The ART of Preventing HIV: Clinical Utility and Implications of Pre-Exposure Prophylaxis

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Learning Objectives
1. Recognize the need for more effective HIV prevention strategies, including chemoprophylaxis.
2. Critique current clinical evidence evaluating the use of pre-exposure prophylaxis (PrEP).
3. Identify mechanisms that potentially mitigate the benefits of the widespread application PrEP.
4. Select appropriate high-risk populations eligible for PrEP in conjunction with other prevention strategies.
Introduction

I. UNAIDS “Getting to Zero” initiative to halt and reverse the AIDS epidemic by 2015
   a. Zero new infections – reduce sexual transmission by half and eliminate vertical transmission
   b. Zero AIDS-related deaths – access to antiretroviral therapy (ART) for all eligible persons
   c. Zero discrimination – reduce punitive laws, HIV-related restrictions, gender-related violence

II. Epidemiology
   a. Prevalence
      i. More than 34 million people worldwide living with HIV
      ii. Annual AIDS-related mortality
         1. Decreased from peak of 2.2 million in mid-2000s to 1.7 million in 2011
         2. Estimated 2.5 million deaths averted since 1995 due to ART
      iii. ART coverage reached ~8 million people, up from 6.65 million in 2010

   b. Incidence
      i. Newly acquired HIV infections decreased globally by 35% since peak in 1997 but trends vary by region
         1. Decreasing – sub-Saharan Africa, Asia, Oceania
         2. Increasing – Eastern Europe, Central Asia, Middle East, North Africa
         3. Stable – Latin America, North America, Western and Central Europe
      ii. Primary modes of transmission globally
         1. Unprotected sex between men who have sex with men (MSM)
         2. Unprotected transactional sex in commercial sex workers (CSW)
         3. Sharing of contaminated needle-injecting equipment
   c. HIV in the United States
      i. More than 1.2 million living within the United States (~60% increase from 1997)

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Clinical Pearls #1: Trends in HIV epidemiology

- Global rates of newly infected persons decreasing but trends vary by region
- Stable incidence in the United States but increased in specific groups
- Sexual activity accounts for ~75% of transmission in the US and 90% globally
- High risk groups for sexual transmission include MSM, SDC, and CSW

MSM = men who have sex with men; SDC = serodiscordant couples; CSW = commercial sex workers
ii. Roughly 50,000 new infections annually with ~75% acquired through sexual activity
   1. MSM account for ~60% of new cases of HIV in US
   2. Heterosexuals account for ~18% of all new HIV infections but >80% of new cases in women

iii. Stable incidence but increasing among specific communities – African Americans, Hispanics, and Latinos, MSM, injection drug users (IDUs)

III. Mechanism of sexual transmission

   a. Transfer of viral particles from infected host
      i. Penetration of epithelial barrier of genital/rectal mucosa
         1. Damage secondary to physical or chemical stress
         2. Can cross intact mucosa via trafficking by dendritic cells (DCs)
      ii. Initial infection of local target cells, by viral “founder population”

   b. Propagation of infection
      i. Local expansion required before spread to distant lymph nodes
      ii. Infected DCs mature and migrate to deeper submucosal tissue and regional lymph nodes
      iii. Dependent on continual seeding from infected latent CD4+ T-cells

   c. Dissemination and systemic infection
      i. Subclinical inflammation and cellular signaling induces recruitment of more DCs and CD4+ T-cells
      ii. Spread of infection to secondary lymphatic tissue and distant sites

IV. Risk of sexual transmission

   a. Risk during acute HIV infection 30-300 times higher than during post-acute phase
   b. Higher risk with greater viral loads \( \rightarrow \) 2.5-fold increased risk per log_{10} increase in viral load
   c. Estimates of HIV transmission per sexual contact
      i. 1 in every 10-1600 encounters between MSM
      ii. 1 in every 200-2000 encounters between an infected male and uninfected female
      iii. 1 in every 700-3000 encounters between an uninfected male and infected female

<p>| Table 1: Per-act relative risk (RR) of transmission with various sexual behaviors^{12} |
|-------------------------------------|-----------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th>Partner status</th>
<th>Sex Act</th>
<th>Condom use</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterosexual</td>
<td>Insertive oral</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Negative HIV test</td>
<td>Insertive vaginal</td>
<td>No</td>
<td>20</td>
</tr>
<tr>
<td>Unknown serostatus</td>
<td>Insertive anal</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>HIV positive</td>
<td>Recipient anal</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>MSM</td>
<td>Recipient anal</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Negative HIV test</td>
<td>Recipient anal</td>
<td></td>
<td>4706</td>
</tr>
<tr>
<td>Unknown serostatus</td>
<td>Recipient anal</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>HIV positive</td>
<td>Recipient anal</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

* Assumes independent and multiplicative risk and estimated per-act risk of HIV transmission of 0.1% from an infected male to uninfected female during unprotected receptive vaginal sex (e.g. RR of ~ 9,400,000 with unprotected receptive anal sex with an HIV-positive partner with an absolute risk of 5 per 1,000 sex acts)
V. Current prevention strategies
   a. Behavioral and structural interventions\textsuperscript{6,9-11,13}
      i. General education and counseling about HIV prevention
         1. Provide adequate information about HIV and effective prevention methods
         2. Identify and correct misconceptions about HIV transmission
         3. Reduce exposure to HIV by providing knowledge and increasing awareness
         4. Emphasize need for safer practices and behaviors to protect own health
      ii. Screening for behavioral risk factors\textsuperscript{13}
         1. Reduce high risk sexual behaviors to lessen risk for HIV infection
         2. Important behaviors to address
            a. Number/sex of partners
            b. HIV status of partners
            c. Types of sexual activities
            d. Barriers to abstinence
      iii. Condom use
         1. Consistent condom use in serodiscordant heterosexual cohort studies reduced HIV transmission by \( \sim 80\% \textsuperscript{14} \)
         2. Risk of transmission increased 20-fold per sex act with no condom use\textsuperscript{12,13}
      iv. Male circumcision
         1. Findings from three recent randomized controlled trials conclude reduction of HIV transmission by \( \sim 60\% \) from infected women to men\textsuperscript{11}
         2. Benefit thought to be derived directly from removal of target cell-rich inner foreskin or indirectly by decreasing inflammation/susceptibility to STIs\textsuperscript{11,13}
      v. Screening and treatment of STIs
         1. STI treatment reduces HIV incidence by \( \sim 40\% \textsuperscript{15} \)
         2. Increased susceptibility through breakdown of mucosal barrier and increased recruitment of target cells through inflammation\textsuperscript{10,11}
         3. Presence of STIs suggest recent or ongoing sexual behaviors that may result in HIV transmission\textsuperscript{13}

\begin{table}
\centering
\begin{tabular}{|l|c|}
\hline
Study                          & Effect size (95\% CI) \\
\hline
Antiretroviral treatment for prevention  \\
HPTN 052, Africa, Asia, Americas\textsuperscript{5} & 96\% (73-99) \\
PreP for discordant couples  \\
Partners PreP, Uganda, Kenya\textsuperscript{1} & 73\% (49-85) \\
PreP for heterosexual men and women  \\
TFF2, Botswana\textsuperscript{6} & 63\% (21-84) \\
Medical male circumcision  \\
Orange Farm,\textsuperscript{7} Rakai,\textsuperscript{7} Kisumu,\textsuperscript{8} & 54\% (38-66) \\
PreP for MSMs  \\
IPLEX Americas, Thailand, South Africa\textsuperscript{4} & 44\% (15-63) \\
Sexually transmitted diseases treatment  \\
Mwanza, Tanzania\textsuperscript{9} & 42\% (21-58) \\
Microbicide  \\
CAPRISA 004, South Africa\textsuperscript{2} & 39\% (6-60) \\
HIV vaccine  \\
RV144, Thailand\textsuperscript{11} & 31\% (1-51) \\
\hline
\end{tabular}
\caption{Comparative effectiveness of current HIV prevention strategies\textsuperscript{15}}
\end{table}
b. Chemoprophylactic strategies
   i. Perinatal prophylaxis\textsuperscript{5,16}
      1. Use of ART to prevent HIV transmission from mother-to-child
      2. Incidence of newly infected children with HIV drastically reduced (~40%) from peak of 570,000 in 2003 to 330,000 in 2011
   ii. Post-exposure prophylaxis (PEP)\textsuperscript{17}
      1. Use of ART after mucosal, percutaneous, or intravenous exposure outside of perinatal situations (e.g. accidental needlesticks, sexual assault)
      2. Not as effective as prevention of HIV transmission by avoiding exposures
         a. Less likely to be effective if initiated >72 hours after exposure
         b. Not likely to benefit persons with frequent, repeated exposures
   iii. Current chemoprophylactic strategies only target specific populations during or immediately after periods of high risk exposure

c. Need for better prevention strategies due to greater burden on healthcare systems\textsuperscript{18,19}
   i. Increasing coverage of HIV-infected persons with ART $\Rightarrow$ decreased mortality
   ii. Increased survival of HIV-infected patients with HAART $\Rightarrow$ increased persons requiring life-long therapy for HIV/AIDS and associated sequelae
   iii. Estimates that more than 60 million new HIV infections could occur in the theoretical 15-20 year wait for an effective preventative vaccine

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**Pre-Exposure Prophylaxis (PrEP)**

1. Overview of PrEP
   a. Pre-exposure prophylaxis = provision of drugs to prevent infection in uninfected individuals with high exposure or vulnerability to a given pathogen\textsuperscript{18}
   b. Not initially feasible for HIV – no agent met criteria for long-term use in healthy individuals\textsuperscript{20}
   c. Rationale supporting ART as PrEP for HIV\textsuperscript{18,21}
      i. Currently utilized in the prevention of other infections (e.g. malaria prophylaxis in travelers to endemic areas, opportunistic infections)
      ii. Analogous concepts to perinatal prophylaxis and PEP
         1. Limit size of “founder population” of infected cells below a theoretical threshold under which infection cannot be established
         2. Block viral replication to allow host responses to eradicate small inoculum
   d. Single agent versus combination therapy\textsuperscript{18,19,21-23}
      i. High risk of inadvertent monotherapy with single agent use leading to resistance in inappropriately screened or seroconverted individuals
      ii. PrEP with monotherapy will likely require far more intensive HIV testing than has ever been achieved to date to prevent resistance
      iii. Greater protection through differential mechanisms with additional agents
         1. Initial animal models with simian immunodeficiency virus (SIV) in macaques demonstrated more robust protection with combination therapy
         2. Similar animal models demonstrated higher potential for single-agent resistance regardless of frequency of monitoring
         3. Preventative advantages of combination therapy prompted revision of several clinical trial protocols
II. Selection of ART agents for PrEP for HIV\textsuperscript{22-25}
   a. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
      i. Evidence with nevirapine to prevent perinatal transmission
      ii. Low barrier to resistance and significant toxicities and drug interactions
   b. Protease inhibitors (PIs)
      i. High barriers to resistance
      ii. Post-integration activity with increased pill burden and significant toxicities
   c. Nucleoside reverse transcriptase inhibitors (NRTIs)
      i. Intermediate barrier to resistance between NNRTIs and PIs
      ii. Active in latent CD4 T-cells and during pre-integration phase
      iii. Newer agents with lower pill burden and safer toxicity profiles

<table>
<thead>
<tr>
<th>Table 2: Comparative characteristics of select ART agents for consideration as use for PrEP\textsuperscript{22-28}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>NRTI</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
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<td>PI</td>
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<tr>
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</tr>
<tr>
<td></td>
</tr>
<tr>
<td>INSTI</td>
</tr>
<tr>
<td>CCR5</td>
</tr>
<tr>
<td>F1</td>
</tr>
</tbody>
</table>

\textsuperscript{QD = once daily dosing; BID = twice daily dosing; PRE = pre-integration phase; POST = post-integration phase; NA = not applicable
ZDV = zidovudine; ABC = abacavir; FTC = lamivudine; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate; EFV = efavirenz; NVP = nevirapine; ATV = atazanavir; DRV = darunavir; IDV = indinavir; LPV = lopinavir/r; IDV = indinavir; LPV = lopinavir/r; RAL = raltegravir; MVC = maraviroc; ENF = enfuvirtide
NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitors; INSTI = integrase inhibitors; CCR5RA = CCR5 receptor antagonists; F1 = fusion inhibitors}

III. Topical formulations\textsuperscript{11,23,26}
   a. Tenofovir (TFV) 1% vaginal gel
      i. Higher vaginal concentrations compared to oral dosing with no risk of renal toxicity
      ii. Hyperosmolarity → disruption of epithelial cervical and colorectal tissue
      iii. Not formulated as tenofovir disoproxil fumarate (TDF) prodrug due to instability
         1. Disoproxil enables greater tissue penetration resulting in higher intracellular concentrations and more potent antiviral activity
         2. Studies with intravenous TFV and oral TDF showed larger reductions in HIV RNA with oral TDF with similar plasma TFV exposures
   b. CAPRISA-004\textsuperscript{30}
      i. Evaluated use of pericoital TFV vaginal gel to prevent HIV infection in South African HIV-negative women compared with placebo (N=889)
      ii. Used “BAT24” dosing strategy – within 12 hours before and 12 hours after and no more than two doses in a 24-hour period
      iii. Demonstrated 39% reduction in incidence rate of HIV with 30 months of follow-up (95% confidence interval [CI], 6-60)
   c. VOICE\textsuperscript{26,29,31}
      i. Compared use of daily TFV vaginal gel and oral regimens with placebo to prevent infection in HIV-negative women (N=5029)
      ii. TFV and placebo gel discontinued due to futility but trial still ongoing to evaluate effectiveness of oral regimens
IV. Tenofovir-emtricitabine (TDF-FTC) for PrEP
   a. Clinical pharmacology\textsuperscript{18,22-24}
      i. Mechanism of action
         1. Terminates elongation of HIV DNA chain by competing with endogenous nucleic acids
         2. Requires sequential phosphorylation by host enzymes to pharmacologically active triphosphate (TP) analogues
         3. Additive to synergistic antiretroviral activity with TDF-FTC combination
      ii. Long plasma and intracellular half-lives
         1. Intracellular half-life 4- to 10-fold longer than plasma half-life
         2. Allows for decreased dosing frequencies and sustained activity during periods suboptimal adherence
      iii. Tissue concentrations at site of entry
         1. TDF-FTC detected in cervicovaginal fluid 2 hours after first dose and remain above plasma levels during most of the dosing interval
         2. Intracellular TPs detected in CD4 T-cells at similar concentrations compared with peripheral blood mononuclear cells
      iv. Activity in active and resting CD4 T-cells
         1. Prevents establishment of latent reservoir in resting CD4 T-cells
         2. Activated CD4 cells may have increased ratios of endogenous nucleoside phosphates to NRTI-TPs
   b. Toxicity profiles\textsuperscript{23}
      i. Inhibition of DNA polymerase gamma \(\rightarrow\) mitochondrial dysfunction \(\rightarrow\) lactic acid production and oxidative damage
      ii. Lower binding affinities than other NRTIs with no increased or additive toxicities
      iii. Tenofovir toxicities
         1. Renal dysfunction – toxicity due to accumulation in proximal tubule\textsuperscript{23,33,34}
            a. Mostly subclinical tubular dysfunction but rare instances of severe toxicity (e.g. acute kidney injury, Fanconi syndrome)
            b. Post-marketing surveillance data in HIV-infected individuals
               i. Increased serum creatinine (SCr) levels \(\geq 0.5\) mg/dL and \(\geq 2\) mg/dL in 2.2% and 0.6% of patients, respectively
               ii. Decreased glomerular filtration rate (GFR) by 3.9 mL/min
               iii. Severe renal toxicity reported in < 0.1% of patients
            c. Risk factors – age, low body weight, baseline renal dysfunction, concomitant use of nephrotoxic agents
         2. Decreased bone mineral density (BMD) – changes associated with altered phosphate metabolism secondary to subclinical tubular dysfunction\textsuperscript{23,34}
            a. Reports of reduced BMD but no increased incidence of fractures
            b. Post-marketing surveillance data in HIV-infected individuals – bone abnormalities in <0.1% of patients
      c. Drug interaction profiles
         i. TDF-FTC not metabolized by cytochrome P450
         ii. Few major clinically relevant interactions with non-ART medications\textsuperscript{32}

\begin{table}[h]
  \centering
  \caption{Clinical Pearls #4: Common and serious toxicities with TDF-FTC\textsuperscript{32}}
  \begin{tabular}{|l|}
    \hline
    - Gastrointestinal \\
    - Hepatomegaly with steatosis \\
    - Lactic acidosis \\
    - Worsening renal impairment* \\
    - Decreased bone mineral density* \\
    \hline
  \end{tabular}
  \textsuperscript{*Associated with TDF only}
\end{table}
### Table 3: Grant RM, et al. *N Engl J Med* 2010; 363 (27): 2587-99 (iPrEx)\(^3\)

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To evaluate the safety and efficacy of once-daily oral TDF-FTC as compared with placebo for the prevention of HIV acquisition among MSM</th>
</tr>
</thead>
</table>
| Design | • Prospective, randomized, multinational, placebo-controlled, event-driven trial  
• 11 sites in 9 cities in Peru, Ecuador, South Africa, Brazil, Thailand, and the US |
| Methods | • 2499 subjects randomized 1:1 from July 2007 to December 2009  
• Prevention package – HIV testing, condoms, risk-reduction counseling, and screening and treatment of sexually transmitted infections (STIs)  
• Prespecified subgroup analysis to correlate drug levels with protective effect |
| Patient Population | • **Inclusion criteria:** HIV-seronegative subjects who were males at birth  
• **Exclusion criteria:** previously diagnosed active and serious infections, active clinically significant medical problems, receipt of other ART or nephrotoxic agents |
| Outcomes | • **Primary:** incidence of HIV seroconversion  
• **Secondary:** adherence rates, risk compensation, and effect on early HIV-1 disease |
| Results | • **Baseline demographics**  
  - Baseline characteristics similar between groups including age, race, baseline STIs, and HBV status  
  - Most patients enrolled in Peru (56%), Ecuador (12%), Argentina (12%), and the US (9%)  
  - Median duration of follow-up = 1.2 years (maximum = 2.8 years) |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TDF-FTC N=1251</th>
<th>Placebo N=1248</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (%)</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Mixed race/other (%)</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Risk behaviors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of male partners in last 12 weeks</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>URAI with HIV+/unknown status partner (%)</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Transactional sex in last 6 months (%)</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>

**URAI** = unprotected receptive anal intercourse

### Outcomes analysis

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>TDF-FTC N=1251</th>
<th>Placebo N=1248</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV seroconversion (no.)</td>
<td>36</td>
<td>64</td>
<td>0.56 (0.37, 0.85)</td>
</tr>
<tr>
<td>≥ 50% pill use</td>
<td>23</td>
<td>47</td>
<td>0.50 (0.30, 0.82)</td>
</tr>
<tr>
<td>&lt; 50% pill use</td>
<td>13</td>
<td>17</td>
<td>0.68 (0.33, 1.41)</td>
</tr>
<tr>
<td>Median time to conversion (days)</td>
<td>35</td>
<td>35</td>
<td>--</td>
</tr>
<tr>
<td>Detectable drug levels (no./total)</td>
<td>3/36</td>
<td>0/64</td>
<td>--</td>
</tr>
<tr>
<td>Overall self-reported pill use (%)</td>
<td>95</td>
<td>95</td>
<td>--</td>
</tr>
</tbody>
</table>

- Similar baseline HIV RNA viral load and CD4 count in seroconverters in both groups  
- No difference in sexual practices including number of sexual partners, percentage of receptive anal intercourse, and reported condom use  
- Detectable blood levels 95% concordant with protective effects – adjusted relative risk reduction = 92% (95% CI, 40.99; p<0.001)  

### Authors’ Conclusions

Once-daily oral TDF-FTC provided 44% relative risk reduction from acquiring HIV in high-risk MSM in conjunction with a comprehensive package of prevention services with a high concordance between positive plasma drug detection and seroconversion.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To compare the safety and efficacy of daily oral TDF or TDF-FTC with placebo for PrEP against HIV-1 acquisition among heterosexual HIV-1-serodiscordant partnerships</th>
</tr>
</thead>
</table>
| Design | ● Prospective, randomized, multisite, double-blind, placebo-controlled trial  
● 9 sites in Kenya and Uganda |
| Methods | ● 4758 couples randomized 1:1:1 between July 2008 and November 2010  
● Comprehensive prevention package – HIV-1 testing and counseling; risk-reduction counseling, screening and treatment for STIs, and free condoms |
| Patient Population | ● **Inclusion criteria:** sexually active couples with plans to remain in the relationship for study period  
○ Seronegative: HIV-1 uninfected  
○ Seropositive: HIV-1 infected with CD4 ≥ 250 cells/mm³ and no AIDS-defining diagnoses  
● **Exclusion criteria:**  
○ Seronegative subjects: previously diagnosed active and serious infections, active clinically significant medical problems, receipt of other ART or nephrotoxic agents  
○ Seropositive subjects: current use of ART |
| Outcomes | ● **Primary:** incidence of HIV-1-seroconversion among HIV-1 uninfected individuals  
● **Secondary:** adherence rates and risk compensation |
| Results | ● **Baseline demographics:**  
○ Baseline characteristics were balanced between groups including age, gender, education, circumcision status, and baseline risk behaviors  
○ Total follow-up = 7830 person-years (median = 23 months, range 1-36 months) |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TDF N=1584</th>
<th>TDF-FTC N=1579</th>
<th>Placebo N=1584</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>62</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>34</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Sex with nonstudy partner (%)</td>
<td>10</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Index partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CD4 count (cells/mm³)</td>
<td>551</td>
<td>561</td>
<td>550</td>
</tr>
<tr>
<td>Median HIV-1 RNA (log₁₀ copies/mL)</td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Couples characteristics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Married (%)</td>
<td>97</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Mean sex acts in past month (no.)</td>
<td>4</td>
<td>4</td>
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</tr>
<tr>
<td>Unprotected sex in past month (%)</td>
<td>28</td>
<td>26</td>
<td>26</td>
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</table>

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>TDF N=1584</th>
<th>TDF-FTC N=1579</th>
<th>Placebo N=1584</th>
<th>HR (95% CI)*</th>
</tr>
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<tbody>
<tr>
<td>HIV-1 seroconversion (no.)</td>
<td>17</td>
<td>13</td>
<td>52</td>
<td>0.25 (0.13, 0.45)</td>
</tr>
<tr>
<td>Male (no.)</td>
<td>9</td>
<td>4</td>
<td>24</td>
<td>0.16 (0.06, 0.46)</td>
</tr>
<tr>
<td>Female (no.)</td>
<td>8</td>
<td>9</td>
<td>28</td>
<td>0.34 (0.16, 0.72)</td>
</tr>
<tr>
<td>HIV viral load of index partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50,000 copies/mL (no.)</td>
<td>13</td>
<td>9</td>
<td>32</td>
<td>0.28 (0.13, 0.58)</td>
</tr>
<tr>
<td>≥ 50,000 copies/mL (no.)</td>
<td>4</td>
<td>4</td>
<td>18</td>
<td>0.23 (0.08, 0.68)</td>
</tr>
<tr>
<td>CD4 count of index partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250-349 cells/mm³ (no.)</td>
<td>8</td>
<td>4</td>
<td>10</td>
<td>0.39 (0.12, 1.26)</td>
</tr>
<tr>
<td>≥ 350 cells/mm³ (no.)</td>
<td>9</td>
<td>9</td>
<td>42</td>
<td>0.21 (0.10, 0.44)</td>
</tr>
</tbody>
</table>

* TDF-FTC versus placebo  
○ HIV-1-protective effects similar across gender, viral load, and CD4 count  
○ Unprotected sex decreased from 27% to 13% at 12 months and 9% at 24 months

**Authors’ Conclusions** PrEP with TDF or TDF-FTC reduces HIV-1 acquisition in serodiscordant heterosexual populations but effectiveness is highly dependent on adherence.

| Purpose | To evaluate the safety and efficacy of daily oral TDF-FTC in the prevention of HIV infection among sexually active heterosexual adults |
| Design | • Prospective, randomized, double-blind, placebo-controlled trial  
• 2 cities in Botswana |
| Methods | • 1219 heterosexuals randomized 1:1 between February 2007 and October 2009  
• Prevention package – condoms, risk-reduction counseling, and screening and treatment of STIs |
| Patient Population | • **Inclusion criteria:** sexually active HIV-seronegative heterosexuals  
• **Exclusion criteria:** chronic illnesses requiring ongoing prescription medication or history of significant renal or bone disease |
| Outcomes | • **Primary:** rates of HIV-1 seroconversion  
• **Secondary:** adherence rates, risk compensation, and effect on early HIV-1 disease |
| Results | • **Baseline demographics**  
  ○ Baseline characteristics similar between groups including age, gender, education, circumcision status, baseline risk behaviors, and STIs  
  ○ Total follow-up = 1563 person-years (median, 1.1 years; maximum, 3.7 years) |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TDF-FTC N=611</th>
<th>Placebo N=608</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>46</td>
<td>46</td>
<td>0.93</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>18-29 years (%)</td>
<td>92</td>
<td>90</td>
<td>--</td>
</tr>
<tr>
<td>30-39 years (%)</td>
<td>8</td>
<td>10</td>
<td>--</td>
</tr>
<tr>
<td>Single (%)</td>
<td>95</td>
<td>93</td>
<td>0.45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sexual behaviors</th>
<th>TDF-FTC N=611</th>
<th>Placebo N=608</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condom use with last partner (%)</td>
<td>81</td>
<td>79</td>
<td>0.66</td>
</tr>
<tr>
<td>≥ 5 lifetime partners (%)</td>
<td>54</td>
<td>58</td>
<td>0.07</td>
</tr>
<tr>
<td>≥ 2 partner in last month (%)</td>
<td>19</td>
<td>19</td>
<td>0.93</td>
</tr>
<tr>
<td>HIV-positive partner in last month (%)</td>
<td>3</td>
<td>4</td>
<td>0.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary and secondary efficacy analysis</th>
<th>TDF-FTC N=611</th>
<th>Placebo N=608</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 seroconversion (no.)</td>
<td>9</td>
<td>24</td>
<td>62% (22, 83)</td>
</tr>
<tr>
<td>Male (no.)</td>
<td>2</td>
<td>10</td>
<td>80% (25, 97)</td>
</tr>
<tr>
<td>Female (no.)</td>
<td>7</td>
<td>14</td>
<td>49% (-22, 81)</td>
</tr>
<tr>
<td>Adherence rates (%)</td>
<td>84</td>
<td>84</td>
<td>--</td>
</tr>
</tbody>
</table>

| Authors’ Conclusions | Once daily oral TDF-FTC decreased the rate of HIV infection by 62% when combined as part of a comprehensive package of HIV-prevention services. Adherence and careful HIV screening is critical for effectiveness and the prevention of the development of resistance. |

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To assess the efficacy and safety of TDF-FTC in preventing HIV acquisition</th>
</tr>
</thead>
</table>
| Design | • Prospective, randomized, double-blind, placebo-controlled, multinational trial  
• 4 sites in Kenya, South Africa, and Tanzania  
• Study terminated early in April 2011 due to lack of efficacy |
| Methods | • 2120 subjects randomized 1:1 between June 2009 and April 2011  
• Comprehensive prevention package – HIV-1 testing and counseling; risk-reduction counseling, screening and treatment for STIs, and free condoms |
| Patient Population | • **Inclusion criteria**: high risk HIV-seronegative women  
• **Exclusion criteria**: previously diagnosed active and serious infections, active clinically significant medical problems, receipt of other ART or nephrotoxic agents |
| Outcomes | • **Primary**: incidence of HIV-1 seroconversion  
• **Secondary**: adherence rates, risk compensation, and effect on early HIV-1 disease |
| Results | • **Baseline characteristics**  
  o Baseline characteristics were balanced between groups including age, gender, education, and baseline risk behaviors  
  o Total follow-up = 1407 person-years |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TDF-FTC N=1251</th>
<th>Placebo N=1248</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Married (%)</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Primary partner (%)</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Other partners (%)</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Sexual behaviors (in past week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex for money or gifts in past 4 weeks (%)</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Mean number of partners</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unprotected sex acts (no.)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

- **Outcomes analysis**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>TDF-FTC N=1251</th>
<th>Placebo N=1248</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV seroconversion (no.)</td>
<td>33</td>
<td>35</td>
<td>0.94 (0.59, 1.52)</td>
</tr>
<tr>
<td>CD4 count (cells/mm(^3))</td>
<td>561</td>
<td>613</td>
<td>--</td>
</tr>
<tr>
<td>HIV RNA (log(_{10}) copies/mL)</td>
<td>5.2</td>
<td>5.2</td>
<td>--</td>
</tr>
<tr>
<td>TDF resistance (no.)</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>FTC resistance (no.)</td>
<td>4</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Self-reported adherence rates (%)</td>
<td>95</td>
<td>95</td>
<td>--</td>
</tr>
</tbody>
</table>

  o Pill count data consistent with self-reported adherence (~88%)  
  o Most subjects perceived themselves to be at low risk for HIV infection (~70%)  
  o Drug-level testing (level ≥ 10 ng/mL TDF → TDF taken in previous 48 hours)  
    - Seroconverters – target plasma level detected in ~20% of subjects  
    - Non-seroconverters – target plasma level detected in ~30% of subjects  
  o No increased evidence of HIV risk behavior with modest but significant reductions in number of partners and unprotected sex acts  

**Authors’ Conclusions**

Once daily oral TDF-FTC did not reduce HIV acquisition in women compared with placebo, but drug level testing demonstrated poor adherence. The lack of adherence could be explained by low perception of risk for HIV infection and difficulty with adherence to daily pill regimens as evidenced by high pregnancy rates in women receiving oral contraceptives.
Clinical Summary

V. Landmark trials for oral PrEP

a. Included sexually active healthy individuals at high risk of acquiring HIV
   i. Adequate renal function (creatinine clearance [CrCl] ≥ 60 mL/min) and hepatic function (transaminases ≤ 2 times the upper limit of normal [ULN])
   ii. No previously diagnosed active and serious infections or current clinically significant medical problems requiring medication therapy
   iii. All subjects participated in comprehensive prevention program at follow-up visits
      1. HIV screening and testing, provision of condoms, and risk counseling
      2. Screening and treatment of sexually transmitted infections (STIs)

table 7: Summary of efficacy in landmark trials evaluating the use of TDF-FTC for PrEP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>RR (95% CI)</th>
<th>AAR</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM (N=2499)</td>
<td>44% (15, 63)</td>
<td>2.2%</td>
<td>Daily oral TDF-FTC reduced risk of acquiring HIV by 44% in high-risk MSM</td>
</tr>
<tr>
<td>Partners-PrEP</td>
<td>SDC (N=4758)</td>
<td>75% (55, 87)</td>
<td>2.5%</td>
<td>Daily oral TDF-FTC reduced acquisition of HIV by 75% in SDCs</td>
</tr>
<tr>
<td>TDF2</td>
<td>High-risk heterosexuals (N=1219)</td>
<td>62% (22, 83)</td>
<td>2.4%</td>
<td>Daily oral TDF-FTC reduced the rate of HIV infection by 62% in high-risk heterosexuals</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>High-risk females (N=2120)</td>
<td>6% (-52, 41)</td>
<td>0.2%</td>
<td>Daily oral TDF-FTC did not reduce HIV acquisition in high-risk females</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>49%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| RR = relative risk reduction; ARR = absolute risk reduction; MSM = men who have sex with men; SDC = serodiscordant couples |

b. Safety

i. Phase II study – no difference in safety patterns compared with placebo in HIV-uninfected women taking daily TDF (N=936) with 217 person-years of follow-up
ii. Phase III studies – no difference in frequency of serious adverse events (AEs), specifically rates of renal and hepatic toxicity as well as bone fractures
   1. Overall risk of serious AEs with daily TDF-FTC = 1.00 (95% CI, 0.83-1.19) over roughly 2 years of follow-up across 4 trials
   2. Similar rates of discontinuation due to AEs with resolution of all toxicities

table 8: Summary of adverse events with TDF-FTC in landmark PrEP trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Elevated SCr (%)</th>
<th>Elevated AST (%)</th>
<th>Elevated ALT (%)</th>
<th>Bone fracture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx*</td>
<td>2</td>
<td>14</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Partners-PrEP*</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>TDF2*</td>
<td>&lt;1</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>FEM-PrEP*</td>
<td>7</td>
<td>15</td>
<td>18</td>
<td>--</td>
</tr>
</tbody>
</table>

SCr = serum creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase
* All values not statistically significant compared with placebo

| RR = relative risk reduction; ARR = absolute risk reduction; MSM = men who have sex with men; SDC = serodiscordant couples |

C. Conclusions

i. Most patients in trials enrolled in regions with high prevalence of HIV ~10-30%
ii. Daily TDF-FTC – efficacious in preventing HIV in high-risk persons (absolute risk-reduction ~2-3%)^{35-40}
   1. High-risk MSM – many sexual partners → significant downstream effects
   2. Serodiscordant couples with untreated HIV-positive partner – life-long high-risk exposure in married couples
   3. High-risk heterosexuals living in regions of high prevalence of HIV – less likely to be applicable to heterosexuals living in areas with low prevalence
iii. Efficacy correlated with adherence – FEM-PrEP self-reported adherence rates of 95% by pill counts but drug testing detected levels in < 40% of sampled subjects
iv. No increased rates of serious adverse events over about 2 years of follow-up
Current Controversies

I. Divergent results from clinical trials
   a. Trials showing efficacy – iPrEx, Partners-PrEP, TDF2
   b. Trials showing futility – FEM-PrEP

II. Impact of adherence
   a. Disparate estimates of adherence based on self-reporting, pill counts, and drug-level testing
      i. Lack of standardized adherence measures
         1. Limited accuracy of self-reporting
         2. Exposes need for objective measures of adherence
      ii. FEM-PrEP study reported adherence rates of 95% by self-reporting and 88% by pill counts but drug testing detected levels in only < 40%
   b. Effectiveness dependent upon higher levels of adherence – iPrEx study demonstrated differential effectiveness based on adherence thresholds
      i. Pill use ≥ 50% → risk reduction by 50% (95% CI, 18%-70%)
      ii. Pill use ≥ 90% → risk reduction by 73% (95% CI, 41%-88%)
   c. Prophylactic effect strongly correlated with detectable drug levels
      i. Detectable levels indicative of recent pill use (e.g. TDF plasma level = 10 ng/mL evidence of use in past 48 hours)
      ii. Drug levels in TDF2 study significantly lower in seroconverters
         1. TDF – 0.3 ng/mL versus 30.6 ng/mL
         2. FTC – 0.5 ng/mL versus 103.3 ng/mL
      iii. Low percentage of detectable levels in seroconverted subjects
   d. Factors impacting adherence in individuals taking PrEP
      i. Trust and commitment within established serodiscordant relationships
      ii. Cultural differences leading to altered perception of risk → ~70% of women in FEM-PrEP perceived themselves to be at no or low risk for HIV infection
      iii. Difficulty with adherence to daily pill regimens → high pregnancy rates among women taking oral contraceptives in FEM-PrEP

Table 4: Impact of adherence and detectable drug levels on effectiveness in landmark PrEP trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Adherence estimates (%)</th>
<th>Seroconverters</th>
<th>Non-seroconverters</th>
<th>RR with detectable levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>95*</td>
<td>9</td>
<td>51</td>
<td>92%</td>
</tr>
<tr>
<td>Partners-PrEP</td>
<td>92</td>
<td>31</td>
<td>82</td>
<td>90%</td>
</tr>
<tr>
<td>TDF2</td>
<td>84</td>
<td>50</td>
<td>88</td>
<td>--</td>
</tr>
<tr>
<td>FEM-PrEP**</td>
<td>95*</td>
<td>26</td>
<td>35</td>
<td>--</td>
</tr>
</tbody>
</table>

* Self-reported adherence
** Target TDF level = 10 ng/mL in the FEM-PrEP study
RR = relative risk reduction

III. Risk compensation
   a. Increased risk-taking behavior resulting from greater protective measures but degree of compensation dependent on efficacy of various prevention strategies
   b. Risk homeostasis model
      i. Target set point of acceptable estimated risk in exchange for benefits received
      ii. Discrepancies in perceived risk and target set point → risk compensatory behavior
      iii. Risk reduction preventative technologies → altered estimates of personal risk → change in risk-taking behaviors
   c. Non-PrEP settings
      i. Meta-analysis of impact of HAART on risk behavior
         1. HIV-positive patients receiving HAART did not exhibit increased sexual risk behavior even at undetectable viral loads

Clinical Pearls #5: Potential pitfalls of PrEP
- Non-adherence
- Increased risk compensation
- Development of resistance
- Inappropriate baseline screening
- Diverting resources from treatment of infected individuals
2. Subjects not receiving HAART that believed HAART and undetectable viral load decreased risk were more likely to engage in unprotected sex

ii. Male circumcision
   1. Mixed results from observational studies but evidence of increased risk compensation in two of three randomized, controlled studies
      a. Circumcised participants reported more sexual contacts
      b. Increased condom use in circumcised patients but significantly greater increased condom use in uncircumcised subjects
   2. Increased risk of ulcerative STIs with decreased condom use \(\rightarrow\) amplified long-term HIV risk

iii. Non-occupational PEP
   1. Longitudinal cohort study in patients provided an advance supply of PEP – no evidence of increases in risk behavior
   2. Offers uncertain protection from HIV infection at expense of considerable adverse events and financial cost \(\rightarrow\) no risk compensation

d. Clinical trial data\(^{35-38}\)
   i. No evidence of increased risk compensation behaviors in landmark trials with some demonstrating reductions in number of sexual partners and rates of unprotected sex
      1. FEM-PrEP – significant reductions in risk behaviors \(\rightarrow\) supporting evidence that futility due to adherence issues not risk compensation
      2. Partners-PrEP – reduced rates of unprotected sex from 27% at baseline to 13% at 12 months and 9% at 24 months
   ii. Decreased risk-taking likely byproduct of intensive risk-reduction counseling

### Table 5: Sexual behaviors of individuals taking PrEP in landmark trials\(^{35-38}\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Unprotected intercourse</th>
<th>Number of partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Partners-PrEP</td>
<td>Decreased</td>
<td>Stable*</td>
</tr>
<tr>
<td>TDF2**</td>
<td>Stable</td>
<td>Decreased</td>
</tr>
<tr>
<td>FEM-PrEP**</td>
<td>Significant reduction</td>
<td>Significant reduction</td>
</tr>
</tbody>
</table>

\(^*\) Number of outside sexual partners

### e. Studies characterizing risk behaviors in potential PrEP candidates\(^44,45\)
   i. Individuals most likely to be willing to use PrEP were subjects with highest risk of acquiring HIV but had low self-perceived risk
   ii. Predicted decreased condom use while using PrEP associated with arousal and risk perception barriers, and decreased likelihood to use multiple prevention methods
   iii. Reinforces need for education about sexual transmission and risk-reduction strategies and continuation of traditional prevention methods

### f. Anecdotal reports of underground use
   i. Media reports of TDF being sold in combination with other drugs, such as Viagra and Valium, at gay dance clubs\(^46,47\)
   ii. Initial survey found that 7% of attendees of gay-pride events in four US cities had previously tried PrEP with TDF but follow-up surveys reported <1%\(^48,49\)

### IV. Resistance
   a. Mechanisms of resistance\(^50,51\)
      i. FTC resistance \(\rightarrow\) M184V
         1. Rapidly selected for within 15 days of monotherapy
         2. Confers high level resistance to 3TC and FTC but reduces replicative capacity of mutated virus
      ii. TDF resistance \(\rightarrow\) K65R
         1. May not develop for up to 28 days with TDF monotherapy
2. Confers intermediate resistance to other NRTIs but paradoxically increases susceptibility to ZDV

iii. Combination TDF-FTC
   1. Most frequent resistance mutation = M184V (not K65R) with dual therapy
   2. M184V delays emergence of K65R due to decreased replicative capacity
   3. Activity of other NRTIs may be spared with PrEP failure with TDF-FTC

b. Clinical trial data35-38
   i. No resistance mutations detected in subjects that seroconverted after enrollment but likely attributed to lack of adherence in seroconverters
   ii. All subjects receiving TDF-FTC with unrecognized HIV infection at enrollment (N=6) developed FTC resistance and one had both M184V and K65R mutations
   iii. Clear emphasis on HIV testing and screening before administering PrEP

c. Mathematical modeling
   i. Impact of circulating resistance on effectiveness of PrEP52
      1. PrEP may only confer partial protection to circulating drug-resistant viruses
      2. May be counterbalanced by reduced fitness of mutant viruses → decreased viral loads → decreased risk of transmission
      3. Circulating drug resistance not likely to impact effectiveness of PrEP but depends on prevalence, sexual behaviors, and viral characteristics
         a. Decreased effect if PrEP use coincides with decreased condom use
         b. Increased effect if resistant strains less transmissible than wild-type
   ii. Impact of PrEP on transmitted drug resistance
      1. Resource-rich settings (e.g. MSM in San Francisco)53
         a. Risk compensation → higher proportion of new cases with resistant virus due to decreased transmission of wild-type virus but increased transmission of resistant virus
         b. Stable risk → higher proportion of new cases with resistant virus due to decreased transmission of resistant virus with even greater reduction in transmission of wild-type virus (paradox of PrEP)
      2. Resource-limited settings (e.g. Botswana)54
         a. Increased number of treatment-naïve individuals with resistant strains regardless of adherence levels but reduced number of treatment-experienced patients requiring second-line therapy
         b. Greatest impact on poor quality treatment programs defined as low success in viral suppression and high rates of drug resistance
         c. High adherence levels (> 90%) likely to reduce treatment costs and increase sustainability of programs in resource-limited settings
      3. Discrepancy in transmitted drug resistance likely due to difference in ambient levels of resistance
Interim Guidelines

I. Interim CDC guidelines for MSM and heterosexuals\textsuperscript{55,56}
   a. Document negative HIV antibody tests and test for acute HIV if patient has symptoms
   b. Confirm substantial, ongoing, high risk for acquiring HIV and that CrCl ≥ 60 mL/min
   c. Screen and treat for STIs and vaccinate or treat for hepatitis B if susceptible
   d. Prescribe no more than a 90-day supply of once-daily TDF-FTC only renewable after HIV testing confirms patient is HIV-uninfected in conjunction with risk-reduction and counseling
   e. Assess HIV status, risk behaviors, adherence, and STIs every 2-3 months
   f. Establish linkage to HIV care or risk-reduction support services depending on HIV status when PrEP is discontinued

II. WHO guidance on oral PrEP\textsuperscript{57}
   a. Recommends PrEP in MSM and heterosexuals with similar algorithms to CDC guidelines
   b. Suggests potential benefit of PrEP in other groups at high-risk for sexual transmission
   c. Emphasizes need for demonstration projects to determine true benefit of PrEP

Additional Considerations

I. Diversion of resources from HIV treatment\textsuperscript{58,59}
   a. Combination TDF-FTC only available as branded medication \(\rightarrow\) significant costs of PrEP with daily TDF-FTC (\(\sim\)$700-900 per month)
   b. Diversion of resources in resource-poor settings could shift ARTs needed for treatment for HIV-infected individuals to prevention in uninfected persons

II. Cost-effectiveness models
   a. MSM in the US
      i. Desai et al. – high-risk MSM in New York City\textsuperscript{60}
         1. Base-case scenario reduced new infections by \(\sim\)9% over 5 years resulting in $31,972 per quality-adjusted life year (QALY) saved
         2. PrEP cost-effective \(\sim\)90% of the time across all assumptions with threshold of $100,000 per QALY saved
         3. Did not include emergence of drug resistance or renal impairment
      ii. Paltiel et al. – high risk MSM populations\textsuperscript{61}
         1. Base-case scenario reduced lifetime risk from 44% to 25% costing $298,000 per QALY gained
         2. Incremental costs per QALY gained lowered to $100,000 if greater efficacy of PrEP and higher annual incidence in target population
      iii. Juusola et al. – analysis in general MSM and high-risk MSM populations\textsuperscript{62}
         1. Base-case scenario reduced new infections by \(\sim\)13% resulting in 550,166 QALYs gained over 20 years costing $172,091 per QALY
         2. Use of PrEP in only high-risk MSM (average of 5 annual partners) improved cost-effectiveness to $50,000 per QALY gained
      iv. Significant expense if used in all MSM with greatest cost-effectiveness achieved in high-risk MSM (e.g. average of 5 annual partners)
         1. No current threshold for acceptable cost per QALY for PrEP
         2. Acceptable cost per QALY for general health interventions \(\sim\)$113,000 per QALY (range, $109,000 to $297,000)\textsuperscript{63}
Table 6: Summary of base-case scenarios of cost-effectiveness models of PrEP in MSM in the United States<sup>60-62</sup>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>High-risk MSM</td>
<td>MSM, 24-44 years</td>
<td>MSM, 13-64 years</td>
</tr>
<tr>
<td>Annual incidence (%)</td>
<td>1.35</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Use of PrEP (%)</td>
<td>25</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Efficacy (%)</td>
<td>50</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Adherence</td>
<td>50</td>
<td>Incorporated in efficacy</td>
<td>Incorporated in efficacy</td>
</tr>
<tr>
<td>Behaviors</td>
<td>Up to 20% more partners</td>
<td>Incorporated in efficacy</td>
<td>No change</td>
</tr>
<tr>
<td>Monthly cost of PrEP ($)</td>
<td>930</td>
<td>724</td>
<td>776</td>
</tr>
<tr>
<td>ICER per QALY gained ($)</td>
<td>31,972</td>
<td>298,000</td>
<td>172,091</td>
</tr>
</tbody>
</table>

*MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.*

b. South African women
   i. Two cost-effectiveness analyses examining the impact of PrEP with TFV vaginal gel in high-risk South African women<sup>64,65</sup>
      1. Cost-effectiveness in base-case scenario = $2700 per year of life saved<sup>64</sup>
      2. Greatest cost-effectiveness in targeted populations with highest incidence and risk with potential for cost-savings
   ii. Cost-effectiveness PrEP likely to diminish as coverage with ART expands particularly beyond 65% of HIV-infected individuals<sup>65</sup>

Summary and Conclusions

I. Beginning of the end of AIDS?
   a. PrEP – new biomedical intervention to help stem the AIDS epidemic but not magic bullet
   b. Part of comprehensive prevention package including risk-reduction and condom use
      i. Ensure adequate testing and screening to prevent inadvertently suboptimal ART
      ii. Emphasize importance of adherence for efficacy and to prevent resistance
      iii. Encourage continued use of traditional prevention methods with PrEP

II. Know your epidemic
   a. Greater impact and cost-effectiveness in target high-risk populations (e.g. MSM, SDC)
   b. Not likely to benefit high-risk populations where sexual transmission not predominant cause of newly acquired infections (e.g. IDUs)
   c. Evaluate resource capacity to absorb increased costs of PrEP and assess optimal combination of preventative strategies which may or may not include PrEP
   d. Use CDC and WHO guidelines as baseline to establish program-specific criteria for use and develop strict criteria for high-risk populations

III. Proposed criteria for use
   a. Not for use in general population – reserved for high-risk persons
      i. MSM with high risk sexual behaviors
      ii. SDC with untreated HIV+ partner and consistent intercourse
   b. Competency assessments following comprehensive education and counseling to identify optimal PrEP candidates
   c. Monthly follow-up visits initially for intensive counseling with HIV testing every 3 months
   d. Provision of condom supply with each prescription of TDF-FTC for PrEP

“A pill a day keeps the HIV away... ...but don't forget the condoms.”
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