Status of Pre-Exposure HIV Prophylaxis (PrEP) -2008

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IF pre-exposure HIV prophylaxis is demonstrated to be effective for humans, ¿which one of the following patients would you consider the best candidate to receive a prescription?

a) An intravenous heroin addict
b) An 18 year old sex worker whom works alone on the streets of a city with a high rate of HIV seropositivity
c) A surgeon who asks for a prescription because he will be operating on a patient with advanced AIDS.
d) A 21 year old man who presents to a sexually transmitted disease clinic for treatment of his 4th episode of gonorrhea in the past year.
e) An HIV negative woman who is married to a hemophiliac man with asymptomatic HIV infection. They wish to have children.
f) I do not know, I'm coming to learn.

Why Pre-Exposure HIV Prophylaxis Should Be Considered

- Education and behavior modification have not worked.
- A vaccine is not yet available
- Precendents for pre exposure prophylaxis exist
  - Malaria
  - Post-coital antibiotics prevention of UTIs.
  - Penicillin to prevent streptococcal infections and Rheumatic fever
  - Surgical prophylaxis.

Pre-Exposure Prophylaxis

- Observation #1: antiretrovirals suppress HIV replication
- Observation #2: antiretrovrials administered to pregnant women prevent vertical transmission
- Observation #3: post-exposure prophylaxis prevents transmission to healthcare workers

Estimated Risk of HIV transmission (Eurosurveil)

• Needlestick	0.3%
• Receptive oral sex	0 - 0.04%
• Insertive vaginal sex	<0.1%
• Insertive anal sex	<0.1%
• Receptive vaginal sex	0.01-0.15%
• Receptive anal sex	<3%
• IDU sharing needle	0.7%

Non-Occupational Post Exposure Prophylaxis Protocols

- Extension of occupational prophylaxis
- **Guidelines:**
  - **Eurosurveillance monthly Archives, volume 9, Issue 6, June 2004**
    - **Stratifies by known HIV + source, unknown HIV status source**
    - **Stratifies by type of exposure**
    - **Regimen – two or three drug regimen.**

Animal Models of PrEP

- Utilize Macaque monkeys & SIV
- Most studied & favored agent: tenofovir
- Intra-rectal inoculation
- Intra-vaginal inoculation
- Single high-dose inoculation
- Multiple low-dose inoculations
- Correlates with human exposures presumed but unproven.

Simian Model Data

- Rhesus Macaque intra-rectal innoculation with single high dose Simian HIV
  - Reliable transmission 100% of animals infected.
- Relevance to the human experience?
  - Use of non-physiologic doses once
  - Human exposure typically to low amounts but repetitively

Experimental Animal Studies of PEP

- Tasi et al. - SIV infection prevented in Macaques with PMPA (R)-9-[2-phosphonylmethoxypropyl] adenine with PEP 24 after iv inoculation
- Bottiger et al. - 2,3'-dideoxy-3'hydroxy-methyl cytidine (BEA-005) showed similar protection.
- Otten et al showed protection in macaques exposed intravaginally to SIV with tenofovir at 12 & 36 h but with failure in 1 of 4 given tenofovir at 72 h

Refined SHIV/Macaque Model

Kim et al, J Med Primatol, 2006;35:210

- Simian-human immunodeficiency virus (SHIVSF162P3 - an R5-using, subtype B HIV-1 envelope) to study microbiocides
- Doses of 10 tissue culture infectious doses per exposure - approximately HIV in semen during acute HIV infection
- Control animals infected after 3-4 intravaginal exposures
- Experimental group - 3 of 4 animals uninfected after 12 exposures

Refined SHIV/Macaque Model

Kaizu et, JID, 2006

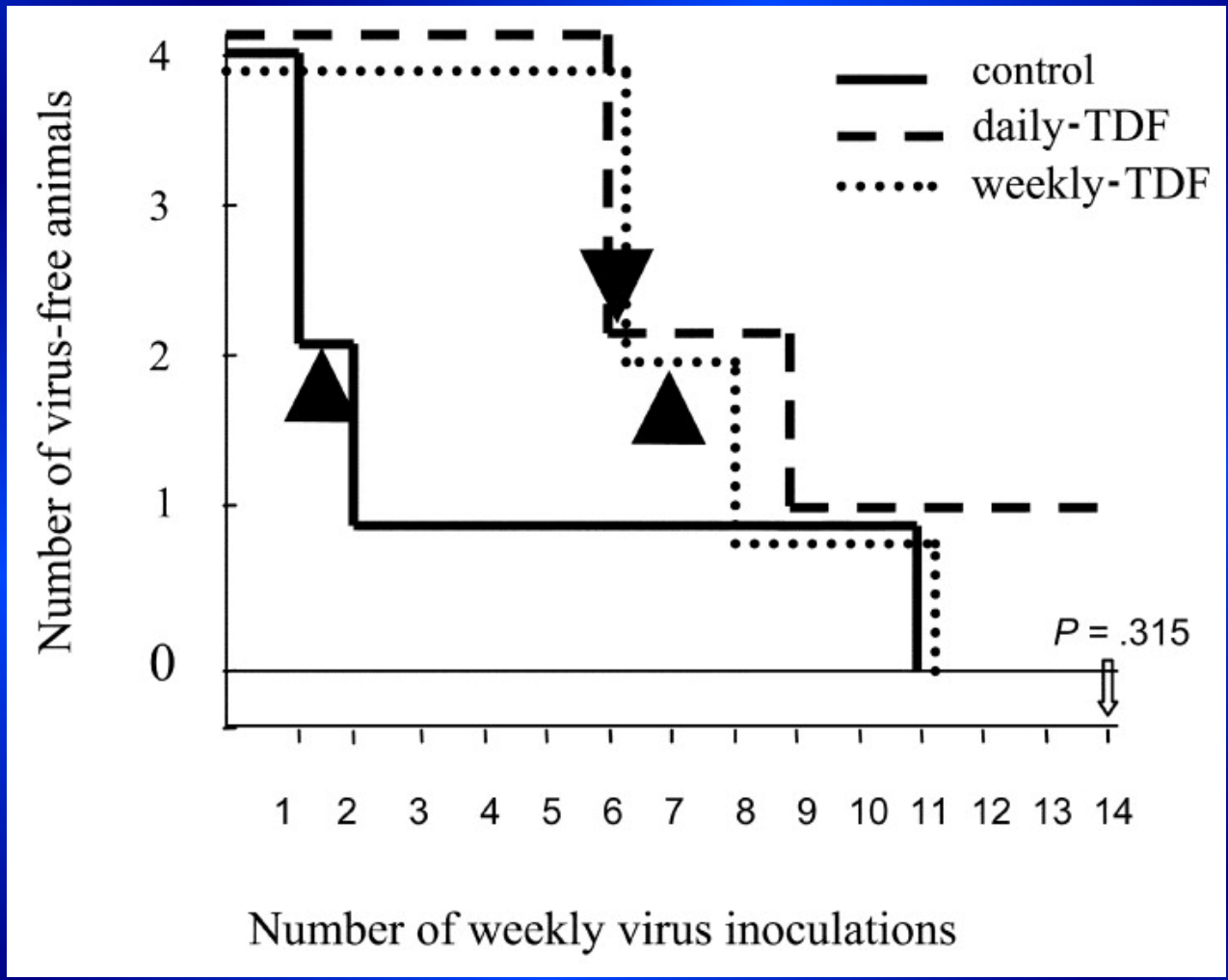
- Purpose: to develop a relevant animal model of intravaginal hiv transmission
- Attempted to match human experience
  - Semen contains both cell-free & cell-associated HIV
  - Men with urethitis have increased lymphocytes.
  - Women with vaginal inflammation/ulcers more vulnerable
- Results: Demonstrated transmission with repeated, low dose cell-associated HIV inoculations – in the absence of clinically apparent inflammation.

J Infect Dis. 2006 Oct 1

Chemoprophylaxis with Tenofovir Disoproxil Fumarate Provided Partial Protection against Infection with Simian Human Immunodeficiency Virus in Macaques Given Multiple Virus Challenges

Shambavi Subbarao,[1] Ronald A. Otten,[1] Artur Ramos,[1] Caryn Kim,[1] Eddie Jackson,[2] Michael Monsour,[1] Debra R. Adams,[1] Sheila Bashirian,[1] Jeffrey Johnson,[1] Vincent Soriano,[4] Ana Rendon,[4] Michael G. Hudgens,[3] Salvatore Butera,[1] Robert Janssen,[1] Lynn Paxton,[1] Alan E. Greenberg,[1] and Thomas M. Folks[1]

Subbarao et al: Survival Curve of 3 groups of 4 Macaques given weekly intrarectal inoculations of SHIV



Tenofovir for PrEP

- Several randomized placebo controlled trials to test Tenofovir alone or with FTC for PrEP among high risk populations (heterosexual, MSM and IDU) are underway in Africa, Asia and the USA.
- Data collected will include efficacy, development of resistance in sero-converters, adherence and changes in risk-behaviors.

Tenofovir for Pre-Exposure Prophylaxis (PrEP)

- Tenofovir- a reverse transcriptase inhibitor used in triple combination HIV treatment
- Is also combined with FTC, another reverse transcriptase inhibitor, in a single pill
- Once daily dosing, low incidence of side effects

Human Trials

- Several initiated, two terminated by activist objections.
- Single trial ungoing data with results expected later this year.
- On the basis of knowledge of human behavior, animal studies and pharmacokinetic information, one would predict a favorable outcome. However, full protection will not be found. Therefore, what will be the basis for recommending PrEP as standard of care?”

Off label and Unapproved uses of PrEP

- Reports of off- label prescriptions to high risk persons for use at circuit parties, sex clubs, etc., with ectasy and sildenafil
- This use could promote risky behaviors and contribute to drug resistance
- Clinical trial settings are placebo-controlled and all participants are counseled on proven prevention methods and frequently tested for HIV

Liu et al.JAMA. 2006.

Arguments Against Pre-Exposure HIV Prophylaxis

- Encourages risky behavior.
- Increases indiscriminate use of antiretrovirals -
  - Engenders false sense of security.
  - Increases risks for adverse reactions.
  - Abets emergence of antiretroviral strains.

The Two Perspectives

- **Primary Care Giver:**
  - **Protect the patient**
- **Public Health Official:**
  - **Protect society through cost effective preventive health measures**

Conclusions

- In theory, pre-exposure prophylaxis is a welcome addition to our efforts to reduce HIV transmission.
- In reality, utility will be limited to selected circumstances.
- Pending the outcome of ungoing studies, pre-exposure prophylaxis should not be used.
- Pre-exposure prophylaxis not yet (if ever) ready for prime time.

Risk for HIV Transmission
Cardo et al, NEJM, 1997

- Retrospective case control study
  - Factors associated with increased risk of transmission:
    - large inoculum (deep injury, hollow bore needle, needle had punctured a vein or artery, visible blood on instrument)
    - advanced stage of disease (high viral load &/or other factors)
  - **Zidovudine PEP decreased risk by ~ 80%**

Tenofovir for PrEP

- Pre-exposure to tenofovir decreases the risk of SIV transmission in macaque monkeys after rectal, vaginal and intravenous inoculation
- Newer studies have also shown efficacy of the combination of Tenofovir/FTC.
- There is no data to support single vs. combination agents

Liu et al. JAMA 2006

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