PEP, nPEP, & PrEP: The State of the Evidence

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Asst. Clin. Professor of Medicine, HIV/AIDS and Infectious Diseases, SFGH, UCSF
INTRODUCTION

- Post-exposure prophylaxis
  - Occupational (PEP)
  - Non-Occupational (nPEP)

- Pre-Exposure Prophylaxis (PrEP)
PEP Case 1

- A 27 year-old resident is on an ED night shift at SFGH. An HIV+ IVDU is admitted in respiratory distress, and a blood gas is necessary. The patient is agitated, and access is difficult. On the second attempt, the patient jumps, and the resident sticks himself in the finger.
Occupational PEP

- Recommended by CDC guidelines: 2001
- Limited Efficacy data (No RCT data)
  - Animal
  - Observational
    - 81% reduction in seroconversion from case-control study (Cardo NEJM 1997)
  - Analogy from perinatal transmission research
    - SD AZT within 48 hrs after birth 65% reduction (Wade NEJM 1998)
PEP ~ Occupational exposure

- **Risk Factors for transmission** (AORs Cardo NEJM 1997)
  - Large-gauge (<18-gauge) hollow-bore needle
  - Deep injury AOR=15
  - Visible blood on the device (AOR= 6.2)
  - Procedure with needle in a blood vessel (AOR=4.3)
  - Terminal AIDS in the source patient (AOR=5.6) (↑VL)
PEP ~ Who to treat

- Triage according to:
  - What kind of fluid
    - Blood: documented risk
    - Semen and vaginal: presumed risk
    - Saliva is NOT infectious unless bloody
    - CSF, synovial, pleural, peritoneal, pericardial, amniotic: unknown risk
  - What was exposed
    - Percutaneous: 0.3% infection rate or 3/1000
    - Mucous membrane/non-intact skin: 0.9% infection rate or 9/10,000
  - Infection status of source
    - HIV +, unknown status, negative
<table>
<thead>
<tr>
<th>Exposure type</th>
<th>HIV-positive, class 1†</th>
<th>HIV-positive, class 2†</th>
<th>Source of unknown HIV status§</th>
<th>Unknown source¶</th>
<th>HIV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small volume**</td>
<td>Consider basic 2-drug PEP††</td>
<td>Recommend basic 2-drug PEP</td>
<td>Generally, no PEP warranted§§</td>
<td>Generally, no PEP warranted</td>
<td>No PEP warranted</td>
</tr>
<tr>
<td>Large volume¶¶</td>
<td>Recommend basic 2-drug PEP</td>
<td>Recommend expanded ≥3-drug PEP</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings in which exposure to HIV-infected persons is likely</td>
<td>No PEP warranted</td>
</tr>
</tbody>
</table>

* For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).
† HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
§ For example, deceased source person with no samples available for HIV testing.
¶ For example, splash from inappropriately disposed blood.
** For example, a few drops.
†† The recommendation “consider PEP” indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.
§§ If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.
¶¶ For example, a major blood splash.
<table>
<thead>
<tr>
<th>Exposure type</th>
<th>HIV-positive, class 1*</th>
<th>HIV-positive, class 2*</th>
<th>Source of unknown HIV status†</th>
<th>Unknown source§</th>
<th>HIV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less severe†</td>
<td>Recommend basic 2-drug PEP</td>
<td>Recommend expanded ≥3-drug PEP</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors† †</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely</td>
<td>No PEP warranted</td>
</tr>
<tr>
<td>More severe§§</td>
<td>Recommend expanded 3-drug PEP</td>
<td>Recommend expanded ≥3-drug PEP</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors† †</td>
<td>Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely</td>
<td>No PEP warranted</td>
</tr>
</tbody>
</table>

* HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, acquired immunodeficiency syndrome, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† For example, deceased source person with no samples available for HIV testing.

§ For example, a needle from a sharps disposal container.

¶ For example, solid needle or superficial injury.

** The recommendation “consider PEP” indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

† † If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ For example, large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient’s artery or vein.
PEP ~ How to manage/treat

- Within 72 hours of exposure (<1 ideal)
- Four weeks (28 days) recommended
- Favor agents that are well tolerated
- Follow up testing at 4-6 wks, 12 wks and 6 months
- Tx failure associated with
  - Delay in treatment
  - Level of exposure
  - Adherence
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Daily Pill Burden</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-drug regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir–emtricitabine (Truvada)‡</td>
<td>One tablet (300 mg of tenofovir with 200 mg of emtricitabine) once daily</td>
<td>1</td>
<td>Well tolerated; once-daily dosing</td>
<td>Potential nephrotoxicity</td>
</tr>
<tr>
<td>Zidovudine–lamivudine (Combivir)§</td>
<td>One tablet (300 mg of zidovudine with 150 mg of lamivudine) twice daily</td>
<td>2</td>
<td>Preferred in pregnancy</td>
<td>Twice-daily dosing; less well tolerated than tenofovir–emtricitabine (nausea, asthenia, neutropenia, anemia, abnormal liver-enzyme levels)</td>
</tr>
<tr>
<td>Three-drug regimens¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir–lopinavir (Kaletra) (plus either tenofovir–emtricitabine or zidovudine–lamivudine)</td>
<td>Two tablets (50 mg of ritonavir with 200 mg of lopinavir per tablet) twice daily, or four tablets once daily</td>
<td>5 or 6</td>
<td>Either once-daily or twice-daily dosing; one copayment; no refrigeration required; most experience in pregnancy; high genetic barrier to resistance</td>
<td>Gastrointestinal side effects such as diarrhea; may cause elevated liver-enzyme levels or hepatitis</td>
</tr>
<tr>
<td>Ritonavir plus atazanavir (plus either tenofovir–emtricitabine or zidovudine–lamivudine)</td>
<td>100 mg of ritonavir plus 300 mg of atazanavir once daily</td>
<td>3 or 4</td>
<td>Once-daily dosing; well tolerated</td>
<td>Ritonavir must be refrigerated; potential for asymptomatic jaundice, renal stones; may cause elevated liver-enzyme levels or hepatitis</td>
</tr>
<tr>
<td>Ritonavir plus darunavir (plus either tenofovir–emtricitabine or zidovudine–lamivudine)</td>
<td>100 mg of ritonavir plus two tablets, each containing 400 mg of darunavir, once daily</td>
<td>4 or 5</td>
<td>Once-daily dosing; high genetic barrier to resistance</td>
<td>Ritonavir must be refrigerated; gastrointestinal side-effects; may cause elevated liver-enzyme levels or hepatitis</td>
</tr>
</tbody>
</table>
What drug should never be used for PEP?

- Nevirapine

Grayson J Clin Path 2008
## Testing and Follow-Up

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommended during Treatment</th>
<th>Recommended at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Symptom-Directed†</td>
</tr>
<tr>
<td>ELISA for HIV antibodies</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Creatinine, liver function, and complete blood count with differential count</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HIV viral load</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-HBs antibodies</td>
<td>Yes ‡</td>
<td>No</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Yes ‡§</td>
<td>No</td>
</tr>
<tr>
<td>HCV antibodies</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HCV RNA¶</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Screening, including rapid plasma reagin test, for other sexually transmitted infections</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Institutional Obligations

- Evaluate the circumstances of the exposure, the type of fluid, and possible entry points
- Evaluate the source patient
- Perform baseline HIV antibody testing of the exposed worker
- Counsel the exposed employee about the possible risks and benefits of PEP
- Offer or recommend PEP as soon as possible after the exposure, preferably within the first several hrs
Post PEP Counseling

- Counsel re: avoiding secondary transmission to others (safer sex and other risk-reduction practices)
- Support and maintain the confidentiality of the worker
- For workers taking PEP, monitor for medication toxicity and adherence.
- Repeat HIV testing at 4-6 weeks, 3 and 6 mos.
- Report exposure as required by federal and state regulations
Hepatitis B

- For patients with potential exposure to HBV who have not been vaccinated against HBV
  - Hepatitis B immune globulin (HBIG) as a 0.06-mL/kg IM and initiate the vaccination series

- For patients who received the vaccine series but did not develop protective antibody (HBV surface antibody positive > 10 IU)
  - HBIG at the time of the postexposure workup and repeat in 1 month

- For patients with immunity to hepatitis B, no Rx
Hepatitis C

- Baseline HCV antibody test
- If source patient HCV+ → ALT and HCV viral load testing at 4-6 weeks
- HCV antibody testing should be repeated at 4-6 months
- If HCV seroconversion occurs (indicated by ALT elevation, detectable HCV viral load, or confirmed positive HCV antibody test), refer to a hepatologist because early treatment of HCV may be indicated
Acute HIV Infection

- Symptoms of primary HIV infection
  - fever, rash, and lymphadenopathy
- Counsel about the symptoms of primary HIV infection
- Instruct to return for reevaluation as soon as possible if symptoms develop
- If symptoms c/w acute HIV appear within 4-6 weeks → evaluate and refer for further evaluation and care/enrollment in clinical trials
The same resident is treated for 28 days with a three drug regimen, and undergoes repeat testing for six months without seroconversion. Two months later, he is again working a night shift. A young woman comes into the ED, and says she was sexually assaulted by a stranger during her evening run in Golden Gate Park.
Non-occupational PEP

- Recommended by CDC guidelines: 2005
- Endorsed by state, national, international health
- Limited implementation:
  - Source patient less often available for HIV testing
  - The genital and oral tracts are unique compartments whose secretions and immunologic milieu vary unpredictably from those of the plasma compartment
  - Mechanisms for accessing care quickly and confidentially have not been adequately developed
TABLE 1. Estimated per-act risk for acquisition of HIV, by exposure route*

<table>
<thead>
<tr>
<th>Exposure route</th>
<th>Risk per 10,000 exposures to an infected source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>9,000</td>
<td>74</td>
</tr>
<tr>
<td>Needle-sharing injection-drug use</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>50</td>
<td>76, 77</td>
</tr>
<tr>
<td>Percutaneous needle stick</td>
<td>30</td>
<td>78</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse</td>
<td>10</td>
<td>76, 77, 79</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>6.5</td>
<td>76, 77</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>5</td>
<td>76, 77</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>1</td>
<td>77†</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>0.5</td>
<td>77†</td>
</tr>
</tbody>
</table>

*Estimates of risk for transmission from sexual exposures assume no condom use.
†Source refers to oral intercourse performed on a man.
When to give nPEP?

- Within 72 hrs (NYS 36 hrs)
- If the source patient is known HIV positive
- Who is considered a high-risk source patient?
  - Men who have sex with men (MSM)
  - Men who have sex with men and women (MSM/W)
  - Commercial sex workers
  - Injection drug users
  - Those who resided in a country where HIV is endemic (prevalence > 1%)
  - Those who have been incarcerated
- And sexual partners of the above categories
FIGURE 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures

Substantial exposure risk

- ≤72 Hours since exposure
  - Source patient known to be HIV positive
    - nPEP recommended
  - Source patient of unknown HIV status
    - Case-by-case determination

- >72 Hours since exposure
  - nPEP not recommended

Negligible exposure risk

Substantial Risk for HIV Exposure

- Exposure of vagina, rectum, eye, mouth, or other mucous membrane, nonintact skin, or percutaneous contact
  - With blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood
  - When the source is known to be HIV-infected

Negligible Risk for HIV Exposure

- Exposure of vagina, rectum, eye, mouth, or other mucous membrane, intact or nonintact skin, or percutaneous contact
  - With urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood
  - Regardless of the known or suspected HIV status of the source
nPEP: Special Considerations

- Teachable Moment
  - Risk compensation or behavioral disinhibition
- PEP regimen should always be offered in the context of risk-reduction counseling
  - Health referral to regular primary care
  - Mental health practitioners
  - Substance use services
  - HIV Prevention Program services in the community
- Cost and Insurance Coverage
nPEP Follow up

- Immediate and serial HIV testing
  - 4-6 weeks
  - 3 months
  - 6 months
  - Rapid testing to exclude chronic HIV infection
  - Hepatitis B virus infection (if not known to be previously immune) → vaccinate
  - Hepatitis C virus infection
  - STI screening (syphilis, gonorrhea, chlamydia, etc.)
A 40 year-old man is a regular patient in your practice. His partner is HIV-positive, and he also reports approximately 20 casual sex partners in the past year. He uses condoms most of the time for anal sex, but will on occasion have sex without a condom after a night of heavy drinking. He has used PEP twice in the past year after risky episodes. He gets HIV testing regularly and tested negative about 3 months ago. He recently heard about “the HIV prevention pill”.
PrEP

- Preexposure prophylaxis (PrEP) is an investigational biomedical prevention strategy that cannot be recommended for routine use.
- Ongoing studies are attempting to answer safety and efficacy questions and whether the perceived protection afforded by PrEP leads to an increased incidence of high-risk behaviors that negate or, worse, overwhelm any protective benefit of this HIV-prevention strategy.
PrEP ~ to the Birth Control Pill?

- PrEP
  - Daily pill during a period of heightened risk, irrespective of the occurrence of sexual activity or the lack thereof
  - Use of PrEP is currently being investigated in clinical trials in different populations at high risk of exposure to HIV
PrEP ~ Theory and evidence

- Prevention is the cornerstone of HIV strategy
- Pre-exposure administration increases ARV efficacy
- Possible increased efficacy vs. PEP for
  - Those at very high risk of exposure
  - Those whose pre and post exposure periods overlap
- Animal trials have promising results
- Human trials show it is safe and no disinhibition
PrEP ~ Theory and evidence cont...

But....

- No large human efficacy trials have been completed
- No evidenced-based guidelines

Evidence Based Medicine: when best evidence from research meets clinical information and patient values, optimal decisions are possible.
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# PrEP ~ Primate studies

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Animal model</th>
<th>PrEP agent</th>
<th>Virus/Route</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tsai</strong></td>
<td>35 juvenile long-tailed macaques</td>
<td>SQ 20-30 mg/kg PMPA SQ 48 h pre/4 h post, or 24 h post</td>
<td>IV SIV (10^3 cell culture infectious dose) once</td>
<td>25/25 treated protected; 10/10 controls infected</td>
</tr>
<tr>
<td><strong>Van Rompay</strong></td>
<td>40 newborn rhesus macaques</td>
<td>SQ 30 and 4 mg/kg PMPA given pre/post at various intervals</td>
<td>Oral SIVmac251 IV SHIV-SF33</td>
<td>75% protected at 30 mg/kg; 50-75% protected at 4 mg/kg</td>
</tr>
<tr>
<td><strong>Van Rompay</strong></td>
<td>8 newborn macaques</td>
<td>SQ 30 mg/kg PMPA daily x 4 weeks</td>
<td>Oral SIVmac055 (PMPA resistant)</td>
<td>2/5 treated protected; 3/5 w/ delayed viremia</td>
</tr>
<tr>
<td><strong>Subbarao</strong></td>
<td>12 adult male Chinese rhesus macaques</td>
<td>Oral TDF (22 mg/kg) daily or weekly</td>
<td>Rectal weekly SHIV SF162P3 (10 TCID&lt;sub&gt;50&lt;/sub&gt;)</td>
<td>TDF delayed but did not prevention infection</td>
</tr>
<tr>
<td><strong>Garcia-Lerma</strong></td>
<td>33 rhesus macaques</td>
<td>SQ FTC +/- tenofovir (QD vs. pre/post); Oral FTC/TDF</td>
<td>Rectal weekly SHIV SF162P3 (10 TCID&lt;sub&gt;50&lt;/sub&gt;)</td>
<td>SQ FTC/TDF fully protective; otherwise partial protection</td>
</tr>
<tr>
<td><strong>Denton</strong></td>
<td>13 BLT humanized mice</td>
<td>IP FTC (3.5 mg) and TDF (5.2 mg) x 7d started 48h prior</td>
<td>Vaginal HIV-1 JR-CSF Once</td>
<td>5/5 treated mice protected; 7/8 controls infected</td>
</tr>
<tr>
<td><strong>Parikh</strong></td>
<td>18 female pigtailed macaques</td>
<td>Vaginal Gel: 1% TFV 1% TFV/5% FTC</td>
<td>Vaginal 2x/week SIV SF162pp3</td>
<td>12/12 protected with either gel; 6/6 controls infected</td>
</tr>
</tbody>
</table>
# On-going PrEP Trials

## Ongoing ARV-based Prevention (Oral PrEP and Topical Microbicide) Trials (December 2009)

<table>
<thead>
<tr>
<th>Study; Study phase</th>
<th>Location</th>
<th>Sponsor; Funder</th>
<th>Population (mode of exposure)</th>
<th>Intervention arm(s)</th>
<th>Status/ Expected completion</th>
</tr>
</thead>
</table>
| **US Extended Safety Trial (CDC 4323)**  
Phase II, safety | United States | CDC | 400 gay men and other men who have sex with men (penile/rectal) | Daily oral TDF | Fully enrolled / 2009  
Final data analysis Q1/10 |
| **Bangkok Tenofovir Study (CDC 4370)**  
Phase II/III, safety and efficacy | Thailand | CDC | 2,400 injecting drug users (parenteral) | Daily oral TDF | Enrolling / 2010 |
| **CAPRISA 004**  
Phase II, Safety and Effectiveness | South Africa | CAPRISA, FHI, CONRAD, USAID, LIFElab | 1,200 heterosexual women (vaginal) | Coitally dependent topical tenofovir gel | Fully enrolled / 2010  
Final data analysis Q3/2010 |
| **iPrEx**  
Phase III, safety and efficacy | Brazil, Ecuador, Peru, South Africa, Thailand, US | NIH, BMGF | 3,000 gay men and other men who have sex with men (penile/rectal) | Daily oral TDF/FTC | Fully enrolled / 2011 |
| **TDF2 (CDC 4940)**  
Phase II, safety and adherence | Botswana | CDC | 1,200 heterosexual men and women (penile and vaginal) | Daily oral TDF/FTC; switched from TDF Q1 2007 | Fully enrolled / 2010 |
| **Partners PrEP**  
Phase III, safety and efficacy | Kenya, Uganda | BMGF | 3,900 serodiscordant heterosexual couples (penile and vaginal) | Daily oral TDF; daily oral TDF/FTC | Enrolling / 2012 |
| **FEM-PrEP**  
| **VOICE (MTN 003)**  
Phase IIb, safety and effectiveness | South Africa, Uganda, Zambia, Zimbabwe | MTN, NIH | 4,200 heterosexual women (vaginal) | Daily oral TDF; daily oral TDF/FTC; daily topical tenofovir gel | Enrolling / 2013 |
| **IAVI E001 & E002**  
Phase II, safety, acceptability, adherence | Kenya, Uganda | IAVI | 150 serodiscordant couples and men and women (vaginal and penile/rectal) | Daily oral TDF/FTC; intermittent oral TDF/FTC (twice weekly + coital dosing) | Fully enrolled / 2010 |
| **PrEP in YMSM (ATN 082)**  
Phase II, safety, acceptability, feasibility | United States | ATN, NICHD | 99 young men who have sex with men (YMSM) (penile/rectal) | Daily oral TDF/FTC | Enrolling / 2011 |

ATN – Adolescent Trial Network; BMGF – Bill & Melinda Gates Foundation; CAPRISA – Centre for the AIDS Programme of Research in South Africa; CDC – US Centers for Disease Control and Prevention; FHI – Family Health International; FTC – emtricitabine; IAVI – International AIDS Vaccine Initiative; MTN – Microbicide Trials Network; NICHD – National Institute of Child Health and Human Development; NIH – US National Institutes of Health; Q1–4 – quarters 1-4; TDF – tenofovir disoproxil fumarate; USAID – United States Agency for International Development

PrEP ~ Human studies

Timeline for Ongoing PrEP Trials* (August 2009)

* The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor trial progress and will update the timeline accordingly. To view or download an updated timeline visit www.prepwatch.org.
Risk compensation/ behavior change

The New York Times
Magazine

IDEA LAB

Protect or Disinhibit?

By JON COHEN
Published: January 22, 2006

The Next Condom Conundrum

Why use a rubber when you can just pop a pill? That’s what HIV-negative guys across the country are asking themselves -- and their doctors.

ADVOCATE.COM

January 2009
Controversies around PrEP

- Long-term safety in HIV-seronegative persons
- Risk Compensation of Behavioral Disinhibition
- Emergence of drug-resistant HIV if seroconversion occurs during PrEP
  - Case Report of Wild Type Virus (low-level viremia, delayed seroconversion, attenuated clinical course)
- Two vs. Three Drugs?
  - Smaller inoculum vs. toxicities/adherence
- Daily vs. Intermittent Dosising
Various intermittent dosing concepts have been discussed by various members of our communities. This lexicon attempts to establish a common vocabulary so that we literally can understand what we are talking about. The intent is to facilitate a discussion about the intermittent PrEP research agenda. Hopefully, it will also facilitate a dialogue among community and research leaders to understand if the growing community interest in PrEP fits with research questions under consideration by sponsors. The discussion about oral prep assumes the agent will be tenofovir or Truvada, although their efficacies in humans are still unknown. Even if the current therapies are proven safe and effective, future PrEP and PEP studies may involve other agents and considerations of their safety, efficacy, and cost. This lexicon is a work in progress that will develop along with these discussions.

**ONCE-DAILY DOSING**

Tenofovir or Truvada taken orally once daily (as is current licensed for use as treatment) without regard to the timing of exposure to HIV. Currently, all completed and on-going trials are based upon once-daily dosing strategies. Some animal model studies in macaques (a type of primate) and mice have incorporated daily dosing.

**WEEKLY-BASED DOSING**

Tenofovir or Truvada taken orally based on a weekly schedule that might include 1, 2, 3, 4, or 5 doses per week, independent of the timing of exposure to HIV. The optimal strategy for timing the doses is unclear. Undoubtedly, this strategy would attempt to balance cost, adherence, and drug levels, but the optimal balance is not known. Small planned pharmacokinetic (PK) studies in seronegative humans and in human tissue-culture models might provide clues to how many weekly doses will provide adequate prophylaxis, if any. Animal model studies have generally followed exposure with a specifically timed pre-exposure dose and may not provide relevant information about weekly dosing that is completely independent of exposure.

**EVENT-BASED DOSING**

Tenofovir or Truvada taken orally based on exposure events, whether anticipated or completed (i.e., before sex is anticipated and/or after it happens). Presumably this strategy would depend upon a single pre-exposure dose and one or more post-exposure doses. Although PrEP use in the community appears to be rare, terms such as “disco dosing” or “Taking a T” probably envision this type of strategy. Some experiments in animal models (macaques) provide data relevant to event-based dosing. A “Pocket-PEP” study in Brazil provided data about how well individuals who are at risk can identify or act on significant exposure events by self-administering post-exposure antiretrovirals that are readily available.

**ROUTINE PLUS EVENT-BASED DOSING**

Tenofovir or Truvada taken orally based on a weekly schedule that might include 1, 2, or 3 routine doses, independent of anticipated or completed exposure. Exposures would be followed by one or more specifically timed post-exposure doses, independent of the routine weekly dose schedule. Small-scale PK studies might be informative. Many animal model experiments have used variably timed pre-exposure doses with specifically timed post-exposure doses.

**PERIODIC DOSING**

Tenofovir or Truvada taken orally, based on any one or more than one of the dosing strategies above during periods of potential sexual or IV exposure. Disruptions in access to a regular partner or partners, voluntary or involuntary periods of abstinence, carefully planned periods of serostenting, including seroconcordant monogamy, or other life events may effectively reduce or avoid exposure, even among individuals frequently at high risk for exposure to HIV. Animal model data may indicate how long before or after exposure prophylactic efficacy is required and may be informative for planning periodic dosing studies.

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**Intermittent PrEP**

- Growing interest in intermittent PrEP
- Macaque studies show potential high efficacy of intermittent PrEP
  - Both pre- and post-exposure doses important
- Small (phase I-II) studies looking at adherence, risk behavior, and drug levels with intermittent dosing are being planned

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From www.avac.org
Stay tuned for PrEP results....

- Current PrEP trials will provide important data on safety, efficacy, risk behavior, adherence, and resistance (PrEP currently unproven)
- PrEP trial results will be available in the next 1-4 years
- Future research will be needed
  - Safety in women desiring pregnancy and pregnant women, breastfeeding women, and adolescents
  - Different dosing patterns and drugs
  - Prevalence, duration, and impact of resistance
  - How best to deliver PrEP
- PrEP will need to be implemented as part of a larger prevention package with counseling and other prevention strategies
- Important to manage expectations of PrEP and current trials
Viral Load and HIV Transmission

- In individuals, suppressing HIV viral load reduces perinatal and may reduce sexual transmission.

- At the population level, it is unclear if reductions in the community viral load reduces new HIV infections.
  - Cohort data and modeling (“Test and Treat”) are supportive.

Community Viral Load (CVL)

- Population-based measure of a community’s viral burden
- Potential biologic indicator of the effectiveness of:
  - Antiretroviral treatment
  - HIV prevention

**Hypothesis:** Reductions in SF’s CVL would be associated with fewer HIV infections
Mean CVL and New HIV Infections, 2004-08

- **Mean CVL & HIV-incidence**, p=0.3
- **Mean CVL & newly diagnosed HIV cases**, p=0.005

Mean CVL copies/ml vs. Number of HIV cases


- **Mean CVL**
  - 2004: 798 (CI: 658, 1212)
  - 2005: 642 (CI: 552, 1033)
  - 2006: 523 (CI: 462, 781)
  - 2007: 518
  - 2008: 434

- **Newly diagnosed and reported HIV cases**
  - 2004: 935 (CI: 658, 1212)
  - 2005: 792 (CI: 552, 1033)
  - 2006: 621 (CI: 462, 781)
  - 2007: 518
  - 2008: 434

- **HIV Incidence**
  - 2004: 658
  - 2005: 1212
  - 2006: 1033
  - 2007: 781
  - 2008: 379
Summary

- PEP: standard of practice for occupational exposure
- nPEP: recommended for sexual or needle-sharing exposures but many barriers to widespread use
- PrEP: still being studied, has potential, but many policy and other considerations as to how PrEP will fit into HIV Prevention Armamentarium
- Take advantage of these unfortunate events to harness the teachable moment—both for occupational and non-occupational exposures
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Resources

- CDC Guidelines 2005; DHHS MMWR 2007
- NYS DOH 2008
- OSHA refers to CDC and DHHS
- [http://www.nccc.ucsf.edu/home/](http://www.nccc.ucsf.edu/home/)
- Warmline 800-933-3413
- PEPline 888-448-4911
- Perinatal HIV Hotline 888-448-8765
ARS Question