In 2011:
New HIV infections: 2.5 million [2.2, 2.8]
Deaths due to AIDS: 1.7 million [1.5, 1.9]
Adult (aged 15-49) prevalence 0.8%
U.S. Preventive Services Task Force (UPSTF) Draft Recommendations (12/12)

- Screen adolescents and adults ages 15 to 65 for HIV infection.
- Younger adolescents and older adults who are at increased risk should also be screened.
- This is a grade A recommendation.

New HIV infections among 13–24 year olds — U.S., 2010

- Of all new HIV infections in 2010, 26% occurred in 13-24 year olds
- 60% are not aware they are infected
- 72% were MSM
- 20% were heterosexuals
- 13% were IDU

HIV Prevention Strategies

Adapted from Ramjee IAS Meeting 2006, #TUPL02
Abstain, Be faithful, Condoms, Counseling & testing

ABC

Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2007-2010—46 States and 5 U.S. Dependent Areas

- Male-to-male sexual contact
- Heterosexual contact
- Injection drug use
- Male-to-male sexual contact and injection drug use

New infections each year ~32,000

HIV Prevention Strategies

Adapted from Ramjee IAS Meeting 2006, #TUPL02
Abstain, Be faithful, Condoms, Counseling & testing

ABC

Circumcision
Cervical HPV vaccine
Castration
Dapivirine in female-controlled microbicides
Diaphragms
Exposure prophylaxis with ART
Genital tract infection control
HIV-2 suppressive treatment
HIV/AIDS testing
Immune restoration therapy
Immunization
Retroviral prophylaxis
SABRINA
Secondary prevention, herpetic labialis
Secondary prevention, herpes zoster vacc
Secondary prevention, varicella zoster vacc
Secondary prevention, hepatitis B vacc
Secondary prevention, hepatitis B vacc
Secondary prevention, hepatitis A vacc
Secondary prevention, hepatitis C vacc
Antiretroviral Therapy (ART) and Prevention

- Vertical transmission – Prevention of Mother to Child Transmission (PMTCT)
  - AZT alone reduced MTCT from 25% to 8% Connor NEJM 1994
  - Current ART reduces MTCT to <0.5%

HPTN 052: ART as Prevention

- 1,763 discordant couples (97% heterosexual) in Africa, Asia, Americas with HIV+ with CD4 350-550
- HIV+ partner randomized to start cART immediately or deferred until CD4 <250
- DSMB Interim analysis:
  - 90% on ART had HIV RNA <400
  - 40 incident cases of HIV
  - 29 linked genetically to partner
  - 96% reduction in transmission!
  
Cohen #MOAX0102 and NEJM 2011;365:493

Guidelines for Initiation of ART

<table>
<thead>
<tr>
<th></th>
<th>AIDS/CD4</th>
<th>CD4 200-350</th>
<th>CD4 350-500</th>
<th>CD4 &gt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>US DHHS ’12</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>IAS-USA ’12</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>BHIVA ’12</td>
<td>YES</td>
<td>YES</td>
<td>certain</td>
<td>certain</td>
</tr>
</tbody>
</table>

Mathematical Modeling
Universal Test and Treat

Utopian Assumptions

- South Africa
- High uptake of annual testing by all individuals >15 year old
- Treat all HIV+
- 99% decrease in infectiousness
- High adherence and low failure with 1st line ART

Prevention and Antiretroviral Therapy (ART)

- Post-exposure prophylaxis (PEP)
  - AZT reduced risk of seroconversion in HCW by 81% in a case-control study Cardo NEJM 1997
  - Current CDC Guidelines recommend 2- or 3-drug antiretroviral treatment for 4 weeks following exposure
  PHS Guidelines 1/21/05 and 9/30/05 <www.aidsinfo.nih.gov>
Definitions

- Microbicides
  - compounds that can be applied inside the vagina or rectum to protect against sexually transmitted infections (STIs), including HIV
  - formulated as gels, creams, films, or suppositories

- PREP
  - Pre-exposure prophylaxis
  - Strategy of administering ART to uninfected, at-risk individuals

Criteria: DAIDS Working Group

- 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 rx regimens
- Affordable, easy to use and implement

DAIDS Working Group Report 4/09

Antiretroviral Drugs: 2013

- nucleoside/tide RTIs (NRTIs)
  - zidovudine (ZDV, AZT)
  - didanosine (ddI)
  - stavudine (d4T)
  - lamivudine (3TC)
  - abacavir (ABC)
  - emtricitabine (FTC)
  - tenofovir (TDF)

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

- protease inhibitors (PIs)
  - saquinavir (SQV)
  - ritonavir (RTV)
  - indinavir (IDV)
  - nelfinavir (NFV)
  - lopinavir/ritonavir (LPV/r)
  - atazanavir (ATV)
  - fosamprenavir (FPV)
  - tipranavir (TPV)
  - darunavir (DRV)

- entry inhibitors (EIs)
  - enfuvirtide (T-20, fusion inhibitor)
  - maraviroc (MVC, CCR5 inh)

- integrase inhibitors (IIs)
  - raltegravir (RAL)
  - elvitegravir (EVI)

Antiretroviral Drug Approval: 1987 - 2013

CAPRISA 004: 1% vaginal TFV gel

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

- Overall
  - Placebo
  - Tenofovir DF gel

- By Adherence
  - Placebo
  - Tenofovir DF gel

**PREP: Animal Model**

Effect of daily and intermittent PREP in monkeys: SHIV rectal challenge

*Garcia-Lerma PLoS Med 2008*

**TDF and FTC/TDF for PrEP**

Optimal PrEP candidates: potency, safety, tolerability, and convenience

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

Potential concerns:
- Used widely; preferred first-line treatment
- Drug resistance
- Toxicities: renal, bone
- Cost >$10,000/year

**Completed and Current Studies of Oral PrEP**

14 studies and projects, up to 16 countries

32,000+ participants

**IPREX: PrEP in MSM**

Phase III study of PREP with TDF/FTC or placebo
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

64 new infections
36 new infections
44% reduction (95% CI, 15%-63%, p=0.005)
92% effective if drug level detectable

**IPREX: Recorded Adherence and Efficacy**

Grant et al, CROI 2010

**Adverse events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TDF/FTC</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Elevated</td>
<td>25 (2%)</td>
<td>28</td>
<td>14 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>56 (4%)</td>
<td>66</td>
<td>41 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (2%)</td>
<td>22</td>
<td>9 (&lt;1%)</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>27 (2%)</td>
<td>34</td>
<td>14 (1%)</td>
</tr>
</tbody>
</table>

Grant NEJM 2010;363:2587
CDC Guidance for PrEP for MSM: (Interim; 1/27/11)

- Before starting:
  - document HIV Ab and r/o acute infection
  - CrCl ≥ 60, screen for STIs and HBV
  - Rx TDF/FTC 1 po daily X 90 days
    - provide risk reduction, adherence counseling, condoms
- On treatment:
  - check HIV Ab every 2-3 months
  - check BUN/creat at 3 months and yearly
  - risk reduction, condoms, STI assessments/rx

http://www.cdc.gov/hiv/prep/index.htm

U.S. Food and Drug Administration (FDA) Approval of PrEP (7/16/12)

- U.S. FDA approves Truvada for pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.

PrEP Studies

Study (reference) | Study population | Design | Results: Reduction in HIV Infection
--- | --- | --- | ---
CDC – TDF-2 | Thigpen NEJM 2012;367:423 | TDF/FTC vs. placebo | TDF/FTC: 63%
Partners PREP | Baeten NEJM 2012;367:399 | TDF vs. TDF/FTC vs. placebo | TDF: 67% TDF/FTC: 75% (86-90% if TFV detected)
FEM-PREP | Van Damme NEJM 2012;367:411 | TDF/FTC vs. placebo | TDF/FTC: 6% (overall adherence was <40%)
VOICE | Press release 9/29/11 | 1% TDF gel vs. placebo gel; oral TDF vs. TDF/FTC vs. placebo | DSMB: TDF oral arm stopped early due to futility; TDF gel not effective

PrEP Studies

Drug Resistance

<table>
<thead>
<tr>
<th>Genotypic Resistance</th>
<th>HIV Status at Enrollment</th>
<th>Placebo N=8</th>
<th>FTC/TDF N=2</th>
<th>Placebo N=3</th>
<th>FTC/TDF N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>65R</td>
<td>Infected (N=10)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>70E</td>
<td>Uninfected (N=100)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>184I</td>
<td></td>
<td>0 (0%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>184V</td>
<td></td>
<td>1 (13%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TDF Resistance</td>
<td></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>FTC Resistance</td>
<td></td>
<td>1 (13%)</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
### CDC Guidance for PrEP for heterosexuals (8/9/12)
- Targeted to high-risk individuals, such as those with an HIV+ sex partner.
- It is critical to take PrEP consistently.
- Discuss risks/benefits with pregnant women or those trying to conceive; data are incomplete and mostly from HIV+ women.
- PrEP is not a stand-alone solution.
- Individuals must be confirmed HIV- prior to PrEP; monitor HIV status, side effects, adherence, and risk behaviors.

### WHO Guidance for PrEP (7/20/12)
- Ensure that people seeking PrEP are HIV-.
- Encourage continued condom use.
- Check for pre-existing medical conditions (e.g., kidney or bone disease).
- Monitor for adverse events.
- Help people adhere to daily medication.
- Ensure uninterrupted supply.
- Test regularly for HIV infection and check for drug resistance if infection is found.
- Gather cost-benefit information.

### Ongoing PrEP Efficacy Studies

<table>
<thead>
<tr>
<th>Study/Location</th>
<th>Sponsor</th>
<th>Population</th>
<th>N</th>
<th>PrEP Agent</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bangkok TDF Study</em> Thailand</td>
<td>CDC</td>
<td>IDU</td>
<td>2413</td>
<td>TDF</td>
<td>Fully enrolled: Results End of 2012</td>
</tr>
<tr>
<td><em>VOICE / MTN 003</em> South Africa, Uganda, Zimbabwe</td>
<td>MTN / NIH</td>
<td>women</td>
<td>5029</td>
<td>TDF/FTC</td>
<td>Fully enrolled: Results 2013</td>
</tr>
<tr>
<td><em>FACTS 001</em> South Africa</td>
<td>women</td>
<td>2200</td>
<td>TFV gel</td>
<td>Enrolling: Results 2014</td>
<td></td>
</tr>
</tbody>
</table>

### IPREX F/U: Modeling PK
- Using data from a separate PK study (STRAND):
  - 2 doses/week: 76% risk reduction
  - 4 doses/week: 97% risk reduction
  - 7 doses/week: 99% risk reduction

  Anderson Sci Transl Med 2012:4:151ra125

### Antiretroviral Drugs: 2012
- *Nucleoside/tide RTIs (NRTIs)*
  - lamivudine (3TC)
  - emtricitabine (FTC)
  - tenofovir (TDF)
- *Entry inhibitors (EIs)*
  - maraviroc (MVC, CCR5 inh)
- *Integrase inhibitors (IIs)*
  - raltegravir (RAL)

### HPTN 069: NEXT-PrEP
- Design: Phase II, 4-arm, multisite, study
- Study population (N=400)
- At-risk HIV-negative gay men
- Study Treatment:
  - MVC monotherapy
  - MVC + FTC
  - MVC + TDF
  - TDF + FTC (control)
- Duration: 48 weeks
- Primary endpoint: Grade ≥3 toxicities; time to study treatment discontinuation

Amendment: Cohort of 200 women
Newer PrEP Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Dosing Route</th>
<th>Dosing Frequency</th>
<th>PrEP Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>rilpivirine-LA</td>
<td>NNRTI</td>
<td>Injectable, SC</td>
<td>Once monthly</td>
<td>Phase 1 pilot</td>
</tr>
<tr>
<td>S/GSK 1265744 ('744)</td>
<td>Integrase inhibitor</td>
<td>Injectable, SC</td>
<td>Once monthly (or less)</td>
<td>Phase 1 pilot</td>
</tr>
<tr>
<td>ibalizumab</td>
<td>CD4 attachment inhibitor</td>
<td>Injectable, SC</td>
<td>Once every 1-4 weeks</td>
<td>Phase 1 pilot</td>
</tr>
</tbody>
</table>

HIV Prevention Strategies

- **Study**
  - Antiretroviral treatment for prevention
  - PrEP for discordant couples
  - FemPrEP (vaginal, injectable)
  - PrEP for heterosexuals
  - PrEP for inhalation
  - Medical male circumcision
  - Diaphragm/condom (new and/or different) (expected)
  - PrEP for MSM
  - PrEP - America, Botswana, South Africa
  - CTC treatment
  - HIV vaccine

- **Effect size (CI)**
  - [95% CI: 95%
  - [75% CI: 85]
  - [65% CI: 75%
  - [45% CI: 55%
  - [35% CI: 45%
  - [25% CI: 35%
  - [15% CI: 25%

HIV Prevention 2012

- **Conclusions**
  - Newer prevention strategies are needed, particularly in MSM.
  - PrEP was effective in reducing HIV infections in MSM and heterosexual men.
  - Updated CDC guidelines anticipated.
  - Logistical and implementation issues.
  - Additional research in progress.
**Acknowledgments**

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Medical College of Cornell University
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH
- The patient volunteers!