HIV: Practice and Prevention, 2017

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HIV: Practice and Prevention, 2016

Epidemiology
Who should be tested
The initial visit/Routine testing and Prophylaxis
Starting antiretroviral therapy
Antiretroviral agents
Resistance
Drug interactions
Conception and Expectations
Prevention: Pre-Exposure Prophylaxis
Adults HIV Prevalence: 2015

- 36.7 millions infected
- 1.1 million deaths
Rates of Adults and Adolescents Living with Diagnosed HIV Infection, by Area of Residence, Year-end 2014 — United States and 6 Dependent Areas

N = 970,319 Total Rate: 360.0

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data are based on address of residence as of December 31, 2014 (i.e., most recent known address).
Stage 3 (AIDS) Classifications, Deaths, and Persons Living with Diagnosed HIV Infection Ever Classified as Stage 3 (AIDS) 1985–2014—United States and 6 Dependent Areas

Note. Deaths of persons with HIV infection, stage 3 (AIDS) may be due to any cause.
Trends in Annual Rates of Death due to the 6 Leading Causes among Persons 25-44 Years Old, 1987–2014—United States

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
Adults and Adolescents Living with Diagnosed HIV Infection, by Sex and Race/Ethnicity, Year-end 2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.

*Includes Asian/Pacific Islander legacy cases.*

*Hispanics/Latinos can be of any race.*
Rates of Diagnoses of HIV Infection among Adults and Adolescents, by Area of Residence, 2015 — United States and 6 Dependent Areas

N = 39,920 Total Rate: 14.7

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay.
Diagnoses of HIV Infection among Adults and Adolescents, by Sex 2010–2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.
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*a* Hispanics/Latinos can be of any race.
Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Transmission Category, 2015—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay. Data have been statistically adjusted to account for missing transmission category. “Other” transmission category not displayed as it comprises less than 1% of cases.

*a Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
HIV Prevalence by County, 2010-14

People Diagnosed and Living with HIV Infection by County
Washington State, 2010-2014

1 blue dot = 1 prevalent case of HIV infection in 2014, randomized by census tract of current residence. Note: prevalence limited to 9,186 cases (73%) with current residence information; 3,466 cases excluded due to missing data.

New Diagnoses and Deaths

Prevalence
Who should be tested?
Case 1

• A 32 year old woman comes to your office for her annual pap smear. She is G2P1 (son is 4 years old). She has a remote history of HPV but no other medical problems.
• She is divorced from her first husband for 4 years and recently remarried.
• Her review of symptoms and exam are normal.
Case 1

Should she be tested for HIV?

YES!
Testing Guidelines: Who to Test

• Which of the following patients should have HIV testing?
  – 30 year old heterosexual man in monogamous relationship
  – 22 year old MSM, multiple partners
  – 45 year old man diagnosed with TB
  – 34 year old pregnant woman
  – 38 year old married woman with no identifiable risk factors
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings
CDC Guidelines

- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.
Rationale for Testing Guidelines

- Increase testing
- Diagnose early before symptomatic
- Decrease stigma associated with testing
- Remove barriers to clinicians to implement testing
Multi-step Deterministic Model of HIV Infections in the US

Number of Infections by Step Along the HIV Care Continuum

Undiagnosed (18.1%) and not retained in care (45.2%) were responsible for 91.5% of all new HIV infections

(Skarbinski, JAMA Int Med, 2015)
New Washington State HIV Testing Recommendations, 2010

- No longer linked to counseling and partner services
- Obtain informed consent separately or with general consent for care
- Inform patient in writing or verbally that HIV testing is included
- Offer opportunity to ask questions or decline testing
- Notify local health officer of + test results

- Pregnant women – must still document patient refusal
HIV Care Cascade: USA

Only 28% of HIV+ persons in the US are engaged in care, on therapy, and have suppressed HIV

(MMWR, 2011)
HIV Care Cascade: Washington State

70% of HIV+ persons in the Washington State are engaged in care, on therapy, and have suppressed HIV (2015)
HIV Care Cascade: King County

75% of HIV+ persons in the King County are engaged in care, on therapy, and have suppressed HIV (June, 2016)
The initial visit:
Routine Testing
Opportunistic Infection Prophylaxis
Case 1

• A 23 year old gay man presents after testing positive for HIV by “rapid test” at a night club.

• This is his first ever HIV test. He is sexually active with men exclusively, has ~ 10 partners per year and does not regularly use protection.

• He is well and without symptoms

• His PMH is notable for depression, a history of methamphetamine use, gonorrhea and syphilis

• He is a college graduate, works in retail, drinks 6 beers on weekend nights, smokes ½ ppd and no longer uses illicit drugs

• His physical exam is normal
Case 1

- Perform a comprehensive history and exam
  - Dates of HIV testing (negative and first positive)
  - ARV history (including adherence, drug resistance and drug intolerances), CD4 nadir and HIV RNA zenith
  - HIV related illnesses
  - Cardiac, renal and hepatic disease history
  - TB exposure and risk
  - Travel and residence history (exposure to dimorphic fungi)
  - Mental health and substance abuse history
  - Sexual and STD history
  - Partner’s HIV status
  - Medications (watch for significant drug interactions)
  - Physical exam – particular attention to skin, mouth, lymphnodes, neurological and cognitive exam, anogenital exam, fat distribution and evidence for liver disease
Case 1

What laboratory testing is indicated at the initial visit?
- HIV serology
- CD4 count (absolute and percent)
- HIV RNA level
- HIV genotypic resistance testing
- CBC, chemistries and urinalysis
- Fasting lipids
- G6PD level
- TST or IGRA (repeat if negative with low CD4 after ART)
- Toxoplasma serology
- Syphilis serologies (IgG if no h/o disease, otherwise RPR or VDRL)
- Hepatitis B sAG, sAB, cAB – if isolated cAB, check HBV DNA
- Hepatitis C AB (repeat annually if at risk), if AB+, check HCV RNA
- Hepatitis A AB
- CMV AB (if at low risk for infection)
Case 1

• What about an STD evaluation?
  - All women should be screened for *Trichomoniasis*
  - Men and women should be screened for GC and *Chlamydia*

• Anal cancer screening?
  - Anyone practicing RAI or with a history of genital warts and women with abnormal pap smears should have an anal pap smear (weak recommendation, moderate quality evidence)

• CXR?
  - In those testing + for latent tuberculosis
# Follow-up Care

## Cancer screening: Cervical Cancer Screening

### < 30 years of age

<table>
<thead>
<tr>
<th>FREQUENCY</th>
<th>WOMEN WITHOUT HIV USPSTF/ACS/ASCCP</th>
<th>WOMEN WITH HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap every 3 years</td>
<td></td>
<td>Annually x 3, if 3 consecutive normal, then every 3 years</td>
</tr>
</tbody>
</table>

### ≥ 30 years of age

<table>
<thead>
<tr>
<th>FREQUENCY</th>
<th>WOMEN WITHOUT HIV USPSTF/ACS/ASCCP</th>
<th>WOMEN WITH HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Pap testing only</td>
<td>Pap every 3 years</td>
<td>Annually x 3, if 3 consecutive normal, then every 3 years</td>
</tr>
<tr>
<td>If Pap and HPV Co-testing</td>
<td>Pap and HPV negative → co-test in 5 yrs</td>
<td>Pap and HPV negative → co-test in 3 years</td>
</tr>
</tbody>
</table>


Case 1

• Vaccinations?
  - Influenza (inactivated) annually
  - *S. pneumonia*: PCV-13 once and Pnvax23 twice, 5 years apart
  - HPV: women 9-26, men 9-21 and consider 22-26
  - HAV: if HAV AB negative
  - HBV: (40ug Recombivax x 3 OR 2-20ug doses of Energix B x 4) if sAG negative and sAB < 10. Consider, if isolated cAB+ and HBV DNA negative
  - MMR: if not immune and CD4 > 200
  - TDAP: once as an adult
  - Varicella: if not immune and CD4 > 200
  - Zoster vaccine: consider in those > 60 and with CD4 > 200
  - *N. meningitidis*: 2 shot series, then every 5 years
Opportunistic Infection Prophylaxis
Case 2

- A 38 yo man presents to HMC ED with fatigue, weight loss, night sweats and diarrhea for 4 months.
- On exam he is emaciated and has slow response times. BP 95/65, HR 110, Temperature 38.2, RR 16. He has thrush, seborrhea and mild abdominal tenderness. His gait is unsteady and he walks gingerly complaining of pain in both feet.
- Laboratory exam: BUN 12, creatinine 1.8, HCO3 14, Hct 24, WBC 3.0, Plts 85K. Rapid HIV test +, CD4 24
- CXR clear
- BCs are taken, he is given IV fluids and admission is recommended. He refuses but is willing to follow up in the Madison Clinic in a while.
- What prophylaxis would you provide?
Risk of Opportunistic Infection

Normal CD4 = 750-1500

Bacterial Pneumonia, HSV, Zoster, Diarrhea

Oral Candidiasis (Thrush), Molluscum Contagiosum, Dermatitis, Folliculitis

Cryptococcal Meningitis, Toxoplasmosis, Non-Hodgkin’s Lymphoma

Pneumocystis jirovecii Pneumonia (PCP), Kaposi’s Sarcoma

Cryptococcal Meningitis, Toxoplasmosis, Non-Hodgkin’s Lymphoma

Mycobacterium avium (MAC), CMV (Retinitis, Colitis), Progressive Multifocal Leukoencephalopathy (PML), Microsporidiosis, Primary CNS Lymphoma (EBV)

Mycobacterium tuberculosis (TB)

Years after infection

CD4 Cell Count
Prophylaxis to Prevent Opportunistic Infections

Considerations for Prophylaxis

• Infection should be common and/or predictable
• Infection should be clinically significant
• Treatment (prophylaxis) should be effective, non-toxic and affordable
# Primary Prophylaxis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Criteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>CD4 &lt; 200 or CD4% &lt; 14 or Thrush or ADI</td>
<td>TMP/SMX or dapsone or atovaquone or aerosolized pentamidine</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>PPD &gt; 5 mm</td>
<td>INH</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>IgG+ and CD4 &lt; 100</td>
<td>TMP/SMX or dapsone + pyrimethamine + leukovorin</td>
</tr>
<tr>
<td>MAC</td>
<td>CD4 &lt; 50</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>VZV</td>
<td>CD4 &gt; 200</td>
<td>Vaccine</td>
</tr>
<tr>
<td>HAV</td>
<td>CD4 &gt; 200</td>
<td>Vaccine</td>
</tr>
<tr>
<td>HBV</td>
<td>CD4 &gt; 200</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
<td>Vaccine</td>
</tr>
<tr>
<td>Influenza</td>
<td>CD4 &gt; 200</td>
<td>Vaccine</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>CD4 &gt; 200</td>
<td>Vaccine</td>
</tr>
</tbody>
</table>
Starting Anti-retroviral Therapy
Cases 3-5

- A 52 yo Hispanic man presents with fever and seizures. He is diagnosed with *Toxoplasma* encephalitis. His CD4 count is 90 and his HIV RNA level is 256,000.

- A 43 yo asymptomatic woman is applying for life insurance and is found to be HIV+ with a CD4 count of 386 and a viral load of 65,000.

- An irritable 78 yo man had been HIV+ for 23 years. He’s never had an HIV related illness, his CD4 count is 790 and his viral load is 6000.
HIV Infection: Pathogenesis

A lot of important stuff happens here
Early Vs Deferred HAART
Strategic Timing of AntiRetroviral Treatment (START) Study

START: 2015

• Randomized study to start ART immediately (when CD4 > 500) or defer until CD4 < 350
• 215 sites in 35 countries, opened enrollment March 2011
• N = 4685 men and women > 18 (median age 36), all with CD4 > 500
• Median age 36, M:F 63%:27%, median CD4 651, VL 12,759
• Median follow-up: 2.8 years
• Countries include low, middle and high income
• Outcome: combination of serious AIDS events, serious non-AIDS events and death

START: 2015

- DSMB analysis of data from March 2015:
  - Early Rx group: 42 events
  - Deferred group: 96 events
  - 57% reduction in the primary endpoint in the early Rx group
  - Benefit regardless of age, sex, race, country, CD4 count, smoking status and FRS

### Early Vs Deferred HAART

**Strategic Timing of AntiRetroviral Treatment (START) Study**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Immediate Rx</th>
<th>Deferred Rx</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>#/100 py</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite primary endpoint</td>
<td>42</td>
<td>0.60</td>
<td>96</td>
<td>1.38</td>
</tr>
<tr>
<td>Components of endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious AIDS event</td>
<td>14</td>
<td>0.20</td>
<td>50</td>
<td>0.72</td>
</tr>
<tr>
<td>Serious non-AIDS event</td>
<td>29</td>
<td>0.42</td>
<td>47</td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td>12</td>
<td>0.17</td>
<td>21</td>
<td>0.30</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6</td>
<td>0.09</td>
<td>20</td>
<td>0.28</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>0.01</td>
<td>11</td>
<td>0.16</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3</td>
<td>0.04</td>
<td>10</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-AIDS cancer</td>
<td>9</td>
<td>0.13</td>
<td>18</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12</td>
<td>0.17</td>
<td>14</td>
<td>0.20</td>
</tr>
</tbody>
</table>

HAART 2011: Effect on Transmission

HPTN 052: Immediate vs Delayed ART for HIV Prevention in Sero-discordant Couples

**HIV-infected, heterosexual sero-discordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm$^3$**
(N = 1763 couples)

**Immediate HAART***
Initiate HAART at CD4+ cell count 350-550 cells/mm$^3$
(n = 886 couples)

**Delayed HAART**
Initiate HAART at CD4+ cell count $\leq$ 250 cells/mm$^3$†
(n = 877 couples)

Primary efficacy endpoint: virologically linked HIV transmission

Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death

HPTN 052: HIV Transmission Reduced by 93% in Sero-discordant Couples

Total HIV-1 Transmission Events: 78
(3 in immediate arm and 43 in delayed arm; \(P < .001\))

Linked Transmissions: 46

Unlinked or TBD Transmissions: 32

Delayed Arm: 43
Immediate Arm: 3

\(P < .001\)

No transmissions occurred if the + partner was suppressed
ART is recommend for **all** HIV infected patients

### CD4+ Cell Count

<table>
<thead>
<tr>
<th>CD4+ Cell Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 350 cells/mm³</td>
<td>Start ART (AI)</td>
</tr>
<tr>
<td>350-500 cells/mm³</td>
<td>Start ART (AI)</td>
</tr>
<tr>
<td>&gt; 500 cells/mm³</td>
<td>Start ART (AI)</td>
</tr>
</tbody>
</table>

### Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count

- History of AIDS-defining illness (AI)
- Pregnancy (AI)
- HIV-associated nephropathy (AII)
- HBV co-infection (AII)
- Patients at risk of transmitting HIV to sexual partners (AI, heterosexuals; AIII, others)
- HCV co-infection* (BII)
- Patients > 50 years of age (BIII)
Case 6

• A 24 yo gay man presents with fever, sore throat, cervical adenopathy and a faint rash 12 days after an ill-advised visit to a bath house while intoxicated.

• His HIV Ab/Ag test is +, immunoblot is negative, WB is negative, plasma HIV RNA + at 500,000 copies

• What is this illness?

• Should he be offered ART?
Treatment of Early HIV

ACTG 5217: The Setpoint Study

HIV infected with seroconversion within the last 6 months

Immediate HAART (IT)
- for 36 weeks – then stop

Delayed HAART (DT)

Primary endpoint: composite of needing ART (CD4 < 350 or VL > 200,000 or clinical category B or C event) + log HIV RNA at 72 weeks

Study halted by DSMB after 130 of 150 enrolled: 10% in IT Vs 50% in DT group needed to start or restart ART

Treatment of Early HIV

ACTG 5217: The Setpoint Study

Time to Initiation or Re-initiation of ART

### Treatment of Early HIV

Fiebig I patients: no HIV DNA in PBMC or $T_{CM}$ cells before and after ARV (Ananworanich and SEARCH study group, CROI 2013 #47)

<table>
<thead>
<tr>
<th></th>
<th>Fiebig I (RNA +) N=19</th>
<th>Fiebig II (P24+) N=3</th>
<th>Fiebig III (AB+) N=25</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC-DNA Total (copies/10^6)</td>
<td>7</td>
<td>2191</td>
<td>289</td>
<td>0.0002</td>
</tr>
<tr>
<td>PBMC-DNA Integrated % Undetectable</td>
<td>100%</td>
<td>67%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>$T_{CM}$ $T_{TM}$ $T_{EM}$ DNA (copies/10^6) (leukophoresis)</td>
<td>0, 0, 0 (N=3)</td>
<td>446, 2830, 1898 (N=4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBMC-DNA 24wks ARV % Undetectable</td>
<td>100% (N=11)</td>
<td>67% (N=3)</td>
<td>72% (N=18)</td>
<td></td>
</tr>
<tr>
<td>Sigmoid-DNA Integrated (copies/10^6)</td>
<td>0 (N=8)</td>
<td>9263 (N=11)</td>
<td>149</td>
<td>0.01</td>
</tr>
<tr>
<td>Sigmoid-DNA Integrated, 24 wks ARV, % Undetectable</td>
<td>100% (N=4)</td>
<td>67% (N=9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HIV Rebound Post Treatment Interruption In Persons Suppressed in Fiebig 1 Acute HIV

• Methods:
  - 8 subjects (7 men, 1 woman) on ART with VL < 20 for a median of 2.8 years (2.5-5.5)
  - VL monitoring every 3-7 days post treatment interruption (TI)

• Subjects:
  - Median age 29 (22-34)
  - Pre-treatment VL 4.2 logs, HIVDNA 66 copies per $10^6$ CD4 cells, median CD4 413
  - Pre-treatment interruption: median CD4 561, HIVDNA and inducible HIV RNA in $10^6$ CD4 cells = 0

Colby, Abst #124
HIV Rebound Post Treatment Interruption In Persons Suppressed in Fiebig 1 Acute HIV

- Results

Treatment of very early HIV infection, while leading to small reservoir size, is insufficient to eradicate the reservoir.

Colby, Abst #124
Patients presenting with early HIV infection should be offered ART

- Decreases severity of acute infection
- Lowers the virologic set point
- Leads to improved CD4 recovery that can affect disease progression
- Limits the size of the HIV reservoir
- Decreases transmission events
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What to use?
Antiretroviral Therapy

Five Drug Classes

- Nucleoside Reverse Transcriptase Inhibitors (NRTI)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
- Protease Inhibitors (PI)
- Integrase Inhibitors
- Cell Entry Inhibitors
HIV Life Cycle
### DHHS Recommendations (2016): Recommended Regimens Regardless of CD4 or Viral Load

#### PI-Based
- **Darunavir/R** + **TDF/FTC (Truvada)** = 3 pills/d

#### Integrase-Based
- **Raltegravir** + **TDF/FTC** = 3 pills (bid regimen)
- **Elvitegravir + cobi** + **TDF/FTC** = Strabilid = 1 pill/d
- **Dolutegravir** + **TDF/FTC or 3TC/ABC (Triumeq)**
  - = 1 or 2 pills/d
New Medications: Tenofovir alafenamide (TAF)

• A prodrug of tenofovir with reduced plasma concentrations and consequently reduced renal and bone adverse effects

• Currently available in fixed dose tablets:
  - Cobisistat + elevitegravir + FTC + TAF = Genvoya
  - Rilpivirine + FTC + TAF = Odefsey
  - FTC + TAF = Descovy
Initiating Antiretroviral Therapy

**DHHS Recommendations (2017): Recommended Regimens Regardless of CD4 or Viral Load**

### PI-Based
- **Darunavir/R** + TDF or TAF/FTC

### Integrase-Based
- **Raltegravir** + TDF or TAF/FTC
- **Elvitegravir + cobi** + TDF or TAF/FTC
- **Dolutegravir** + TDF or TAF/FTC or 3TC/ABC
LATTE-2: Long Acting Cabotegravir + Rilpivirine

- **Cabotegravir**
  - Novel integrase inhibitor
  - Analogue of dolutegravir
  - 2 formulations:
    - Oral: $T_{1/2}$ 40 hours (previous phase 2 study showed efficacy & safety 30-90 mg/day)
    - **LA nanosuspension $T_{1/2}$ 20-40 days (200 mg/mL)**

- **Rilpivirine**
  - FDA approved NNRTI (25 mg/day PO)
  - **LA nanosuspension $T_{1/2}$ ~30-90 days (300 mg/mL)**
LATTE-2: Participants and Study Overview

309 pts: 91% male, 15% AA, VL $4.3 \log_{10}$, 18% $>100K$, CD4 489

CAB 30 mg + ABC/3TC PO for 20 wks

VL $<50$ on PO

+PO RPV 4 wks

Induction Phase (24 wks)

289 entered maintenance
2 injections of 2 or 3 mL at a time

1º endpoint: VL % $< 50$ by FDA snapshot analysis

400 mg CAB + 600 mg RPV IM q4 wks (N=115)*

600 mg CAB + 900 mg RPV IM q8 wks (N=115)**

CAB + ABC/3TC PO q day (N=56)

Maintenance Phase (96 wks)

32 wk results

* Loading dose of CAB at day 1
** Loading doses of CAB at day 1 & wk 4

Margolis, D et al. CROI 2016
LATTE-2 Week 32 Primary Virologic Results

% with HIV RNA <50 c/mL

- Q4W: 99%
- Q8W: 95%
- Oral CAB: 98%
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Failure and Drug Resistance
Case 7

• A 38 year old man with AIDS was started on HAART (EFV, TDF, FTC) a year ago with an excellent response: his HIV RNA dropped from 248,000 copies to < 30 copies and his CD4 increased from 87 to 360 cells.

• Unfortunately, he’s missed several recent appointments and when he finally does make it to the office you find he has thrush and seborrheic dermatitis. His CD4 count has decreased to 240 cells and his HIV RNA is now detectable at 37,000 copies.

• What is going on?

• What, in particular, are you worried about?
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- Insufficient drug level
- Viral replication in the presence of drug
- Resistant virus

Factors:
- Poor adherence
- Social/personal issues
- Regimen issues
- Toxicities

Factors:
- Poor potency
- Wrong dose
- Host genetics
- Poor absorption
- Rapid clearance
- Poor activation
- Drug interactions
Adherence and Drug Resistance Relationship
## When to Use Resistance Testing

<table>
<thead>
<tr>
<th>Patient Status</th>
<th>IAS-USA¹</th>
<th>DHHS²</th>
<th>European³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/acute</td>
<td>Recommend</td>
<td>Recommend ‡</td>
<td>Recommend</td>
</tr>
<tr>
<td>Post-exposure prophylaxis</td>
<td>—</td>
<td>—</td>
<td>Recommend</td>
</tr>
<tr>
<td>Chronic, treatment naïve</td>
<td>Consider*</td>
<td>Recommend ‡</td>
<td>Strongly consider*</td>
</tr>
<tr>
<td>Failure</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Recommend †</td>
<td>Recommend</td>
<td>Recommend †</td>
</tr>
<tr>
<td>Pediatric</td>
<td>—</td>
<td>—</td>
<td>Recommend †</td>
</tr>
</tbody>
</table>

*Especially if exposure to someone receiving antiretroviral drugs is likely or if prevalence of drug resistance in untreated patients ≥5% (European: ≥10%); †When viral load is detectable; ‡December 1, 2007: The panel recommends performing genotypic drug resistance testing for all treatment-naïve patients entering into clinical care, regardless of whether antiretroviral therapy is to be initiated. This recommendation is based on the fact that transmitted resistance mutation may be detected at a time point more proximal to the time of infection than later. Repeat testing may be considered at the time when therapy is to be initiated.

Drug interactions
Case 8

• A 25 year old woman is recently diagnosed with advanced HIV. Her CD4 count is 10, her plasma HIV RNA level is > 1,000,000.

• Her PMH is notable for GERD, anxiety, opiate addiction, hyperlipidemia, primary pulmonary hypertension, hepatitis C, hepatitis B and a seizure disorder.

• Current medications are omeprazole, diazepam, methadone, lovastatin, sildenafil, dilantin, pegylated interferon, ribavirin and estradiol.

• Besides bactrim and azithromycin you prescribe HAART selecting ddI, 3TC and atazanavir/ritonavir.

• The clinic pharmacist approaches you shaking her head in disgust. What is the problem?
Case 8

Drug Interactions

- NNRTIs (EFV, NVP, ETR, RLP) induce the cytochrome P450 system
- Protease inhibitors (esp RTV) and cobicistat inhibit the cytochrome P450 system
- Ribavirin increases the toxicity due to ddI
- NNRTIs decrease estradiol concentrations and, paradoxically, so do protease inhibitors
- Methadone metabolism is increased by NNRTIs and variably affected by protease inhibitors
- Atazanavir and rilpivirine absorption is decreased with co-administration of PPI

- Watch out for significant drug interactions with all antiretrovirals, especially those metabolized through the cytochrome P450 system
For this patient:

- Change omeprazole to ranitidine
- Change diazepam to lorazepam
- Watch for methadone withdrawal
- Change lovastatin to pravastatin
- Talk to pulmonologist about sildenafil dose
- Transition from dilantin to other anticonvulsant (Keppra)
- Don’t use ddI with ribavirin
- Don’t use 3TC alone in patient with hepatitis B
- Don’t rely on OCPs alone for birth control in patient on HAART
Case 9: HIV: 2015

- A 38 yo HIV+ male is married to a 30 yo HIV negative woman who wants to conceive a child.
- He has been on ART for 6 years, his HIV RNA level is always non-detectable
- They practice safe sex most of the time. She is tested for HIV twice a year.
- He worries that he won’t be around to raise the child and is concerned about transmitting HIV to his wife should they go forward with her plan

- How do you consul them?
HIV and Age Associated Comorbidities: 2015

• Cross sectional study of Age Associated Non-communicable Comorbidities (AANCCs) (2010 - 2012)
• 540 HIV+ patients > 45 years followed at an outpatient HIV clinic in Amsterdam.
• 524 HIV uninfected patients were recruited from the sexual health clinics in Amsterdam or from uninfected cohorts existing in Amsterdam cohort studies on HIV/AIDS

Schouten, Clin Infect Dis 2014; 59(12):1787-97
HIV and Age Associated Comorbidities: 2015

- Cross sectional study of AANCCs 2010 – 2012
- HTN, myocardial infarction, vascular disease and impaired renal function were more common in HIV+ subjects
- Risk of AANCCs was independently associated with age, smoking, FH, higher waist to hip ratio and HIV (OR 1.58)

Schouten, Clin Infect Dis 2014; 59(12):1787-97
HIV: 2015: Life Expectancy

- NA ACCORD study of 22,937 adults on ART
- Crude mortality rate was 19.8/1000 person-years
- Life expectancy increased from 36.1 to 51.4 years from 2000-2 to 2006-7
- Life expectancy was lower for non-whites, IDU and those with baseline CD4 < 350
- A 20 year old HIV+ adult in the US or Canada is expected to live into their early 70s

HIV: 2015: Life Expectancy

- NA ACCORD study of 22,937 adults on ART
- Life expectancy
  - Overall (A)
  - By sex (B)
  - By transmission group (C)
  - By race (D)
  - By baseline CD4 (E)

Conception

Conception Between HIV Discordant Couples (Positive partner suppressed on ART)

HIV Negative Woman

HIV Prevention Methods
- PrEP alone
- Timed IC + PrEP
- Sperm washing + IUI + PrEP
- SW + IVF
- SW + IVF + ICSI

HIV Negative Man

HIV Prevention Methods
- Collect semen – vaginal insemination
- PrEP alone
- Male circumcision + PrEP
- Timed IC + PrEP
- IVF, ICSI
Conception

Cost and HIV Transmission Risk by Method

<table>
<thead>
<tr>
<th>Variable</th>
<th>IUI + SW</th>
<th>IVF + SW</th>
<th>ICSI + SW</th>
<th>Self Insemination</th>
<th>Intercourse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ave # cycles</td>
<td>2.8</td>
<td>1.4</td>
<td>0.6</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Cost/cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PrEP</td>
<td>$1265</td>
<td>$12,513</td>
<td>$15,128</td>
<td>$30</td>
<td>Free (sort of)</td>
</tr>
<tr>
<td>+ PrEP</td>
<td>$2195</td>
<td>$13,443</td>
<td>$16,058</td>
<td>$960</td>
<td>$930</td>
</tr>
<tr>
<td>Cost/birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PrEP</td>
<td>$12,635</td>
<td>$41,132</td>
<td>$46,256</td>
<td>$30</td>
<td>Free (sort of)</td>
</tr>
<tr>
<td>+ PrEP</td>
<td>$16,835</td>
<td>$42,062</td>
<td>$47,156</td>
<td>$5145</td>
<td>$5115</td>
</tr>
<tr>
<td>Preg rate</td>
<td>19%</td>
<td>38.1%</td>
<td>23%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>HIV Risk</td>
<td>0.1-0.5%</td>
<td>0-0.4%</td>
<td>0-0.09%</td>
<td>0.03-0.5%</td>
<td>0.03-0.5%</td>
</tr>
</tbody>
</table>

## Conception

### Conception in discordant couples

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barriero, AIDS Rev, 2006</td>
<td>62 couples: infected partner (22 F and 40 M) suppressed on ART</td>
<td>Timed unprotected intercourse</td>
<td>68 live births: no transmission b/n partners</td>
</tr>
<tr>
<td>Vernazza, AIDS, 2011</td>
<td>53 couples: infected partner (all male) suppressed on ART</td>
<td>PrEP (TDF alone 36 and 12 hours) before timed intercourse</td>
<td>Conception rate 26-75% (1 to 12 cycles), no HIV Tx</td>
</tr>
<tr>
<td>Semprini, Am J Obst and Gyn, 2013</td>
<td>635 couples (2113 cycles)</td>
<td>SW-IUI</td>
<td>41% of women had a live birth; no HIV transmissions</td>
</tr>
<tr>
<td>Lampe, Am J Obst and Gyn, 2011</td>
<td>2003 women with HIV+ male partners</td>
<td>SW followed by IUI, IVF or ICSI</td>
<td>1080 pregnancies; no HIV transmissions</td>
</tr>
</tbody>
</table>
Case #10: PrEP

• A 26 yo HIV negative MSM who has been treated for rectal gonorrhea and syphilis twice in the last year presents asking about HIV Pre-Exposure Prophylaxis (PrEP)

• A 30 yo HIV negative woman is married to an HIV+ man. He is not perfectly adherent to his HIV treatment and they do not consistently use condoms. She asks if PrEP is right for her.
What is PrEP?

- **PEP**
- **Daily PrEP**
- **Intermittent PrEP**

**Single exposure**

**Frequent regular exposures**

**Occasional exposures**
The importance of being adherent

<table>
<thead>
<tr>
<th></th>
<th>Efficacy in randomized comparison</th>
<th>% of blood samples with tenofovir detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP</strong></td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td><strong>TDF2</strong></td>
<td>62%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>44%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>FEM-PrEP</strong></td>
<td>6%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td>-</td>
<td>29%</td>
</tr>
</tbody>
</table>

Grant et al N Engl J Med 2010
Marrazzo et al CROI 2013 #26LB
When taken, PrEP works

- iPrEx: 51% adherence / 44% efficacy
- Bangkok: 67% adherence / 49% efficacy
- Partners PrEP: 81% adherence / 75% efficacy
- TDF2: 79% adherence / 62% efficacy

HIV protection effectiveness

% adherence
When taken, PrEP works

% adherence

FEM-PrEP and VOICE
≤30% adherence / No efficacy

HIV protection effectiveness
FDA Approves First Medication to Reduce HIV Risk

“It is still better to prevent HIV than to treat a life-long infection of HIV.”

Deborah Birnkrant, director of the Division of Antiviral Products, FDA
July 16, 2012
CDC provides interim guidance for use of PrEP in MSM and heterosexuals.
Intermittent PrEP: ipergay

- Truvada: 2 pills 2-24 hours before sex – then 1 pill 24 and 48 hours later
- N=400 MSM who practice unprotected RAI

(Molina, NEJM, 2015)
Intermittent PrEP: ipergay

- Results: 86% reduction in HIV transmission
- Participants took a median of 15 Truvada pills per month

(Molina, NEJM, 2015)
Who is PrEP for?

- Anyone with an HIV-positive sex partner or injecting partner
- Recent bacterial STD (chlamydia, gonorrhea, or syphilis)
- High number of sex partners
- Inconsistent or no condom use
- Commercial sex work
- Anyone in an area with a high prevalence of HIV infection

- HIV-negative
- Good kidney function
Is PrEP safe?

- **Start-up syndrome**
  - 1-18.5% with gastrointestinal symptoms

- **Renal safety**
  - 0.2% changes in creatinine

- **Bone safety**
  - 0.4 to 1.5% loss of BMD
  - Return towards baseline with withdrawal
  - Not associated with increased fracture risk

- **Longer term follow-up in diverse populations needed**

How often do I need to be monitored?

Every 3 months for

- HIV testing
- Medication refills
- Talk about side effects and adherence

Every 6 months (at least) for

- Monitoring kidney function
- STD testing (more frequently in high risk patients)
Pre-Exposure Prophylaxis Drug Assistance Program (PrEP DAP)

What is PrEP?

Pre-Exposure Prophylaxis (PrEP) is an HIV prevention method in which HIV-negative people take a daily pill to reduce their risk of becoming infected.

When used consistently, PrEP has been shown to reduce the risk of HIV-1 infection among adult men and women at very high risk for HIV infection through sex or injection drug use. TRUVADA® has been approved by the Federal Drug Administration for use in PrEP.

If you are interested, your prescribing medical provider can answer your questions.

Where can I find additional information on PrEP?

- [What is PrEP?](#)
- [PrEP Facts](#)

What is PrEP DAP?

PrEP DAP is a drug assistance program for HIV-negative people who have risk factors that expose them to HIV. PrEP DAP will pay for TRUVADA® for people who want to be on PrEP.

Learn about PrEP DAP in our brochure - [English (PDF)](#)

PrEP DAP brochure - [Spanish version (PDF)](#)
How can I learn more?

General Information
www.cdc.gov/hiv/basics/prep.html
www.facebook.com/groups/PrEPFacts
www.prepfacts.org

How to Pay for PrEP
Gilead’s Medication Assistance Program
www.gilead.com/responsibility/us-patient-
iaccess/truvada%20for%20prep%20medication%20assistance%20program

Washington PrEP DAP (also has list of PrEP providers by county)
www.doh.wa.gov/YouandYourFamily/IllnessandDisease/HIVAIDS/HIVCareClientServices/PrEPDAP
Summary

- HIV is a human retrovirus that infects and kills CD4+ T-cells causing a progressive loss of immune function and susceptibility to opportunistic infections and cancers.
- HIV treatment has evolved from being ineffective and toxic → effective and toxic → effective and relatively non-toxic.
- Non-traditional consequences of HIV (e.g., cardiovascular disease) are now among the most prominent problems patients face.
- Most patients who adhere to antiretroviral therapy can lead relatively normal lives that includes offspring, if desired.
- Pre-Exposure Prophylaxis (PrEP) is an effective strategy for preventing HIV infection in high-risk patients where other strategies may not be completely protective.