significance of the finding is unclear. It could mean that women are immune to hepatitis B or it could mean they are still at risk and should be vaccinated. We looked at what factors are associated with this finding in the WIHS. We found that very few women (1.8%) with isolated hepatitis B core antibody had evidence of active hepatitis B. We found that women with active hepatitis C infection and HIV infection were more likely to have this laboratory finding and that the cause may be interference by hepatitis C in developing the protective hepatitis B antibody (hepatitis B surface antibody). Further study is still needed to completely understand the clinical significance of isolated hepatitis B core antibody.

**Title:** Negative-strand hepatitis C virus (HCV) RNA in peripheral blood mononuclear cells from anti-HCV-positive/HIV-infected women

**Lay Language Summary:** Infection with both hepatitis C virus (HCV) and HIV is common and may negatively affect the course of both infections. HCV has been reported to multiply, or replicate, in certain blood cells outside the liver, particularly in patients infected with both HIV and HCV. However, little is known about the factors affecting HCV replication in blood cells. We investigated HCV RNA in blood cells of 144 HCV- and HIV infected women enrolled in WIHS. HCV RNA inside blood cells indicates that HCV is multiplying in those cells. HCV RNA was detected in 42% of the 144 women. HCV was more likely to replicate in blood cells in women who had the highest level of HCV RNA in their blood and who drank seven or more alcoholic drinks per week. It was less likely to replicate in blood cells of women with activated CD4 cells in the range of 10-20% and CD4+ cell counts in the range of 200-500 cells/mm3 as well as women who injected drugs in the last 6 months. We concluded that HCV replication in blood cells is common among women also infected with HIV and appears to be related to lifestyle and health of the immune system. The presence of HCV infection in cells outside of the liver needs to be considered in the evaluation and treatment of HCV infection.

**Title:** Hepatitis C virus quasispecies in HIV-infected women: role of injecting drug use and highly active antiretroviral therapy (HAART)

**Lay Language Summary:** Despite the high frequency of hepatitis C virus (HCV) and HIV co-infection, little is known about how the HCV virus swarms "quasispecies" acts in HIV-positive patients. We looked at 236 HIV+/anti-HCV+ women enrolled in the Women's Interagency HIV Study (WIHS) and looked at the effect of various factors such as drug use and ethnicity and age on changes in the HCV virus over time and in relation to HAART. We found that age over 40 and high HCV RNA load were the only factors that were significantly associated how complex the HCV virus or "quasispecies" is when we counted the number of bands in an assay called SSCP. We also found that very high HCV and HIV plasma loads were associated with stability of HCV "quasispecies" over time while women who were actively injecting drugs were five times more likely to experience changes in these "quasispecies" than their non-injecting counterparts. No affect on HCV quasispecies was noted in relation to CD4 count or highly active antiretroviral therapy. Active drug use may result in repeated HCV infections with new HCV strains causing these changes that we observed. This needs to be considered when planning treatment and prevention strategies for HCV in co-infected individuals.


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**Title:** Prevalence and long-term effects of occult hepatitis B virus infection in HIV-infected women

**Lay Language Summary:** This study looks at the frequency of "occult" hepatitis B infection (infection not detected using conventional serological testing) among WIHS women at the time of enrollment. We found only a small number (approximately 2%) of women had occult hepatitis B. When we followed these women over time, it did not seem that their infection was linked to any adverse effects on their liver, as determined by liver blood tests (hepatitis B is a virus that primarily effects the liver). The small number of cases of occult HBV infection in WIHS and the unclear long term role of occult HBV infection on the health of the liver led us to conclude that regular screening for HBV in the blood in all women with occult HBV infection may not be indicated at this time.

**Citation:** Tsui JI, French AL, Seaberg EC, Augenbraun M, Nowicki M, Peters M and Tien PC. Prevalence and long-term effects of occult hepatitis B virus infection in HIV-infected women. *Clin Infect Dis* 2007;45:736-740.
HIV Medications & Adherence
**Title:** Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women

**Lay Language Summary:** The effect of highly active antiretroviral therapy (HAART) use by HIV positive women on human papillomavirus (HPV), the viral cause of cervical cancer and precancerous cervical lesions, is still unclear. Therefore, the purpose of this study was to assess changes in the rates of cervical HPV and squamous intraepithelial lesions (SIL) related to the use of HAART among women who took their medications regularly (were adherent) and whose viral loads responded to treatment. We compared the rates of HPV and SIL in women before and after the start of HAART. Significantly lower levels of HPV and cervical dysplasia were seen in women who reported taking their HAART medications at least 95% of the time and whose viral loads decreased after the start of HAART. These findings showing a protective effect of HAART may help explain why rates of cervical cancer have not increased during the HAART era, even though women with HIV are living longer.


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**Title:** CYP1A1 genotype modifies the impact of smoking on effectiveness of HAART among women

**Lay Language Summary:** We have previously shown that women in the WIHS who smoke cigarettes do less well on HAART than women who do not smoke. This could happen for several reasons. For example, women who smoke may take more risks, in general, and less health care precautions such as not taking their medicines all the time. Another reason may be that smoking interferes with the efficacy of antiretroviral therapy. When we examined women who reported taking their medications all the time, smokers still had poorer outcomes suggesting that there may be a biological basis for this. In the present study we looked at differences in outcomes between smokers and non-smokers in women taking HAART who have variations in several genes that could influence the impact of smoking. We found that in women who smoke, a variant form of the CYP1A1 gene was associated with an inferior response to therapy. If this finding is repeated in other studies, it could have an impact in how smokers with HIV infection are treated.

**Title:** Protease inhibitor levels in hair strongly predict virologic response to treatment

How patients do on HIV therapy depend on lots of factors, including the type of virus they have, the strength of their immune system, and how much of the HIV drug they actually get into their system. Although adherence to the drug (taking the medication at the right time every day) makes a difference in terms of how much drug people get into their system, different people also see different levels of drug because of biologic differences in how they absorb and clear medications from their system. Analyzing hair levels of medications is one way to figure out how much drug someone gets into their system over a period of about a month. Hair medication levels can be better than just looking at a single blood medication level since hair levels give an idea of the average level of exposure to a medication over a period of time. This study in WIHS looked at the relationship between hair levels of two protease inhibitors (Kaletra and Reyataz) and doing well on therapy (in terms of a virologic response) in 224 participants. Besides the amount of adherence to the medication, hair levels of these medications were the strongest predictor of doing well on the meds virologically. Therefore, all those times that you gave hair to our study finally paid off! We will continue to analyze hair levels for other drugs and look next at if people with higher hair drug levels get more side effects on these meds. Thanks so much for your participation.


**Title:** Serum lipid profiles among patients initiating ritonavir-boosted atazanavir versus efavirenz-based regimens

To date, there have been no studies comparing the impact of two different therapies (Sustiva, EFV, and Reyataz, TAZ) on various lipid (fat) levels in the blood. Given the aging of the HIV-infected population, the risk of heart disease and the effects of HIV and therapies on lipids, it is important to compare the effects of these preferred regimens among a racially diverse group of patients who are representative of the current HIV epidemic. To this end, we conducted a study utilizing data from three ongoing cohort studies (WIHS, MACS, and the US Navy HIV Program). We found that while EFV use was associated with greater increases in HDL-c than TAZ, the greater increase in non-HDL-c with EFV resulted in similar declines in TC/HDL ratio with both regimens (which itself is an important marker). These beneficial changes in serum lipids occurred while maintaining improved immunological and virologic marker profiles.

**Citation:** Ganesan A, Benning L, Golub ET, Riddle M, Crum-Cianflone N, Tasker S, Jacobson L, and Gange SJ. Serum Lipid Profiles among Patients Initiating Ritonavir-Boosted Atazanavir versus Efavirenz-Based Regimens. AIDS Research and Therapy 2009,6:13.
Title: Disclosure of complementary and alternative medicine use to health care providers among HIV-infected women

Lay Language Summary: We analyzed longitudinal data collected from October 1994 to March 2002 from HIV-infected CAM-using women enrolled in the Women's Interagency HIV Study (WIHS) to determine prevalence and predictors of nondisclosure of CAM use to health care providers among HIV-infected women. Of the 2056 HIV-infected women in the WIHS, 1377 reported use of CAM at least once during study follow-up and contributed a total of 4691 CAM-using person visits. The overall nondisclosure prevalence was 64% across study visits. Compared to their non-Hispanic White counterparts, non-Hispanic Black and Hispanic women were more likely not to disclose their CAM use, whereas college educated women were less likely not to disclose than those with less than a high school education. Fewer health care provider visits, fewer CAM modalities used, and lower health care satisfaction score all had significant relationships with increased nondisclosure of CAM use. From our study, we found that knowledge of factors associated with nondisclosure and interventions targeted towards modifiable determinants would help enhance CAM disclosure.


Title: Association of child care burden and household composition with adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study

Lay Language Summary: HIV is no longer considered an acute disease where physician, patient and family concentrate on immediate survival. Generally, if patients are adherent with their medicine regimens, HIV can become a chronic controlled disease. Unfortunately the drug regimens that make it possible for HIV to be well controlled are often cumbersome, expensive and associated with multiple side effects. Any of these stresses may affect an individual's ability to adhere with drug regimens. As HIV positive women live longer, more productive lives, the stress that their children and social factors place on them will likely impact adherence. We plan to examine familial relationships and the role they play in adherence, with a long-term goal of improving the effectiveness of interventions that positively impact HIV survival.

**Title:** Effect of HAART on salivary gland function in the Women's Interagency HIV Study (WIHS)

**Lay Language Summary:**
Dry mouth is a common complaint among patients with Human Immunodeficiency Virus (HIV) infection in general and those who are taking multiple medications in particular. The purpose of this study was to look at possible relationships among Highly Active Antiretroviral Therapy (HAART), the complaint of dry mouth and unstimulated and stimulated saliva flow rates in a selected group of HIV positive participants in WIHS. Our study included 668 HIV positive women who received comprehensive medical and dental evaluations every six months. The pattern of findings indicated that Protease Inhibitor (PI) based HAART was a significant risk factor for developing decreased unstimulated and stimulated salivary flow rates as well as salivary gland enlargement as compared with non-PI based HAART. We concluded that PI-based HAART therapy is a significant risk factor for developing reduced salivary flow rates and salivary gland enlargement in HIV positive patients.

**Citation:**

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**Title:** Self-Perception of Body Fat Changes and HAART Adherence in the Women's Interagency HIV Study

**Lay Language Summary:**
We were interested in studying whether perceived changes in body fat in the chest, abdomen, upper back, face, arms, legs, and buttocks among WIHS women taking HIV medications affected their compliance taking these medications. Data from 1,671 HIV+ positive women taking HIV medications from April 1999 to March 2006 were analyzed. The chest, abdomen, and upper back were grouped as central body sites and the face, arms, legs and buttocks were grouped as peripheral body sites. After taking into account the effects of other factors such as age, race, drinking alcohol, drug use, waist and hip measurements, body weight, and amount of HIV virus in the body, we found that women who perceived fat gain in the central sites and those who perceived fat loss in the peripheral sites were less likely to take their HIV medications compared to the women who did not perceive these changes. It is important for WIHS women to discuss honestly how they are feeling about any changes in body fat with their physician before deciding to stop taking their HIV medications.

**Citation:**
Title: Age and racial/ethnic differences in the prevalence of reported symptoms in human immunodeficiency virus-infected persons on antiretroviral therapy

Lay Language Summary: Clinical symptoms, such as headaches and fatigue, are very common in HIV-infected persons, and directly impact quality of life. However, few have evaluated age and racial/ethnic differences in the prevalence of clinical symptoms in HIV patients. We studied this issue in two distinct but key segments of the current HIV/AIDS epidemic, that is, MSM and women from minority racial/ethnic groups. We determined that women ≥40 and men ≥50 years of age had the highest prevalence of symptoms. Individual symptoms elevated in older age groups for both men and women were body fat changes, muscle aches, tingling in hands and feet, and dizziness. Finally, Caucasian women had a higher prevalence of many symptoms compared to other races, but few racial/ethnic differences were noted for men. These findings indicate that close monitoring of symptoms, particularly for older patients and Caucasian women, may reduce adverse effects on quality of life and unnecessary interruption of HAART.


Title: Factors associated with preclinical disability and frailty among HIV-infected and HIV-uninfected women in the era of cART

Lay Language Summary: HIV-infected adults taking highly active antiretroviral therapy (HAART) are living longer. As part of ongoing evaluations of HIV and its treatment, we were interested in assessing whether treated adults are at increased risk for disability or impaired physical functioning. In 2005, we asked participants to answer questions on their physical activity and ability to perform daily activities as well as perform the timed-walk and grip strength tests. We analyzed their results and compared it to CD4+ counts and history of clinical AIDS. We assessed the role of CD4+ counts and history of clinical AIDS, both measures of immune suppression, on disability. Women with CD4+ counts <100 cells/mL were at increased risk for being slower, weaker, and frail compared to HIV-uninfected women. Similar results were observed for history of clinical AIDS. Findings from this study suggest that HIV-infected adults with a history of HAART have a limited risk for disability, though a subset might benefit from target screening and prevention.

Finding the best treatment for an HIV-positive person can be challenging for clinicians. This is because there are many different medicines to choose from and many different combinations to put them in. Studies on HAART come out so quickly that it may be difficult for clinicians to keep up. To help solve these problems, the United States Department of Health and Human Services writes guidelines on how to use antiretroviral therapy. These guidelines recommend certain regimens. Not all patients will get these recommended regimens for many reasons, including side effects, resistance, and other patient likes and dislikes. This study looked to see how many WIHS participants used HAART regimens that were recommended by U.S. HIV treatment guidelines and whether patients who got these regimens had higher CD4 counts or lower viral loads. This study only looked at information that was already collected in WIHS from April 1998 to October 2004. The study found that 17% of WIHS women starting their first HAART medicines said they used a combination that the U.S. HIV treatment guidelines recommended against using. These combinations were not recommended to be used because they were not powerful enough, have too many side effects, or are a combination of interacting drugs. Women who used HAART combinations the guidelines were against did not gain as many CD4 cells and continued to have detectable viral loads in 2 years compared to women who used guideline HAART or HAART not mentioned at all in the guidelines. It is unclear why these women were using these poor HAART combinations that the guidelines recommended against but it was not related to race, education, income, and insurance. If a woman had a higher viral load, or started her first HAART after the year 2001, she was less likely to get a HAART regimen the guidelines advised against.

Title: Constructing inverse probability weights for marginal structural models

Lay Language Summary: The method of inverse probability weighting (henceforth, weighting) can be used to adjust for measured confounding and selection bias under the four assumptions of consistency, exchangeability, positivity, and no misspecification of the model used to estimate weights. In recent years, several published estimates of the effect of time-varying exposures have been based on weighted estimation of the parameters of marginal structural models because, unlike standard statistical methods, weighting can appropriately adjust for measured time-varying confounders affected by prior exposure. As an example, the authors describe the last three assumptions using the change in viral load due to initiation of antiretroviral therapy among 918 human immunodeficiency virus-infected US men and women followed for a median of 5.8 years between 1996 and 2005. The authors describe possible tradeoffs that an epidemiologist may encounter when attempting to make inferences. For instance, a tradeoff between bias and precision is illustrated as a function of the extent to which confounding is controlled. Weight truncation is presented as an informal and easily implemented method to deal with these tradeoffs. Inverse probability weighting provides a powerful methodological tool that may uncover causal effects of exposures that are otherwise obscured. However, as with all methods, diagnostics and sensitivity analyses are essential for proper use.

Citation: Cole SR and Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656-664.
Patterns, predictors, and consequences of initial regimen type among HIV-infected women receiving highly active antiretroviral therapy

Highly active antiretroviral therapy (HAART) for HIV infection usually consists of three drugs; three nucleoside reverse transcriptase inhibitors (NRTIs), or two NRTIs with either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Because patient characteristics and clinical outcomes may differ by therapy type (PI-based, NNRTI-based or 3-NRTI-based HAART), it is important to understand which patients are receiving which type of therapy, who is more likely to change their therapy, and whether some therapy types work better than others. We therefore investigated these two types of HAART regimens in the WIHS cohort, with regard to patient characteristics and short-term response to therapy. We studied 1,555 women initiating HAART between April 1996 and March 2005. Trends have changed over time, but currently, women in the WIHS are least likely to begin HAART with a 3-NRTI-based regimen. Between 1996 and 2000, women with higher CD4+ counts were more likely to take NNRTI-based HAART, and women with a history of injection drug use were less likely. From 2000 to 2002, women with high viral load were more likely to take NNRTI-based HAART, and older women were more likely to take 3-NRTI-based HAART. From 2002 to 2005, Black and Hispanic women were least likely to take NNRTI-based HAART. Women taking all 3 regimen types were equally likely to switch treatment regimens. By one year after starting HAART, women taking 3-NRTI-based regimens had lower CD4+ cell counts than those taking PI-based HAART. Women starting HAART now are least likely to take a 3-NRTI-based regimen, and those regimens don’t seem to work as well as the PI-based and NNRTI-based HAART regimens.

**Title:** Longitudinal anthropometric patterns among HIV-infected and HIV-uninfected women

**Summary:** Previous studies suggest that HIV infection, antiretroviral therapy, or both may affect body fat distribution, especially waist and hip size. In women, the waist is typically smaller than the hips, resulting in a waist-to-hip ratio of less than one. Larger waist size and larger waist-to-hip ratio may be related to future risk of heart disease. This study looks at the patterns in waist and hip size, as well as weight, among women in WIHS over a five year period. We found that HIV-uninfected women's waist and hip size and their weight increased steadily over five years, while the HIV-infected women's waist and hip size, and weight stayed the same. We also found that although HIV-infected women had smaller waist and hip size than the HIV-uninfected women, HIV-infected women had a larger waist-to-hip ratio. Among the HIV-infected women, waist-to-hip ratio was larger among white women and if Hepatitis C virus infection was present, but waist-to-hip ratio was not affected by the use of antiretroviral medications. Since HIV-infected women have smaller waists but disproportionately large waist-to-hip ratios, their risk of future heart disease is not clear. HIV infected women should therefore be monitored regularly for diabetes, high blood pressure and high cholesterol and those conditions should be treated if present.


**Title:** Impact of drug abuse treatment modalities on adherence to ART/HAART among a cohort of HIV seropositive women

**Summary:** Previous studies looked at how methadone maintenance programs influence adherence to antiretrovirals. Less is known about how different kinds of drug treatment programs have an effect on adherence. This report used data collected for the WIHS between 1998 and 2002. We looked at how different types of drug treatment program have an effect on adherence. In this study, women who were in any kind of drug abuse treatment program were more likely to report better adherence. Also, we found that women who were in a medication-based or medication-free program had the same likelihood of reporting better adherence. In summary, more efforts to enroll women who use drugs in treatment programs are needed.

Title: Association between living with children and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study

Lay Language Summary: HIV is no longer considered an acute disease where physician, patient and family concentrate on immediate survival. Generally, if patients are adherent with their medicine regimens, HIV can become a chronic controlled disease. Unfortunately the drug regimens that make it possible for HIV to be well controlled are often cumbersome, expensive and associated with multiple side effects. Any of these stresses may affect an individual's ability to adhere with drug regimens. As HIV positive women live longer, more productive lives, the stress that their children and social factors place on them will likely impact adherence. We plan to examine familial relationships and the role they play in adherence, with a long-term goal of improving the effectiveness of interventions that positively impact HIV survival.


Title: Association of complementary and alternative medicine use with highly active antiretroviral therapy initiation

Lay Language Summary: Different forms of complementary and alternative medicine (CAM) are commonly used in the United States and appear to be gaining in popularity. CAM is defined by the National Institutes of Health's, National Center for Complementary and Alternative Medicine, as, "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." CAM usage is very common among HIV-infected individuals. However, concerns regarding whether its use will affect HAART initiation, are not well studied. Previous studies have shown that CAM has delayed cancer treatment in some patient groups. The data collected regularly from the WIHS cohort will allow us to further examine CAM's influence on HIV-infected women's initiation to HAART treatment.

Title: Highly active antiretroviral therapy reduces urinary albumin excretion in women with HIV infection

Lay Language Summary: The appearance of small amounts of protein in the urine is common in people with HIV infection. This study looks at the changes in urine protein levels after initiating antiretroviral therapy. Stored urine specimens of 162 women were tested for levels of protein in samples at two consecutive visits 6 months apart. Changes in the level of protein excretion were compared based on antiretroviral initiation. Women of black race and with lower CD4+ lymphocyte count and hematocrit; greater age, HIV-1 RNA level, and systolic and diastolic blood pressures; the presence of diabetes mellitus or hypertension; and prior report of an AIDS-defining illness had a higher level of urine protein excretion at first measurement. Women not initiating therapy had a greater increase in the amount of protein they excreted in their urine over six months as compared to those initiating antiretroviral therapy or initiating HAART. This increase in urine protein excretion was greater in women with a lower CD4+ lymphocyte count, higher HIV RNA level, and without diabetes mellitus or hypertension (p=0.01 and 0.005, respectively). Beginning HAART therapy is associated with a lesser increase in urine protein excretion as compared to non-HAART antiretroviral regimens or no therapy. HAART as a treatment strategy for elevated urine protein excretion should be tested further.

Citation: Szczech LA, Golub ET, Springer G, Augenbraun M, Young M, Gandhi M, Gillespie BS, and Anastos K. Highly active antiretroviral therapy reduces urinary albumin excretion in women with HIV infection. J Acquir Immune Defic Syndr 2008;48:360-361.
Title: Antiretroviral therapy exposure and insulin resistance in the Women's Interagency HIV study

Lay Language Summary: The study looks at insulin resistance in WIHS women over a five and a half year period from 2000 to 2006 in association with antiretroviral therapy use. We found that HIV infected women regardless of type of ART regimen reported at the last visit had greater insulin resistance than HIV-uninfected women, with the association strongest in those reporting recent use of a PI-containing HAART regimen. Interestingly, among HIV infected women, cumulative use of PI or NNRTI was not associated with greater insulin resistance; rather longer cumulative use of NRTI (in particular, stavudine and lamivudine) was associated with greater insulin resistance. Because nucleoside reverse transcriptase inhibitors are the backbone of highly active antiretroviral therapy, HIV infected women should be monitored regularly for diabetes.


Title: The association of bone mineral density with HIV infection and antiretroviral treatment in women

Lay Language Summary: Studies in HIV infected men have indicated that either HIV itself or the use of HAART regimens can be associated with osteoporosis (low bone density). Because women in general are more likely than men to develop osteoporosis, they may be at greater risk than men for this complication of anti-HIV therapy. However, at least one recent study of HIV infected women and men found that women were less likely than men to develop this problem. In this study 272 WIHS women had DEXA scans to assess their bone density. We found that in general the WIHS women had very good bone density, with only 5 women (2%) having osteoporosis. This is much lower than what is found in most studies of HIV infected men. But, while mostly in the normal range, the bone density was lower in the HIV infected women, whether or not they were taking HAART, and they were more likely to have DEXA results that showed slightly "weak" bones, also called osteopenia. Because most of the WIHS women in the study are premenopausal, this may mean they will be at higher risk for osteoporosis after menopause. Further study is needed.

Title: Association of Serum Lipid Levels With HIV Serostatus, Specific Antiretroviral Agents, and Treatment Regimens

Lay Language Summary: After puberty, cholesterol levels differ between women and men, with premenopausal women having lower total cholesterol (total-C) and LDL (the "bad" cholesterol). But after menopause women have higher total cholesterol and LDL (natural or surgical). HDL (the "good" cholesterol), is higher in women throughout adulthood, and higher in American blacks than in American whites. There are multiple cholesterol abnormalities in HIV infected people even without antiretroviral therapy (HAART), but most studies have been done on men. If HIV or HAART causes changes in cholesterol in women, it could increase their chance of heart disease. We found that HAART use, but not HIV infection, was associated with abnormal values of triglycerides and total and LDL cholesterol levels. These abnormalities may give women an increased risk for heart disease or strokes. HIV infection was associated with lower HDL, which was improved by HAART, but not completely so, a pattern different from that reported in men.


Title: HIV status, trust in health care providers, and distrust in the health care system among Bronx women

Lay Language Summary: HIV status, trust in doctors, and distrust in the health care system Trust in doctors and the health care system is important. The goal of this study was to look at things related to trust in doctors and distrust in the system in black and Hispanic women who were HIV-infected or at-risk for HIV infection. We interviewed 102 women from the WIHS Bronx site about trust, drug and alcohol use, depression, mental health medications, and feelings of discrimination. Many people distrusted the health care system about HIV issues, and most people trusted their doctors. People who distrusted the system were more likely to feel depressed and not have health insurance. People who trusted their doctors were more likely to be HIV positive, have a job, take mental health medications, and have white, black or Hispanic doctors (compared to "other" doctors). Even though many people distrusted the system, most people trusted their doctors. HIV-positive women trusted their doctors more than HIV-negative women. Studies are needed to understand how to get and keep trust, and how trust is related to HIV health.

Citation: Cunningham C, Sohler N, Korin L, Gao W and Anastos K. HIV Status, trust in health care providers, and distrust in the health care system among Bronx women. AIDS Care 2007;19(2):226-234.
Mortality among participants in the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study

People with HIV infection are living longer due to the new drugs that fight the infection and keep the virus from replicating. These medications are preventing disease and death from HIV-related causes so now we would expect to see other causes of death becoming more common. Causes of death due to accident (such as drug overdose) or injury (such as car crash) are now emerging as an area for investigation and ultimately prevention. We examined accident and injury causes of death among the women in the WIHS and the men in the MACS to look at trends over time (especially since the introduction of HAART) and the factors that are associated with these causes of death. We found enrollment in the WIHS, unemployment, cigarette smoking, injection drug use, and depression independently increase the risk of death but did not find an association between HIV infection or calendar year and risk of accidental or injury deaths.


Within-individual stability of obesity-related biomarkers among women

One of the side effects of "HAART", also called the "combination cocktail" of medicines for the treatment of HIV infection and AIDS, is a loss of fat in the arms, legs and buttocks (known as lipoatrophy) and/or a gain in the fat in the abdomen, back and neck (known as lipohypertrophy). There has recently been evidence that the levels of some hormones that are made in the fat are unusually high (a hormone called leptin in people with fat gain) or unusually low (leptin and another hormone, called adiponectin, in people with fat loss). In addition, these hormone levels have been shown to be associated with insulin resistance, also known as "pre-diabetes", and perhaps with high blood pressure. Leptin may also have an impact on T-cell counts. We propose to look at the levels of these hormones in the stored samples of blood from women in the "DEXA" study at the Bronx and San Francisco sites. In addition, we propose to identify women in the WIHS as a whole who have developed this fat loss or fat gain, and look at the blood levels of these hormones before and after starting HAART, compare them to women who started HAART but did not develop this syndrome, and determine if there is an association between the blood levels of leptin and adiponectin with prediabetes or with high blood pressure, or with CD4 cell count increases in women taking HAART. In this manuscript, we are examining whether levels of these hormones change over time in women, and whether they are affected by body weight.

**Title:** HIV-1 drug resistance in variants from the female genital tract and plasma

**Summary:**
In most HIV-infected individuals, HIV medication decreases virus levels and improves immune systems. After several months, however, treatment fails due to the emergence of drug resistance. Drug resistant viruses can be transmitted to sexual partners or to infants via mother-to-child-transmission. Noncompliance to HIV medication will facilitate the emergence of drug resistance in infected patients. Drug resistance in the female genital tract is not well studied. In this study we documented the presence of HIV-1 drug resistance in the blood and genital tract of women during and after antiretroviral therapy. The findings of drug resistant viruses in the female genital tract is important for sexual and mother to child transmissions. This study emphasizes the importance of compliance with medication and avoiding high-risk activities including having sex with multiple partners and using any kind of illicit drug use.


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**Title:** Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women

**Summary:**
Very high adherence to highly active antiretroviral therapy (HAART) is central to successful treatment of HIV infection. Prior studies have primarily examined determinants of adherence at a single point in time and few studies have evaluated factors associated with changes in adherence, especially in both men and women. We studied factors associated with changes (increasing or decreasing) in adherence to HAART among men and women. We found that antiretroviral adherence is a dynamic process, and identified risk factors associated with increasing and decreasing adherence potentially suggesting specific interventions.

**Citation:** Lazo-Elizondo M, Gange S, Wilson T, Anastos K, Ostrow D, Witt J and Jacobson L. Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women. CID 2007;45:1377–85.
Title: Association between complementary and alternative medicine use and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study

Lay Language Summary: Complementary and alternative medicine (CAM) use has been prevalent among HIV infected population even in the highly active antiretroviral therapy (HAART) era. Our study was designed to assess whether CAM use affects HAART adherence among women in the Women's Interagency HIV Study (WIHS). We used data collected between October 1998 and March 2002 in WIHS when CAM use and HAART adherence data were available. The primary outcome of this study was self-reported adherence to HAART = 95% over past six months. A special statistical method (logistic regression with repeated measurements) was employed to assess effect of CAM use on HAART adherence after controlling for the effects of other factors. From our analysis, CAM use showed only a positive trend in being associated with adherence to HAART after controlling for possible confounders, but did not negatively affect HAART adherence. Further research of the impact of specific CAM types on HAART use should be explored.

Title: Differences among U.S. states in estimating the number of people living with HIV/AIDS: impact on allocation of federal Ryan White funding

Lay Language Summary: Under the U.S. Ryan White Care Act (RWCA), surveillance data from AIDS case reporting are used to guide allocation of federal funds for HIV/AIDS care and treatment. Since all diagnosed persons living with HIV (PLWH) drive care and treatment needs, not just persons living with AIDS (PLWA), Congress has mandated that surveillance data on HIV (non-AIDS) be incorporated into PLWA prevalence estimates used in RWCA allocation formulas. However, differences in each state's reporting requirements for HIV (non-AIDS) surveillance, particularly laboratory reporting requirements, may affect comparability in PLWA prevalence estimates across states, potentially resulting in inequitable resource allocation. We conducted a simulation study using clinical and laboratory data on 1,337 HIV-positive women with HIV/AIDS from the Women's Interagency HIV Study, 477 (36%) of whom had not yet progressed to AIDS at the beginning of the 4 year study period. To assess the impact of differing laboratory reporting scenarios on the completeness of PLWA ascertainment, we estimated the completeness of prevalent HIV (non-AIDS) case ascertainment and the total number of PLWA that would have been ascertained over a four year period for three laboratory reporting scenarios, each in the context of AIDS case reporting and death certificate surveillance: CD4<200 cells/µL and detectable viral load (Scenario A); CD4<500 cells/µL and no viral load reporting (Scenario B); and CD4<500 cells/µL and detectable viral load (Scenario C).

Title: Cervical shedding of HIV-1 RNA among women with low levels of viremia while receiving highly active antiretroviral therapy

Lay Language Summary:
HIV may act differently between blood and other bodily fluids, like from the cervix or vagina (the genitals). Currently, most HIV-infected patients can control the virus in their blood very well with treatment, but we don't yet know who will still have virus in their genital fluids. This is the first study to look at which women from WIHS still have virus in their genital fluid, even though they have controlled the virus in their blood very well with medicines. We found that using drugs like crack, and receiving a type of medicine called a non- nucleoside reverse transcriptase inhibitor instead of another kind of medicine called a protease inhibitor made it easier to find virus in genital secretions, even when virus in the blood was really low. These results suggest that protease inhibitors may be better able to control virus in the blood and the genital fluids than non-nucleoside reverse transcriptase inhibitors.

Citation:

Title: Live birth patterns among human immunodeficiency virus-infected women before and after the availability of highly active antiretroviral therapy

Lay Language Summary:
The number of women living with HIV infection and AIDS has been increasing steadily worldwide, and women now account for approximately 50% of the 40 million adults living with HIV/AIDS globally. In the United States during 2001-2004, an estimated 75% of women diagnosed with HIV/AIDS were aged 13-44 years. Since 1996, highly active antiretroviral therapy (HAART) has been available in the United States, and has been shown to dramatically improve survival for individuals with HIV, and to markedly reduce the rate of mother-to-child transmission of HIV. However, it is unclear whether these advantages have affected women's childbearing plans. Since the majority of HIV infected women are in the years of highest fertility, it is important to understand the interplay between their reproductive activities and HIV serostatus, and the factors that influence childbearing decisions. In this study, we compared the relationship between HIV infection and childbearing before and after the availability of HAART in a cohort of HIV-infected and at-risk women.

Citation:
**Title:** Antiretroviral therapies associated with lipoatrophy in HIV-infected women

**Lay Language Summary:** Fat distribution changes or the "lipodystrophy syndrome" was first thought to be a result of protease inhibitors (PI). Fat changes that were described included fat loss in peripheral body sites (arms, legs, face and buttocks) and fat gain in central body sites (dorsocervical area and abdomen). Since then, factors other than PI have been associated with fat distribution changes. First, recent studies including from the WIHS show that fat loss and not fat gain is associated with HIV infection. Second, studies in men that have measured the amount of fat in various parts of the body find that stavudine (d4T) is associated with fat loss. Our study investigated the association of individual antiretroviral drugs on fat changes from 1999 to 2003, using circumference measurements collected from women in the WIHS. During this period, stavudine use decreased by half. We found fat loss in HIV+ women over a four-year period in the trunk and legs. The use of didanosine (ddI) for at least 12-months may further worsen the fat loss.

**Keywords:** HIV; Fat Changes


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**Title:** Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study

**Lay Language Summary:** The study looks at new diagnoses of diabetes in WIHS women over a five year period from 2000 to 2005 in association with antiretroviral therapy use. While studies have found that protease inhibitors are associated with diabetes, we found that longer exposure to the nucleoside reverse transcriptase inhibitors were associated with new cases of diabetes. Because nucleoside reverse transcriptase inhibitors are the backbone of highly active antiretroviral therapy, HIV-infected women should be monitored regularly for diabetes.

**Keywords:** Diabetes Mellitus; diagnosis; HAART; Incidence; Reverse Transcriptase Inhibitors; Risk

Sexual Practices/Risk Behaviors
**Title:** Impact of menopause on condom use by HIV-seropositive and comparison seronegative women

Lay Language Summary: Women with HIV may use condoms during sex both to prevent pregnancy and to prevent transmission of sexually transmitted diseases, including HIV. After menopause, the contraceptive value of condoms goes away, since women can no longer become pregnant. For this reason, condom use may decline with menopause. We looked at how regularly women used condoms around the time when they thought they were going through menopause. Women used condoms at 74% of visits before reporting menopause and 70% of visit afterward. This drop was not significant. Even after comparing women with and without HIV, as well as after controlling for other factors associated with condom use, there was still no effect of menopause on condom use.


**Title:** Contraceptive use among U.S. women with HIV

Lay Language Summary: We looked at contraception use and sterilization over time in WIHS, using information on 2,784 women and 26,832 visits. We found that most women at risk for pregnancy in WIHS do not use the most effective forms of birth control, and in fact women with HIV are less likely to use hormonal contraception than HIV-women. Most women don't use condoms, and HIV+ women are not more likely to use condoms than HIV- ones. Use didn't change much across time. Older women were less likely to use birth control. Women who'd been sterilized were less likely to use barriers. We concluded that barrier use and highly effective contraception are underused among US women with HIV, placing them at risk for unwanted pregnancy.

Title: Acquisition of new sexual partners among women with HIV infection: patterns of disclosure and sexual behavior within new partnerships

Lay Language Summary: In order to best design prevention programs to reduce sexual risk among women with HIV-infection, it is important to understand sexual behaviors and the factors that influence them. This analysis focuses on the extent to which women with HIV-infection acquire new sexual partners over time, and describes HIV disclosure patterns within these partnerships. In this paper, we report that nearly one-third of all partnerships reported among HIV+ women over a one-year period were started since the last study visit, and that in newer relationships, women tended to be less likely to report disclosure but more likely to report condom use consistency. We also found that women who believed that HIV therapy protects their partners from getting HIV were associated with less condom use among those women.

Substances of Abuse
Title: Smoking cessation among women with and at risk for HIV: are they quitting?

Cigarette smoking is an important health risk factor for HIV-infected persons. It is very common and carries high risk causing early illness and death. We studied 747 women who participated in the Women's Interagency HIV Study (WIHS) who smoked cigarettes and were followed for ten years. The study was designed to determine the rate of quitting smoking for at least 12 months and the predictors of quitting smoking. Among the women in the WIHS, on average, 1.8% per year quit smoking for one year or more. This rate of quitting smoking is well below US population cessation rates of 3.4-8.5% per year. Predictors of higher rates of cessation were Hispanic ethnicity and more years of education. Cessation was lower for heavier smokers and women with current or former illicit drug use. Given the high prevalence of smoking, the high risk of adverse health events from smoking, and low rates of cessation, this study supports efforts to overcome barriers to help these women quit smoking.


Title: Longitudinal trends in hazardous alcohol consumption among women with human immunodeficiency virus infection, 1995-2006

We evaluated the drinking patterns of 2767 HIV-positive women over the time period 1995-2006. Based on their responses to the WIHS questionnaires, WIHS women were divided into three drinking categories, based on their alcohol consumption at each visit. The first group was hazardous drinking, defined as more than 7 drinks a week or 4 or more drinks in a day. The second group was moderate drinking, or any alcohol consumption that was not hazardous. The final group was non-drinkers. During the study period, between 14% and 24% of WIHS women drank at hazardous levels. Women were more likely to drink at hazardous levels if they were unemployed, not a high-school graduate, enrolled in the original cohort (1994-1995), had a CD4 count between 200 and 500 cells/ml, were hepatitis C seropositive, or had depressive symptoms. Other studies have shown that HIV-positive women with hazardous drinking are more likely to miss taking their medications, to engage in risky sexual behavior, and to progress in their disease more rapidly. Therefore, doctors and prevention programs are encouraged to do more to help women recognize their hazardous drinking and to provide options to help them cut back on their drinking.

Title: Relationship of injection drug use, antiretroviral therapy resistance, and genetic diversity in the HIV-1 pol gene

Lay Language Summary: One of the major problems confronting the development of effective vaccines and therapies for HIV-1 is the high rate at which this virus undergoes genetic mutation. Such mutation allows the virus to escape from the host immune response and from the effects of antiretroviral therapy. Previous studies from our laboratory have shown that viruses from injection drug users show a higher rate of mutation in the viral coat or envelope protein than do viruses from non-injection drug users. In this study we examined whether a higher mutation rate in the viral protein that is targeted by antiretroviral therapy was also observed in viruses from injection drug users. We found that in injection drug users this viral protein did show evidence of greater genetic mutation. Furthermore, the genetic patterns observed for this protein also showed a higher level of resistance to antiretroviral therapy. However, this higher level of resistance could not be explained simply by the higher rate of genetic mutation among viruses from injection drug users. These findings may have important implications for which antiretroviral regimens should be used initially in those with a history of injection drug use.

Title: Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women

Lay Language Summary: Use of crack cocaine by women with HIV/AIDS may make the disease progress faster in terms of low CD4 count, high viral load, illness, and death. To see if this is true in the WIHS, this study looked at the relationship of crack use in the WIHS to these four disease outcomes, from 1996-2004. Of the 1686 HIV+ women included in the study, almost a third reported crack use at some point over the 9 years (29% of the women). Most reported crack use at some but not all of their WIHS study visits, but 3% (54 women) reported crack use at all their visits. Women who reported persistent crack use (that is, use at all study visits) were over three times as likely as women who didn't report crack at all to die from AIDS related causes, to have low CD4, and high viral load, even if taking HAART as prescribed, and regardless of age, race, income, education, and study site. Women who reported crack use at some or all of their study visits were more likely than non-users to develop new AIDS-defining illnesses. This study found that crack use does make HIV disease progress faster, although it doesn't explain how. This suggests that women with HIV should be able to receive treatment for crack addiction along with their HIV medications and therapies. This may require providers to do more follow-up with women who use crack, to be more understanding of their life situations, to help them toward quitting by focusing on positive things in their lives, and to arrange easy access to counseling.


Title: Illicit drug use, depression and their association with highly active antiretroviral therapy in HIV-positive women

Lay Language Summary: Depression and use of illicit drugs like crack/cocaine/heroin are serious problems for HIV positive women in the WIHS cohort. In addition, prior research on other groups with HIV/AIDS suggests that both types of problems may be related to a woman's tendency not to seek or follow through with health care services, such as being on HAART. We used WIHS study data to explore how depression and illegal drug use were related to whether women were on HAART. We found that when we looked at them individually, both depression and illicit drug use were related to not being on HAART. But when we looked at them together, women with both depression and illicit drug use were the least likely to be on HAART, followed by women with illicit drug use but no depression. We concluded that women with both problems need specialized treatment for both their depression and their drug use if they are to have an opportunity to use the most potent HIV/AIDS treatments.

Title: Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts

Lay Language Summary: At each study visit, information regarding the antiretroviral drugs that WIHS participants are taking and how well they are taking them is collected. This same information is also collected in the MACS, an HIV study of men who have sex with men, and the ALIVE study, an HIV study of injection drug users. Using this information, we compared the trends over time in the use of HAART and antiretrovirals between these three studies. Additionally, we investigated the timing and determinants of a change in HAART use once a participant has begun HAART. Participants in the ALIVE study were more likely to modify their HAART use earlier than in the MACS and WIHS. This is in addition to the overall lower uptake of HAART that has been previously cited. Other factors that were associated with earlier modification of HAART treatment were higher HIV RNA levels, depression, Hispanic ethnicity, and to a lesser extent lower CD4 counts.

Study Methods
Title: Using marginal structural measurement-error models to estimate the long-term effect of antiretroviral therapy on incident AIDS or death

Lay Language Summary: The present study will estimate the long-term effect of highly active antiretroviral therapy (HAART) on time to AIDS or death. In addition, the present study will account for actual therapy reported rather than assuming that once initiated individuals remain on therapy. Further, the present work will account for imperfections in reported HAART use rather than assume reports are completely accurate.

Citation: Cole SR, Jacobson LP, Tien PC, Kingsley L, Chmiel JS, and Anastos K. Using marginal structural measurement-error models to estimate the long-term effect of antiretroviral therapy on incident AIDS or death. *Am J Epidemiol* 2010;171(1):113-122.

Title: An instrumental variables evaluation of the effect of antidepressant use on employment among HIV-infected women using antiretroviral therapy in the United States: 1996-2004

Lay Language Summary: HIV medications extend the lives of people living with HIV, and allow them to continue to work. Many HIV-positive persons also suffer from depression, and may not be able to work. The question we ask is: Can people work more if they take both HIV and anti-depression medication? The logic is that drugs to combat depression help people with HIV in two ways. First, antidepressants improve how people feel mentally. Second, antidepressants also help people to take the HIV drugs correctly, and thus feel better physically. Those two effects combined will help HIV-positive persons in their employment activities. The study shows that for some patients, HIV medications by themselves may no be sufficient. Some will need antidepressants to be able to work. Efforts to screen, diagnose, and treat depression can help people with HIV have better physical and mental health, and also help them to be more productive.

Title: Time scale and adjusted survival curves for marginal structural cox models

Lay Language Summary: Past uses of causal inference models have used the time spent on study to count how long people are at risk for the outcome. We show how to count the time spent on anti-HIV treatment. Also, we show how to make a picture to depict the effect of anti-HIV treatment. We use the example of anti-HIV treatment and time to AIDS. In this example, use of time spent on treatment showed that anti-HIV treatment was better than using time spent on study.


Title: Retention and attendance of women enrolled in a large prospective study of HIV-1 in the United States

Lay Language Summary: Our objective was to measure study retention (returning for follow-up visits) and attendance for two recruitment waves of participants in the Women's Interagency HIV Study (WIHS), since recruiting strategies were modified between the two waves. After 10 study visits (five years), the overall retention rate in the new WIHS cohort (enrolled in 2001-2002) was 86 percent for both the HIV-uninfected and HIV-infected women. In the original cohort (enrolled in 1994-1995), after 24 study visits (12 years), the retention rate was 75 percent for the HIV-infected women and 62 percent for the HIV-uninfected women. In analysis of the HIV-infected women, risk factors for early (visits 2 and 3) non-attendance were temporary housing, moderate alcohol consumption, use of crack/cocaine/heroin, having a primary care provider, WIHS site of enrollment, lower CD4 cell count, and higher viral load. Among HIV-uninfected women, the risk factors for early non-attendance were recruitment into the original cohort, household income >=$12,000 per year, temporary housing, unemployment, use of crack/cocaine/heroin, and WIHS site of enrollment. In analysis of HIV-infected study participants, risk factors for non-attendance at later visits (7 through 10) were younger age, White race, not having a primary care provider, not having health insurance, WIHS site of enrollment, higher viral load, and non-attendance at a previous visit. In analysis of HIV-uninfected study participants, younger age, White race, WIHS site of enrollment, and non-attendance at a previous visit were significantly associated with non-attendance at later visits. Preventing early study dropout resulted in better study retention early on, but dropout at later study visits may require different prevention strategies.

Title: Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution

Lay Language Summary: This is a methodological paper whose purpose is to present and illustrate a hazard taxonomy for the generalized gamma family of parametric survival distributions. Preliminary work for this manuscript was presented by Christopher Cox during the May 2005 WIHS/MACS meeting. Our hope is to encourage the wider use of this family, which will ultimately benefit investigators in both MACS and WIHS. This manuscript uses the same data as the paper entitled, "Patterns of the Hazard of Death after AIDS through the Evolution of Antiretroviral Therapy: 1994-2004," written by Schneider, Gange, Williams, Anastos, Greenblatt, Kingsley, Detels and Muñoz, which was recently accepted by AIDS. It does not present any new scientific results, but uses the data to illustrate this taxonomy.

Citation: Cox C, Chu H, Schneider MF and Muñoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. Stat Med 2007;26:4352-4374.
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