Conflicts of Interest

Disclosures

• **Grant/Research Support**: GSK, Merck, Gilead, BMS, N&N Pharmaceuticals Inc., Taimed Biologics, Inc.

• **Advisory Board**: Viiv Healthcare, Gilead

• **Stock Shareholder**: Merck, Phizer, Johnson&Johnson, GSK, Gilead
Objectives

1. Review the strategies for prevention of HIV infection in the US
2. Review the concept of treatment as prevention for HIV infection
3. Understand the principles of pre-exposure prophylaxis and guidelines for pre-exposure prophylaxis for HIV
4. Review the principles of post-exposure prophylaxis for HIV
HIV in the United States: At A Glance

Gay & Bisexual Men of All Races

Are the Most Severely Affected by HIV

1 in 6 Living with HIV

About 1 in 4 New HIV Infections is Among Youth Ages 13-24

Are Unaware of Their Infection

Most of Them Do Not Know They Are Infected, Are Not Getting Treated, and Can Unknowingly Pass the Virus on to Others

www.Aids.gov
START Study: Initiation of ART in Early Asymptomatic HIV Infection

Multicontinental Study (n=4685)
- HIV-positive adults
- Treatment-naive
- CD4 >500 cells/mm³

Randomization 1:1

Immediate ART (n=2326)

Deferred ART (n=2359)
(CD4 Declined to <350 cells/mm³ or AIDS-related event)

5/2015: DSMB recommends stopping trial: Deferred arm offered ART

Primary outcome was a composite outcome of 2 major components:

- Any serious AIDS-related event
  - Death from AIDS or any AIDS-defining event, Hodgkin’s lymphoma
- Any serious non–AIDS-related event
  - CVD (myocardial infarction, stroke, or coronary revascularization) or death from CVD, end-stage renal disease (initiation of dialysis or renal transplantation) or death from renal disease, liver disease (decompensated liver disease) or death from liver disease, non–AIDS-defining cancer (except for basal cell or squamous cell skin cancer) or death from cancer, and any death not attributable to AIDS

Immediate ART Prevents AIDS- and Non-AIDS Related Events

Number of Serious Events

Component (Serious Events)

- TB, KS, lymphoma — most common AIDS-related events — all less frequent in immediate-ART group
- Cancer rates (combining AIDS/non-AIDS) lower in immediate-ART group
- Greatest benefit: age >50, VL >50,000, CD4:CD8 <0.5, Framingham score >10%

Deferred ART (n=2359) vs Immediate ART (n=2326)

- 57% Reduction (P<0.001)
- 72% Reduction (P<0.001)
- 39% Reduction (P=0.04)

**ART recommended for all HIV+ individuals, regardless of CD4 cell count**

<table>
<thead>
<tr>
<th>CD4 Cell Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 350</td>
<td>AI</td>
</tr>
<tr>
<td>350-500</td>
<td>AI</td>
</tr>
<tr>
<td>&gt;500</td>
<td>AI</td>
</tr>
</tbody>
</table>

AI: strong recommendation, data from randomized clinical trials

WHO on Sept 30, 2015: “Treat-all”
Primary Goals of HIV Treatment

- Maximally and durably suppress plasma HIV viral load
- Reduce HIV associated morbidity and prolong survival
- Improve quality of life
- Restore and preserve immunologic function
- Prevent HIV transmission
  - “Treatment as prevention” - TASP
- May also decrease inflammation and immune activation – thought to contribute to higher rates of cardiovascular and other comorbidities
In the 1990s...

...2015
In the 1990s...

...2015

Courtesy of: http://hivpositivemagazine.com/2016_Healthy_Aging.html
Commonly Used Medications for HIV

NRTIs
- Abacavir (ABC)/3TC
- Tenofovir*/FTC

* Tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)

NNRTI:
- Rilpivirine (RPV)** (if VL <100K, CD4>200)
- Efavirenz (EFV)+

Boosted PI: ritonavir or cobicistat plus
- Darunavir (DRV/r or DRV/c)
- Atazanavir (ATV/r or ATV/c)

Integrase inhibitor:
- Raltegravir (RAL)
- Elvitegravir (EVG)/cobicistat**
- Dolutegravir (DTG)**

**Coformulated with TDF/FTC and TAF/FTC; +Coformulated with TDF/FTC; ++Coformulated with ABC/3TC
Drug specific side effects of Newer NRTIs

**Tenofovir (nucleotide)**

- **Tenofovir disoproxil fumarate (TDF)**
  - Renal toxicity - ↑Scr, proteinuria, hypophosphatemia
  - Fanconi-like syndrome
  - Osteomalacia
  - Decrease in bone mineral density

- **Tenofovir alafenamide (TAF)**
  - TAFs reduced dose and improved stability, plasma exposure of tenofovir is 90% lower with TAF (vs TDF) – 25 mg vs 300 mg
  - Less renal toxicity, less bone mineral density loss

- **Abacavir**
  - 3 – 9% fatal hypersensitivity reaction if HLA B5701 positive
  - Requires screening for HLA B5701
  - The association between ABC and increased risk of myocardial infarction remains controversial – first raised by the D:A:D study
  - Abacavir should be used with caution in patients who have or who are at high risk for cardiovascular disease
Commonly Used Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI’s)

- Efavirenz (Sustiva™)
- Rilpivirine (Edurant™)

- Long half-life, may take two weeks to clear
- A single mutation can cause resistance to the entire class (with the exception of Etravirine) – low genetic barrier to resistance
- Efavirenz – insomnia, abnormal dreams, depression, suicidal ideation
- Rilpivirine – less CNS side effects, but do not give with PPIs, and must be taken with food
HIV Protease Inhibitors

Atazanavir (Reyataz™)
Darunavir (Prezista™)

• Gastrointestinal distress
• Bleeding in hemophiliacs
• Hyperglycemia, insulin resistance
• Hyperlipidemia
• Lipodystrophy – (abdominal lipo hypertrophy)
• Hepatotoxicity
• Needs to be boosted with Ritonavir or Cobicistat
  • Metabolized by and inhibit CYP3A4
  • Drug Interactions are very challenging!!
• Atazanavir can also cause a Gilbert syndrome with increased bilirubin (Bili ~ 2 - 4)
Ritonavir Boosting - Pharmacoenhancing - of Fortovase

- PIs traditionally coupled with RTV (100-400 mg QD) as a pharmacologic booster
- RTV inhibits CYP3A4 in the liver, increasing PI exposure and half-life
- Boosting allows less frequent PI administration and lower daily dose
- RTV associated with diarrhea and nausea, increased lipids, many drug–drug interactions

Now in practice - Atazanavir/r, Darunavir/r
Lipid lowering agents and PIs: Drug interactions

- **Pravastatin**: Use cautiously
- **Atorvastatin**: Low interaction potential
- **Rosuvastatin**: Use cautiously
- **Lovastatin**: Contraindicated
- **Simvastatin**: Contraindicated

**SQV/RTV**
- Atorvastatin $\uparrow$ 347% AUC
- Simvastatin $\uparrow$ 3059% AUC
- Pravastatin $\downarrow$ 50% AUC
Newer Pharmacoenhancers

- Cobicistat extends the half-life of elvitegravir an integrase inhibitor that is part of Stribild
- Cobicistat is potent CYP3A inhibitor
- It also inhibits tubular secretion of creatinine
- To use this drug, the pre-ART creatinine clearance must be above 70
- Potential for other drug-drug interactions
Integrase Strand Transfer Inhibitors

- Raltegravir (Isentress®)
- Dolutegravir (Tivicay®)
- Elvitegravir + Cobicistat (component of Stribild® and Genvoya®)

- Overall well tolerated – have become the “darlings”
- Can cause insomnia and depression
- Very minimal drug-drug interaction for Raltegravir & Dolutegravir
- Eltegravir combined with cobicistat is well tolerated but beware of drug-drug interaction
- COBI and DTG: inhibits Cr secretion without reducing renal glomular function
HPTN 052: Stable Heterosexual Couples

Phase 3 study
Americas, African, Asian sites
(n=1763 couples)
Stable, healthy, sexually active,
serodiscordant couples
CD4 350-550 cells/mm$^3$

Randomization
1:1

Delayed ART
CD4 $\leq 250$ cells/mm$^3$
Similar baseline demographic characteristics
and sexual history/behavior both arms
and between HIV-negative partner and HIV-positive,
treatment naïve index patient

Early ART
CD4 350 to 550 cells/mm$^3$

Primary Endpoints

- Transmission
  - Virologically linked transmission events

- Clinical
  - WHO stage 4 clinical events
  - Pulmonary TB
  - Severe bacterial infection and/or death

HPTN 052: HIV Treatment as Prevention

- DSMB halts trials after a median follow-up: 1.7 years
  - HIV RNA <400 copies/mL
    - Early ART: 90%
    - Delayed ART: 93%
- Linked HIV transmission to HIV-negative partner (n=39)
  - Early therapy (n=1)
    - 0.1 per 100 person-years
  - Delayed therapy (n=27)
    - 1.7 per 100 person-years
- Early ART that suppressed HIV RNA led to a 96% reduction of sexual transmission of HIV in serodiscordant couples

HPTN 052 (Final Results): Stable Heterosexual Couples

Phase 3 study
Americas, African, Asian sites
Stable, healthy, sexually active, serodiscordant couples
CD4 350-550 cells/mm³

Randomization 1:1

Delayed ART
CD4 ≤250 cells/mm³
Similar baseline demographic characteristics and sexual history/behavior both arms and between HIV-negative partner and HIV-positive, treatment naïve index patient

Early ART
CD4 350 to 550 cells/mm³

Primary Endpoints
- Transmission
  - Virologically linked transmission events
- Clinical
  - WHO stage 4 clinical events
  - Pulmonary TB
  - Severe bacterial infection and/or death

Status of Participants
Enrolled (2010; n=1763 enrolled)
Remained in trial
  2011 (n=1702)
  2015 (n=1536)

The early initiation of ART led to a sustained decrease in genetically linked HIV-1 infections in sexual partners.

Relative Reduction: 69%

Relative Reduction: 93%

HPTN 052: Final Results of HIV Prevention in Stable Heterosexual Couples

- Linked HIV transmission to HIV-negative partner (n=46)
  - Overall 93% reduction in risk of transmission with early therapy
- Linked partner infections diagnosed after index partner started ART (n=8)*
  - Recently initiated ART (n=4)
  - Virologic failure (n=4)
- No HIV transmission among people who were suppressed
  - Timing of the linked transmission events supports the model that HIV transmission is very unlikely in the setting of viral suppression

*Early arm (n=3) and delayed arm (n=5). Phylogenetic methods compared HIV pol sequences from index partner pairs and controls. Linkage probability was further assessed by comparing the genetic distances between pol sequences (Bayesian analysis).

HIV Cascade of Care: Missed Opportunities in the US

HIV-Infected: >25 Years of Age (n=896,800)

- Diagnosed: ~88%
- Linked to Care: ~73%
- Retained in Care: ~40%
- Viral Suppression: ~28%

HIV-Infected: 13-29 Years of Age (n=78,949)

- Diagnosed: 40%
- Linked to Care: 25%
- Retained in Care: 11%
- Viral Suppression: 6%

14% (approximately 1 in 7 people living with HIV) were unaware of their infection.
Only 3 Out Of 10 People Living With HIV Had The Virus Under Control.

**Achieving Viral Suppression: More People with HIV Need to be in Medical Care**

- **People living with HIV**
  - 30% Virally suppressed
  - 70% Not virally suppressed

- **People living with HIV who were not virally suppressed**
  - 4% In care but not on ART*
  - 10% On ART but not virally suppressed
  - 20% Not diagnosed
  - 66% Diagnosed but not in care

*Sources: CDC National HIV Surveillance System and Medical Monitoring Project, 2011.
Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Multinational study
HIV-negative men or transgender women who have sex with men
Screened (n=4905)

Randomization 1:1

Emtricitabine/tenofovir DF (n=1251)
Similar baseline demographic characteristics (except mean age), sexual risk factors, STIs, and HBV status
Follow-Up 3324 person-years (median 1.2 years)

Placebo (n=1248)

Study Outcomes
- HIV seroconversion
- Adverse events
- Metabolic effects
- HBV exacerbations
- Risk behavior and STIs (including HSV)
- Adherence

Drug resistance, HIV RNA level, immunologic response, and CD4 cell count assessed in people who become HIV positive during the study.

• Overall efficacy was a 44% reduction in incidence of HIV.

• In subjects with detectable blood levels of FTC-TDF efficacy was 92%.

iPrEx Open-Label Extension (OLE): HIV Incidence and Risk Reduction by Detectable Drug

![Graph showing HIV incidence and risk reduction by detectable drug levels.](graph.png)

**Tablets/Week (％ patients):**
- <2 (26)
- 2 to 3 (12)
- 4 to 6 (21)
- 7 (12)

**Risk Reduction:**
- <2: 44%
- 2 to 3: 84%
- 4 to 6: 100%
- 7: 100%

Grant RM, et al. 20th IAC. Melbourne, 2014. Abstract TUAC0105LB.
PROUD Study: PrEP Use in a Real-World Setting (2012-2014)

Multicenter UK Study
13 Sexual Health Clinics
Open label
HIV-negative MSM
Condomless anal intercourse
No HBV

Immediate
Emtricitabine/Tenofovir DF (n=276)

Deferred (12 months)
Emtricitabine/Tenofovir DF (n=269)

10/2014: DSMB recommends stopping trial:
MSM in the deferred arm offered PrEP

Web-based randomization. Follow-up: 3 times monthly for up to 24 months.
Primary endpoint: HIV infection in the first 12 months.
Baseline characteristics:
- Age: 35 years.
- White: 81%.
- No current relationship: 54%.
- Full-time employment: 72%.
- Recreational drug use in the past 90 days: 70%.

PROUD Study: Results

- Significantly fewer new HIV infections with immediate versus deferred PrEP (3 versus 19 cases)
  - 86% reduction ($P=0.0002$)
  - Number needed to treat to prevent 1 infection: 13
- PEP used by 31% in deferred arm
- Preliminary analysis found that risk behaviors were similar between the 2 arms

HIV Incidence

PEP: post-exposure prophylaxis.
ANRS Ipergay Trial Open-Label Extension Study: On-Demand PrEP in High-Risk MSM

Double-Blind/Open-Label Study
France and Canada

HIV-negative
High-risk MSM with ≥2 partners within 6 months without the systematic use of a condom
eGFR >60 mL/min
ALT <2.5x ULN
Hemoglobin 10 g/dL
No HBV or HCV

Double-Blind
Emtricitabine/Tenofovir DF
Before and After Sex
(n=206)

86% Relative Reduction
(P=0.002)
NNT to prevent 1 HIV Infection: 18

Open-Label Extension (Safety)
Emtricitabine/Tenofovir DF
Before and After Sex
(n=362)

Placebo
Before and After Sex
(n=208)

Open-label study extension study:
Pre-planned, implemented 8 days after discontinuation of the placebo arm.
Full prevention services (counseling, condoms and gels, testing and treatment for STIs, HBV/HAV vaccination, PEP).
Peer counseling on risk reduction and adherence.
Follow-up every 2 months.
Emtricitabine/tenofovir DF: 2 tablets 2 to 24 hours before sex, 1 tablet at 24 and 48 hours later.

Open-label extension baseline characteristics:
Age: 35 years.
White: 93%.
STI diagnosed at entry: 33%.
Use of psychoactive drugs: 43%.
Number of sexual acts in prior 4 weeks: 9.5.
Number of sexual partners in prior 2 months: 7.

ANRS Ipergay Trial: Results

- Significantly fewer new HIV infections with intermittent PrEP versus placebo (2 versus 14 cases)
  - 86% reduction after a mean follow-up of 13 months ($P=0.002$)
  - Number needed to treat to prevent 1 HIV infection: 18
- Safety of on-demand PrEP was similar to placebo except for GI adverse events
- Adherence to PrEP was good, supporting the acceptability of on-demand PrEP

ANRS Ipergay Trial Open-Label Extension Study: Efficacy of On-Demand PrEP in High-Risk MSM

- Median follow-up: 18.4 months
- Single incident HIV infection
  - Subject had not used PrEP in 40 months
  - Neither emtricitabine nor tenofovir were detectable at time of HIV diagnosis
- Estimated efficacy
  - 97% relative reduction in HIV transmission versus placebo

HIV Seroconversion Rates

ANRS Ipergay Trial Open-Label Extension Study: Adherence, Safety, and STIs

- Slight increase in correct adherence
- PrEP was well tolerated
- No significant change in median number of partners or sexual acts
- High rate of STIs, suggesting a potential for HIV exposure
  - Incidence rate of first STI increased from 35 to 41 per 100 person-years (double-blind to open-label extension)

### Additional Outcomes With “On-Demand” PrEP

<table>
<thead>
<tr>
<th></th>
<th>Double-Blind</th>
<th>Open-Label Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>42</td>
<td>50*</td>
</tr>
<tr>
<td>Sub-optimal</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>No PrEP</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Discontinuations due to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse events (%)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>STIs (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>37</td>
<td>58</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>Syphilis</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>HCV</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*P=0.007 versus double-blind PrEP.

Pre-Prophylaxis for HIV in Women

Kenya, South Africa and Tanzania

South Africa, Uganda and Zimbabwe
FEM - PrEP

- 1,951 women randomized to receive Truvada or placebo
- Kenya, South Africa and Tanzania
- Study stopped because of futility
  - 56 HIV endpoints:
    - Truvada N = 28
    - Placebo N = 28
- Possible explanations for lack of efficacy
  - Poor adherence or drug sharing
  - Differential compartmental PK
  - Chance
VOICE enrolled 5,029 women, but the final analysis of study data is based on 5,007 participants; 22 women were not included because they were later identified to have been infected at the time of enrollment.

1:1:1:1:1 Randomization to daily oral TDF, FTC/TDF, oral placebo, tenofovir, vaginal gel or gel placebo

TDF: No HIV protection
FTC/TDF: No HIV protection
Tenofovir gel: No HIV protection

<30% samples had tenofovir detected.
>50% of women in each of the active arms never had tenofovir detected, at any time during their follow-up.
<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Participants</th>
<th>Type of medication</th>
<th>mITT efficacy*</th>
<th>Adherence-adjusted efficacy based on TDF detection in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>Injecting drug users</td>
<td>TDF</td>
<td>49</td>
<td>(10–72)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>HIV discordant couples</td>
<td>TDF</td>
<td>67</td>
<td>(44–81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>75</td>
<td>(55–87)</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexually active men and women</td>
<td>TDF/FTC</td>
<td>62</td>
<td>(22–83)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Men who have sex with men</td>
<td>TDF/FTC</td>
<td>42</td>
<td>(18–60)</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>Heterosexually active women</td>
<td>TDF/FTC</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>VOICE</td>
<td>Heterosexually active women</td>
<td>TDF</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>NS</td>
<td>–</td>
</tr>
</tbody>
</table>

**Abbreviations:** mITT = modified intent to treat analysis, excluding persons determined to have had HIV infection at enrollment; CI = confidence interval; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NS = not statistically significant; NA = data not available.

* % reduction in acquisition of HIV infection.
### Completed trials (ordered by decreasing HIV risk reduction in primary intention-to-treat analysis)

<table>
<thead>
<tr>
<th>Study (location)</th>
<th>Population</th>
<th>Design</th>
<th>Relative reduction in HIV incidence in intention-to-treat analysis</th>
<th>PrEP detection in blood samples from non-seroconverters</th>
</tr>
</thead>
</table>
| **Partners PrEP Study** (Kenya, Uganda) | 4747 heterosexual men and women with HIV infected partners (serodiscordant couples) | 1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo | **TDF: 67%**  
(95% CI 44-81%, p<0.0001) | 82%  
Detection of tenofovir in blood associated with 86-90% HIV protection. |
| **TDF2 Study** (Botswana) | 1219 heterosexual men and women | 1:1 randomization to daily oral FTC/TDF or placebo | **FTC/TDF: 63%**  
(95% CI 22-83%, p=0.01) | 79% |
| **iPrEx** (Brazil, Ecuador, Peru, South Africa, Thailand, US) | 2499 MSM and transgender women | 1:1 randomization to daily oral FTC/TDF or placebo | **FTC/TDF: 44%**  
(95% CI 15-63%, p=0.005) | 51%  
Detection of tenofovir associated with 92% HIV protection, high adherence with >95% protection. |
| **CAPRISA 004** (South Africa) | 889 women | 1:1 randomization to intercourse-associated use of tenofovir vaginal gel or placebo | **Tenofovir gel: 39%**  
(95% CI 6-60%, p=0.02) | Detection of high concentrations of tenofovir (>1000 ng/mL) in cervicovaginal fluid associated with 74% reduced HIV risk. |
| **FEM-PrEP** (Kenya, South Africa, Tanzania) | 2120 women | 1:1 randomization to daily oral FTC/TDF or placebo | FTC/TDF: No HIV protection | 35-38% at a single visit, 26% at two consecutive visits |
| **VOICE** (South Africa, Uganda, Zimbabwe) | 5029 women | 1:1:1:1 randomization to daily oral TDF, FTC/TDF, oral placebo, tenofovir vaginal gel, or gel placebo | **TDF: No HIV protection**  
FTC/TDF: No HIV protection  
Tenofovir gel: No HIV protection | <30% of samples had tenofovir detected.  
≥50% of women in each of the active arms never had tenofovir detected, at any time during their follow-up |
FDA Approves Truvada for PrEP

Truvada:
tenofovir disoproxil fumarate (TDF) + Emtricitabine

Descovy (tenofovir alafenamide + emtricitabine) not approved
PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE
### Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th></th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detecting substantial risk of acquiring HIV infection</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
</tr>
<tr>
<td></td>
<td>Recent bacterial STI</td>
<td>Recent bacterial STI</td>
<td>Sharing injection equipment</td>
</tr>
<tr>
<td></td>
<td>High number of sex partners</td>
<td>High number of sex partners</td>
<td>Recent drug treatment (but currently injecting)</td>
</tr>
<tr>
<td></td>
<td>History of inconsistent or no condom use</td>
<td>History of inconsistent or no condom use</td>
<td></td>
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<tr>
<td></td>
<td>Commercial sex work</td>
<td>Commercial sex work</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In high-prevalence area or network</td>
<td>In high-prevalence area or network</td>
<td></td>
</tr>
<tr>
<td>Clinically eligible</td>
<td>Documented negative HIV test result before prescribing PrEP</td>
<td>No signs/symptoms of acute HIV infection</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Normal renal function; no contraindicated medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Documented hepatitis B virus infection and vaccination status</td>
<td></td>
</tr>
<tr>
<td>Prescription</td>
<td>Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other services</td>
<td>Follow-up visits at least every 3 months to provide the following:</td>
<td></td>
<td>Access to clean needles/syringes and drug treatment services</td>
</tr>
<tr>
<td></td>
<td>HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At 3 months and every 6 months thereafter, assess renal function</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Every 6 months, test for bacterial STIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do oral/rectal STI testing</td>
<td>Assess pregnancy intent</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pregnancy test every 3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Access to clean needles/syringes and drug treatment services</td>
<td></td>
</tr>
</tbody>
</table>

STI: sexually transmitted infection

Gay and Bisexual Men Face Highest – and Rising – Number of Syphilis Infections

† Men who have Sex with Men     ‡‡ Men who have Sex with Women
Note: Based on available data from states reporting sex of sex partners
From 12/1/14 – 1/30/2015, in King County, Washington, 4 cases of ocular syphilis, defined as clinical signs or symptoms consistent with ocular disease in a person with syphilis were reported.

- All 4 cases were MSMs
- 3 out of 4 patients were had HIV
- 3 patients received treatment with aqueous crystalline penicillin G for 14 days, and 1 was treated with 10 days of procaine penicillin and probenecid
- All 4 patients had initial improvement in ocular symptoms after treatment.
  - However, 1 patient still had a blind spot in one eye 1 month after treatment
  - 2 patients were considered legally blind after 5 months
  - 4\textsuperscript{th} patient was lost to follow-up.
CT & GC Screening for Men

• MSM
  – A least for urethral GC and CT if insertive intercourse in the past year*
  – A least for rectal GC and CT if receptive intercourse in the past year*
  – A least for pharyngeal GC if receptive oral sex in the past year
• Rescreen anyone with a positive test 3 months after treatment

*regardless of reported condom use
Is an ounce of prevention worth a pound of cure?
My Final Recommendations

- PrEP works but significant ethical and operational challenges persist
- *Adherence is everything in PrEP* – efficacy requires patient’s ongoing commitment to adherence
- The right drug at the right place at the right time
- Achieves higher levels in the rectum than in the cervix
  - Women have lower leeway for non-adherence – must take it at least 6 out of 7 days; most likely need all 7 days
  - For anal sex: 4 + doses of PrEP/week likely confers protection but your message should be to take TDF + Emtricitabine (Truvada) *EVERY SINGLE DAY*
- Advise condom use to prevent other STDs
- At a minimum: must use condoms until tenofovir DF achieves intracellular drug concentrations that protect against HIV
  - 7 days after starting PrEP for patients engaging in receptive anal sex
  - 21 days for patients engaging in receptive vaginal sex (women)
**My Final Recommendations**

- PrEP should be continued until the HIV infected partner has achieved a *stably suppressed* VL *(6 months after initiation of ART)*
  - The concept of treatment as prevention
- No refills – give only a 90 day supply *(renewable only after HIV test is back)*
- HIV 4\(^{th}\) generation test every 3 months – check for symptoms of acute seroconversion
  - If symptoms of acute seroconversion – then HIV VL PCR
- Check for STIs
  - CDC recommends 6 months; I recommend **3 months**
  - *High risk exposure homosexual*: Z72.52 *(ICD 10)*
  - *High risk exposure heterosexual*: Z72.51 *(ICD 10)*
- Cost of PrEP ~ $1,425/month in the US
  - many public & private insurances cover – co-pay may vary
Simultaneous Use of Different Classes of Prevention Strategies

**Combination HIV Prevention**

- Biomedical Interventions
- Structural Interventions
- Community Interventions
- Individual and Small Group Behavioral Interventions
- HIV Testing, Linkage to Care, Expanded ART Coverage
Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016

from the
Centers for Disease Control and Prevention,
U.S. Department of Health and Human Services
Guidelines for health care professionals on the management of nonoccupational exposure to HIV, including recommendations for postexposure prophylaxis. CDC. http://stacks.cdc.gov/view/cdc/38856

Table 1. Estimated per-act risk for acquiring human immunodeficiency virus (HIV) from an infected source, by exposure act

<table>
<thead>
<tr>
<th>Exposure type</th>
<th>Rate for HIV acquisition per 10,000 exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9,250</td>
</tr>
<tr>
<td>Needle sharing during injection drug use</td>
<td>63</td>
</tr>
<tr>
<td>Percutaneous (needlestick)</td>
<td>23</td>
</tr>
<tr>
<td>Sexual</td>
<td></td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>138</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse</td>
<td>8</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>11</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>4</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>Low</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>Low</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Biting</td>
<td>Negligible</td>
</tr>
<tr>
<td>Spitting</td>
<td>Negligible</td>
</tr>
<tr>
<td>Throwing body fluids (including semen or saliva)</td>
<td>Negligible</td>
</tr>
<tr>
<td>Sharing sex toys</td>
<td>Negligible</td>
</tr>
</tbody>
</table>

Source: http://www.cdc.gov/hiv/policies/law/risk.html

Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and preexposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

HIV transmission through these exposure routes is technically possible but unlikely and not well documented.
Guidelines for health care professionals on the management of nonoccupational exposure to HIV, including recommendations for postexposure prophylaxis. CDC. http://stacks.cdc.gov/view/cdc/38856
Table 2. Recommended schedule of laboratory evaluations of source and exposed persons for providing nPEP with preferred regimens

<table>
<thead>
<tr>
<th>Test</th>
<th>Source</th>
<th>4–6 weeks after exposure</th>
<th>3 months after exposure</th>
<th>6 months after exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Ag/Ab testing a (or antibody testing if Ag/Ab test unavailable)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatitis B serology, including:</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>hepatitis B surface antigen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis B surface antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis B core antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C antibody test</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Syphilis serology e</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gonorrhea f</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chlamydia f</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pregnancy h</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Serum creatinine (for calculating estimated creatinine clearance) i</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alanine transaminase, aspartate aminotransferase</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HIV viral load</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HIV genotypic resistance</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Guidelines for health care professionals on the management of nonoccupational exposure to HIV, including recommendations for postexposure prophylaxis. CDC. http://stacks.cdc.gov/view/cdc/38856
### Recommendations for nPEP

**Table 5. Preferred and alternative antiretroviral medication 28-day regimens for nPEP \(^{a,b}\)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Preferred/alternative</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents aged ≥ 13 years, including pregnant women, with</td>
<td>Preferred</td>
<td>A 3-drug regimen consisting of tenofovir DF 300 mg <em>and</em> fixed dose combination emtricitabine 200 mg (Truvada(^{c})) once daily <em>with</em> raltegravir 400 mg twice daily <em>or</em> dolutegravir 50 mg once daily</td>
</tr>
<tr>
<td>normal renal function (creatinine clearance ≥ 60 mL/min)</td>
<td>Alternative</td>
<td>A 3-drug regimen consisting of tenofovir DF 300 mg <em>and</em> fixed dose combination emtricitabine 200 mg (Truvada) once daily <em>with</em> darunavir 800 mg (as 2, 400-mg tablets) once daily <em>and</em> ritonavir(^{b}) 100 mg once daily</td>
</tr>
</tbody>
</table>


- Since 1991, the CDC has investigated all cases of HIV infection reported as acquired occupationally by healthcare workers
- Confirmed cases of occupationally acquired HIV infection (n=58)
  - Nurse (41%), laboratory clinician (35%), physician (10%), other (14%)
  - 1985 to 1998 (n=57)
    - HIV-infected blood (n=49), concentrated virus in a laboratory (n=3), visibly bloody fluid (n=1), unspecified body fluids (n=4)
  - 1999 to 2013 (n=1)
    - Laboratory technician sustaining needle puncture while working with a live HIV culture (2008)
