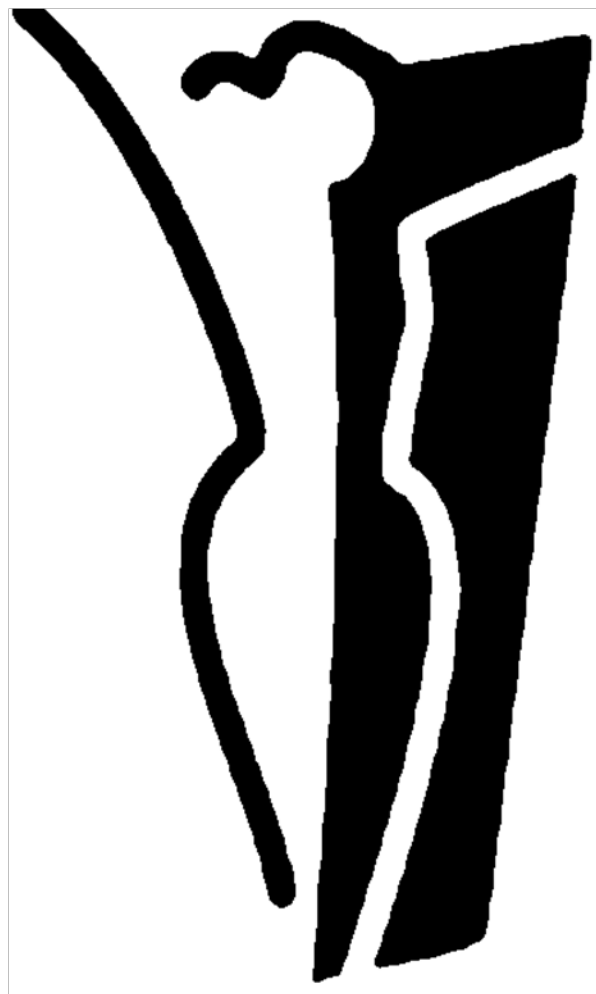


**1995-2012 WIHS Findings:  
Lay Language Summaries for  
the Community**

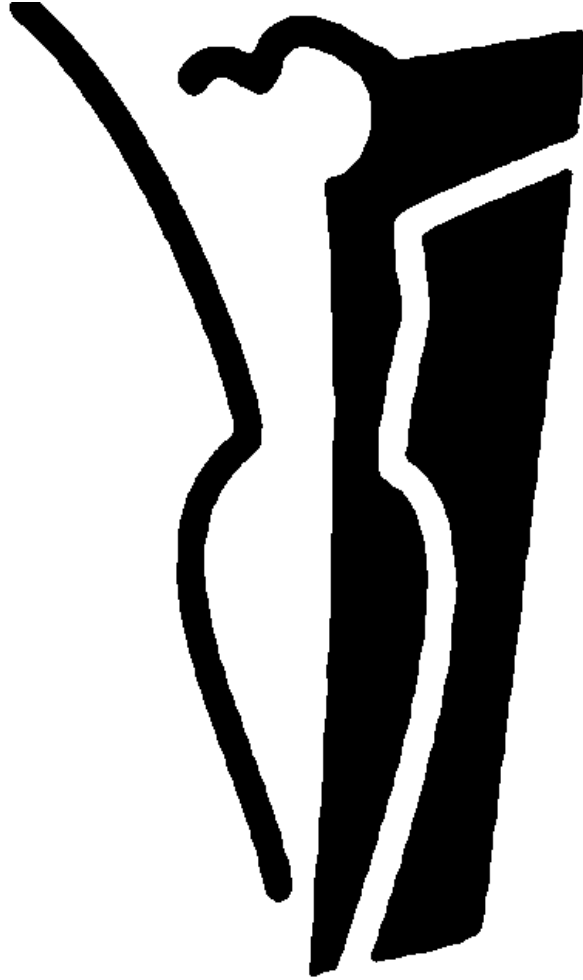


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# Bacterial Vaginosis and Microflora





### **The Association of HIV Status with Bacterial Vaginosis and Vitamin D in the United States**

Bacterial vaginosis is an imbalance of the bacteria in the vagina where the normal healthy bacteria are overgrown by less healthy bacteria. We found that WIHS women with vitamin D deficiency were more likely to have bacterial vaginosis than women with normal vitamin D levels. We also found that vitamin D deficiency was very common among WIHS women. We cannot tell from this study whether increasing vitamin D levels by supplements or by more sun exposure will prevent bacterial vaginosis.

French AL, Adeyemi OM, Agniel DM, Evans CT, Yin MT, Anastos K, Cohen MH. The Association of HIV Status with Bacterial Vaginosis and Vitamin D in the United States. *J Women's Health* 2011;20(10):1497-1503. **PMC3233211**

### **Pyrosequencing of the genital microbiotas of HIV-seropositive and -seronegative women reveals *Lactobacillus iners* as the predominant *Lactobacillus* Species**

All women have bacteria in the vagina, but some kinds of bacteria are considered to be of benefit to health while others are not. This study looked at the kinds of bacteria that were found in 21 women from the WIHS and found that the bacteria that were in most of the women were less beneficial than what was expected.

Spear GT, Gilbert D, Landay AL, Zariffard R, French AL, Patel P, and Gillevet PM. Pyrosequencing of the genital microbiotas of HIV-seropositive and -seronegative women reveals *Lactobacillus iners* as the predominant *Lactobacillus* Species. *Appl Environ Microbiol* 2011;77(1):378-381. **PMC3019699**

### **Analysis of standard methods for diagnosing vaginitis: HIV infection does not complicate the diagnosis of vaginitis**

here 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/m<sup>3</sup>. 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.

Sha BE, Gaweel SH, Hershov RC, Passaro D, Augenbraun M, Darragh TM, Stek A, Golub ET, Cashin L, Moxley MD, Weber KM and Watts DH. Analysis of standard methods for diagnosing vaginitis: HIV infection does not complicate the diagnosis of vaginitis. *J Low Genit Tract Dis* 2007;11:240-250.

### **Utility of Amsel Criteria, Nugent Score, and Quantitative PCR for *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Lactobacillus* spp. for Diagnosis of Bacterial Vaginosis in Human Immunodeficiency Virus-Infected Women**

Many women have bacterial vaginosis or BV; this occurs when certain bacteria overgrow in the vagina and results in discharge and bad odor. There are different ways of diagnosing BV. In the clinic, a provider may use the Amsel criteria which combines some of your symptoms and exam with a slide with vaginal discharge to look at bacteria. A provider may also send a slide with vaginal discharge to a special lab to count several the different types of bacteria using the Nugent method or a Quantitative PCR. This study found that in women with HIV, the lab method did a better job of detecting BV than the Amsel method.

Sha BE, Chen HY, Wang QJ, Zariffard MR, Cohen MH, and Spear GT. Utility of Amsel Criteria, Nugent Score, and Quantitative PCR for *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Lactobacillus* spp. for Diagnosis of Bacterial Vaginosis in Human Immunodeficiency Virus-Infected Women. *J Clin Microbiol* 2005;43:4607-4612. **PMC1234056**



### **Female genital-tract HIV load correlates inversely with Lactobacillus species but positively with bacterial vaginosis and Mycoplasma hominis**

Several types of bacteria and microorganisms normally live in a healthy vagina. However, bacterial vaginosis or BV can occur when certain types of bacteria take over. This study found that in HIV+ women, lower levels of “good” bacteria (lactobacillus) and higher levels of “bad” organisms (M. hominis, Candida vaginitis and Herpes Simplex Virus or HSV) were related to higher levels of HIV in the genital tract. This suggests that women with BV, Candida, and HSV may be shedding more HIV virus.

Sha BE, Zariffard MR, Wang QJ, Chen HY, Bremer J, Cohen MH, and Spear GT. Female genital-tract HIV load correlates inversely with Lactobacillus species but positively with bacterial vaginosis and Mycoplasma hominis. *J Infect Dis* 2005;191:25-32.

### **Detection of bacterial vaginosis-related organisms by real-time PCR for Lactobacilli, Gardnerella vaginalis and Mycoplasma hominis**

Many types of “good” organisms, including lactobacilli, live in a healthy vagina. When “bad” organisms (like Gardnerella vaginalis) invade, bacterial vaginosis (BV) can happen. Researchers tested a new method, called real-time PCR, to detect which organisms were in a sample of vaginal fluid. This may help researchers determine what causes BV

Zariffard MR, Saifuddin M, Sha BE, and Spear GT. Detection of bacterial vaginosis-related organisms by real-time PCR for Lactobacilli, Gardnerella vaginalis and Mycoplasma hominis. *FEMS Immunol Med Microbiol* 2002;34:277-281.

### **Human immunodeficiency virus type 1 stimulatory activity by Gardnerella vaginalis: relationship to biotypes and other pathogenic characteristics**

Gardnerella vaginalis is a “bad” type of bacteria that can infect the vagina and cause bacterial vaginosis (BV). This study found that it can also cause HIV in the vagina to become more active. Whether the Gardnerella vaginalis was resistant to certain drugs used to treat BV did not affect its ability to make HIV more active.

Simoes JA, Hashemi FB, Aroutcheva AA, Heimler I, Spear GT, Shott S, and Faro S. Human immunodeficiency virus type 1 stimulatory activity by Gardnerella vaginalis: relationship to biotypes and other pathogenic characteristics. *J Infect Dis* 2001;184:22-27.

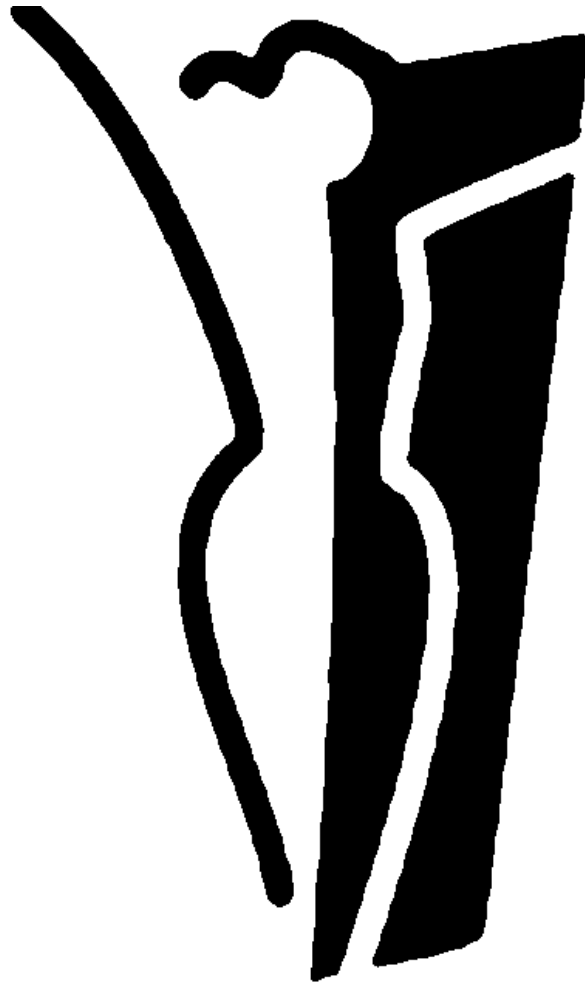
### **Bacterial vaginosis-associated microflora isolated from the female genital tract activates HIV-1 expression**

A healthy vagina is home to many types of “good” organisms. The presence of “bad” bacteria can result in bacterial vaginosis (BV) and lead to increased HIV activity and transmission. This research looked at several types of “bad” bacteria to see which ones could activate HIV; they suggest that Mycoplasma hominis may be involved.

Al Harthi L, Roebuck KA, Olinger GG, Landay A, Sha BE, Hashemi FB, and Spear GT. Bacterial vaginosis-associated microflora isolated from the female genital tract activates HIV-1 expression. *J Acquir Immune Defic Syndr* 1999;21:194-202.



# Cardiovascular





### **Cytomegalovirus IgG antibody is associated with subclinical carotid artery disease among HIV-infected women**

Adults with HIV infection have a higher risk of cardiovascular events. Cytomegalovirus (CMV) infection may be associated with vascular disease in HIV-infected adults. We used WIHS data to examine CMV IgG in relation to several cardiovascular variables. We found that CMV IgG was higher in HIV-infected women compared to HIV-uninfected women, and was associated with subclinical cardiovascular disease in HIV-infected women.

Parrinello CM, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, Xue X, Hunt PW, Deeks SG, Hodis HN, and Kaplan RC. Cytomegalovirus IgG antibody is associated with subclinical carotid artery disease among HIV-infected women. *J Infect Dis* 2012 205(12):1788-96.

**PMC3415890**

### **Association of subclinical atherosclerosis with lipid levels amongst antiretroviral-treated and untreated HIV-infected women in the Women's Interagency HIV study**

HIV infection results in abnormal lipid levels, which may increase risk of cardiovascular disease. HIV treatment has been shown to increase lipid levels in persons with HIV, which has also been linked to increased risk of cardiovascular disease. We examined lipid levels in both persons with and without HIV, to see if they were associated with atherosclerosis (as measured by CIMT). In women without HIV, higher lipids were associated with atherosclerosis. In women with HIV, we only found associations between lipids and atherosclerosis in the women who were treated. In the HIV-infected women who were treated, lipids measured 10 years earlier had stronger associations with atherosclerosis than the lipids measured at the same time as the CIMT measurement.

Parrinello CM, Landay AL, Hodis HN, Gange SJ, Norris PJ, Young M, Anastos K, Tien PC, Xue X, Lazar J, Benning L, Tracy RP, Kaplan RC. Association of subclinical atherosclerosis with lipid levels amongst antiretroviral-treated and untreated HIV-infected women in the Women's Interagency HIV study. *Atherosclerosis* 2012 225(2):408-411.

### **Chronic Depressive Symptoms and Framingham Coronary Risk in HIV-Infected and Uninfected Women**

Depression is common in people with cardiovascular diseases (CVD) and is a risk factor for CVD-related death. However, little is known about whether HIV infection influences the relationship between depression and cardiovascular risk. 526 HIV-infected and 132 uninfected women in the WIHS study were included in this analysis. We found that cardiovascular risk was similar between the HIV-infected and uninfected women. We also found that experiencing symptoms of chronic depression increased cardiovascular risk scores for both HIV-infected and uninfected women. The diagnosis and treatment of depression may be an important consideration in cardiovascular risk reduction for both HIV-infected and uninfected women.

Schwartz RM, Mansoor A, Wilson TE, Anastos K, Everson-Rose SA, Golub ET, Goparaju L, Hessol NA, Mack W, and Lazar J. Chronic Depressive Symptoms and Framingham Coronary Risk in HIV-Infected and Uninfected Women. *AIDS Care* 2012;24(3):394-403. **PMC3243818**

### **T-cell activation and senescence predict subclinical carotid artery disease in HIV-infected women**

Prior studies of people living with HIV infection show that having low CD4 counts may be bad for the heart and blood vessels. In earlier studies, we showed that this was true among women in the WIHS. This paper is a more detailed study of HIV-infected and HIV uninfected WIHS participants who volunteered to have measurements of their neck arteries taken ("carotid artery substudy"). By making measurements of the types of immune cells (Tcells) in the blood specimens donated by WIHS participants, we learned some new information about what specific types of immune cells might be involved in developing heart and blood vessel diseases in HIV-infected women. The results will not change what doctors are currently doing to prevent and treat heart disease in HIV-infected women, but help researchers better understand the biological processes that are involved.

Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, Xue X, Hunt P, Karim R, Kern DM, Hodis HN, and Deeks SG. T-cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. *J Infect Dis* 2011;203(4):452-463. **PMC3071219**

### **T-cell activation predicts carotid artery stiffness among HIV-infected women**

Some women with HIV infection may have high risk of developing diseases of the heart and blood vessels. This study used data from the carotid ultrasound substudy, which included ~75% of women in the WIHS. We found that HIV+ women who had abnormal immune function had more stiff neck arteries. This may suggest a higher risk of heart attack and stroke in women who have HIV and whose disease is not well-controlled by antiretroviral treatment

Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gandhi M, Xue X, Parrinello C, Hunt P, Deeks SG, and Hodis H. T-cell activation predicts carotid artery stiffness among HIV-infected women. *Atherosclerosis* 2011;217(1):207-213. **PMC3139014**



### **Oxidant stress in HIV-infected women from the Women's Interagency HIV Study**

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.

Glesby MJ, Hoover DR, Raiszadeh F, Lee I, Shi Q, Milne G, Sanchez SC, Gao W, Kaplan RC, Morrow JD, and Anastos K. Oxidant stress in HIV-infected women from the Women's Interagency HIV Study. *Antivir Ther* 2009;14(6):763-769.

### **The association of HIV infection with left ventricular mass/hypertrophy**

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).

Mansoor A, Golub ET, DeHovitz J, Anastos K, Kaplan RC, and Lazar J. The association of HIV infection with left ventricular mass/hypertrophy. *AIDS Res Hum Retroviruses* 2009;25(5):475-481.

### **Plasma Homocysteine Is Not Associated With HIV Serostatus or Antiretroviral Therapy in Women**

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.

Raiszadeh F, Hoover DR, Lee I, Shi Q, Anastos K, Gao W, Kaplan R, and Glesby MJ. Brief Report: Plasma Homocysteine is Not Associated with HIV Serostatus or Antiretroviral Therapy in Women. *J Acquir Immune Defic Synd* 2009;51(2):175-178.





### **Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV- infected women and men**

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.

Kaplan R, Kingsley L, Gange S, Benning L, Jacobson L, Lazar J, Anastos K, Tien P, Sharrett R, and Hodis H. Low CD4+ T-cell count as major atherosclerosis risk factor in HIV-infected women and men. *AIDS* 2008;22:1615-1624.

### **Interarm blood pressure differences in the women's interagency HIV study**

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.

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.

### **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.

Kaplan RC, Kingsley LA, Sharrett AR, Li X, Lazar J, Tien PC, Mack WJ, Cohen MH, Jacobson L and Gange SJ. Ten-year predicted coronary heart disease risk in HIV-infected men and women. *Clin Infect Dis* 2007;45:1074-1081.



### **Correlates of prevalent hypertension in a large cohort of HIV- infected women: Women's Interagency HIV Study**

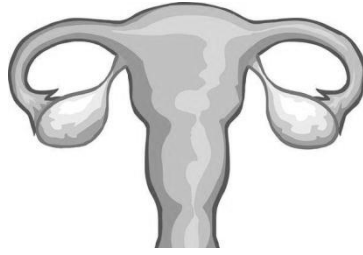
High blood pressure (hypertension) has been associated with development of heart disease, stroke, kidney failure and other serious consequences. Hypertension has been studied in HIV infected persons, but the results have not been consistent, with some studies showing an increase in hypertension in HIV 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.

Khalsa A, Karim R, Mack WJ, Minkoff H, Cohen M, Young M, Anastos K, Tien PC, Seaberg E and Levine AM. Correlates of prevalent hypertension in a large cohort of HIV-infected women: Women's Interagency HIV Study. *AIDS* 2007;21:2539-2541.

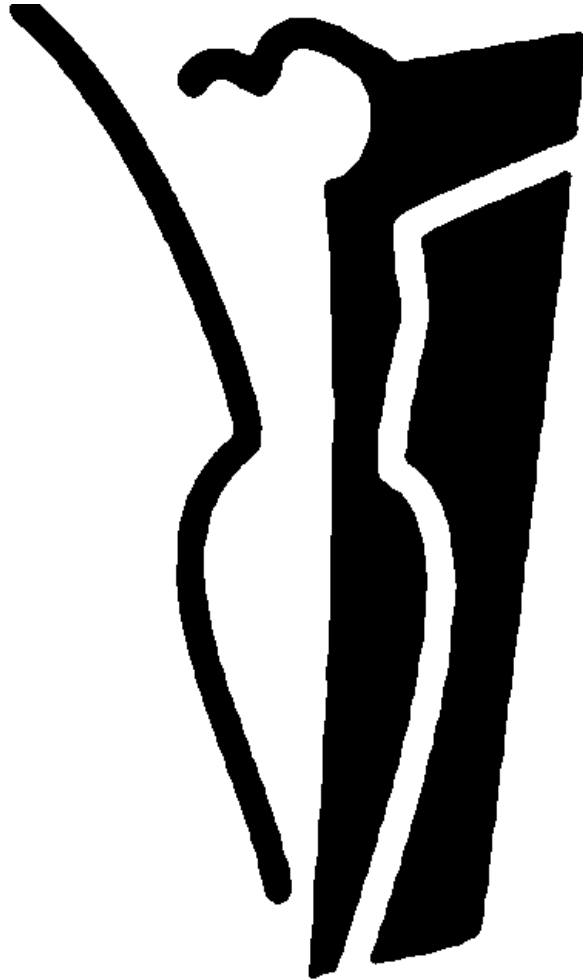
### **Peripheral arterial disease in HIV-infected and uninfected women**

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.

Sharma A, Holman S, Pitts R, Minkoff HL, DeHovitz JA, Lazar J. Peripheral arterial disease in HIV-infected and uninfected women. *HIV Med* 2007;8:555-560.



## **Cervical Cancer and HPV**





### **Risk Factors for oral HPV infection among a high prevalence population of HIV-positive and at-risk HIV-negative adults**

Recently, human papillomavirus (HPV) has been found to cause certain types of oral cancer. People with human immunodeficiency virus (HIV) are more likely to have oral HPV infection, but it is not known why. This study included people from 2 cohort studies: the MACS and the WIHS. 379 HIV-positive and 266 HIV-negative individuals were enrolled in this sub-study. Cells from the mouth and throat were collected by rinsing and gargling with Scope mouthwash. These cells were tested for HPV DNA. Oral HPV infection was common (34%), even though oral cancer is rare. HPV16 (the type responsible for most tonsillar cancers) was found in 5.7% of participants. HIV-negative participants who had had more recent oral sex partners were more likely to have an oral HPV infection. Among HIV-positive participants, lower CD4 cell count and having had more lifetime oral sex partners were strong risk factors for oral HPV infection. This suggests people who are immunosuppressed may be less likely to be able to clear oral HPV infections. Future studies will look at how likely these prevalent oral HPV infections are to clear and what risk factors are related to oral HPV persistence.

Beachler DC, Weber KM, Margolick JR, Strickler HD, Cranston RD, Burk RD, Wiley DJ, Minkoff H, Reddy S, Stammer EE, Gillison ML, and D'Souza GA. Risk Factors for oral HPV infection among a high prevalence population of HIV-positive and at-risk HIV-negative adults. *Cancer Epidemiol Biomarkers Prev* 2012 21(1):122-33.

### **Correlating knowledge of cervical cancer prevention and human papillomavirus with compliance after colposcopy referral**

Women with HIV are at high risk for developing cervical cancer. Cervical cancer is preventable in HIV+ women, but prevention requires multiple visits for Pap testing. Women with abnormal Pap tests need a colposcopy, examination of the cervix with bright light and magnification, to see if they have precancer that really needs treatment. WIHS researchers showed in 1999 that getting women with HIV to come to colposcopy was hard and many women didn't follow up. We set out to look at multiple factors that might predict whether women who need colposcopy follow up. Factors we looked at included knowledge about cervical cancer prevention, stress, depression, study site, trust in doctors, and prior abnormal Pap tests. Things that were associated with actually getting colposcopy done included less education, prior abnormal Pap, study site, and higher stress. Teaching women about cervical cancer seems unlikely to improve follow-up, but changing how sites manage women with abnormal Paps might help.

Massad LS, Weber KM, Wilson TE, Goderre JL, Hessel NA, Henry D, Colie C, Strickler HD, Levine AM, Watts DH, and Evans CT. Correlating knowledge of cervical cancer prevention and human papillomavirus with compliance after colposcopy referral. *J Lower Genital Tract Dis* 2012;16(2):98-105.

### **Effect of Human Immunodeficiency Virus Infection on the Prevalence and Incidence of Vaginal Intraepithelial Neoplasia**

Women with HIV are more likely to have abnormal Pap tests and cervical precancer than those who do not. Hysterectomy eliminates risk for cervical cancer by removing the cervix. But WIHS and others have shown that HPV, the virus that causes cervical cancer, is still present in the vagina after hysterectomy. How often HIV+ women still have abnormal Paps after hysterectomy isn't known. Neither is how often HIV+ women can get precancers in the vagina. We looked at these questions and found that after 5.6 years of follow-up Paps were abnormal in 89% of visits for HIV+ women after hysterectomy compared to only 4% of HIV- women. But these abnormal Paps were often of low grade. Only 14% of women who'd had hysterectomy had abnormal Paps every year. Abnormal Paps were more common among women with lower CD4 counts and smokers. About a third of HIV+ women with abnormal Paps cleared them over 5 years. True precancers found on biopsy were pretty uncommon in HIV+ women (0.2% per year), though more common than in HIV- women. Two women developed vaginal cancer during follow-up, but both appear to have been cured after radiation treatment. In conclusion, women with HIV often have abnormal Paps, even after hysterectomy, but these don't often lead to high grade precancer or cancer.

Massad LS, Xie X, Greenblatt RM, Minkoff H, Sanchez-Keeland L, Watts DH, Wright RL, D'Souza GA, Merenstein D, and Strickler H. Effect of Human Immunodeficiency Virus Infection on the Prevalence and Incidence of Vaginal Intraepithelial Neoplasia. *Obstet Gynecol* 2012;119(3):582-9. **PMC3285255**



### **Cervicovaginal HPV Infection Before and After Hysterectomy: Evidence of Different Tissue Tropism for Oncogenic and Non-Oncogenic HPV Types in a Cohort of HIV-positive and HIV-negative Women**

This study evaluated how common the different types of human papillomavirus (HPV) are in HIV-infected women. Oncogenic HPV (the types that can cause cancer) reduced significantly in HIV-infected women who had hysterectomy but non-oncogenic HPV (the types of HPV that do not cause cancer) remained common in the vagina of women who had hysterectomy. This suggests that oncogenic HPV types may have a special affinity for the cervix and that may be why these HPV types are an important cause of cervical cancer, but do not cause as much vaginal cancer.

D'Souza GA, Burk R, Zhong Y, Minkoff H, Massad LS, Xue X, Watts DH, Anastos K, Palefsky J, Levine AM, Colie C, Castle P, and Strickler HD. Cervicovaginal HPV Infection Before and After Hysterectomy: Evidence of Different Tissue Tropism for Oncogenic and Non-Oncogenic HPV Types in a Cohort of HIV-positive and HIV-negative Women. *Int J Cancer* 2011 10.1002/ijc.27363. **PMC3321069**

### **Genital Warts and Vulvar Intraepithelial Neoplasia: Natural History and Effects of Treatment and Human Immunodeficiency Virus Infection**

Immunosuppressed women are at high risk for genital warts. The viruses that cause warts can also lead to cancer and precancer of the vulva, the skin around the vagina. WIHS has previously shown that HIV+ women are more likely to get warts and vulvar precancer. In this study, including the 2001-2 cohort, we showed that again. About a third of HIV+ women got genital warts during follow-up periods extending up to 13 years.

We also showed that most WIHS women who get genital warts have them go away, often without treatment, and usually within the first year after they're seen. Women who smoke and those with lower CD4 counts are at higher risk for warts, although women who'd quit smoking were not at higher risk. Usual treatments seem to be effective for HIV+ women with warts, though warts were more likely to come back after treatment in HIV+ than HIV- women.

Warts are hard to distinguish from precancers. HIV+ women were more likely to need biopsy of changes in vulvar skin and were more likely to have precancer. Risk for vulvar precancer was only high among women with lowest CD4 counts, suggesting that women with minimal to moderate immunosuppression may be able to control the virus that leads to vulvar cancer.

Only two women were found to have vulvar cancer through all of WIHS. Both had early cancers that were treated surgically, apparently with cure.

Massad LS, Xie X, Darragh T, Minkoff H, Levine AM, Watts DH, Wright R, D'Souza D, Colie C, and Strickler H. Genital Warts and Vulvar Intraepithelial Neoplasia: Natural History and Effects of Treatment and Human Immunodeficiency Virus Infection. *Obstet Gynecol* 2011;118(4):831-839. **PMC3178036**

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

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.

D'Souza G, Palefsky JM, Zhong Y, Minkoff H, Massad LS, Anastos K, Levine AM, Moxley M, Xue XN, Burk RD, and Strickler HD. Marijuana use is not associated with cervical human papillomavirus natural history or cervical neoplasia in HIV-seropositive or HIV-seronegative women. *Cancer Epidemiol Biomarkers Prev* 2010;19(3):869-872.



### **Knowledge of cervical cancer prevention and human papillomavirus among women with HIV**

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.

Massad LS, Evans C, Wilson T, Goderre J, Hessol N, Henry D, Colie C, Strickler H, Levine AM, Watts DH, and Weber K. Knowledge of cervical cancer prevention and human papillomavirus among women with HIV. *Gynecol Oncol* 2010;217:70-76.

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

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.

Massad LS, Xie X, Darragh T, Minkoff H, Levine AM, D'Souza G, Cajigas A, Colie C, Watts DH, and Strickler H. Histologic correlates of glandular abnormalities in cervical cytology among women with HIV. *Obstet Gynecol* 2009;114(5):1063-1068

### **Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women**

Infection with anal human papillomavirus (HPV), the viral cause of anal cancer, is common in HIV-infected women. However, few studies have looked at the risk factors for anal intraepithelial neoplasia (AIN) in HIV-infected and other high-risk women. We studied AIN in a subset of the WIHS women from San Francisco Bay Area, Chicago, and Brooklyn. Participants were interviewed and received a gynecological examination, including anal and cervical cytology testing and, if abnormal, colposcopy or anoscopy-guided biopsy of visible lesions. A total of 657 (471 HIV-infected and 186 HIV-uninfected) women were enrolled. Anal and cervical HPV-related disease and anal HPV infection were very common in the HIV-infected women, even in the HAART era. The most important risk factors for LGAIN were history of receptive anal intercourse and anal HPV infection (both high risk and low risk for cancer types). The most important risk factor for HGAIN was anal HPV infection (only high risk for cancer types).

Hessol NA, Holly EA, Efird JT, Minkoff H, Schowalter K, Darragh TM, Burk RD, Strickler HD, Greenblatt RM and Palefsky JM . Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women. *AIDS* 2009;23(1):59-70.

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

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.

Xue X, Gange SJ, Zhong Y, Burk RD, Minkoff H, Massad LS, Watts H, Kuniholm M, Anastos K, Levine AM, D'Souza G, Moxley M, Palefsky JM, and Strickler HD. Marginal and Mixed Effects Models in the Analysis of HPV Natural History Data. *Cancer Epidemiol Biomarkers Prev* 2010;19(1):159-169.



### **Long-term incidence of cervical cancer in women with human immunodeficiency virus**

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.

Massad LS, Seaberg EC, Watts DH, Minkoff H, Levine AM, Henry D, Colie C, Darragh TH, and Hessel N. Long-term incidence of cervical cancer in women with human immunodeficiency virus. *Cancer* 2009;115(3):524-530.

### **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.

Harris TG, Burk RD, Yu H, Minkoff H, Massad LS, Watts DH, Zhong Y, Gange S, Kaplan RC, Anastos K, Levine AM, Moxley M, Xue X, Fazzari M, Palefsky JM and Strickler HD. Insulin-like growth factor axis and oncogenic human papillomavirus natural history. *Cancer Epidemiol Biomarkers Prev* 2008;17:245-248.

### **High-grade cervical disease in adolescents with HIV**

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.

Massad LS, Evans CT, D'Souza G, Darragh T, Minkoff H, Henry D, Goparaju L, Muderspach LI, and Watts DH. High-grade cervical disease in adolescents with HIV. *J Low Genit Tract Dis* 2008;12:199-203.

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

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.

Massad LS, Seaberg EC, Wright R, Darragh T, Lee Y, Colie C, Burk R, Strickler H and Watts H. Squamous cervical lesions in women with HIV: Long-term follow-up in the Women's Interagency HIV Study. *Ob Gyn* 2008;111:1388-1393.

### **The relationship between cocaine use and human papillomavirus infections in HIV-seropositive and HIV-seronegative women**

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.

Minkoff H, Zhong Y, Strickler HD, Watts DH, Palefsky JM, Levine AM, D'Souza G, Howard AA, Plankey M, Massad LS and Burk R. The relationship between cocaine use and human papillomavirus infections in HIV-seropositive and HIV-seronegative women. *Infect Dis Obstet Gynecol* 2008;2008:587082.



### **Six-month natural history of oral versus cervical human papillomavirus infection**

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.

D'Souza G, Fakhry C, Sugar E, Seaberg EC, Weber K, Minkoff H, Anastos K, Palefsky J and Gillison M. Six-month natural history of oral versus cervical HPV infection. *Int J Cancer* 2007;121(1):143-150.;11(2):90-97.

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

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 like 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.

Harris TG, Burk RD, Xue X, Anastos K, Minkoff H, Massad LS, Young MA, Levine AM, Gange SJ, Watts DH, Palefsky JM, and Strickler HD. Association of cutaneous anergy with human papillomavirus and cervical neoplasia in HIV-seropositive and seronegative women. *AIDS* 2007;21:1933-1941.

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

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.

Massad LS, Fazzari M, Anastos K, Klein R, Minkoff H, Jamieson D, Duerr A, Celentano D, Gange S, Cu-Uvin S, Young M, Watts H, Levine A, Schuman P, Harris T and Strickler H. Outcomes after treatment of cervical intraepithelial neoplasia among women with HIV. *J Low Genit Tract Dis* 2007;11(2):90-97.

### **The relationship between prevalent oral and cervical HPV infections in HIV-positive and negative women**

There are many different types of the human papillomavirus (HPV). HPV can infect both the cervix and the mouth/throat and certain types can cause cancer in these places. This study looked at whether women had the same or different types of HPV in the cervix and mouth/throat. The study found that most women did not have infections in the cervix and mouth at the same time, but if they did, the types were often the same. Overall, 25% of HIV+ women had HPV mouth/throat infections and 77% had cervical infections. In HIV- women, 9% had mouth/throat HPV and 45% had cervical HPV.

Fakhry C, D'Souza G, Sugar E, Weber K, Goshu E, Minkoff H, Wright R, Seaberg E, and Gillison M. The relationship between prevalent oral and cervical HPV infections in HIV-positive and negative women. *J Clin Microbiol* 2006;44(12):4479-4485. **PMC1698387**





### **Outcome After Negative Colposcopy Among Human Immunodeficiency Virus-Infected Women With Borderline Cytologic Abnormalities**

Pap smears look at cervical cells to detect early signs of cervical cancer. If there are unusual cells, colposcopy is used to look more closely at the cervix. This study looked at women who had unusual cells on their Pap smear but normal colposcopy results. Of these women, 12% of the HIV+ and 4% of the HIV- women later developed some cervical lesion or cancer. However, infection with certain types of HPV and race were important predictors of whether these women would develop cervical cancer.

Massad LS, Evans CT, Strickler HD, Burk RD, Watts DH, Cashin L, Darragh T, Gange S, Lee YC, Moxley M, Levine A, and Passaro DJ. Outcome After Negative Colposcopy Among Human Immunodeficiency Virus-Infected Women With Borderline Cytologic Abnormalities. *Obstet Gynecol* 2005;106:525-532.

### **Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus**

There are many types of human papillomavirus, which can cause genital warts and cervical cancer. Researchers found that 5 out of every 100 women (per year) with HIV had genital warts, compared to 1.3 out of every 100 HIV negative women (per year). Vulvar intraepithelial neoplasia (a skin change that can sometimes become cancer) was also much more common among women with HIV. Being on HAART decreased the risk of warts or neoplasia, while lower CD4 counts increased the risk. The type of human papillomavirus was also an important factor.

Massad LS, Silverberg MJ, Springer G, Minkoff H, Hessel N, Palefsky JM, Strickler HD, Levine AM, Sacks HS, Moxley M, and Watts DH. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. *Am J Obstet Gynecol* 2004;190:1241-1248.

### **HPV testing for triage of HIV-infected women with papanicolaou smears read as atypical squamous cells of uncertain significance**

Some types of human papillomavirus increase the risk of cervical cancer. Pap smears check for abnormal cells in the cervix in order to prevent cervical cancer. Sometimes the results from a Pap smear can be unclear and a woman may be instructed to have a colposcopy. This study asked if testing the woman for different types of human papillomavirus instead would be useful. However, they found that these tests were not as good as the colposcopy for detecting which women were at risk for cervical cancer.

Massad LS, Schneider MF, Watts DH, Strickler HD, Melnick S, Palefsky J, Anastos K, Levine AM, and Minkoff H. HPV testing for triage of HIV-infected women with papanicolaou smears read as atypical squamous cells of uncertain significance. *J Womens Health* 2004;13:147-153.

### **Natural history of grade 1 cervical intraepithelial neoplasia in women with human immunodeficiency virus**

Grade 1 cervical intraepithelial neoplasias (CIN1) are abnormal areas on the cervix. Sometimes they get worse and become cancer and sometimes they go away on their own. This study looked at HIV+ and HIV- women with CIN1 and followed them over time to see what happened to these areas. None of the HIV- women and only 8 (out of 202) HIV+ women got worse. One-third of the HIV+ women and two-thirds of the HIV- women got better on their own. The type of human papillomavirus was an important factor in whether the abnormal areas went away.

Massad LS, Evans CT, Minkoff H, Watts DH, Strickler HD, Darragh T, Levine A, Anastos K, Moxley M, and Passaro DJ. Natural history of grade 1 cervical intraepithelial neoplasia in women with human immunodeficiency virus. *Obstet Gynecol* 2004;104:1077-1085.

### **Correlating Papanicolaou Smear, Colposcopic Impression, and Biopsy Among Women with HIV-1: Results from the WIHS**

Pap smears and colposcopies are used to examine the cervix to prevent cervical cancer. The ability of these tests to find early signs of cervical cancer were slightly better for HIV+ women than for HIV- women. However, the tests did not always agree with each other.

Massad LS, Schneider M, Watts DH, Darragh T, Abulafia O, Salzer E, Munderspach L, Sidaway M, and Melnick S. Correlating Papanicolaou Smear, Colposcopic Impression, and Biopsy Among Women with HIV-1: Results from the WIHS. *J Lower Genital Tract Dis* 2001;5:212-218.



### **Evolution of cervical abnormalities among women with HIV-1: Evidence from surveillance cytology in the Women's Interagency HIV Study**

Pap smears look for cervical signs that may lead to cancer. Sometimes these lesions get better on their own (regress) and sometimes they become cancer (progress). While 73% of HIV+ women had at least one abnormal Pap smear, only 6% ever developed a serious lesion that meant a risk for cancer. HIV+ women with high CD4 counts and low viral loads were similar to HIV- women in terms of risk of progressing to cancer. Most HIV+ women were less likely than HIV- women to have lesions regress and disappear.

Massad LS, Ahdieh L, Benning L, Minkoff H, Greenblatt RM, Watts H, Miotti P, Anastos K, Moxley M, Muderspach LI, and Melnick S. Evolution of cervical abnormalities among women with HIV-1: Evidence from surveillance cytology in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2001;27:432-442

### **Association of vitamin A deficiency with cervical squamous intraepithelial lesions in human immunodeficiency virus-infected women**

Some types of human papillomavirus can cause genital warts or cervical cancer. Women with low levels of vitamin A and HIV were more likely to have cervical lesions that could be early signs of cervical cancer.

French AL, Kirstein LM, Massad LS, Semba RD, Minkoff H, Landesman S, Palefsky J, Young M, Anastos K, and Cohen MH. Association of vitamin A deficiency with cervical squamous intraepithelial lesions in human immunodeficiency virus-infected women. *J Infect Dis* 2000;182:1084-1089.

### **Adherence to colposcopy among women with HIV infection**

Colposcopy is used to examine the cervix for signs of cancer if a woman has an abnormal Pap smear. However, many women do not get a colposcopy when recommended. This study found that 65% of WIHS women got a colposcopy when recommended by their doctor. Women with HIV, who use crack or cocaine, who were too ill to get care or who were less concerned about their children were less likely to get a colposcopy when recommended. Among HIV+ women, low CD4 counts and high viral loads were related to not getting a colposcopy. This information can help providers make sure their patients get colposcopies when needed.

Cejtin HE, Komaroff E, Massad LS, Korn A, Schmidt JB, Eisenberger-Matiyahu D, and Stier E. Adherence to colposcopy among women with HIV infection. *J Acquir Immune Defic Syndr* 1999;22:247-252.

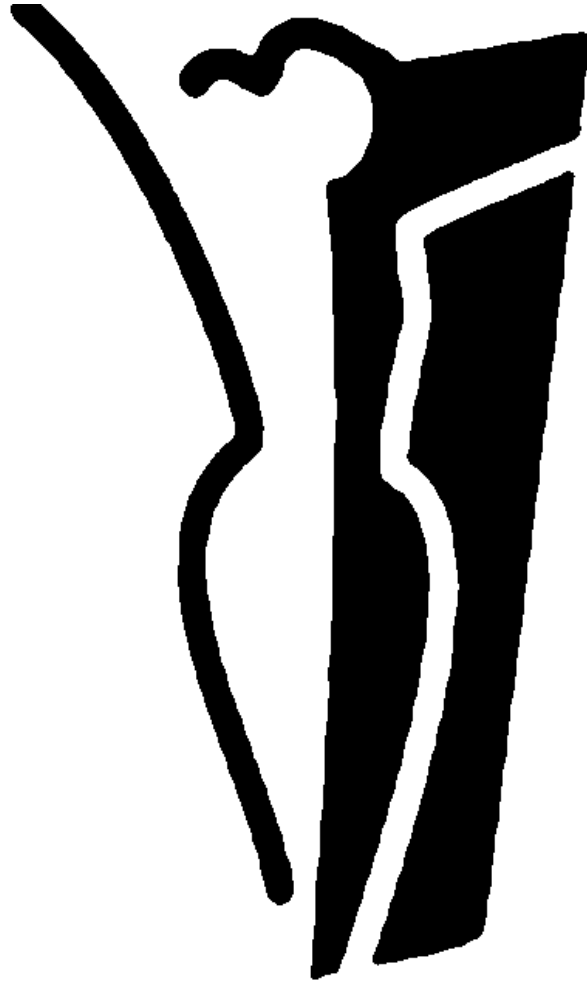
### **Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1**

Women with HIV had higher rates of abnormal cervical cells (38%) compared to HIV- women (16%). However, few women went on to have signs of cervical cancer or pre-cancer. Women with low CD4 counts, higher viral loads, human papillomavirus and higher number of recent male sex partners were all more likely to have abnormal cervical cells.

Massad LS, Riestler KA, Anastos KM, Fruchter RG, Palefsky JM, Burk RD, Burns D, Greenblatt RM, Muderspach LI, and Miotti P. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr* 1999;21:33-41.



# Depression





### **Depressive symptoms are increased in the early perimenopausal stage in ethnically diverse HIV+ and HIV- women**

A number of recent research studies have demonstrated that women experience more depressive symptoms as they enter menopause or “the change” compared to when they were younger. We looked at whether depressive symptoms are higher at different stages of the menopause compared to before the onset of menopause. It’s helpful to describe some definitions that we used to define different stages of the menopause. “Premenopause” means “before menopause” and refers to the stage when women are fertile and have menstrual cycles that come once a month (about every 28 days). The menopause includes three stages: early perimenopause, late perimenopause, and postmenopause. “Peri” means “around” so “perimenopause” means around the menopause. Early perimenopause is when women start to notice that their cycles do not come as regularly as they used to when they were younger. Late perimenopause is when women start to skip periods. “Post” means “after,” so “postmenopause” is after menopause, specifically 12 months after periods have stopped completely.

In this study, we examined whether WIHS participants also were more likely to show depressive symptoms during the menopause. We also wanted to determine whether women who were HIV-infected were more likely to show depressive symptoms during the perimenopause. Our results were similar to other research studies and showed that women in the WIHS were more likely to experience depressive symptoms in the early perimenopause. We found that HIV-infected women and HIV-uninfected women showed a similar level of depressive symptoms during that perimenopausal stage. Women with hot flashes were also more likely to show elevated depressive symptoms regardless of what menopausal stage they were in. Overall, these findings suggest that HIV-infected and HIV-uninfected women may be more likely to show depressive symptoms when their menstrual cycles first start to become irregular.

Maki PM, Rubin LH, Cohen M, Golub ET, Greenblatt RM, Young M, Schwartz RM, Anastos K, & Cook JA. Depressive symptoms are increased in the early perimenopausal stage in ethnically diverse HIV+ and HIV- women. *Menopause* 2012.

### **Perinatal Depressive Symptoms in HIV-Infected versus HIV-Uninfected Women: A Prospective Study from Preconception to Postpartum**

Many women who have HIV also experience depression. It is important to look at women with both HIV and depression because it can affect HIV being passed on to the baby and how regularly a woman takes her prescribed medication. We examined perinatal depressive symptoms by following women from before pregnancy through childbirth. Perinatal is the time occurring during pregnancy and one year after birth. 139 HIV-infected and 105 uninfected women participated in the study. The results show that rates of perinatal depressive symptoms did not differ between HIV-infected and uninfected women. The best predictor of high perinatal depressive symptoms in HIV-infected woman was if they had depressive symptoms prior to pregnancy. If an HIV-infected woman used crack, cocaine or heroin, they were also at a slightly higher risk for perinatal depressive symptoms. Finally, all women were at a higher risk for perinatal depressive symptoms if they used available mental health services or did not graduate from high school. Results from this study show that these risk factors, especially depression prior to pregnancy, should be examined and treated because it can help to prevent HIV being transmitted to the baby and to improve post pregnancy outcomes for mothers and children.

Rubin LH, Cook JA, Grey DD, Weber K, Wells C, Golub ET, Wright RL, Schwartz RM, Goparaju L, and Maki PM. Perinatal Depressive Symptoms in HIV-Infected versus HIV-Uninfected Women: A Prospective Study from Preconception to Postpartum. *J Women’s Health*

### **An instrumental variable evaluation of antidepressant use on employment among HIV-infected women using highly-active antiretroviral therapy in the United States: 1996-2004**

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 that the HIV drugs cofrectly 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 not 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.

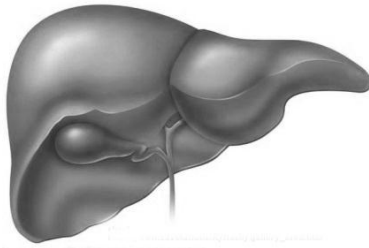
Galarraga O, Salkever S, Cook JA, and Gange SJ. An instrumental variable evaluation of antidepressant use on employment among HIV-infected women using highly-active antiretroviral therapy in the United States: 1996-2004. *NBER Working Paper* 2006;12619:1-42.



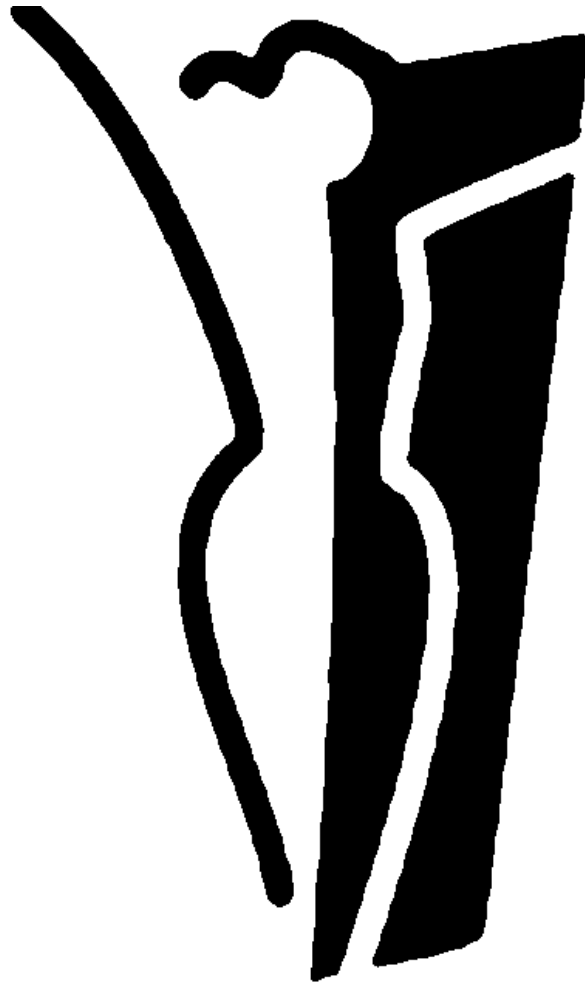
### **Depressive Symptoms and AIDS-Related Mortality Among a Multisite Cohort of HIV-Positive Women**

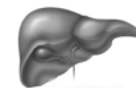
Many women with HIV also suffer from depression. This study found that even when accounting for other health factors, women with chronic depressive symptoms were at higher risk for dying from AIDS. Women who had worse depression also had faster progression of HIV/AIDS. However, receiving mental health services seemed to decrease the risk of dying.

Cook JA, Grey D, Burke J, Cohen MH, Gurtman AC, Richardson JL, Wilson TE, Young MA, and Hessel NA. Depressive Symptoms and AIDS-Related Mortality Among a Multisite Cohort of HIV-Positive Women. *Am J Public Health* 2004;94:1133-1140. **PMC1448411**



# Liver Disease and Hepatitis





### **Assessing Mortality in Women with Hepatitis C Virus and Human Immunodeficiency Virus using Indirect Markers of Fibrosis**

It is very important to find out how much damage hepatitis C has done to the liver. If a patient has a lot of damage or fibrosis then treatment is important. If there is very little or no damage then treatment can wait. How do we decide how much damage there is in the liver? The main way has been by performing a liver biopsy. Liver biopsy has been used to determine the amount of fibrosis and to evaluate the level of inflammation. However biopsies only sample a small piece of liver; there may be areas with more or less scar tissue leading to underestimating the amount of scar tissue or fibrosis. So we are very interested in finding out if blood tests can tell us how much damage there is to the liver. This study used blood tests that are done routinely and shows that those with the most severe score on the blood tests had the worst survival.

Bambha K, Pierce C, Cox C, French AL, Tien PC, Strickler HD, Sharp GB, Augenbraun M, Glesby MJ, Villacres M, Plankey M, Gange SJ, and Petes MG. Assessing Mortality in Women with Hepatitis C Virus and Human Immunodeficiency Virus using Indirect Markers of Fibrosis. *AIDS* 2012; 26(5):599-607.

### **Liver diffusivity in healthy volunteers and patients with chronic liver disease: comparison of breathhold and free-breathing techniques**

We compared the liver image of patients with chronic liver disease (fatty liver disease and HCV) to healthy subjects using two different ways of doing MRI. We found a moderate correlation between the two techniques at best, meaning two techniques should not be used interchangeably. Additionally, the consistently higher ADC value with free-breathing technique compare to breath-hold technique. The findings of this study will improve how we use MRI to study the liver. The long term goal of our study is to see if MRI (which does not require sticking a needle into the liver) can be used in place of a liver biopsy to study scarring of the liver.

Eatesam M, Noworolski SM, Tien PC, Nystrom M, Dodge JL, Merriman RB, and Qayyum A. Liver diffusivity in healthy volunteers and patients with chronic liver disease: comparison of breathhold and free-breathing techniques. *J Magn Reson* 2012 35(1):103-9. **PMC3241899**

### **Lower Liver-Related Death in African American Women With HIV/HCV Co-Infection Compared to Caucasian and Hispanic Women**

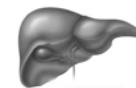
Racial/ethnic differences in how hepatitis C progresses have been well described. The ability to spontaneously clear HCV from the body is lower among African Americans compared to Caucasians and Hispanics. However African Americans appear to develop less fibrosis and inflammation once they have chronic HCV. We studied whether there are differences in deaths from hepatitis C depending upon race of women in WIHS. We found that African American women who have both HIV and hepatitis C were much less likely to die from liver disease as compared to Caucasians and Hispanics. There were no differences in death form other causes.

Sarkar M, Bacchetti P, French AL, Tien P, Glesby MJ, Nowicki M, Plankey M, Gange S, Sharp G, Minkoff H and Peters MG. Lower Liver-Related Death in African American Women With HIV/HCV Co-Infection Compared to Caucasian and Hispanic Women. *Heptology* 2012.

### **Responses to Hepatitis A Virus Vaccine in HIV-Infected Women: Effect of Hormonal Contraceptives and HIV Disease Characteristics**

We studied the effect of hormonal contraceptives and other HIV disease characteristics on antibody responses to hepatitis A vaccine of HIV-infected women. Antibodies are measures commonly used to determine if vaccines are working well in an individual. We found that antibody responses to hepatitis A vaccine were neither decreased nor increased by the use of hormonal contraceptives in HIV-infected women. However, antibody responses to hepatitis A vaccine were overall low in HIV-infected women and were lower in those with lower CD4+ cells. Many women had antibodies against hepatitis A before vaccination and in these women vaccination was not beneficial. We conclude that HIV-infected women should be tested for the presence of antibodies against hepatitis A before vaccination to determine if they may benefit from the vaccine. If they do, it is best to administer the vaccine when the CD4+ cell numbers are high.

Weinberg A, Allshouse AA, MaWhinney S, Canniff J, Benning L, Wentz EL, Minkoff H, Young M, Nowicki M, Greenblatt R, Cohen M and Golub E. Responses to Hepatitis A Virus Vaccine in HIV-Infected Women: Effect of Hormonal Contraceptives and HIV Disease Characteristics. *J Acquir Immune Defic Syndr* 2012 1;60(1):e15-e18. **PMC3332075**



## **The Relation of HLA Genotype with Hepatitis C Viral Load and Markers of Liver Fibrosis in HIV-Infected and HIV-Uninfected Women**

This study analyzed the effect of WIHS women's genes on the progression of hepatitis C virus (HCV) disease. We found that one of the genes associated with resistance to HCV infection was also associated with lower amounts of HCV in blood and also, possibly, with a lower risk of getting liver disease, in women who are HCV infected. The public health implications of this work are two-fold. Firstly, this study represents an important step toward personalization of HCV 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 HCV disease progression may be useful in the effort to create new and more effective HCV treatments.

Kuniholm MH, Gao X, Xue X, Kovacs K, Marti D, Thio CL, Peters MG, Greenblatt RM, Goedert JJ, Cohen MH, Minkoff H, Gange SJ, Anastos K, Fazzari M, Young MA, Strickler HD, and Carrington M. The Relation of HLA Genotype with Hepatitis C Viral Load and Markers of Liver Fibrosis in HIV-Infected and HIV-Uninfected Women. *J Infect Dis* 2011; 203(12):1807-1814. **PMC3100515**

## **Hepatitis C virus infection and biological false-positive syphilis tests**

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.

Augenbraun M, French A, Glesby M, Sanchez-Keeland, L, Young MA, Greenblatt RM, and Sharma A. Hepatitis C Virus (HCV) Infection and False Positive Syphilis Tests. *Sex Transm Infect* 2010;86(2):97-98.

## **Activation of CD8 T cells predicts progression of HIV infection in women coinfecting with hepatitis C virus**

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.

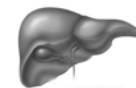
Kovacs A, Karim R, Mack W, Xu J, Chen Z, Operskalski E, Frederick T, Landay AL, Voris J, Spencer L, Young MA, Tien P, Augenbraun M, Strickler HD, and Al-Harthi L. Activation of T cells Predicts Progression in Women: Role of Hepatitis C and Immune Activation. *J Infect Dis* 2010;201(6)823-834.

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

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.

Kuniholm MH, Kovacs A, Gao X, Xue X, Marti D, Thio CL, Peters MG, Terrault NA, Greenblatt RM, Goedert JJ, Cohen MH, Minkoff H, Gange SJ, Anastos K, Fazzari M, Harris TG, Young MA, Strickler HD, and Carrington M. Specific HLA Class I and II Alleles Associated with Hepatitis C Virus Viremia. *Hepatology* 2010;51(5):1514-1522.





### **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)**

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/mm<sup>3</sup> 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.

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.

### **Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure**

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.

Ouyang DW, Shapiro D, Lu M, Brogly S, French AL, Thompson B, Tuomala RE, and Hershov R. Increased Risk of Hepatotoxicity in HIV-infected Pregnant Women Receiving Antiretroviral Therapy Independent of Nevirapine Exposure. *AIDS* 2009;23(18):2425-2430.

### **Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the women's interagency HIV study**

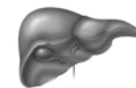
There is concern that HIV-positive persons may be at higher risk of cardiovascular disease. Infection with hepatitis C might worsen and speed up the process. Few studies have looked at the association of HIV/HCV coinfection with cardiovascular disease. Studies comparing persons with HCV infection only 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.

Tien PC, Schneider MF, Cole S, Cohen M, Glesby M, Lazar J, Nowicki M, Young M, and Kaplan RC. Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the Women's Interagency HIV Study. *AIDS* 2009;23(13):1781-1784.

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

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.

Tsui J, Vittinghoff E, Anastos K, Augenbraun M, Young M, Nowicki M, Cohen MH, Peters MG, Golub ET, and Szczech L. Hepatitis C Seropositivity and Kidney Function Decline Among Women with HIV: Data From the Women's Interagency HIV Study. *Am J Kidney Dis* 2009;54(1):43-50.



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

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.

Operskalski EA, Mack WJ, Strickler HD, French AL, Augenbraun M, Tien PC, Villacres MC, Spencer LY, DeGiacomo M and Kovacs A. Factors associated with hepatitis C viremia in a large cohort of HIV-infected and -uninfected women. *J Clin Virol* 2008;41:255-263.

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

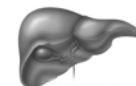
This study examined the association between the risk of liver disease in HIV/HCV co-infected and a growth factor, called insulin-like growth factor I (IGF-I). IGF-I has been shown to stimulate the replication of cells in the liver that play a major role in the development of liver fibrosis. Our results 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.

Strickler HD, Howard AA, Peters M, Fazzari M, Yu H, Augenbraun M, French AL, Young M, Gange S, Anastos K and Kovacs A. The insulin-like growth factor axis and risk of liver disease in hepatitis C virus/HIV-co-infected women. *AIDS* 2008;22:527-531.

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

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 coinfecting 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.

Villacres MC, Literat O, DeGiacomo M, Du W, Frederick T and Kovacs A. Defective response to Toll-like receptor 3 and 4 ligands by activated monocytes in chronic hepatitis C virus infection. *J Viral Hepat* 2008;15:137-144.



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

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 starting 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.

Bacchetti P, Tien PC, Seaberg EC, O'Brien TR, Augenbraun MH, Kral AH, Busch MP and Edlin BR. Estimating past hepatitis C infection risk from reported risk factor histories: implications for imputing age of infection and modeling fibrosis progression. *BMC Infect Dis* 2007;7:145.

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

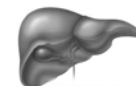
In the U.S. a large number of women with HIV are also infected with Hepatitis C. Although it is recommended that people with both HIV and Hepatitis C be evaluated for treatment for hepatitis C, that doesn't always happen. In the WIHS, almost one of three women tested positive for antibody to Hepatitis 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.

Cohen MH, Grey D, Cook JA, Anastos K, Seaberg E, Augenbraun M, Burian P, Peters M, Young M and French A. Awareness of hepatitis C infection among women with and at risk for HIV. *J Gen Intern Med* 2007;22:1689-1694.

### **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.

French AL, Operskalski E, Peters M, Strickler H, Tien P, Sharp G, Glesby M, Young M, Augenbraun M, Seaberg EC and Kovacs A. Isolated hep B core antibody is associated with HIV and ongoing but not resolved Hep C infection in a cohort of US women. *J Infect Dis* 2007;195(10):1437-1442.



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

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/mm<sup>3</sup> 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.

Laskus T, Operskalski E, Radkowski M, Wilkinson J, Mack WJ, DeGiacomo M, Al-Harhi L, Chen Z, Xu J and Kovacs A. Negative-strand hepatitis C virus (HCV) RNA in peripheral blood mononuclear cells from anti-HCV-positive/HIV-infected women. *J Infect Dis* 2007;195:124-133.

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

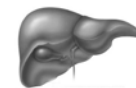
Despite the high frequency of hepatitis C virus (HCV) and HIV co-infection, little is known about how the HCV virus swarms "quasispecies" acts in HIV-positive patients. We looked at 236 HIV+/anti-HCV+ women enrolled in the Women's Interagency HIV Study (WIHS) and looked at the effect of various factors 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.

Laskus T, Wilkinson J, Karim R, Mack W, Radkowski M, DeGiacomo M, Nasseri J, Chen Z, Xu J and Kovacs A. Hepatitis C virus quasispecies in HIV-infected women: role of injecting drug use and highly active antiretroviral therapy (HAART). *Hepatology* 2007;46:359-370.

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

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.

Tsui JJ, 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.



### **Evaluating the impact of HCV on HAART-mediated immune responses in HCV/HIV co-infected women: Role of HCV on expression of memory T-cells**

A growing number of HIV infected women are also positive for the hepatitis C (HCV) virus. It is therefore critical to understand the impact that HCV may have on HIV therapy (HAART). In this study, we examined the impact of HCV on the ability of HAART to reconstitute the immune system in three groups of HIV+ women: 1) women that are HCV negative (HCV-); 2) women that are HCV+ but did not clear HCV infection (HCV+RNA+), and 3) women that are HCV+ but cleared the infection (HCV+RNA-). We found that HCV does not impact the majority of expected immune changes related to HAART but that HCV causes the expansion of a certain subset of T cells, called memory T cells. The significance of the expansion of this subpopulation remains to be determined.

Al Harthi L, Voris J, Du W, Wright DJ, Nowicki M, Frederick T, Landay A, and Kovacs A. Evaluating the impact of HCV on HAART-mediated immune responses in HCV/HIV co-infected women: Role of HCV on expression of memory T-cells. *J Infect Dis* 2006;193(9):1202-1210.

### **Longitudinal effect of antiretroviral therapy on markers of hepatic toxicity: impact of hepatitis C coinfection**

Many women with HIV also have hepatitis C, which is a virus that can attack the liver. There was some concern that HAART drugs might damage the liver as well. However, this study looked at over 300 women who had both HIV and hepatitis C and were on HAART. They found that few women had abnormal liver chemical levels and that these levels tended to go down over time. This suggests that HAART is safe for women with hepatitis C.

French AL, Benning L, Anastos K, Augenbraun M, Nowicki M, Sathasivam K, and Terrault NA. Longitudinal effect of antiretroviral therapy on markers of hepatic toxicity: impact of hepatitis C coinfection. *Clin Infect Dis* 2004;39:402-410.

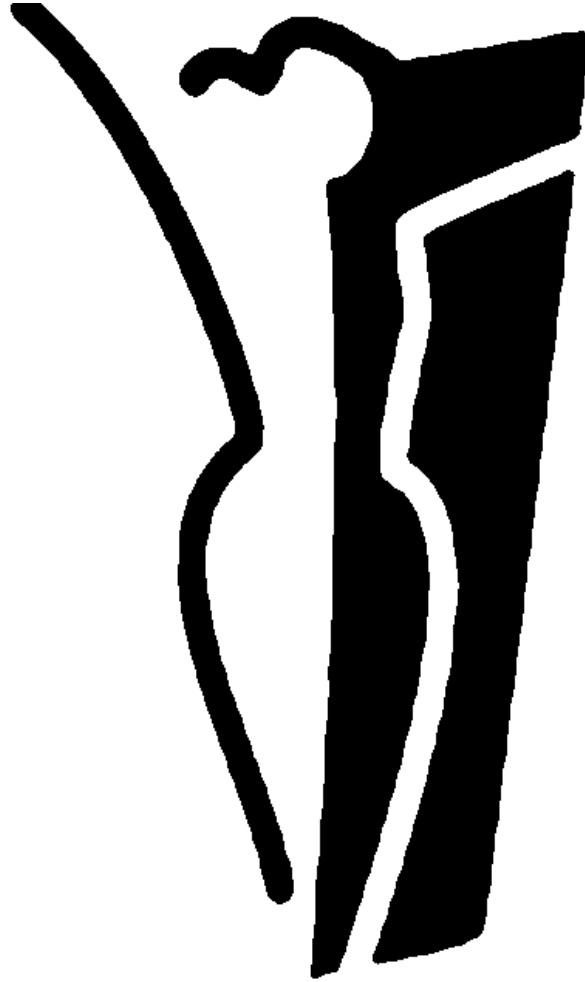
### **Hepatitis C virus infection in Chicago women with or at risk for HIV infection: evidence for sexual transmission**

Hepatitis C is a virus that can damage the liver. Researchers are not sure if it can be sexually transmitted, though it can be transmitted in blood. This study found that injection drug use was the biggest risk for hepatitis C, but that there was evidence for sexual transmission as well.

Hershow RC, Kalish LA, Sha B, Till M, and Cohen M. Hepatitis C virus infection in Chicago women with or at risk for HIV infection: evidence for sexual transmission. *Sex Transm Dis* 1998;25:527-532.



# Metabolic Disorders





### **The association between diet and physical activity on insulin resistance in the Women's Interagency HIV Study**

We evaluated the relationship between diet and physical activity with insulin resistance (IR) in HIV-infected and uninfected women the San Francisco Bay Area (n=113) and Chicago (n=65) Women's Interagency HIV Study (WIHS) sites. In analysis including all women, being from San Francisco and having a higher BMI were associated with greater IR; heavy intensity physical activity and annual household income >\$36,000 was associated with a lower IR. In analysis limited to HIV-infected women, being menopausal and having a higher BMI were associated with greater IR; heavy intensity activity and higher CD4 cell count was associated with lower IR. Among urban women with or at risk for HIV-infection, heavy intensity physical activity was associated with lower IR while dietary macronutrients were not. Given the overall health benefits of physical activity, these behaviors should be encouraged whenever possible and may reduce a common metabolic complication of HIV infection in women.

Hessol NA, Ameli N, Cohen M, Urwin S, Weber KM, Tien PC. The association between diet and physical activity on insulin resistance in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2012.

### **Investigating the Effects of Metabolic Dysregulation on Hair Follicles: A Comparison of HIV-Infected Women With and Without Central Lipohypertrophy**

The objective of this study was to determine whether HIV-infected women with altered hair characteristics had moderate to severe fat changes had compared to HIV-infected women who did not report these changes. We analyzed answers to questions about hair characteristics and scalp inflammation that were asked of all HIV-infected women in the Women's Interagency HIV Study (WIHS) during visit 29. Other data that were analyzed included age, race, education, cigarette smoking, highly active anti-retroviral therapy use, current CD4 cell count and HIV RNA viral load.

We found that history of injection drug use and shorter eyelashes were associated with and increased risk of fat gain. We did not find an association of either abnormal scalp hair growth or increased inflammatory scalp symptoms with fat gain in this cohort. Our findings are important as they may teach us something about a possible link between hair disorders and fat gain in both HIV-infected and uninfected women.

Mirmirani P, Maurer T, Cohen M, D'Souza G, Karim R, Plankey M, Robison E, Sharma A, Tien PC, Hessol NA. Investigating the Effects of Metabolic Dysregulation on Hair Follicles: A Comparison of HIV-Infected Women With and Without Central Lipohypertrophy. *International Journal of Dermatology*. 2012.

### **Association of HIV infection with Incident Diabetes Mellitus: Impact of using Hemoglobin A1C as a Criterion for Diabetes**

There has been some question in published studies whether HIV infection is associated with an increased risk of diabetes. Some studies show that HIV infection is associated with an increased risk, while others show that the risk is the same or possibly lower when compared to uninfected persons. A possible reason for these differences is how diabetes was defined in these studies and if these studies were able to take into account other important factors associated with diabetes, such as obesity, older age, and family history of diabetes.

Recently the American Diabetes Association has also changed the criteria for how diabetes is diagnosed by allowing an elevated hemoglobin A1C (>6.5%) to be considered a diagnosis for diabetes. However, it is not clear whether hemoglobin A1C can be used to diagnose diabetes in the setting of HIV infection, because factors such as anemia can affect the hemoglobin A1C level.

In our study, we examined the association of HIV infection with developing diabetes defined using definitions that included an elevated hemoglobin A1C and those that did not. We found that HIV was consistently associated with a greater risk of diabetes. Regardless of the diabetes definition used, traditional risk factors such as older age, obesity, and family history of DM were strongly associated with diabetes risk. Hemoglobin A1C can be used in the HIV setting, as it only slightly underestimates the effects of HIV on DM risk.

Tien P, Schneider M, Cox C, Karim R, Cohen M, Sharma A, Young M and Glesby M. Association of HIV infection with Incident Diabetes Mellitus: Impact of using Hemoglobin A1C as a Criterion for Diabetes. *J Acquir Immune Defic Syndr* 2012 61(3):334-340. **PMC3480977**

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

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.

Womack JA, Scherzer R, Cole SR, Fennie K, Williams AB, Grey M, Minkoff H, Anastos K, Cohen MH, and Tien PC. Hormonal Contraception and Metabolic Outcomes in Women With or at Risk for HIV Infection. *J Acquir Immune Defic Syndr* 2009;52(5):581-587.

#### **Short-term bone loss in HIV-infected premenopausal women**

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.

Yin MT, Lu D, Cremers S, Tien PC, Cohen MH, Shi Q, Shane E, Golub ET, and Anastos K. Short term bone loss in HIV infected premenopausal women. *J Acquir Immune Defic Syndr* 2010;53(2):202-208.

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

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.

Sobieszczyk ME, Hoover D, Anastos K, Mulligan R, Tan T, Shi C, Hyman C, Cohen M, Cole S, Plankey M and Justman J. Prevalence and predictors of metabolic syndrome among HIVpositive and negative women in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2008;48:272-280.

#### **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.

Womack J, Tien PC, Feldman J, Shin JH, Fennie K, Anastos K, Cohen MH, Bacon MC and Minkoff H. Obesity and immune cell counts in women. *Metabolism* 2007;56:998-1004.

#### **Body composition in HIV-infected women**

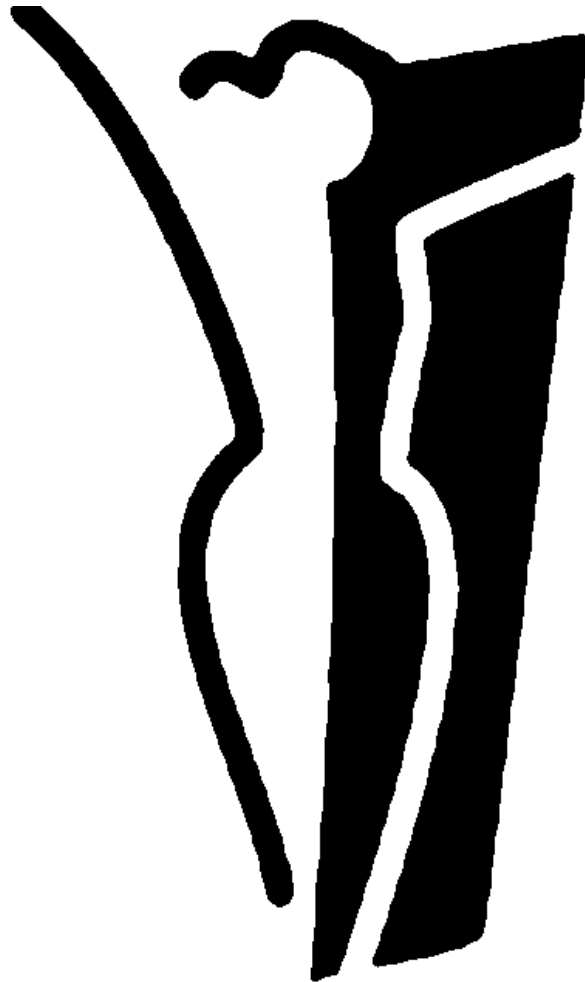
Doctors know that HIV can cause patients to lose weight, especially muscle (instead of fat). This study looked specifically at women. Overall, HIV+ and HIV- women were similar in weight and fat. While HIV viral load was not related to body weight, women with higher CD4 counts had more fat. This shows some differences compared to men's weight changes with HIV.

Swanson B, Hershov RC, Sha BE, Benson CA, Cohen M, and Gunfeld C. Body composition in HIV-infected women. *Nutrition* 2000;16:1064-1068.





# Neurocognition





### **Effects of hepatitis C and HIV on cognition in women: Data from the Women's Interagency HIV Study**

Some persons who are infected with HIV are also infected with the hepatitis C virus. The hepatitis C virus always infects the liver, but sometimes infection with this virus can affect other organs. Some research has suggested that the hepatitis C virus also can affect the brain by causing memory problems and problems with concentration. Other research has found that persons infected with both HIV and hepatitis C have more problems with memory and thinking than persons infected with only one of these viruses. However, not all previous studies have shown this. Women in WIHS have had testing of the speed of their thinking processes. We used this information to find out whether infection with HIV or with hepatitis C influences the speed of thinking. We found that hepatitis C usually did not affect the speed of thinking.

Crystal HA, Kleyman I, Anastos K, Lazar J, Cohen MH, Liu C, Pearce L, Golub ET, Valcour V, Ho A, Strickler H, Peters M, Kovacs A, Kreek MJ, and Manly J. Effects of hepatitis C and HIV on cognition in women: Data from the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2012 1;59(2):149-54. **PMC3319079**

### **Insulin Resistance and Cognition among HIV-infected and HIV-uninfected Adult Women**

Insulin resistance is a condition where the body does not metabolize glucose efficiently and is often considered to be the stage before diabetes. There are some publications to suggest that people with insulin resistance do worse on tests of memory and thinking. This study looked to see if having insulin resistance was related to testing performance on memory and thinking tests done about 5 years ago in the WIHS. We found some evidence for a relationship between insulin resistance and test performance. Much of this relationship could be explained by other risk factors in the cohort. Overall, this suggests that more research is needed; and firm conclusions from this study could be strengthened by current work underway using a bigger testing battery among more women.

Valcour V, Maki PM, Bacchetti P, Anastos K, Crystal HA, Young MA, Mack WJ, Cohen MH, Golub ET, and Tien PC. Insulin Resistance and Cognition among HIV-infected and HIV-uninfected Adult Women. *AIDS Res Hum Retroviruses* 2011 28(5):447-53. **PMC3332367**

### **Associations of cardiovascular variables and HAART with cognition in middle-aged HIV-infected and uninfected women**

Some people are better at concentrating and solving problems in their head than others. Many factors influence the ability to concentrate. We studied how high blood pressure, hardening of the arteries, HIV infection, AIDS, drug use, and aging influence concentration in women from WIHS. WIHS participants were given tests of concentration at several of their visits. We measured hardening of the arteries by taking pictures using sound waves of the artery that carries blood to the brain. We found that hypertension, AIDS, and hardening of the arteries were associated with worse ability to concentrate. HIV infection without AIDS was not associated with worse concentration. Women who were cigarette smokers when they took the tests of concentration did worse than non-smokers. Women who never consumed any alcoholic beverages had worse concentration than women who consumed a moderate amount of alcohol. This work suggests another reason why control of high blood pressure is important in young women with or without HIV.

Crystal HA, Weedon J, Randesi M, Lazar J, Manly J, Valcour V, Cohen MH, Anastos K, Liu C, Mack WJ, Golub ET, Ho A, Holman S, Kreek MJ, and Kaplan RC. Associations of cardiovascular variables and HAART with cognition in middle-aged HIV-infected and uninfected women. *J Neurovirol* 2011;17(5):469-476. **NIHMSID 409645**

### **Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV+ and HIV- women: The WIHS Neurocognitive Substudy**

The goal of this study was to demonstrate the normal range of scores on two cognitive measures, among a large group of ethnically and educationally diverse HIV-uninfected, high risk women. We examined the relationships of age, years of school, quality of school, and race/ethnicity on scores on measures of speed and executive function. Then, using these normative expectations, we determined whether there was any effect of HIV infection on cognitive test performance. We found that HIV-infected women obtained lower scores than HIV-uninfected women on all the measures, but after taking into account age, years of education, racial/ethnic classification, and reading level, only the difference on one measure of speed remained significant. These results suggest that researchers need to take into account educational and cultural background when diagnosing cognitive impairment in HIV-infected women.

Manly JJ, Smith C, Crystal H, Richardson J, Golub ET, Young MA, Greenblatt RM, and Robison E. Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV+ and HIV- women: The WIHS Neurocognitive Substudy. *J Clin Exp Neuropsychol* 2011;33(8):853-863. **PMC33837**



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

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.

Maki PM, Cohen MH, Weber K, Little DM, Fornelli D, Perschler P, Gould F, and Martin E. Impairments in Memory and Hippocampal Function in HIV+ Versus HIV- Women: A Preliminary Study. *Neurology* 2009;72(19):1661-1668.

### **Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women**

Both HIV and hepatitis C virus can affect certain brain functions. This study found that women with both hepatitis C and HIV infection had poorer brain functions compared to women with neither infection, especially if the infected women were not on HAART. Women with HIV and hepatitis did worse with lower CD4 counts.

Richardson JL, Nowicki M, Danley K, Martin EM, Cohen MH, Gonzalez R, Vassileva J, and Levine AM. Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. *AIDS* 2005;19:1659-1667.

### **Neuropsychological functioning in a cohort of HIV infected women: importance of antiretroviral therapy**

This study found that HIV+ women who did not take HAART did worse on certain brain function tests. However, HIV+ women on HAART did about the same as HIV- women.

Richardson JL, Martin EM, Jimenez N, Danley K, Cohen M, Carson VL, Sinclair B, Racenstein JM, Reed RA, and Levine AM. Neuropsychological functioning in a cohort of HIV infected women: importance of antiretroviral therapy. *J Int Neuropsychol Soc* 2002;8:781-793.

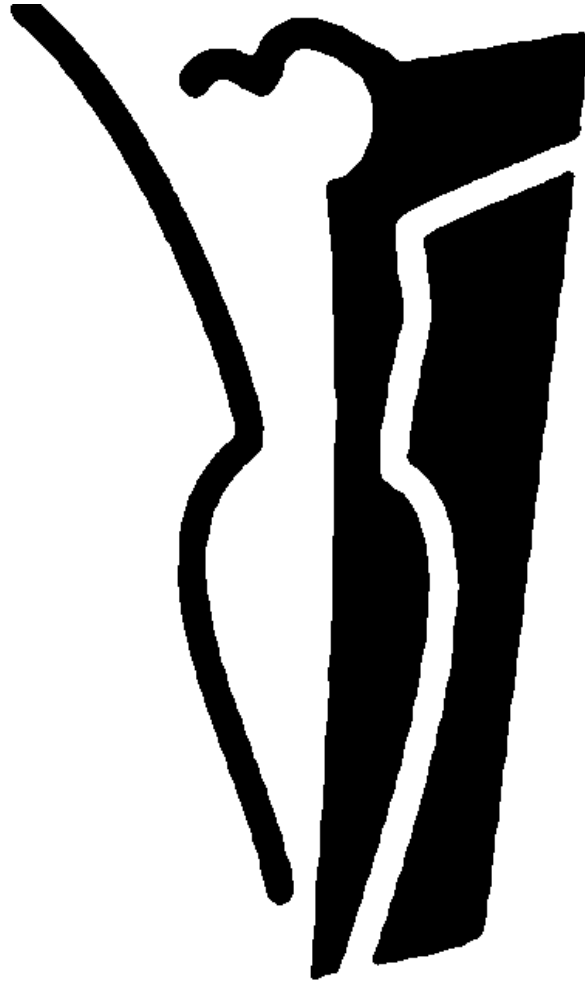
### **Neurobehavioral functioning in asymptomatic HIV-1 infected women**

This study looked at the brain functions of women with HIV; previous studies had only looked at men. They found that there was no difference in brain function between HIV- women and HIV+ women who did not have AIDS symptoms.

Stern RA, Arruda JE, Somerville JA, Cohen RA, Boland RJ, Stein MD, and Martin EM. Neurobehavioral functioning in asymptomatic HIV-1 infected women. *J Int Neuropsychol Soc* 1998;4:172-178.



# Oral Health





### **Factors associated with use of dental services among HIV-infected and high-risk uninfected women**

Dental health is important but often ignored. This study found that at-risk HIV negative women were less likely to go to the dentist compared to HIV+ women. This may be because HIV+ women can access dentists through government programs. The researcher also found that women who were non-white or afraid of dentists or thought they had bad teeth were less likely to go to the dentist.

Shiboski C, Cohen M, Weber K, Shansky A, Malvin K, and Greenblatt R. Factors associated with use of dental services among HIV-infected and high-risk uninfected women. *J Am Dent Assoc* 2005;136(9):1242-1255.

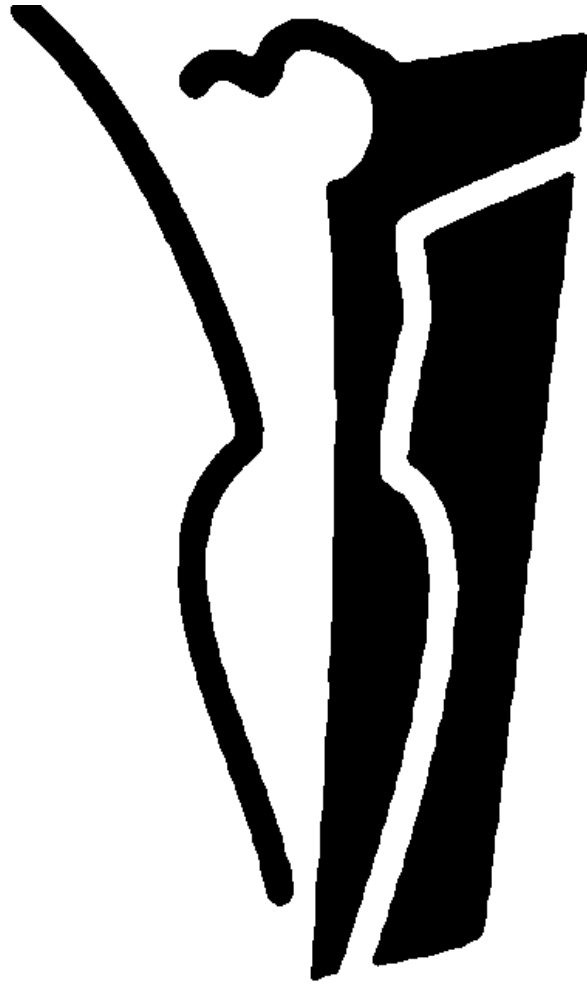
### **Baseline characteristics of participants in the oral health component of the Women's Interagency HIV Study**

One of the substudies in WIHS looked at oral health. At the beginning of the study, HIV+ and HIV- women had similar oral health. However, HIV+ women did have fewer teeth than HIV- overall. Also, among HIV+ women, lower CD4 counts related to more decayed or missing teeth.

Mulligan R, Phelan JA, Brunelle J, Redford M, Pogoda JM, Nelson E, Seirawan H, Greenspan JS, Navazesh M, Greenspan D, and Alves ME. Baseline characteristics of participants in the oral health component of the Women's Interagency HIV Study. *Community Dent Oral Epidemiol* 2004;32:86-98.



# Other Medical Conditions





### **The relationship between race and HIV-associated sensory neuropathy in a large cohort of US women**

This study examines neuropathy, or nerve damage, specifically in people with HIV. This nerve damage has an unknown cause but causes severe pain. We investigated various factors associated with developing neuropathy, and found that it was more common in people with diabetes, Hepatitis C, and older age. In addition, this neuropathy was less common in Hispanics, compared to African-Americans (the main component of the study's subjects), for unknown reasons

Anziska T, Helzner E, Crystal H, Glesby M, Plankey M, Weber K, Golub E and Burian P. The relationship between race and HIV-associated sensory neuropathy in a large cohort of US women. *J Neuro Sci* 2012 15; 315(1-2):129-32.

### **Insomnia symptoms and HIV infection among participants in the Women's Interagency HIV Study**

Insomnia is a common problem among women with HIV. In this study, we assessed the prevalence of insomnia symptoms among women with and without HIV-infection and examined factors associated with insomnia. We studied 1682 women who were enrolled in the Women's Interagency HIV Study (WIHS), a multisite prospective cohort study of HIV-infected women in the United States. Our analysis focused on sociodemographics, sleep measures, depressive symptoms, drug use, alcohol consumption, medication (antiretroviral and others), and HIV-related clinical variables. We found that among women 40 years old and younger, 69% of those with HIV infection reported insomnia symptoms compared with 61% of uninfected women. Among women ages 41 to 50 years old, 75% of HIV infected women reported insomnia symptoms and 78% of uninfected women reported such symptoms. Among women older than 50 years old, 83% of those with HIV infection reported insomnia symptoms compared with 82% of uninfected women. We also found no significant differences in the likelihood of reporting insomnia symptoms based on various HIV treatment types. HIV-infected women with depression were more likely to report insomnia symptoms than those reporting no depressed moods, irrespective of their age group. In summary, insomnia symptoms were common among both HIV-infected and uninfected women. Prevalence of insomnia did not vary significantly by HIV status, except among women 40 years old and younger. Younger women with HIV infection are at greater risk for experiencing insomnia symptoms.

Jean-Louis G, Weber K, Aouizerat B, Levine AM, Maki P, Liu C, Anastos K, Milam J, Althoff KN, and Wilson TE. Insomnia symptoms and HIV infection among participants in the Women's Interagency HIV Study. *Sleep* 2012 1;35(1):131-7. **PMC3242680**

### **Urinary Markers of Kidney Injury and Kidney Function Decline in HIV-Infected Women: Biomarkers and Kidney Decline**

HIV-infected persons have higher risks of kidney disease, but current blood tests cannot detect kidney disease until it has become advanced. We tested new urine tests for early kidney disease to determine whether they could predict which women would develop more advanced kidney disease later in the study. In the WIHS, we measured levels of four proteins in urine from 908 HIV-infected and 289 uninfected participants. Kidney function was measured three times over eight years. As we hypothesized, higher levels of three of the biomarkers predicted worse progression of kidney disease, independent of all other risk factors for kidney disease. These findings are completely new, and have never been demonstrated in persons with HIV disease. Our research has importance for the clinical care of patients with HIV infection. Current strategies to screen for kidney disease in HIV-infected patients rely on the creatinine blood test, which usually is not abnormal until the kidney is heavily diseased. These new tests could detect kidney disease many years earlier, allowing for changes in medication or lifestyle strategies to prevent more advanced kidney disease.

Shlipak MG, Scherzer R, Abraham A, Tien PC, Grunfeld C, Peralta CA, Devarajan P, Bennett M, Butch AW, Anastos K, Cohen MH, Nowicki M, Sharma A, Young MA, Sarnak MJ, Parikh CR. Urinary Markers of Kidney Injury and Kidney Function Decline in HIV-Infected Women: Biomarkers and Kidney Decline. *J Acquir Immune Defic Syndr* 2012 61(5):565-573. **PMC3509242**

### **Sero-incidence of 2009 H1N1 infection in HIV-infected and HIV-uninfected women in the US prior to vaccine availability**

In April 2009, a new strain of influenza, called H1N1 or swine flu, caused outbreaks of flu in the United States. The strain quickly spread all over the world, causing a flu pandemic. This study will use blood specimens from WIHS participants collected during study visits to determine how many women may have been infected with this new H1N1 flu between March 1 – September 30, 2009. The information from this study helps determine: 1) whether HIV-infected and –uninfected women have similar risk of flu; and 2) whether HIV-infected women who have greater immune suppression have a similar risk of flu compared to women with healthier immune systems.

Althoff KN, Eichelberger M, Gange SJ, Sharp G, Gao J, Glesby MJ, Young MA, Greenblatt RM, French AL, Villacres M, and Minkoff H. Sero-incidence of 2009 H1N1 infection in HIV-infected and HIV-uninfected women in the US prior to vaccine availability. *AIDS*



### **Lower levels of interleukin-12 precede the development of tuberculosis among HIV-infected women**

Proteins and peptides called cytokines play a major role in the control of cell activity against *M. tuberculosis*, the agent causing tuberculosis (TB). We investigated the relation between peripheral blood mononuclear cells (PBMC) cytokines and the risk to develop TB in ten HIV+ women. The cytokines from PBMC of 10 HIV-infected and 10 HIV-uninfected women served as controls. We compared the production cytokines by PBMC of women who had TB before and after the TB with two control groups. Group 1: 10 women HIV-infection and Group 2: 10 women without HIV infection. Both control groups have not had TB. There was lower production of cytokine IL-12 among women before TB compared with those HIV-infected without TB. Lower IL-12 production by PBMC may be involved in the increased risk among HIV-infected women to TB.

Bordon J, Plankey MW, Young MA, Greenblatt RM, Villacres MC, French AL, Zhang J, Brock G, Appana S, Herold B, Durkin H, Golub JE, and Fernandez-Botran R. Lower levels of interleukin-12 precede the development of tuberculosis among HIV-infected women. *Cytokine* 2011;56(2):325-331. **NIHMSID 408795**

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

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.

Althoff KN, Anastos K, Nelson KE, Celentano DD, Sharp GB, Greenblatt RM, French AL, Diamond DJ, Holman S, Young M, and Gange SJ. Predictors of reported influenza vaccination in HIV-infected women in the United States, 2006-07 and 2007-08 seasons. *Prev Med* 2010;50(5-6):223-229.

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

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.

Levine AM, Seaberg EC, Hessol NA, Preston-Martin S, Silver S, Cohen MH, Anastos K, Minkoff M, Orenstein J, Dominguez G, and Watts DH. HIV as a Risk Factor for Lung Cancer in Women: Data from the Women's Interagency HIV Study (WIHS). *J Clin Oncol* 2010;28(9):1514-1519.

### **Effect of tuberculosis on the survival of women infected with human immunodeficiency virus**

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.

Lopez-Gatell H, Cole S, Hessol N, French A, Greenblatt R, Landesman S, Preston-Martin S and Anastos K. Effect of tuberculosis on the survival of women infected with human immunodeficiency virus. *Am J Epidemiol* 2007;165:1134-1142.





### **Incidence of tuberculin Skin test conversion among HIV-infected and -uninfected women: results of a 6-year study**

Tuberculosis is a dangerous disease for people with HIV and can be checked with a tuberculin skin test. HIV positive and negative women were tested every year for 7 years. Overall, the number of positive tests decreased from 1996 to 2002. African-Americans, women under 40 years old and HIV+ women who had started HAART were more likely to have a positive test. This suggests that testing for tuberculosis after starting HAART is a good idea. However, doctors should be careful about the method they use, since taking the test many times can lead to a positive test, even if the person doesn't actually have tuberculosis.

French AL, Evans CT, Anastos K, Greenblatt RM, Hershov R, Huebner R, Augenbraun M, Young M, Lopez-Gatell H, and Passaro DJ. Incidence of tuberculin Skin test conversion among HIV-infected and -uninfected women: results of a 6-year study. *J Acquir Immune Defic Syndr* 2006;42(5):592-596.

### **Prevalence and predictors of Toxoplasma seropositivity in women with and at risk for human immunodeficiency virus infection**

Toxoplasmosis is a parasite that can infect the brain, eyes, heart, lung and liver. It is found in cats and cat litter. This study found that the rates of toxoplasmosis were about the same in HIV+ and HIV- women. However, older women and those born outside the US had higher rates of toxoplasmosis.

Falusi O, French AL, Seaberg EC, Tien PC, Watts DH, Minkoff H, Piessens E, Kovacs A, Anastos K, and Cohen MH. Prevalence and predictors of Toxoplasma seropositivity in women with and at risk for human immunodeficiency virus infection. *Clin Infect Dis* 2002;35:1414-1417.

### **Women and HIV: creating an ambiance of caring**

Many women with HIV also need mental health care, but not all get the help they need. This paper gives providers tips for how to help their patients with mental health needs.

Cohen MH. Women and HIV: creating an ambiance of caring. *J Am Med Womens Assoc* 2001;56:9-10.

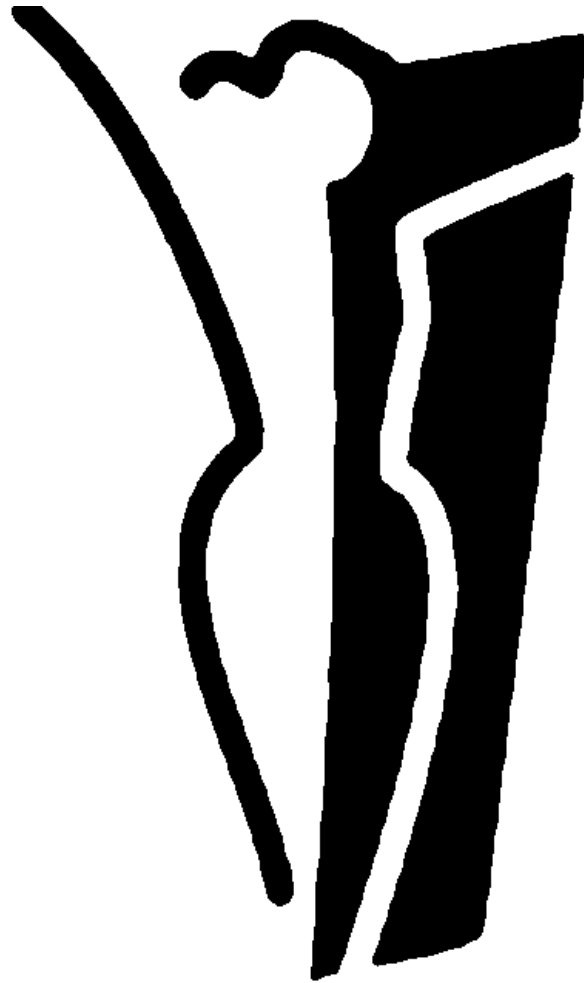
### **HIV-associated distal symmetrical polyneuropathy: clinical features and nursing management**

People with HIV can suffer from distal symmetrical polyneuropathy, meaning pain or weakness in the hands and feet. This paper describes the symptoms and treatment for distal symmetrical polyneuropathy.

Swanson B, Zeller JM, and Paice JA. HIV-associated distal symmetrical polyneuropathy: clinical features and nursing management. *J Assoc Nurses AIDS Care* 1998;9:77-80.



# Pregnancy and Other Gynecology





### **Circulating Vitamin D Predicts Serum Anti-Mullerian Hormone Levels in Late Reproductive-Aged Women: Women's Interagency HIV Study**

Ovarian reserve in women reflects the number of eggs. HIV infected women have low blood levels of vitamin D. Laboratory research revealed that vitamin D plays a role in a gene related to ovarian reserve. We want to study the relationship between ovarian reserve and blood levels of vitamin D in a large cohort of HIV-seronegative and HIV-seropositive women. This study involves analyzing already existing data from the WIHS and will have no impact of the participants.

Merhi ZO, Seifer DB, Weedon J, Adeyemi O, Holman S, Anastos K, Golub ET, Young M, Karim R, Greenblatt R and Minkoff H. Circulating Vitamin D Predicts Serum Anti-Mullerian Hormone Levels in Late Reproductive-Aged Women: Women's Interagency HIV Study. *Fertil Steril* 2012 98(1):228-234. **PMC3389125**

### **Quantitative and qualitative correlates of cervicovaginal herpes simplex virus 2 shedding among HIV-infected women in the Women's Interagency HIV Study**

Herpes Simplex Virus Type 2 (HSV -2) causes a lifelong infection that produces genital sores periodically and can cause women to worry a great deal. It is particularly common among HIV infected women. Genital herpes is transmitted to others when the virus is present (or doctors call it shedding) from the genital tract. Since people with HSV periodically shed infectious virus when a sore is present or even if it is not, it is important to find out if we can predict when shedding can happen, how it changes over time, and also factors that determine who is likely to be shedding the virus and who is not. Knowing more about this will help us to prevent genital herpes and improve treatment for HIV infected women.

Aumakhan B, Gange SJ, Beyrer C, Gaydos CA, Minkoff H, Merenstein DJ, Cohen M, Anastos A, Greenblatt R, Nowicki M, and Quinn TC. Quantitative and qualitative correlates of cervicovaginal herpes simplex virus 2 shedding among HIV-infected women in the Women's Interagency HIV Study. *Int J STD AIDS* 2011;22(5):273-277. **PMC3123901**

### **Clinical reactivations of herpes simplex virus type 2 infection and human immunodeficiency virus disease progression markers**

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 coinfecting 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.

Aumakhan B, Gaydos CA, Quinn TC, Beyrer C, Benning L, Minkoff H, Merenstein DJ, Cohen M, Greenblatt R, Nowicki M, Anastos K, and Gange SJ. Clinical Reactivations of Herpes Simplex Virus Type 2 (HSV-2) Infection and Human Immunodeficiency Virus 1 (HIV-1) Disease Progression Markers. *PLoS ONE* 2010;5(4):e9973.

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

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.

Seifer D, Golub E, Lambert-Messerlain G, Benning L, Anastos K, Watts DH, Cohen M, Karim R, Young M, Minkoff H, and Greenblatt R. Variations in Serum Mullerian Inhibiting Substance Between White, Black and Hispanic Women. *Fertil Steril* 2009;92(5):1674-1678.



### **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

Dolev J, Maurer T, Springer G, Glesby M, Minkoff H, Connell C, Young M, Schowalter K, Cox C and Hessol N. Incidence and risk factors for verrucae in women. *AIDS* 2008;22:1213-1219.

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

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.

Massad LS, Evans CT, Weber K, Cejtin H, Golub ET, DiGilio K, Alpern A and Watts DH. Hysterectomy among women with HIV: indications and incidence. *J Acquir Immune Defic Synd* 2007;44(5):566-568

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

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.

Seifer D, Golub ET, Lambert-Messerlain G, Springer G, Holman S, Moxley M, Cejtin H, Nathwani N, Anastos K, Minkoff H and Greenblatt R. Biologic markers of ovarian reserve and reproductive aging: application in a cohort study of HIV infection in women. *Fertil Steril* 2007;88(6):1645-1652.

### **Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction**

Sometimes women do not get their periods; this is called amenorrhea. One possible reason for amenorrhea is that the ovaries stop producing certain chemicals. This study found that HIV+ women were three times more likely to have amenorrhea (for at least one year) that was not due to ovarian failure, compared to HIV- women. This raises an interesting question of what is causing amenorrhea in HIV+ women.

Cejtin H, Kalinowski A, Bacchetti P, Taylor R, Watts H, Kim S, Massad LS, Preston-Martin S, Anastos D, Moxley M, and Minkoff H. Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction. *Obstet Gynecol* 2006;108(6):1423-1431.

### **Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women**

Sometimes women don't get their period regularly. This study found that there was no difference between HIV+ and HIV- women in terms of having menstrual abnormalities. However, among HIV+ women, having higher CD4 counts and being on HAART was related to fewer menstrual abnormalities.

Massad LS, Evans CT, Minkoff H, Watts DH, Greenblatt RM, Levine AM, Anastos K, Young M, Seifer DB, Golub ET, and Cohen M. Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women. *J Womens Health (Larchmt)* 2006;15:591-598.



### **HIV Type 1 and Cytomegalovirus Coinfection in the Female Genital Tract**

Cytomegalovirus is a virus that can be transmitted through sex or from mother to baby. Researchers found that women with cytomegalovirus in their genital tract had higher levels of HIV virus. They also had more immune signals that can increase HIV replication. This information can help researchers understand how cytomegalovirus might affect HIV infections.

Lurain NS, Robert ES, Xu J, Camarca M, Landay A, Kovacs AA, and Reichelderfer PS. HIV Type 1 and Cytomegalovirus Coinfection in the Female Genital Tract. *J Infect Dis* 2004;190:619-623.

### **Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV**

This study compared how often HIV+ and HIV- women got pregnant and what happened to those pregnancies. HIV+ women were less likely to get pregnant; out of 100 HIV+ women, only 7.4 got pregnant per year compared to 15.2 out of 100 HIV- women per year. However, the same percent of women had live babies, miscarriages, abortions or stillborns, whether they were HIV+ or HIV-. The researchers found that there were fewer abortions once HAART was available.

Massad LS, Springer G, Jacobson L, Watts H, Anastos K, Korn A, Cejtin H, Stek A, Young M, Schmidt J, and Minkoff H. Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV. *AIDS* 2004;18:281-286.

### **Effect of hormonal contraceptive use on plasma HIV-1-RNA levels among HIV-infected women**

Many women take hormonal birth-control, such as depo or the pill. Researchers compared women who were on hormonal birth control and those who were not. There was no difference in CD4 levels nor in the amount of HIV between the two groups.

Cejtin HE, Jacobson L, Springer G, Watts DH, Levine A, Greenblatt R, Anastos K, Minkoff HL, Massad LS, and Schmidt JB. Effect of hormonal contraceptive use on plasma HIV-1-RNA levels among HIV-infected women. *AIDS* 2003;17:1702-1704.

### **Substance use and psychotherapeutic medications: a likely contributor to menstrual disorders in women who are seropositive for human immunodeficiency virus**

Researchers found that women who were on methadone or had injected drugs were more likely to have very long menstrual cycles – 90 days or longer. Women who were on psychotherapeutic drugs also had very long or very short menstrual cycles. Doctors should think about the drugs a woman may be taking if she has abnormal menstrual cycles.

Harlow SD, Cohen M, Ohmit SE, Schuman P, Cu-Uvin S, Lin X, Greenblatt R, Gurtman A, Khalsa A, Minkoff H, Young MA, and Klein RS. Substance use and psychotherapeutic medications: a likely contributor to menstrual disorders in women who are seropositive for human immunodeficiency virus. *Am J Obstet Gynecol* 2003;188:881-886.

### **Effect of HIV infection on menstrual cycle length**

Menstrual cycles less than 18 days or more than 40 days are considered abnormal. This research found that having HIV did not really affect the length of a woman's menstrual cycles. However, among HIV+ women, having higher viral loads and lower CD4 levels may be related to having cycles that vary in length or sometimes not having a period.

Harlow SD, Schuman P, Cohen M, Ohmit SE, Cu-Uvin S, Lin X, Anastos K, Burns D, Greenblatt R, Minkoff H, Muder spach L, Rompalo A, Warren D, Young MA, and Klein RS. Effect of HIV infection on menstrual cycle length. *J Acquir Immune Defic Syndr* 2000;24:68-75.

### **Hormonal levels among HIV-1-seropositive women compared with high-risk HIV-seronegative women during the menstrual cycle**

Hormone levels change throughout a woman's menstrual cycle. Hormones can also affect the immune system. This study found that women with HIV had normal levels of hormones. They also found that hormones were not affected by HAART, viral load or CD4 levels.

Cu-Uvin S, Wright DJ, Anderson D, Kovacs A, Watts DH, Cohn J, Landay A, and Reichelderfer PS. Hormonal levels among HIV-1-seropositive women compared with high-risk HIV-seronegative women during the menstrual cycle. Women's Health Study (WHS) 001 and WHS 001a Study Team. *J Womens Health Gend Based Med* 2000;9:857-863.



### **Effect of menstrual cycle on HIV-1 levels in the peripheral blood and genital tract. WHS 001 Study Team**

Hormone changes during the menstrual cycle can affect the immune system. While menstrual cycle timing didn't change CD4 counts nor HIV levels in a woman's blood, it did affect the amount of virus in the vagina and cervix. Specifically, this study found higher HIV levels during a woman's period

Reichelderfer PS, Coombs RW, Wright DJ, Cohn J, Burns DN, Cu-Uvin S, Baron PA, Coheng MH, Landay AL, Beckner SK, Lewis SR, and Kovacs AA. Effect of menstrual cycle on HIV-1 levels in the peripheral blood and genital tract. WHS 001 Study Team. *AIDS* 2000;14:2101-2107.

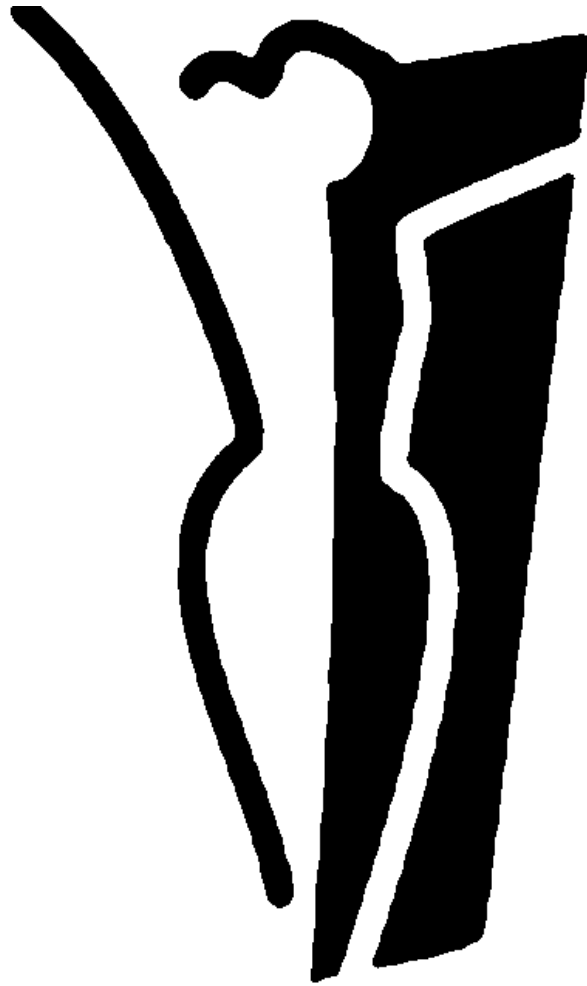
### **Case Report: Verrucous carcinoma of the vulva in a patient infected with the human immunodeficiency virus**

This study reports on a rare type of cancer of the vulva in a patient with HIV.

Massad LS, Ahuja J, and Bitterman P. Case Report: Verrucous carcinoma of the vulva in a patient infected with the human immunodeficiency virus. *Gynecol Oncol* 1999;73:315-318.



# Vitamins





### **Vitamin D insufficiency may impair CD4 recovery among Women's Interagency HIV Study (WIHS) participants with advanced disease on HAART**

Vitamin D plays a role in overall health, and vitamin D deficiency has been reported in high rates in HIV-infected patients. Some small cross sectional studies, vitamin D deficient HIV patients had significantly lower CD4 counts. In our study, we tried to determine the association of vitamin D insufficiency with immune recovery over time after initiation of antiretroviral treatment in HIV-infected women. We found that Vitamin D insufficiency is associated with impaired late CD4 recovery on HAART in the WIHS cohort. The mechanism of this association may be impaired late production of new CD4 cells during recovery of immunity, however this merits further exploration.

Aziz AM, Livak B, Burke-Miller J, French A, Glesby MJ, Sharma A, Young M, Villacres M, Tien PC, Golub E, Adeyemi OM. Vitamin D insufficiency may impair CD4 recovery among Women's Interagency HIV Study (WIHS) participants with advanced disease on HAART. *AIDS* 2012.

### **Association Between Vitamin D, Oral Candidiasis, and Calprotectinemia in HIV**

People with HIV often get overgrowth of yeast in their mouth because of their faulty immune system. Vitamin D is a regulator of calcium metabolism and immune functions. Many people, including people living with HIV, suffer from a lack of vitamin D. We wanted to test the theory that abnormally low level of vitamin D in people with HIV makes them more susceptible to yeast infection in their mouth. Our data support this theory. Additional studies are needed to be able to say whether giving people living with HIV a vitamin D supplement will result in less yeast infection in their mouth.

Sroussi HY, Burke-Miller J, French AL, Adeyemi OM, Weber KM, Lu Y and Cohen M. Association Between Vitamin D, Oral Candidiasis, and Calprotectinemia in HIV. *J Dent Res* 2012 91(7):666-70. **PMC3383847**

### **Vitamin D deficiency in HIV-infected and HIV-uninfected women in the United States**

Vitamin D is an important vitamin that contributes to overall health. Vitamin D deficiency (low levels) is very common in adults living in the US. Our study was performed to see how common vitamin D Deficiency was in WIHS women and if HIV infection increases the chances of having Vitamin D deficiency. Vitamin D testing was performed on stored samples from 1750 WIHS women from all 6 WIHS sites. We found that 2 out of every 3 women had Vitamin D deficiency. Low vitamin D levels were more common in African American and Hispanic women compared with white women and HIV infection did not increase the risk of having low vitamin D levels. It is important to study how these low vitamin D levels affect the overall health of HIV-infected and un-infected WIHS women and ways to increase vitamin D levels to the normal range.

Adeyemi OM, Agniel D, French AL, Tien PC, Weber K, Glesby MJ, Villacres MC, Sharma A, Merenstein D, Golub ET, Meyer W, and Cohen M. Vitamin D deficiency in HIV-infected and HIV-uninfected women in the United States. *J Acquir Immune Defic Syndr* 2011;57(3):197- 204. **PMC3431159**

### **Vitamin A deficiency and genital viral burden in women infected with HIV-1**

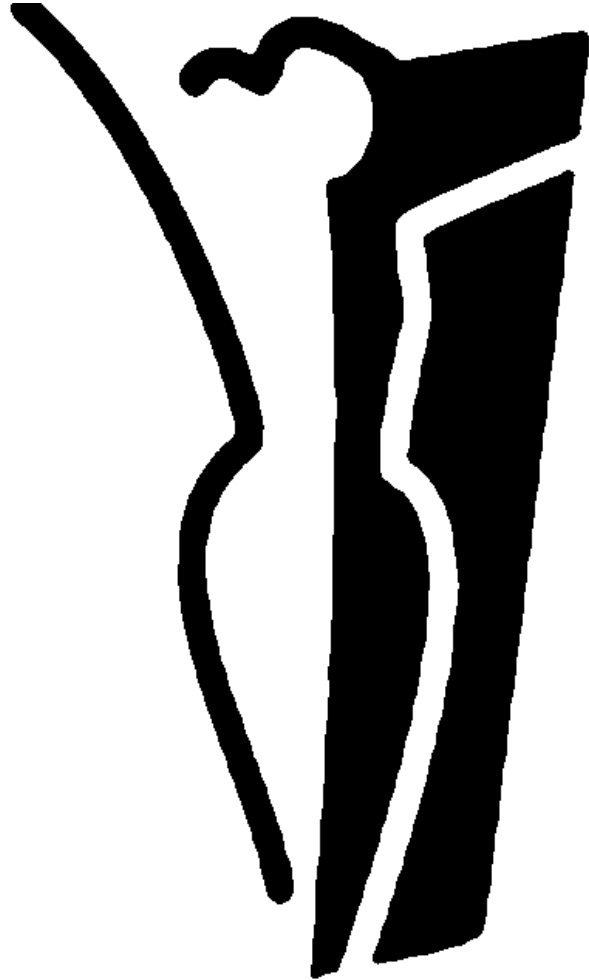
Researchers tested the idea that low levels of vitamin A might increase genital levels of HIV virus.. They found that women with lower vitamin A did not have higher HIV levels in their genital tract fluids. This suggests that vitamin A is unlikely to be related to HIV transmission including to a newborn.

French AL, Cohen MH, Gange SJ, Burger H, Gao W, Semba RD, Meyer WA, III, Robison E, and Anastos K. Vitamin A deficiency and genital viral burden in women infected with HIV-1. *Lancet* 2002;359:1210-1212





# Sexual Practices and Risk Behaviors





### **Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study**

This analysis examined the rate of pregnancy and time to pregnancy for both HIV-infected and HIV-uninfected women in the WIHS from 2002-2009. 766 pregnancies were reported among 1,412 women. For HIV-infected women, the rate of pregnancy was 40% lower compared to HIV-uninfected women and the time to first pregnancy was 73% longer. Age was also a predictor of longer times to pregnancy regardless of HIV status. Women living with HIV now have longer life expectancies due in large part to antiretroviral therapy. As such, they are now better able to plan for their future and those plans often include the desire to become a mother. This desire can be complicated by concerns over how their HIV infection could impact their child and the longevity of their own health. This analysis demonstrated that despite slower times to pregnancy, conception is possible for women with HIV.

Linan B, Minkoff H, Cohen MH, Karim R, Cohan D, Wright R, Young MA, Watts DH, and Golub ET. Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study, 2002-2009. *AIDS* 2011;25(5):707-711. **NIHMSID 417263**

### **Sexual Serosorting among Women with or at Risk of HIV Infection**

HIV seroconcordance between sexual partners has been found to be an important determinant of lower condom use consistency among men who have sex with men and injection drug users, but little evidence supports this practice among women. Using longitudinal data from the Women's Interagency HIV Study, the pattern of HIV seroconcordance between partners over time, as well as its relationship with unprotected sex was examined. From our analysis, a decreased trend of having sex with male partners of unknown HIV status was observed and having HIV seroconcordant partners was significantly associated with increased risk of unprotected sexual intercourse for both HIV-infected and HIV-uninfected women. Our findings may implicate that women in the WIHS is practicing serosorting, i.e. selectively having unprotected sex with partners of the same HIV serostatus, as a risk reduction strategy.

Liu C, Hu H, Goparaju L, Bacchetti P, Weber K, Correa N, Nowicki M, and Wilson TE. Sexual Serosorting among Women with or at Risk of HIV Infection. *AIDS Behav* 2011;15(1):9-15. **PMC2987377**

### **Impact of menopause on condom use by HIV-seropositive and comparison seronegative women**

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.

Massad LS, Evans CT, Wilson TE, Golub ET, Goparaju L, Howard A, Greenblatt RM, Weber K and Schilder K. Impact of menopause on condom use by HIV-seropositive and comparison seronegative women. *J Acquir Immune Defic Syndr* 2008;47(3):401-402.

### **Contraceptive use among U.S. women with HIV**

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.

Massad LS, Evans CT, Wilson T, Golub ET, Sanchez-Keeland I, Minkoff H, Weber K and Watts H. Contraceptive use among US women with HIV. *J Womens Health (Larchmt)* 2007;16(5):657-666.



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

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.

Wilson T, Feldman J, Vega M, Gandhi M, Richardson J, Cohen M, McKaig R, Ostrow E, Robison E and Gange S. Acquisition of new sexual partners among women with HIV infection: patterns of disclosure and sexual behavior within new partnerships. *AIDS Educ Prev* 2007;19(2):151-159.

### **The Effect of Sexual and Physical Violence on Risky Sexual Behavior and STDs Among a Cohort of HIV Seropositive Women**

Many women with HIV have experienced sexual and physical violence in their lifetime. Recent sexual or physical violence was related to increased STDs, number of sexual partners and depression. This suggests that health care providers need to address violence that their patients may be experiencing.

Hogben M, Gange S, Watts DH, Robison E, Young M, Richardson J, Cohen M, and DeHovitz J. The Effect of Sexual and Physical Violence on Risky Sexual Behavior and STDs Among a Cohort of HIV Seropositive Women. *AIDS and Behavior* 2001;5:353-361.

### **Domestic violence and childhood sexual abuse in HIV-infected women and women at risk for HIV**

Many women experience abuse during their lifetime. This study found that HIV+ and HIV- women had similar rates of domestic abuse ever (about 66%) and recently (about 25%). Among HIV+ women, 31% reported childhood sexual abuse; 27% of HIV- women also reported childhood sexual abuse. Childhood sexual abuse was related to later domestic abuse, using drugs, and risky sex. This supports the idea that children who experience sexual abuse may be at higher risk for HIV when they are adults.

Cohen M, Deamant C, Barkan S, Richardson J, Young M, Holman S, Anastos K, Cohen J, and Melnick S. Domestic violence and childhood sexual abuse in HIV-infected women and women at risk for HIV. *Am J Public Health* 2000;90:560-565. **PMC1446192**

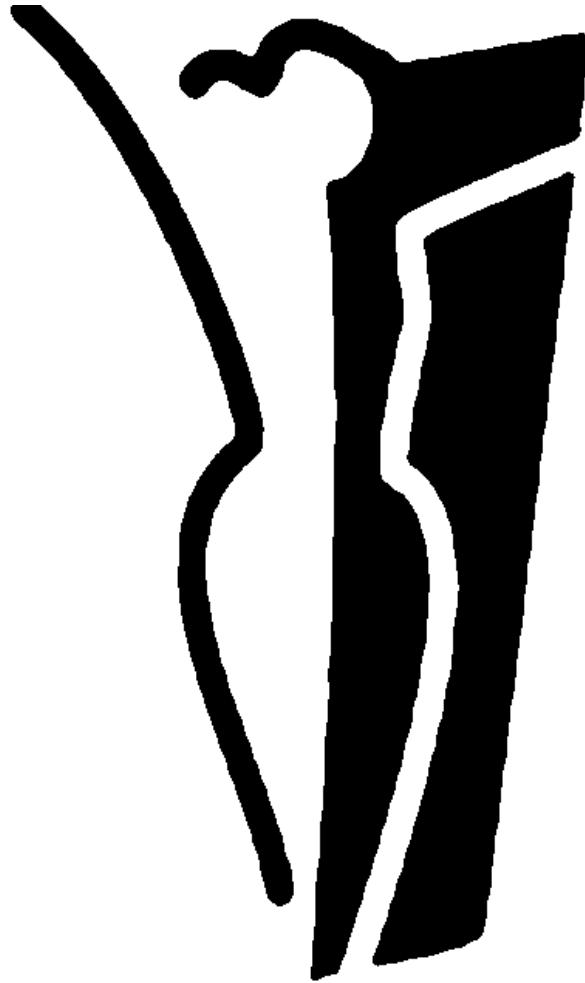
### **Sexual behavior of heterosexual women infected with HIV**

In a survey of 28 straight HIV+ women, 14 reported being sexually active; they all reported being monogamous and 7 had uninfected partners. Four of the sexually active women do not use condoms. 48% of the women reported physical or sexual abuse in their lifetime. Since HIV diagnosis, more women were abstinent and fewer women were on oral birth control.

Massad LS, Farhi MS, Ackatz L, Sha B, and Benson C. Sexual behavior of heterosexual women infected with HIV. *J Womens Health Genet Based Med* 1995;4:681-684. \



# Substances of Abuse





### **Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Cohort (WIHS)**

Some studies suggest marijuana use may reduce HIV-related symptoms. We evaluated marijuana use among HIV-infected women in the WIHS. 21% of women used marijuana in 1994. This decreased to 14% of women by 2009. Daily use of marijuana became more common during the study. Women reported they used marijuana to relax, improve appetite, and help reduce pain. In 2009, half of marijuana users said a doctor had prescribed their marijuana and half used marijuana just for fun. The study suggests that marijuana use is common among HIV-infected women in the WIHS.

D'Souza G, Matson P, Grady CD, Nahvi S, Merenstein D, Weber K, Greenblatt R, Burian P and Wilson TE. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Cohort (WIHS), 1994-2010. *J Acquir Immune Defic Syndr* 2012.

### **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.

Goldberg D, Weber KM, Orsi J, Hessol NA, D'Souza G, Watts DH, Schwartz R, Liu C, Glesby M, Burian P, and Cohen MH. Smoking Cessation Among Women With and At High Risk for HIV: Are They Quitting? *J Gen Intern Med* 2010;25(1):39-44.

### **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.

Cook RL, Zhu F, Herbeck Belnap B, Weber K, Cook JA, Vlahov D, Wilson TE, Hessol NA, Plankey M, Howard AA, Cole SR, Sharp GB, Richardson JL, and Cohen MH. Longitudinal Trends in Hazardous Alcohol Consumption in Women with HIV Infection: 1995-2006. *Am J Epidemiol* 2009;169(8):1025-1032.

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

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.

Kowalski J, Gange SJ, Schneider MF, Tsai H-L, Templeton A, Shao Q, Zhang QW, Yeh MF, Young MJ and Markham RB. Relationship of Injection Drug Use, Antiretroviral Therapy Resistance, and Genetic Diversity in the HIV-1 pol Gene. *J Acquir Immune Defic Syndr* 2009;50(4):381-389.



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

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.

Cook J, Burke-Miller J, Cohen M, Cook R, Vlahov D, Wilson T, Golub ET, Schwartz R, Howard A, Ponath C, Plankey M and Grey D. Crack cocaine, disease progression, and mortality in a multi-center cohort of HIV-1 positive women. *AIDS* 2008;22:1355-1363.

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

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.

Cook J, Grey D, Burke J, Cohen M, Vlahov D, Kapadia F, Wilson T, Schwartz R, Cook R, Golub ET, Anastos K, Ponath C, Goparaju L and Levine A. Illicit drug use, depression, and their association with highly active antiretroviral therapy in HIV-positive women. *Drug and Alcohol Dependence* 2007;89(1):74-81.

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

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.

Morris J, Golub ET, Mehta S, Jacobson L and Gange S. Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts. *AIDS Research and Therapy* 2007;4:12.

### **The relationship between non-injection drug use behaviors on progression to AIDS and death in a cohort of HIV seropositive women in the era of highly active antiretroviral therapy use**

Researchers know that injection drug use leads to poorer outcomes for people with HIV. This study looked at the effects of non-injection drugs. At the beginning of the study, women who currently used or had ever used non-injection drugs had lower CD4 counts and higher viral loads. Women who used non-injection drugs regularly were less likely to use HAART over the course of the study. Non-injection drug use was related to developing AIDS, compared to women who never used drugs.

Kapadia F, Cook JA, Cohen MH, Sohler N, Kovacs A, Greenblatt RM, Choudhary I, and Vlahov D. The relationship between non-injection drug use behaviors on progression to AIDS and death in a cohort of HIV seropositive women in the era of highly active antiretroviral therapy use. *Addiction* 2005;100:990-1002.



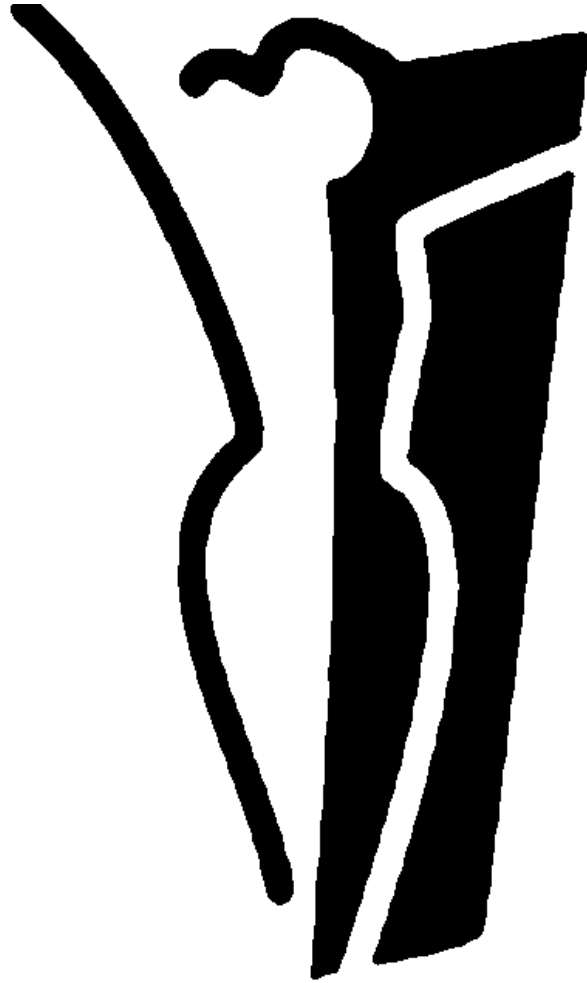
**Correlates of immune activation marker changes in human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women who use illicit drugs**

This study looked at changes in the immune system and how they related to CD4 count, HIV viral load and drug use. The immune system was more active when viral loads were high and when CD4 counts were low. However, drug use was not related to changes in the immune system.

Landay A, Benning L, Bremer J, Weiser B, Burger H, Nowicki M, and Kovacs A. Correlates of immune activation marker changes in human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women who use illicit drugs. *J Infect Dis* 2003;188:209-218.



# HIV Medication and Adherence







### **Pharmacist counseling in a cohort of women with HIV and women at risk for HIV**

Because many HIV-positive women take medicines, having a good relationship with the pharmacy is very important to remain healthy. Not all HIV-positive women use their pharmacies in the best way possible. They may avoid talking with the pharmacist due to concerns about privacy, or other bad experiences. Talking to the pharmacist is an important part of pharmacy care. The pharmacist can explain the medications, can ask insurance companies to pay for medicines, can help people manage side effects, and can talk with you about ways to remember to take your medicines. This study looked at whether the being HIV positive affects the way one uses her pharmacy. In our study, only 30% of all women had spoken to their pharmacist in the last 6 months. Women who were HIV positive were just as likely to talk their pharmacist as HIV negative women. However, women who were younger and who had more education were less likely to talk to the pharmacist. For the HIV positive women in the study, talking with the pharmacist had a small (but not statistically significant) effect on adherence and CD4+ cell counts. In the future, prospective studies should be done to look closely at the effect between talking with a pharmacist and health of HIV positive women.

Cocohoba JM, Althoff KN, Cohen M, Hu H, Cunningham C, Sharma A, Greenblatt RM. Pharmacist counseling in a cohort of women with HIV and women at risk for HIV. *Patient Preference and Adherence*. 2012 6:457-463.

### **Human Leukocyte Antigen (HLA) Genotype and Risk of HIV Disease Progression Before and After Initiation of Antiretroviral Therapy**

This study analyzed the effect of WIHS women's genes on the progression of their HIV disease, both before and after they started to take antiretroviral therapy. We found that three of the genes linked with slower disease progression before therapy predicted faster disease progression after women started therapy. Because poor response to antiretroviral therapy is an important problem for many people, future studies of how these three genes function in people taking antiretroviral therapy may help people get the most benefit possible once they start taking HIV drugs.

Kuniholm MH, Gao X, Xue X, Kovacs K, Marti D, Greenblatt RM, Cohen MH, Minkoff H, Gange SJ, Anastos K, Fazzari M, Young MA, Strickler HD, and Carrington M. Human Leukocyte Antigen (HLA) Genotype and Risk of HIV Disease Progression Before and After Initiation of Antiretroviral Therapy. *J Virol* 2011;85(20):10826-10833. **PMC3187522**

### **A Single Nucleotide Polymorphism in CYP2B6 Leads to >3-fold Increases in Efavirenz Concentrations in Intensive PK Curves and Hair Samples**

A lot of HIV-infected people, including women in the study, are prescribed efavirenz (also known as Sustiva) in their antiretroviral regimens. The medication called Atripla contains efavirenz. However, not everyone can tolerate efavirenz since this drug can lead to side effects such as vivid dreams, dizziness, insomnia, depression, etc. We have been collecting small hair samples from all WIHS women on antiretroviral therapy since 2002 and also performed a substudy called the "Intensive PK study" where women on medications were brought into clinical research centers to obtain plasma samples over 24 hours. This paper tries to find factors that may influence efavirenz medication levels in the blood and in hair, including genetic factors. We found that women with liver problems tend to have higher blood levels of efavirenz, as do women who regularly drink orange juice or eat oranges. We also found that people with a particular pattern in a gene that makes a protein that breaks down efavirenz in the bloodstream (called CYP2B6) have levels of efavirenz in the blood and hair that are 3 times higher than those who don't have that particular gene pattern. Therefore, people who have this particular gene type and take efavirenz may be able to take lower doses of the medication to get the same effect. Thank you for participating in WIHS!

Gandhi M, Greenblatt R, Bacchetti P, Jin C, Huang Y, Anastos K, Cohen M, DeHovitz JA, Sharp GB, Gange SJ, Liu C, Hanson SC and Aouizerat B. A Single Nucleotide Polymorphism in CYP2B6 Leads to >3-fold Increases in Efavirenz Concentrations in Intensive PK Curves and Hair Samples. *J Infect Dis* 2012.



### **Use of Vitamin C on HAART Adherence and Effectiveness among Treated HIV+ Women**

In populations with chronic or terminal diseases, complementary and alternative medicines (CAM) have been shown to have higher usage than the general population, likely due to the belief that CAM may reduce disease symptoms or side effects from conventional treatments. Despite the high rates of CAM use in HIV, there have been few longitudinal, observational studies of the impact of CAM use in large cohorts of HIV positive individuals. CAM modalities have well proven potential benefits and harms. However, due to ethical implications and the vast array of modalities it is difficult to conduct randomized clinical trials to assess benefits and harms. Moreover, because there are so many different CAM modalities and varying characteristics of the same intervention, a clinical trial only addresses a specific modality. However, a cohort study --a true effectiveness study-- allows one to test a plethora of CAM modalities and better understand which ones may hold promise for improving HIV care. We anticipate the knowledge gained will provide physicians and patients with information about a commonly used CAM modality- Vitamin C- and its impact on HIV care.

Merenstein D, Gandhi M, Wang C, Robison E, Levine AM, Schwartz RM, Weber K, and Liu C. Use of Vitamin C on HAART Adherence and Effectiveness among Treated HIV+ Women. *Complement Ther Med*. 2012 Aug;20(4):222-7. **PMC3351689**

### **The effect of HAART on salivary microbiota in the Women's Interagency HIV Study (WIHS)**

Many different types of bacteria and other organisms live in our mouths. This study looked at the different bacteria in HIV+ and HIV- women's mouths. They found that the bacteria in these women's saliva did not differ, regardless of their HIV status. However, they found that women on HAART had fewer yeast cells but more of other types of bacteria.

Navazesh M, Mulligan R, Pogoda J, Greenspan D, Alves M, Phelan J, Greenspan J, and Slots J. The effect of HAART on salivary microbiota in the Women's Interagency HIV Study (WIHS). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;100:701-708.

### **Influence of gender on receipt of guideline-based antiretroviral therapy in the era of HAART**

Treatment of HIV becomes more and more complicated as new antiretroviral medicines become approved by the Federal Drug Administration (FDA). 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. The guidelines also forbid certain regimens. Not all patients will get recommended regimens for many reasons, including side effects, resistance, and other patient likes and dislikes. Despite the guidelines, some patients will get regimens that the guidelines forbid! These regimens are bad regimens because they don't work as well or cause more side effects. This study looked to see how often participants in the WIHS and MACS take HAART regimens that are not recommended by the U.S. guidelines. The WIHS and MACS are good examples of large groups of patients that are affected by HIV in the United States. This study found that being a man or a woman did not raise your risk of getting a nonguideline regimen. Patients that got non-guideline regimens were older and had higher HIV viral loads. A good piece of news is that these non-guideline regimens seemed to be used less and less over time. The results of this study will hopefully make clinicians more aware that certain antiretroviral medicines should not be combined. This study will also highlight the importance of monitoring antiretroviral regimens to make sure that patients get the best therapies possible.

Cocohoba J, Althoff KN, Palella FJ, Godfrey RJ, and Greenblatt RM. Influence of gender on receipt of guideline-based antiretroviral therapy in the era of HAART. *AIDS Care* 2011.

### **Atazanavir Concentration in Hair is the Strongest Predictor of Outcomes on Antiretroviral Therapy**

Although HIV medications (antiretrovirals) have made a huge difference in HIV management and people are doing better and better living with this disease, people are still "failing" these therapies. Some people fail treatment because of side effects and some people have a hard time taking some of the complicated HIV regimens in the right way. However, we do know that people do better on these therapies if they take them every day and get enough medication in their system.

One way to figure out how much medication a patient actually gets in her system is to measure the level of that medication in her bloodstream. That way, we can get a rough idea of how much drug the HIV virus is actually seeing once the medication hits the bloodstream. If we can figure out how much drug a patient is actually getting in her system, we can consider "individualizing" everyone's dose, or making sure a patient gets a dose of antiretroviral that is right for her - a patient with very high blood levels of HIV medications and side effects from the medicines may need a lower dose, for instance. We are looking at blood levels of these medications as part of the WIHS study. However, medications get into the bloodstream quickly and leave quickly and a single blood level can only tell us what medication the patient took over the past 24 hours. Therefore, in the WIHS study, we have started to measure antiretroviral levels in hair, which is why HIV-positive WIHS participants on treatment have



been giving hair to the study every visit. HIV medications accumulate in hair more slowly than in the bloodstream, over a period of weeks to months, in fact. Hair levels tell us how much drug the patient has been seeing over a long time period, which may tell us more about why she is either doing well on therapy or not, including if she is having a lot of side effects.

This paper puts together a lot of the data on hair levels we have been collecting in WIHS over the past 6-7 years. We show in this paper that, for women on atazanavir (Reyataz®)-based therapy, hair levels of drug tell us more than any other factor about the outcomes of treatment. We measured hair levels of atazanavir for women taking this drug between April 2003-April 2008 and looked at the relationship of those hair levels with how well the women do in terms of achieving viral loads that are undetectable. Hair levels of drug strongly predicted how people did, so that women with high atazanavir levels in their hair were more likely to have undetectable viral loads than those with low levels in their hair. We are hoping that these hair levels will eventually allow us to tailor each person's HIV regimen so that it works best for her. Thank you so much for participating in the study.

Gandhi M, Ameli N, Bacchetti P, Anastos K, Gange SJ, Minkoff H, Young MA, Milam J, Cohen MH, Sharp GB, Huang Y, and Greenblatt RM. Atazanavir Concentration in Hair is the Strongest Predictor of Outcomes on Antiretroviral Therapy. *Clin Infect Dis* 2011;52(10):1267-1275. **PMC3079399**

### **The Impact of the AIDS Drug Assistance Program (ADAP) on Use of Highly Active Antiretroviral and Antihypertensive Therapy among HIV-Infected Women**

The AIDS Drug Assistance Program (ADAP) is the nation's primary drug assistance program to help people with HIV to access life-sustaining medications. In light of budget cuts and projected increase in demand for effective therapy, it is vital that we examine the impact of ADAP on use of medication therapy. The objective of our study, titled "The Impact of the AIDS Drug Assistance Program (ADAP) on Use of Highly Active Antiretroviral and Antihypertensive Therapy Among HIV-infected Women", was to evaluate the association between enrollment into ADAP and use of highly active antiretroviral therapy (HAART) and antihypertensive therapy. In addition, differences in state eligibility criteria and drug coverage were examined to see if states with broader coverage were associated with increased medication use. To perform this study, we used data from HAART-eligible women enrolled in the California, New York and Illinois WIHS sites. A subset of women with a history of hypertension were also analyzed. Analyses that measured the association between demographic, behavioral, and health service factors and nonuse of HAART and antihypertensive medication were performed. We found that women without ADAP were less likely to use HAART and trended towards lower likelihood of antihypertensive use compared to women enrolled in ADAP. There was no significant difference in medication use between states. Therefore, we concluded that ADAP enrollment increased the likelihood of HAART use in women who met clinical criteria for taking HAART. While state of residence was not associated with differences in HAART or antihypertensive use, other government programs, such as Medicaid, may have played an important role.

Yi T, Cocohoba J, Cohen M, Anastos K, DeHovitz JA, Kono N, Hanna DB, and Hessol NA. The Impact of the AIDS Drug Assistance Program (ADAP) on Use of Highly Active Antiretroviral and Antihypertensive Therapy among HIV-Infected Women. *J Acquir Immune Defic Syndr* 2011;56(3):253-262. **PMC3042745**

### **Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women**

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.

Minkoff H, Zhong Y, Burk RD, Palefsky JM, Xue X, Watts DH, Levine AM, Wright RL, Colie C, D'Souza G, Massad LS, and Strickler HD. Influence of Adherent and Effective Antiretroviral Therapy Use on Human Papillomavirus Infection and Squamous Intraepithelial Lesions in HIV-Positive Women. *J Infect Dis* 2010;201(5):681-690.



### **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.

Gandhi M, Ameli N, Bacchetti P, Gange SJ, Anastos K, Levine A, Hyman CL, Cohen M, Young M, Huang Y, and Greenblatt RM for the Women's Interagency HIV Study (WIHS). Protease inhibitor levels in hair samples strongly predict virologic responses to HIV treatment. *AIDS* 2009;23(4):471-478.

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

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.

Feldman DN, Feldman JG, Greenblatt RM, Anastos K, Pearce L, Cohen MH, Gange SJ, Leanza S, and Burk R. CYP1A1 genotype modifies the impact of smoking on effectiveness of HAART among women. *AIDS Educ Prev* 2009;21(3 Suppl):81-93.

### **Disclosure of complementary and alternative medicine use to health care providers among HIV-infected women**

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.

Liu C, Yang Y, Gange SJ, Weber K, Sharp G, Wilson TE, Levine A, Robison E, Goparaju L, Gandhi M, and Merenstein D. Disclosure of Complementary and Alternative Medicine Use to Health Care Providers among HIV-infected Women. *AIDS Patient Care and STDS* 2009;23(11):965-971.



### **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.

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.

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

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.

Merenstein DJ, Schneider MF, Cox C, Schwartz R, Weber K, Robison E, Gandhi M, Richardson J and Plankey MW. Association of child care burden and household composition with adherence to Highly Active Antiretroviral Therapy in the Women's Interagency HIV Study. *AIDS Patient Care and STDS* 2009;23(4):289-296.

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

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.

Navazesh M, Mulligan R, Karim R, Mack WJ, Ram S, Seirawan H, Greenspan J, Greenspan D, Phelan J and Alves M. Effect of HAART on salivary gland function in the Women's Interagency HIV Study (WIHS). *Oral Dis* 2009;15(1):52-60.

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

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.

Plankey M, Bacchetti P, Jin C, Grimes B, Hyman C, Cohen M, Howard AA, and Tien PC. Self-Perception of Body Fat Changes and HAART Adherence in the Women's Interagency HIV Study. *AIDS Behav* 2009;13(1):53-59.



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

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.

Silverberg MJ, Jacobson L, French A, Witt MD, and Gange S. Age and Racial/Ethnic Differences in the Prevalence of Reported Symptoms in HIV-Infected Persons on Antiretroviral Therapy. *J Pain Symptom Manage* 2009;38(2):197-207

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

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.

Terzian AS, Holman S, Nathwani N, Robison E, Weber K, Young M, Greenblatt RM, and Gange SJ. Factors associated with preclinical disability and frailty among HIV-infected and -uninfected women in the era of cART. *J Women's Health* 2009;18(12):1965-1974.

### **Consistency of initial antiretroviral therapy with HIV treatment guidelines in a US cohort of HIV-infected women**

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.

Cocohoba J, Wang QJ, Cox C, Gange SJ, Cohen M, Glesby M, DeHovitz JA and Greenblatt RM. Consistency of initial antiretroviral therapy with HIV treatment guidelines in a US cohort of HIV-infected women. *J Acquir Immune Defic Syndr* 2008;47:377-383.



### **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.

Golub ET, Benning L, Sharma A, Gandhi M, Cohen MH, Young M and Gange SJ. Patterns, predictors, and consequences of initial regimen type among HIV-infected women receiving highly active antiretroviral therapy. *Clin Infect Dis* 2008;46:305-312.

### **Longitudinal anthropometric patterns among HIV-infected and HIV- uninfected women**

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.

Justman JE, Hoover DR, Shi Q, Tan T, Anastos K, Tien PC, Cole SR, Hyman C, Karim R, Weber K and Grinspoon S. Longitudinal anthropometric patterns among HIV-infected and HIVuninfected women. *J Acquir Immune Defic Syndr* 2008;47:312-319.

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

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.

Kapadia F, Vlahov D, Wu Y, Cohen MH, Greenblatt RM, Howard AA, Cook JA, Goparaju L, Golub ET, Richardson J and Wilson TE. Impact of drug abuse treatment modalities on adherence to ART/HAART among a cohort of HIV seropositive women. *Am J Drug Alcohol Abuse* 2008;34:161-170.



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

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.

Merenstein DJ, Schneider MF, Cox C, Schwartz R, Weber K, Robison E, Gandhi M, Richardson J and Plankey MW. Association between living with children and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study. *Pediatrics* 2008;121:e787- e793.

### **Association of complementary and alternative medicine use with highly active antiretroviral therapy initiation**

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.

Merenstein D, Yang Y, Schneider M, Goparaju L, Weber K, Sharma A, Levine AM, Sharp GB, Gandhi M and Liu C. Association of Complementary and Alternative Medicine Use with HAART Initiation. *Altern Ther Health Med* 2008;14:18-22.

### **Highly active antiretroviral therapy reduces urinary albumin excretion in women with HIV infection**

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.

Szczec 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.

### **Antiretroviral therapy exposure and insulin resistance in the Women's Interagency HIV study**

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.

Tien P, Schneider M, Cole S, Levine A, Cohen M, DeHovitz J, Young M, and Justman J. Antiretroviral Therapy Exposure and Insulin Resistance in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2008;49:369-376.





### **The association of bone mineral density with HIV infection and antiretroviral treatment in women**

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.

Anastos K, Lu D, Shi Q, Mulligan R, Tien P, Freeman R, Cohen M, Justman J and Hessel N. The association of bone mineral density with HIV infection and antiretroviral treatment in women. *Antivir Ther* 2007;12(7):1049-58.

### **Association of Serum Lipid Levels With HIV Serostatus, Specific Antiretroviral Agents, and Treatment Regimens**

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.

Anastos K, Lu D, Shi Q, Tien P, Kaplan R, Hessel N, Cole S, Vigen C, Cohen M, Young M and Justman J. The association of serum lipid levels with HIV serostatus, specific antiretroviral agents and treatment regimens. *J Acquir Immune Defic Synd* 2007;45(1):34-42.

### **HIV status, trust in health care providers, and distrust in the health care system among Bronx women**

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.

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.

Hessel N, Kalinowski A, Benning L, Mullen J, Young M, Palella F, Anastos K, Detels R and Cohen M. Mortality among participants in the MACS and WIHS. *CID* 2007;44:287-294.



### **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.

Kaplan RC, Ho GYF, Xue X, Rajapthak S, Cushman M, Rohan TE, Strickler HD, Scherer PE and Anastos KA. Within-individual stability of obesity-related biomarkers among women. *Cancer Epidemiol Biomarkers Prev* 2007;16:1291-3.

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

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.

Kemal K, Burger H, Mayers D, Anastos K, Foley B, Kitchen C, Huggins P, Schroeder G, Back S, Gao W, Meyer MA and Weiser B. HIV-1 drug resistance in variants from the female genital tract and plasma. *J Infect Dis* 2007;195(4):535-545.

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

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.

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.



### **Association between complementary and alternative medicine use and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study**

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.

Liu C, Lerch V, Weber K, Schneider MF, Sharp GB, Goparaju L, Sharma A, Levine A, Gandhi M and Merenstein D. Association between complementary and alternative medicine use and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study. *J Altern Complement Med* 2007;13:1053-1056.

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

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 (PLWHA) 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 PLWHA 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 PLWHA 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 PLWHA ascertainment, we estimated the completeness of prevalent HIV (non-AIDS) case ascertainment and the total number of PLWHA 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/ $\mu$ L and detectable viral load (Scenario A); CD4<500 cells/ $\mu$ L and no viral load reporting (Scenario B); and CD4<500 cells/ $\mu$ L and detectable viral load (Scenario C).

Nash D, Andreopoulos E, Horowitz D, Sohler N and Vlahov D. Differences among U.S. states in estimating the number of people living with HIV/AIDS: impact on allocation of federal Ryan White funding. *Public Health Rep* 2007;122:644-656.

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

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.

Neely M, Benning L, Xu J, Strickler H, Greenblatt R, Minkoff H, Young M, Bremer J, Levine A and Kovacs A. Cervical shedding of HIV-1 RNA among women with low levels of viremia while receiving highly active antiretroviral therapy. *J Acquir Immune Defic* 2007;44(1):38-42.

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

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<sup>1</sup>. 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.

Sharma A, Feldman J, Golub ET, Schmidt J, Silver S, Robison E and Minkoff H. Live birth patterns among human immunodeficiency virus-infected women before and after the availability of highly active antiretroviral therapy. *Am J Obstet Gynecol* 2007;196(6):541.e1-6.

#### **Antiretroviral therapies associated with lipoatrophy in HIV-infected women**

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.

Tien PC, Barron Y, Justman J, Hyman C, Cohen M, Young M, Kovacs A and Cole S. Antiretroviral therapies associated with lipoatrophy in HIV-infected women. *AIDS Patient Care and STDs* 2007;21:1739-1745.

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

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.

Tien PC, Schneider MF, Cole SR, Levine AM, Cohen M, DeHovitz J, Young M and Justman JE. Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study. *AIDS* 2007;21:1739-1745.

#### **Longitudinal relationships between use of highly active antiretroviral therapy and satisfaction with care among women living with HIV/AIDS**

This study looked at how satisfied a patient is with her healthcare and if she uses HAART. Overall, HAART use led to higher patient satisfaction with her care and with better access to care. However, whether or not a patient was satisfied with her doctor did not indicate whether she would take HAART in the future. Other factors that related to not taking HAART included illegal drug use, fewer health care visits and being African-American.

Burke-Miller JK, Cook JA, Cohen MH, Hessel NA, Wilson TE, Richardson JL, Williams P and Gange SJ. Longitudinal relationships between use of highly active antiretroviral therapy and satisfaction with care among women living with HIV/AIDS. *Am J Public Health* 2006;96(6):1044-1051. **PMC1470631**

#### **Effects of treated and untreated depressive symptoms on highly active antiretroviral therapy (HAART) use in a U.S. multi-site cohort of HIV-positive women**

Taking HAART is important in controlling HIV. However, researchers know that depressed patients are less likely to stay on HAART. This study looked at depressed patients and found that those who got mental health therapy (with or without antidepressants) were more likely to stay on HAART. This is useful information for providers to help their depressed patients stay on their HAART drugs.

Cook J, Grey D, Burke J, Cohen M, Anastos K, Gandhi M, Richardson J, Wilson T, and Young M. Effects of treated and untreated depressive symptoms on highly active antiretroviral therapy (HAART) use in a U.S. multi-site cohort of HIV-positive women. *AIDS Care* 2006;18(2):93-100.



### **Assessing the effect of HAART on QOL among HIV-infected women**

Researchers know that HAART is important for physical health, but we don't know if taking HAART changes a person's quality of life. This study looked at over 900 women and found that HAART use was related to a short-term improvement in quality of life, especially mental health domains.

Liu C, Weber K, Robison E, Hu Z, Jacobson L, and Gange S. Assessing the effect of HAART on QOL among HIV-infected women. *AIDS Research and Therapy* 2006;3(6):1-11. **PMC1459186**

### **The Association of Race, Sociodemographic, and Behavioral Characteristics With Response to Highly Active Antiretroviral Therapy in Women**

This study looked at whether white and African-American women had the same results after starting HAART. Initially it seemed that white women were more likely to suppress their HIV; however, once the researchers accounted for CD4 counts, drug use, smoking, depression and other important factors, there was no difference between white and African-American women.

Anastos K, Schneider MF, Gange S, Minkoff H, Greenblatt R, Feldman J, Levine A, Delapenha R, and Cohen M. The Association of Race, Sociodemographic, and Behavioral Characteristics With Response to Highly Active Antiretroviral Therapy in Women. *J Acquir Immune Defic Syndr* 2005;39(5):537-544.

### **Medically Eligible Women Who Do Not Use HAART: The Importance of Abuse, Drug Use, and Race**

This study found that 1 in 4 women who met the requirements for taking HAART were not on HAART. Women who used crack/cocaine/heroin, or who had a history of abuse, and African American women were less likely to be on HAART when it was recommended.

Cohen MH, Cook JA, Grey D, Young M, Hanau LH, Tien P, Levine AM, and Wilson TE. Medically Eligible Women Who Do Not Use HAART: The Importance of Abuse, Drug Use, and Race. *Am J Public Health* 2004;94:1147-1151. **PMC1448413**

### **Dissatisfaction with medical care among women with HIV: dimensions and associated factors**

Women with HIV get less health care than men with HIV in the US. One reason may be that women are less satisfied with their care. This study asked women how satisfied they felt about different parts of their health care. Women were most satisfied with their provider's bedside manner and with the cost of care; they were least satisfied with access to care and with technology. Women who were in poor health, who were depressed, who were not on HAART, who did not have a regular doctor or who were Hispanic/Latina were less satisfied with their health care. This helps providers improve care for their patients.

Burke JK, Cook JA, Cohen MH, Wilson T, Anastos K, Young M, Palacio H, Richardson J, and Gange S. Dissatisfaction with medical care among women with HIV: dimensions and associated factors. *AIDS Care* 2003;15:451-462.

### **Effects of depressive symptoms and mental health quality of life on use of highly active antiretroviral therapy among HIV-seropositive women**

Women with HIV may also suffer from depression. Researchers found that, accounting for other health factors, women who were depressed or had poor mental health quality of life were less likely to take HAART. However, they found that receiving mental health services made it more likely to use HAART. This suggests that mental health can be an important in helping women take HAART.

Cook JA, Cohen MH, Burke J, Grey D, Anastos K, Kirstein L, Palacio H, Richardson J, Wilson T, and Young M. Effects of depressive symptoms and mental health quality of life on use of highly active antiretroviral therapy among HIV-seropositive women. *J Acquir Immune Defic Syndr* 2002;30:401-409.

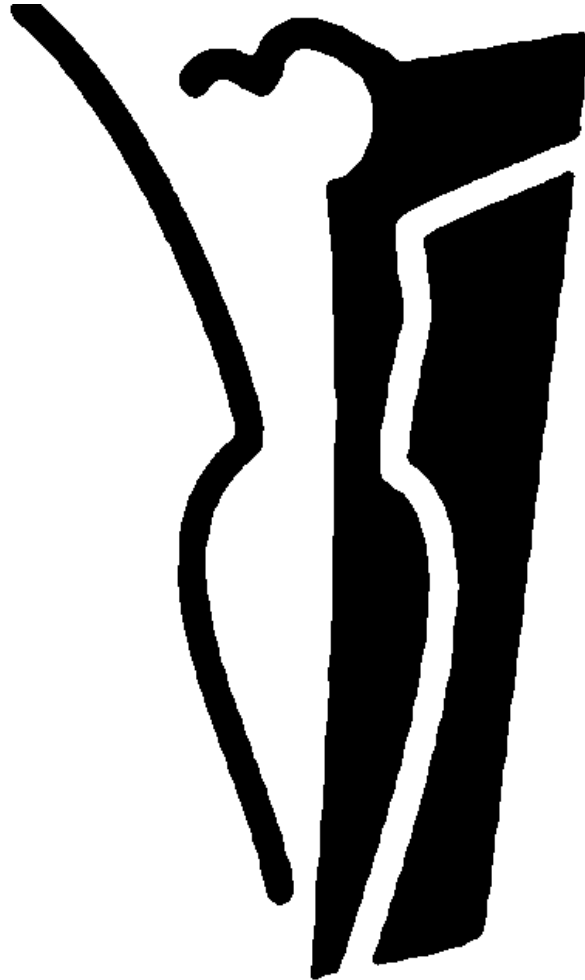
### **Use of highly active antiretroviral therapy in a cohort of HIV- seropositive women**

This study looked at which women were more likely to take antiretroviral medications. Before HAART was available, CD4 count, viral load, and drug/alcohol use were related to using antiretrovirals. Once HAART became available, having a college education and having private insurance made it more likely that a woman was on HAART; being African-American or using injection drugs made it less likely that a woman took HAART.

Cook JA, Cohen MH, Grey D, Kirstein L, Burke J, Anastos K, Palacio H, Richardson J, Wilson TE, and Young M. Use of highly active antiretroviral therapy in a cohort of HIV- seropositive women. *Am J Public Health* 2002;92:82-87. **PMC1447394**



# **HIV Progression and Mortality**





### **Pre-existing albuminuria predicts AIDS and non-AIDS mortality in women initiating antiretroviral therapy**

A small amount of protein in the urine, called “microalbuminuria”, is known to be a marker of heart disease, kidney disease, and mortality in patients with diabetes or high blood pressure. Microalbuminuria is also common in HIV-infected individuals. We previously showed that WIHS participants who had microalbuminuria or higher levels of protein in the urine had a higher risk of mortality compared to women with no protein in the urine. In the current study, we showed that the risk of death was higher in women with microalbuminuria or protein in the urine even after starting HIV medicines. Because the tests for microalbuminuria and urine protein are widely available, these simple tests may be helpful to identify women who would benefit from more aggressive management of HIV and other health problems

Wyatt CM, Hoover DR, Shi Q, Tien PC, Karim R, Cohen MH, Goderre JL, Seaberg EC, Lazar J, Young MA, Klotman PE, and Anastos K. Pre-existing albuminuria predicts AIDS and non-AIDS mortality in women initiating antiretroviral therapy. *Antivir Ther* 2011;16(4):591-596. **PMC3119869**

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

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.

French A, Gawel S, Hershov R, Benning L, Hessel N, Levine A, Anastos K, Augenbraun M, and Cohen M. Trends in Mortality and Cause of Death among Women with HIV in the US: A Tenyear Study. *J Acquir Immune Defic Syndr* 2009;51(4):399-406.

### **Experience of pain among women with advanced HIV disease**

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.

Richardson JL, Heikes B, Karim R, Weber K, Anastos K, and Young M. Experience of pain among women with advanced HIV disease. *AIDS Patient Care and STDS* 2009;23(7):503-511.

### **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**

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.

Simek MD, Rida W, Priddy FH, Carrow E, Laufer DS, Lehrman JK, Boaz M, Tarrogon-Fiol T, Miiro G, Birungi J, Pozniak A, McPhee D, Manigart O, Karita E, Inwoley A, Jaoko W, DeHovitz J, Bekker LG, Pitisuttithum P, Paris R, Poignard P, Wrin T, Fast PE, Burton DR, and Koff WC HIV-1 elite



neutralizers: Individuals with broad and potent neutralizing activity identified using a high throughput neutralization assay together with an analytical selection algorithm. *J Virol* 2009;83(14):7337-7348.

#### **Multiple-infection and recombination in HIV-1 within a longitudinal cohort of women**

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.

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.

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

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.

Nowicki M, Karim R, Mack W, Minkoff H, Anastos K, Cohen M, Greenblatt R, Young M, Gange S and Levine A. Correlates of CD4+ and CD8+ lymphocyte counts in HIV- women: WIHS. *Hum Immunol* 2007;68(5):342-349.

#### **Causes of death among women with human immunodeficiency virus infection in the era of combination antiretroviral therapy**

This study looked at women from 1994-2000 who had died. They found that AIDS-related deaths decreased 39% per year. However, non-AIDS related deaths (such as accidents, overdoses and heart disease) stayed about the same each year. Non-AIDS deaths were related to smoking, older age, depression, injection drug use and hepatitis C infection. This suggests that doctors can help their patients with HIV live longer by also paying attention other problems, like smoking, depression, drug use and hepatitis C.

Cohen MH, French AL, Benning L, Kovacs A, Anastos K, Young M, Minkoff H, and Hessol NA. Causes of death among women with human immunodeficiency virus infection in the era of combination antiretroviral therapy. *Am J Med* 2002;113:91-98.

#### **Marked declines in human immunodeficiency virus-related mortality in Chicago in women, African Americans, Hispanics, young adults, and injection drug users, from 1995 through 1997**

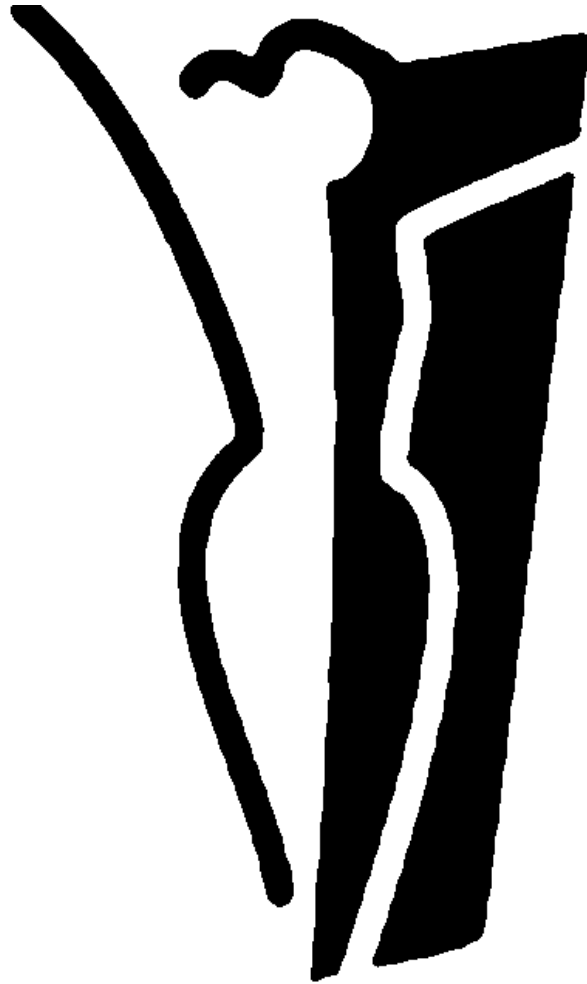
HIV-related deaths in Chicago reached a peak in 1995. From 1995-1997, HIV-related deaths declined 61%. In 1996, the decline was seen mostly in whites, men and middle-age adults. In 1997, however, the decline was also seen in women, African Americans, Hispanics, injection drug users and different age groups. Therefore, while it took longer, even the most at-risk groups did see a decline in deaths from HIV.

Whitman S, Murphy J, Cohen M, and Sherer R. Marked declines in human immunodeficiency virus-related mortality in Chicago in women, African Americans, Hispanics, young adults, and injection drug users, from 1995 through 1997. *Arch Intern Med* 2000;160:365-369.





# HIV Pathogenesis





### **Permissive and Protective Factors Associated With Presence, Level and Longitudinal Pattern of Cervicovaginal HIV Shedding**

This study evaluated whether various behavioral, immunologic, virologic, therapeutic and local factors and conditions are associated with the presence and pattern of HIV shedding in cervicovaginal secretions in a group of women who are part of the WIHS cohort. We found that both the level and pattern of shedding were positively correlated with the amount of HIV in blood plasma as well as factors and conditions that lead to cervicovaginal inflammation, but negatively correlated with the use of HAART. When we evaluated separately the groups of patient-visits with detectable and undetectable HIV in blood plasma, we found that the same factors were strongly associated with higher levels of shedding in the detectable group, and that HAART use was associated with lower shedding level in the undetectable group. In addition, we found a high level of discordance between HIV presence in blood plasma and in cervicovaginal secretions. In a large percentage (58%) of patient-visits with detectable HIV in plasma, HIV was undetectable in cervicovaginal secretions, while in a low but significant percentage (7.6%) of patient-visits with undetectable HIV in plasma, HIV was detectable in cervicovaginal secretions. This information suggests that, with detectable HIV in plasma, additional factors, in particular cervicovaginal inflammatory conditions, may be necessary to permit cervicovaginal shedding in cervicovaginal secretions, and that with undetectable HIV in plasma, HIV may be shed in cervicovaginal secretions and HAART may prevent such shedding.

Homans JD, Christensen S, Stiller T, Wang CH, Mack WJ, Anastos K, Minkoff H, Young M, Greenblatt RM, Cohen M, Stricker HD, Karim R, Spencer LY, Operskalski E, Frederick T, and Kovacs A. Permissive and Protective Factors Associated With Presence, Level and Longitudinal Pattern of Cervicovaginal HIV Shedding. *J Acquir Immune Defic Syndr* 2012 1;60(1):99-110. [PMC3334315](#)

### **Tenofovir use urinary biomarkers among HIV-infected women in the Women's Interagency HIV Study**

This is a study to identify tests that can detect early changes in kidney function of women taking tenofovir (Viread) to assist in identifying those at highest risk for toxicity related to the medication. This study will help to provide new ways to diagnose kidney injury from tenofovir. This study used tests that have already been performed in WIHS (serum creatinine) and utilized stored urine specimens to look for levels of enzymes that are put into the urine when kidney toxicity is occurring (NGAL, NAG, Beta-2-microglobulin). This study will impact future patients by helping to detect kidney injury earlier as creatinine, a current marker of renal injury has been shown to lag behind other more sensitive markers of kidney injury and to provide a greater understanding if changes in kidney function among women on tenofovir may be related to the medication. This study utilized the information already collected and stored urine specimens. No additional participant contact was necessary. In the results, NAG and  $\beta$ 2MG levels rose in women taking tenofovir. Biomarkers levels were also elevated in women who appeared to have baseline kidney abnormalities and elevated HIV virus level.

Oboho I, Abraham A, Benning L, Anastos K, Sharma A, Young M, Burian P, Gandhi M, Cohen M and Szczech L. Tenofovir use urinary biomarkers among HIV-infected women in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2012.

### **IL10 responses are associated with sustained CD4 T cell counts in treated HIV infection**

Inflammation persists in treated HIV infection and may increase the risk for non-AIDS illnesses. We investigated the association of white blood cell factors called cytokines with changes in CD4 levels and co-infection with hepatitis C virus (HCV) during anti-retroviral treatment (HAART). Undetectable HIV RNA (<80 copies/ml) at baseline and secreted IL10 by blood cells were associated with CD4 gains at follow-up. Cytokines mediating inflammation (IL1 $\beta$ , IL6, IL12 and TNF $\alpha$ ) were also produced in blood cell cultures, but only IL10 was associated with sustained CD4 increases. This association was significant only in women with HIV single-infection, indicating that HCV co-infection may limit CD4 gains possibly by contributing to inflammation. Secreted IL10 from white blood cells may balance the inflammatory environment of HIV, resulting in CD4 stability.

Villacres M, Kono N, Mack W, Nowicki M, Anastos K, Augenbraun M, Liu C, Landay A, Greenblatt R, Gange S and Levine A. IL10 responses are associated with sustained CD4 T cell counts in treated HIV infection. *J Infect Dis* 2012 206(5):780-9.

### **Multisite comparison of high-sensitivity multiplex cytokine assays**

People infected with HIV infection often have inflammation, which can contribute to immune deficiency. One way to measure inflammation is to test for inflammation markers in the blood, and these markers are called cytokines. New tests have been developed that can test for multiple cytokines in the same small sample of blood. This study tested how well the new tests performed.



Breen EC, Reynolds SM, Cox C, Jacobson LP, Magpantay L, Mulder CB, Dibben O, Margolick JB, Bream JH, Sambrano E, Martinez-Maza O, Sinclair E, Borrow P, Landay AL, Rinaldo CR, and Norris PJ. Multisite comparison of high-sensitivity multiplex cytokine assays. *Clin Vaccine Immunol* 2011;18(8):1229-1242. **PMC3147360**

### **Absence of reproducibly detectable low-level HIV viremia in highly exposed seronegative men and women**

HIV is not considered highly infectious when one considers the large number of sexual or drug injection exposures that typically lead to infection. Infection is normally detected by the presence of virus or human antibodies against the virus resulting from the production of a large amount of virus. Multiple lines of evidence indicate that the actual number of HIV infections may be underestimated as a consequence of transient, or short-lasting, infections resulting from very low levels of virus and the absence of seroconversion. In this study we tested for very low levels of HIV RNA in 524 HIV-negative plasma samples from 313 highly exposed women and men from 3 longitudinal HIV cohorts. We found that transient viremia was not reproducibly detected in highly exposed HIV-negative men and women.

Delwart E, Bernardin F, Lee TH, Winkelman V, Liu C, Sheppard H, Liu A, Greenblatt RM, Anastos K, DeHovitz J, Nowicki M, Cohen MH, Golub ET, Barbour J, Buchbinder S, Busch MP, NIAID Center for HIV/AIDS Vaccine Immunology (CHAVI). Absence of reproducibly detectable low-level HIV viremia in highly exposed seronegative men and women. *AIDS* 2011;25(5):619-623. **PMC3458706**

### **The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of US women**

This study measured soluble immune markers in the blood of women with or without HIV, including women whose HIV was poorly controlled (not on HIV antiretroviral medicines) and those whose virus was controlled to very low levels with antiretroviral medicines. We found that women with high levels of virus in their blood had abnormal levels of several immune markers. Most but not all of these abnormal markers were normal in subjects on antiretroviral medicines. These studies demonstrate which arms of the immune system are disturbed in HIV infected women and how show that antiretroviral therapy does not fully correct inflammation induced by HIV.

Keating SM, Golub ET, Heitman JW, Lebedeva M, Nowicki M, Young MA, Strickler H, Crystal C, Zhang J, Greenblatt RM, Desai S, Wu S, Landay AL, Gange SJ, Norris PJ, and the Women's Interagency HIV Study. The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of US women. *AIDS* 2011;25(15):1823-1832. **PMC3314300**

### **Elevated caspase-3 expression and T-cell activation in elite suppressors**

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.

Ronquillo RE, Desai SN, Norris PJ, Golub ET, Greenblatt RM, Gange SJ, and Landay AL. Elevated Caspase-3 Expression and T Cell Activation in Elite Suppressors. *J Acquir Immune Defic Syndr* 2010;54(1):110-111.

### **CD8(+) T cell activation in women coinfecting with Human Immunodeficiency Virus Type 1 and hepatitis C virus**

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.

Kovacs A, Al-Harhi L, Christensen S, Mack W, Cohen M and Landay A. CD8(+) T cell activation in women coinfecting with Human Immunodeficiency Virus Type 1 and hepatitis C virus. *J Infect Dis* 2008;197:1402-1407.

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

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.



Strickler HD, Fazzari M, Kovacs A, Isasi C, Napolitano LA, Minkoff H, Gange S, Young M, Sharp GB, Kaplan RC, Cohen M, Gunter MJ, Harris TG, Yu H, Schoenbaum E, Landay AL and Anastos K. Associations of insulin-like growth factor (IGF)-I and IGF-binding protein-3 with HIV disease progression in women. *J Infect Dis* 2008;197:319-327.

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

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- $\alpha$ , 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.

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.

#### **Saliva can mediate HIV-1-specific antibody-dependent cell-mediated cytotoxicity**

HIV is not usually transmitted by saliva. One reason may be that chemicals that attack HIV, called Antibody Dependent Cell Mediated Cytotoxicity or ADCC, may be present in saliva. This study found that about 24% of women, whether HIV+ or HIV-, had HIV-specific ADCC in their saliva. In HIV+ women, the ADCC targeted the gp120 protein of the HIV virus.

Kim JS, Nag P, Landay AL, Alves M, Cohen MH, Bremer JW, and Baum LL. Saliva can mediate HIV-1-specific antibody-dependent cell-mediated cytotoxicity. *FEMS Immunol Med Microbiol* 2006;48:267-273.

#### **Relationship of HIV RNA and cytokines in saliva from HIV-infected individuals**

Cytokines are a group of chemicals released by the body's immune cells; they can help fight off bacteria and viruses in different ways. This study found that the types of cytokines in a woman's saliva and in her blood are different. There was no relationship between the amount of HIV and the amount of cytokines in a woman's saliva. They did find that some cytokines – interferon-gamma – was more common in HIV+ than HIV- women. They also found that a cytokine called interleukin-10 was lower in HIV+ women, but higher in women with lower CD4 counts.

Spear GT, Alves ME, Cohen MH, Bremer J, and Landay AL. Relationship of HIV RNA and cytokines in saliva from HIV-infected individuals. *FEMS Immunol Med Microbiol* 2005;45:129-136.

#### **Induction of tumor necrosis factor- $\alpha$ secretion and toll-like receptor 2 and 4 mRNA expression by genital mucosal fluids from women with bacterial vaginosis**

A healthy vagina has several types of normal bacteria and other organisms. When certain other organisms take over, bacterial vaginosis (BV) can occur. This can make it easier to spread HIV. This study showed that immune cells produce certain factors (tumor necrosis factor- $\alpha$  or TNF $\alpha$ , Toll Like Receptor or TLR2 and TLR4) when exposed to the bacteria that cause BV – but not when exposed to other bacteria. This can help researchers understand the impacts of BV on a woman's health.

Zariffard M, Novak R, Lurain N, Sha B, Graham P, and Spear G. Induction of tumor necrosis factor- $\alpha$  secretion and toll-like receptor 2 and 4 mRNA expression by genital mucosal fluids from women with bacterial vaginosis. *J Infect Dis* 2005;191 (11):1913-1921.

#### **Relationship of U1 cell HIV-stimulatory activity to bacterial vaginosis and HIV genital tract virus load**

Researchers compared genital mucus from women with and without bacterial vaginosis (BV). The mucus from women with BV caused certain cells to have more active HIV. It is uncertain which bacteria caused this change, but this supports the idea that women with BV may be shedding more HIV virus.

Zariffard M, Sha B, Wang Q, Chen H, Bremer J, Cohen M, and Spear G. Relationship of U1 cell HIV-stimulatory activity to bacterial vaginosis and HIV genital tract virus load. *AIDS Res Hum Retroviruses* 2005;21(11):945-948.



### **Women with cervicovaginal antibody-dependent cell-mediated cytotoxicity have lower genital HIV-1 RNA loads**

One way the body fights viruses is with antibody-dependent cell-mediated cytotoxicity (ADCC). Researchers measured how much ADCC was in a woman's blood and how much was in her cervical fluid. They found that women with ADCC in their cervical fluid had lower levels of HIV virus in their genital tract.

Nag P, Kim J, Sapiega V, Landay AL, Bremer JW, Mestecky J, Reichelderfer P, Kovacs A, Cohn J, Weiser B, and Baum LL. Women with cervicovaginal antibody-dependent cell-mediated cytotoxicity have lower genital HIV-1 RNA loads. *J Infect Dis* 2004;190:1970-1978.

### **Trichomonas vaginalis infection activates cells through toll-like receptor 4**

One of the body's normal responses to infections is inflammation. However, HIV can become more active when inflammation happens. *Trichomonas vaginalis* is an organism responsible for the sexually-transmitted infection called "trich". Researchers found that trich can cause inflammation by making immune cells produce a chemical called Toll Like Receptor or TLR4. This information can help researchers understand the effect of trich on HIV in the genital tract.

Zariffard MR, Harwani S, Novak RM, Graham PJ, Ji X, and Spear GT. *Trichomonas vaginalis* infection activates cells through toll-like receptor 4. *Clin Immunol* 2004;111:103-107.

### **Trophoblasts are productively infected by CD4-independent isolate of HIV type 1**

Researchers determined that a certain type of cell that makes up the placenta (call trophoblasts) make chemicals that HIV uses to enter cells and that trophoblasts could be infected by some types of HIV but not by other types. This information may help researchers understand how HIV infects babies before they are born

Al Harthi L, Guilbert LJ, Hoxie JA, and Landay A. Trophoblasts are productively infected by CD4-independent isolate of HIV type 1. *AIDS Res Hum Retroviruses* 2002;18:13-17.

### **Antibody-dependent cell-mediated cytotoxicity in cervical lavage fluids of human immunodeficiency virus type 1-infected women**

Antibody-dependent cell-mediated cytotoxicity (ADCC) is one way the immune system reacts to HIV. This study looked for ADCC in both the blood and cervical fluids of women. 56% of women had ADCC in their blood and 16% in their cervical fluid.

Battle-Miller K, Eby CA, Landay AL, Cohen MH, Sha BE, and Baum LL. Antibody-dependent cell-mediated cytotoxicity in cervical lavage fluids of human immunodeficiency virus type 1-infected women. *J Infect Dis* 2002;185:439-447.

### **A menstrual cycle pattern for cytokine levels exists in HIV-positive women: implication for HIV vaginal and plasma shedding**

Cytokines are chemicals produced by the immune system. This study found that levels of cytokines in the vagina were higher when HIV+ women had their period. The level of cytokines in the blood did not change during their period. They also found that the number of CD4 and CD8 cells did not change during the menstrual cycle.

Al Harthi L, Kovacs A, Coombs RW, Reichelderfer PS, Wright DJ, Cohen MH, Cohn J, Cu-Uvin S, Watts H, Lewis S, Beckner S, and Landay A. A menstrual cycle pattern for cytokine levels exists in HIV-positive women: implication for HIV vaginal and plasma shedding. *AIDS* 2001;15:1535-1543.

### **Myeloid-related protein (MRP)-8 from cervico-vaginal secretions activates HIV replication**

Researchers identified a chemical, MRP-8, that is produced by certain immune cells. In cervical/vaginal fluid, MRP-8 increases HIV production. This could help researchers find ways to eventually decrease HIV shedding in the genital tract.

Hashemi FB, Mollenhauer J, Madsen LD, Sha BE, Nacken W, Moyer MB, Sorg C, and Spear GT. Myeloid-related protein (MRP)-8 from cervico-vaginal secretions activates HIV replication. *AIDS* 2001;15:1-9.

### **Determinants of HIV-1 shedding in the genital tract of women**

Looking at HIV+ women, researchers found 57% had HIV RNA in their genital. However, only 6% had HIV viruses in their genital tract. Although genital tract HIV virus was more common in women with HIV RNA in their blood, even some women with low blood levels still had HIV virus in their genital tract. This is important, as HIV virus in the genital tract can infect sex partners or babies when giving birth.



Kovacs A, Wasserman SS, Burns D, Wright DJ, Cohn J, Landay A, Weber K, Cohen M, Levine A, Minkoff H, Miotti P, Palefsky J, Young M, and Reichelderfer P. Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 2001;358:1593-1601.

### **The impact of the ovulatory cycle on cytokine production: evaluation of systemic, cervicovaginal, and salivary compartments**

The thymus is a small organ in the body that can create T cells; it is most active when we are children but can make new T cells in adults. This study wanted to see if HIV+ patients who were suppressing their HIV were making new T cells. However, they found no difference between the HIV+ and HIV- patients.

Al Harthi L, Wright DJ, Anderson D, Cohen M, Matity AD, Cohn J, Cu-Uvin S, Burns D, Reichelderfer P, Lewis S, Beckner S, Kovacs A, and Landay A. The impact of the ovulatory cycle on cytokine production: evaluation of systemic, cervicovaginal, and salivary compartments. *J Interferon Cytokine Res* 2000;20:719-724.

### **Detection and molecular mass determination of an HIV replication- enhancing female genital tract factor using a blot bioassay**

The researchers describe a method for detecting a chemical in cervical/vaginal fluid that affected HIV activity.

Hashemi FB, Spear GT, Madsen L, and Mollenhauer J. Detection and molecular mass determination of an HIV replication- enhancing female genital tract factor using a blot bioassay. *Biotechniques* 2000;28:478, 480, 482, 484.

### **Induction of human immunodeficiency virus type 1 expression by anaerobes associated with bacterial vaginosis**

Normally, several “good” types of organisms live in the vagina. When “bad” organisms invade the vagina, bacterial vaginosis (BV) can result. BV can lead to increased transmission of HIV. This study found that certain bacteria, increased HIV activity, where other bacteria did not. This can help researchers understand how to better treat BV and reduce HIV transmission.

Hashemi FB, Ghassemi M, Faro S, Aroutcheva A, and Spear GT. Induction of human immunodeficiency virus type 1 expression by anaerobes associated with bacterial vaginosis. *J Infect Dis* 2000;181:1574-1580.

### **Evaluation of thymopoiesis using T cell receptor excision circles (TRECs): differential correlation between adult and pediatric TRECs and naive phenotypes**

The thymus is a small organ in the body that can make T cells. The thymus is most active in young children, but can make some T cells in adults. This study found certain types of T cells that may have been created in the thymus of adults.

Steffens CM, Al Harthi L, Shott S, Yogev R, and Landay A. Evaluation of thymopoiesis using T cell receptor excision circles (TRECs): differential correlation between adult and pediatric TRECs and naive phenotypes. *Clin Immunol* 2000;97:95-101.

### **Activation of human immunodeficiency virus type 1 expression by Gardnerella vaginalis**

A healthy vagina is home to many types of “good” organisms. The presence of “bad” bacteria can result in bacterial vaginosis (BV) and lead to increased HIV activity and transmission. This research found that Gardnerella vaginalis, a bacteria often found in BV, can activate HIV.

Hashemi FB, Ghassemi M, Roebuck KA, and Spear GT. Activation of human immunodeficiency virus type 1 expression by Gardnerella vaginalis. *J Infect Dis* 1999;179:924-930.

### **Association of indicators of bacterial vaginosis with a female genital tract factor that induces expression of HIV-1**

Researchers had found that the cervical/vaginal fluid of some women with HIV could activate HIV. They found evidence in this study that this was possibly because of certain bacteria that cause bacterial vaginosis.

Olinger GG, Hashemi FB, Sha BE, and Spear GT. Association of indicators of bacterial vaginosis with a female genital tract factor that induces expression of HIV-1. *AIDS* 1999;13:1905-1912.

### **Regulation of CCR5 and CXCR4 expression by type 1 and type 2 cytokines: CCR5 expression is downregulated by IL-10 in CD4-positive lymphocytes**



HIV needs certain chemical tags to be able to enter T cells. This study found that certain cytokines (chemical messengers made by the immune system) can increase or decrease the production of these chemical tags. This information helps us understand how HIV is transmitted.

Patterson BK, Czerniewski M, Andersson J, Sullivan Y, Su F, Jiyamapa D, Burki Z, and Landay A. Regulation of CCR5 and CXCR4 expression by type 1 and type 2 cytokines: CCR5 expression is downregulated by IL-10 in CD4-positive lymphocytes. *Clin Immunol* 1999;91:254-262.

### **A human immunodeficiency virus (HIV)-inducing factor from the female genital tract activates HIV-1 gene expression through the kappaB enhancer**

These researchers had found that the cervical/vaginal fluid of some women could activate HIV. They found in this study that this involved two chemical, AP-1 and NF-kappaB, that are made by the immune system.

Al Harthi L, Spear GT, Hashemi FB, Landay A, Sha BE, and Roebuck KA. A human immunodeficiency virus (HIV)-inducing factor from the female genital tract activates HIV-1 gene expression through the kappaB enhancer. *J Infect Dis* 1998;178:1343-1351.

### **Repertoire of chemokine receptor expression in the female genital tract: implications for human immunodeficiency virus transmission**

This study identified some of the tags that HIV uses to enter T cells. They found a molecule called CCR5 was mostly found on cells in the genital tract and a molecule called CXCR4 was found mostly in the bloodstream. There was some evidence that sexually transmitted diseases and progesterone could increase the level of these molecules, which might make it easier for HIV to infect the cells.

Patterson BK, Landay A, Andersson J, Brown C, Behbahani H, Jiyamapa D, Burki Z, Stanislawski D, Czerniewski MA, and Garcia P. Repertoire of chemokine receptor expression in the female genital tract: implications for human immunodeficiency virus transmission. *Am J Pathol* 1998;153:481-490. **PMC1852974**

### **Chemokines are present in the genital tract of HIV-seropositive and HIV- seronegative women: correlation with other immune mediators**

The immune system releases certain chemicals, called chemokines, to fight infection. This study looked at whether three specific chemokines (IL-8, RANTES and MIP-1 alpha) were produced in the cervical/vaginal fluid. They found IL-8 in 81% of the samples, RANTES in 32% and MIP-1 alpha in 15%. This information can help researchers understand how the body defends itself from HIV.

Spear GT, Sha BE, Saarloos MN, Benson CA, Rydman R, Massad LS, Gilmore R, and Landay AL. Chemokines are present in the genital tract of HIV-seropositive and HIV- seronegative women: correlation with other immune mediators. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;18:454-459.

### **Evaluation of immunologic markers in cervicovaginal fluid of HIV- infected and uninfected women: implications for the immunologic response to HIV in the female genital tract**

The researchers compared the cervical/vaginal fluid of women who were HIV positive and HIV negative. They found HIV+ women were more likely to have abnormal cervical cells, but not more likely to have vaginal infections. The immune chemicals detected were about the same in both groups. Women with vaginal infections or abnormal cervical cells did have higher levels of certain chemicals from the immune system (IgG and interferon-gamma).

Sha BE, D'Amico RD, Landay AL, Spear GT, Massad LS, Rydman RJ, Warner NA, Padnick J, Ackatz L, Charles LA, and Benson CA. Evaluation of immunologic markers in cervicovaginal fluid of HIV- infected and uninfected women: implications for the immunologic response to HIV in the female genital tract. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;16:161-168.

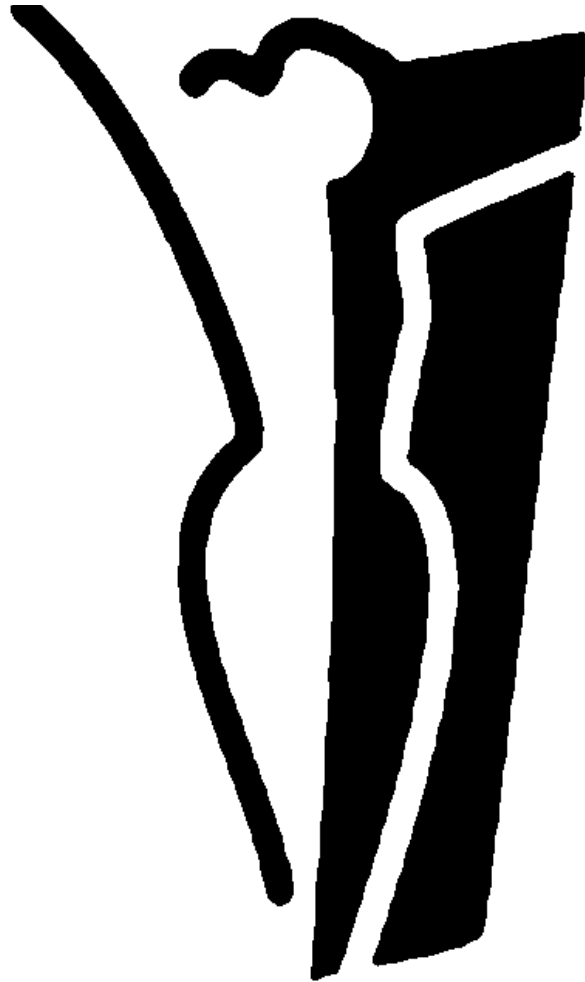
### **A potent activator of HIV-1 replication is present in the genital tract of a subset of HIV-1-infected and uninfected women**

This study determined that the cervical/vaginal fluid of some women (both HIV+ and HIV-) could activate HIV.

Spear GT, Al Harthi L, Sha B, Saarloos MN, Hayden M, Massad LS, Benson C, Roebuck KA, Glick NR, and Landay A. A potent activator of HIV-1 replication is present in the genital tract of a subset of HIV-1-infected and uninfected women. *AIDS* 1997;11:1319-1326.



# Study Methods







### **The parametric g-formula to estimate the effect of highly active antiretroviral therapy on incident AIDS or death**

The parametric g-formula is a viable alternative that can be used in the analysis of complex longitudinal data. We used the parametric g-formula to assess the impact of HAART on time to AIDS or death in both the WIHS and the MACS. We were able to estimate that antiretroviral therapy substantially reduces the risk of AIDS or death.

Westreich D, Cole S, Young J, Palella F, Tien P, Kingsley L, Gange S and Hernan M. The parametric g-formula to estimate the effect of highly active antiretroviral therapy on incident AIDS or death. *Stat Med* 2012 31(18):2000-9.

### **Using marginal structural measurement-error models to estimate the long-term effect of antiretroviral therapy on incident AIDS or death**

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.

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.

### **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**

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 not 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.

Galarraga O, Salkever DS, Cook JA, and Gange SJ. 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. *Health Econ* 2010;19(2):173-188.

### **Time scale and adjusted survival curves for marginal structural cox models**

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.

Westreich D, Cole SR, Tien PC, Chmiel JS, Kingsley L, Funk MJ, Anastos K, Jacobson LP. Time scale and adjusted survival curves for marginal structural cox models. *Am J Epidemiol* 2010;171(6):691-700.

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

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  $\geq$  \$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.

Hessol NA, Weber K, Holman S, Alden C, Goparaju L, Kono N, Robison E, Watts H, and Ameli N. Retention and Attendance of Women Enrolled in a Large Prospective Study of HIV-1 in the United States. *J Women's Health* 2009;18(10):1627-1637.

### **Constructing inverse probability weights for marginal structural models**

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.

Cole SR and Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656-664.

### **Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution**

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.

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.

### **Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models**

This study looked at different mathematical ways to measure the effect of HAART. By considering how CD4 and HIV levels can change over time, they calculated that HAART significantly slows down the time until someone develops AIDS or dies.

Cole SR, Hernan MA, Robins JM, Anastos K, Chmiel J, Detels R, Ervin C, Feldman J, Greenblatt R, Kingsley L, Lai S, Young M, Cohen M, Munoz A. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am J Epidemiol* 2003; 158(7):687-694.

### **Retention of women enrolled in a prospective study of human immunodeficiency virus infection: impact of race, unstable housing, and use of human immunodeficiency virus therapy**

As HIV becomes more common among women of color, it is important to find ways to include and keep women of color in HIV studies. This paper describes how WIHS has been able to keep so many African-American and Hispanic women in the study over a long period of time, so that other researchers can do the same.

Hessol NA, Schneider M, Greenblatt RM, Bacon M, Barranday Y, Holman S, Robison E, Williams C, Cohen M, and Weber K. Retention of women enrolled in a prospective study of human immunodeficiency virus infection: impact of race, unstable housing, and use of human immunodeficiency virus therapy. *Am J Epidemiol* 2001;154:563-573.



### **Comparison of two amplification technologies for detection and quantitation of human immunodeficiency virus type 1 RNA in the female genital tract**

Being able to detect HIV viral load in the blood and genital tract is important for both researchers and doctors. This study compared two new methods with an existing lab technique and found that, when done correctly, all three methods can give similar results.

Bremer J, Nowicki M, Beckner S, Brambilla D, Cronin M, Herman S, Kovacs A, and Reichelderfer P. Comparison of two amplification technologies for detection and quantitation of human immunodeficiency virus type 1 RNA in the female genital tract. Division of AIDS Treatment Research Initiative 009 Study Team. *J Clin Microbiol* 2000;38:2665-2669. **PMC86993**

### **Interrater variability in diagnosis of cervical biopsies from women with HIV-1: results from the Women's Interagency HIV Study**

A biopsy of the cervix removes a small piece to examine for signs of cervical cancer. Biopsy samples were examined by two different pathologists (one at the study site and another central reviewer) to see how often they gave the same results. Overall, the doctors agreed pretty well. The study site doctors were a little more likely to report less severe results than the central review doctors. Disagreement was more likely when a patient had low CD4 counts.

Massad LS, Kirstein L, Darragh T, Bitterman P, Sidaway M, Muderspach L, Abulafia O, Salzer E, Watts H, and Melnick S. Interrater variability in diagnosis of cervical biopsies from women with HIV-1: results from the Women's Interagency HIV Study. *J Lower Genital Tract Dis* 2000;4:190-194.

### **The Women's Interagency HIV Study. WIHS Collaborative Study Group**

This paper describes WIHS study methods and baseline characteristics of the original women enrolled. There were 2,058 HIV+ women and 568 HIV- women from six study sites around the country. Women were aged 16-73; about 25% were Hispanic/Latina and over 50% were African-American. Of the HIV+ women, 34% had injected drugs and 42% had high-risk sex; among HIV- women, 28% had injected drugs and 26% had high-risk sex. More than half of the women were living below the poverty line. These women had been carefully selected to represent women with HIV across the nation.

Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, Young M, Greenblatt R, Sacks H, and Feldman J. The Women's Interagency HIV Study. WIHS Collaborative Study Group. *Epidemiol* 1998;9:117-125.

### **Bioelectrical impedance analysis (BIA) in HIV infection: principles and clinical applications**

This study describes a method of measuring body weight and body fat that might be useful in detecting weight changes before a person with HIV gets seriously sick. This method is called bioelectrical impedance analysis.

Swanson B and Keithley JK. Bioelectrical impedance analysis (BIA) in HIV infection: principles and clinical applications. *J Assoc Nurses AIDS Care* 1998;9:49-54