Pre-Exposure Prophylaxis (PrEP) and Post Exposure Prophylaxis: Strategies for HIV Prevention

Elizabeth Hudson, DO, MPH
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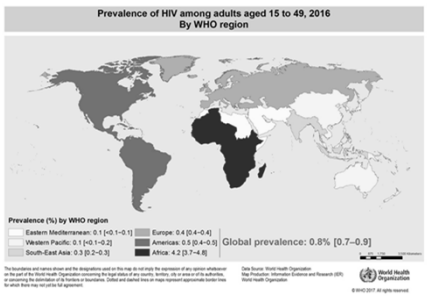
HIV Pandemic

- In 2016, there were 37 million people worldwide living with HIV
  - 1.1 million people older than age 13 are HIV positive in the US
    - 15% of these people do not know they are infected
- Since the start of the epidemic:
  - 76 million people have become infected with HIV
  - 35 million people have died
- Worldwide, 1.8 million people became newly infected with HIV in 2016, down from 3.4 million in 2001
- AIDS-related deaths have fallen by 48% since the peak in 2005 (PEPFAR)
  - 1 million people died from AIDS-related causes in 2016

HIV Prevalence: Ages 15-49



HIV prevalence among Men who Have Sex with Men

- Atlanta, Georgia 16%
- Baltimore, Maryland 38%
- Boston, Massachusetts 12%
- Chicago, Illinois 18%
- Dallas, Texas 26%
- Denver, Colorado 16%
- Detroit, Michigan 14%
- Houston, Texas 26%
- Los Angeles, California 19%
- Miami, Florida 25%
- Nassau-Suffolk, New York 8%
- New Orleans, Louisiana 21%
- New York, New York 29%
- Newark, New Jersey 19%
- Philadelphia, Pennsylvania 11%
- San Diego, California 18%
- San Francisco, California 23%
- San Juan, Puerto Rico 12%
- Saint Louis, Missouri 14%
- Seattle, Washington 15%
- Washington, DC 14%
- Overall average: 19%

Age	HIV prevalence
18-19	7%
20-24	12%
25-29	15%
30-39	21%
40-49	28%
50 or over	25%

Race/Ethnicity	HIV prevalence
Asian	8%
Black, non-hispanic	28%
Hispanic	18%
White, non-hispanic	16%
Other	21%

- **In Los Angeles, reports show that 33 to 36 percent Black men who have sex with men may be HIV-positive**
- **If current trends in the US continue, 50% of Black MSM and 25% of Hispanic MSM will become HIV + in their lifetimes**

Treatment as Prevention (TasP)

A universal approach to HIV prevention that combines both pre-exposure prophylaxis (PrEP) for those engaging in recurrent high-risk sexual practices and other prevention strategies (e.g., antiretroviral therapy for all HIV-infected individuals, post-exposure prophylaxis (PEP),male circumcision) could lead to marked reductions in HIV acquisition

Treatment as Prevention (TasP)

- The World Health Organization (WHO) released updated guidelines in 2015 calling for:
  - Antiretroviral therapy (ART) for everyone diagnosed with HIV regardless of CD4 cell count
  - Pre-exposure prophylaxis (PrEP) for people at substantial risk of HIV infection
- WHO estimates that if these recommendations are widely adopted worldwide, they could avert 21 million deaths and prevent 28 million new infections by the year 2030.

Proposed Candidate Drugs for PrEP

- Excellent tolerability
- Low toxicity
- Pharmacokinetics allowing once-daily dosing
- A high genetic barrier of resistance
- Adequate drug concentrations in blood, rectal mucosa, and genital fluids
- Demonstration of safety, tolerability, and efficacy in clinical trials
- Low cost

Truvada

- Released in 2004 as a combination of two NRTI's (Nucleoside Reverse Transcriptase Inhibitors) Emtriva (FTC, Emtricitibine) and Viread (TDF or Tenofovir disoproxil fumarate) for HIV therapy
- Truvada (FTC/TDF) became the 'backbone' treatment most HIV treatment
  - One pill once a day HIV therapy (e.g.:Atripla)
  - Poor compliance with PrEP issues with treatment if become HIV +
- Very well tolerated, virologically durable, few side effects (N/V)
  - Osteoporosis, Fanconi's Syndrome most serious SE's: rare
- FDA approved Truvada for PrEP use in 2012 based on various studies

PrEP Clinical Trials: Heterosexuals

Partners-PrEP

- Study done in Kenya and Uganda, demonstrated that tenofovir with or without emtricitibine, was efficacious, compared with a placebo, for the prevention of HIV acquisition among 4758 sero-discordant couples (one partner HIV+/one HIV-)
- Use of these medications decreased the risk of HIV infection by 67 and 75 percent, respectively (17 and 13 infections compared with 52 infections in the placebo arm)

TDF2

- Separate trial of 1200 sexually active heterosexual women and men in Botswana the rate of HIV infection was similarly decreased by 62 percent among patients randomly assigned to daily tenofovir and emtricitibine (Truvada) compared with placebo
- Both of these studies demonstrated issues with study participant compliance: 30% or less compliance as measured by drug levels

PrEP Clinical Trials: Women and PrEP

- **FEM-PREP**

- Used oral and topical formulations of Tenofovir among approximately 2000 sexually active African women
- The study was halted when an interim assessment showed no evidence of protective efficacy among those assigned to the Truvada arm
  - They had higher rates of pregnancy compared with those in the placebo arm, suggesting that they were having more unprotected intercourse
  - Less than one quarter of the subset of FEM-PrEP participants who were assigned to receive Truvada and underwent therapeutic drug monitoring had detectable plasma drug levels: Non adherence!

Vaginal and Oral Interventions to Control the Epidemic; VOICE trial

- Conducted among 5000 African women who were randomly assigned to oral tenofovir alone, oral Truvada, a placebo pill; or tenofovir gel or placebo vaginal gel
- In this population of predominately young unmarried women with high HIV incidence, no study drug significantly reduced the risk of HIV acquisition.
- Tenofovir was detected in less than a third of blood samples from women, despite high levels of self-reported product use.

PrEP Clinical Trials: MSM

Pre-exposure Prophylaxis Initiative (iPrEx):NEJM, 2010

- A multinational trial conducted in six countries in four different continents, with 2470 HIV-seronegative men and 29 transgender women randomly assigned to either Truvada prophylaxis or placebo once daily
- All participants received HIV testing, risk reduction counseling, condoms, and management of STDs at enrollment and throughout the trial.
- The participants were followed for a median of 1.2 years
  - pill counts and medication history were taken serially throughout the trial

PrEP Clinical Trials: MSM

iPrEx results:

- 100 patients became infected during follow-up (36 in the intervention arm and 64 in the placebo group) consistent with a **44 percent reduction** in the incidence of HIV with tenofovir-emtricitabine

iPrEx Ole:Off Label Extension 2012:

- For people who take 7 PrEP pills per week, their estimated level of protection is 99%
- For people who take 4 PrEP pills per week, their estimated level of protection is 96%

PrEP Clinical Trials: MSM

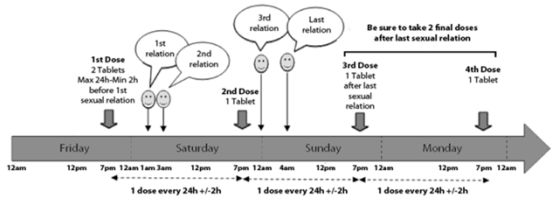
Ipergay "Intervention Prophylactique pour Et avec les Gays"(CROI 2015)

- French researchers wanted to see if taking PrEP only around the time participants were actually exposed to HIV would worked
- Trying to increase adherence, save money and decrease risk of side effects
- Recruited 400 high risk MSM who took *two Truvada* pills (or a placebo) from one day to two hours before they anticipated having sex.

PrEP Clinical Trials: MSM

- If they had sex, then they were to take another pill 24 hours after having sex and a fourth pill 48 hours after
  - The period of taking PrEP would thus cover two to three days
  - If they continued having sex, they were told to continue taking PrEP until 48 hours after their last experience
- All participants also received risk-reduction counseling, were provided with condoms, had three-monthly tests for HIV and other sexually transmitted infections (STIs), and received hepatitis A and B vaccines if needed

Ipergay



PrEP Clinical Trials: Men Who Have Sex with Men

- During this initial study time, two participants allocated to Truvada became HIV positive vs 14 in placebo group
- The annual rate of HIV infection seen per 100 participants was 0.94% in participants taking Truvada and 6.75% in patients on placebo
- This translated to an effectiveness of 86%
- In November 2014, Data and Safety Monitoring Board required all participants to be offered PrEP at once because of high effectiveness

PrEP Clinical Trials: Men Who Have Sex with Men

There was no evidence of behavior change in the study: risk compensation

- The proportion of participants reporting at least one episode of condomless anal sex in the previous two months didn't change from baseline: 70%
- The number of partners remained at just under eight in the last two months
- During the study, 35% of participants were diagnosed with an STD including 20% with gonorrhea and 10% with syphilis
  - Hep C seen in two
- There was a higher rate of gastrointestinal side-effects such as N/V/D in Truvada arm
  - only one person in the entire study discontinued *Truvada* due to an adverse event – a suspected drug/drug reaction.

PrEP Clinical Trials: Men Who Have Sex with Men

- **PROUD study: CROI 2015**

- PROUD was an open-label randomized trial done at 13 sexual health clinics in England
- Enrolled HIV negative gay men who had had at least one episode of receptive or insertive anal intercourse without a condom in the previous 90 days. Participants were randomly assigned (1:1) to receive daily Truvada either immediately (275 patients) or after a deferral period of 1 year (269 patients)
- People in the immediate group had an 86% relative reduction in risk of acquiring HIV compared with the deferred group.

PrEP Clinical Trials: Men Who Have Sex with Men

- Again, no change in STD rates
- The incidence of new HIV infections recorded in the deferred group was roughly seven-times higher than UK's national estimate for MSM
- "The difference suggests that the PROUD study population was highly selective, despite broad eligibility, and that the offer of PrEP generally attracts those men who are most likely to benefit from it."

"No new HIV infections seen among Kaiser PrEP users"

- Kaiser Permanente San Francisco Medical Center, 32 month observation study of 657 people placed on PrEP
- The average length of use during the study period was 7.2 months, resulting in 388 person-years of observation of PrEP use
- The average age of PrEP users was 37, and 99 percent were MSM
- Compared with people who did not use the PrEP protocol, users were more likely to report multiple sex partners, and were not more likely to report having an HIV-infected sexual partner.

Kaiser PrEP Study

- No new HIV infections were identified in those on PrEP during the observation period!
- At six months after initiation, 30% of PrEP users had been diagnosed with at least one STI
- At 12 months, 50 % of PrEP users had been diagnosed with any STI
  - 33 percent had a rectal STI, 33 percent had chlamydia, 28 percent had gonorrhea, and 5.5 percent had syphilis
- "Without a control group, we don't know if these STI rates were higher than what we would have seen without PrEP."

Limitations of Kaiser Study

- No comparator group the study, so cannot formally evaluate the efficacy of PrEP
- Were subjects who had the initiative to start PrEP more likely to serosort, or PrEP-sort, or to engage in other risk reduction activities at the same time?
- Claims of 100% efficacy in the Kaiser Permanente study (which by the way the authors themselves did not make) are not supported by IPrEx, Ipergay and PROUD

Limitations of Kaiser Study: Risk Compensation

- Risk compensation is a theory which suggests that people typically adjust their behavior in response to the perceived level of risk, becoming more careful where they sense greater risk and less careful if they feel more protected
- After a year of PrEP use, fully 50% of people who took Truvada were diagnosed with a sexually transmitted infection and 41% indicated their condom usage had decreased
- Could PrEP use could undercut other risk reduction activities?
- Are we just observing what is happening anyway with STI's, PrEP or no PrEP?

What's Next in PrEP?

Other medications and treatment modalities for PrEP being considered

- Rilpivirine
- Maraviroc
- Cabotegravir
- Injectable PrEP with nanosuspension: long lasting

Truvada and Tissue Uptake

- For blood and cervicovaginal tissues to be fully protected, it takes about **three weeks** of daily Truvada use
- For rectal tissue to be maximally protected, it takes only about **7 days**
- About the same amount of time would be needed for these drugs to wash out from these different tissue types
  - waning anti-HIV protection as those levels drop, over time

Pre-Exposure Prophylaxis (PrEP) for Prevention of HIV

What is it?

- Once daily Truvada (Tenofovir/Emtricitibine) taken to prevent acquisition of HIV

Who is it for?

- Serodiscordant partners (HIV +/HIV-)
- Men who have sex with men (MSM) who have recently reported high-risk sexual behaviors (eg, unprotected anal sex) or had a documented sexually transmitted infection
- Heterosexually active men and women who infrequently use condoms and have sex with partners who are at high risk of HIV-infection
- IDU's
- Individuals who have used post-exposure prophylaxis more than twice in the past year

KP So Cal Guidelines for PrEP

ELIGIBILITY CRITERIA FOR PrEP:

- Patients should be at least 18 years of age
- Patients should have no laboratory evidence of HIV via ELISA or HIV RNA (qualitative or quantitative; if acute infection suspected)
- Patients should be determined by KP provider to be at increased risk for HIV acquisition
- Patient should understand that PrEP is not a guarantee against contracting HIV
- Patients should understand the possible risk of toxicity (renal, bone, etc.) and the risk of potential resistance development should they acquire HIV
- Patients should have creatinine clearance ≥ 60 mL/min
- Female patients should not be pregnant and are actively employing effective contraceptive methods prior to starting PrEP, unless PrEP is part of a safer conception strategy for serodiscordant couples

KP So Cal Guidelines for PrEP: ID Referral

- Consult with ID physician or provider
  - Counseling about risk/sexual practices, benefits/risks of Truvada, review of our PREP program and patient responsibilities
  - Baseline labs obtained
  - Consult notes routed to the referring physician/provider and HIV PharmD
- TAV to start RX 3 MONTH TAV (Provider) + labs + risk reduction counseling
- 6 MONTH TAV (Provider) + labs + risk reduction counseling, STI testing
- 12 MONTH APPT(Provider+/- PharmD) + labs + risk reduction counseling

KP So Cal Guidelines for PrEP

LABS	Baseline	3 weeks	*Every 3 months thereafter- labs and follow up*	
HIV Screening Test (Antigen/Antibody)	X	X	X	
HIV RNA test for recent exposure at baseline only	X			
Risk Reduction Counseling	X		X	
Sexually Transmitted Infection Screening(STIs)	X		X	
Creatinine	X	X	X	
Urinalysis	X		X	
Hepatitis Serologies	X			
For Women Only: Pregnancy Testing	X	X	X	

Pre-Exposure Prophylaxis (PrEP) for Prevention of HIV

- This treatment is not for everyone!
  - Drug is $1200/month so compliance is key!
    - Recent Stanford study (9/15) showed PrEP, from a cost standpoint, should **NOT** be the priority
- Need to be aware of high level of STI's in this population and that condom use is considered a key part of this treatment
  - STI screening is key!
- Risks associated with Truvada include:
  - Osteoporosis
  - Renal dysfunction
- ID is overseeing this program; will likely change in future due to volume

Post-Exposure Prophylaxis for HIV Prevention: Occupational Exposures

- Risk of potentially becoming infected with HIV is a concern for all Health Care Workers (HCWs)
- All facilities have procedures in place to try to decrease the risk for these types of exposures
- The risk of a HCW becoming infected with HIV in an occupational setting is quite low
  - 58 documented seroconversions in HCWs from 1985-2013
  - Higher risk depends on type of exposure
    - Hollow bore needle versus solid needle
    - Deep Injury
    - Source with high HIV Viral Load

Post-Exposure Prophylaxis for HIV Prevention: Occupational Exposures

- First response is always cleaning the potentially exposed area
- Need to determine if the HCW would benefit from PEP
- Percutaneous or mucous membrane exposure?
- Bodily fluids involved?
  - Infectious:
    - Blood, semen, vaginal secretions or bodily fluids with visible blood
  - Not Infectious:
    - Feces, saliva, urine, sputum, sweat, tears, vomitus

Post-Exposure Prophylaxis for HIV Prevention: Occupational Exposures

Determine HIV status of SOURCE patient!

- If source patient is HIV positive, find out
  - If on treatment
  - Last T cell and Viral load count
- If unknown HIV status AND source patient is available
  - Obtain a rapid HIV test: if negative -> no PEP
- If source patient's HIV status can not be determined, need for PEP is dependent on many factors
  - Contact ID

Post-Exposure Prophylaxis for HIV Prevention: Occupational Exposures

Counseling and baseline testing for HCWs

- Order Blood Borne Pathogen (BBP) panel
  - HIV Ab, Hep C Ab Hep B S ag
- Baseline labs: Bun/Creat, LFTs, Lytes and CBC
- Recommend safer sex until all serologic testing is complete
- Discuss risks and benefits of PEP
  - HCWs of child-bearing age should have a serum HCG

Post-Exposure Prophylaxis for HIV Prevention: Occupational Exposures

PEP Treatment Options

- Want to initiate PEP, ideally, within 2 hours of exposure
  - Can receive up to 72 hours post exposure
- For exposures where the source pt's HIV status is unknown, PEP options are
  - Dolutegravir (50 mg) QD PLUS Truvada (300/200)QD X 28 days

    or
  - Raletegravir (400 mg) BID PLUS Truvada (300/200) X 28 days
    - Best choice for pregnant HCWs

Post-Exposure Prophylaxis for HIV Prevention: Occupational Exposures

- If the source patient is HIV +, and is well controlled on their HIV medications, HCW should receive same medications for their PEP
- If the source patient is HIV + and is not well controlled, can consider the previously mentioned regimens
- ID physicians should always be consulted to ensure correct PEP is given AND that the HCW gets follow up in ID clinic

Post-Exposure Prophylaxis for Prevention Occupational Exposures to Other BBPs

- Source patient should be tested for Hep C Ab and Hep B S Ag
- HCW should be assessed for Hep B immunization status, Hep B S Ab, previous Hep C Ab testing (if done)
- All HCWs should be immune to Hep B as immunization is required for employment
  - Hep B S Ab titers can decrease and HCW is still immune
- Many scenarios for Hep B and HCWs, depending on vaccine status
  - Hep B Immunoglobulin is available; 7 days to use

Post-Exposure Prophylaxis for Prevention Occupational Exposures to Other BBPs

- There is no post-exposure prophylaxis for Hep C exposure
- If source pt is Hep C Ab neg or Hep C Ab + but Hep C RNA neg, HCW is not at risk for acquiring Hep C
- If the source pt is Hep C Ab + and has detectable Hep C RNA, then HCW should have Hep C Ab AND Hep C RNA obtained at baseline
  - Requires Hep C Ab Q 2 months for 6 months total
- If source pt is unknown Hep C status, HCW will get follow up Hep C Ab testing every 2 months for 6 months total

Post-Exposure Prophylaxis for HIV Prevention: Non-Occupational Exposures (nPEP)

- Patients who present within 72 hours of a potential HIV exposure are candidates for Non-Occupational PEP (nPEP)
- These patients should have baseline HIV, Hep C and Hep B tests
  - Also, screen for Syphilis and STIs (GC/CT)
  - Remember to swab all orifices used for sex for GC/CT
- Options for nPEP are the same as those for PEP
  - Truvada plus Raltegravir or Truavada plus Dolutegravir X 28 days
- If source patient is known, can do rapid HIV test
  - If source pt is known HIV + and is on ARVs, can place patient on same ARVs for their nPEP
    - Check HIV VL and CD4-> helps to determine risk
    - Repeat testing for HIV at 4 weeks and 3 months post exposure

Post-Exposure Prophylaxis for Prevention of Hep B: Non-Occupational Exposures (nPEP)

- If exposed patient is not known to be Hep B immune, by history, when they present, they should receive Hep B immunoglobulin immediately
- Obtain Hep B serology tests **before** giving Hep B Ig
  - These patients should also be started on the Hep B vax series
- Patients who are given Hep B Ig get retested in 6 months

Post-Exposure Prophylaxis for Prevention of Hep C: Non-Occupational Exposures

- Test patient for Hep C Ab at baseline
- If know the source patient, obtain Hep C Ab and Hep C RNA
- If source Hep C RNA is +, check pts Hep C RNA at 4 weeks and then Hep C Ab and Hep C RNA at 3 and 6 months from time of potential exposure
- If source's Hep C RNA is negative, no risk for patient
- If source's Hep C status is not known, recheck patient's Hep C Ab in 6 months from time of exposure
- No post-exposure prophylaxis treatment for Hep C exposure

Questions/Comments?

Thank You!