Truvada for HIV Pre-Exposure Prophylaxis

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Objectives

- Review the Pre-exposure prophylaxis methods for HIV
- Discuss the characteristics of Truvada
- Review the current data for Truvada for Pre-exposure prophylaxis (PrEp) for HIV
- Identify future considerations for PrEP

HIV Epidemiology

- 48,100 new HIV diagnoses in 2009
  - 503 in Baltimore City (~1%)

	United States	Baltimore
# of New Diagnoses	48,100	503 (~1%)
Heterosexual	27%	38%
MSM	64%	36.2%
MSM/IVDA	2%	1.3%
IVDA		24.1%

http://www.cdc.gov/hiv/topics/surveillance/basic.htm#hivinfection
http://ideha.dhmh.maryland.gov/OIDEOR/CHSE/Shared%20Documents/Baltimore_City_HIV_AIDS_Epidemiological_Profile_12_2010.pdf

Current Management for HIV

- Treatment
  - What we do!
- Post-Exposure Prophylaxis
  - Needle-stick, sexual
  - Occupational or non-occupational
- Pre-Exposure Prophylaxis
  - IVDA, MSM, heterosexual
  - Tenofovir 1% gel
  - Truvada

Pre-Exposure Prophylaxis

- Education/Elimination of risk factors
  - Unsafe sex practices
  - High number of partners
  - Sharing of needles
    - Needle exchange programs
- Condom use
- Test
  - Identify all those that are infected
- Treat
  - Decrease infected patients viral load

What is Truvada?

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Tenofovir, Viread®, TDF
- Lamivudine, Epivir®, 3TC
- Emtricitabine, Emtriva®, FTC
- Abacavir, Ziagen®, ABC
- Zidovudine, Retrovir®, AZT
- Didanosine, Videx EC®, ddI
- Stavudine, Zerit®, d4T
- *Zalcitabine, Hivid®, ddC*

- Truvada
  - Tenofovir +Emtricitabine
- Epzicom
  - Abacavir + Lamivudine
- Combivir
  - Zidovudine + Lamivudine
- Trizivir
  - Abacavir + Zidovudine + Lamivudine

Truvada: Tenofovir/Emtricitabine

	Column A			Column B
	NNRTI	**PI**	**II**	**2-NRTI**
Preferred	Efavirenz	Atazanavir/r daily Darunavir/r daily	Raltegravir	Tenofovir/ Emtricitabine
Alternative	Rilpivirine	Fosamprenavir/r BID Fosamprenavir/r daily Lopinavir/r daily Lopinavir/r BID	Elvitegravir/c	Abacavir/ Lamivudine OR

r = ritonavir boosting; c = cobicistat boosting

Tenofovir, Viread®, TDF

- Nucleotide reverse transcriptase inhibitor
- Dose: 300 mg po daily
  - Renal dosage adjustment needed
- Effective against Hepatitis B
- Adverse Effects:
  - Acute Renal Failure
  - Fanconi's Syndrome
  - Decrease in bone mineral density
- Common mutations:
  - K65R

Emtricitabine, Emtriva®, FTC

- Dose: 200 mg po daily
  - Renal dosage adjustment needed
- Effective for Hepatitis B
- Adverse Effects
  - Clinically significant: none
- Common mutation
  - M184V

Truvada for Pre-Exposure Prophylaxis Trials

- iPrex
- Partners PrEP
- FEM-PrEP
- TDF2

iPrex

- Population:
  - Men at birth ≥ 18 years of age
  - MSM and transgender
- Region:
  - Peru, Ecuador, South Africa, Brazil, Thailand, US
- Intervention:
  - Truvada vs. Placebo
  - Every 4 week visits
  - Drugs dispensed, pill counts, adherence counseling, rapid HIV testing, medical histories, high-risk behaviors
- July 10, 2007- December 17, 2009

Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99.

iPrex

- 2499 HIV negative patients enrolled
- Infections:
  - 100 infected during enrollment
    - 36 in Truvada group
    - 64 in Placebo group
    - 44% reduction in incidence (p=0.005)
- Resistance
  - No patients infected after randomization developed resistance with K65R or M184V

iPrex Adherence Related to Infection Rates

	HIV+ N= 34		HIV – N = 43	
	Drug Detected	Drug Not Detected	Drug Detected	Drug Not Detected
≥50% pill use	8%	92%	54%	46%
< 50% pill use	14%	86%	0%	100%

iPrex

- Sexual Practices
  - No difference between the group
  - Condom use increased
    - ~50% to ~75% of patients using condoms
  - Number of anal receptive partners in last 12 weeks decreased
    - ~ 12 to ~5 partners
- Safety
  - Nausea and vomiting > in Truvada group ($p<0.001$)
  - Renal discontinuations > in Truvada group
    - 7 in Truvada group
    - 3 in Placebo group

iPrex: Overall Results

- 44% reduction in incidence in adult males
- Limited renal dysfunction seen in Truvada but significantly more than Placebo
- No resistance mutations seen in those infected during the study
- High-risk sexual behaviors decreased in both groups

Partners PrEP

- Population:
  - Men and Women ≥ 18 years of age
  - Discordant heterosexual couples
- Region:
  - Kenya and Uganda
- Intervention:
  - Tenofovir vs. Truvada vs. Placebo
  - Every 4 week visits
  - HIV-1 testing, drugs dispensed, medication collection, adherence counseling, high-risk behavior assessment, medical histories
- July 2008 – November 2012

Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367:399-410.

Partners PrEP

- 4747 HIV negative patients enrolled
- Infections:
  - 82 infected during enrollment
    - 13 in Truvada group
    - 17 in tenofovir group
    - 52 in Placebo group
    - 67% reduction in incidence: tenofovir ($p<0.001$)
    - 75% reduction in incidence: Truvada ($p< 0.001$)
- Resistance
  - No patients infected after randomization developed resistance with K65R or M184V

Partners PrEP
Adherence Related to Infection Rates

	Cohort of Truvada and Tenofovir Group	
	HIV + N =29	HIV – N = 198
Drug Detected	31%	82%

Partners PrEP

- Sexual Practices
  - No difference between the groups
  - Condom use increased
    - ~70% to ~90% of patients using condoms
- Safety
  - Similar GI toxicities seen in all groups
  - Renal discontinuations :
    - 1 in Tenofovir group
    - 0 in Truvada and Placebo group

Partners PrEP: Overall Results

- 67% reduction in incidence in adult male/female
- Limited renal dysfunction seen in Truvada/tenofovir
- No resistance mutations seen in those infected during the study
- High-risk sexual behaviors decreased in both groups

PrEP for African Women (FEM-PrEP)

- Population:
  - Women 18-35 years old
  - Women with 1 or more vaginal sex acts in last 2 weeks or more than one sex partner in previous month
- Region:
  - Kenya, South Africa, Tanzania
- Intervention:
  - Truvada vs. Placebo
  - Every 4 week visits
  - HIV-1 testing, pregnancy testing, toxicities, high risk behavior assessment/counseling, adherence counseling, drugs dispensed, medication collection, medical histories
- June 11, 2009 – April 15, 2011

FEM-PrEP

- 2120 HIV negative patients enrolled
- Infections
  - 68 infections during enrollment
    - 33 in Truvada group
    - 35 in Placebo group
    - Hazard ratio: 0.94 (p=0.81)
- Resistance
  - M184V/I mutation
    - 4 in Truvada group who were infected
    - 1 in Placebo group who were infected

Damme LV, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med 2012; 367:411-422.

FEM-PrEP
Adherence Related to Infection Rates

	Cohort of Truvada Group	
	HIV + N =27	HIV – N = 78
Drug Detected	26%	35%

FEM-PrEP

- Sexual Practices
  - No difference between the groups
  - Minimal reduction in # of partners: 0.14
  - Minimal reduction in vaginal sex acts: 0.58
  - Minimal reduction in sex without a condom use: 0.46
  - P<0.001 for all
- Safety
  - More nausea and vomiting seen in Truvada group (p=0.03)
  - Rise in SCr discontinuations :
    - 20 in Truvada group
    - 5 in Placebo group

FEM-PrEP: Overall Results

- 0.94 hazard ratio for Truvada
- Higher rates of renal dysfunction seen in Truvada group
- More M184V/I mutations seen in the Truvada group
- High-risk sexual behaviors decreased in both groups
- Study stopped early in April 2011 due to lack of efficacy

TDF2

- Population:
  - Men and Women 18-39 years of age
  - Discordant heterosexual couples
- Region:
  - Botswana
- Intervention:
  - Truvada vs. Placebo
  - Every 4 week visits
  - HIV-1 testing, pregnancy testing, toxicities, high risk behavior assessment/counseling, adherence counseling, drugs dispensed, medication collection, medical histories
- March 22, 2007 – October 23, 2009

Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. 2012;367:423-434.

TDF2

- 1219 HIV negative patients enrolled
- Infections:
  - 33 infected during enrollment
    - 9 in Truvada group
    - 24 in Placebo group
    - 62.2% efficacy with Truvada (p=0.03)
- Resistance
  - 1 patient in Placebo group had K65R

TDF2
Adherence Related to Infection Rates

	Cohort of Truvada Group	
	HIV +	HIV –
Drug Detected	2/4 patients	55/69 patients

TDF2

- Sexual Practices
  - No difference between the group
  - No change in condom use during study: ~80%
  - Number of sexual partners in last month decreased
    - ~1.2 to ~0.9
- Safety
  - Nausea and vomiting > in Truvada group ($p<0.001$/$p=0.008$)
  - Rise in SCr discontinuations :
    - 1 in Truvada group
    - 0 in Placebo group

TDF2: Overall Results

- 62.2% efficacy with Truvada
- No differences in SCr toxicities between groups
- No increase in resistance
- High-risk sexual behaviors decreased in both groups
  - Stable condom use
- Study stopped early due to low retention and logistics

Resistance with PrEP: For those exposed to Truvada/tenofovir

	Infected at enrollment		Infected during study	
	Resistance	No Resistance	Resistance	No Resistance
iPrex	2 (M184V, M184I)	0	0	36
Partners-PrEP	2 (K65R, M184V)	6	0	30
FEM-PrEP	1		4 (M184V, M184I)	33
TDF2	1		1 (K65R, M184V, A62V)	8

Resistance to Truvada

- M184V/I
  - Resistance to emtricitabine and lamivudine
  - Can decrease replicative capacity
  - Can increase susceptibility to tenofovir and zidovudine
  - May protect against development of K65R
  - With dual therapy
    - Resistance can occur in as low as 12 weeks
- K65R
  - Intermediate resistance to tenofovir, abacavir, lamivudine, emtricitabine
  - Increases susceptibility to zidovudine

- Is this risk of resistance low?
- Should we be worried about the rates of resistance in those identified HIV positive at enrollment?

Hurt CB, Eron JJ, Cohen MS. Pre-exposure prophylaxis and antiretroviral resistance: HIV Prevention at a cost? Clin Infec Dis 2011;53:1265-1270.

High-Risk Sexual Behavior

- No increase in high-risk behavior in any of the studies
  - Potential decline
- Qualitative study interviewing patients with the potential for PrEP
  - 64% indicated would increase sexual risk with PrEP
  - 60% would decrease condom use
- Can we provide the education and counseling to every patient at risk for HIV as done in all studies?

Brooks RA, Landovitz RL, Kaplan RL, et al. Sexual risk behaviors and acceptability of HIV Pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: a mixed methods study. AIDS Patient Care STDs 2012;26:87-94.

Provider Willingness

- "Compliance with this medication is the key to it working"
- "The challenge is identifying people who are at risk who will actually take the pills as prescribed"
- "..there is a big chasm between 'biologically working' and actually having people in the real world use it"
- "The use of this medication is not a license for unsafe sex and it's not a Saturday night special"

- Concerns by providers
  - Amount of adherence and high risk education provided in the studies
  - What is the high risk population?

Arnold EA, Hazelton P, Lane T, et al. A qualitative study of provider thoughts on implementing pre-exposure prophylaxis (PrEP) in clinical settings to prevent HIV infection. Plos One 2012;7:e40603.

Cost-Effectiveness of PrEP

- Cost of PrEP in MSM with high risk:
  - $298,000/QALY gained
  - $32,000/QALY gained
  - $50,000/QALY gained
- Cost of PrEP in 20% of all MSM in the US
  - $177,091/QALY gained
- Cost of PrEP in all MSM in the US
  - $216,480/QALY gained
- PrEP for all high risk MSM for 20 years
  - $75 billion more than…
  - Current $600,000 for every HIV infection prevented

Juusola JL, Brandeau ML, Owens DK, et al. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. Ann Intern Med 2012;156:541-550.

Cost-Effectiveness of PrEP

- Basically, the math doesn't add up
- Conclusion
  - PrEP needs to cost < $15/day to help all MSM patients
  - Current Cost:
    - $1149.01/month
    - $38/day

CDC Interim Guidelines

- Contraindicated in patients with unknown or positive HIV status
- Women and Men who are high risk from penile-vaginal sex
  - Truvada can used daily to reduce infections
- Discordant couples
  - Used as an option for prevention especially if trying to conceive
- Do not use if pregnant
  - Once pregnant discontinue PrEP

Future Considerations

- iPrEP
- Other medications with less systemic absorption
  - Gels
    - Tenofovir, efavirenz, raltegravir
- Targeted Population Cost-effectiveness studies
- How will insurance companies pay for this?

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