

Management of HIV-Infected Women

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Objectives

- Provide appropriate support and counseling to HIV-infected women who desire to conceive
- Differentiate important characteristics of HIV-infected women and men in terms of the selection of optimal ARV therapy
- Apply the US Department of Health and Human Services perinatal treatment guidelines when counseling and caring for HIV-infected women of childbearing potential
- Select the preferred antiretroviral agents for use before and during pregnancy

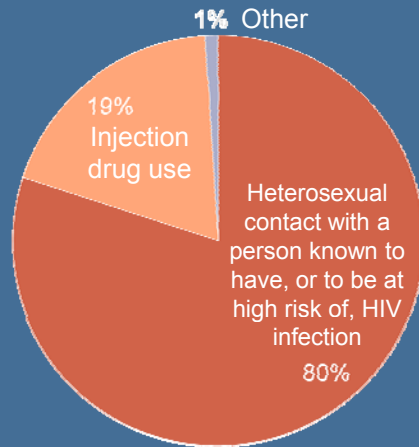
HIV Prevalence Among Women in the US Is Increasing

- 1992: 14% of patients with AIDS were women¹
- 2005: 23% were women²
- 2001-2005: transmission ↓ thru IDU and ↑ through high-risk heterosexual contact
- 90% of the 6726 children with HIV/AIDS were exposed perinatally

¹CDC. HIV/AIDS Surveillance Report 1998;10(No. 2):1-43. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/past.htm#surveillance>. Accessed February 13, 2008.

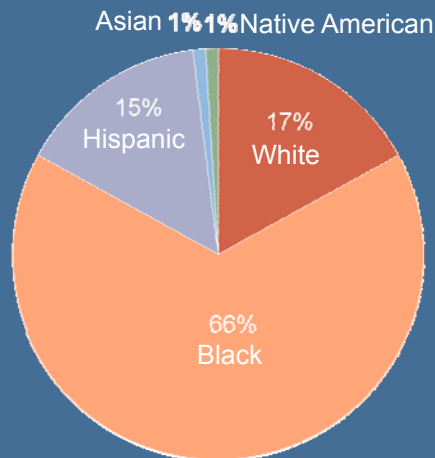
²CDC. Cases of HIV infection and AIDS in the United States and Dependent Areas, 2005. Revised June 2007. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2005report/default.htm>. Accessed February 20, 2008.

HIV/AIDS Cases Among Women by Transmission Category (33 States, 2005)



Adapted from HIV/AIDS Surveillance in Women. <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/women/index.htm>.

HIV/AIDS Cases Among Women by Race (33 States, 2005, n = 9708)

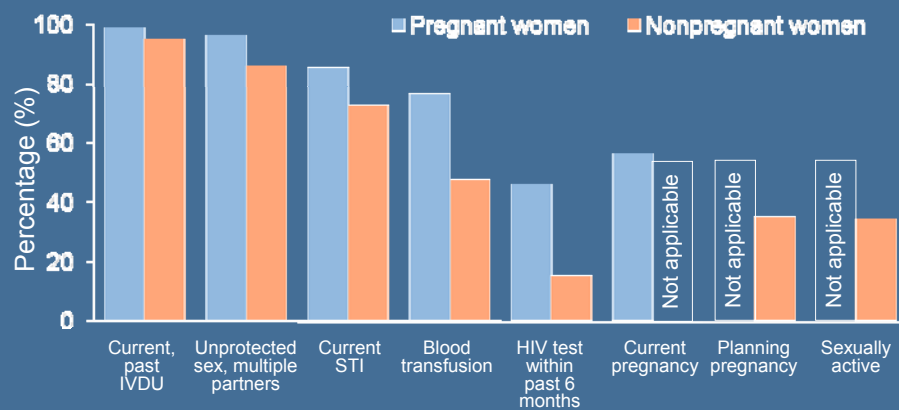


Adapted from HIV/AIDS Surveillance in Women. <http://www.cdc.gov/hiv/topics/surveillance/resources/slides/women/index.htm>.

HIV Screening Strategies for Women

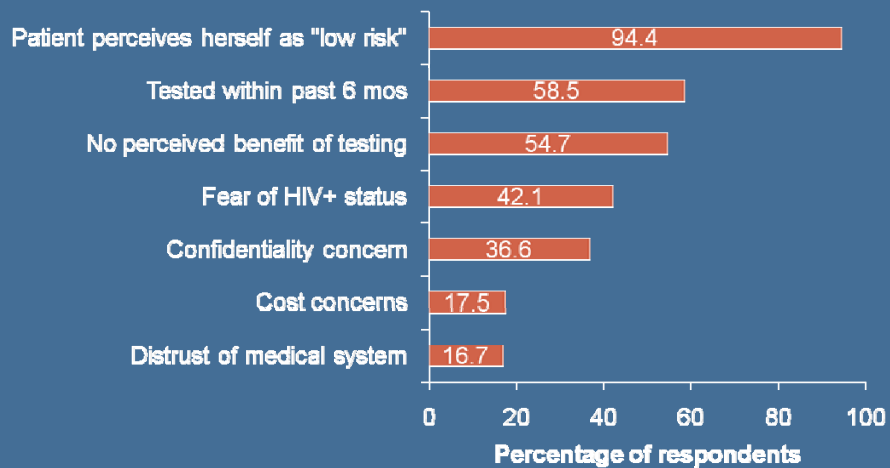
- OB/GYN is often first to diagnose HIV through STD testing, prenatal screening, or testing during delivery
- “Opt-out”: universal testing with patient notification and right of refusal
- “Opt-in”: voluntary testing with pretest counseling regarding risks and benefits

When OB/GYNs Recommend HIV Testing



Gray et al. *Obstet Gynecol.* 2007;110(5):1019-1026.

Why Patients Decline HIV Testing



Gray et al. *Obstet Gynecol.* 2007;110(5):1019-1026.

Additional Screening of HIV+ Women

- Sexually transmitted infections¹
- Risk behavior¹
- Domestic violence²
- Cervical dysplasia/cancer
 - Pap smears at initial screening and 6 months later; if results are negative, repeat annually¹
- Depression

¹Aaron and Levine. *AIDS Read.* 2005;15(8):420-423, 426-428.

²Baeten et al. *Guide to the Clinical Care of Women With HIV/AIDS.* 2005. Chapter 3.

Considerations for HIV+ Women

- HIV Therapy for Women of Childbearing Age
- Effective Contraception

Initial Treatment Recommendations Are the Same for Men AND Women, Except...

NNRTI Option

•efavirenz^a

OR

PI Options

- atazanavir + ritonavir
- fosamprenavir + ritonavir (BID)
- lopinavir/ritonavir (BID)

+

NRTI Options

- tenofovir + emtricitabine^b
- abacavir^c + lamivudine^b

^aAvoid for pregnant women and women who may become pregnant.

^bEmtricitabine can be used in place of lamivudine and vice versa.

^cFor patients who test negative for HLA B*5701.

DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, 2008. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

Pregnancy and HIV Infection

- Most HIV⁺ women are of reproductive age¹
- 50% of pregnancies in the US are unintended²
- Pregnancy rate 7.4/100 person-years for HIV⁺ women and 15.2/100 person-years in HIV⁻ women ($P < .0001$)³
- In HAART era⁴
 - 150% ↑ in live birth rate among HIV⁺ women
 - 5% ↑ among HIV⁻ women

¹Aberg et al. *Clin Infect Dis*. 2004;39(5):609-629.

²Finer and Henshaw. *Perspect Sex Reprod Health*. 2006;38(2):90-96.

³Massad et al. *AIDS*. 2004;18(2):281-286.

⁴Sharma et al. *Am J Obstet Gynecol*. 2007;196(6):541.e1-541.e6.

Preventing Pregnancy for HIV⁺ Women

- Condoms, when used correctly: can prevent HIV transmission, effective for pregnancy prevention¹
- Intrauterine devices (IUDs): complication rates similar in HIV⁺ and HIV⁻ women²
- Diaphragm, tubal sterilization
- Combined hormonal contraceptives, progestin-only hormonal contraceptives
- Nonoxynol-9 spermicides may increase genital ulceration, HIV transmission³

¹Aaron and Levine. *AIDS Read*. 2005;15(8):420-423,426-428. ²Sinei et al. *Lancet*. 1998; 351(9111):1238-1241. ³Kreiss et al. *JAMA*. 1992;268(4):477-482.

ARV & Hormonal Contraceptive Interactions

Antiretroviral	Interaction	Recommendation
Atazanavir (ATV)	EE, AUC ↑ 48% NE, AUC ↑ 110%	Use lowest effective dose or alternative methods
Fosamprenavir (FPV) ^a	NE, EE ↑ with APV APV ↓ 20%	Do not coadminister
Darunavir + ritonavir (DRV/r)	EE, potentially ↓	Use alternative or additional contraception
Efavirenz	EE, ↑ 37%	Use alternative or additional contraception
Indinavir	EE, ↑ 24% NE, ↑ 26%	No dose adjustment needed
Lopinavir + ritonavir (LPV/r)	EE, ↓ 42%	Use alternative or additional contraception
Nelfinavir (NFV)	EE, ↓ 47% NE, ↓ 18%	Use alternative or additional contraception
Nevirapine	EE, ↓ 20%	Use alternative or additional contraception
Ritonavir (RTV)	EE, ↓ 40%	Use alternative or additional contraception
Saquinavir (SQV)	No data available	...
Tipranavir + ritonavir (TPV/r)	EE, AUC, C _{max} ↓ 50%	↑ risk of rash; monitor for estrogen deficiency
Maraviroc (MVC)	None	Safe to use in combination

There is no clear interaction between hormonal contraceptives and NRTIs.

EE, ethinyl estradiol; NE, norethindrone; AUC, area under the curve

^aFPV is the phosphate ester prodrug of amprenavir (APV)

DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, 2008. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

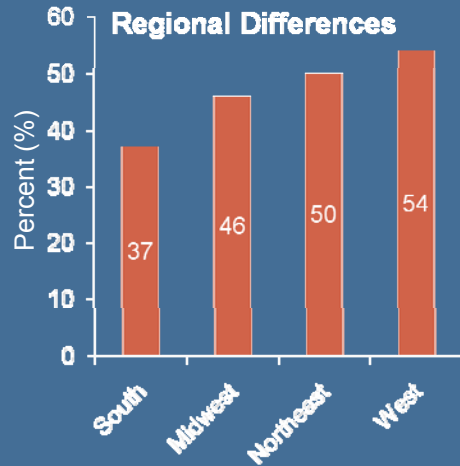
Antiretroviral Therapy:

Differences Between Women and Men

Essential Patient-Provider Discussions

Differential Effects of HIV Medication

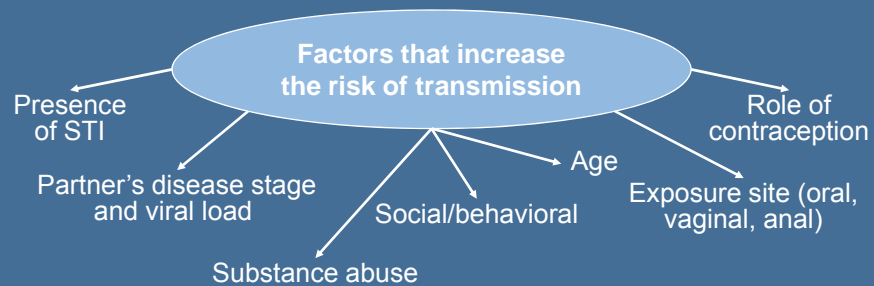
- 55% of women have never discussed with their provider how HIV medications may affect them differently than men
- Of women who DID discuss this, 96% said their provider answered their questions satisfactorily and 95% said they felt comfortable with the discussion

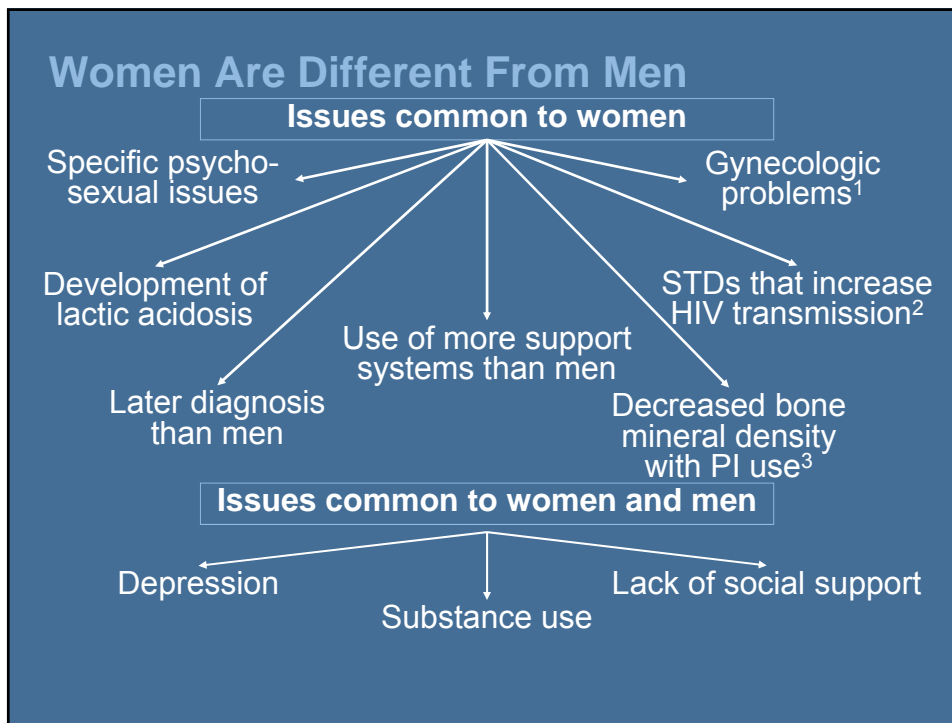


Women Living Positive Survey. http://www.thewellproject.org/en_US/Tools/PressReleases/WS_Women_Brochure_FINAL.pdf. Accessed February 13, 2008.

Risk Factors for HIV Transmission

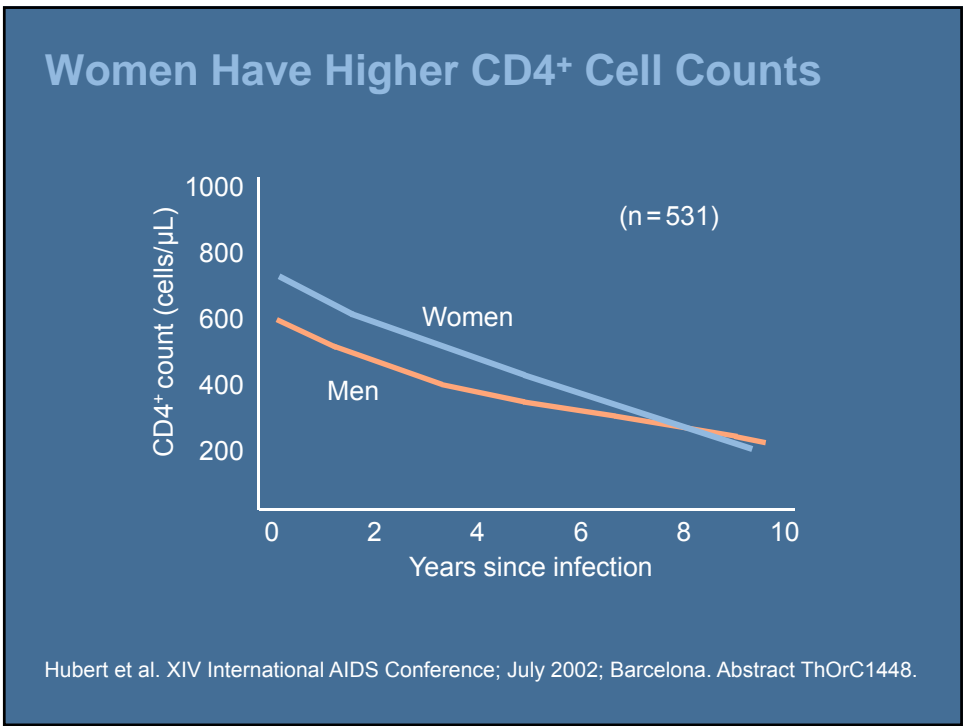
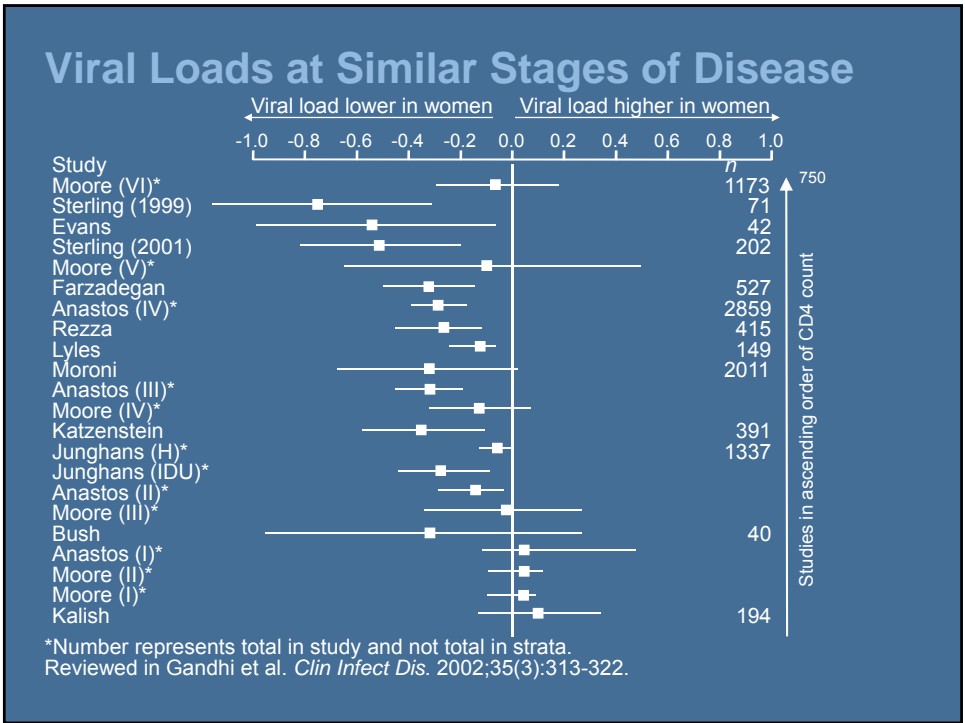
Women are more susceptible than men to contracting HIV during unprotected heterosexual intercourse



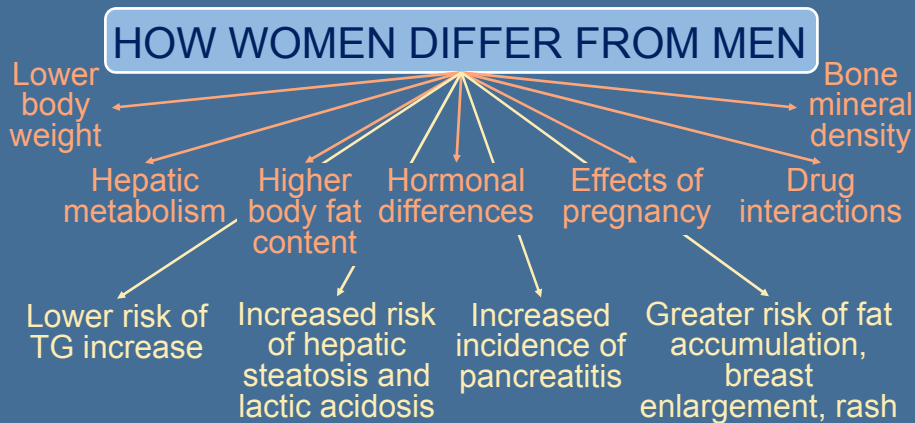


Biologic Differences: *Compared to Men, Women Have...*

- 2x-6x lower viral load in early disease; the difference disappears within 5-15 years
- Higher CD4⁺ cell counts earlier in disease process
- But women have a similar disease progression rate



Factors Affecting Treatment



Pharmacokinetic Differences: Compared to Men, Women...

- Saquinavir¹: 50% ↓ clearance
- Tipranavir/r²: ↑ plasma concentrations
- Darunavir³: ↑ AUC
- Ritonavir³: ↑ AUC
- Nevirapine⁴: ↑ drug levels
- Zidovudine, lamivudine⁵: ↑ intercellular concentrations

¹Dolan et al. 14th CROI; February 25-28, 2007; Los Angeles, CA. Abstract 777.

²Walmsley et al. 4th International AIDS Society Conference on HIV Pathogenesis and Treatment; July 22-25, 2007; Sydney, Australia. Abstract MOPDB04.

³Sekar et al. 9th International Workshop on Clinical Pharmacology of HIV Therapy; April 7-9, 2008; New Orleans, LA. Abstract O16.

⁴Clark. *Drug Saf.* 2005;28(12):1075-1083.

⁵Anderson et al. *AIDS.* 2003;17(15):2159-2168.

Tolerability Differences: Compared to Men, Women...

- Darunavir/r¹: ↑ nausea, ↑ headache, ↓ fatigue
- Didanosine²: ↑ pancreatitis
- Fosamprenavir³: ↑ upper respiratory tract infections, ↑ headache, ↓ diarrhea
- Nelfinavir⁴: ↓ diarrhea
- Nevirapine⁵: ↑ hepatotoxicity
- Ritonavir⁶: ↑ peak concentration
↑ abdominal pain, nausea, vomiting

¹Collier et al. 46th ICAAC; September 27-30, 2006; San Francisco, CA. Abstract H-1396.

²Moore et al. *AIDS*. 2001;15(5):617-620.

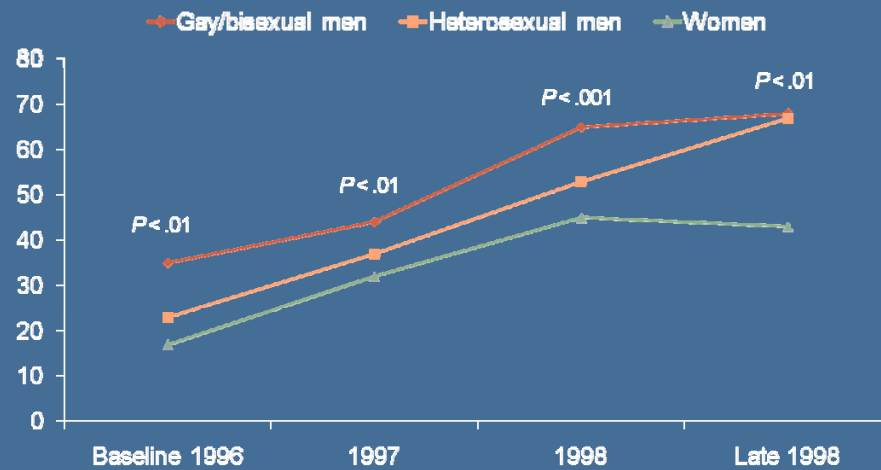
³Currier et al. 46th ICAAC; September 27-30, 2006; San Francisco, CA. Abstract A-2593.

⁴Gerstein et al. National Conference on Women and HIV; May 4-7, 1997; Los Angeles, CA. Abstract 304.1.

⁵Bersoff-Matcha et al. *Clin Infect Dis*. 2001;32(1):124-129.

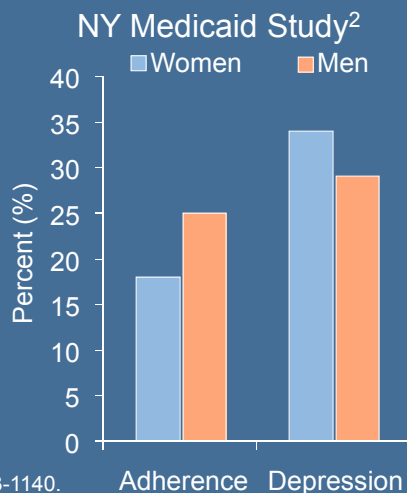
⁶Gatti et al. 39th ICAAC; September 26-29, 1999; San Francisco, CA. Abstract 2210.

Women Have More Limited Access to HIV Healthcare Than Men



Depression Worsens HIV Outcomes in Women: Results of 2 Studies

- WIHS Study¹
- AIDS-related mortality rates significantly higher among women with depression
- Women with chronic depression 2.3 times more likely to die than those without
- Depression risk increased with late-stage disease, HIV symptoms, age 30-39 years
- Adherence not associated with mortality rates



WIHS, Women's Interagency HIV Study

¹Cook et al. *Am J Public Health*. 2004;94(7):1133-1140.

²Turner et al. *J Gen Intern Med*. 2003;18(4):248-257.

Issues and Responses for HIV+ Women

Common Issues	Potential Responses
Lack of trust	Nonjudgmental attitude Female staff
Low self-esteem	Respectfulness Empowerment
Caregiver priority	Child care One-stop-shop models
Domestic violence	Counseling Legal aid
Mental illness	Integrated medical healthcare
Complex personal situations	Multiservice coordination
Stigma	Social support groups

Reviewed by Squires. *Gen Med*. 2007;4(4):294-307. Adapted from HRSA HIV/AIDS Bureau. A guide to the clinical care of women with HIV/AIDS, 2005 edition. <http://hab.hrsa.gov/publications/womencare05/>.

Conception in HIV infected women

The Risks of Reproduction *Transmission to a Partner*

In a study of 415 discordant heterosexual couples

- 23% of HIV⁻ partners seroconverted
- In this study, transmission rates from men to women = transmission rates from women to men (~11.8/110 person-years)
- No transmissions < 1500 copies/mL;
23 transmissions/100 py > 50,000 copies/mL
 - Each log₁₀ increment in viral load = 2.45-fold increased risk of transmission (95% CI 1.85–3.26)

Quinn et al. 7th CROI; January 30-February 4, 2000; San Francisco, CA. Abstract 193.
Quinn et al. *NEJM*. 2000;34(13):921-929.

The Risks of Reproduction *Transmission To a Newborn*

Intrapartum transmission is correlated with¹

- Late (3rd trimester) access to care ($P < .001$)
- HIV RNA > 1000 copies/mL close to delivery ($P < .001$)
NOTE: 0.07% transmission with RNA < 1000 copies/mL
- Preterm (before wk 37) delivery ($P = .03$)

Transmission during breastfeeding²

- 999 (23%) of 4343 breastfed children became infected
 - 58% acquired infection before 4 wks of age
 - 42% acquired infection after 4 wks of age

¹Warszawski et al. 12th CROI; February 22-25, 2005; Boston, MA. Abstract 97.

²Read et al. 10th CROI; February 10-14, 2003; Boston, MA. Abstract 97.

Assisted Reproduction Strategies for Reducing Risk of Transmission

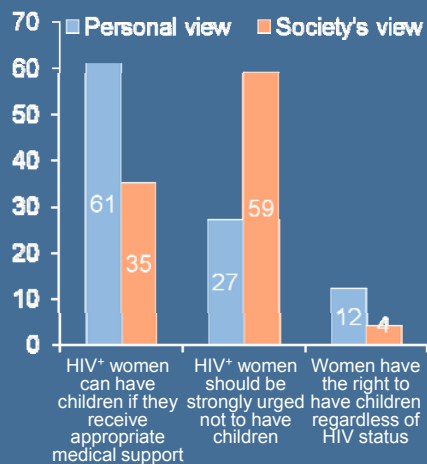
- For any discordant couple: counsel about using donor sperm, considering adoption, or not having children¹
- HIV⁺ woman, HIV⁻ man: homologous insemination
- HIV⁻ woman, HIV⁺ man: semen washing, IVF/ICSI
 - Antiretroviral treatment
 - Semen analysis (hypogonadism in HIV⁺ men with ↓ serum testosterone; abnormal semen analyses)
 - Screen for genital tract infections
 - Timed intercourse (ovulation predictors)
 - Peri-exposure prophylaxis

¹Ethics Committee of the American Society for Reproductive Medicine. *Fertil Steril.* 2002;77(2):218-222.

Essential Patient-Provider Discussions

Treatment Options During Pregnancy

- 57% of women who are or were pregnant did not discuss pregnancy-appropriate HIV treatments before conception
- Most HIV-infected women believe they can have children if they receive appropriate medical care



Women Living Positive Survey. http://www.thewellproject.org/en_US/Tools/PressReleases/WS_Women_Brochure_FINAL.pdf. Accessed February 13, 2008.

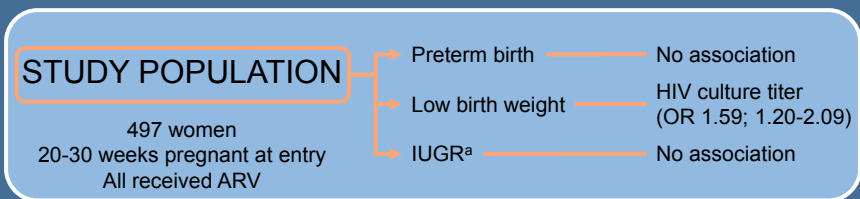
Preconception Counseling for HIV+ Women

- Impact of HIV on pregnancy, pregnancy on HIV progression, ARV treatment on pregnancy
- Maternal risk factors: drug/alcohol use, advanced maternal age, comorbid conditions
- General pregnancy issues
- Guardianship issues
- Risk, prevention of perinatal transmission
- Discussion of assisted reproductive technologies with the HIV-treating provider and the OB/GYN

Adapted from: Anderson J. A Guide to the Clinical Care of Women With HIV/AIDS. 2005. Chapter VII

Impact of HIV on Pregnancy

- Fertility: HIV+ women have lower likelihood of pregnancy with longer duration of infection^{1,2}
- Pregnancy outcome: PACTG 185 trial evaluated the effect of CD4+ cell count, viral load, HIV culture titer on pregnancy by using multivariate analysis³



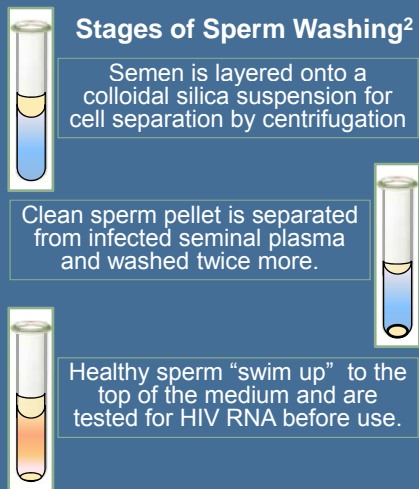
^aBirth weight below 10th percentile for gestational age compared with large database.
¹Lee et al. *Am J Epidemiol.* 2000;151:1020-1028.
²Anderson. *A Guide to the Clinical Care of Women With HIV/AIDS.* 2005. Chapter VI.
³Lambert et al. *AIDS.* 2000;14:1389-1399.

ART for HIV-Serodiscordant Couples

Centers Offering ART to HIV-Discordant Couples¹

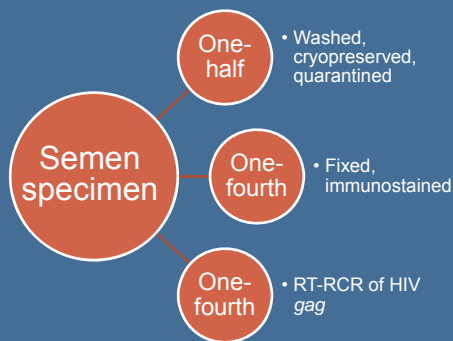
- Columbia University, New York, NY
- Eastern Virginia Medical College, Norfolk, VA
- Albert Einstein Medical College, Bronx, NY
- Washington University, St. Louis, MO
- University of Colorado, Denver, CO
- UMDNJ-New Jersey Medical Center, Newark, NJ

Stages of Sperm Washing²



¹Adapted from Sauer. 2005. http://depts.washington.edu/cfas/WHIN/2005_sanjuan/Sauer.ppt
²Thornton et al. *Top HIV Med.* 2004;12(2):61-67.

Example Protocol: Bedford Research Foundation



- Cryopreserved sperm from 2 HIV- specimens shipped to fertility treatment center
- Pregnancy attempted by IVF or oligospermia cup (NOT IUI)
- Woman tested for HIV at 3 wks, 3 mos, and 6 mos after insemination, regardless of pregnancy status

Kiessling et al. Society of Assisted Reproductive Technology Prize Paper. American Society for Reproductive Medicine. Washington, DC. October, 2007.

Reproduction by Discordant Couples

Outcome	Intrauterine insemination	In vitro fertilization/ intracytoplasmic sperm injection
Couples (n)	581	160
Number of cycles (n)	2400	283
Pregnancies (n)	456	65
Pregnancy rate per cycle (%)	19	23
Multiple pregnancy rate (%)	4	10
Maternal seroconversion (n)	0	0
Offspring seroconversion (n)	0	0

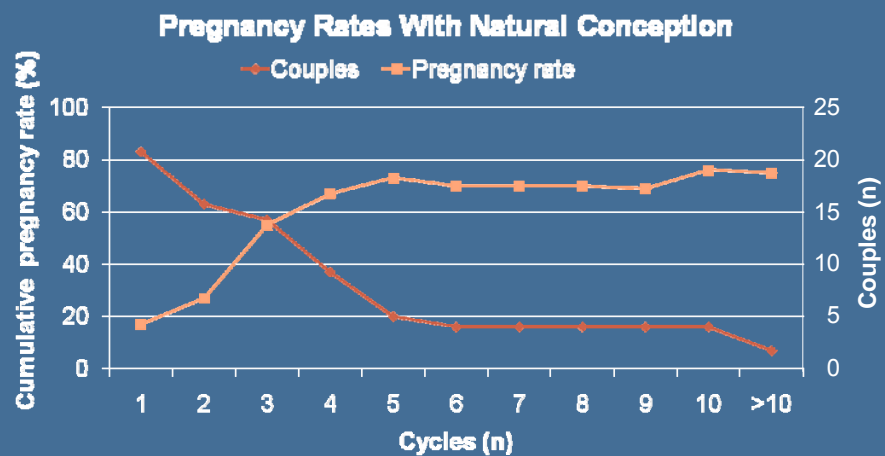
Savasi et al. *Hum Reprod.* 2007;22(3):772-777.

Results of Assisted Reproduction

Procedures	IUI	IVF	ICSI	FET	Total	P value
Couples	853	76	262	40	1231	
Cycles	2840	107	394	49	3390	
Pregnancy per cycle	15.1	29.0	30.6	20.4	17.5	< .001
Multiple pregnancy rate	4.9	17.2	20.8	20.0	9.12	< .01
Delivery per cycle	11.5	38.2	43.1	25.0	41.9	< .05
Pregnancy per couple	42.7	26.3	21.0	17.5	30.9	> .05
Delivery per couple	35.1	26.3	21.0	17.5	30.9	< .01

Bujan et al. *AIDS*. 2007;21(14):1909-1914.

Timed Intercourse With Pre-Exposure Prophylaxis



Vernazza et al. 4th IAS; July 22-25, 2007; Sydney, Australia. Abstract MOPDC01.

Unassisted Conception by HIV-Discordant Couples

76 natural conceptions, 68 newborns

52 couples with 1 pregnancy
6 couples with 2 consecutive pregnancies
4 couples with 3 consecutive pregnancies

9 fetal deaths
7 in 30 pregnancies among HIV⁺ women
2 in 42 pregnancies among HIV⁻ women
OR=6.1; 95% CI, 1.02-46.68; *P*=.02

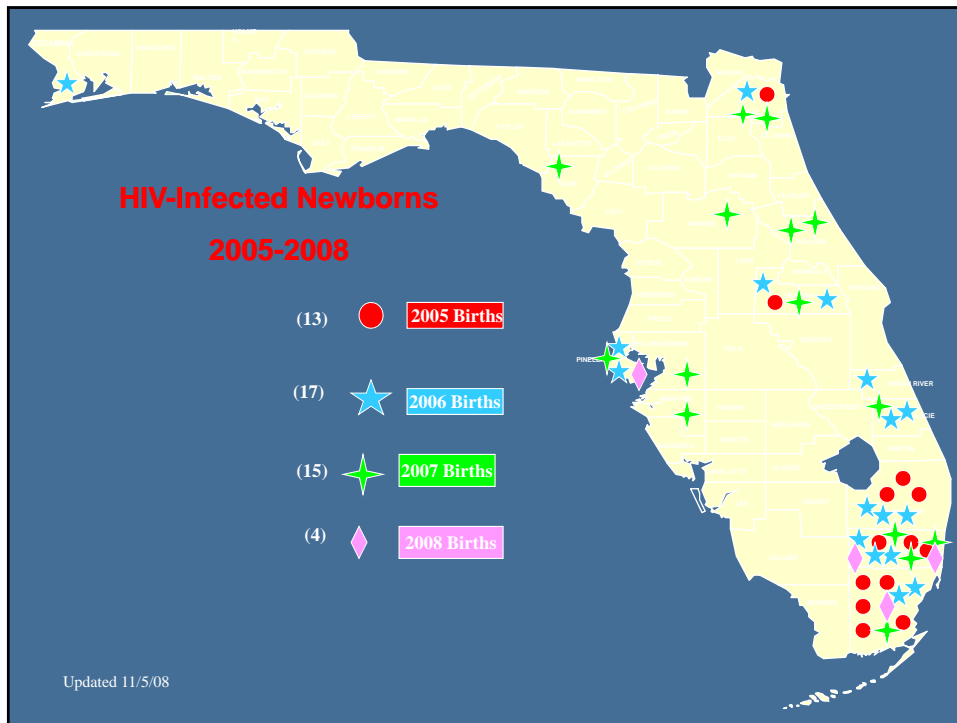
HIV transmission
sexual: 0 in 76 pregnancies
maternofetal: 1 in 23 pregnancies among HIV⁺ women

Barreiro et al. *J Acquir Immune Defic Syndr.* 2006;43(3):324-326

Reduce Risk of Perinatal Transmission

- Antiretroviral therapy recommended for all pregnant women
- Reduce HIV viral load to < 1000 copies/mL
- Include zidovudine, if possible
- Recommend 3-part zidovudine prophylaxis regimen to reduce perinatal transmission for all pregnant women with HIV infection, regardless of viral load

DHHS guidelines, November 2, 2007. Available at <http://AIDSinfo.nih.gov>.



Antiretroviral Therapy and Pregnancy

Hepatitis Treatment in Pregnancy

- Pegylated interferon-alfa
 - Is not recommended for pregnant women¹
 - Is contraindicated when combined with ribavirin for pregnant women or for men whose partners are pregnant²
- Ribavirin is contraindicated during pregnancy²
 - May persist in non-plasma compartments for 6 months³
 - If either partner has used ribavirin, extreme care must be taken to avoid pregnancy during therapy and for 6 months after³

¹DHHS guidelines, November 2, 2007. Available at <http://AIDSinfo.nih.gov>.

²PEGASIS package insert. <http://www.fda.gov/cder/foi/label/2007/103964s5120lbl.pdf>

³COPEGUS package insert. <http://www.fda.gov/cder/foi/label/2007/021511s014lbl.pdf>

Protecting Infants From Hepatitis

- “Infants born to women with hepatitis B infection should receive hepatitis B immune globulin (HBIG) and initiate the three-dose hepatitis B vaccination series within 12 hours of birth.”
- “Infants born to women with HCV/HIV co-infection should be evaluated for HCV infection by HCV RNA testing between 2 and 6 months of age and/or HCV antibody testing after 15 months of age.”

DHHS guidelines, November 2, 2007. Available at <http://AIDSinfo.nih.gov>.

Antiretroviral Treatment for Pregnant Women

- For women not already being treated with ARVs, consider delaying treatment until 10 to 12 weeks' gestation
- For women already being treated with ARVs, consider continuing therapy, although effects of ARVs on fetus in first trimester are uncertain
- Perform resistance testing before beginning ARV therapy or prophylaxis and for women on ARV therapy with detectable HIV RNA levels

DHHS guidelines, November 2, 2007. Available at <http://AIDSinfo.nih.gov>

FDA Pregnancy Categories

A	Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B	Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C	Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D	Positive for human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X	Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

DHHS. <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed February 21, 2008.

ART Safety During Pregnancy

Class	FDA Category		
	B	C	D
NRTIs	Didanosine Emtricitabine Tenofovir	Abacavir Lamivudine Stavudine Zidovudine	
NNRTIs	Etravirine Nevirapine	Delavirdine	Efavirenz
Protease inhibitors	Atazanavir Darunavir Nelfinavir Ritonavir Saquinavir	Amprenavir Fosamprenavir Indinavir Lopinavir/ritonavir Tipranavir	
Entry inhibitors	Enfuvirtide Maraviroc		
Integrase inhibitor		Raltegravir	

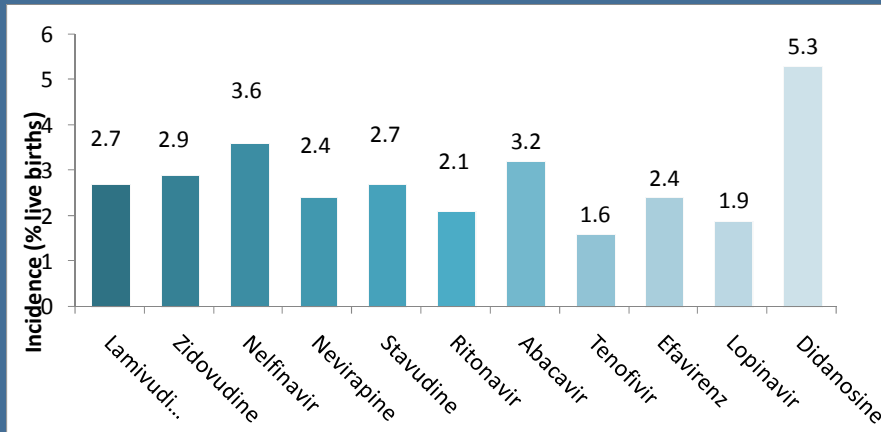
DHHS. <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed February 21, 2008.

Antiretroviral Agents and Pregnancy

	NRTI	NNRTI	Protease Inhibitor	Entry Inhibitor	Integrase Inhibitor
Recommended	Zidovudine Lamivudine	Nevirapine	Lopinavir/r		
Alternate	Didanosine Emtricitabine Stavudine Abacavir		Indinavir Ritonavir Saquinavir HGC		
Insufficient data	Tenofovir		Atazanavir Darunavir Fosamprenavir Tipranavir	Enfuvirtide Maraviroc	Raltegravir
Not recommended		Efavirenz Delavirdine	Nelfinavir		

DHHS. <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed February 21, 2008.

Prevalence of Birth Defects After First-Trimester Exposure to ART



Registry Coordinating Center. The Antiretroviral Pregnancy Registry Interim Report, December 2007. http://www.apregistry.com/forms/interim_report.pdf. Accessed April 9, 2008.

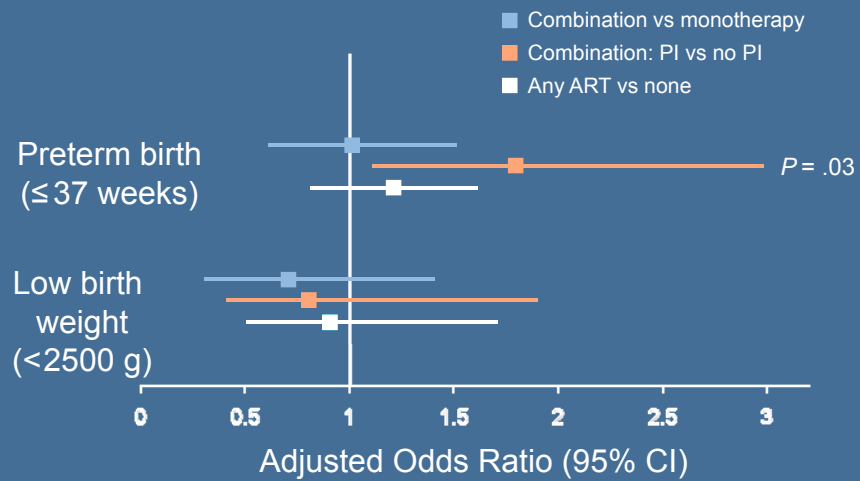
Infant Toxicities and ARV Drug Exposure

- Potential for
 - mutagenic and carcinogenic effects¹
 - mitochondrial dysfunction¹
- Zidovudine-related infant toxicity: anemia¹
- HIV-negative infants exposed in utero and neonatally (n = 1820) have lower hematologic measurements than unexposed infants (n = 351)²
 - 0-2 months:
 - ↓ hemoglobin concentrations
 - ↓ platelet, neutrophil, lymphocyte, CD4⁺, CD8⁺ cell counts
 - 6-24 months:
 - ↓ platelet, lymphocyte, CD4⁺, CD8⁺ cell counts

¹Thorne and Newell. *Expert Opin Drug Saf.* 2005;4(2):323-335.

²Pacheco et al. *J Infect Dis.* 2006;194(8):1089-1097.

Pregnancy Outcomes by ARV Regimen



Cotter et al. *J Infect Dis.* 2006;193:1195-1201.

Conclusion

Any healthcare provider who has female patients of reproductive age can protect that woman's health and the health of her children, planned or unplanned.