



2013-2014 WIHS Findings: Lay Language Summaries for the Community

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Bacterial Vaginosis

Colonization by Candida species of the oral and vaginal mucosa in HIV-infected and noninfected women

Yeast infections, scientifically called candidiasis, commonly occur for all women vaginally and about 90% of AIDS patients have had oral candidiasis, also called thrush. In this study, WIHS researchers tested for yeast infections in mouth and vaginal tissues of both HIV-infected and HIV-uninfected women for 90 days. Both groups of women had substantial rates of yeast infections during the study period, though HIV-infected women had higher rates of infection. One surprising finding was how common oral candidiasis was among both groups--more than half of the women studied had at least one oral yeast infection.

Merenstein D, Hu H, Wang C, Hamilton P, Blackmon M, Chen H, Calderone R, Li D. AIDS Res Hum Retroviruses 2013 Jan;29(1):30-4. (PMC3537294)

Comparison of lower genital tract microbiota in HIV-infected and uninfected women from Rwanda and the US

The HIV infection is mostly spread by sexual contact between men and women. The types of bacteria in the vagina affect how much HIV infection there is. Since HIV infections occur more frequently in Africa, we thought that the types of bacteria in the vaginas of African women might be different than bacteria in women in the US. However, we found that in general, the types of bacteria were very similar between African and US women.

Benning L, Golub ET, Anastos K, French AL, Cohen M, Gilbert D, Gillevet P, Munyazesa E, Landay AL, Sikaroodi M, Spear GT. PLoS One 2014 May 9;9(5):e96844. (PMC4016010)

Free glycogen in vaginal fluids is associated with Lactobacillus colonization and low vaginal pH

While all women have bacteria in the vagina, Lactobacillus when present helps protect women from infections and therefore can be regarded as good or beneficial bacteria. We found that a substance that women make in their vaginas called glycogen, appears to help the Lactobacillus survive in the vagina.

Mirmonsef P, Hotton AL, Gilbert D, Burgad D, Landay A, Weber KM, Cohen M, Ravel J, Spear GT. Plos One 2014 Jul 17;9(7):e102467. (PMC4102502)

Impact of Eating Probiotic Yogurt on Colonization by Candida Species of the Oral and Vaginal Mucosa in HIV-Infected and HIV-Uninfected Women

Have you heard that yogurt may be beneficial during a yeast infection? Yeast infections (scientifically called candidiasis) of the mouth, throat, and vagina are common among people infected with HIV. Fungal infections (like yeast infections) are often difficult to treat, since fungi like bacteria and viruses can become drug-resistant. Probiotics, including yogurt, are live microorganisms which can improve our health, and are commonly taken by women when they suspect they have a vaginal yeast infection. In this small study, WIHS researchers asked several HIV-infected as well as HIV-uninfected women to eat probiotic yogurt daily for 15 days, then tested swabs from their mouths and vaginas for fungal colonies. Yeast infections were more commonly seen in HIV-infected women, but while probiotic yogurts were eaten there were fewer yeast infections. Even after probiotics were stopped, HIV-infected women had fewer yeast infections compared to before they began the probiotics. While this data is limited and more studies are needed for conclusive evidence on probiotics, it shows promising evidence that probiotic yogurt could take on a valuable role in maintaining women's health.

Hu H, Merenstein DJ, Wang C, Hamilton PR, Blackmon ML, Chen H, Calderone RA, Li D. *Mycopathologia* 2013 Oct;176(3- 4):175-181. (PMC3903393)

Cardiovascular

Gonadotropin and Sex Steroid Levels in HIV-infected Premenopausal Women and Their Association with Subclinical Atherosclerosis in HIVinfected and -uninfected Women in the Women's Interagency HIV Study (WIHS)

Many HIV-infected women experience irregular periods, thought to be related to irregular levels of sex hormones and a similar hormone called gonadotropin. Irregular levels of these hormones can indicate that other problems such as hardening of the arteries (atherosclerosis) are present from an overall imbalance of hormone regulation. WIHS researchers studied early markers of artery disease through blood tests and ultrasound measurement of the carotid artery in the neck in premenopausal women with and without HIV infection. HIV-infected women had lower levels of estrogen and testosterone compared to HIV-uninfected women. Lower levels of testosterone was associated with carotid artery stiffness for all HIV-infected women, while lower levels of estrogen was only linked with arterial stiffness for women with weakened immune systems.

Karim R, Mack WJ, Kono N, Tien PC, Anastos K, Lazar J, Young M, Cohen M, Golub E, Greenblatt RM, Kaplan R, Hodis HN. *J Clin Endocrinol Metab* 2013;98(4):E610-618. (PMC3615203)

Macrophage Inflammatory Markers Are Associated With Subclinical Carotid Artery Disease in Women With Human Immunodeficiency Virus or Hepatitis C Virus Infection

We developed a panel of serum biomarkers that were found to be correlated with cardiovascular disease outcomes in women with HIV or HCV infection. These serum biomarkers were associated with innate immune cell (monocyte) production of inflammatory mediators. The study developed a novel assay that can be potentially used to predict non AIDS co morbidities in the WIHS.

Shaked I, Hanna DB, Gleißner C, Marsh B, Plants J, Tracy D, Anastos K, Cohen M, Golub ET, Karim R, Lazar J, Prasad V, Tien PC, Young MA, Landay AL, Kaplan RC, Ley K. *Arterioscler Thromb Vasc Biol* 2014 May;34(5):1085-1092. (PMC4067091)

Mean platelet volume is decreased in HIV infected women

Platelets are an important component of our blood and help form blood clots. HIV infection is associated with lowered platelet counts and an increased risk for cardiovascular events (such as a heart attack). These conditions can be caused by platelets being larger on average, referred to as a higher mean platelet volume (MPV), which can occur when platelets are not destroyed by the body at the appropriate time. In this study, WIHS researchers found that HIV-infected

women actually had lower MPV values compared to HIV-uninfected women, meaning there may instead be a problem with platelet production rather than destruction.

Qadri S, Weedon J, Holman S, DeHovitz J, Crystal H, Minkoff H, Lazar J. HIV Med 2013 Oct;14(9):549-55. (PMC3775876)

Microvascular Endothelial Dysfunction and Enhanced Thromboxane and Endothelial Contractility in Patients with HIV

Highly active antiretroviral therapy (HAART) has prolonged the life of those infected with HIV significantly, but sadly, they suffer from an increased burden of many diseases usually encountered by older subjects, including heart attacks and strokes. WIHS researchers are committed to finding out why this is happening in order to eliminate this burden in the future. In this study, tiny blood vessels under the skin were biopsied and examined their health and inflammation levels. The results showed that premenopausal HIV positive women had early signs of cardiovascular disease, which could later develop into circulation problems.

Wang D, Melancon JK, Verbese J, Hu H, Liu C, Aslam S, Young M, Wilcox CS. J AIDS Clin Res 2013; 4(12): 267. (PMC4066983)

RyR3 gene variants in subclinical atherosclerosis among HIV infected women in the Women's Interagency HIV Study (WIHS)

Did you know that HIV causes more heart attacks and deaths from heart disease in women than men? One way to catch heart disease early on is to look at the hardening and narrowing of a large artery in your neck, which can show changes before they could be detected as early heart disease by other tests. HIV-infected people may have a faster progression of artery narrowing than HIV-uninfected people, but there are also genetic factors that speed up the decline. In this study, WIHS researchers found an association between early artery narrowing and one gene, or region of our DNA, including slight racial differences.

Shendre A, Irvin MR, Aouizerat BE, Wiener HW, Vazquez AI, Anastos K, Lazar J, Liu C, Karim R, Limdi NA, Cohen MH, Golub ET, Zhi D, Kaplan RC, Shrestha S. Atherosclerosis 2014 Apr;233(2):666-72. (PMC3965606* incorrect in publication list)

T-Cell Activation, Both Pre- and Post-HAART Levels, Correlates With Carotid Artery Stiffness Over 6.5 Years Among HIV-Infected Women in the WIHS

Because of several factors, including higher smoking rates and HIV-infection itself, HIV-infected individuals have a higher risk of cardiovascular disease (heart disease) and atherosclerosis (stiffening of arteries). A major one of those factors could be a specific immune response (T-cell activation) that curiously continues throughout infection, even during successful treatment

with antiretroviral therapy when other factors like CD4 cell count and viral load are generally improved. WIHS women were studied 6.5 years apart to detect progression of arterial stiffness, and from their data this particular immune response predicted stiffness in HIV-infected women, especially for those co-infected with HCV.

Karim R, Mack WJ, Kono N, Tien PC, Anastos K, Lazar J, Young M, Desai S, Golub ET, Kaplan RC, Hodis HN, Kovacs A. JAIDS 2014 Nov 1;67(3):349-56. (PMC4197806)

Cervical Cancer and HPV

Abnormal pap tests and human papillomavirus infections among HIV-Infected and uninfected women who have sex with women

Infections with human papillomaviruses (HPVs), the viruses that cause cervical and other cancers, are more common in HIV+ than HIV- women. Cancer-causing HPVs are spread through sexual contact. Women who have sex only with women may believe that their risk for HPV infection is lower. We investigated the frequency of HPV and abnormal Pap tests in WIHS women who reported sex only with women in the 5 years before study. Only 73 of 3766 WIHS women (49 HIV+, 24 HIV-) met this definition. Over time, 20% of Pap tests in HIV+ women were abnormal, compared to 6% in HIV- women ($P = 0.002$). In multivariable analysis, compared to women who had sex with men those who had sex with women had a 47% lower risk of HPV, a non-significant 40% lower risk of cancer-causing HPV, and a 41% lower risk of abnormal Pap. HIV+ women who had sex with women had a higher risk for all these findings than HIV- women who had sex with women. We concluded that HIV infection increases risk for HPV infection and abnormal Pap in women who have sex with women. While their risk was lower than HIV+ women who have sex with men, it still seems high enough to merit regular Pap testing.

Massad LS, Xie X, Minkoff H, Darragh TM, D'Souza G, Sanchez-Keeland L, Watts DH, Colie C, Strickler HD. *J Low Genit Tract Dis* 2014 Jan;18(1):50-56. (PMC3905442)

Cervical human papillomavirus testing to triage borderline abnormal Pap tests in HIV-co-infected women

Correspondence - small study of 140 women, will become paper in the future

D'Souza G, Burk RD, Palefsky J, Massad LS, Strickler HD, for the WIHS HPV Working Group. *AIDS* 2014 Jul 17;28(11):1696-8. (PMC4196721)

Concomitant anal and cervical HPV infections and intraepithelial neoplasia in HIV-infected and uninfected women

Human papillomavirus (HPV) infections are fairly common and mostly clear on their own, but for some women the infection persists and can even lead to invasive squamous cell carcinoma (cancer) for certain strains of HPV. HPV infections in women can occur both on the cervix and in the anus, and for some women they have HPV at both sites. WIHS researchers analyzed data from women who had both cervical and anal HPV infections to see if these infections differed for women with and without HIV infection as well. Women with HIV infection were more likely to have the same HPV strain in the anus and cervix compared to women without HIV infection,

and having a weaker immune system (having a lower CD4+ count) was also associated with HPV infections that had the potential to cause cancer.

Hessol NA, Holly EA, Minkoff H, Weber KM, Efird JT, Darragh T, Burk RD, Strickler S, Greenblatt RM, Palefsky JM. AIDS 2013;27(11):1743- 1751. (PMC3917497)

Invasive cervical cancer risk among HIV-infected women: A North American multi-cohort collaboration prospective study

Human papillomavirus (HPV) infections are fairly common and mostly clear on their own, but for some women the infection persists and can lead to invasive cervical cancer. HIV-infected women are more likely to be infected with HPV and to have that infection persist compared to HIV-uninfected women, and having a lower CD4+ T-cell count (immunosuppression) increases this risk. In this study, data from WIHS as well as 17 other cohorts was used to show that HIV-infection and immunosuppression were linked to higher rates of invasive cervical cancer.

Abraham AG, Strickler HD, Jing Y, Gange SJ, Sterling TR, Silverberg M, Saag M, Rourke S, Rachlis A, Napravnik S, Moore RD, Klein M, Kitahata M, Kirk G, Hogg R, Hessol NA, Goedert JJ, Gill MJ, Gebo K, Eron JJ, Engels EA, Dubrow R, Crane HM, Brooks JT, Bosc. J Acquir Immune Defic Syndr 2013 Apr 1;62(4):405-413. (PMC3633634)

Long-term cumulative detection of human papillomavirus among HIV seropositive women

WIHS and others have shown that women with HIV often have genital infections with human papillomavirus (HPV), the virus that causes genital warts and cancers of the cervix, vagina, vulva, and anus. Few long-term studies have been done, however. WIHS has followed women for HPV infection throughout its course, and we have results extending up to 10 years. These results show that up to 90% of HIV+ women will have an HPV infection at some point, significantly more often than HIV- women, though HIV- women seem to catch up if followed long enough. Most people in WIHS have at least one HPV infection. This high frequency of HPV may explain the increased risk of cervical cancer they face, although the greatest increase in HPV was among types not usually linked to cancer.

Massad LS, Xie X, Burk R, Keller MJ, Minkoff H, D'Souza G, Watts DH, Palefsky J, Young M, Levine AM, Cohen M, Strickler HD. AIDS 2014 Sep 3 [E-pub ahead of print]. (In Progress)

Long-term cumulative incidence of cervical intraepithelial neoplasia grade 3 or worse after abnormal cytology: impact of HIV infection

Regular Pap tests for abnormal cervical cells are important for female health. Sometimes there is unnecessary stress and anxiety when Pap test results are abnormal, indicating a colposcopy has to be done, but later results are normal or show minimal damage from human

papillomavirus (HPV). However, despite possible false positive results, these tests are especially necessary for HIV-infected women, as shown by WIHS researchers who found that HIV-infected women have an increased risk of progression to cancer from abnormal Pap tests compared to women without HIV-infection.

Massad LS, Pierce CB, Minkoff H, Watts DH, Darragh TM, Sanchez-Keeland L, Wright RL, Colie C, D'Souza G. *Int J Cancer* 2014 Apr 15;134(8):1854-61. (PMC3947413)

Depression

Do HIV-Positive Women Receive Depression Treatment that Meets Best Practice Guidelines?

We analyzed data from women who reported high levels of depression symptoms, to determine whether they received high quality depression treatment and, if so, what was related to receiving good treatment. We found that around 60% of women with high levels of depressive symptoms received some depression treatment and over two-fifths (42%) received best practice treatment. These rates were much higher than those in the general population, indicating that women in the WIHS cohort have higher than average depression treatment likelihood. The most important predictor of receiving good depression treatment was seeing the same medical provider on a consistent basis. This highlights the importance of provider continuity in receiving good depression care.

Cook JA, Burke-Miller JK, Grey DD, Cocohoba J, Liu C, Schwartz RM, Golub ET, Anastos K, Steigman PJ, Cohen MH. *AIDS Behav* 2014 Jun;18(6):1094-1102. (PMC4020946)

Resilience moderates the association between childhood sexual abuse and depressive symptoms among women with and at-risk for HIV

The study investigated the relationships between resilience, childhood sexual abuse, depressive symptoms, and health related quality of life among a sample of women with HIV and uninfected women. The sample consisted of 202 women (138 HIV+ and 64 HIV-), mostly African American, at the Chicago CORE Center site of the Women Interagency HIV Study. Resilience is the ability to function well in negative environments or after negative experiences. Resilience, depressive symptoms, and health related quality of life were measured with self-report questionnaires. Among both infected and uninfected women, women with higher resilience reported lower depressive symptoms and higher health related quality of life. Women with both a history of childhood sexual abuse and low resilience scores reported higher depressive symptoms, but women with a history of childhood sexual abuse and high resilience scores did not report higher depressive symptoms. Interventions to promote resilience, especially in women with a childhood sexual abuse history, might reduce depressive symptoms and poor health related quality of life among HIV infected and uninfected women.

Dale SK, Weber KM, Cohen MH, Kelso GA, Cruise RC, Brody LR. *AIDS Behav* 2014 Aug 2 [E-pub ahead of print]. (In Progress)

Single-nucleotide polymorphisms in TrkB and risk for depression: Findings from the Women's Interagency HIV Study

Did you know that major depressive disorder (MDD) is more prevalent in HIV-infected individuals than non-infected individuals, particularly for women? Understanding MDD within HIV infection is especially important because it may be linked to cognitive impairment. Genetics may play a role in fighting depression, and WIHS researchers looked at two genes, or areas in our genetic code that can vary slightly between people. They found that differences in one of these genes could account for a lack of self-reported depression and racial differences among HIV-infected women.

Avdoshina V, Mocchetti I, Liu C, Young MA, Anastos K, Cohen M, Crystal H, Pearce CL, Golub ET, Tractenberg RE. *J Acquir Immune Defic Syndr* 2013 Oct 1;64(2):138-141. (PMC3780967)

HIV Medication and Adherence

Abuse and resilience in relation to HAART medication adherence and HIV viral load among women with HIV in the United States

The study investigated the relationships between resilience, abuse, HAART medication adherence, viral load, and CD4+ cell count among a sample of women with HIV. The sample consisted of 138 women, mostly African American, at the Chicago CORE Center site of the Women Interagency HIV Study. Resilience is the ability to function well in negative environments or after negative experiences and was assessed with the Connor-Davidson Resilience Scale. Abuse and HAART medication adherence were reported during structured interviews. HIV viral load and CD4+ cell count were measured with blood specimens. Women with higher resilience had higher HAART adherence and undetectable viral load. Women with both high resilience scores and a history of sexual abuse reported higher HAART adherence, but not women with low resilience scores and a history of sexual abuse. Interventions to promote resilience among women with HIV, especially women with sexual abuse history, might assist women in improving HAART medication adherence and achieving undetectable viral loads.

Dale S, Cohen M, Weber K, Cruise R, Kelso G, Brody L. AIDS Patient Care STDs March 2014;28(3):136-143. (PMC3948478)

Association between U.S. State AIDS Drug Assistance Program (ADAP) Features and HIV Antiretroviral Therapy Initiation, 2001-2009

U.S. AIDS Drug Assistance Programs (ADAPs) are federally funded to provide antiretroviral therapy for their eligible residents living with HIV infection, but states do not contribute money to these programs equally. WIHS was included in this study of 14 U.S. cohorts of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) to test how living in different states affected HIV care, including how soon antiretroviral therapy is started. The results of this analysis showed that states that did not contribute extra money into the ADAP budget had delayed initiation of antiretroviral therapy when treatment was clinically indicated, meaning that state-led funding for these programs is important for adequate care.

Hanna DB, Buchacz K, Gebo KA, Hessel NA, Horberg MA, Jacobson LP, Kirk GD, Kitahata MM, Korthuis PT, Moore RD, Napravnik S, Patel P, Silverberg MJ, Sterling TR, Willig JH, Collier A, Samji H, Thorne JE, Althoff KN, Martin JN, Rodriguez B, Stuart EA, Gange. PLOS One 2013 Nov;8(11):e78952. (PMC3832515)

Common clinical conditions - age, low BMI, ritonavir use, mild renal impairment - affect tenofovir pharmacokinetics in a large cohort of HIV-infected women

Tenofovir is one of the most widely taken antiretroviral drugs for HIV management, particularly in conjunction with emtracitabine in the drug Truvada, and it is now used to prevent HIV-infection as part of PrEP therapy. While its dosage was determined in clinical trials most of the study populations were small in size and relatively homogeneous, so WIHS researchers conducted what are called pharmacokinetic studies to test the levels tenofovir in the blood of WIHS women already taking the drug. They found that among these women taking recommended dosages, those who were older, had lower BMIs, had decreased kidney function, or were also taking ritonavir were being exposed to higher than recommended levels of tenofovir.

Baxi SM, Greenblatt RM, Bacchetti P, Scherzer R, Minkoff H, Huang Y, Anastos K, Cohen M, Gange SJ, Young M, Shlipak MG, Gandhi M. *AIDS* 2014 Jan 2;28(1):59-55. (PMC3956315)

Increase in single-tablet regimen use and associated improvements in adherence-related outcomes in HIV-infected women

Single-tablet treatment use was associated with better adherence and virologic suppression. However, 15% of women on ART in this study were still not adherent; other interventions are needed to increase treatment benefits.

Hanna DB, Hessel NA, Golub ET, Cocohoba JM, Cohen MH, Levine AM, Wilson TE, Young M, Anastos K, Kaplan RC. *JAIDS* 2014 Apr 15;65(5):587-596. (PMC3999284)

Trends and disparities in antiretroviral therapy initiation and virologic suppression among newly treatment-eligible HIV-infected individuals in North America, 2001-2009

WIHS is part of a collection of research cohorts called the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which means that when data is collected by all of these separate cohorts and pooled together into a huge dataset researchers can present convincing arguments for trends seen in the North American population of people living with HIV. In one analysis from this collaboration, researchers looked at the quality of HIV treatment from 2001 to 2009, focusing on how improved antiretroviral therapies have led to patients starting antiretrovirals earlier and becoming virologically suppressed. They found that there was little difference in these two measures of care across states and provinces, and although certain barriers such as past drug use were associated with starting antiretrovirals on time, once patients started therapy these barriers did not limit how well they could suppress the HIV virus once they consistently took their medications.

Hanna DB, Buchacz K, Gebo KA, Hessel NA, Horberg MA, Jacobson LP, Kirk GD, Kitahata MM, Korthuis PT, Moore RD, Napravnik S, Patel P, Silverberg MJ, Sterling TR, Willig JH, Lau B, Althoff KN, Crane HM, Collier AC, Samji H, Thorne JE, Gill MJ, Klein MB, Mar. *Clin Infect Dis* 2013;56(8): 1174-1182. (PMC3657490)

Understanding the disparity: predictors of virologic failure in women using highly active antiretroviral therapy vary by race and/or ethnicity

The development of highly active antiretroviral therapy (HAART) was revolutionary for helping people living with HIV infection live longer lives with fewer AIDS-related illnesses without also causing severe side-effects, as the early antiretroviral drugs did. The goal of HAART is long-term viral suppression, but sometimes HIV levels rise after an initial suppression (called virologic failure), and a goal of the WIHS is to study how and why this happens to develop strategies that help continued viral suppression. WIHS researchers found that virologic failure was fairly common among HIV-infected WIHS women, but factors associated with it varied by race and ethnicity. For example, virologic failure was associated with lack of health insurance only among Hispanic women, while it was associated with depressive symptoms only among African American women.

McFall AM, Dowdy DW, Zeleya CE, Murphy K, Wilson TE, Young MA, Gandhi M, Cohen MH, Golub ET, Althoff KN; for the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2013 Nov 1;64(3):289-98. (PMC3816935)

Gender role behaviors of high affiliation and low self-silencing predict better adherence to antiretroviral therapy in women with HIV, AIDS Patient Care and STDs

The current study investigated how three gender role behaviors: self-silencing (hiding feelings to avoid conflict or rejection), unmitigated communion (caring for others at the expense of self-care), and affiliation (valuing interpersonal relationships) related to medication adherence, viral load and CD4 count in women with HIV. Better adherence was significantly associated with lower self-silencing and higher affiliation, and higher affiliation was related to a higher CD4 count in all women and to lower viral load among women who were lower in self-silencing. Results suggest that interventions that focus on women's gender role behaviors should be developed to improve HIV health outcomes.

Brody, LR, Stokes, LR, Kelso, GA, Dale, SK, Cruise, RC, Weber, KA, Burke-Miller, JK, & Cohen, MH. *AIDS Patient Care and STDs*. 2014 Jul 9. (Epub ahead of print).. (PMC4135315)

HIV Pathogenesis

Comparison of Antibodies That Mediate HIV Type 1 gp120 Antibody-Dependent Cell-Mediated Cytotoxicity in Asymptomatic HIV Type 1-Positive Men and Women

Comparison of results from two earlier studies of antibody dependent cell mediated cytotoxicity (ADCC), one of men and another of women, suggested that seropositive men might have more ADCC antibodies against HIV than seropositive women. There were, however several other variable between the individuals in these studies. This study was done to compare men and women where those other variables were controlled. We obtained samples from the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) that were carefully matched with respect to race, age, CD4 T cell number and viral load. This study clearly shows that gender was not the reason for the differences seen in earlier studies.

Mata MM, Iwema JR, Dell S, Neems L, Jamieson B, Phair J, Cohen M, Anastos K, Baum L. *AIDS Res Hum Retroviruses* 2014 Jan;30(1):50-57. (PMC3887406)

Epigenetic analysis of HIV-1 proviral genomes from infected individuals: Predominance of unmethylated CpG's

Have you heard of epigenetics? There is more to our DNA than just its sequence; how our bodies use the genetic information encoded from our DNA is affected by the absence or presence of tags called methyl groups. In HIV infection, the virus integrates some of its DNA into its host's DNA. WIHS researchers looked at whether these viral DNA regions had methyl groups because that would indicate these DNA regions are probably not actively making the host sick. Some people living with HIV never show a decreased immune response despite having the infection for years (we call them long-term nonprogressors) and this study suggests that part of their relatively healthy immune system may be a result of having methylated viral DNA regions.

Weber S, Weiser B, Kemal KS, Burger H, Ramirez CM, Korn K, Anastos K, Kaul R, Kovacs C, Doerfler W. *Virology* 2014 Jan 20;449:181-189. (PMC4060985)

HIV RNA Levels in Plasma and Cervical Vaginal Lavage Fluid in Elite Controllers and HAART Recipients

We show that in a rare group of HIV+ women that control HIV without therapy ("elite" controllers) that they have low level HIV in their blood compared to HIV+ subjects on therapy. The majority of samples from both groups had undetectable HIV in the genital tract. This study has implication for designing new therapies for HIV+ women.

Landay A, Golub ET, Desai S, Zhang J, Winkelman V, Anastos K, Durkin H, Young M, Villacres MC, Greenblatt RM, Norris PJ, Busch MP for the Women's Interagency HIV Study. AIDS 2014 Mar;28(5):739-43. (PMC4160049)

The S40 residue in HIV-1 Gag p6 impacts local and distal budding determinants, revealing additional late domain activities

WIHS researchers are not limited to clinical research; some of the efforts of the WIHS contribute to understanding the mechanism through which HIV infects cells, so one day that knowledge could help develop new antiviral treatments and maybe even a cure.

Watanabe SM, Chen MH, Khan M, Ehrlich L, Kemal KS, Weiser B, Shi B, Chen C, Powell M, Anastos K, Burger H, Carter CA. Retrovirology 2013 Nov;10:143. (PMC3907034)

Treatment-related changes in serum lipids and inflammation: clinical relevance remains unclear

Research letter - confirmed and expanded results of Piconi et al. AIDS 2013 for women

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. Analyses from the Women's Interagency HIV Study. (PMC3909663)

HIV Progression and Mortality

Association of self-reported race with AIDS death in continuous HAART users in the women's interagency HIV study (WIHS)

Highly active antiretroviral therapy (HAART) has revolutionized HIV care so that many people on HAART are able to live relatively normal lives with life expectancies similar to the general population. However, sometimes even individuals continually on HAART can experience an AIDS-defining illness (ADI) and die of AIDS. WIHS researchers examined the racial effects of these clinical outcomes, finding that even after adjusting for known confounding variables (such as drug use, depressive symptoms, and adherence) African American women were twice as likely as caucasian women to develop an ADI and die from AIDS while on HAART. Future studies are needed to examine behavioral and biologic factors that may explain these racial differences.

Murphy K, Hoover DR, Shi Q, Cohen M, Gandhi M, Golub ET, Gustafson DR, Pearce C, Young M, Anastos K. AIDS 2013 Sep 24;27(15):2413-2423. (PMC3815041)

Cause-Specific Life Expectancies After 35 Years of Age for Human Immunodeficiency Syndrome-Infected and Human Immunodeficiency Syndrome-Negative Individuals Followed Simultaneously in Long-term Cohort Studies, 1984-2008

The introduction of highly active antiretroviral therapy (HAART) was a real game changer for the HIV-infected community. In this study, WIHS researchers teamed up with researchers from the Multicenter AIDS Cohort Study (MACS) to study how affected the life spans and causes of death for men and women living with HIV infection. By comparing these patients with HIV-uninfected controls, researchers found that HIV-infected individuals who did not die from an AIDS-related condition had shorter lifespans than similarly matched uninfected controls by only 7-9 years. Factors that increased risk of dying younger were unemployment, depression, and hepatitis B or C infection. These types of studies are important for understanding the current state of the population infected with HIV.

Wada N, Jacobson LP, Cohen M, French A, Phair J, Muñoz A. Am J Epidemiol 2013 Jan;177(2):116-25. (PMC3590031)

Cause-specific mortality among HIV-infected individuals, by CD4+cell count at HAART initiation, compared with HIV-uninfected individuals

During the earlier days of antiretroviral therapy there were many serious side effects of the drugs, so physicians would wait until an HIV-infected patient's immune system was

compromised beyond a threshold that seems relatively severe compared to current treatment recommendations. Current therapy, known as highly active antiretroviral therapy (HAART), is more effective and has fewer side effects than earlier drugs, so physicians are now recommending starting HAART before the immune system functions at dangerously low levels. In this study, researchers looked at deaths of WIHS and MACS participants to see whether starting HAART early can prevent death at a younger age from both AIDS- and non-AIDS-related causes. Their results showed that for the most part HIV-infected persons who started HAART before their immune system was severely affected by HIV had similar life spans and causes of death compared to HIV-uninfected persons. The exception was for people infected both with HIV and hepatitis B or C, but that means that getting treated for hepatitis is that much more important for people who are living with HIV infection.

Wada N, Jacobson LP, Cohen M, French A, Phair J, Muñoz A. AIDS 2014 Jan 14;28(2):257-65. (PMC4164055)

Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada

Powerful research conclusions can be made when large study groups work together to form massive datasets. In this study WIHS teamed up with other research groups to form the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) to examine how combination antiretroviral therapy has led to changes in life expectancy from 2000-2007. Using data from nearly 23,000 HIV-infected patients, it was estimated that a 20-year-old HIV-positive adult on antiretroviral therapy in the U.S. or Canada is expected to live into their early 70s, which means they have a life expectancy close to that of the general population.

Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, Burchell AN, Cohen M, Gebo KA, Gill MJ, Justice A, Kirk G, Klein MB, Korthuis PT, Martin J, Napravnik S, Rourke SB, Sterling TR, Silverberg MJ, Deeks S, Jacobson LP, Bosch RJ, Kitahata MM, Goede. PLoS One 2013 Dec;8(12):e81355. (PMC3867319)

Liver Disease and Hepatitis

Association of HIV Infection, Hepatitis C Virus Infection, and Metabolic Factors with Liver Stiffness Measured by Transient Elastography

Liver biopsies are still considered the "gold standard" for assessing how healthy liver tissue is; however, there is a new brief, noninvasive ultrasound-based test that estimates the degree of fibrosis, or liver stiffness/scarring, called the Fibroscan. Cirrhosis is what we call severe fibrosis, so monitoring liver stiffness is important for preventing more severe liver complications from cirrhosis like liver cancer and liver failure. Hepatitis C has been well studied via Fibroscans, including HIV/HCV-coinfection, but WIHS was one of the first groups to study Fibroscan results from HIV-infected HCV-uninfected adults. Women with both infections had the highest degree of liver stiffness, followed by either HIV or HCV infection, and lastly having neither infection.

Bailony MR, Scherzer R, Huhn G, Plankey MW, Peters MG, Tien PC. *J Infect Dis* 2013 Dec 1;208(11):1776-1783. (PMC3814832)

Association of the IFNL4- Δ G Allele With Impaired Spontaneous Clearance of Hepatitis C Virus

Did you know that about 20-30% of individuals who are infected with hepatitis C (HCV) will clear the virus on their own without any treatment? There is a gene, named IFNL4, which may help eliminate the virus or improve chances of responding well to treatment if you have what is believed to be the more favorable genotype (or "flavor"). We looked at which "flavor" of this gene HCV-positive WIHS women had and found that having the more favorable one meant you were more than 3 times as likely to clear your HCV. However, for those who did not completely clear the virus, having this favorable genotype meant they had more copies of the virus in their system (measured by HCV RNA).

Aka PV, Kuniholm MH, Pfeiffer RM, Wang AS, Tang W, Chen S, Astemborski J, Plankey M, Villacres MC, Peters MG, Desai S, Seaberg EC, Edlin BR, Strickler HD, Thomas DL, Prokunina-Olsson L, Sharp GB, O'Brien TR. *J Infect Dis* 2014 Feb;209(3):350-354. (PMC3883162)

Genome-wide association study of spontaneous resolution of hepatitis C virus infection: data from multiple cohorts

Did you know that Hepatitis C (HCV) will spontaneously be eliminated by 40% of people who are infected by it? Racial and other genetic effects were explored during this study, which looked at many regions of DNA for almost 2,500 WIHS women who either currently have HCV or have in the past and spontaneously cleared the virus from their systems. Comparing the groups who either cleared the virus or still had active HCV infection showed that women of

African descent may have a reduced ability to clear HCV on their own because of several specific points in their DNA. Moving forward, those points will be investigated to see how they may play a role in fighting HCV.

Duggal P, Thio CL, Wojcik GL, Goedert JJ, Mangia A, Latanich R, Kim AY, Lauer GM, Chung RT, Peters MG, Kirk GD, Mehta SH, Cox AL, Khakoo SI, Alric L, Cramp ME, Donfield SM, Edlin BR, Tobler LH, Busch MP, Alexander G, Rosen HR, Gao X, Abdel-Hamid M, Apps R. *Ann Intern Med* 2013;158 (4):235-245. (PMC3638215)

Hepatitis C viremia is associated with cytomegalovirus IgG antibody levels in HIV-infected women

Cytomegalomavirus (CMV) is a common virus related to other herpes viruses that can infect almost anyone. Most people do not know they have CMV because it rarely causes symptoms, except for people with weakened immune systems, such as infants, the elderly, and people infected with HIV. For these more vulnerable groups, CMV infection requires a large proportion of the body's immune cells to exclusively fight CMV. Long-term infection with hepatitis C virus (HCV) may affect overall immune health and lead to CMV having a stronger effect on the immune system, similar to how CMV affects people with HIV infection. WIHS researchers found that women with both HIV and HCV infections had more CMV-specific immune cells compared to HIV-infected women without HCV, indicating that HCV infection can make an individual's immune system fight even harder against CMV infection and may lead to CMV-related diseases such as heart disease.

Kuniholm MH, Parrinello CM, Anastos K, Augenbraun M, Plankey M, Nowicki M, Peters M, Golub ET, Lurain N, Landay AL, Strickler HD, Kaplan RC. *PLoS One* 2013 Apr 17;8(4):E61973. (PMC3629158)

Microbial Translocation and Liver Disease Progression in HIV/ Hepatitis C Co-infected Women

Early in HIV infections, immune cells in the gut are destroyed which causes the gut to be "leaky," in other words, allowing bacteria from intestinal tract to leak into the circulation (bacterial translocation). In diseases such as alcoholism, leaky gut has been associated with more rapid progression of liver fibrosis and cirrhosis. We looked at markers of leaky gut from stored samples from 21 women with hepatitis C and HIV who experienced liver fibrosis over a 5 year period and compared them to markers from 23 women who experienced little liver disease progression. We found that some of the markers of bacterial leakage across the gut wall and some markers of inflammation were higher in the women who experienced liver disease progression. This suggests, but is not definitive, that bacterial translocation may be part of the reason that hepatitis C associated liver disease progression is more rapid in HIV-infected persons than in persons without HIV.

French AL, Evans CT, Agniel DM, Cohen MH, Peters M, Landay AL, Desai SN. J Infect Dis 2013;208(4):679-689. (PMC3719907)

Systemic Cytokine and Interferon Responsiveness Patterns in HIV and HCV Mono and Co-Infections

Did you know that for HIV-infected persons, about half of the deaths that are not related to AIDS involve the liver? Having both HIV and HCV infections can accelerate and worsen the effects of HCV infection alone. In this study WIHS researchers examined how HIV+/HCV+ and HIV+/HCV- WIHS women have altered anti-inflammatory and other immune responses compared to their HIV- control groups, which may contribute to their more severe HCV disease progression.

Fernandez-Botran R, Joshi-Barve S, Ghare S, Barve S, Young M, Plankey M, Bordon J. J Interferon Cytokine Res 2014 Nov;34(11):885-93. (PMC4217006)

Metabolic Disorders

Antiretroviral therapy modifies the genetic effect of known type 2 diabetes-associated risk variants in HIV-infected women

Preventing type 2 diabetes mellitus is especially important for those with HIV-infection, but this can be challenging since some types of antiretroviral medications can increase your risk of developing diabetes. From the general population, we know some specific genetic variations among different races can increase your risk of developing diabetes. In this study WIHS researchers looked at the effects of diabetes risks from both antiretroviral drug use and inherited risks. They determined that women with a higher risk for diabetes based on their genetics were at an even greater risk when on a certain combination of antiretroviral therapy, meaning that genetics should be considered when choosing the right combination of anti-HIV drugs to prevent developing diabetes.

Frasco MA, Karim R, Van Den Berg D, Watanabe RM, Anastos K, Cohen M, Gange SJ, Gustafson DR, Liu C, Tien PC, Mack WJ, Pearce CL. AIDS 2014 Jun 31;28(12):1815-23. (In Progress)

Changes in Body Mass Index Following HAART Initiation among HIV Infected Women in the Women's Interagency HIV Study

Increasing body mass index (BMI) is known to be a common part of the aging process, for both HIV-infected and -uninfected women, but the effect of highly active antiretroviral therapy (HAART) on BMI is less certain. Many studies of BMI and HAART were short term and mostly focused on men, so in this study WIHS investigators looked at these effects on WIHS women over a period of 15 years. Different classes of drugs that make up HAART showed slight differences in BMI, but overall their effects were minimal.

Sharma A, Bynum SA, Schneider MF, Cox C, Tien PC, Hershov RC, Gustafson D, Plankey MW. J AIDS Clin Res 2014 Jun 25;5:323. (In Progress (not in Pubmed))

Investigating the effects of metabolic dysregulation on hair follicles: a comparison of HIV-infected women with and without central lipohypertrophy

What do eye lash length and belly fat have in common? They both may be related to your fat metabolism, as researchers investigated in a survey of HIV-infected WIHS women. Though they were expecting there to be an association between increased belly fat and hair loss, instead it appears that belly fat is associated with shorter eye lashes.

Mirmirani P, Maurer T, Cohen M, D'Souza G, Karim R, Plankey M, Robison E, Sharma A, Tien PC, Hessol NA. Int J Dermatol 2014 Oct;53(10):e443-8. (PMC3785560)

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. *J Acquir Immune Defic Syndr* 2013;62(1):74-80. (PMC3529765)

The association of self-perception of body fat changes and quality of life in the Women's Interagency HIV Study

Changes in body fat are common for people living with HIV infection, and these changes can have an effect on quality of life. In this study, self-perceived fat loss of any kind among HIV-infected WIHS women was associated with overall lower quality of life. Reported fat loss from the limbs and face (called peripheral fat loss) was associated with many quality of life areas, including physical functioning, pain, emotional well-being, and energy/fatigue, while fat loss from the abdomen and other central areas of the body was associated with lower social and cognitive functioning. Central fat gain was associated with lower quality of life as well. These findings help reinforce how important self-perception of body image is when striving for overall health of women living with HIV infection.

Plankey M, Bacchetti P, Jin C, Dass-Brailsford P, Gustafson D, Cohen MH, Karim R, Yin M, Tien PC. *AIDS Care* 2013;25(12):1544-1550. (PMC3769511)

Neurocognition

An investigation of menopausal stage and symptoms on cognition in HIV-infected women

Large studies in HIV-uninfected women demonstrate that menopause and menopausal symptoms—particularly mood changes, sleep disturbance, and hot flashes—negatively impact memory and other mental abilities. Here we evaluated the individual and interactive effects of menopausal stage, menopausal symptoms, and HIV status on memory and other mental abilities. We found that hot flashes, depressive, and anxiety symptoms are associated with worse performance on memory and other mental abilities in both HIV-infected and uninfected women, although elevated anxiety symptoms were associated with learning difficulties more in HIV-infected women. Since problems with memory and other mental abilities can interfere with everyday functioning including treatment adherence, it may be important to screen and treat anxiety in midlife HIV-infected women.

Rubin LH, Sundermann EE, Cook JA, Martin EM, Golub ET, Weber KM, Cohen MH, Crystal H, Cederbaum JA, Anastos K, Young M, Greenblatt RM, Maki PM. Menopause 2014 Sept;21(9):997-1006. (PMC4119867)

Anthropometric measures and cognition in middle-aged HIVinfected and uninfected women. The Women’s Interagency HIV Study

Have you heard about a relationship between obesity and cognitive impairment? They have been associated within the HIV-uninfected population, and mid-life obesity has also been linked with a higher risk of developing Alzheimer's Disease. Highly active antiretroviral therapy (HAART) may reduce the risk of developing HIV-associated dementias, but it does not seem to prevent cognitive impairments. WIHS researchers found that middle-aged overweight women with HIV infection overall performed worse on cognitive tests, but on some tests being overweight was associated with a better performance. These results show that HIV infection and its associated changes in metabolism can have complex and variable effects on cognition.

Gustafson DR, Mielke MM, Tien PC, Maki P, Valcour V, Cohen M, Anastos K, Liu C, Pearce L, Golub E, Minkoff H, Crystal H. Journal of Neurovirology 2013 Dec;19(6):574-585. (PMC3957488)

Other Medical Conditions

Atypical autonomic regulation, auditory processing, and affect recognition in women with HIV

This study examined the effect of HIV on heart rate, heart rate variability, auditory processing, and affect recognition. Relative to at risk HIV seronegative women, HIV-infected women had less heart rate variability (i.e., respiratory sinus arrhythmia) and had poorer performance on auditory processing and affect recognition tasks. Additionally, there was a significant negative correlation between CD4 and accuracy to detect specific emotions. The observed indices of atypical autonomic and behavioral regulation may contribute to greater difficulties in social behavior and social communication among HIV infected women and individuals in their social network.

Heilman KJ, Harden ER, Weber KM, Cohen M, Porges SW. *Biol Psychol* 2013;94(1):143- 151. (PMC3742727)

Cochlear function among HIV-Seropositive and HIV-Seronegative men and women

Our hearing gets worse as we age, but HIV-infection may also contribute to hearing loss. WIHS and MACS researchers used very sophisticated technology to measure hearing damage in the very early stage before hearing loss can be detected by other tests. They hypothesized that HIV antiretroviral therapy could be a factor causing hearing damage; however, in this particular study there was not a strong association between HIV-infection or HIV medications and early hearing loss.

Torre P 3rd, Hoffman HJ, Springer G, Cox C, Young M, Margolick JB, Plankey M. *Ear Hear* 2014 Jan-Feb;35(1);56-62. (PMC3872496)

Critical consciousness, racial and gender discrimination, and HIV disease markers in African American women with HIV

This study suggests that raising awareness of social oppression and joining others to enact social change may be an important step for improving HIV outcomes in African American HIV-infected women who experience high levels of gender and racial discrimination.

Kelso GA, Cohen MH, Weber KM, Dale SK, Cruise RC, Brody LR. *AIDS Behav* 2014 Jul;18(7):1237-46. (PMC4010552)

Does HIV infection promote early kidney injury in women?

Among HIV-infected persons, it is estimated that as many as one in three people have chronic kidney disease. While HIV-infection has been linked to a 10x risk of developing kidney failure, having decreased kidney function if you are HIV-infected increases your risk of dying from non-kidney-related deaths as well. Unfortunately, kidney function is difficult to measure in HIV-infected persons because many tests for kidney health among the general population are not accurate within HIV-infection. Here, WIHS researchers used measures of kidney damage from urine to detect increased kidney disease in HIV-infected women.

Jotwani V, Scherzer R, Abraham A, Estrella MM, Bennett M, Devarajan P, Anastos K, Cohen MH, Nowicki M, Sharma A, Young M, Tien PC, Grunfeld C, Parikh CR, Shlipak MG. *Antivir Ther* 2014;19(1):79-87. (PMC3933452)

Food insecurity with hunger is associated with obesity among HIV-infected and at risk women in Bronx, NY

Having uncertain access to nutritious food, or food insecurity, unfortunately has an association with obesity, particularly in women of color. For women living with HIV infection, obesity can add to an already increased risk of cardiovascular disease, so it is especially important to understand how food insecurity relates to obesity among WIHS demographics. Before the Food Insecurity Questionnaire was added to other WIHS sites it was piloted at our Bronx site, and the results showed that food insecurity with hunger (smaller meals or fewer in number) was associated with higher rates of obesity for both HIV-infected and HIV-uninfected women. Stress and mental health are suggested as having roles in this relationship, so further studies exploring those connections are being pursued by WIHS researchers.

Sirotin N, Hoover DR, Shi Q, Anastos K, Weiser SD. *PLoS One* 2014 Aug 27;9(8):e105957. (PMC4146558)

Gender roles and mental health in women with and at risk for HIV

This study investigated women's roles in their sexual relationships and how these roles related to their depressive symptoms and quality of life, both at present and averaged over 11 years. Compared to HIV- women, HIV+ women reported significantly higher levels of several aspects of self-silencing (not expressing their own needs for fear of relationship loss or conflict), unmitigated communion (caring for others at the expense of self-care), and multi-year averaged depressive symptoms. HIV+ women also reported lower levels of decision-making power in sexual relationships and lower recent and multi-year averaged quality of life. For both HIV+ and HIV- women, higher self-silencing and unmitigated communion significantly related to recent or multi-year averaged higher depressive symptoms and lower quality of life. Intervention strategies designed to increase self-care and self-advocacy in the context of sexual relationships could potentially minimize depressive symptoms and enhance quality of life in women with and at risk for HIV.

Brody LR, Stokes LR, Dale SK, Kelso GA, Cruise RC, Weber KM, Burke-Miller JK, Cohen M. Psychology of Women Quarterly 2014;38(3):311-326. (In Progress)

Prevalence and correlates of cryptococcal antigen positivity among AIDS patients--United States, 1986-2012

Report

McKenney J, Smith RM, Chiller TM, Detels R, French A, Margolick J, Klausner JD; Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2014 Jul 11;63(27):585-7. (Exempt)

Psychosocial correlates of gender-based violence among HIV-infected and HIV-uninfected women in three US cities

Gender-based violence (GBV) is woman's experience of psychological, physical or sexual abuse at any age. GBV is common among women with and at risk for HIV, yet little is known about psychological factors associated with GBV that could be changed through behavioral interventions. The current study examined the associations between psychosocial variables (i.e., hopelessness, consideration of future consequences, self-esteem), mental health symptoms, substance use, and GBV among a sample of 736 HIV-infected and HIV-uninfected participants in the Women's Interagency HIV Study (WIHS) from the Chicago, Brooklyn and Washington DC sites. Results indicated high rates of lifetime GBV among the sample (58%) as well as high rates of childhood sexual abuse (CSA), specifically (22.2%). HIV-infected women were more likely to be hopeless and to experience lower consideration of future consequences as compared to uninfected women. Multivariable analyses indicated that current non-injection drug use and a history of injection drug use were the main correlates of GBV and CSA. Being born outside of the US was associated with a reduced likelihood of GBV and CSA. Results of this study can be used to develop interventions that simultaneously address trauma and substance use while incorporating cognitive approaches to assisting HIV-infected women, in particular, in working through hopelessness and poor future orientation.

Schwartz RM, Weber KM, Schechter GE, Connors NC, Gousse Y, Young MA, Cohen MH. AIDS Patient Care and STDs 2014 May;28(5):260-7. (PMC4011431)

Pulmonary symptoms and diagnoses are associated with HIV in the MACS and WIHS cohorts

With effective combination antiretroviral therapy, the HIV epidemic is aging and hinting that there may be increased risk of breathing-related (pulmonary) conditions among people with HIV-infection. In collaboration with our men's cohort, MACS, WIHS researchers found that HIV-infection was associated with sleep apnea (stopping breathing during sleep) and wheezing among both cohorts, while HIV-infected MACS men additionally were associated with more

severe conditions like chronic obstructive pulmonary disease, which includes emphysema.
More reasons to stop smoking!

Gingo MR, Balasubramani GK, Rice TB, Kingsley L, Kleerup EC, Detels R, Seaberg EC, Greenblatt RM, Holman S, Huang L, Sutton SH, Bertolet M, Morris A. BMC Pulm Med 2014 Apr 30;14:75. (PMC4021087)

Resilience among women with HIV: Impact of silencing the self and socioeconomic factors

The study investigated the relationship between resilience, gender roles, education, employment, and income among a sample of women with HIV and uninfected women. The sample consisted of 120 women (85 HIV+ and 35 HIV-), mostly African American, at the Chicago site of the Women Interagency HIV Study. Resilience is the ability to function well in negative environments or after negative experiences. Resilience was measured with the Connor-Davidson Resilience Scale -10 item scale (CD-RSC) and was also coded from personal narratives told by participants. Gender roles are social expectations for acceptable female and male behaviors, attitudes, feelings, thoughts, career choices and personality traits. Gender Roles were measured using five questionnaires. Participants showed high levels of resilience. Women with higher egalitarian (less traditional) gender role scores had higher resilience scores compared to women with more traditional gender roles, as shown both by their autobiographical narratives and CDRISC-10 scores. Employment, higher levels of education, and income were related to higher resilience as measured by the CD-RISC. Prevention and intervention strategies for HIV+ women and HIV-uninfected women should promote more non-traditional gender roles, such as higher decision-making in sexual relationships.

Dale SK, Cohen MH, Kelso GA, Cruise RC, Weber KM, Watson C, Burke-Miller JK, Brody LR. Sex Roles 2014 Mar 1;70(5-6):221-231. (PMC4051411)

Risk of Breast Cancer with HIV-Using CXCR4 Defined by V3-Loop Sequencing

Have you heard that HIV-infection can reduce risk of breast cancer? When HIV infects cells it may have the ability to attach to a specific protein (CXCR4) found on both immune cells and breast cancer cells. Not all types of HIV are able to use CXCR4 in their infection cycle, but women with AIDS whose viruses prefer the CXCR4 receptors have a significantly reduced risk of developing breast cancer. WIHS researchers investigated different techniques to sequence HIV viral genetic codes and accurately determine whether a specific HIV sample could attach to CXCR4, while confirming its anti-breast cancer association.

Goedert JJ, Swenson LC, Napolitano LA, Haddad M, Anastos K, Minkoff H, Young M, Levine A, Adeyemi O, Seaberg EC, Aouizerat B, Rabkin CS, Harrigan PR, Hessel NA. JAIDS 2014 Oct 15 [E-pub ahead of print]. (In Progress)

Serum Albumin and Kidney Function Decline in HIV-Infected Women

It is increasingly important to understand what the aging process is for persons living with HIV infection, since development of effective antiretroviral therapy means they are living longer and longer. Kidney health during aging can be measured with a common blood test for albumin, a common protein in blood, so WIHS researchers wanted to see how effectively albumin levels reflect kidney health over time in HIV-infected women. They found that lower serum albumin levels corresponded strongly with declining kidney function, which means that monitoring kidney health for HIV-infected women can be accomplished with a simple routine blood test.

Lang J, Scherzer R, Tien PC, Parikh CR, Anastos K, Estrella MM, Abraham AG, Sharma A, Cohen MH, Butch AW, Nowicki M, Grunfeld C, Shlipak MG. *Am J Kidney Dis* 2014 Oct;64(4):584-91. (PMC4177337)

Serum biomarkers of immune activation and subsequent risk of non-Hodgkin B cell lymphoma among HIV-infected women

The most common cancer among people with HIV infection who have access to highly active antiretroviral therapy (HAART) is AIDS-associated B-cell non-Hodgkin lymphoma (AIDS-NHL). HIV infection over time causes problems with the immune system, including a weakened immune system and B-cell hyperactivation. In this study, WIHS researchers tested blood markers of long-term immune activation in women with HIV infection and found that they were associated with a two to three-fold increase in the risk of developing AIDS-NHL.

Hussain SK, Hessel NA, Levine AM, Crabb Breen E, Anastos K, Cohen M, D'Souza G, Gustafson DR, Silver S, Martinez-Maza O. *Cancer Epidemiol Biomarkers Prev* 2013 Nov;22(11): 2084-2093. (PMC3833437)

Taking it one day at a time: African American women aging with HIV and co - morbidities

WIHS researchers are very interested in what the aging process is like for women living with HIV. In this study, focus groups made of African American women enrolled at our Washington DC WIHS site shared their personal experiences about living and aging with HIV and other co-morbidities. It turned out that co-morbidities, such as diabetes and hypertension, seemed to be more difficult to self-manage than HIV due to daily struggles such as insufficient income/health insurance, hectic work schedule, and loneliness. Caring for family and other social responsibilities were shown to help participants find motivation to stay healthy.

Warren-Jeanpier L, Dillaway H, Hamilton P, Young M, Goparaju L. *AIDS Patient Care STDs* 2014 28(7):372-380. (PMC4074760)

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

One of the most commonly prescribed antiretroviral drugs, tenofovir, has been associated with kidney damage. It is important for doctors to monitor kidney health, especially for patients

taking an antiretroviral regimen that includes tenofovir. WIHS researchers are committed to finding ways of detecting very early signs of kidney decline so a patient could be switched to a non-tenofovir regimen before serious kidney damage occurs. In this study, WIHS researchers found that one biomarker believed to indicate early kidney damage was elevated in patients taking tenofovir.

Oboho I, Abraham A, Benning L, Anastos K, Sharma A, Young M, Burian P, Gandhi M, Cohen M and Szczech L. *J Acquir Immune Defic Syndr* 2013 Apr;62(4):388-395. (PMC3692572)

The impact of HAART on the respiratory complications of HIV infection: longitudinal trends in the MACS and WIHS cohorts

Respiratory health is a well-known concern for people living with HIV infection, but not a lot is known about how the introduction of highly active antiretroviral therapy (HAART) affected the risk of respiratory diseases. In this study, MACS and WIHS researchers compared HIV-infected men and women to HIV-uninfected men and women over time, noting how often patients developed respiratory diseases and whether those were associated with death. Respiratory diseases were classified as either non-infectious, such as chronic obstructive pulmonary disease (which includes chronic bronchitis and emphysema), or infectious. While HIV-infected individuals with access to HAART did not appear to have a higher risk of developing non-infectious respiratory diseases, compared to HIV-uninfected individuals they did have a higher risk for infectious respiratory diseases and a higher risk for dying from those diseases.

Gingo MR, Balasubramani GK, Kingsley L, Rinaldo CR, Alden CB, Detels R, Greenblatt RM, Hessel NA, Holman S, Huang L, Kleerup EC, Phair J, Sutton SHM, Seaberg EC, Margolick JB, Wisniewski SR, Morris A. *PLOS One* 2013;8(3) e58812. (PMC3595204)

Urinary biomarkers of kidney injury are associated with all-cause mortality in the Women's Interagency HIV Study (WIHS)

Unfortunately, the WIHS Study has lost a significant number of participants who have passed away during the course of our study. We are very grateful to all past and present WIHS participants, and one way we can express gratitude for those who have died during this study is to look at what factors may have contributed to their death, in hopes of improving the care for HIV-infected women in the future. Common blood tests for kidney disease in HIV infections tend to miss detecting the earliest phase of disease when interventions could prevent further damage. In this study, WIHS researchers found that early kidney disease as detected by urine tests could predict death from all causes. This means that catching kidney disease early on through simple urine tests could have a life-saving effect for HIV-infected women.

Peralta C, Scherzer R, Grunfeld C, Abraham A, Tien P, Devarajan P, Bennett M, Butch A, Anastos K, Cohen M, Nowicki M, Sharma A, Young M, Sarnak M, Parikh C, Shlipak M. HIV Med 2014 May;15(5):291-300. (PMC3975680)

Antiretroviral-Treated HIV-Infected Women Have Similar Long-Term Kidney Function Trajectories as HIV-Uninfected Women

There are many factors that are considered when choosing an effective HAART regimen. Kidney disease is a strong risk factor for death among HIV-infected individuals, so choosing drugs that do not cause undue harm to kidney function is very important. One of the most commonly-prescribed HIV antiretroviral drugs is tenofovir, which in past studies has been linked to faster kidney decline, but to a variable extent. WIHS researchers compared HIV-infected women just starting a HAART regimen which either does or does not include tenofovir to a group of women without HIV infection, examining their kidney function over time. While HIV-infected women tended to have slightly worse kidney function at the start of the experiment compared to the HIV-uninfected women, both groups had similar rates of gradual kidney decline, suggesting that tenofovir and other antiretrovirals may not have any noticeable effect on speeding up kidney disease.

Estrella MM, Abraham AG, Jing Y, Parekh RS, Tien PC, Merenstein D, Pearce CL, Anastos K, Cohen MH, Dehovitz JA, Gange SJ. AIDS Res Hum Retroviruses 2013;29(5):755-760. (PMC3636577)

HIV-Uninfected Women

Women are historically under-studied when it comes to many aspects of HIV infection, and their pulmonary health (also called respiratory or breathing health) is especially important to investigate, since sex differences are known to occur in the progression of lung disease. In this study, WIHS researchers found that HIV-infected women have a harder time getting rid of the respiratory waste product, carbon dioxide, when they exhale compared to HIV-uninfected women. This trend along with the tendency for HIV-infected women to have blockages in their airflow may cause respiratory symptoms such as difficulty breathing.

Fitzpatrick ME, Gingo MR, Kessinger C, Lucht L, Kleerup E, Greenblatt RM, Claman D, Ponath C, Fong S, Huang L, Morris A. JAIDS 2013 Nov;64(3):284-288. (PMC3857225)

Sexual Practices and Risk Behaviors

Computational modeling reveals distinct effects of HIV and history of drug use on decisionmaking processes in women

Drug users and HIV-seropositive individuals often show deficits in everyday decision-making. Different psychological processes may underlie these deficits and there is still lack of understanding of the nature of these deficits. This study used new statistical methods based on mathematical cognitive modeling to explore the effects of drug use and HIV on decision-making. We classified a subset of women enrolled at the Chicago site of the Women's Interagency HIV Study (WIHS) into one of four groups based on their HIV status and history of crack, cocaine and/or heroin use. We then measured their decision-making with a widely used laboratory task called the Iowa Gambling Task (IGT). Using new statistical methods, we identified four distinct psychological processes underlying their performance on the IGT. Results showed that drug use was associated with problems with learning/memory and less of a reaction to loss. HIV infection was associated only with a reaction to loss. This study contributes to an understanding of how HIV and drug use may be associated with problem with decision-making which could impact day to day functioning.

Vassileva J, Ahn W, Weber KM, Busemeyer JR, Stout JC, Gonzalez R, Cohen MH. PLOS One 2013 Aug;8(8): e68962. (PMC3737214)

Facilitators and barriers to discussing HIV prevention with adolescents: perspectives of HIV-infected parents

Parents have been considered an underutilized resource for educating children about HIV prevention. Parents and other family members can play a critical role in prevention efforts by using effective parenting practices, communicating their values and expectations, and modeling strategies that reduce the risk of acquiring HIV. Despite the potential protective role of parent-child communication on adolescent sexual and drug use behavior, much remains unknown about the processes and contexts in which these communication encounters occur. This study will examine parent-adolescent communication about HIV prevention in families affected by HIV. Specifically, the project will use a mixed methods approach to identify the strategies parents living with HIV/AIDS use to discuss HIV prevention with their 10-17 year old adolescents. Whereas in-depth interviews will shed light on what motivates and/or prevents parents from discussing HIV prevention with adolescents, a questionnaire will collect information on theoretical concepts previously identified as important to research in this field. Overall, this project will be useful in identifying ways to help parents more effectively communicate with adolescents about safer sex, drug use, and HIV infection.

Edwards LL, Reis JS, Weber KM. Am J Public Health 2013 Aug;103 (8) 1468-1475. (PMC3908917)

HIV serostatus differs by catechol-O-methyltransferase Val158Met genotype

We all have a gene, the catechol-o-methyltransferase (COMT) gene, which comes in different forms or alleles. One variation of the gene, the Met allele, has been associated with risk behaviors including illicit drug use and unprotected sex. Since these risk behaviors increase the risk of contracting HIV, we looked to see if having the COMT Met allele is more common in women with HIV versus women without HIV. In a sample of 1848 HIV-infected women and 612 HIV-uninfected controls, we found that the HIV-infected women were more likely to carry the Met allele versus the uninfected controls. We report a link between one's COMT allele form and HIV serostatus that may be due to the association between the Met allele and risk-taking.

Sundermann EE, Bishop JR, Rubin LH, Aouizerat B, Wilson TE, Weber KM, Cohen M, Golub E, Anastos K, Liu C, Crystal H, Pearce CL, Maki PM. AIDS 2013 Jul 17;27(11):1779-1782. (PMC3897122)

Sexual minority status and violence among HIV infected and at-risk women

Women who have sex with women or with both men and women may identify as lesbian, bisexual or even straight. Some research has found that these women are at risk for violence and drug use. This study found that women who identified as bisexual or had sex with both men and women were more likely to experience sexual and domestic abuse, and especially physical violence. Having sex for drugs or money, having multiple sex partners and using drugs explained some of the increased risk for violence. We also found that women who only had sex with women were less likely to report sexual abuse and physical violence.

Pyra M, Weber K, Wilson TE, Cohen J, Murchison L, Goparaju L, Cohen MH. J Gen Intern Med 2014 Aug;29(8):1131-8. (PMC4099466)

Study Methods

Identifying the appropriate comparison group for HIV-infected individuals

Review article

Wong C, Althoff K, Gange SJ. *Curr Opin HIV AIDS* 2014 Jul;9(4):379-85. (PMC4105851)

Predictive accuracy of the veterans aging cohort study index for mortality with HIV infection: a North American cross cohort analysis

One important contribution from the WIHS is its work with other large research groups in the North American AIDS Cohort Collaboration (NA-ACCORD). Together, the NA-ACCORD collaborators were able to use data from over 10,000 people living with HIV infection to test the accuracy of a certain index, the Veterans Aging Cohort Study (VACS) index, for determining risk of death within the next several years. The results indicated that the VACS index accurately estimates risk of dying over one to five years after taking antiretroviral therapy across different patient subgroups.

Justice AC, Modur SP, Tate JP, Althoff KN, Jacobson LP, Gebo KA, Kitahata MM, Horberg MA, Brooks JT, Buchacz K, Rourke SB, Rachlis A, Napravnik S, Eron J, Willig JH, Moore R, Kirk GD, Bosch R, Rodriguez B, Hogg RS, Thorne J, Goedert JJ, Klein M, Gill J, D. *JAIDS* 2013;62(2):149-163. (PMC3619393)

Substances of Abuse

Alcohol consumption trajectories in adult women with HIV Infection

Drinking more alcohol than recommended can have bad health consequences. Most previous research has looked at alcohol consumption at a single time point. The current paper presents information about drinking trends over time. We included information from all WIHS study participants, with information provided between 1996 and 2006. We used a statistical program to group women into 5 different groups, depending on their long-term drinking behavior. We found that most women (80%) either drank at low levels during the entire period, or did not drink at all. However, some women either continued to drink above recommended levels for the entire period, or increased their drinking to heavy levels during the follow-up period. Women were most likely to have long-term patterns with heavy drinking if they had a past history of heavy drinking, used tobacco or other drugs at the beginning of the study, or if they had less education. The study had no direct impact on WIHS participants, since the information was already collected. The information will help women and their healthcare providers to identify whether they are at risk for long-term drinking problems. Then, such women might receive better alcohol treatment interventions in the future.

Cook RL, Zhu F, Belnap BH, Weber KM, Cole SR, Vlahov D, Cook JA, Hessel NA, Wilson TE, Plankey M, Howard AA, Sharp GB, Richardson JL, Cohen MH. *AIDS Behav* 2013 Jun;17(5):1705-1712. (PMC3534826)

Crack cocaine use impairs anterior cingulate and prefrontal cortex function in women with HIV infection

An earlier WIHS study showed that among women with a history drug use HIV-infected women had worse verbal memory (for example, remembering a grocery list, while non-verbal memory could be remembering a picture) compared to HIV-uninfected women. Since cocaine was shown to be the main factor in that result, this follow-up paper examines the functional MRI results of which areas in the brain were activated during memory tests, specifically tests of semantic clustering, or organizing words into categories (such as organizing an artichoke into the vegetable category). Both current and past crack cocaine users showed decreased activity during the learning portion in brain regions known for helping form memories and later showed decreased activity during the recognition portion in an important area known to be altered from cocaine use and from HIV-infection.

Meyer VJ, Little DM, Fitzgerald DA, Sundermann EE, Rubin LH, Martin EM, Weber KM, Cohen MH, Maki PM. *J Neurovirol* 2014 Aug;20(4):352-61. (PMC4090256)

HIV and Recent Illicit Drug Use Interact to Affect Verbal Memory in Women

HIV infection and illicit drug use are both associated with cognitive deficits. This study looked at the effects of HIV and recent illicit drug use on the Hopkins Verbal Learning Task (HVLT) and the Stroop task. The HVLT is a task of verbal learning and memory. The Stroop task measures processing speed and executive function. Participants included 947 HIV-infected and 443 HIV-uninfected women. Three drug use groups were compared: recent illicit drug users, former users, and non-users. We found that HIV infection was associated with worse verbal learning and recent illicit drug use was associated with worse verbal memory. Importantly, there was an interaction between HIV serostatus and recent illicit drug use. Women with HIV who recently used drugs performed worse on verbal learning and memory than women with HIV who had never used drugs. However, among women who were not infected with HIV, recent illicit drug use had no effect on verbal learning and memory. When we looked at the effects of specific drugs, we found that cocaine use negatively impacted verbal memory and heroin use negatively impacted verbal learning (but only among HIV-infected women). We did not find an interaction between HIV and illicit drug use on the Stroop task. The interaction between HIV and illicit drug use on verbal memory, but not executive function or processing speed, suggests that recent illicit drug use among HIV-infected women may negatively affect the brain circuits underlying verbal memory.

Meyer VJ, Rubin LH, Martin E, Weber KM, Cohen MH, Golub ET, Valcour V, Young MA, Crystal H, Anastos K, Aouizerat BE, Milam J, Maki PM. *J Acquir Immune Defic Syndr* 2013;63(1):67-76. (PMC3628722)

Smoking cessation and recidivism in the Women's Interagency HIV Study

We know smoking can lead to cancer, heart disease, and premature death, but you may not know that smoking is especially harmful for HIV-infected people. In 1995, 57% of WIHS women were smokers, but almost every year that amount decreased until only 39% were smokers in 2011. Only 20% of women who smoked when they joined WIHS have quit, and about half of them have since started again. Quitting took longer for women who drink alcohol, smoked for a long time, have high blood pressure, and have a low CD4 count (in those with HIV), but those who were recently pregnant could quit in less time.

Hessol NA, Weber KW, D'Souza G, Burton D, Young M, Milam J, Murchison L, Gandhi M, Cohen MH. *Amer J Prev Med* 2014 Jul;47(1):53-69. (PMC4065848)

Vitamins

Relationship of vitamin D, HIV, HIV treatment and lipid levels in the Women's Interagency HIV study (WIHS) of HIV-infected and un-infected women in the US

Research suggests that people with low vitamin D levels have a greater chance of having heart disease and death from heart disease. Reports of very low vitamin D levels in treated HIV positive patients, mostly men, have also recently appeared. The vitamin D levels may be affected by HIV medications. High cholesterol and early heart disease are also seen in treated HIV positive patients. We aimed to study the relationship between vitamin D levels and cholesterol (and other lipid levels) in HIV-infected women.

Schwartz JB, Moore KL, Yin M, Sharma A, Merenstein D, Islam T, Golub ET, Tien PC, Adeyemi OM. *J Int Assoc Provid AIDS Care* 2014 May;13(3):250-259. (PMC4016117)

Vitamin D and insulin resistance in non-diabetic women's interagency HIV study participants

Some studies have shown that low vitamin D levels are associated with a higher risk of diabetes in the general population. In this WIHS study, we looked at the association between Vitamin D levels and insulin resistance (a measure that suggests a higher risk of developing diabetes) in HIV-infected and HIV-uninfected WIHS women. Among 981 women, there was a high rate of vitamin D deficiency but this was not associated with insulin resistance. Other known factors such as body weight, ethnicity, hepatitis C and menopause were associated with insulin resistance. In summary, while low vitamin D levels and insulin resistance are both commonly seen in HIV infected and uninfected women, we did not find that low vitamin D levels directly contributed to insulin resistance in the WIHS.

Adeyemi OM, Livak B, Orsi J, Glesby MJ, Villacres MC, Weber KM, Sharma A, Golub E, Young M, Cohen M, Tien PC. *AIDS Patient Care STDs* 2013 Jun;27(6):320-325. (PMC3671624)

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 ET, Cohen M, Adeyemi OM. AIDS 2013 Feb 20;27(4):573-8. (PMC3902982)