Special Considerations in HIV Care and Prevention for Women

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Describe sex differences in HIV progression and treatment outcomes
• Cite important updates in HIV prevention for women over the past two years
Faculty and Planning Committee
Disclosures

Please consult your program book.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
ARS question: What is the #1 cause of death or disability among women of reproductive age (15-44) worldwide?

1. Maternal mortality related to birth
2. Cervical cancer
3. HIV/AIDS
4. Accidents
5. Breast cancer
Massive impact in women

- **Women and health: today's evidence tomorrow's agenda** released by the World Health Organization (WHO) on November 9, 2009

- “Globally, the leading cause of death and disease among women of reproductive age (between the ages of 15 and 44) is HIV/AIDS...”

Proportion of all AIDS cases in women: 7% in 1985 to 26% today
Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Race/Ethnicity, 2009—40 States and 5 U.S. Dependent Areas

**Males**
- N=32,538
- American Indian/Alaska Native: 31%
- Asian: 20%
- Black/African American: 46%
- Multiple races: <1%

**Females**
- N=10,255
- Hispanic/Latino*: 16%
- Native Hawaiian/Other Pacific Islander: 17%
- White: 65%
- Multiple races: <1%

2008 census (women in U.S): 14% AA, 11% Hispanic

Note: Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.

*Hispanics/Latinos can be of any race.
Risks in women cluster with poverty, disempowerment

HIV-infected women versus men in U.S.

- Poorer
- Cluster in South and Northeast
- Lower education levels
- Lower rates of having health insurance
- More food insecurity
- More competing priorities (childcare, etc.)
- More depression
- More substance use
- More domestic violence

Women’s Interagency HIV Study (WIHS)

San Francisco
Chicago
Los Angeles
Washington, D.C.
Bronx, NY
Brooklyn, NY

2012 re-competition: 13 Southern sites have applied
ARS question: How often does the IOM recommend HIV testing in women?

1. At least once between the ages of 13-64
2. Based on her risk factors
3. Once every 5 years unless a new risk factor occurs
4. Yearly
Bold new guideline from IOM committee

- Institute of Medicine (IOM) report July 19, 2011
  - Recommendation 5.4: Counseling and screening for human immunodeficiency virus infection on an annual basis for sexually active women

- Gestational DM, HPV, counseling on STDs, contraception, lactation, DV, yearly visits
ISIS/HPTN 064: Higher HIV Incidence Among At-Risk Women in US

- 2099 women recruited from US communities with high HIV prevalence\(^1\)
  - 88% black, 12% Hispanic, 8% white
  - 1.5% of women newly diagnosed with HIV at baseline

<table>
<thead>
<tr>
<th>Events Analyzed</th>
<th>Women Analyzed, n</th>
<th>Events, n</th>
<th>Window Period</th>
<th>Annual Incidence Estimates, %</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infection at enrollment</td>
<td>2064</td>
<td>2</td>
<td>2 wks</td>
<td>2.52</td>
<td>0.60-10.7</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>1951</td>
<td>4</td>
<td>--</td>
<td>0.24</td>
<td>0.09-0.65</td>
</tr>
</tbody>
</table>

- Annual HIV incidence 5x higher than CDC’s 0.05% estimate for black women\(^2\)
  - Adult incidence rates in Sub-Saharan Africa (0.28% Congo; 0.53% Kenya)\(^3\)

Case

37 yr old AA female with HIV, never on HAART, Current CD4 230; viral load 70,000.

Pt single mother of two children; has been historically reluctant to start meds; recently in new relationship with HIV- male partner who refuses to use condoms. Her sister has an HIV+ husband. She asks what is the best way to protect her brother-in-law (“Since my boyfriend is too dumb to protect himself, we should protect someone in the family”)
ARS question: Of the following interventions, which has the best evidence of efficacy (level I RCT data) in preventing HIV transmission to women?

1. Microbicides
2. Circumcising the male partner
3. HIV vaccine
4. Male condoms
5. Using HIV treatment for HIV+ male partner
# Major RCTs of microbicides

<table>
<thead>
<tr>
<th>Trial location</th>
<th>Candidate microbicide</th>
<th>Efficacy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand, South Africa</td>
<td>Nonoxynol-9</td>
<td>Increased transmission</td>
<td>Van Damme. AIDS 2000</td>
</tr>
<tr>
<td>Africa, India</td>
<td>Cellulose sulfate</td>
<td>No protective effect</td>
<td>Van Damme. NEJM 2008</td>
</tr>
<tr>
<td>Africa</td>
<td>PRO2000 gel</td>
<td>No protective effect</td>
<td>McCormack. Lancet 2010</td>
</tr>
<tr>
<td>Africa, USA</td>
<td>BufferGel</td>
<td>No protective effect</td>
<td>Abdool-Karim. AIDS 2011</td>
</tr>
<tr>
<td>South Africa</td>
<td>1% tenofovir gel</td>
<td>39% reduction in HIV acquisition (54% in high gel adherers)</td>
<td>Abdool-Karim. Science 2010</td>
</tr>
<tr>
<td>Africa</td>
<td>1% tenofovir gel</td>
<td>No protective effect</td>
<td>VOICE trial. Press release 11/25/11</td>
</tr>
</tbody>
</table>
## Circumcision works for heterosexual men

<table>
<thead>
<tr>
<th>Trial location</th>
<th>Trial design</th>
<th>Target group</th>
<th>Age range (yrs)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange County, South Africa&lt;sup&gt;1&lt;/sup&gt;</td>
<td>RCT</td>
<td>Heterosexual men</td>
<td>18-24 yrs</td>
<td>60% ITT 76% per protocol</td>
</tr>
<tr>
<td>Kisumu Kenya&lt;sup&gt;2&lt;/sup&gt;</td>
<td>RCT</td>
<td>Heterosexual men</td>
<td>18-24 yrs</td>
<td>53% ITT 68% per protocol</td>
</tr>
<tr>
<td>Uganda&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RCT</td>
<td>Heterosexual men</td>
<td>15-49 yrs</td>
<td>51% ITT 55% per protocol</td>
</tr>
<tr>
<td>Uganda&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Observational</td>
<td>Female partners of circumcised men</td>
<td>15-49 yrs</td>
<td>No protective effect</td>
</tr>
<tr>
<td>U.S.&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>MSM</td>
<td>Not specified</td>
<td>No protective effect</td>
</tr>
</tbody>
</table>

Case (continued)

• Your patient is considering ART, but first asks if the meds work equally as well in women than men
ARS question: Most recent studies have shown that--

1. Women do as well as men on antiretroviral therapy (ART)
2. Women do worse than men on ART
3. Men do worse than women on ART
Women have lower viral loads and higher CD4 counts than men - baseline

\[ \log_{10} \text{ difference in viral load between men and women } \]

Viral load lower in women

Viral load higher in women

Study

- Moore, 1999 (VI)
- Sterling, 1999
- Evans, 1997
- Sterling, 2001
- Moore, 1999 (V)
- Anastos, 2000 (IV)
- Rezza, 2000
- Lyles, 1999
- Moroni, 1999
- Anastos, 2000 (III)
- Moore, 1999 (IV)
- Katzenstein, 1996
- Junghans, 1999* (H)
- Junghans, 1999* (IDU)
- Anastos, 2000 (II)
- Moore, 1999 (III)
- Bush, 1996
- Anastos, 2000 (I)
- Moore, 1999 (II)
- Moore, 1999 (I)
- Kalish, 2000

Clinical progression or mortality: Trends of observational studies across time

Differential use of ARVs
Unknown infection date
Differential access to care
Differential provider treatment
Social factors
Higher rates of IVDU

Better outcomes in women
Same in men and women
Worse outcomes in women

Higher uptake of ARVs (IVDU Spain)
?Lower viral load & higher CD4
?Higher drug levels
Higher baseline life expectancies
?Better cardiovascular outcomes
?Less viral resistance

Rothenberg 1987; Reeves 1988
Friedland 1991; Lemp 1992; Melnick 1994

Cozzi Lepri 1994; Chaisson. 1995
Brettle 1996; Prins 1999
Pezzotti 1999; Junghans 1999
Sterling 2001; Lewden 2001; Gebo 2003;
Porter 2003; Moore A 2003; Perez-Hoyos 2007; Hoffman 2007; Soon G.
ICAAC 2010

Moore A. 2002; Perez-Hoyos. 2003
Nicastri 2007; Collazos 2007; Jarrin
WIHS: Black HIV+ Women Twice as Likely to Die of AIDS Than White HIV+ Women

- N = 1471 women on continuous HAART

Other significant predictors of AIDS death: depression, peak HIV-1 RNA, nadir CD4+ cell count, HCV coinfection, illegal drug use, < 95% adherence to ART

Black race, depression predicted reduced adherence to HAART, but black race remained associated with AIDS death after adjusting for adherence

The patient agrees to start an “easy” regimen
You start medroxyprogesterone injections and the EFV/TFV/FTC combination tablet and book the patient for a return appointment in three weeks
Pt returns a week later with nightmares and insomnia (as well as a shocking fantasy of switching providers)
### Higher rates of ART side effects in women

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Adverse event</th>
<th>Ratio</th>
<th>Statistical analysis</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter <em>et al.</em> (38)</td>
<td>Dyslipidemia</td>
<td></td>
<td>AHR 1.39</td>
<td>(1.05–1.45)</td>
</tr>
<tr>
<td>Richter <em>et al.</em> (38)</td>
<td>Glucose abnormalities</td>
<td></td>
<td>AHR 0.65</td>
<td>(0.45–0.93)</td>
</tr>
<tr>
<td>Galli <em>et al.</em> (39)</td>
<td>Lipoatrophy</td>
<td></td>
<td>AHR 1.84</td>
<td>(0.47–7.14)</td>
</tr>
<tr>
<td>Galli <em>et al.</em> (39)</td>
<td>Lipohypertrophy</td>
<td></td>
<td>AHR 3.23</td>
<td>(1.17–8.91)</td>
</tr>
<tr>
<td>Bonfanti <em>et al.</em> (40)</td>
<td>Lipodystrophy</td>
<td></td>
<td>ARR 1.5</td>
<td>(1.20–2.10)</td>
</tr>
<tr>
<td>Heath <em>et al.</em> (41)</td>
<td>Lipoatrophy</td>
<td></td>
<td>AOR 2.06</td>
<td>(1.03–4.12)</td>
</tr>
<tr>
<td>Heath <em>et al.</em> (41)</td>
<td>Lipohypertrophy</td>
<td></td>
<td>AOR 2.36</td>
<td>(1.17–4.74)</td>
</tr>
<tr>
<td>Santos <em>et al.</em> (42)</td>
<td>Lipohypertrophy</td>
<td></td>
<td>AOR 1.84</td>
<td>(1.17–2.91)</td>
</tr>
<tr>
<td>Floridia <em>et al.</em> (45)</td>
<td>Rash</td>
<td></td>
<td>AOR 1.65</td>
<td>(1.00–2.72)</td>
</tr>
<tr>
<td>Boulassel <em>et al.</em> (44)</td>
<td>Hypersensitivity reactions</td>
<td></td>
<td>AHR 4.4</td>
<td>(2.10–9.30)</td>
</tr>
<tr>
<td>van Leth <em>et al.</em> (46)</td>
<td>Rash</td>
<td></td>
<td>UOR 2.0</td>
<td>(1.20–3.40)</td>
</tr>
</tbody>
</table>

Ratios (+/- 95% CI) of different adverse events by sex with HAART (2002-07)

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Treatment discontinuation in women is frequent and has consequences.

- ICONA: Women 2x more likely to stop ART due to toxicity.
  
- Swiss Cohort 2010: Women 1.68 (1.14-2.48) more likely to change 1st line due to toxicity.

- Early discontinuation of ART linked to lower rates of survival.

References:
• Landmark study—67% women (84% black or Hispanic), comparing outcomes on DRV/r- therapy
• 32.8% of women (vs 23.2% men, p 0.042) d/c’d ART
• Trend - worse virologic responses in women (ITT), driven by higher d/c rates
• Conclusion: Real world and even clinical studies in HIV lose HIV-infected women, discontinuation rates high

Pharmacokinetics: The explanation of sex differences?

• If women have higher ARV levels than men, could explain
  ➢ Increased risk of toxicities
  ➢ Improved outcomes
  ➢ Drug levels in experienced patients may be determinative of outcome

Possible sex differences in 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 (↓ AAG)

Metabolism
- In vitro: F>M trend
- Progesterone ↓ CYP3A4 activity
- Hepatic g-gp M>F

Elimination
- M>F trend
- Smaller organs
- HepC and liver status

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

Sex differences in ARV pharmacokinetics

• Most studies show higher plasma concentrations, troughs, or AUCs of ARVs in women: IDV, LPV, SQV, NVP, EFV, TPV, DRV/r (prelim); RTV

• But few powered to look at association between levels and toxicities or outcomes by sex

Sex differences in ART side effects and HIV complications
NNRTI-induced rashes/ liver toxicity more common in women

Rash

- Nevirapine (Viramune®)
  - More common (15.8% vs 8.4%; RR 4-6)\(^1-4\)
  - More severe (RR 7.3); 2% rate
  - ↑ at higher CD4 (trend)\(^5-8\)

- Etravirine (Intelence®)
  - 34% women vs 18% men; p 0.02\(^9\)

Hepatotoxicity

- Nevirapine
  - *Women*: 12x ↑ sx hepatotoxicity with CD4 >250
  - *Men*: 5x ↑ risk CD4 >400

General pattern of fat changes differ by sex

- More total body fat in women
- Equal rates of peripheral lipoatrophy in both sexes\(^{11,12}\)
- More central adiposity in HIV+ women \(^{12}\)
- Patient-described\(^8\): “Beach ball on sticks”
- “d” drugs and IDV\(^{1-10}\)

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ARS question: What is the increase in odds of HIV patients being osteoporotic?

1. OR 1.5
2. OR 2.5
3. OR 3.5
4. OR 4.5
5. OR 5.5
Bone loss common in HIV

- Osteopenia (OR 6.4) and osteoporosis (OR 3.7; 15% prevalence) common\(^1\)
- OR 3.02 (95% CI 1.26-7.25) for women:men\(^2\)

\(^{1}\)Brown. AIDS 2006; \(^{2}\)Fausto. Bone 2006; \(^{3}\)Cazanave AIDS 2008; \(^{4}\)Bruera. AIDS 2003; \(^{5}\)Anastos. Antiviral Ther 2007; \(^{6}\)McComsey. AIDS 2008; \(^{7}\)Negredo. AIDS 2005; \(^{8}\)Mondy JAIDS 2005; \(^{9}\)Guaraldi. HIV Clin. Trials 2004; \(^{10}\)McCamsey CID 2010
ARS question: When should you screen a woman with HIV infection and no other known risk factors for bone disease via DEXA?

1. Starting at age 40
2. Starting at age 50
3. Starting at menopause
4. Starting at age 65
When to screen (DEXA)

Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers

McComsey G et al. CID
Case (continued)

• The patient’s symptoms resolve after about a week and she stays on the combination regimen
• By her 2 month visit, her viral load is undetectable and her CD4 320
• She then comes in 3 months later saying that her new partner wants to have a baby with her and she has stopped her birth control, although she is scared to expose her baby to HIV
In 2012, what is the rate of perinatal transmission of HIV in the US?

1. 25%
2. 10%
3. 5%
4. 3%
5. <2%
Mother-to-Child Transmission in the US Over Time

Decline due to:
- More HIV testing in prenatal visits
- Increase in use of HAART in pregnancy
- C-section if viral load >1000 copies/ml

Stigma towards HIV+ women childbearing high and internalized

- Nat’l survey (4831 general population) 3/31/08, AMFAR
  - Only 14% believed HIV+ women should have children (even less than those with schizophrenia 17% or Down’s 19%)

- Nat’l survey (700 HIV+ women)²
  - 27% felt HIV+ women should be “strongly urged” not to have children
  - 59% felt societal pressure to forego child bearing
  - Only half even asked by their providers if they desired pregnancy

K.Squires. AIDS Patient Care and STDs. 2011
Practical tips for providers with HIV+ women

- Don’t *initiate* NVP if CD4 > 250
- Efavirenz class D FDA agent (but not an emergency)
- Lipodystrophy changes different than men
- Women do equally as well or better than men on ARVs
- May have more side effects on therapy due to PK and more discontinuation
- Think about bone
- Talk about women-specific and reproductive issues
- Encourage more clinical research in HIV+ women

Expert opinion
Stop AIDS. Make the Promise.

Each of us can help stop the spread of HIV and reduce the impact of AIDS. You don’t have to be a top scientist working on a cure to make a difference. Protecting yourself and others from HIV infection, welcoming someone living with HIV into your life or even just talking about HIV and AIDS can help.

Are you taking action?

Make your promise now at www.worldaidscampaign.org