PEP, PREP, HPTN052 and MLN2238
Understanding the alphabet soup of HIV prevention and cure strategies

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Pharmacy Grand Rounds
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Presentation Objectives

1. Restate differences between PEP and PREP
2. Explain changes in clinical practice resulting from the HPTN052 trial
3. Recall the proposed mechanism of action of MLN2238 for HIV reservoir eradication
Human Immunodeficiency Virus
HIV 101

HIV Can Be Transmitted By

- Sexual Contact
- Sharing Needles to Inject Drugs

HIV Is **NOT** Transmitted By

- Air or Water
- Saliva, Sweat, Tears, or Closed-Mouth Kissing
- Insects or Pets
- Sharing Toilets, Food, or Drinks
HIV Incidence

- Black MSM: 10,315
- White MSM: 7,570
- Hispanic/Latino MSM: 7,013
- Black Heterosexual Women: 4,142
- Black Heterosexual Men: 1,926
- Hispanic/Latina Heterosexual Women: 1,010
- White Heterosexual Women: 968

Source: CDC.gov
Untreated HIV
HIV 101
Protect Yourself From HIV

- Get tested at least once or more often if you are at risk.
- Use condoms the right way every time you have anal or vaginal sex.
- Choose activities with little to no risk like oral sex.
- Limit your number of sex partners.
- Don’t inject drugs, or if you do, don’t share needles or works.

- If you are at very high risk for HIV, ask your health care provider if pre-exposure prophylaxis (PrEP) is right for you.
- If you think you’ve been exposed to HIV within the last 3 days, ask a health care provider about post-exposure prophylaxis (PEP) right away. PEP can prevent HIV, but it must be started within 72 hours.
- Get tested and treated for other STDs.
• PEP is the use of antiviral agents started within 72 hours of single exposure for HIV prevention.
HIV negative or unknown status persons

**oPEP**
- Needle Sticks
- Blood or body fluids

**nPEP**
- Sexual assault
- IV drug use
Who is a PEP candidate?

- HIV exposure likely
- <72 hours from exposure
- Source HIV+ or high risk
# HIV Transmission Risk

<table>
<thead>
<tr>
<th>Type of Exposure</th>
<th>Risk per 10,000 Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral</strong></td>
<td></td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>9,250</td>
</tr>
<tr>
<td>Needle-Sharing During Injection Drug Use</td>
<td>63</td>
</tr>
<tr>
<td>Percutaneous (Needle-Stick)</td>
<td>23</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
<td></td>
</tr>
<tr>
<td>Receptive Anal Intercourse</td>
<td>138</td>
</tr>
<tr>
<td>Insertive Anal Intercourse</td>
<td>11</td>
</tr>
<tr>
<td>Receptive Penile-Vaginal Intercourse</td>
<td>8</td>
</tr>
<tr>
<td>Insertive Penile-Vaginal Intercourse</td>
<td>4</td>
</tr>
<tr>
<td>Receptive Oral Intercourse</td>
<td>Low</td>
</tr>
<tr>
<td>Insertive Oral Intercourse</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Estimated Per-Act Probability of Acquiring HIV from an Infected Source by Exposure Act* 

Patel P, et al. AIDS. 2014
PEP Components

- Expert Counseling
- One time medication course
- Baseline & repeat STI/lab testing
PEP Preferred Regimens

Emtricitabine/Tenofovir DF + Dolutegravir = PEP 5 +23 days

Emtricitabine/Tenofovir DF + Raltegravir* = PEP 5 +23 days

*Preferred in pregnancy (data)

2016 CDC/DHHS nPEP Guidelines Update
PEP Alternative Regimens

Emtricitabine/ Tenofovir DF + Darunavir/ ritonavir = PEP 28 days

Lamivudine / zidovudine + Raltegravir or Dolutegravir = PEP 28 days

2016 CDC/DHHS nPEP Guidelines Update
Medication Adherence

Antiviral resistance

Adverse Drug Reactions

Cost

Effect on Risky Behaviors
PEP Medication Counseling

- **Start ASAP**
- Make up a missed dose = 12 hours
- Complete the entire course
- Take 2 hr before/6 hr after divalent cations
- Adverse effects mild
  - Insomnia – take in AM, sleep hygiene
  - Headaches – OTC analgesics
  - Nausea/diarrhea – take with food
Learning Assessment Q1

• Patient LR is a 52 yoF is a sexual assault victim from an HIV known + assailant. Which of the following is a guideline recommended PEP option?

1. Emtricitabine + Tenofovir DF + Raltegravir x23d
2. Lamivudine + Zidovudine + Dolutegravir x28d
3. Lamivudine + Abacavir + Dolutegravir x28d
4. Lamivudine + Zidovudine + Darunavir x28d
What if there were a pill that could help prevent HIV?

There is.

Ask your doctor if PrEP is right for you.

Pre-exposure prophylaxis: A daily pill to reduce risk of HIV infection

www.cdc.gov/hiv/basics/prep.html
Who is a PrEP candidate?

HIV + partner
High # partners
Bacterial STI
No condom use
Commercial sex worker
CrCl >60 ml/min

HIV + injection partner
Sharing equipment
CrCl >60 ml/min

PrEP

2014 CDC PrEP Clinical Practice Guideline
PrEP Evidence

- Men who have sex with men (MSM)
  - iPrEX
  - US MSM safety trial
- Serodiscordant couples
  - Partners PrEP
  - FEM PrEP
- Intravenous drug users (IVDU)
  - Bangkok Tenofovir Study

2014 CDC PrEP Clinical Practice Guideline
iPrEx Study (2010)

2500 males

58 excluded

1,224 PrEP 1,217 Placebo

36 HIV + 64 HIV +

Grant et al. N Engl J Med 363;27
Risk Reduction

>90
With verified adherence

73
>90% reported adherence

50
>50% reported adherence

PrEP Components

- Expert Counseling
- Chronic Medication
- Ongoing lab testing
Only PrEP FDA Approved Regimen

- Emitricitabine + Tenofovir DF 1 tablet daily ongoing
PrEP Medication Counseling

- Daily therapy, not to be taken periodically
  - Risk of viral resistance if inconsistent
- Better adherence = better protection
- Take with or without food
- Monitor LFTs, renal function
- Adverse effects mild
  - Hepatotoxicity – usually mild, reversible
  - Rash – often resolves, antihistamines
Learning Assessment Q2

• Which of the following patients would be considered the best PrEP candidate (all HIV-)?

1. Exclusive MSM 16 yoM with 6 sexual partners in the past year

2. Presented to the ER a 23 yoF post sexual assault

3. Monogamous 50 yoM partner of HIV + male with CKD stage 3-4

4. Transgender 32 yoM to F commercial sex worker engaging in anal receptive intercourse
The end of AIDS?

How 5 million lives have been saved, and a plague could now be defeated
Prevention of HIV-1 Infection with Early Antiretroviral Therapy


ABSTRACT

BACKGROUND
HPTN052 Basics

1,763 HIV+/couples

Active TB, HIV +/+ excluded

886 Early cART
877 Late cART

1 HIV +
28 HIV +

# HPTN052 Design

<table>
<thead>
<tr>
<th>Study Enrollment</th>
<th>13 sites</th>
<th>9 countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation</td>
<td>1:1 Randomization</td>
<td>Permutated block</td>
</tr>
<tr>
<td>Groups</td>
<td>Early = At enrollment</td>
<td>Late = CD4&lt;250 or ADI</td>
</tr>
<tr>
<td>Interventions</td>
<td>2 NRTIs + NNRTI or PI, risk reduction counseling</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Quarterly HIV testing for uninfected partner</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td>Kaplan-Meier</td>
<td>Event free probability</td>
</tr>
<tr>
<td></td>
<td>Cox Regression</td>
<td>Relative Risks</td>
</tr>
<tr>
<td></td>
<td>Chi squared</td>
<td>Adverse effects</td>
</tr>
</tbody>
</table>

HPTN052 Results

97% heterosexual

94% married

Early therapy

CD4 - 442
VL 4.4 log10
89% VL<400

Late therapy

CD4 - 428
VL 4.4 log10
9% VL<400

HPTN052 Results

RRR=96%

Cost
Unaware of infection
Extrapolation to other HIV+ populations
Long term treatment ADRs
Adherence
Learning Assessment Q3

• True or False

Based on the results of HPTN052, it is acceptable for commercial sex workers who are HIV+ with a sustained undetectable viral load (<20 copies/mL) to engage in unprotected intercourse since the risk of HIV transmission is very low.
HIV Cure Strategies

- Vaccines
- Drugs
- BMT
- Herbals
- Heavy metals
- Detoxification methods
Latent HIV Reservoir

https://smhs.gwu.edu/timetoendhiv/hiv-aids/finding-a-cure
Latent HIV as Target

- Host cells have intrinsic suicide pathways to limit viral replication
- Viruses evolved to inhibit cell death pathways
- HIV is resistant to apoptosis
  - Regulates endogenous apoptosis proteins
- Latent (memory) → active cells do not die
  - Antagonism of cell apoptosis pathways
  - Potential target: promote cell apoptosis
MLN2238, Ixazomib

Promotes cell apoptosis

Ixazomib towards HIV Cure

• The Effect of Ixazomib on the Latent HIV Reservoir
  • ClinicalTrials.gov Identifier: NCT02946047
  • “Pilot Study of Ixazomib to Reduce the Number of HIV DNA Positive Lymphoid Cells”
    • Phase I/II study
    • Primary outcome: safety
    • Secondary outcome: effect on HIV reservoir
• Actively enrolling!

https://clinicaltrials.gov/ct2/show/NCT02946047
Ixazomib towards HIV Cure

• Treatment: oral Ixazomib on days 1, 8 and 15 of a 28 day cycle

• Study subject criteria
  • Adults aged >18
  • On a stable regimen of ART that suppresses HIV replication
  • Good renal, liver function
  • No viral co-infection
  • Females of non-childbearing potential
    • Males agree to barrier protection

https://clinicaltrials.gov/ct2/show/NCT02946047
Learning Assessment Q4

• A patient asks you to explain how ixazomib works against HIV. Best response:

1. Shock and kill theory
2. Decreasing the number of latent HIV cells
3. Acting as chemotherapy against active HIV virus
4. Utilizes the “Bob Beck” Protocol and methodology
Summary

• PEP is a 28 day course of 3 drug therapy given after a one time suspected exposure to HIV that should be started soon as possible

• PREP is an ongoing use of 2 drug therapy that is taken daily to prevent HIV for those at high risk of exposure

• MLN2238, ixazomib, is proteasome inhibitor undergoing clinical research for potential curative intent of HIV infection
Questions?

BECOME AN AGENT OF CHANGE

HOPE FOR A CURE

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