MICHIGAN
HIV CONSULT
PROGRAM

Provider to Provider Advice from HIV experts at Henry Ford Hospital
- HIV disease management
- Drug interactions
- PEP, nPEP, PrEP
- Perinatal HIV treatment

TWO WAYS TO CONTACT US

For urgent questions: (313) 575-0332
Submit non-urgent questions henryford.com/HIVconsult

Henry Ford Health System
Henry Ford Hospital
Michigan Department of Health & Human Services

The Michigan HIV Consult Program is a partnership between Henry Ford Hospital in Detroit and Michigan Department of Health and Human Services.
PrEP & nPEP
HIV Prophylaxis & Treatment Updates

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Senior Staff Henry Ford Hospital
Clinical Associate Professor Wayne State University

For

Michigan HIV Consult Program
Disclosures

• Have received research grants, served on regional and national boards and have been a lecturer for:
  • Abbott Molecular
  • ViiV Healthcare
  • Gilead Sciences
  • BMS

• All the information provided will be published data and current guidance by national institutions or boards (CDC, NIH, DHHS, FDA, etc).

• No off-label use will be discussed.
Key Topics

- US Prevention Methods Against HIV

- PrEP
  - HIV prophylaxis
  - In whom, what is the data?
  - Regimens available
  - How to get started
  - Summary

- PEP (oPEP, nPEP)
  - Define the categories
  - Risks for HIV
  - Data for use
  - Recommended regimens
  - Summary
Proven HIV Prevention Methods (CDC)

- HIV testing and linkage to care
- HIV medications
- Access to condoms
- Prevention programs for people with HIV and their partners
- Prevention programs for people at high risk for HIV infection
- Substance abuse treatment and access to sterile syringes
- STI screening and treatment

CDC FACT SHEET. Proven HIV Prevention Methods. CDC.gov
HIV Testing and Linkage to Care

- CDC recommends that all Americans ages 13-64 get tested at least once for HIV as a routine part of medical care, and
- Gay and bisexual men and others at high risk get tested at least once a year.
- HIV testing is the only way to identify the nearly one in eight Americans currently living with HIV who are unaware of their infection and may be unknowingly transmitting the virus to others.
- Knowledge of HIV status is empowering. When people test negative, they are in a better position to assess – and modify – their risk behaviors to help them stay uninfected.
- When people learn they are infected, research shows they take steps to protect their own health and prevent transmission to others. Linkage to care after a positive test helps ensure people receive life-saving medical care and treatment and helps reduce their risk of transmitting HIV.

CDC FACT SHEET. Proven HIV Prevention Methods. CDC.gov
Biomedical Prevention Methods: Treatment as Prevention

- Treating people with HIV lowers the amount of virus in their bodies and can dramatically reduce their risk of transmitting HIV to others.

- In fact, a landmark clinical trial in 2011 showed that people with HIV who began taking anti-HIV medications early (before their immune systems were significantly weakened) experienced a 96 percent reduction in their risk of transmitting HIV to sexual partners.

- This supports the continued expansion of HIV testing remains a primary prevention strategy for CDC – so that people who are infected with HIV can quickly be linked to care and can begin treatment.

- Other strategies
  Pre-exposure prophylaxis, post-exposure prophylaxis and prevention of mother to child transmission

CDC FACT SHEET. Proven HIV Prevention Methods, CDC.gov
What should HIV prophylaxis look like?

• Ideally- An effective vaccine!
• In view of lacking effective vaccines, the alternative strategies include:
  • Reduce exposure risks:
    • Reduce number of partners
    • Use of barrier protection and reduction of high risk encounters
    • Reduce rates of STDs
    • Improve natural barrier to disease acquisition- circumcision
    • Behavioral interventions
    • Needle exchanges
  
• Reduce disease burden
  • Reduction in known positive partners HIV viral load
  • Reduction in “population” viral load

• Chemoprophylaxis
HIV Chemoprophylaxis or PrEP

- Otherwise known as **Pre-Exposure Prophylaxis (PrEP)**
- Ideal candidates
  - Agent not use for HIV therapy
  - Excellent tolerability & Low Toxicity
  - Good PK- once daily to longer dosing schedules
  - High genetic barrier to resistance
  - Good penetration into tissues, semen, genital/rectal mucosa & fluids
  - Low costs, widely available
  - Discrete
Chemoprophylaxis

- First approved PrEP - Truvada (tenofovir DF/emtricitabine)
- Is it an ideal candidate??
  - Agent not use for therapy - YES
  - Excellent tolerability & Low Toxicity - YES
  - Good PK - once daily to longer dosing schedules - YES
  - High genetic barrier to resistance - NO
  - Good penetration into tissues, semen, genital/rectal mucosa & fluids - YES
  - Low costs, widely available - YES
  - Discrete - YES
Where does the proof for PrEP come from?

- Landmark trial in macaques from Tsai CC, et al, Science 1995
  - PMPA was administered sc once daily 48 hrs prior, 4 hrs after and 24hrs post inoculation with SIV, followed by treatment for 4 weeks
  - PMPA prevented SIV infection in all macaques as compared to controls
- Other animal studies show that TDF/FTC is effective as chemoprophylaxis if given in less than 24hrs of exposure (PEP)
PrEP in Humans

- TDF was evaluated for PreEP as a single pill, vaginal gel and in dual combination with FTC
- Other agents have been evaluated but have not shown consistent benefits (eg, Maraviroc)
- Several key large clinical trials have evaluated the use of PrEP
  - iPrEX study
  - PrEP Partners study
  - TDF2
  - FEM-PrEP
  - VOICE
  - HPTN 052 (serodiscordant couples)
  - CAPRISA 004 (women with TDF gel)
iPrEX Study

- Male sex at birth
- N = 2499
- 18 yrs of age or older
- HIV-seronegative status
- Evidence of risk for acquisition of HIV infection

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Overall (N = 2499)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Younger than 25 yrs</td>
<td>50</td>
</tr>
<tr>
<td>25-39 yrs</td>
<td>40</td>
</tr>
<tr>
<td>40 yrs or older</td>
<td>10</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>17</td>
</tr>
<tr>
<td>Black</td>
<td>9</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
</tr>
<tr>
<td>Mixed/other</td>
<td>69</td>
</tr>
<tr>
<td>Latino</td>
<td>72</td>
</tr>
<tr>
<td>Completed some college</td>
<td>43</td>
</tr>
</tbody>
</table>

iPrEx: Efficacy

- Efficacy through study end (mITT): 42% (95% CI: 18% to 60%)

Partners PrEP: TDF vs TDF/FTC vs Placebo in HIV-Serodiscordant Couples

HIV-negative partners in HIV-serodiscordant heterosexual couples (N = 4747)

Oral Tenofovir QD (n = 1584)

Oral Tenofovir/Emtricitabine QD (n = 1579)

Oral Placebo* (n = 1584)

Follow-up: 36 mos

*Placebo arm terminated early on July 10, 2011, by data and safety monitoring board.

Partners PrEP: Both PrEP Strategies Significantly Reduce HIV Acquisition

Both PrEP strategies associated with significant reduction in HIV acquisition vs placebo in both men and women

- TDF efficacy: 71% in women, 63% in men
- TDF/FTC efficacy: 66% in women, 84% in men

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TDF2: PrEP With TDF/FTC in HIV-Negative Heterosexuals in Botswana

HIV-uninfected adults, heterosexually active, aged 18-39 yrs
(N = 1219)*

Oral Tenofovir/Emtricitabine
(n = 601)

Oral Placebo
(n = 599)

≥ 12-mo follow-up

*n = 19 patients excluded for failure to start study medication or HIV infection.
TDF2: PrEP With TDF/FTC Significantly Reduces HIV Acquisition

- 9 vs 24 patients seroconverted in TDF/FTC vs placebo arms, respectively
- Overall protective efficacy of TDF/FTC: 62.2% (95% CI: 21.5-83.4; P = 0.03)
- Reduction in HIV acquisition with TDF/FTC observed in both men and women but study underpowered to demonstrate sex-based differences in outcomes

![Graph showing failure probability over weeks for TDF/FTC and Placebo treatments.](image)
But not all studies were successful
Disappointing Results of PrEP in Women: FEM-PrEP and VOICE

- **FEM-PrEP**: Phase III study of oral TDF/FTC planned for 3900 high-risk women in Africa (2120 randomized)
  - Announced April 18, 2011, that study was ended early because of lack of efficacy
  - 35 vs 33 new HIV infections in the placebo and TDF/FTC arms\(^1\)
  - TFV blood levels suggest that use was too low (< 40%) to assess efficacy
  - 4 vs 1 patient with M184V/I in the TDF/FTC and placebo arms

- **VOICE**: Phase IIB placebo-controlled trial of > 5000 women in South Africa, Uganda, and Zimbabwe\(^2\)
  - Daily oral TDF; daily oral TDF/FTC; daily vaginal TFV 1% gel
  - DSMB stopped the daily oral TDF arm in September 2011 and the daily vaginal gel arm in November 2011, both for lack of efficacy
  - Daily oral TDF/FTC arm continued

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1. Van Damme L, et al N Engl J Med. 2012 Jul 11. [Epub ahead of print]. 2. These data are available in press release format only, have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format before conclusions should be made from these data.
What were the limitations in these trials?

- Adherence?
- Penetration into vaginal tissue?
  - The PrEP Partners study work better in women (TDF2 as well)
- Degree of HIV Exposure?
- Genital inflammation?
PrEP Adherence

- iPrEX study

Drug Detection at Visit with First Evidence of HIV Infection for Case

HIV infection occurred during periods of low drug exposure

PrEP (Like ART) Works When Taken

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>TDF2[2]</td>
<td>79</td>
</tr>
<tr>
<td>iPrEx[3]</td>
<td>51</td>
</tr>
</tbody>
</table>

*TDF/FTC arm

There is a clear dose-response between evidence of PrEP use and efficacy

iPrEP Safety

- BMD changes were small (~1%); no evidence of negative effect on health\textsuperscript{[1]}
- No differences in fracture rates between groups\textsuperscript{[1,2]}
- All fractures were trauma related
- Need longer follow-up to evaluate effects on bone density and fracture risk over time

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TDF/FTC (n = 1251)</th>
<th>Placebo (n = 1248)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 event</td>
<td>12</td>
<td>13</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>Events</td>
<td>%</td>
</tr>
<tr>
<td>Death</td>
<td>&lt; 1</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>5</td>
<td>76</td>
<td>5</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>2</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine elevation confirmed on next visit</td>
<td>0.4</td>
<td>7.0</td>
<td>0</td>
</tr>
</tbody>
</table>
Partners PrEP and TDF 2: Safety

- **Partners PrEP**\(^1\)
  - Rates of death, serious adverse events, laboratory events low and not significantly different between arms
  - Mild GI effects and fatigue, primarily during Month 1

- **TDF2**\(^2\)
  - Rates of serious adverse events similar between arms
  - Higher rates of nausea, vomiting, and dizziness in FTC/TDF group, lessened after first month
  - Decrease in BMD, but no increase in fractures

CAPRISA 004

- Double blind, randomized study (n=444)
- 1% vaginal gel formulation of TDF vs. placebo placed within 12hrs before and after sex
- Women assigned to **tenofovir gel** had a **39 percent** reduction in the risk of HIV acquisition (5.6 versus 9.1 infections per 1000 persons). The protective effect of tenofovir gel was evident irrespective of other risks of HIV acquisition
- Higher level of adherence corresponded to a lower incidence of HIV infection (risk reduction 54, 38, and 28 percent, respectively, among those with high, intermediate, and low rates of adherence).
- No tenofovir resistance found in the study
- 40% of women had adherence of less than 50% despite intensive follow up
- VOICE trial- TDF gel arm was terminated by IDSMB
No Evidence of Risk Compensation in PrEP Clinical Trials

**iPrEx**

- Patients Reporting URAI (%)
- Wks Since Randomization
- Placebo
- FTC/TDF

**Partners PrEP**

- HIV-Negative Participants With Any Unprotected Sex (%)
- Follow-up Time (Mos)
- Placebo
- FTC/TDF
- TDF

iPrEx: Self-Reported Condom Use With High-Risk Sex

Receptive Intercourse Using Condoms (% of Partners)

Wks Since Randomization

PrEP and HIV Resistance

- Resistance was rare in clinical trials of PrEP, except for those with acute infection at baseline
- Resistance mutations seen: K65R (TDF) or M184V/I (FTC)

<table>
<thead>
<tr>
<th>Trial</th>
<th>HIV Infected After Enrollment, n/N</th>
<th>Seronegative Acute HIV Infection at Enrollment, n/N</th>
<th>HIV Infections Averted, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx(^{[1,2]})</td>
<td>0/36</td>
<td>2/2</td>
<td>28</td>
</tr>
<tr>
<td>Partners PrEP(^{[3]})</td>
<td>0/30</td>
<td>2/8</td>
<td>74</td>
</tr>
<tr>
<td>TDF2(^{[4]})</td>
<td>0/10</td>
<td>1/1</td>
<td>16</td>
</tr>
</tbody>
</table>

Limitations of Data

- Only ~ 10% of iPrEx population from the US
  - Arguably, prevention benefit should not differ by geography
- Long-term adherence and adherence at time of HIV exposure unknown (in those who became infected)
- Long-term health effects of TDF/FTC in HIV negative and HIV seroconverters unknown
- Adherence, risk behavior, PrEP interest likely to be different now that results are known compared with clinical trial population

How Much Is Enough?  
A Primary Prevention Comparison

<table>
<thead>
<tr>
<th></th>
<th>iPrEx[1]</th>
<th>WOSCOPS[2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>TDF/FTC daily</td>
<td>Pravastatin daily</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>HIV</td>
<td>MI</td>
</tr>
<tr>
<td>Population</td>
<td>Men 18-67 yrs of age (N = 2499)</td>
<td>Men 45-65 yrs of age (N = 6595)</td>
</tr>
<tr>
<td>Risk factor</td>
<td>MSM behavior</td>
<td>High cholesterol</td>
</tr>
<tr>
<td>Frequency of outcome in placebo arm</td>
<td>4% per yr</td>
<td>1.6% per yr</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>44% (95% CI:15% to 63%)</td>
<td>31% (95% CI:17% to 43%)</td>
</tr>
</tbody>
</table>

### Preexposure Prophylaxis for the Prevention of HIV Infection in the United State – 2017 Update

**Clinical Practice Guideline. CDC. Published online March 2018**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Analyses— HIV incidence (mITT)</th>
<th>Effect — HR [Efficacy Estimate] (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Agent</strong> 36 infections among 1224 persons 64 infections among 1217 persons</td>
<td>0.56 [44%] (0.37–0.85)</td>
</tr>
<tr>
<td>iPrEx (MSM)</td>
<td><strong>Control</strong> 3 infections among 201 persons (all 3 in delayed arm, not on TDF) 4 infections among 199 persons (1 acute infection at enrollment)</td>
<td>Not Reported</td>
</tr>
<tr>
<td></td>
<td><strong>Partners PrEP (heterosexual men and women)</strong> TDF 17 infections among 1572 persons 52 infections among 1568 persons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC 13 infections among 1568 persons</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>TDF</strong> 9 infections among 601 persons 1.2 infections/100 person-years 24 infections among 599 persons 3.1 infections per 100 person-years</td>
<td>0.38 [62%] (0.17–0.79)</td>
</tr>
<tr>
<td></td>
<td><strong>Control</strong> 1.2 infections/100 person-years 3.1 infections per 100 person-years</td>
<td></td>
</tr>
<tr>
<td>TDF2 (heterosexual men and women)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>FEM-PrEP (heterosexual women)</strong> 33 infections among 1024 persons 4.7 infections per 100 person-years</td>
<td>0.94 [6%] (0.59–1.52)</td>
</tr>
<tr>
<td></td>
<td>35 infections among 1032 persons 5.0 infections per 100 person-years</td>
<td></td>
</tr>
<tr>
<td>West African Trial (heterosexual women)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 infections among 427 persons 0.86 infections per 100 person-years 6 infections among 432 persons 2.48 infections per 100 person-years</td>
<td>0.35 [65%] (0.03–1.93)</td>
</tr>
<tr>
<td>VOICE (heterosexual women)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>TDF</strong> 52 infections among 993 persons 6.3 infections per 100 person-years TDF/FTC 61 infections among 983 persons 4.7 infections per 100 person-years</td>
<td>TDF 1.49 [-50 %] (0.97–2.3) TDF/FTC 1.04 [-4 %] (0.73, 1.5)</td>
</tr>
<tr>
<td></td>
<td>35 infections among 999 persons 4.2 infections per 100 person-years</td>
<td></td>
</tr>
<tr>
<td>BTS (persons who inject drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 infections among 1204 persons 0.35 infections per 100 person-years 33 infections among 1207 persons 0.68 infections per 100 person-years</td>
<td>0.51 [49%] (9.6, 72.2)</td>
</tr>
</tbody>
</table>

* mITT: modified intent to treat analysis; HR: hazard ratio.

* Not statistically significant.
CDC Guidelines and Clinical Application of PrEP

TDF/FTC was approved in July 16\textsuperscript{th}, 2012 for PrEP
## Guidance for PrEP Use

<table>
<thead>
<tr>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Persons Who Inject Drugs</th>
</tr>
</thead>
</table>
| Detecting substantial risk of acquiring HIV infection | HIV-positive sexual partner  
Recent bacterial STI†  
High number of sex partners  
History of inconsistent or no condom use  
Commercial sex work | HIV-positive sexual partner  
Recent bacterial STI‡  
High number of sex partners  
History of inconsistent or no condom use  
Commercial sex work  
In high HIV prevalence area or network | HIV-positive injecting partner  
Sharing injection equipment |
| Clinically eligible | Documented negative HIV test result before prescribing PrEP  
No signs/symptoms of acute HIV infection  
Normal renal function; no contraindicated medications  
Documented hepatitis B virus infection and vaccination status | | |
| Prescription | Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply | | |
| Other services | Follow-up visits at least every 3 months to provide the following:  
HIV test, medication adherence counseling, behavioral risk reduction support,  
side effect assessment, STI symptom assessment  
At 3 months and every 6 months thereafter, assess renal function  
Every 3-6 months, test for bacterial STIs  
Do oral/rectal STI testing | For women, assess pregnancy intent  
Pregnancy test every 3 months | Access to clean needles/syringes and drug treatment services |

STI: sexually transmitted infection

Preexposure Prophylaxis for the Prevention of HIV Infection in the United State – 2017 Update Clinical Practice Guideline. CDC. Published online March 2018
Risk Behavior Assessment for MSM

In the past 6 months:

• Have you had sex with men, women, or both?
• (if men or both sexes) How many men have you had sex with?
• How many times did you have receptive anal sex (you were the bottom) with a man who was not wearing a condom?
• How many of your male sex partners were HIV-positive?
• (if any positive) With these HIV-positive male partners, how many times did you have insertive anal sex (you were the top) without you wearing a condom?
• Have you used methamphetamines (such as crystal or speed)?
Risk Behavior for Heterosexual Men and Women

In the past 6 months:

- Have you had sex with men, women, or both?
- *(if opposite sex or both sexes)* How many men/women have you had sex with?
- How many times did you have vaginal or anal sex when neither you nor your partner wore a condom?
- How many of your sex partners were HIV-positive?
- *(if any positive)* With these HIV-positive partners, how many times did you have vaginal or anal sex without a condom?
MSM-Initiating PrEP

**Document eligibility**
- Must be HIV negative by 4th generation test
- Test for acute HIV (HIV viral load)
- Confirm patient is High risk for HIV acquisition
  - Frequent partner changes, HIV-positive or unknown status partners, living in a high HIV prevalence region, inconsistent use of condoms
- Screen for HBV, STIs (gonorrhea, chlamydia, syphilis, etc)
- Check creatinine clearance and Cockcroft-Gault formula with CrClr >60mL

**Beginning PrEP**
- Prescribed Truvada (TDF/FTC) 1 pill QD, for 3 months
- Repeat HIV testing q3mo prior to next refill
- If HBV diagnosed, consider using Truvada for both PrEP and tx of HBV
- Provide risk reduction and PrEP medication adherence, counseling and condoms
MSM PrEP

- **Follow up**
  - Q2-3 months HIV testing
  - PrEP adherence monitoring
  - Assess risk behaviours, provide risk reduction counseling, condoms
  - Assess for STIs
  - Repeat CrClr in 3 months after starting and then yearly

- **Stopping PrEP**
  - HIV infection confirmed, link to care
  - Check Genotype if HIV positive
  - HBV therapy needed
  - Poor adherence* to medications or risk reductions
Heterosexual recommendations

When PrEP is used by heterosexually active adults, it is important to ensure that
1) PrEP is targeted to persons at very high risk for HIV acquisition (11), especially uninfected persons whose regular sexual partners are known to have HIV infection;
2) The importance of adherence to daily medication and its influence on efficacy is clearly discussed;
3) Couples understand that although no adverse effects have been found among infants exposed to TDF/FTC during pregnancy and breastfeeding, these data are incomplete for women in HIV-discordant couples using TDF/FTC to prevent acquisition of HIV;
4) PrEP is delivered as part of a comprehensive set of prevention services, including risk-reduction, PrEP medication adherence counseling, and ready access to condoms;
5) Sexually transmitted infection treatment is provided when indicated by laboratory screening tests conducted at least every 6 months, and
6) PrEP is accompanied by monitoring of HIV status, pregnancy status, side effects, adherence, and risk behaviors at each quarterly follow-up visit.
PrEP in high risk heterosexuals

**Determine eligibility**

- Document negative HIV antibody test immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection or reports unprotected sex with an HIV-positive person in the preceding month.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Confirm that patient is at ongoing, very high risk for acquiring HIV infection.
- If any sexual partner is known to be HIV-infected, determine whether receiving antiretroviral therapy; assist with linkage to care if not in care or not receiving antiretroviral therapy.
- Confirm that calculated creatinine clearance is ≥60 mL per minute (Cockcroft-Gault formula†).
- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision regarding prescribing PrEP.
- Screen and treat as needed for sexually transmitted infections (STIs).
- Disclose to women that safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP to women who are breastfeeding.

**Beginning PrEP regimen**

- Prescribe tenofovir disoproxil fumarate (TDF) 300 mg plus emtricitabine (FTC) 200 mg (i.e., one Truvada [Gilead Sciences] tablet) daily.

- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.
PrEP in high risk heterosexuals

Follow-up while PrEP medication is being taken

- Every 2–3 months, perform an HIV antibody test (or fourth generation antibody/antigen test) and document negative result.
- At each follow-up visit for women, conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal-care provider.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STIs as needed.
- Every 6 months, test for bacterial STIs, even if asymptomatic, and treat as needed.
- Three months after initiation, then every 6 months while on PrEP medication, check serum creatinine and calculate creatinine clearance.

On discontinuing PrEP

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV-positive, order and document results of resistance testing, establish linkage to HIV care.
- If HIV-negative, establish linkage to risk reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B infection.
- If pregnant, inform prenatal-care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding.
FDA Approval

- Extended indication for TDF/FTC to include use as PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV infection in adults at high risk

- Strengthened TDF/FTC boxed warning
  - TDF/FTC for PrEP must be used only by individuals who are confirmed to be HIV negative prior to prescribing the drug and at least every 3 months during use

- Approval accompanied by REMS
  - Goal is to minimize risk of acquiring HIV infection and to reduce the risk of development of resistant HIV-1 variants in those receiving PrEP
  - Central component is training and education program to assist prescribers in counseling individuals who are taking or considering TDF/FTC for PrEP
FDA Approval

- October 3rd, 2019- FDA\(^1\) approved Descovy (emtricitabine 200mg and tenofovir alafenamide 25mg) in at-risk adults and adolescents for HIV-1 pre-exposure prophylaxis (PrEP)
  - Weighing more than 35kg
  - At risk due to sex
- Excluded were patients at risk due to receptive vaginal sex (cis-gender women).
- The key trial evaluated the effectiveness of Descovy for PrEP in a multinational study of 5387 HIV negative men and transgender women who have sex with men and were at risk for HIV-1 infection. (DISCOVER Trial)\(^2\)

1. FDA.gov
2. Hare, C. THE PHASE 3 DISCOVER STUDY: DAILY F/TAF OR F/TDF FOR HIV PREEXPOSURE PROPHYLAXIS. Abstract 104. CROI 2019
PrEP Counseling

- Continued behavioral risk reduction
- Importance of PrEP adherence
- Adverse events
- Very well tolerated and safe
- May experience mild nausea in first few weeks
### Clinical Signs and Symptoms of Acute (Primary) HIV Infection – Most Check!

<table>
<thead>
<tr>
<th>Features</th>
<th>Overall (n = 375)</th>
<th>Sex</th>
<th>Route of transmission</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Male (n = 355)</td>
<td>Female (n = 23)</td>
<td>Sexual (n = 324)</td>
</tr>
<tr>
<td>Fever</td>
<td>75</td>
<td>74</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68</td>
<td>67</td>
<td>78</td>
<td>71</td>
</tr>
<tr>
<td>Myalgia</td>
<td>49</td>
<td>50</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>Skin rash</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>Headache</td>
<td>45</td>
<td>45</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>40</td>
<td>40</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>30</td>
<td>30</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Night sweats</td>
<td>28</td>
<td>28</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>27</td>
<td>21</td>
<td>28</td>
</tr>
</tbody>
</table>

Preexposure Prophylaxis for the Prevention of HIV Infection in the United State – 2017 Update Clinical Practice Guideline. CDC. Published online March 2018
Summary

- TDF/FTC was approved in July 2012, and is the only formulation currently approved for adults at high risk.
- Daily TDF/FTC have been shown to have moderate efficacy in HIV-1 prevention among MSM.
- Efficacy is highest with higher adherence.
- October 3rd, 2019- FDA approved TAF/FTC for men and transgendered women.
- More data is needed in women, especially for TAF/FTC.
- Provide risk counseling, risk assessment, and monitoring.
- New agents are in trials including long half live agents.
Post-Exposure Prophylaxis
Occidental Blood-borne Exposures
Relative Risk of Seroconversion with Percutaneous Injury

PEP Categories

- **oPEP** - for occupational exposures
  - HCWs who may experience a cut, needle stick, or other potentially infectious body fluid exposure “on the job”

- **nPEP** - for non-occupational exposures
  - Persons who are potentially exposed to HIV through consensual or forced intercourse, accidental puncture wounds, or IVDU
HIV Exposure Definitions

- Percutaneous injury or contact of mucous membrane or non-intact skin with blood, tissue, or other potentially infectious body fluids.

- Infectious body fluids
  - semen, vaginal secretions, CSF, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, amniotic fluid

- Non-infectious Body Fluids
  - feces, nasal secretions, saliva, sputum, sweat, tears, urine, vomitus
Non-Occupational HIV Exposures

- Sexual contact, consensual or forced
- Accidental cuts or punctures with sharp objects
- Intentional use of contaminated or shared needles for IVDU
nPEP Need by Exposure

<table>
<thead>
<tr>
<th>PEP recommended, if source HIV + or at risk of HIV</th>
<th>PEP <em>NOT</em> recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Unprotected receptive &amp; insertive vaginal or anal intercourse</em></td>
<td><em>Kissing, or oral-oral contact &amp; no mucosal damage</em></td>
</tr>
<tr>
<td><em>Unprotected receptive penile-oral contact with ejaculation</em></td>
<td><em>Bites without blood</em></td>
</tr>
<tr>
<td><em>Oral-vaginal contact with blood exposure</em></td>
<td><em>Needles/sharps exposure not in contact with HIV + or at-risk person</em></td>
</tr>
<tr>
<td><em>Needle-sharing</em></td>
<td><em>Mutual masturbation – intact skin</em></td>
</tr>
<tr>
<td><em>Injury with blood exposure</em></td>
<td></td>
</tr>
<tr>
<td>- needle stick, bite, accident</td>
<td><em>Oral-anal contact</em></td>
</tr>
<tr>
<td><em>Receptive penile-oral contact without ejaculation</em></td>
<td><em>Receptive penile-oral contact</em></td>
</tr>
<tr>
<td><em>Insertive penile-oral contact</em></td>
<td><em>Oral-vaginal – no blood exposure</em></td>
</tr>
</tbody>
</table>
Evaluation of Non-Occupational Exposures

- HIV status of the potentially exposed person
  - baseline rapid testing should be conducted to ensure they are not already HIV-positive

- Timing and frequency of exposure
  - nPEP should be initiated within 72 hours of exposure

- Risk of HIV acquisition based on type of exposure

- HIV status of the exposure source
  - often difficult to obtain for non-occupational exposures
Other Considerations for Possible Sexual Exposures

- Prophylaxis for bacterial STIs, trichomoniasis
- Testing for Hepatitis B and C
- Pregnancy prevention for female patients
- Counseling and other support for survivors of sexual assault
Principles of PEP

• Importance of quick initiation of PEP following possible HIV exposure
• Importance of HIV tests for the potentially exposed patient
• Use of a “complete” three-drug regimen for PEP
• Duration of treatment is 28 days
• Follow-up testing required at 6 weeks and 3 months (with newest, 4th-generation Ag/Ab tests)
Step by Step
Assessment/Determinations

- What is the risk for contracting HIV?
- Are there factors that might affect this risk?
- How effective is PEP?
- Is it too late to start PEP?
- What is the current PEP regimen
- How long should the HCW be followed

Other Issues
- Advice about getting pregnant
- What if the HCW was breast feeding
Estimated Transmission HIV Risk

- Higher HIV viral load, increased risk of transmission
- Non-intact mucous membranes increases risk for transmission during sexual exposures.

<table>
<thead>
<tr>
<th>Exposure Type if Source HIV-infected</th>
<th>Estimated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle-sharing exposure</td>
<td>0.67% (1/150)¹</td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>0.5% (1/200) to 3% (6/200)²,³</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>0.1% (1/1000)³,⁴</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>0.065% (1/1500)³,⁴</td>
</tr>
<tr>
<td>Insertive vaginal intercourse</td>
<td>0.05% (1/2000)³,⁴</td>
</tr>
<tr>
<td>Oral sex with ejaculation</td>
<td>Conflicting data, but felt to be low-risk. PEP recommended for performer of oral sex who receives ejaculate.⁵,⁶</td>
</tr>
</tbody>
</table>
Risk for HIV Exposure

**Substantial Risk**

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

**Negligible Risk**

- **Exposure of:** vagina, rectum, eye, mouth or other mucous membrane, intact or nonintact skin, or percutaneous contact
- **With:** urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood
- **Regardless:** of the known source or suspected HIV status of the source
When should PEP be started?

Tenofovir (PMPA) for HIV-2 PEP in Macaques

### Study Design

- **Methods**
  - HIV-2 inoculated intravaginally
  - N = 16 female macaques

- **Regimens**
  - Control vs. Tenofovir regimens
  - PEP started @ 12, 36, or 72 h
  - PEP Rx for 28d

### Results (% Infected)

Algorithm for Evaluation and Treatment of non-occupational HIV Exposure

2019 AETC and CDC Recommendations
How Long Should PEP be Administered? Tenofovir (PMPA) for SIV PEP in Macaques

Study Design

- **Methods**
  - SIV inoculated IV
  - N = 24 macaques

- **Regimens**
  - Control vs. Tenofovir regimens
  - PEP started @ 24, 48, or 72 h
  - PEP Rx for 3, 10, or 28d

Results for PEP Started @ 24h

Preferred 28-day ARV medications Regimens for nPEP

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>A 3-Drug Regimen</th>
</tr>
</thead>
</table>
| Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function (creatinine clearance ≥ 60 mL/min) | Tenofovir DF 300 mg and emtricitabine 200 mg (Truvada®) Fixed dose combination once daily +  
  raltegravir 400 mg twice daily  
  or  
  dolutegravir 50 mg once day |

Risk for neural tube defects with dolutegravir exposure in women who may become pregnant. Recommendations are to discuss with the patient risks and benefits. Consider alternative regimens.  
CDC 2016 Guidelines  
https:\\AIDSETC.ORG
### Preferred nPEP regimen for adolescents and adults (≥13 years of age) with normal renal function (creatinine clearance >59 mL/min):

<table>
<thead>
<tr>
<th>Option</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPTION 1</strong></td>
<td>Tenofovir DF/emtricitabine (TDF/FTC) 300/200 mg (Truvada®), 1 tablet PO daily</td>
<td>+ dolutegravir (Tivicay®)* 50 mg, 1 tablet PO daily</td>
<td>-</td>
<td>28 days**</td>
</tr>
<tr>
<td><strong>OPTION 2</strong></td>
<td>TDF/FTC 300/200 mg (Truvada®) 1 tablet PO daily</td>
<td>+ raltegravir (Isentress®) 400 mg, 1 tablet PO BID</td>
<td>-</td>
<td>28 days</td>
</tr>
<tr>
<td><strong>ALTERNATIVE</strong></td>
<td>TDF/FTC 300/200 mg (Truvada®) 1 tablet once daily</td>
<td>+ darunavir (Prezista®) 800 mg, 1 tablet daily</td>
<td>+ ritonavir 100 mg, 1 tablet daily</td>
<td>28 days</td>
</tr>
</tbody>
</table>

**CDC 2016 Guidelines**
https://AIDSETC.ORG
PEP Following Exposure at Henry Ford

**STOP PEP**

---

**COMPLETE 28-DAY REGIMEN:**

Recommended PEP Regimen

- Tenofovir 300 mg PO qd
- Emtricitabine* 200 mg PO qd

**PLUS**
- Raltegravir 400 mg PO bid

- Perform baseline confidential HIV testing of the exposed worker and refer to experienced clinician within 3 days of initiating PEP.
- See Tables 4 and 5 for alternative regimens.

---

*Has the source patient been at risk for HIV exposure in previous 6 weeks?*

- **YES**
  - Obtain HIV RNA assay from source patient; continue PEP until results are available.
  - **HIV RNA NEGATIVE**
    - **STOP PEP**
  - **HIV RNA POSITIVE**

- **NO**
  - Source patient does not have capacity to consent
  - Source patient refuses HIV testing
  - **STOP PEP. PEP not indicated.**
nPEP Take Home Points

• Assess patient’s HIV exposure

• If exposure occurred:
  • Test both the patient and the source for HIV infection at baseline
  • 1st dose of ART to begin ideally within 2hrs after exposure (don’t wait for results if credible exposure)

• All exposed persons to be offered a 3 drug regimen of Truvada + Raltegravir/Dolutegravir for 28 days.

• Repeat HIV testing at 6 weeks and 3 months if needed.
### Payment Options for Post-Exposure Prophylaxis Following Non-Occupational Exposures Including Sexual Assault (nPEP)

<table>
<thead>
<tr>
<th>Insurance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private Insurance</td>
<td>PEP is covered. Large co-pay may be a consideration.</td>
</tr>
<tr>
<td>No Insurance</td>
<td>Gilead Patient Assistance Merck Patient Assistance Program</td>
</tr>
<tr>
<td>Medicaid in MI</td>
<td></td>
</tr>
</tbody>
</table>
HIV: PEP Resources

- Clinician’s PEP Hotline 888-448-4911
- Reporting to CDC 404-893-0485
- In all states, sexually assaulted persons are eligible for reimbursement of medical expenses through the U.S. Department of Justice Victim’s Compensation Program in cases where the sexual assault is reported to the police (http://www.ojp.usdoj.gov/ovc/map.html).
HIV Consult Line

• Free service for providers
• Access to HIV expert 24 hours a day, 7 days a week
• Can reach us
  – Urgent, call: (313)-575-0332
Thank you
Extra Slides
**PrEP Results**

### TABLE 1. Study design and methods used in four PrEP efficacy trials with daily oral TDF/FTC*

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. and sex of participants</th>
<th>Design</th>
<th>Total follow-up time (per participant median)</th>
<th>No. of Incident HIV Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>2,499 (100% male)</td>
<td>RDBPCT</td>
<td>3,324 person-yrs (1.8 yrs)</td>
<td>Placebo: 64, TDF/FTC: 36, Total: 100</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>HIV-discordant couples</td>
<td>4,758 couples (38% female)</td>
<td>RDBPCT</td>
<td>7,830 person-yrs (23 mos)</td>
<td>Placebo: 52, TDF/FTC: 13, Total: 65†</td>
</tr>
<tr>
<td></td>
<td>Heterosexual men and women</td>
<td>1,216 (46% female)</td>
<td>RDBPCT</td>
<td>1,563 person-yrs (1.1 yrs)</td>
<td>Placebo: 24, TDF/FTC: 9, Total: 33</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexual women</td>
<td>2,056 (100% female)</td>
<td>RDBPCT</td>
<td>1,407 person-yrs (NR)</td>
<td>Placebo: 35, TDF/FTC: 33, Total: 68</td>
</tr>
</tbody>
</table>

### TABLE 2. Measures of efficacy in four PrEP efficacy trials with daily oral TDF/FTC,* by medication adherence

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>mITT† % reduction in HIV incidence (95% CI)</th>
<th>Combined self-report and pill-count medication adherence measures (95% CI)</th>
<th>Pill-count medication adherence measures (95% CI)</th>
<th>TDF blood detection† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>MSM</td>
<td>44% (15%–63%)</td>
<td>&gt;50%† (18%–70%)</td>
<td>73% (41%–88%)</td>
<td>92% (40%–99%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All: Men: Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>HIV-discordant couples</td>
<td>75% (55%–87%)</td>
<td>100%* (87%–100%)</td>
<td>90% (58%–98%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterosexual men and women</td>
<td>62% (22%–83%)</td>
<td>84% (54%–95%)</td>
<td>84% (-62%–98%, NS)</td>
<td></td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexual women</td>
<td>66% (28%–84%)</td>
<td>100%* (54%–95%)</td>
<td>84% (-62%–98%, NS)</td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Heterosexual women</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*No. of Incident HIV Infections

**MMWR / August 10, 2012 / Vol. 61 / No. 31**
THE PHASE 3 DISCOVER STUDY: DAILY F/TAF OR F/TDF FOR HIV PREEXPOSURE PROPHYLAXIS

Author(s):
Charles B. Hare1, Josep Coll2, Peter Ruane3, Jean-Michel Molina4, Kenneth H. Mayer5, Heiko Jessen6, Robert M. Grant1, Joss J. DeWet7, Melanie Thompson8, Edwin DeJesus9, Ramin Ebrahimi10, Robertino Mera Giler10, Moupali Das10, Diana Brainard10, Scott McCallister10

Abstract Body:
Emtricitabine/tenofovir disoproxil fumarate (F/TDF) prevents HIV infection when used as daily pre-exposure prophylaxis (PrEP). Compared to TDF, tenofovir alafenamide (TAF) has higher intracellular tenofovir (TFV)-DP levels, lower plasma TFV levels, and improved renal and bone safety when used for HIV treatment. This study describes the efficacy and safety of F/TAF vs F/TDF for PrEP in cis-men who have sex with men (MSM) and transgender women (TGW) who are at high risk of HIV acquisition.

This randomized (1:1), double-blind, active-controlled study was conducted in North America and Europe at sites with high HIV prevalence in MSM. Entry required ≥2 episodes of condomless anal sex (CAS) in past 12W or rectal gonorrhea/chlamydia or syphilis in past 24W. Participants received daily blinded F/TAF (200/25 mg) or F/TDF (200/300 mg), with matching placebo; pill counts and blood levels were used to measure adherence. Primary endpoint was the HIV infection rate per 100 person years (PY) when 50% completed 96W. Renal safety, 3 anatomic site sexually transmitted infection (STI) testing and risk behavior were assessed every 12W. Using CDC reported HIV surveillance data we calculated the background 'HIV incidence rate' in at risk individuals not on PrEP from 105 US metropolitan statistical areas (MSAs) for comparison.

5387 adults were treated at 94 sites in 11 countries, with 3226 (60%) in the US. Mean age was 36, range 18-76 years, 9% Black, 1% TGW, 23% had prior PrEP use and 41% had >3 receptive CAS partners in the 90 days before study entry. 90% of participants completed ≥48W on study, with median follow up of 84W. For this analysis, 85% remained on study drug: 6% discontinued by participant choice and 6% were lost to follow up. On-study sexual HIV risk persisted with an STI rate of 99.5/100PY. Across both arms, there were 21 HIV diagnoses—an infection rate of 0.26/100 PY—a figure significantly lower than the expected HIV infection rate for those at risk but not on PrEP in the US (Table). Both drugs were tolerated well with 1.5% AE-related discontinuations, with GI most common.

In a multinational population of cis-MSM and TGW at risk of sexual HIV infection, the HIV incidence rate on either F/TAF or F/TDF was very low and significantly less than the background rate in those at risk but not on PrEP in the US. In almost 2 years of follow up, both F/TAF and F/TDF, given daily, were tolerated and had low discontinuation rates.