ART and Prevention: What do we know?

*Biomedical Issues*

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ART for Prevention: Rationale

Having HIV drugs present at the site of exposure should reduce the risk of infection.
ART for Prevention: HIV+ Mother to Child Transmission

- Prevention of Mother to Child Transmission
  - AZT alone reduced transmission from 25% to 8%
    *Connor NEJM 1994*
  - Current ART reduces transmission to <0.5%

![Graph showing Stage 3 (AIDS) Classifications among Perinatally Infected Persons, 1985–2011—United States and 6 Dependent Areas.](chart.png)
ART for Prevention: HIV-Exposed

• Post-exposure prophylaxis (PEP)
  • Occupational PEP
    • AZT reduced risk in health care workers by 81% Cardo NEJM 1997
    • Updated CDC Guidelines recommend 3 antiretroviral drugs for 4 weeks following occupational exposure (9/13)

• Non-Occupational PEP (nPEP)
  • CDC Guidelines recommend 3 antiretroviral drugs for 4 weeks following non-occupational exposure within 72 hours (1/05)

www.aidsinfo.nih.gov/guidelines
ART for Prevention: HIV+

HPTN 052

- 1,763 discordant couples (97% heterosexual) in Africa, Asia, Americas with HIV+ with CD4 350-550
- HIV+ partner randomized to start HIV treatment immediately or deferred until CD4 <250
- DSMB Interim analysis:
  - 29 new infections linked to partner

96% reduction in transmission!

Cohen IAS 2011 #MOAX0102 and NEJM 2011;365:493
ART for Prevention: HIV-

- **Microbicides**
  - gels, creams, films, or suppositories that can be applied inside the vagina or rectum to protect against sexually transmitted infections, including HIV

- **PrEP**
  - *Pre-exposure prophylaxis*
  - Giving HIV drugs to uninfected individuals who are at-risk for HIV infection to protect against HIV acquisition
CAPRISA 004: 1% vaginal TFV gel

Study population:
18-44 year old South African HIV-uninfected women (N=889)

HIV Incidence Rate (%)

<table>
<thead>
<tr>
<th>Follow-Up (months)</th>
<th>Placebo</th>
<th>Tenofovir DF gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>10.5%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td>(P=0.007)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>9.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td>(P=0.017)</td>
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</tbody>
</table>

Overall

NIH: PrEP Drug Criteria

- Safe
- Penetrates target tissues
- Protects against HIV infection in tissues
- Long-lasting activity for convenient dosing
- Unique resistance profile or high barrier to resistance
- No significant drug-drug interactions
- Possibly, not a part of current HIV treatment
- Affordable, easy to use and implement

NIH/DAIDS Working Group Report 4/09
### Antiretroviral Drugs: 2013

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>PIs</th>
<th>EIs</th>
<th>IIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (ZDV, AZT)</td>
<td>saquinavir (SQV)</td>
<td>enfuvirtide (T-20, fusion inhibitor)</td>
<td></td>
</tr>
<tr>
<td>didanosine (ddI)</td>
<td>ritonavir (RTV)</td>
<td>maraviroc (MVC, CCR5 antagonist)</td>
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<tr>
<td>stavudine (d4T)</td>
<td>indinavir (IDV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td>nelfinavir (NFV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>lopinavir/r (LPV/r)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td>atazanavir (ATV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td>fosamprenavir (FPV)</td>
<td></td>
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</tr>
</tbody>
</table>

### NNRTIs
- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)

### Protease Inhibitors (PIs)
- rilpivirine (RPC)
- darunavir (DRV)

### Integrase Inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
TDF and TDF/FTC for PrEP

Optimal PrEP candidates: potency, tolerability, and convenience

- TDF (tenofovir) = TDF (tenofovir)
- TDF/FTC (co-formulated tenofovir + emtricitabine)

FDA approved TDF/FTC for PrEP (7/16/12):
“in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.”
iPrEx: PrEP in MSM

Study population: HIV-uninfected MSM or transgendered women from South America, South Africa, Thailand and U.S. (N=2499)

Ten were HIV-infected at enrollment

If drug levels measurable, 92% reduction in risk

Grant NEJM 2010;363:2587; IAS 2011 #WELBC04
<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Reduction in HIV Infection</th>
</tr>
</thead>
</table>
| **Partners PREP**  
*Baeten NEJM 2012;367:399* | 4758 discordant Kenyan and Ugandan couples | TDF vs. TDF/FTC vs. placebo | TDF: 67%  
TDF/FTC: 75%  
(86-90% if drug detected) |
| **CDC – TDF-2**  
*Thigpen NEJM 2012;367:423* | 1200 Botswanan adults (45% women) | TDF/FTC vs. placebo | TDF/FTC: 63%  
(84% if drug detected) |
| **Bangkok IDU**  
*Choopanya Lancet 2013;382:855* | 2413 Thai IDU (20% women) | TDF vs. placebo | TDF: 49%  
(70% if drug detected) |
<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study population</th>
<th>Design</th>
<th>Results: Reduction in HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEM-PREP Van Damme NEJM 2012;367:411</td>
<td>2120 women in Kenya, South Africa, Tanzania</td>
<td>TDF/FTC vs. placebo</td>
<td>TDF/FTC: 6% (overall adherence was &lt;40%)</td>
</tr>
<tr>
<td>VOICE Marrazzo CROI 2013</td>
<td>&gt;5000 women in South Africa, Uganda, Zimbabwe</td>
<td>1% TDF gel vs. placebo gel; oral TDF vs. TDF/FTC vs. placebo</td>
<td>No study drug effective (overall adherence was &lt;30%)</td>
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</table>
CDC PrEP Guidance

- MSM 1/27/11
- Heterosexuals 8/9/12
- IDU 6/14/13

- Document HIV status and r/o acute HIV infection
- TDF/FTC one pill daily X 90 days
- Counseling (risk reduction, condoms, adherence, drug use)
- Follow kidney function and HIV status every 3 months

www.aidsinfo.nih.gov/guidelines
PrEP: Status in the U.S.
Nationally survey representing 55% of U.S. pharmacies

N=1774 unique PrEP users:
- median age 37
- 48% women

N=1674 PrEP prescribers:
- 16% FP
- 15% IM
- 14% ER
- 12% ID
- 9% NP
- 8% PA

Mera ICAAC 2013 #H663a
ART for Prevention: Issues

- Biomedical
  - Adherence
  - Side effects and toxicities
  - Drug resistance
- Behavioral
  - Adherence
  - Risk compensation
- Practical
  - Access
  - Cost
  - Coverage
ART for Prevention: Future

ART for HIV+
• ↑ HIV testing, linkage and retention in care

ART for HIV-
• PEP
• PrEP
  • Intermittent dosing
  • Other antiretroviral drugs (e.g. maraviroc)
  • Long-acting ART formulations
• Microbicides – vaginal and rectal

Scale-up, Demonstration Projects + Research
VACCINE COUNSELING ARV TREATMENT CIRCUMCISION ART TOPICAL PrEP ART ORAL PrEP ORAL PrEP ACUTE HIV INFECTION ART PMTCT
Acknowledgments

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- Division of AIDS, NIAID, NIH