Graying of the HIV Epidemic: The Intersection of Menopause and HIV

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Objectives

• Outline prevention challenges regarding HIV in older women.
• Describe the current literature regarding antiretroviral therapy in post menopausal women.
• Describe the impact of menopause on women.
Program Overview

- Introduction
- Epidemiologic Trends
- HIV screening/Testing
- Menopause
- Treatment options and Treatment response
- Management Considerations
- Prevention Challenges

HIV/AIDS and Aging (1 of 2):
NIH Statement (9/09/10)

- “HIV clearly poses a risk to individuals 50 years and older and presents complex treatment challenges”
  - “In those with long-term HIV infection, the persistent activation of immune cells by the virus likely increases the susceptibility of these individuals to inflammation-induced diseases and diminishes their capacity to fight certain diseases. Coupled with the aging process, the extended exposure of these adults to both HIV and antiretroviral drugs appears to increase their risk of illness and death from cardiovascular, bone, kidney, liver and lung disease, as well as many cancers not associated directly with HIV infection...”

NIH Statement (9/09/10)

“HIV clearly poses a risk to individuals 50 years and older and presents complex treatment challenges”
- “HIV disease progresses more quickly in older compared with younger adults, and antiretroviral therapy restores immune system cells less effectively, placing this older group at greater risk for illness and death from HIV infection than younger people who are infected for comparable periods of time. Moreover, the higher rate of pre-existing conditions in people of advanced age often complicates their treatment for HIV infection.”


Epidemiology
By 2015, Approximately 50% of People Living With HIV Will Be >50 Years of Age

Smith G. Senate Committee on Aging. 2005
Available at: http://aging.senate.gov/events/hr141gs.pdf.

New HIV Cases in 2011 by Age at Diagnosis (50 States)

New HIV Cases in the US (2011): Age and Race/Ethnicity (50 States)

<table>
<thead>
<tr>
<th>Years of Age</th>
<th>White (n=13,846)</th>
<th>Hispanic/Latino (n=10,159)</th>
<th>Black (n=23,168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 34</td>
<td>4000</td>
<td>4000</td>
<td>4000</td>
</tr>
<tr>
<td>&gt;50</td>
<td>6000</td>
<td>6000</td>
<td>6000</td>
</tr>
<tr>
<td>35 to 49</td>
<td>8000</td>
<td>8000</td>
<td>8000</td>
</tr>
<tr>
<td>&gt;50</td>
<td>10000</td>
<td>10000</td>
<td>10000</td>
</tr>
</tbody>
</table>


Persons Living With HIV (50 States)

<table>
<thead>
<tr>
<th>Years of Age</th>
<th>2008 (n=822,638)</th>
<th>2009 (n=851,040)</th>
<th>2010 (n=879,335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.5%</td>
<td>1.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>20 to 34</td>
<td>16.8%</td>
<td>16.8%</td>
<td>16.8%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>50.7%</td>
<td>48.5%</td>
<td>46.1%</td>
</tr>
<tr>
<td>35 to 49</td>
<td>31.0%</td>
<td>33.3%</td>
<td>36.8%</td>
</tr>
</tbody>
</table>

Life Expectancy Among Treated HIV Patients in the US and Canada (2000-2007)

• NA-ACCORD participants ≥20 years of age (n=22,937)
  – Treatment-naive before initiating ART
• Crude mortality rate (2000-2007)
  – 19.8 per 1000 person-years (n=1622 deaths)
• Life expectancy at 20 years of age
  – Increased from 36.1 to 51.4 years from 2000-2002 to 2006-2007
• A 20-year-old HIV-positive person is expected to live into their early 70s

NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design.
Hogg RS, et al. PLOS one. 2013

Time to AIDS Diagnosis After a Diagnosis of HIV Infection in 2009 (46 States)

AIDS diagnosis after HIV diagnosis
- <12 months (overall: 32.4%)
- ≥12 months (overall: 67.6%)

Available at: http://www.cdc.gov/hiv/surveillance/resources/reports/2010report/.
Survival After AIDS Diagnosis (1998-2005)

Available at: http://www.cdc.gov/hiv/surveillance/resources/reports/2010report/.

HIV Screening/Testing
CDC Recommendations for
HIV Testing in Healthcare Settings

- Routine voluntary testing for patients ages 13 to 64 years in healthcare settings
  - Not based on patient risk
- Opt-out testing
- No separate consent for HIV
- Pretest counseling not required
- Repeat HIV testing left to discretion of provider
  - Based on patient risk


HIV Screening:
Guidelines From Other Organizations

  - Strongly recommends clinicians screen for HIV in all adolescents and adults 15 to 65 years of age (endorsed by AAFP, but beginning at 18 years of age)
    - Younger adolescents and older adults at increased risk should also be screened
    - Recommends clinicians screen all pregnant women for HIV

- American College of Physicians (2008) (endorsed by the HIV Medicine Association)
  - Recommends clinicians adopt routine screening for HIV and encourage patients to be tested
    - Regardless of whether HIV risk factors are present
    - Recommends clinicians determine the need for repeated screening on an individual basis

AAFP. Available at: http://www.aafp.org/patient-care/clinical-recommendations/all/hiv.html.
Factors Associated With Late or Missed Diagnosis of HIV Infection in Older Adults

- Routine screening uncommon in this age group
- Poor awareness of HIV risk factors (including safe sex practices)
  - Lack of HIV prevention education targeting older adults
- Health care provider belief that older adults are not sexually active
- Failure of some health care providers to consider HIV infection in this patient population
- Confusion about HIV-specific or opportunistic infection symptoms with symptoms of other diseases

HIV Risk in Older Adults: Unprotected Sexual Activity

- Use of erectile dysfunction drugs contributes to increased rates of sexual activity
- Menopause
  - No risk for pregnancy=no need for condom
- Vaginal dryness due to estrogen depletion leads to greater likelihood of trauma and increased risk of HIV acquisition


Project ROADMAP: Sexual Risk Behaviors of Older HIV-Positive Patients

- Sexually active, HIV-positive men and women
- Baseline demographics
  - Age (years): 51 (45-71)
  - Race
    - Black (82%), Hispanic (12%), white (5%)
  - On HAART: 92%
  - Transmission through heterosexual contact: 94%
  - Age at HIV diagnosis
    - Mean: 39.7 years
    - ≥45 years of age: 25%

<table>
<thead>
<tr>
<th>Exploratory Findings</th>
<th>Men (n=125)</th>
<th>Women (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual preference (%)</td>
<td>84</td>
<td>94</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Homosexual</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Bisexual</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>≥1 sexual partner (%)</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>Vaginal sex</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Anal sex</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Number of sexual acts in past 6 months</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>With only women (%)</td>
<td>85.6</td>
<td>--</td>
</tr>
<tr>
<td>With only men (%)</td>
<td>12.0</td>
<td>--</td>
</tr>
<tr>
<td>Both (%)</td>
<td>2.0</td>
<td>--</td>
</tr>
</tbody>
</table>

ROADMAP: Re-educating Older Adults in Maintaining AIDS Prevention (UM/JMH).
Project ROADMAP: Sexual Risk Behaviors of Older HIV-Positive Patients

- Approximately 20% of sexually active participants reported not using condoms consistently
- 60% reported having anal or vaginal sex at least once with HIV negative/unknown serostatus partners
  - Of these, 17.3% reported not using condoms
- Interventions are needed to help older patients engage in safer sexual practices

ROADMAP: Re-educating Older Adults in Maintaining AIDS Prevention (UM/JMH).

Vulnerability to HIV Acquisition in Women Varies Across the Age Spectrum

- Adolescence
  - Biologic: cervical ectopy
  - Behavioral: lack of knowledge, lack of condom use, multiple partners, STD’s
- Child bearing potential
  - Biologic: hormonal contraception
  - Behavioral: safe sex practices decrease
- Pregnancy
  - Biologic: increase risk of acquisition
- Post-menopausal
  - Biologic: physiologic changes in genital tract, increase number of CCR5 receptors (Clinical relevance)
  - Behavioral: No worry about becoming pregnant, therefore, less condom use
HIV Acquisition in Older Women

- Older women are not targeted by education and prevention messages
- Many older women are newly single by divorce or death of spouse
- Some older women practice a “self-silencing” of their thoughts and feelings about their sexual behaviors to avoid confrontation and conflict, which compromises condom negotiation skills and safe sex practices
- Societal norms may suggest that older women do not have sex, which may be a barrier to HIV testing and discussion about risk behaviors
- Women >50 years of age may view condom use as a means to prevent pregnancy only—not as a way to prevent HIV transmission

References:

Menopause
Menopause

- All women transition from a reproductive period (regular ovulation and cyclic menstrual bleeding) to a post menopausal period marked by amenorrhea.
  - Hormone levels are variable
  - Estrogen levels fall markedly and levels of FSH increase
  - As ovaries fail to produce estrogen, the menstrual cycle is erratic, followed by amenorrhea. (12 months=menopause)

Menopause in HIV+ Women

- Data are inconclusive in terms of age of menopause.
  - There are multiple confounding factors: tobacco use, substance abuse, weigh loss/low BMI, African-American, low socioeconomic status
  - WIHS: mean age HIV (47.7 yrs) vs non-HIV (48.0). This study used recall as well as measurement of FSH. 53% of HIV+ women with prolonged amenorrhea had FSH <25 mIU/ml.
Summary of Key Physical Changes with Menopause

- Vasomotor instability
- Metabolic Changes
- Coronary Artery Disease
- Accelerated bone loss
- Skin changes
- Urogenital atrophy
- Cognition (?)
- Libido (?)
Impact of Menopause

- Increases osteopenia and osteoporosis
- Dyslipidemia
- Metabolic Changes
- Weight Changes
- Cardiac Risk
- Inflammation/immune response

Unintended Pregnancy

- In 2006, there were 235,000 pregnancies in women older than 40 yrs
  - Total pregnancy rate 21/1000 women
  - 112,000 unintended (48%)

Finer. Contraception. 2011
## DHHS Guidelines: Preferred Regimens

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Efavirenz&lt;sup&gt;1&lt;/sup&gt;/emtricitabine&lt;sup&gt;2&lt;/sup&gt;/tenofovir DF&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Atazanavir&lt;sup&gt;4&lt;/sup&gt; + ritonavir + emtricitabine&lt;sup&gt;2&lt;/sup&gt;/tenofovir DF&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Darunavir + ritonavir (qd) + emtricitabine&lt;sup&gt;2&lt;/sup&gt;/tenofovir DF&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>INSTI</td>
<td>Raltegravir + emtricitabine&lt;sup&gt;2&lt;/sup&gt;/tenofovir DF&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/cobicistat/emtricitabine/tenofovir DF&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + abacavir/lamivudine&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Lopinavir/r bid + zidovudine/lamivudine&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Efavirenz should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.

<sup>2</sup>Lamivudine may substitute for emtricitabine or visa versa.

<sup>3</sup>Tenofovir DF should be used with caution in patients with renal insufficiency.

<sup>4</sup>Atazanavir + RTV should not be used in patients who require >20 mg omeprazole equivalent/day.

<sup>5</sup>Patients with creatinine clearance <70 mL/min.

<sup>6</sup>Patients who are HLA-B*5701 negative.

DHHS. Available at: [http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf).

Revision February 12, 2013.


Update October 30, 2013.
COHERE Study

- Collaboration of Observational HIV Epidemiological Research Europe
  - Multi-cohort collaboration of 33 European cohorts
- Patients starting HAART (n=67,659)
  - Stratified by 10 age groups (<2 to >60 years of age)
- Pre-HAART baseline in older patients
  - Distribution of HIV transmission categories similar with exception of IDU (lower in older versus younger patients)
  - Higher HIV RNA levels
  - Lower CD4 cell counts
  - Higher percentage of AIDS diagnoses
    - 13 to 49 years of age: 18% to 29%
    - >50 years of age: 32% to 33%


COHERE Study: Baseline Virologic and Immunologic Profile by Age

COHERE Study: Response by Baseline Age

Achieving CD4 Count >200 Cells/mm³ at 12 Months

New AIDS Event At 12 Months

**COHERE Study: Continuation of HAART by Baseline Age**

- Similar rates of discontinuing or switching >1 antiretroviral agent during the first 12 months of HAART
- Complete treatment discontinuation was rare
  - Lower rates were observed among those ≥40 years of age

**Discontinuation of All ARTs at 12 Months**

<table>
<thead>
<tr>
<th>Age at Baseline (years)</th>
<th>Discontinuation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 (n=2259)</td>
<td>15.3%</td>
</tr>
<tr>
<td>40-49 (n=1834)</td>
<td>14.8%</td>
</tr>
<tr>
<td>≥50 (n=997)</td>
<td>9.2%</td>
</tr>
<tr>
<td>&gt;60</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

*P* < 0.0001 for trend


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**Kaiser Permanente Northern California: Older Age and Response/Tolerability to HAART**

- Retrospective, observational, cohort study of HIV patients with known dates of HAART initiation (n=5090)
- Patients ≥50 years of age at HAART initiation
  - Higher percentage with a CD4 count <200 cells/mm³ and AIDS diagnosis
  - Higher modified Charlson comorbidity index scores
  - Higher levels of HAART adherence in the year after HAART initiation

<table>
<thead>
<tr>
<th>Baseline (years of age)</th>
<th>CD4 &lt;200 cells/mm³ (%)</th>
<th>HIV RNA ≥10K copies/mL (%)</th>
<th>AIDS (%)</th>
<th>Adherence (%)</th>
<th>Modified Charlson Comorbidity Index score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39 (n=2259)</td>
<td>43.0</td>
<td>66.3</td>
<td>61.7</td>
<td>83.7</td>
<td>80.0</td>
</tr>
<tr>
<td>40-49 (n=1834)</td>
<td>45.8</td>
<td>62.6</td>
<td>69.4</td>
<td>85.7</td>
<td>76.0</td>
</tr>
<tr>
<td>≥50 (n=997)</td>
<td>47.6*</td>
<td>61.6</td>
<td>72.1†</td>
<td>88.9†</td>
<td>68.5†</td>
</tr>
</tbody>
</table>

Kaiser Permanente Northern California: Virologic Response and Age

Achieving HIV RNA <500 Copies/mL at 12 Months

Experiencing HIV RNA Rebound Within 2 Years

Age at Baseline (years)

Hazard Ratio (95% CI)

18-39 40-49 >50

0 0.97 1.15 1.15

(0.88-1.06) (0.99-1.37) (1.04-1.27)

*P=0.009 and †P=0.01. Adjusted for age only. Similar results when adjusted for all potential predictors.


HAART and HIV in Older Persons

- Better adherence
- Similar virologic response
- Slower CD4 recovery in some cohorts
- Higher risk of progressing to AIDS
- Increased mortality

CDC: HIV-Infected Persons Engaged in Selected Stages of the Continuum of Care (2009)

CDC and Prevention National HIV Surveillance System

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 to 34</td>
<td></td>
</tr>
<tr>
<td>35 to 44</td>
<td></td>
</tr>
<tr>
<td>45 to 54</td>
<td></td>
</tr>
<tr>
<td>55 to 64</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
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</table>

n=1,148,200 HIV-infected persons, 18% of whom are unaware of their infection.

VACS Virtual Cohort: Comorbidities Among Older HIV-Infected Patients

Age was associated with all comorbidities except liver disease ($P<0.001$).
VACS Virtual Cohort: Comorbidities Among Older HIV-Infected Patients


HAART in Post menopausal women

- 267 HIV-infected racially and ethnically diverse women (220 premenopausal and 47 postmenopausal) demonstrated that the median change in absolute CD4 cell counts and percentages did not differ between premenopausal and post-menopausal women after two years of ART (260 versus 273 cells/mm3, $P = 0.51$; 11.0% versus 12.0%, $P = 0.79$)

- There were also no differences between premenopausal and post-menopausal women in the proportions achieving plasma HIV RNA viral loads <50 copies/mL after two years of HAART (75% versus 77%, $P > 0.99$; OR: 0.82, 95%CI: 0.36–1.89)

Patterson, et al. CID 2009
Management Considerations

Management of Postmenopausal Women and HIV

- Diagnosis
- Management of vasomotor symptoms
- HRT risk vs. benefit
- Estrogen interaction with ART
- Exercise - Aerobic and weight bearing
- Smoking cessation
- Calcium supplementation/Vitamin D
- Osteoporosis screening
- Healthy diet
- STI counseling/screening
- Screening colonoscopy
- Routine mammograms
Sexually Transmitted Infections (STIs) in Older Women

• STIs among older adult adults (45-64 yr) have more than doubled in the past 10 years
  – Chlamydia: 6700 cases (2000) > 19,000 (2010) CDC
  – Trichomoniasis: 7,593 US women 18-89 yrs old (2010): highest rates (13%) in those >50 yrs, second highest in those in their 40’s (11%). *

• Possible delay in diagnosis due to stigma or lack of symptom recognition

*Gaydos et al. 2011
Hot Flushes (aka Hot Flashes)

- “Sudden onset of reddening of the skin over the head, neck, and chest accompanied by a feeling of intense body heat and sometimes concluded by profuse perspiration”
- Number 1 complaint to physicians
- Few seconds to several minutes
- Rare to recurrent every few minutes
- Most severe at night and during times of stress
- More common among overweight women
- Usually last for 1-2 years
- 25% will last for more than 5 years

Hot Flushes May Continue Years After Menopause

Number of years women report having hot flushes as estimated by a survey of 501 untreated women who experienced hot flushes

Mean age of natural menopause was 49.5 years; mean age of surgical menopause was 43.7 years.
Kronenberg F. Ann NY Acad Sci. 1990;592:52-86. Used with permission.
HRT

- Vasomotor symptoms are the most common indication for HRT and estrogen is the most effective treatment
- Consider potential contraindications
- Drug interactions
- Women with a uterus should receive progestin to prevent endometrial cancer

Alternative Approaches for Vasomotor Symptoms: Lifestyle Adaptations

Guidelines from NAMS

- Limited effectiveness
  - Cooling body core temperature
  - Exercise
  - Paced respirations (catecholamine control)
  - Relaxing activities
    - yoga, massage, meditation, paced respiration, leisurely bath
  - Avoid Triggers
    - spicy food, hot drinks, caffeine, alcohol

Clinical Management
Mod-Severe Vasomotor Symptoms

• Hormone therapy is only FDA approved treatment
  – “gold standard”
• SSRI’s and gabapentin
  – have efficacy in early studies
• Progestogens effective
  – however large doses required
• Clonidine (oral or transdermal)

Sleep and Mood Disturbances

• Vasomotor episodes have an adverse impact on quality of sleep
• Sleep disturbances lead to a reduced ability to handle problems and stresses
• Women with a history of depression are at risk of reoccurrence during menopause
• HRT may provide additional benefit to antidepressants in the management of postmenopausal depression
Prevention Challenges

- Late diagnosis
- Shorter HIV to AIDS survival
- Lower perceived risk by patients and providers
- Sexual risk factors
  - Continued sexual activity after being widowed or divorced so less likely to use condoms when there is little concern for pregnancy
  - Physiologic changes may increase risk of HIV acquisition
  - Less likely to discuss (or be asked) sexual habits with providers

Conclusions

- The HIV population is aging
- There are unique challenges caring for women who are aging with HIV
- Continue to screen sexually active women for STIs
- Discuss and offer contraception in perimenopausal women
Issues For Women Aging With HIV Disease

• Unprotected sex
  – No concern about pregnancy
  – “I’m too old to catch HIV”

• Unintended pregnancies

• Delay in testing

• Menopause and physiologic changes

• Limited incomes

• Immune restoration

• Comorbid illnesses

• Polypharmacy

• Insufficient data on drug interactions in older population


Thank You
Questions?
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