HIV Prevention and Treatment: Optimizing Biomedical and Behavioral Treatments: Lessons from the Field

Frederick L. Altice, M.D., M.A.
Director of Clinical and Community Research
Schools of Medicine & Public Health
Yale University
The Need for HIV Prevention

Continued HIV Risk in the US

- Estimated new HIV infections in the United States for the most affected subpopulations, 2008-2011

- ~50,000 NEW HIV infections annually – no change in the past 15 years

### Gaps that Reduce Test and Treat Strategies for HIV Prevention

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
<td>11,783,500</td>
<td>100%</td>
</tr>
<tr>
<td>HIV Diagnosed</td>
<td>9,419,500</td>
<td>81%</td>
</tr>
<tr>
<td>Linked to Care</td>
<td>7,253,020</td>
<td>77%</td>
</tr>
<tr>
<td>Retained in Care</td>
<td>4,803,950</td>
<td>66%</td>
</tr>
<tr>
<td>Prescribed ART</td>
<td>4,265,900</td>
<td>89%</td>
</tr>
<tr>
<td>Viral Suppression</td>
<td>3,284,750</td>
<td>77%</td>
</tr>
</tbody>
</table>

~850,000 (75%) are not virally suppressed.

MMWR, 2011
Major Contributors to Disengagement in the HIV Treatment Continuum

- **Health disparities**
  - Black and Latino MSM and women
  - Criminal justice-involved populations
  - Adolescents

- **Social co-morbidities**
  - Homelessness

- **Medical and psychiatric co-morbidities**
  - Substance use disorders (alcohol, drugs)
  - Mental illness
Eco-Social Model: Need to Address ALL Key Issues

- HIV testing guidelines
- HIV treatment guidelines
- Siloed funding sources
  - CDC, HRSA
  - SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Policy

Community
- HIV testing guidelines
- HIV treatment guidelines
- Siloed funding sources
  - CDC, HRSA
  - SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Relationships
- Sex Partners
- Family
- Friends
- Social Networks
- Med Providers
- Case Managers

Siloed funding sources
- CDC, HRSA
- SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Health System
- Organization
- ASOs/CBOs
- Clinic proximity
- Clinic culture
- Appointments
- Supportive svcs
- Integrated svcs

Communication Factors
- Trust
- Communication
- Longevity
- Concordance

Need
- Severity
- Comorbidities
- Health beliefs
- Past experiences

Enabling
- Insurance
- Housing
- Transport
- Income
- Social support
- Food security
- CJ status

Predisposing
- Age
- Race/ethnicity
- Sex
- Sexuality
- Mental health
- Substance use

Individual

Community

Need

Relationships

Policy

Siloed funding sources
- CDC, HRSA
- SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Eco-Social Model: Need to Address ALL Key Issues

- HIV testing guidelines
- HIV treatment guidelines
- Siloed funding sources
  - CDC, HRSA
  - SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Policy

Community
- HIV testing guidelines
- HIV treatment guidelines
- Siloed funding sources
  - CDC, HRSA
  - SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Relationships
- Sex Partners
- Family
- Friends
- Social Networks
- Med Providers
- Case Managers

Siloed funding sources
- CDC, HRSA
- SAMHSA
- Health Depts
  - ACA, ADAP
  - Ryan White
- Quality indicators
- Service coordin.
- Reimbursement
- Workforce
- Incarceration

Health System
- Organization
- ASOs/CBOs
- Clinic proximity
- Clinic culture
- Appointments
- Supportive svcs
- Integrated svcs

Communication Factors
- Trust
- Communication
- Longevity
- Concordance

Need
- Severity
- Comorbidities
- Health beliefs
- Past experiences

Enabling
- Insurance
- Housing
- Transport
- Income
- Social support
- Food security
- CJ status

Predisposing
- Age
- Race/ethnicity
- Sex
- Sexuality
- Mental health
- Substance use

Individual
HIV Testing
The First Step of the Continuum
2006 Recommendations From CDC: Routine Opt-Out Testing for HIV

- Routine voluntary testing for patients aged 13-64 yrs in healthcare settings — not based on patient risk
- Opt-out testing
- No separate consent for HIV
- Pretest counseling not required
- Repeat HIV testing at least annually for persons at high risk

### Ongoing Community Randomized Trials

<table>
<thead>
<tr>
<th>Location</th>
<th>Location</th>
<th>Location</th>
<th>Location</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zambia</td>
<td>Tanzania</td>
<td>South Africa</td>
<td>Botswana</td>
<td>Brooklyn</td>
</tr>
<tr>
<td>South Africa</td>
<td>10,000</td>
<td>1,250</td>
<td>5,000</td>
<td>Washington</td>
</tr>
<tr>
<td>Clusters</td>
<td>Clusters</td>
<td>Clusters</td>
<td>Clusters</td>
<td>Clusters</td>
</tr>
<tr>
<td>24</td>
<td>24</td>
<td>34</td>
<td>30</td>
<td>38 HCT</td>
</tr>
<tr>
<td>55,000</td>
<td>10,000</td>
<td>1,250</td>
<td>5,000</td>
<td>39 Care</td>
</tr>
<tr>
<td>Arms</td>
<td>Arms</td>
<td>Arms</td>
<td>Arms</td>
<td>Arms</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Interventions</td>
<td>Interventions</td>
<td>Interventions</td>
<td>Interventions</td>
<td>Interventions</td>
</tr>
<tr>
<td>HCT, Circumcision</td>
<td>HCT, Circumcision</td>
<td>HCT, Circumcision</td>
<td>HCT</td>
<td>Structural &amp; behavioral</td>
</tr>
<tr>
<td>ART to all HIV+</td>
<td>ART to HIV+ (CD4&lt;350)</td>
<td>ART to all HIV+</td>
<td>Circumcision ART to HIV+ (CD4&lt;350; VL&gt;10,000)</td>
<td></td>
</tr>
<tr>
<td>Incidence Outcome</td>
<td>Incidence Outcome</td>
<td>Incidence Outcome</td>
<td>Incidence Outcome</td>
<td>Incidence Outcome</td>
</tr>
<tr>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
<td>Cumulative 2 years</td>
<td>HCT, Linkage, VL</td>
</tr>
</tbody>
</table>

None involving MSM  

El Sadr CROI 2012
Chronic HIV in the US: New Infections and Awareness of HIV Serostatus

Number (in ‘000s)

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,106,400-1,200,000</td>
<td>874,056-960,000</td>
</tr>
</tbody>
</table>

~20 Unaware of Infection
~54% of New Infections
~80% Diagnosed
~46% of New Infections

Acute HIV Infection (AHI)

- Earliest phase of HIV infection between HIV acquisition and seroconversion (several weeks to 2 months)

- Acute HIV infection and primary HIV infection often used interchangeably, although primary infection can refer to a longer period (first 6 months)
Symptomatic Acute HIV Infection

Occurs in estimated 40-90% of HIV-infected persons roughly 21-28 days after infection.

40 patients with AHI compared to 164 uninfected patients with flu-like illness*

Diagnosis: Serologic Tests are Negative

- **EIA**
  - 1\textsuperscript{st} generation (HIV IgG): 60 days post-infection
  - 2\textsuperscript{nd} generation (HIV IgG): 45 days
    - Most rapid tests are equivalent to 2\textsuperscript{nd} generation
  - 3\textsuperscript{rd} generation (HIV IgG and IgM): 21 days
  - 4\textsuperscript{th} generation (HIV IgG, IgM and p24): 15 days

- Western blot can be negative very early after infection

- RNA testing (individual or pooled NAAT samples)

- **Testing guidelines†**
  - In a person with self-reported symptoms and risk behavior. If acute retroviral syndrome suspected, HIV serology + HIV VL to diagnose AHI (BIII)*.
  - AHI patients should have repeat serologic testing over next 3 months (AI)**.

* Moderate recommendation based on non-randomized clinical trials +/- or cohort studies
** Strong recommendation based on randomized clinical trials.

† Guidelines for use of ART in HIV-infected Adults and Adolescents, 2012
Detection of Early HIV Infection

- HIV RNA (plasma)
- HIV p24 antigen
- HIV antibody

Time Since Infection, d

First-generation EIA
Second-generation EIA
Third-generation EIA
Fourth-generation EIA
NAAT

Patel et al. Archive Int. Med, 2010
New Diagnostics for Detecting Acute HIV Infection

4th Generation IA Test

Acute HIV Infection (55.6%)
Median VL = 3.7M

CDC, MMWR 2013: 62(24);489-494
Acute HIV Infection Conundrums

- How frequent & who should be tested?
- Should AHI algorithms be expanded?
- Counseling & Testing reduces risk in chronically infected patients (AHI?)
- Does immediate ART reduce HIV transmission?
  - SABES Trial – RCT of immediate vs delayed ART (Peru)
  - Includes adherence/coping strategies of HPTN 052
  - Additional contributors of “new” diagnosis
  - But ........
Contribution of Alcohol & Drug Use to Risk Behaviors Associated with HIV Transmission

Ludford K et al. PLoS One, 2013
Alcohol & Adherence: Peruvian MSM

Ferro E et al, IAS 2013

Perfect adherence:
- No AUD (N=148): 91.9%
- AUD (N=116): 80.2%

Optimal adherence:
- No AUD (N=148): 64.2%
- AUD (N=116): 44.0%

P values:
- ≥90% Optimal: P=0.005
- 100% Perfect: P<0.001
How to Manage Risk Behaviors and/or Adherence

- They are often linked – but not always!
- Comprehensive behavioral intervention that incorporates alcohol & drug reduction?
  - Very few DEBIs address drug/alcohol use
- Pharmacotherapies?
  - Naltrexone
    - Oral
    - XR-NTX
  - Acamprosate
  - Disulfiram
2009 CDC Guidance for HIV Testing in Correctional Settings

- 10 million released annually
- HIV prevalence 4x greater among prisoners than in the community
- 14-18% of all HIV+ patients cycle through annually
- 95% enter CJS via jails
  - More challenging with rapid turnover
- High HIV risk behaviors after release (HIV+s & HIV-s)

Centers for Disease Control and Prevention
HIV Testing Implementation Guidance for Correctional Settings
January 2009

Opt-out (if feasible)
Risk-based testing
Opt-in
Randomized Controlled Trials of Routine Opt-Out HIV Testing in Jails

**Men’s Jail**

<table>
<thead>
<tr>
<th></th>
<th>Immediate (n=103)</th>
<th>Early (n=98)</th>
<th>Delayed (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid HIV Test (%)</strong></td>
<td>45%*</td>
<td>53%†</td>
<td>33%</td>
</tr>
</tbody>
</table>

*P=0.01 and †P=0.001 versus delayed.

**Women’s Jail**

<table>
<thead>
<tr>
<th></th>
<th>Immediate (n=108)</th>
<th>Early (n=108)</th>
<th>Delayed (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid HIV Test (%)</strong></td>
<td>55%</td>
<td>73%*</td>
<td>50%</td>
</tr>
</tbody>
</table>

*P=0.007 (versus immediate), P<0.001 (versus delayed).

Immediate: during a mandatory initial medical screen the night of admission; early: during required physical examination the following evening; delayed: 7 days after arrival to the facility.

AIDS-Related Mortality Achieves Parity in Prisons and the General Population

HIV Treatment Outcomes During and After Incarceration

**HIV RNA Change**

<table>
<thead>
<tr>
<th>Change (log_{10} copies/mL)</th>
<th>DURING (N=292)</th>
<th>AFTER (3 MO) (N=292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA Change</td>
<td>-1.04</td>
<td>+1.14</td>
</tr>
</tbody>
</table>

**P < 0.0001**

**Viral Suppression (%)**

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Suppression (%)</td>
<td>59%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Prison Release

Where's the safety net?

Recidivism to Prison

Homelessness
Drug Relapse
Unemployment
Mental Illness
Intimate Partner Violence
Risk Behaviors

Altice FL

Family
Insurance
Overdose
RCT of DAART for Released HIV+ Prisoners

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>DAART (N=103)</th>
<th>SAT (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>46.3</td>
<td>43.8</td>
</tr>
<tr>
<td>Racial/ethnic minority</td>
<td>85 (85)</td>
<td>22 (70)</td>
</tr>
<tr>
<td>Women</td>
<td>18 (18)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Opioid Dependence</td>
<td>64 (64)</td>
<td>30 (59)</td>
</tr>
<tr>
<td>Cocaine Abuse</td>
<td>89 (89)</td>
<td>R21 46 (90)</td>
</tr>
<tr>
<td>Alcohol Dependence</td>
<td>26 (26)</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Axis I Disorder</td>
<td>42 (42)</td>
<td>24 (47)</td>
</tr>
<tr>
<td>HIV-1 RNA&lt;400</td>
<td>80 (80)</td>
<td>39 (76)</td>
</tr>
<tr>
<td>Mean CD4</td>
<td>414</td>
<td>350</td>
</tr>
</tbody>
</table>

P=ns for all comparisons

*Altice, CROI, 2011*
Altice, CROI 2011
## Correlates of Achieving VL<400 at 6 Months (N=154)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAART (vs SAT)</td>
<td>2.91</td>
<td>(1.29-6.57)</td>
<td>0.010</td>
</tr>
<tr>
<td>Baseline VL&lt;50</td>
<td>5.54</td>
<td>(2.52-12.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>0.36</td>
<td>(0.15-0.83)</td>
<td>0.016</td>
</tr>
<tr>
<td>Prescribed BPN (among those meeting OD criteria)</td>
<td>3.62</td>
<td>(1.32-9.92)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* NS were age, gender, race/ethnicity, homeless at time of release, mental illness, duration of incarceration

*Altice, CROI 2011*
Retention on BPN Treatment (N=50)

Substudy (N=94)
- 50 (53%) started BPN
- BPN preferred by \( \frac{3}{4} \)
- Clients changed their mind pre/post release

## Independent Correlates of Maximal Viral Suppression at 6 Months (N=94)

<table>
<thead>
<tr>
<th>Among Subjects with Opioid Dependence (N=94)</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention on BPN (24 weeks)</td>
<td>5.37 (1.15-25.1)</td>
</tr>
<tr>
<td>Male gender</td>
<td>4.23 (1.01-18.0)</td>
</tr>
<tr>
<td>Black (ref: White)</td>
<td>0.13 (0.03-0.68)</td>
</tr>
<tr>
<td>Hispanic (ref: White)</td>
<td>0.47 (0.09-2.31)</td>
</tr>
<tr>
<td>Baseline VL&lt;50</td>
<td>10.5 (3.21-34.1)</td>
</tr>
<tr>
<td>DAART (no longer significant)</td>
<td>1.56 (0.65-3.74)</td>
</tr>
</tbody>
</table>

*Springer, PLoS One, 2012*
Post-Release Impact of Methadone Treatment

Kinlock, J Sub Abuse Treat, 2009
Impact of Methadone Dose on Treatment Retention Post-Release in Malaysia

Wickerhsham, *Drug Alcohol Depend*, 2013
Retention in Care Among HIV+ Jail Detainees: Results from a Multi-Site Study (N=867)

Althoff, AIDS Behav, 2012
# Independent Correlates of Sustained Retention in HIV Care

<table>
<thead>
<tr>
<th>Covariate</th>
<th>AOR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>2.10</td>
<td>1.42, 3.11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Having an HIV provider (pre-incarceration)</td>
<td>1.67</td>
<td>1.09, 2.56</td>
<td>0.02</td>
</tr>
<tr>
<td>Heroin use (30 days pre-incarceration)</td>
<td>✔</td>
<td>1.49, 2.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Discharge planning (within jail)</td>
<td>1.50</td>
<td>1.06, 2.12</td>
<td>0.02</td>
</tr>
<tr>
<td>Disease management session (within jail)</td>
<td>2.25</td>
<td>1.51, 3.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Needs assessment (post-release)</td>
<td>1.59</td>
<td>1.06, 2.37</td>
<td>0.02</td>
</tr>
<tr>
<td>HIV-related education (post-release)</td>
<td>2.03</td>
<td>1.37, 2.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transportation assistance (post-release)</td>
<td>1.54</td>
<td>1.0, 2.22</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Althoff, AIDS Behav, 2012*
HIV+ Jail Detainees

Heightened Instability Post-Release

Meyer JP et al, AJPH, In Press
Transitions from Housing Among HIV+ Jail Detainees

● Transition to housing
  - Not ever having OR decreasing food insecurity
  - Not using alcohol (? Rx effect of BPN)

● Transition to homeless
  - Becoming food insecure
  - Cocaine use
  - Depression / deterioration

Housing contributed on average to 15.6% increase in VL<400

Zelenev A et al, AIDS Behav, 2013
Do Other Treatments for Substance Use Disorders Improve Outcomes

- XR-NTX for alcohol use disorders
  - Acceptability of injections
  - Retention and Safety
- XR-NTX for opioid dependence
  - Acceptability of injections
  - Retention and Safety
  - Overdose
- Methadone for opioid dependence (Malaysia)
- ARTAS-II (Ukraine)
Reasons for missing:

1. Incarceration
2. Missed Timeframe
3. Lost
4. Work
5. Relapsed to alcohol after release – detoxed
6. Interviews too long
7. Medical need for opioid pain meds - never received injections
8. Hospitalization
Treatment of HIV-Infected Persons for Prevention of HIV Transmission

The Role of HIV Treatment Providers
CDC: Breaks in the Continuum of Care in HIV-Infected Patients in the US

- CDC study shows that only ~ 25% of US patients with HIV have suppressed HIV-1 RNA

Treatment of HIV-Infected Persons for Prevention of HIV Transmission

Altice FL et al, JAIDS, 2011

P<0.5 for all comparisons between subjects on BPN/NX < 3 Quarters and those on longer duration. Using GEE and incorporating being on BPN/NX 3 or 4 Quarters, β=1.34 95% CI:(1.18, 1.53).

P<0.5 for all comparisons between subjects on BPN/NX < 3 Quarters and those on longer duration and for comparisons from baseline. Using GEE and incorporating being on BPN/NX 3 or 4 Quarters, β=1.25 95% CI: (1.10, 1.42).
Treatment of HIV-Infected Persons for Prevention of HIV Transmission
HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm$^3$ (N = 1763 couples)

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

- **Delayed ART**
  Initiate HAART at CD4+ cell count ≤ 250 cells/mm$^3$* (n = 877 couples)

*Based on 2 consecutive values ≤ 250 cells/mm$^3$.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage IV events, pulmonary TB, severe bacterial infection and/or death
- Couples received *intensive counseling* on risk reduction and use of condoms

# Observational Studies: ART Decreases Risk of Transmitting HIV


<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musicco 1994</td>
<td>436 monogamous HIV-uninfected female sexual partners of HIV-infected men in Italy</td>
<td>0.88 (0.36-2.16)</td>
</tr>
<tr>
<td>Melo 2008</td>
<td>93 heterosexual Brazilian couples</td>
<td>0.10 (0.01-1.67)</td>
</tr>
<tr>
<td>Sullivan 2009</td>
<td>2993 HIV-discordant couples in Rwanda and Zambia</td>
<td>0.21 (0.08-0.56)</td>
</tr>
<tr>
<td>Del Romero 2010</td>
<td>648 heterosexual couples in Madrid</td>
<td>0.21 (0.01-3.75)</td>
</tr>
<tr>
<td>Donnell 2010</td>
<td>3408 heterosexual African couples; index partner HIV positive and HSV positive</td>
<td>0.08 (0.01-0.57)</td>
</tr>
<tr>
<td>Lu 2010</td>
<td>1927 heterosexual couples for testing and treatment at county hospitals in China</td>
<td>1.44 (0.85-2.44)</td>
</tr>
<tr>
<td>Reynolds 2011</td>
<td>250 HIV-discordant couples from Rakai, Uganda</td>
<td>0.10 (0.01-1.64)</td>
</tr>
<tr>
<td>Birungi 2012</td>
<td>550 heterosexual couples attending a clinic in Uganda</td>
<td>0.91 (0.38-2.20)</td>
</tr>
<tr>
<td>Jai 2012</td>
<td>Large population-based cohort (&gt;38,000 couples) of HIV-positive persons and their HIV-negative partners in China</td>
<td>0.74 (0.65-0.84)</td>
</tr>
<tr>
<td><strong>SUMMARY</strong></td>
<td></td>
<td><strong>0.58 (0.35-0.96)</strong></td>
</tr>
</tbody>
</table>
Limitations of Current Data on ART for HIV Prevention

- Only 2 couples from US included in HPTN 052\textsuperscript{[1]}
- ART may mediate different degree of risk reduction when other modes of transmission (eg, needles, anal intercourse) taken into account
- Adherence to lifelong ART may be difficult when initiated in asymptomatic individuals
- Observational studies of the effect of ART on transmission among HIV serodiscordant couples have shown lower HIV risk reduction, likely as a result of lower adherence to ART\textsuperscript{[2]}
- 28\% of infections in HPTN 052 occurred from outside of study partnerships, for which ART use by the HIV-infected partner offered no protection\textsuperscript{[1]}

Pre-Exposure Prophylaxis (PrEP) for HIV-Uninfected Persons to Reduce Risk of HIV Acquisition
PrEP Clinical Trials

- Phase III clinical trials of PrEP tested daily oral TDF-based tablets (alone or in combination with FTC)
- Factors that supported testing of TDF-based PrEP in clinical trials
  - Potency: rapid antiretroviral activity
  - Safety: high tolerability, substantial treatment safety experience
  - Ease: once-daily dosing, few drug–drug interactions
  - Preclinical/early clinical evidence: animal model data found high efficacy of PrEP for HIV protection[1]

PrEP Trials Have Shown Efficacy in MSM, Heterosexual Men and Women, and PWIDs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population/Setting</th>
<th>Intervention</th>
<th>HIV Infections, n</th>
<th>HIV Risk Reduction, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEX[^1^]</td>
<td>MSM, transgender women, 11 sites in US, South America, Africa, Thailand</td>
<td>TDF/FTC</td>
<td>36</td>
<td>44 (15-63)</td>
</tr>
<tr>
<td>(N=2499)</td>
<td></td>
<td></td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>(N=4747)</td>
<td></td>
<td>TDF/FTC</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>(N=1219)</td>
<td></td>
<td></td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Thai PWID[^4^]</td>
<td>PWIDs from 17 drug treatment centers in Thailand</td>
<td>TDF</td>
<td>17</td>
<td>49 (10-72)</td>
</tr>
<tr>
<td>(N=2413)</td>
<td></td>
<td></td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Adherence: Key Contributor to Outcome in PrEP Trials (Detectable TDF Levels)

Differences in Adherence Translated to Relative Risk Reduction in Transmitting HIV

Bangkok TDF Study: Adherence to PrEP and Risk of HIV Acquisition

Pts Uninfected By Level of Adherence

Adherence

Uninfected Pts (%)

mITT | > 67% | > 75% | > 90% | > 95% | > 97.5%

49 | 54 | 58 | 68 | 72 | 84

PrEP (Like ART) Works When Taken

<table>
<thead>
<tr>
<th>Study</th>
<th>Blood Samples With Tenofovir Detected, %</th>
<th>HIV Protection Efficacy in Randomized Comparison, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP[1]</td>
<td>81</td>
<td>75</td>
</tr>
<tr>
<td>TDF2[2]</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>iPrEx[3]</td>
<td>51</td>
<td>44</td>
</tr>
<tr>
<td>Thai IDU[4]</td>
<td>67</td>
<td>49</td>
</tr>
</tbody>
</table>

2 additional trials of PrEP (FEM-PrEP and VOICE), both conducted among high-risk African women, did not demonstrate protection against HIV; in both trials, PrEP adherence was very low (< 30%)

Caveat Emptor: PrEP Trials Found Decreasing Risk Behavior Over Time

**iPrEx**[1]

**Partners PrEP**[2]

PrEP Works Together With Other HIV Prevention Strategies

- Example from Partners PrEP Study: package of HIV prevention services, including ongoing risk-reduction counseling, HIV testing, ART according to national policies, treatment of STIs, and other strategies plus PrEP synergize to maximally reduce HIV risk.

HIV Incidence

- Serodiscordant Couples Outside of Clinical Trials\(^1\): 10% to 15%/yr
- Partners PrEP Placebo Arm\(^2\): 2%/yr
- Partners PrEP TDF/FTC Arm\(^2\): 0.5%/yr

Long-Acting GSK1265744 and TMC278

- Nanosuspensions: drug nanocrystals suspended in liquid
  - Increased drug dissolution rate
  - Nanocrystal design allows for low injection volume
- Potential utility as long-acting injections for ART regimens, PrEP
  - GSK1265744 (DTG analogue) dosed monthly or quarterly
  - TMC278 nanosuspension of RPV dosed monthly

Favorable Drug Concentrations With GSK1265744 and TMC278 Injections

- PK results
  - GSK1265744 injected every 4 wks or every 12 wks achieved plasma levels > protein-adjusted IC$_{90}$
  - TMC278 dosed every 4 wks achieved plasma levels comparable to those achieved by oral RPV 25 mg/day in HIV-infected patients
- GSK1265744 safe, well tolerated alone and in combination with TMC278
- Findings support phase II study of GSK1265744 + TMC278 as 2-drug ART regimen

Sustained Released Pharmacotherapies

- Emerging sustained pharmacotherapies for treatment of substance use disorders
  - XR-NTX
  - XR-BPN
  - Implantable NTX and BPN

<table>
<thead>
<tr>
<th>Part 1. Overview Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participating Organization(s)</td>
<td>National Institutes of Health (NIH)</td>
</tr>
<tr>
<td>Components of Participating Organizations</td>
<td>National Institute of Allergy and Infectious Diseases (NIAID)</td>
</tr>
<tr>
<td></td>
<td>Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)</td>
</tr>
<tr>
<td></td>
<td>National Institute of Mental Health (NIMH)</td>
</tr>
<tr>
<td>Funding Opportunity Title</td>
<td>Sustained Release of Antivirals for Treatment or Prevention of HIV (SRATP) (R01)</td>
</tr>
<tr>
<td>Activity Code</td>
<td>R01 Research Project Grant</td>
</tr>
<tr>
<td>Announcement Type</td>
<td>New</td>
</tr>
<tr>
<td>Related Notices</td>
<td>None</td>
</tr>
<tr>
<td>Funding Opportunity Announcement (FOA) Number</td>
<td>PAR -13-349</td>
</tr>
</tbody>
</table>
## Key Questions for ART as Prevention and PrEP

<table>
<thead>
<tr>
<th>Components</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost</strong></td>
<td>How to pay for ARVs? Prioritize some individuals/populations?</td>
</tr>
<tr>
<td><strong>Uptake</strong></td>
<td>Do those who may benefit most from ART and PrEP want it?</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td>Will adherence to PrEP and ART be high enough to achieve benefits?</td>
</tr>
<tr>
<td><strong>Sexual behavior</strong></td>
<td>Does taking PrEP or ART result in more risk-taking behavior? Enough to undermine the prevention benefits?</td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>What will the effect be on HIV incidence at the population level?</td>
</tr>
</tbody>
</table>
"Half of everything we teach you is wrong... unfortunately, we don't know which half."