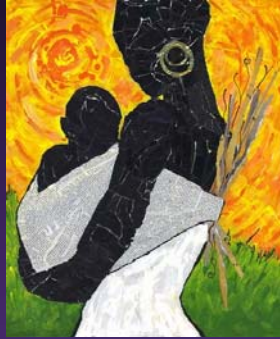


Women and HIV: A case-based approach



The Medical Management of HIV/AIDS
December 14, 2007

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Women's HIV Program, Positive Health Practice, UCSF

Case#1

- **HPI:** 58 yo Caucasian woman presented to my clinic Aug 2006 with 4-5 years of cognitive decline – from employed as printer to sporadic homelessness, all thought 2^o profound depression. Admitted to UCSF inpatient psychiatric unit 7/06



Case

- **PMH** significant for Non-Hodgkin's lymphoma dx'd 8 years previously treated with CHOP (had PCP PNA, CMV PNA, & disseminated VZV in context of chemo) and in remission since. Has had multiple episodes of bacterial pneumonias since and progressive affect loss, cognitive decline, failure to care for self, depression

Case

- **MEDS:** Multiple psych meds
- **ALL:** NKDA
- **SHx:** No smoking; social EtOH; occasional MJ; no IVDU or other drugs; sex with men only (3 sexual partners in last 20 years); educated and successful woman in printing and journalism prior to decline
- **FHx:** Noncontributory

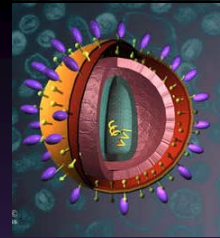
Case

- **PE:** 130/70; 92%RA; 37.0; 110; 22
Thin, white woman NAD; Somnolent, flat affect, would track, but sits with dazed expression and answers questions slowly; only oriented to self; can follow 1-step, but not 2-step commands; poor effort on neuro exam, but no clear focal deficits; flexor plantar response; no thrush; RRR S1 S2 no mgr; clear lungs; abdomen soft; no peripheral edema or rash

Case

- **LABS:** WBC 5.6; Hct 34.2; Plt 316; SPEP – general increase in gamma region suggestive of polyclonal gammopathy; ESR 46; lytes, LFT's unremarkable
- **CXR:** Increased lung markings in a nodular-reticular pattern; **Head CT:** Parenchymal loss; periventricular white matter T2 prolongation nonspecific

Diagnosis?



- *Pneumocystis jiroveci* on bronch
- HIV Ab positive
- CD4 46 (6%) with viral load >500,000 copies/mL
- Probable HIV encephalopathy (PML and CMV ruled out) causing progressive (and preventable) cognitive decline
- Now. . Improving gradually on HIV therapy, but residual organic brain damage

¼ of HIV-infected people in U.S. unaware of infection status

People living with HIV/AIDS	1,039,000 to 1,185,000
Percent unaware of HIV status	24% to 27% (>250,000)
Relative risk of transmission from unaware patient compared to aware	3.5 times

Marks G. *AIDS*. 2006;20(10):1447-1450.

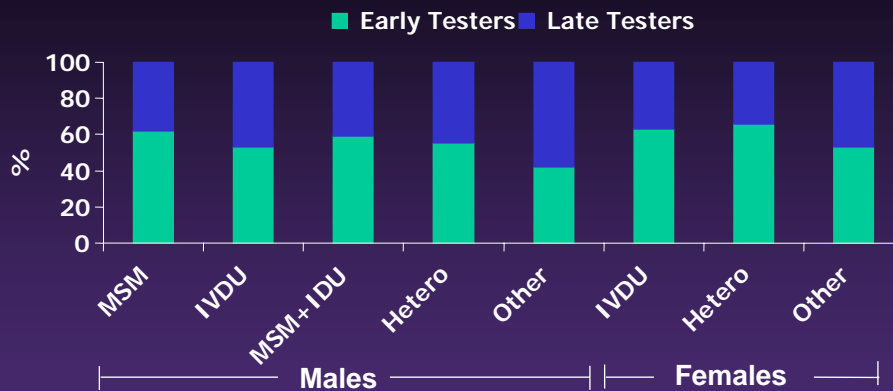
Women may be less likely to identify risk for HIV (WIHS)

Exposure Category:	1994/1995 cohort	2000/2001 cohort
Intravenous drug use	34%	10%
Heterosexual risk	42%	41%
Transfusion risk	4%	--*
No identified risk	20%	48%

* Transfusion risk not assessed in 00/01 cohort

Barkan SE et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. *Epidemiology*. 1998; Bacon et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. *Clin Diagn Lab Immunol* 2005; Division of HIV/AIDS Prevention/CDC. National Women and AIDS Collective. November 2007

"Late Testers" Account for Almost 40% of HIV Diagnoses

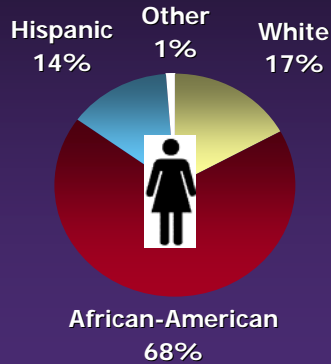


Risk factors for later presentation and OP's: racial/ethnic minority, **no perceived risk factors**, older age²

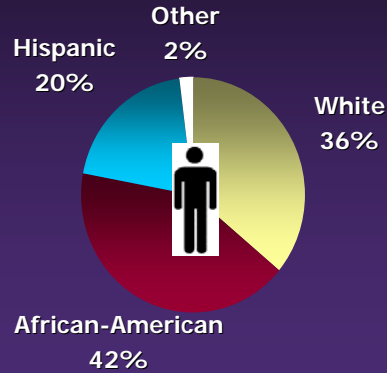
HIV/AIDS Surveillance Report, 2004. Vol. 16. Atlanta: US Department of Health and Human Services, CDC: 2005:1-46. Available at: <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/default.htm>.²Ostermann et al. Trends in HIV testing and differences between planned and actual testing in the United States, 2000-2005. *Archives Internal Medicine* Oct 2007; Hanna et al. AIDS-defining opportunistic illnesses in the HAART era in New York City. *AIDS Care* Feb 2007

Epidemic in women skewed towards minorities

HIV/AIDS among U.S. women

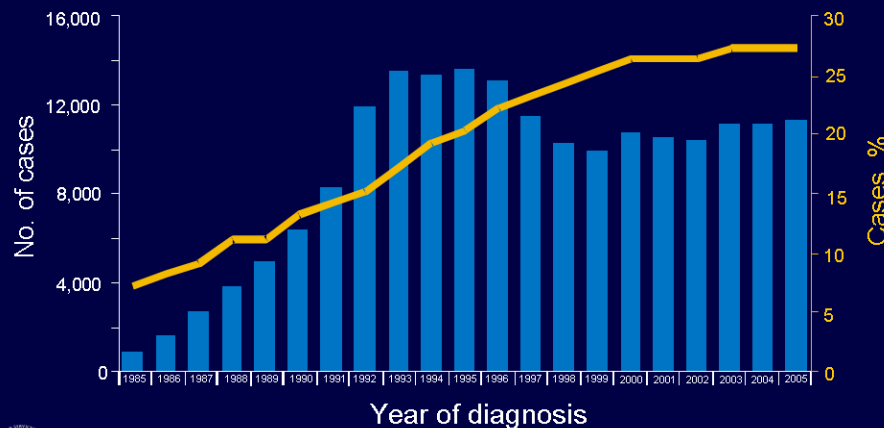


HIV/AIDS among U.S. men



CDC. Available at: www.cdc.gov/hiv/topics/surveillance/resources/slides/index.htm

Rising rates of AIDS cases in women in U.S. – 46% HIV cases worldwide



•Proportion of all AIDS cases in women has more than tripled in 15 years, from 7% in 1985 to 29% today

•Leading cause of death in black women ages 25-34 (3rd in black women ages 35-44; 5th overall in women 35-44)

Cases of HIV and AIDS in the U.S. (6/28/07). <http://www.cdc.gov/hiv/topics/women/resources.htm>

CDC guidelines (routine, not risk-based) 9/21/06 may benefit women

- HIV screening in all health-care settings ages 13-64 after patient notified (opt-out screening – assent inferred unless patient declines)¹.
- HIV testing for those at high risk for HIV infection at least qyear
- General consent for medical care implied; separate written consent not required
- Prevention counseling requirement relaxed
- (Some controversy, state-by-state)²

Branson BM et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006 Sep 22;55(RR-14):1-17 ; ²Wynia MK. Routine screening: informed consent, stigma and the waning of HIV exceptionalism. Am J Bioeth. 2006 Jul-Aug;6(4):5-8.

Screening in pregnant women

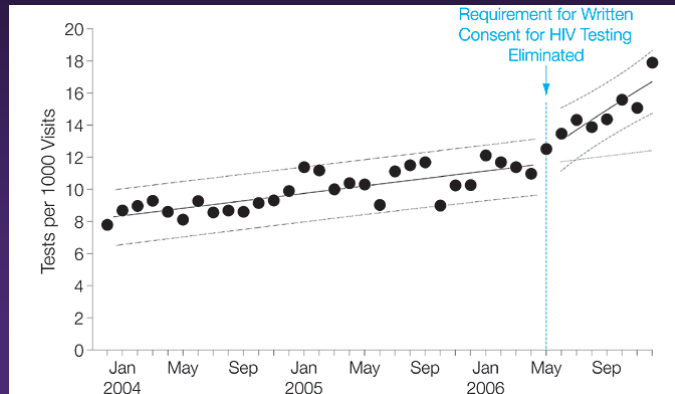
- HIV screening should be included in the routine prenatal panel for all pregnant women
- Opt-out screening after the patient is notified about testing
- Repeat screening in the 3rd trimester in areas of elevated rates of HIV in pregnant women or high-risk patient
- Rapid testing during labor if no HIV test documented

Branson BM et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006 Sep 22;55(RR-14):1-17



AB682 signed by Gov. Schwarznegger in CA 10/12/07

- AB 682 (California HIV Routine Screening bill)
 - Repeals written consent for HIV testing
 - Part of unwritten consent for routine medical care



Zetola N et al. Association Between Rates of HIV Testing and Elimination of Written Consents in San Francisco. JAMA 2007

Case#2



HPI: 39 year old AA female with HIV contracted in '97 2° heterosexual sex, never on HAART (except during pregnancy), presents to clinic 6 months ago after sporadic f/u for past 8 years. Current CD4 count 260 and viral load 80,000.

Pt single mother of two children and has been reluctant to start ARVs (although took during pregnancy). Finally comes to clinic stating "I am willing to try your drugs, but they *better* not give me side effects"

Case



- PMH remarkable for chronic hypertension with mild renal insufficiency, anemia and grade I peripheral neuropathy
- Meds: HCTZ, iron supplements, gabapentin
- Allergies: NKDA
- Social history: Smokes ½-1 PPD; drinks 2-3 glasses of beer per night; sporadic MJ and crack use; h/o heroin use in past; works in convenience store sporadically; 2 children at home

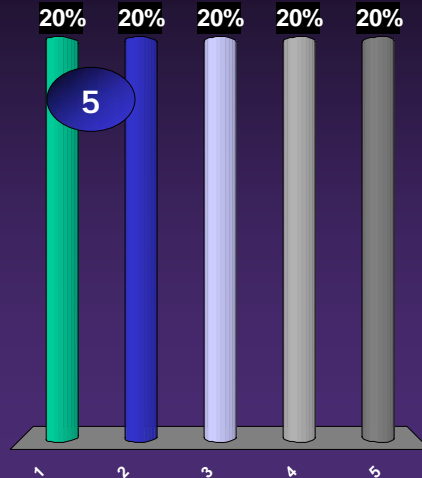
Case



- PE: BP 145/92; Anxious thin AA woman, NAD; OP clear; old track marks, but no current skin abnormalities; S4 present, otherwise exam unremarkable
- LABS:
 - WBC 3.9; Hct 32.6; Plt 150; BUN 15; Crea 1.4
 - Baseline HIV phenotype -full sensitivity to all agents except ddl (fold-change 1.94).
- Question: What NRTI backbone would you consider for this patient with renal insufficiency, anemia and neuropathy, hoping for no side effects?

ARS question: What NRTI backbone would you choose?

1. Tenofovir + Didanosine
2. Tenofovir + Emtricitabine (Truvada®)
3. Zidovudine + Lamivudine (Combivir®)
4. Abacavir + Lamivudine (Epzicom®)
5. Stavudine + Lamivudine



NRTIs in women



- Mono or dual therapy era, had sex differences in NRTI toxicities (pancreatitis, lactic acidosis, neuropathy)¹⁻⁵
- Women still at higher risk for anemia with AZT than men⁶
- TFV-associated renal insufficiency (EAP) higher with lower body weights, lower CD4, older age⁷
- At higher risk for neuropathy than men

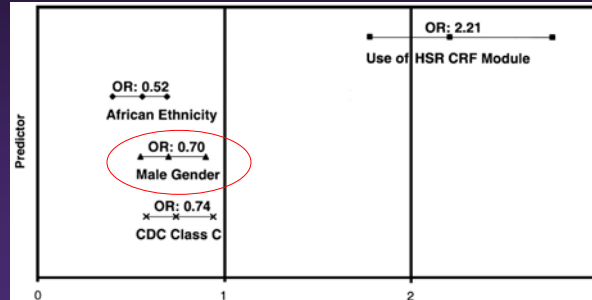
¹Moore RD. Amer. J Med 1996; ²Currier. JAIDS 2000; ³Squire. CROI 2000, #516; ⁴Boxwell ICAAC 1999, #1284; ⁵Moyle. AIDS 2002; ⁶Ssali Prevalence, incidence and predictors of severe anaemia with AZT-containing regimens in African adults with HIV infection within the DART trial. Antiretroviral therapy 2006; ⁷Nelson. The safety of tenofovir for the treatment of HIV infection in adults: the first 4 years. AIDS 2007; ⁸Dragovic. NRTI usage and the incidence of peripheral neuropathy in HIV/AIDS patients. Antivir Chem Chemotherapy 2003

I chose ABC/3TC – As safe in women?



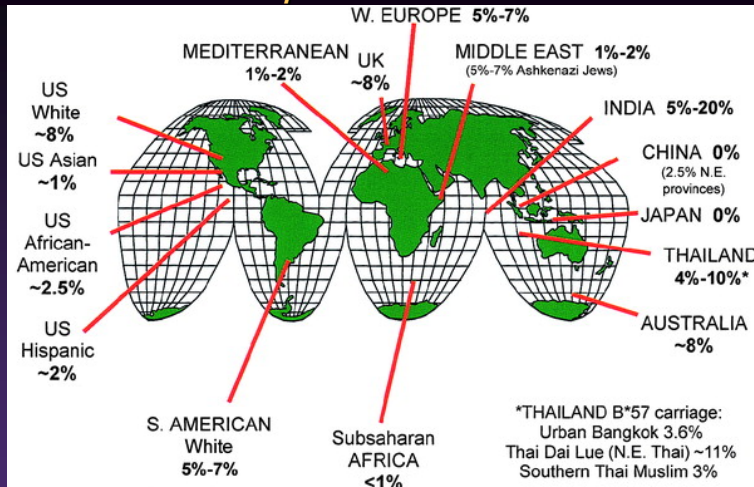
• Risk factors for HSR

- Retrospective analysis of 8038 ABC-treated subjects¹
- Female sex ↑ odds (OR 1.42) for developing ABC HSR



¹ Cutrell. Updated risk factor analysis of suspected hypersensitivity reactions to ABC. *Ann Pharmacol*. 2004; ²Hetherington et al. Hypersensitivity reactions during therapy with the NRTI abacavir. *Clin Ther* 2001

HLA *B5701 prevalence worldwide¹



Now know about HLA *B5701 association with ABC HSR (PREDICT-1², SHAPE), so should test our patient prior to starting ABC³

¹Phillips. Genetic screening to prevent ABC HSR: Are we there yet? *CID* 2006; ²Mallal. PREDICT-1: a novel randomised prospective study to determine the clinical utility of HLA-B*5701 screening to reduce abacavir hypersensitivity in HIV-1 infected subjects (study CNA106030). *IAS* 2007; ³DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Updated December 1, 2007; <http://aidsinfo.nih.gov>

Case (continued)



- Pt HLA*B5701 negative, so started ABC/3TC/ATZ/RTV
- No ABC HSR
- Had GI side effects on ATZ/RTV and didn't like food restriction, so switched to Fosamprenavir/RTV (100mg daily^{1,2})
- Still GI side effects on RTV



¹Ruane et al. Plasma amprenavir pharmacokinetics and tolerability following administration of 1,400 milligrams of fosamprenavir once daily in combination with either 100 or 200 milligrams of ritonavir in healthy volunteers. *Antimicrob Agents Chemother* FebS 2007; ²FDA Approves Administration of LEXIVA with Lower Dose of "Boosting" Medication Ritonavir. *Press Release*. October 12, 2007

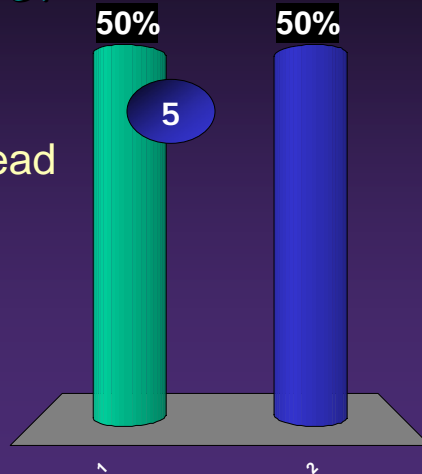
Case (cont.)



- Pt very frustrated and asks
All my girlfriends have more side effects on these medications than my men friends – Do women with HIV get more sick from these meds you give out???

What will you tell her about sex differences in adverse events on ARVs?

1. Yes, sex differences in adverse effects exist
2. No, this is all in your head



Sex differences in adverse effects of ARVs

- NRTI toxicity differences well-known and reviewed¹⁻⁷
- Sex differences in HAART era frequent^{8,9} and have clinical consequences
 - 1st HAART discontinuation rates 2^o to toxicities >2x as common in women than men (IcoNa)¹⁰⁻¹²

¹Moore RD. Amer. J Med 1996; ²Currier. JAIDS 2000; ³Squire. CROI 2000, #516; ⁴Boxwell ICAAC 1999, #1284; ⁵Moyle. AIDS 2002; ⁶Bolhaar et al. CID July 2007; ⁷Currier J. CID 2007; ⁸Nicastri. JAC 2007; ⁹Collazos J. AIDS 2007; ¹⁰D'Arminio Monforte. AIDS 2000; ¹¹Murri. JAIDS 2003; ¹²Spire. AIDS Care 2004

NVP-induced rashes more common in women



- More common (15.8% vs 8.4%; RR 4-6)¹⁻⁴
- More severe (RR 7.3); 2% rate
- ↑ risk at higher CD4 (trend)
- Same or ↓ rash in pregnancy (5-8%)⁵⁻⁸

¹Bersoff-Matcha. CID 2001; ²Mazhude. AIDS 2002; ³Ananworanich. AIDS 2005; ⁴Antinori AIDS 2001; ⁵Timmermans. AIDS 2005; ⁶Joao. Am J Ob/Gyn 2006; ⁷Phanuphak. HIV Med 2007; ⁸Natarajan. HIV Med 2007

NVP related hepatotoxicity more common in women

- **Safety data of NVP¹:**
 - *Women:* 12x ↑ sx hepatotoxicity with CD4 >250 vs. ≤ 250
 - *Men:* 5x ↑ risk CD4 >400 vs. ≤ 400
- **S. African trial with NVP²**
 - Women 20% grade 3,4 toxicity (12.8% men)
 - 50% hepatotoxicity in women BMI <18.5

¹“Dear Health Care Professional Letter”, Boehringer-Ingelheim, 2004; ²Sanne. JID 2005

Risk factors for NVP-related hepatic toxicity in women

- Toxicity with systemic sx (rash) 3.2x as common in women
- Pregnancy (19% vs. 4.2%)²⁻⁴
- Low BMI⁵
- Common to sexes: AST/ALT ↑, HBV, HCV⁶, especially genotype 3 (HR 1.9)⁷ (treatment of HCV protective⁸), prior toxicity

¹ Stern. JAIDS. 2003; ²Timmermans. AIDS 2005; ³Jamisse JAIDS 2007; ⁴ Phanuphak HIV Med 2007; ⁵Sanne. JID 2005 ⁶Maggiolo JAC 2007; ⁷Torti. JAIDS. 2006; ⁸Labarga JID 2007

Sex differences in CVD events (M>F) most likely not HAART-related

- Triglyceride (TG) and LDL increases, HDL decreases relatively more in men than women on HAART (pre-menopausal)¹⁻⁴
- ↑ MI rate in men versus women in DAD, median age 39 (RR 1.99)⁵⁻⁷
 - Sex-difference not related to differences in HAART usage
 - Most likely secondary to baseline CVD risk factors
- ↑ in high-risk CVD in males vs females (17 vs 12%) in WHS/MACS⁹
 - Driven by non-HAART factors (smoking, BP, age, overweight, low income)



Need more comparison data with post-menopausal women

¹Theibaut. HIV Med 2001; ²Leitner. Atherosclerosis 2005; ³Santos. Int J STD AIDS 2005; ⁴van Leth. PLoS Medicine 2004; ⁵Law. HIV Med. 2003; ⁶Friis-Moller. NEJM. 2003; ⁷Friis-Moller. AIDS 2003; ⁸Neumann. Eur J. Med Res. 2004; ⁹Kaplan CID 2007

General pattern of fat changes differ by sex

- ↑ central adiposity in women
- Equal rates of peripheral lipoatrophy in both sexes
- ddI^{1,9}, IDV² and d4T^{2,11}
- Patient-described:
“Beach ball on sticks”



¹Galli. Antiviral Ther. 2003; ²Martinez. Lancet 2001; ³Thiebaut. CID 2000; ⁴Saves. CID 2002; ⁵Heath. Int J. of Epidemiology 2002; ⁶European Pediatric Lipodystrophy Group. AIDS 2004; ⁷Benson JO. JAIDS 2000; ⁸The Body; The Complete HIV/AIDS resource" www.thebody.com; ⁹Tien. AIDS Patient Care and STDs 2007; ¹⁰FRAM. JAIDS 2006; ¹¹Jacobson CID 2005

Summary of adverse events more common in women on HAART

- NVP rashes and hepatotoxicity
- More GI intolerance to older PI regimens¹⁻⁴, not newer⁵⁻⁶
- Lipid changes less than men, but unclear effect on CVD outcomes
- Women more central adiposity (some role of HAART: d4t→LA; IDV→central fat; ddI→fat loss)
- Ecologic increases in preterm, pre-eclampsia and fetal death with HAART in pregnancy
- Osteopenia HIV-related AND HAART-associated (PIs⁷⁻¹¹) so watch in women

¹Gatti. AIDS 1999; ²Dieleman. AIDS 2002; ³Lucas. Ann Intern Med 1999; ⁴Bonfanti. JAIDS 2000; ⁵Eron. Lancet 2000; ⁶Hoffman. HIV Clin Trials 2007; ⁷Vescini. JAIDS 2003; ⁸Fausto. Bone 2005; ⁹Brown. J. Clin Endo & Metab 2003; ¹⁰Bruera. AIDS 2003; ¹¹Anastos. The association of bone mineral density with HIV infection and antiretroviral treatment in women. Antiviral Ther 2007

Why do women have more adverse effects? – Probably PK

Pharmacokinetics

Bioavailability

- Women ↓ acid, slower gastric emptying time (OCPs, pregnancy)
- Diet differences
- No consistent differences in gut CYP or p-gp

Distribution

- Women weigh less
- More proportional fat
- Varying plasma volumes
- Less organ flow
- Estrogen has effects on plasma binding proteins

Metabolism

- In vitro: F>M trend
- Progesterone ↑ CYP2A4 activity
- Hepatic g-gp M>F

Elimination

- Smaller organs
- HepC and liver status

Administration of concomitant medications can affect each stage & vary by sex

Gandhi. Annu Rev Pharm Tox 2004; ²Mirfazaelian. E. J.. Clin. Pharm. 2002; ³Wobold. Hepatol 2003

Sex differences in ARV pharmacokinetics

- Most studies generally show higher plasma concentrations or AUCs of ARVs in women¹: IDV^{2,3}, LPV⁴, SQV^{5,6}, NVP⁷⁻⁹, EFV^{10,11}
- But few powered to look at association between levels and toxicities or outcomes *by sex (WIHS performing¹²)*

¹Otokun. Gender Med 2007; ²Csajka. AAC 2004; ³Burger. JAIDS 2002; ⁴Burger. 3rd Intl' Conf Clinical Pharm of HIV Therapy 2002; ⁵Pai. Pharmacotherapy 2004; ⁶Fletcher JID 2004; ⁷Regazzi. AIDS 2003; ⁸la Porte. 4th Intl' Conf Clinical Pharm of HIV Therapy 2003; ⁹von Hentig. Br. J. Clin. Pharm 2006; ¹⁰Burger. 4th Intl' Conf Clinical Pharm of HIV Therapy 2003; ¹¹Burger. Br. J Clin. Pharm 2005; ¹²Gandhi. Clin Pharm and Therapeutics 2007

Case (continued)

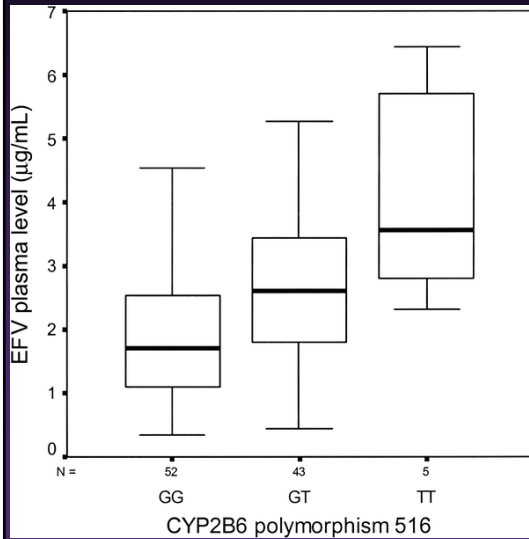


- Given GI side effects with PIs, consider NNRTIs
- Concerned about NVP given CD4 >250
- Pt gingerly started on efavirenz 600mg po qhs with her ABC/3TC tablet (pt counseled on pregnancy)
- Pt starts having horrible nightmares and insomnia (as well as fantasies of switching providers), but has an amazing immunologic and virologic response
- Question: Any specific reason to think our patient would have more side effects on efavirenz?

ARS: What pharmacogenomic trait may lead to an increase in EFV exposure in our patient?

1. HLA*B5701 rates lower in patients of African descent
2. Cytochrome p450 3A4 (CYP3A4) activity higher in patients of African descent
3. CYP2C19 activity lower in African-Americans than Caucasians
4. CYP2B6 activity lower in African-Americans than Caucasians

Genetic effects on EFV

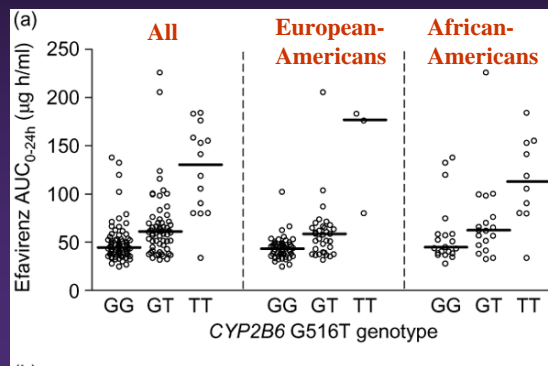


- CYP450-2B6 is responsible for β -hydroxylation of EFV and 90% of its clearance
- G→T change at codon 516 reduces CYP2B6 activity¹
- Homozygous TT genotype with highest EFV levels
- MDR1 (p-gp) may also affect EFV levels²

¹Rodriguez-Novoa et al. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. CID 2005; Fellay et al. Lancet 2002

CNS symptoms on EFV and CYP2B6 variation

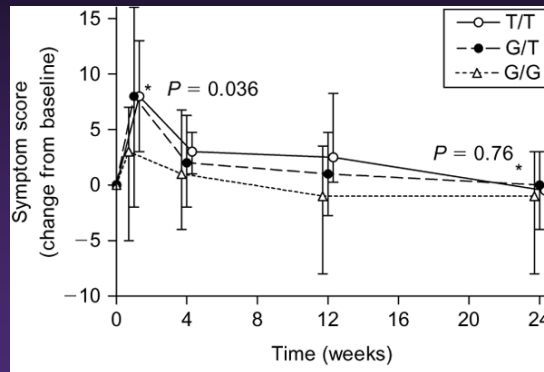
- ACTG study in 89 (57%) European-Americans; 50 (32%) African-Americans; and 15 (10%) Hispanics¹
- CYP2B6 TT genotype more common in AA (20%) than EA (3%) and associated with higher EFV AUC (p 0.0001)



¹Haas et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS. 2004

CNS symptoms on EFV and CYP2B6 variation

- CNS symptoms in the CYP2B6 TT patients were higher at week 1 of therapy ($p = 0.036$)¹

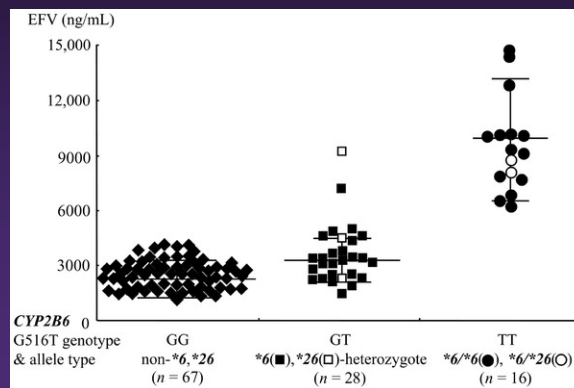


- But no relationship between CYP2B6 TT and virologic response/resistance²

¹Haas et al. Pharmacogenetics of efavirenz and central nervous system side effects. AIDS. 2004; ²Haas et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir. JID 2005

Trial of reducing EFV dose in TT patients

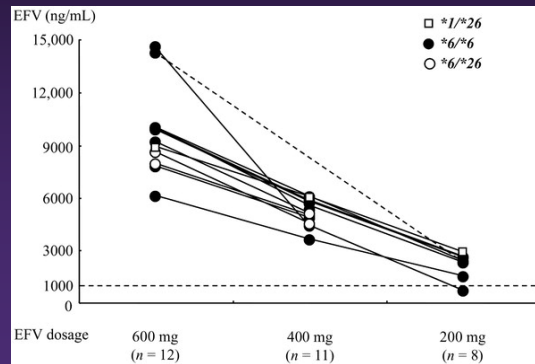
- Looked at CYP2B6 516 genotype of 111 Japanese patients and saw same trend



¹Gatanaga et al. Successful efavirenz dose reduction in HIV Type1-infected individuals with cytochrome p450 2B6 *6 and *26. CID November 1, 2007

Reducing EFV dose for CYP2B6 TTs

- Reduced dose to 400mg or 200mg of 12 of those treated TT patients (also started 5 naives on 400mg)
 - All remained undetectable and levels >minimum target [].
 - All reported improvement in CNS symptoms



¹Gatanaga et al. Successful efavirenz dose reduction in HIV Type1-infected individuals with cytochrome p450 2B6 *6 and *26. CID November 1, 2007

Case (continued)



- You send 10 strands of pt's hair to Gandhi project and find that EFV levels exceed those of 90% in her study¹ (CYP2B6 516 indeed TT)
- Reduce dose of EFV to 400mg po qhs
- New regimen of Epzicom 1 tab po qhs and EFV 400mg po qhs → good immunologic and virologic response, side effect free
- **Question:** Do men and women do equally as well on therapy, besides the side effects?

¹Gandhi et al. Hair levels of antiretrovirals are an independent predictor of virologic success (submitted, December 2007)

ARS: Do men and women have different clinical responses on therapy?

1. Yes, women have better virologic responses than men
2. Yes, women have worse virologic responses than men
3. Yes, women have lower rates of survival than men
4. No, men and women do equally as well on antiretroviral therapy in terms of virologic and clinical responses

Virologic, immunologic responses similar



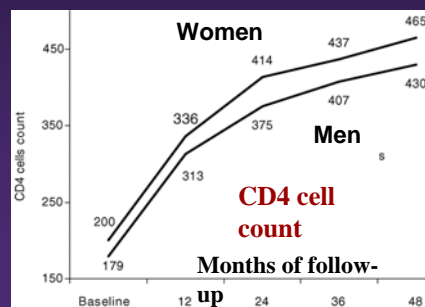
• Virologic responses

- Baseline viral loads lower in women, but responses similar¹⁻³



• Immunologic responses

- Higher baseline CD4 counts in women, but parallel increases²⁻⁶



¹Kuyper. JAIDS 2004; ²Moore A. JAIDS 2003; ³Nicastrì. AIDS 2005; ⁴Finkel. AIDS 2003; ⁵Bersoff-Matcha. CROI 2006; paper 887; ⁶Nicastrì AIDS 2005

Progression to new AIDS diagnoses or death same in both sexes if adjusted

Follow-up	Cohort
~2 yrs	Johns Hopkins clinic cohort ^{1,2}
3 yrs	Swiss HIV Cohort Study ²
4 yrs	London clinic cohort, 1 st HAART on ³
5.4 yrs	Italian Antiretroviral Treatment Group, 1 st HAART onwards ⁴ ; CASCADE (22 cohorts) ⁵
6-7 yrs	EuroSIDA cohort, 1 st HAART on ⁶ ; Spanish hospital network, '97-'04 ⁷

¹Sterling. AIDS 2001; ²Junghans. AIDS 1999; ³Moore A. JAIDS 2002; ⁴Nicastrì. AIDS 2005; ⁵CASCADE. Lancet 2003; ⁶Moore A. JAIDS 2003; ⁷Perez-Hoyos. J Women's Health 2007

Reasons for mortality in HIV patients may differ by sex

- Comparison study of causes of mortality in Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS)¹
- Higher rates accident or injury-related mortality in women vs men (2.96 vs. 0.79/1000)
- Risk factors for death varied by gender

WOMEN

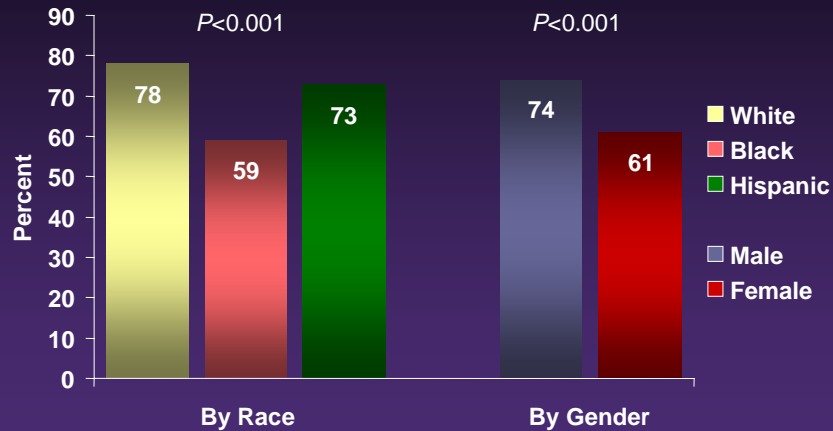
- Decreased CD4
- Unemployment
- Higher EtOH use
- IVDU

MEN

- Higher education
- Depression
- Higher # of sex partners

¹Hessol N. Mortality among participants in the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study. CID 2007

Disparities usually explained by access: Use of HAART in the USA by Race and Gender



Cunningham WE et al. *JAIDS* 2000; McNaughten et al. *JAIDS*. 2003; Pence. The Influence of Psychosocial Characteristics and Race/Ethnicity on the Use, Duration, and Success of Antiretroviral Therapy. *JAIDS* 2007

Community beliefs about HIV

500 African Americans surveyed by phone

(51% high school and 49% some college or more; 53.4% <\$35,000 and 46.6% >\$35,000 annual income)

- Institutions are trying to stop HIV 75.4 %
- AIDS is a form of genocide 15.2 %
- AIDS was produced in a government lab 26.6 %
- People who take new meds are guinea pigs 43.6 %
- Cure for AIDS exists, but withheld from poor 53.4 %
- Information about AIDS is being withheld 58.8 %

Bogart LM et al. Are HIV/AIDS conspiracy beliefs a barrier to HIV prevention among African Americans? *JAIDS* 2005 Feb 1;38(2):213-8

Case (continued)



- The patient feels well. Had been counseled on EFV and teratogenicity prior to starting new regimen and stated she had no intention of pregnancy
- However, new boyfriend (HIV-negative) tells pt that he wants to have baby with her and pt agrees

Special preconception points with serodiscordant couples

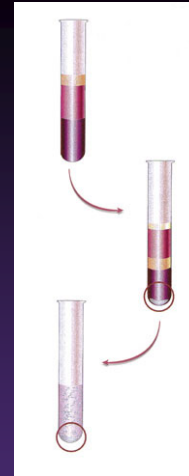


- Surveys indicate 25-33% of HIV-positive women desire childbearing¹⁻³ (63% in Nigeria⁴)
- Preconception labs:
 - Rubella, Varicella immunity screen
 - Toxo IgG
 - Hep A, B, C serology
 - Hb electrophoresis
- Preconception vaccines
 - MMR if CD4 >200
 - Pneumovax, Tdap, Influenza
 - Hepatitis A/B
- Prenatal vitamins (400-800mcg folate)
 - Increase folate to 4-10mg a day if on folate antagonist (TMP-SMZ)
- Counseling
 - Domestic violence, drug/EtOH abuse, supports, milk bank/formula

Chen. Family Plan Perspect 2001; Stanwood. Contraception 2007; Ogilvie. AIDS 2007; ⁴Oladapo. J Natl Med Assoc 2005

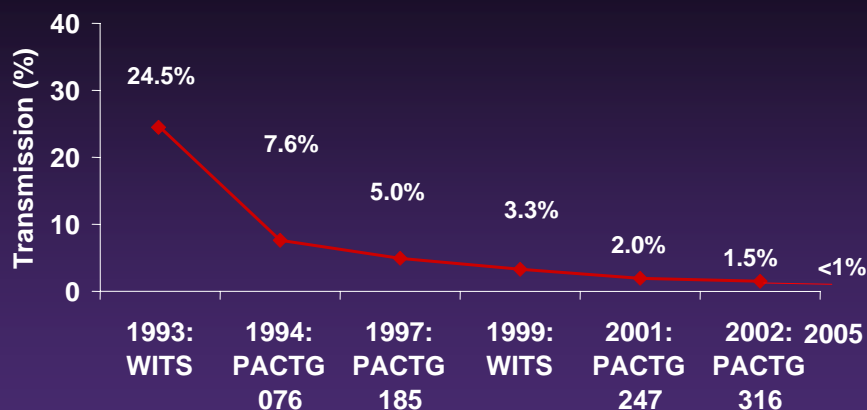
Insemination options

- HIV+ ♀ with HIV- ♂: Assisted insemination (?role for PREP/PEP with timed coitus)
- HIV- ♀ with HIV+ ♂:
 - Wash sperm (spermatozoa lack CD4/CCR5/CXCR4, so HIV RNA in non-sperm cells/fluid) x 2 after gradient centrifugation (>99.99% HIV free¹)
 - Controversy about testing for HIV PCR after washing² (no seroconversions³⁻⁵)
 - IUI, IVF or intracytoplasmic sperm injection
 - CA Senate law bill allows sperm washing in CA as of 1/08⁶



¹Politch. *Fert Steril.* 2004; ²Pasquier. *J Virol Methods* 2006; ³Sauer *Human Reprod* 2007; ⁴Savasi. *Human Reprod.* 2007; ⁵Bujan *AIDS* 2007; ⁶California Senate Approves Bill That Would Allow HIV-Positive Men to Have Sperm Washed, Used for Fertility Treatments. *Kaiser Daily HIV/AIDS Report*

Mother-to-Child Transmission in the US Over Time



Decline due to: —More HIV testing in prenatal visits
 —Increase in use of HAART by HIV+ women
 —Increase in elective C-section by HIV+ women

ARS: Can this patient remain on her same regimen? She is happy on it

1. No, the efavirenz should be switched to nelfinavir
2. No, the abacavir should be switched to zidovudine
3. Yes, we finally found a regimen that works!
4. No, the efavirenz should be switched to a non-nelfinavir PI

Which ARVs NOT to use in pregnancy



- Efavirenz - teratogen
 - Retrospective Antiretroviral Pregnancy Registry reports
 - 4 Cases human infants with significant CNS defects with 1st trimester exposure to EFV (meningomyelocele, Dandy-Walker)
- ddI/d4T combination (lactic acidosis, hepatic)
- NVP if CD4 >250
- Nelfinavir with EMS (ethylmethyl sulfonate) contamination²

Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Nov 2 2007. aidsinfo.nih.gov; DHHS Panel on Antiretroviral Therapy Guidelines for Adults and Adolescents-Notice on Nelfinavir FDA- Pfizer Letter 9/13/2007

ARVs and Pregnancy – Start 2nd trimester

	NRTI/ NtRTI	NNRTI	PI	FI/Other
Recommended	AZT 3TC	NVP ¹	LPV/r (3 rd trim: increase dose)*	
Alternate	ddl, FTC, d4T, ABC		IDV RTV SQV(sgc)/r	
Not recommended	ddC ²	EFV ³ DLV ⁴	NFV ⁷	
Insufficient data	TFV		FPV, ATV ⁵ , Darunavir, Tipranavir	T-20, Mavariroc, Raltegravir

¹Not with CD4 counts < 250/mm³ due to liver toxicity.

²Rodent studies show potential for teratogenicity and developmental toxicity.

³ Primate/human studies show teratogenicity.

⁴Rodent data shows potential for teratogenicity and carcinogenicity.

⁵Theoretical concern for hyperbilirubinemia' accumulating data on safety

⁶Increase dose from 2 tabs po bid to 3 tabs po bid (Maltrex) in 3rd trimester; ⁷EMS as preservative

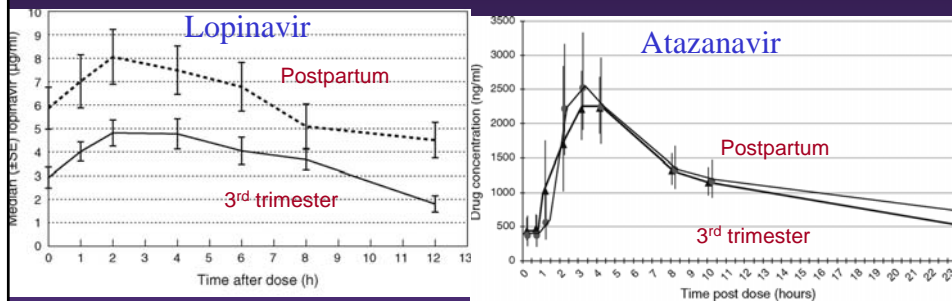
November 2007 DHHS Guidelines.
Available at <http://AIDSinfo.nih.gov>

ARS: You switch patient to ABC/3TC/Kaletra. Can she stay on same dose throughout pregnancy?

1. No, the abacavir should be increased during the 3rd trimester
2. No, the Kaletra dose should be decreased during the 3rd trimester
3. Yes
4. No, Kaletra dose should be increased during the 3rd trimester

Remember dosing changes

- Kaletra – Increase to 3 tabs po bid during 3rd trimester (from 2 tabs bid) due to PK changes¹
- Atazanavir – No PK differences during 3rd trimester², so no dose adjustment



¹Stek AIDS 2006; ²Ripamonti. AIDS 2007

Current USPHS Guidelines for Prevention of Mother-to-child Transmission

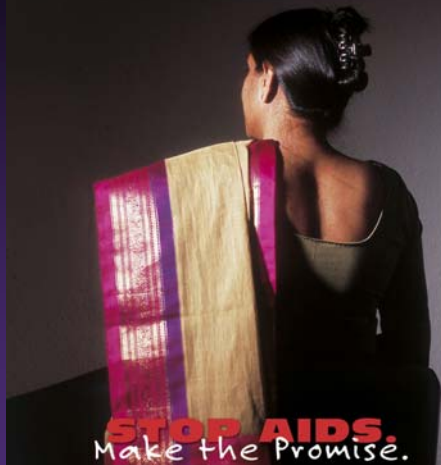
- **Mother's plasma HIV-1 RNA >1,000 copies/mL**
 - Combination highly active antiretroviral therapy (HAART)
 - Elective C-section if HIV-1 RNA >1,000 copies/mL near delivery
- **Maternal plasma HIV-1 RNA <1,000 copies/mL**
 - HAART or use of AZT alone
- **No treatment prior to labor**
 - During birth and after birth (for baby) of regimens of AZT, AZT/3TC, nevirapine, or AZT/nevirapine, single dose of Truvada® may decrease NVP resistance²
- **No treatment prior to or during labor**
 - Infant prophylaxis for 6 weeks with AZT after birth
 - Some clinicians use combination therapy (HAART)



¹Public Health Service Task Force Recommendations; November 2007. Available at: <http://AIDSInfo.nih.gov>; ²Chi et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. Lancet 2007.

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