ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals

Activity Code: SM393
Breakfast with the Experts
Women and Reproductive Health

Saturday, April 22, 2017
7:45am – 8:45am

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When someone evolves, everything that surrounds him or her also evolve. When we try to become a better person, everything around us also improves.

Paulo Coelho
The Alchemist
Upon completion of this presentation learners should be better able to:

1. Describe the treatment differences of sexually transmitted infections for women living with HIV in contrast to the general population
2. Identify which family planning methods are appropriate for women living with HIV
3. Recognize issues relating to pregnancy and breastfeeding for women living with HIV
4. Describe potential barriers to the implementation of PrEP during pregnancy
Treatment differences of sexually transmitted infections for women living with HIV in contrast to the general population
What is the link between STDs and HIV infection?

• Individuals who are infected with STDs are at least 2-5 times more likely than uninfected individuals to acquire HIV infection sexually.

• If an HIV-infected individual is also infected with another STD, that person is more likely to transmit HIV through sexual contact than other HIV-infected persons.

• http://www.cdc.gov/std/hiv/STDFact-STD-HIV.htm
Link between STIs and HIV infection

**Increased susceptibility**
- Genital **ulcers** (e.g., syphilis, HSV, or chancroid)
- **Inflammation** resulting from genital ulcers or non-ulcerative STIs

**Increased infectiousness**
- Shedding of HIV in genital secretions
- The median **concentration of HIV** in semen is 10 times higher in men who are infected with both GC and HIV

http://www.cdc.gov/std/hiv/STDFact-STD-HIV.htm
STI treatment reduce HIV transmission

• Studies of STI treatment **reduced incidence** of HIV in countries (Quinn et al*)
• Some of the microbicides also reduced the incidence of HSV-2 (CAPRISA 004) (Tenofovir gel)**

*http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)06439-3/abstract


Links to 2015 CDC treatment guidelines (app)

Question 1:
The three diseases most frequently associated with **vaginal discharge** are: (select the correct statement)

a. Bacterial vaginosis (BV), trichomoniasis and candidiasis  
b. Herpes Simplex, Bacterial vaginosis (BV), and candidiasis  
c. Gonococcus (NG), Bacterial vaginosis (BV), and candidiasis  
d. HPV, Herpes simplex and Bacterial vaginosis (BV)  
e. None of the above
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Vaginal Infections

- Vaginitis is usually characterized by a **vaginal discharge** and/or vulvar itching and irritation, and a vaginal odor might be present.

- The three diseases most frequently associated with vaginal discharge are **BV** (replacement of the normal vaginal flora by an overgrowth of anaerobic microorganisms, myco-plasmas, and *Gardnerella vaginalis*), **trichomoniasis** (*T. vaginalis*), and **candidiasis** (usually caused by *Candida albicans*).

- BV is the most prevalent cause of vaginal discharge or malodor; but, in a nationally representative survey, most women with BV were asymptomatic https://www.cdc.gov/std/tg2015/bv.htm
A 28 y/o female living with HIV, at present on HAART (undetectable VL) complains of fetid vaginal discharge most common after menses or after coitus. She was Rx a vaginal anti-fungal cream without results.

What would be the findings on her pelvic exam if this was BV?

a. Thick white vaginal discharge
b. Vaginal warts
c. Thin white vaginal discharge
d. External ulcers
e. All of the above
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https://api.cvent.com/polling/v1/api/polls/sp-utrfjm

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Bacterial Vaginosis (BV) Clinical Criteria

- Homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- Presence of clue cells on microscopic examination;
- pH of vaginal fluid >4.5; and
- A fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).

BV and HIV

• BV appears to recur with **higher frequency** in women who have HIV infection.

• Women with HIV who have BV should receive the **same treatment** regimen as those who do not have HIV infection.

Pregnancy and BV

• All pregnant women who have symptomatic disease require treatment.

• BV has been associated with adverse pregnancy outcomes (e.g., PROM, chorioamnionitis, PTL, PTB, intraamniotic infection, post-partum and wound infection).

• Some prefer using systemic Rx to treat possible subclinical upper genital infections.

• Treatment of BV in asymptomatic pregnant women at high risk for preterm delivery with oral Rx has reduced preterm delivery in 3 of 4 RCTs.

• Intravaginal clindamycin cream should only be used during the first half of pregnancy. Metronidazole has low risk in pregnancy. https://www.cdc.gov/std/tg2015/bv.htm
BV and PrEP (oral vs. microbicide)

- The efficacy of **oral pre-exposure prophylaxis (PrEP)** for women was not affected by bacterial vaginosis (BV). *(CROI 2017 abstract 85).*
- Tenofovir levels were compared between women with BV bacterial species and those without, both after 7 days of **microbicide gel or film** use at home, and subsequently after a single application at the trial center (FAME-04). Women with **no Lactobacillus were more likely to have undetectable levels of tenofovir** *(CROI 2017 abstract 86LB).*
Pelvic Inflammatory Disease (PID)

• PID includes any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.

• *N. gonorrhoeae* and *C. trachomatis*, in many cases; however, microorganisms that comprise the vaginal flora also have been associated with PID.

• All women diagnosed with acute PID should be tested for *N. gonorrhoeae and C. trachomatis* and HIV.

• Screening and treating sexually active women for chlamydia reduces their risk for PID.

• Although BV is associated with PID, whether PID can be reduced by treating BV is unclear.

https://www.cdc.gov/std/tg2015/pid.htm
Clinical diagnosis of PID

• Presumptive treatment for PID should be initiated if pelvic or lower abdominal pain, no cause other than PID, and if one or more are present on pelvic examination:
  - cervical motion tenderness
  - uterine tenderness
  - adnexal tenderness.

• Additional criteria:
  • fever >101°F (>38.3°C);
  • cervical mucopurulent discharge or cervical friability;
  • abundant numbers of WBC on saline microscopy of vaginal fluid;
  • Elevated Sed Rate;
  • elevated CRP; and
  • cervical infection with GC/Chlam.

https://www.cdc.gov/std/tg2015/pid.htm
PID and HIV

• In previous observational studies, HIV-infected women with PID were more likely to require surgical intervention.
• They were more likely to have a tubo-ovarian abscess but responded equally well to standard IV and oral antibiotic regimens.
• Whether the management of immunodeficient HIV-infected women with PID requires more aggressive interventions (e.g., hospitalization or parenteral antimicrobial regimens) has not been determined.
• https://www.cdc.gov/std/tg2015/pid.htm
Question 3:
Select the **incorrect** statement

a. Many genital herpes infections are transmitted by persons unaware that they have it or who are asymptomatic when transmission occurs.

b. Immuno-compromised patients might have prolonged or severe episodes of genital, perianal, or oral herpes.

c. The majority of HPV infections are asymptomatic, unrecognized, or subclinical.

d. The quadrivalent HPV “vaccine” is recommended for females only from ages 9-26 years.

e. In previous observational studies, HIV-infected women with PID were more likely to require surgical intervention.
<table>
<thead>
<tr>
<th>Statement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many genital herpes infect...</td>
<td>0%</td>
</tr>
<tr>
<td>Immuno-compromised pat...</td>
<td>0%</td>
</tr>
<tr>
<td>The majority of HPV infec...</td>
<td>0%</td>
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<tr>
<td>The quadrivalent HPV “va...</td>
<td>0%</td>
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<tr>
<td>In previous observational ...</td>
<td>0%</td>
</tr>
</tbody>
</table>
Genital Ulcers

• In the USA, the majority of young, sexually active patients who have genital ulcers have:
  • genital herpes, syphilis, or chancroid.
• The frequency of each condition differs by geographic area and patient population;
  • genital herpes is the most prevalent of these diseases.
• More than one of these diseases can be present in a patient who has genital ulcers. All three of these diseases has been associated with an increased risk for HIV infection.
• Not all genital ulcers are caused by sexually transmitted infections.

Genital HSV

• Genital herpes is a chronic, life-long viral infection.
  • Two types of HSV have been identified, HSV-1 and HSV-2.

• The majority of cases of recurrent genital herpes are caused by HSV-2 although HSV-1 might become more common as a cause of first episode genital herpes. At least 50 million persons in the United States have genital HSV infection.
  • The majority of persons infected with HSV-2 have not been diagnosed with genital herpes.

https://www.cdc.gov/std/tg2015/herpes.htm
HSV and HIV

- Immunocompromised patients can have **prolonged or severe episodes**.
- Lesions are common and might be severe, painful, and atypical.
- HSV **shedding is increased** in persons with HIV.
- Whereas ARV therapy reduces the severity and frequency of symptomatic genital HSV, frequent **subclinical shedding still occurs**.
- Clinical manifestations of genital HSV might **worsen during immune reconstitution** early after HAART.

- **Suppressive or episodic** therapy with oral antiviral agents is effective in decreasing the clinical manifestations.
- Daily Acyclovir in persons with HIV infection did not reduce the risk for either **HIV transmission or HSV-2 transmission** to susceptible sex partners.
HSV and HIV

**Recommended Regimens for Daily Suppressive Therapy in Persons Infected with HIV**

- **Acyclovir** 400–800 mg orally twice to three times a day
  - OR
- **Famciclovir** 500 mg orally twice a day
  - OR
- **Valacyclovir** 500 mg orally twice a day

**Recommended Regimens for Episodic Infection in Persons Infected with HIV**

- **Acyclovir** 400 mg orally three times a day for 5–10 days
  - OR
- **Famiciclovir** 500 mg orally twice a day for 5–10 days
  - OR
- **Valacyclovir** 1.0 grams orally twice a day for 5–10 days

https://www.cdc.gov/std/tg2015/herpes.htm
Question 4. Select the correct statement

a. HPV testing is used to determine cervical cytology frequency in HIV-negative women
b. Testing for HPV is recommended for all women younger than 30 years old
c. The prevalence of HPV is the same for women living with HIV as those who are HIV-negative
d. The treatment of HPV includes acyclovir
e. All of the above
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https://api.cvent.com/polling/v1/api/polls/sp-zbqr6s

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
## Current Cervical Cancer Screening Recommendations in HIV

### DHHS Cervical Cancer Screening Guidelines for HIV-Infected Women

<table>
<thead>
<tr>
<th>Test</th>
<th>Women &lt; 30 Yrs of Age</th>
<th>Women ≥ 30 Yrs of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to Start</strong></td>
<td></td>
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<tr>
<td>Younger than 21 yrs</td>
<td>Pap test</td>
<td>Pap test only</td>
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<td></td>
<td>old</td>
<td>Pap and HPV Cotest</td>
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<td>- Within 1 yr of</td>
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<tr>
<td>sexual activity</td>
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<tr>
<td>onset; no later</td>
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<tr>
<td>than 21 yrs</td>
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<tr>
<td>Age 21-29 yrs</td>
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<tr>
<td>- At time of initial</td>
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<tr>
<td>HIV diagnosis</td>
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<tr>
<td><strong>Repeat Screening</strong></td>
<td>Every 12 mos; after 3</td>
<td>Every 12 mos; after 3</td>
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<td></td>
<td>consecutive normal</td>
<td>consecutive normal</td>
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<tr>
<td></td>
<td>tests, switch to every</td>
<td>tests, switch to every</td>
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<td></td>
<td>3 yrs</td>
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<td></td>
<td></td>
<td>Continue lifelong</td>
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</table>

*For normal/negative test results.

DHHS. Adult and adolescent opportunistic infection.

Slide credit: clinicaloptions.com
Current Recommendations for HPV Vaccination in HIV

- HPV vaccination indicated for all HIV-infected individuals aged 9-26 yrs

### HPV Vaccination Recommendations for HIV-Infected Women

- Use either bivalent, quadrivalent, or 9-valent HPV recombinant vaccine
  - 9 valent: types 6, 11, 16, 18, 31, 33, 45, 52, 58
  - Quadrivalent: types 6, 11, 16, 18
  - Bivalent: types 16, 18
- Each is administered at 0, 1-2, and 6 mos

DHHS. Adult and adolescent opportunistic infection.
Family planning methods appropriate for women living with HIV

https://itunes.apple.com/ca/app/contraception/id595752188?mt=8

App
Contraception
By Centers For Disease Control and Prevention
Open iTunes to buy and download apps.
What ARVs Are Compatible With Contraception?

• Several PIs, EFV, and EVG/COBI-based regimens have drug interactions with combined oral contraceptives
  • Decrease or increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate could potentially:
    • Decrease contraceptive efficacy
    • Increase estrogen- or progestin-related adverse effects (eg, thromboembolism)
• Women taking ARVs with significant interactions with hormonal contraceptives should use an additional or alternative contraceptive, consider ARV switch

## Drug Interactions Between Hormonal Contraceptives and ARVs

<table>
<thead>
<tr>
<th>Hormonal Contraceptive</th>
<th>NRTI Any*</th>
<th>PI ATV</th>
<th>LPV</th>
<th>DRV</th>
<th>RTV</th>
<th>NNRTI EFV</th>
<th>NVP</th>
<th>ETR</th>
<th>RPV</th>
<th>INSTI DTG</th>
<th>RAL</th>
<th>EVG/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
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<td>Etonogestrel or levonorgestrel implant</td>
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<td>Transdermal ethinyl estradiol</td>
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<td>Norethisterone (norethindrone)</td>
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<tr>
<td>DMPA injectable</td>
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</tbody>
</table>

*Includes 3TC, ABC, AZT, ddI, d4T, FTC, TDF.

- **No clinically significant interaction or interaction unlikely**
- **Potential interaction that may require monitoring or regimen alteration**

Truly, every problem seems simple after being solved. The greatest achievement (that might seem simple today) was the result of a series of small victories that today might have been overlooked.

Paulo Coelho
Issues relating to pregnancy and breastfeeding for women living with HIV
**DHHS Recommendations: Initial ART in Pregnant Women**

<table>
<thead>
<tr>
<th>Guideline Status</th>
<th>NRTIs</th>
<th>Pls</th>
<th>Integrase Inhibitors</th>
<th>NNRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>3TC/ABC</td>
<td>Atazanavir/RTV*</td>
<td>Raltegravir*</td>
<td></td>
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<tr>
<td></td>
<td>FTC/TDF</td>
<td>Darunavir/RTV*†</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3TC + TDF</td>
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<tr>
<td>Alternative</td>
<td>3TC/ZDV</td>
<td>Lopinavir/RTV*</td>
<td>Efavirenz*</td>
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<td></td>
<td></td>
<td></td>
<td>Rilpivirine*‡</td>
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<tr>
<td>Insufficient data to</td>
<td>FTC/TAF</td>
<td></td>
<td>Dolutegravir</td>
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<td>recommend</td>
<td></td>
<td>Fosamprenavir</td>
<td>EVG/COBI</td>
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<td></td>
<td></td>
<td></td>
<td>EVG/COBI</td>
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</tbody>
</table>

*In addition to 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if pretreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm³. §If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.
Trans-placental transfer of newer drugs*

• Higher Rates of Neuropsychiatric Adverse Events Leading to Dolutegravir Discontinuation in Women and Older Patients (Insomnia, sleep disturbances, Poor concentration, slow thinking, Dizziness, Headache, paraesthesia, Depression) http://www.medscape.com/viewarticle/873541?nlid=112427_721&src=WNL_mdplsfeat_170131_mscpedit_aids&uac=17333MK&spon=1&implID=1281938&faf=1

• Dolutegravir concentrations at delivery (13 h post-dose) were 1730 ng/ml in maternal blood and 2211 ng/ml in cord blood, suggesting significant in-utero exposure (Ratio 1.27 in 2 cases) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856184/pdf/aids-30-1313.pdf

• Ratio of Darunavir cord blood to maternal delivery concentration was 0.1076 (Zorrilla et al).*** and 0.18 (Stek et al) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4579345/

• Elvitegravir cord blood to maternal delivery concentration was 0.30 mg/L (ratio of 1.0 /case report) https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/450/elvitegravir--stribild--evg-cobi-tdf-ftc-

• Median Rilpivirine cord blood/maternal concentration ratio was 0.55 (Tran IMPAACT 1026) https://www.ncbi.nlm.nih.gov/pubmed/26918544

*INSTIs are smaller molecules (<500 Dalton mw) and are expected to “cross the placenta”
True or False

• HIV-infected pregnant women receiving ART who present for care during the first trimester should continue treatment during pregnancy, assuming the regimen is tolerated and effective in suppressing viral replication
  a. True
  b. False
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DHHS Recommendations: Women onSuppressive ART who Become Pregnant

• “In general, HIV-infected pregnant women receiving ART who present for care during the first trimester should continue treatment during pregnancy, assuming the regimen is tolerated and effective in suppressing viral replication”

• How to manage ART when women become pregnant while receiving newer antiretroviral drugs (with limited PK and safety data in pregnancy) as part of effective and well-tolerated regimens?
  • DHHS emphasizes that maintaining viral suppression is paramount for both maternal health and prevention of perinatal transmission
  • If uncertain about pregnancy safety of drugs within ART regimen, consultation with HIV perinatal specialist is recommended before considering a change
  • Report all ART exposures in pregnant women to Antiretroviral Pregnancy Registry
PROMISE: Efficacy and Safety at Median Follow-up of Approximately 2 Yrs

Between treatment arms, no significant difference in primary safety or efficacy endpoints

- Time to first grade 3/4 sign or symptom or grade 2-4 chemistry or hematology result ($P = .08$)
- Time to AIDS-defining event, serious non-AIDS event, or any-cause death ($P = .54$)

- Secondary endpoints: continuing ART associated with lower HIV event rate

<table>
<thead>
<tr>
<th>Outcome, n (rate per 100 PY)</th>
<th>Continue ART (n = 827)</th>
<th>Stop ART (n = 825)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of HIV/AIDS-related or WHO stage 2/3 events</td>
<td>57 (3.09)</td>
<td>99 (5.49)</td>
<td>0.56 (0.41-0.78)</td>
</tr>
<tr>
<td>WHO stage 2/3 events</td>
<td>38 (2.02)</td>
<td>80 (4.36)</td>
<td>0.47 (0.32-0.68)</td>
</tr>
</tbody>
</table>

• There is a time when we need to understand things: when we try to change them.

• We not always achieve the change, but at least we learn because we dare to explore new roads.

• Paulo Coelho
PrEP during pregnancy
Counseling Patients about PrEP Use During Conception, Pregnancy, and Breastfeeding
DHHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission

• For serodiscordant couples who want to conceive, initiation of antiretroviral therapy (ART) for the HIV-infected partner is recommended (AI for CD4 T-lymphocyte (CD4-cell) count \(\leq 550 \text{ cells/mm}^3\), BIII for CD4-cell count \(>550 \text{ cells/mm}^3\) ). If therapy is initiated, maximal viral suppression is recommended before conception is attempted (AIII).

• Periconception administration of antiretroviral pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission (CIII).

• The utility of PrEP of the uninfected partner when the infected partner is receiving ART has not been studied.

PrEP during pregnancy: potential barriers

• No specific guidelines
• Concerns for fetal exposure to a drug given for “maternal indications”
• No studies available
• Are there any benefits?
• Case reports
Before making any important decision—declaring a war, moving with his companions to another plain, choosing a field in which to sow seed—the warrior asks himself: “How will this affect the fifth generation of my descendants?”

A warrior knows that everything a person does has enduring consequences and he needs to understand what kind of world he is leaving behind for that fifth generation.

Paulo Coelho
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