



Pharmacologic Strategies in HIV Prevention: Small Steps Toward HIV Control

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Disclosures

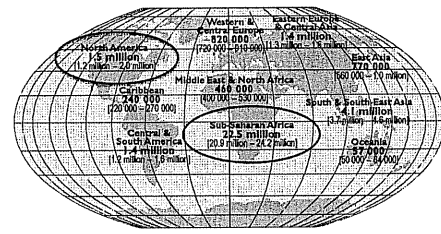
- Financial Conflict of Interest: None
- Unapproved Use of Drugs:
 - Tenofovir as Microbicide
 - Tenofovir and Tenofovir/Emtricitabine as Pre-Exposure Prophylaxis
 - Maraviroc as Microbicide

Objectives

At the end of the presentation, the audience should be able to:

- Discuss the reasons why new HIV prevention strategies are needed, in the US and globally
- Identify different ways where antiretroviral drugs can play a role in HIV prevention
- Discuss the benefits and limitations of the current studies using different antiretroviral-associated strategies

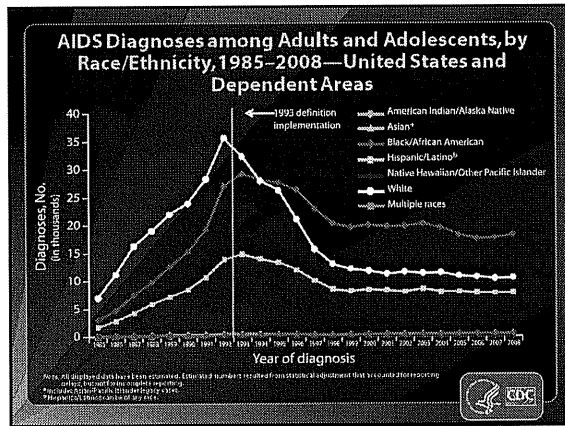
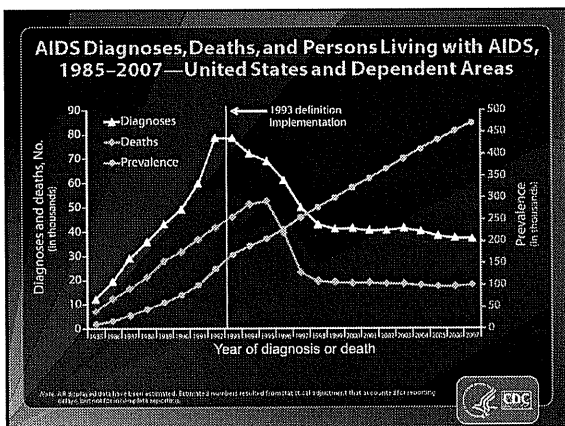
Adults and children estimated to be living with HIV - 2009



| Region | Estimated HIV Prevalence (in millions) |
|-------------------------------|--|
| Western & Central Europe | ~1.4 million |
| Eastern Europe & Central Asia | ~1.3 million |
| North America | ~1.3 million |
| Latin America | ~1.2 million |
| Caribbean | ~740,000 |
| Middle East & North Africa | ~440,000 |
| Central & South America | ~1.4 million |
| Sub-Saharan Africa | ~22.5 million |
| South & South-East Asia | ~4.1 million |
| East Asia | ~3.7 million |
| Oceania | ~377,000 |
| Other | ~50,000 |

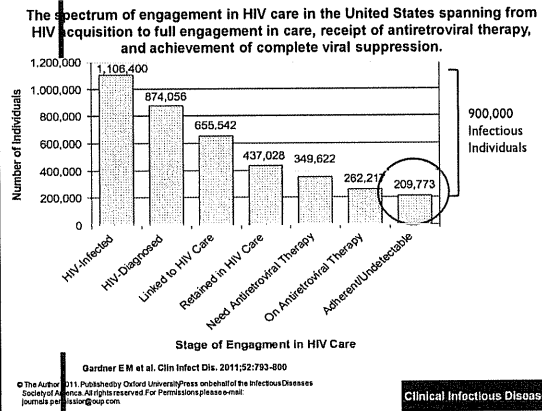
Total: 33.3 million [31.4 million – 35.3 million]

Source: WHO/UNAIDS 2011



30 Years of HIV – State of 2011

- HIV Treatment – Improves patient survival in the US and globally
- In the US,
 - 56,000 new infection/yr,
 - 16,000 deaths/yr –
 - net increase of 40,000 HIV-infected person/yr
- Many infected patients are unaware of their status
- HIV Vaccine - None
- Traditional prevention measures – not effective enough



Primary Goals

- Reducing HIV incidence
- Increasing access to care and optimizing health outcomes
- Reducing HIV-related health disparities

Effective HIV Prevention Strategies

| | |
|------------------------|---|
| Behavioral | Abstinence Be Faithful Reduction of high risk behavior Clean needle use |
| Biomedical | Condom use (>80% effective) Male circumcision (50-70% effective) Prevention & Treatment of STIs Blood product screening (>95% effective) Universal precaution |
| Informational | Public Education HIV Testing |
| Pharmacological | To be discussed |

Pharmacologic Strategies of HIV Prevention

ART for HIV (-) High Risk Individuals

- Post-Exposure Prophylaxis (PEP)
- Pre-Exposure Prophylaxis (PrEP)

Effective ART for HIV+ → ↓ HIV RNA → ↓ HIV transmission

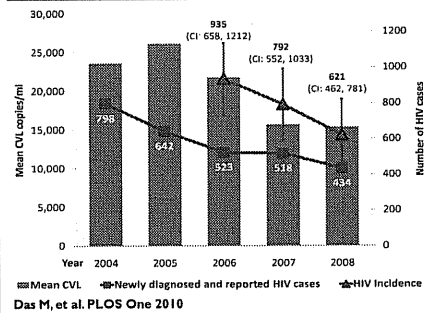
“Treatment as Prevention” - not a new concept, successes reported in –

- **Perinatal ART** in Pregnant HIV-infected women – prevention of mother-to-child HIV transmission
- **Maternal ART post-partum** – reduced transmission associated with breastfeeding
- **HIV discordant monogamous couples** in Uganda

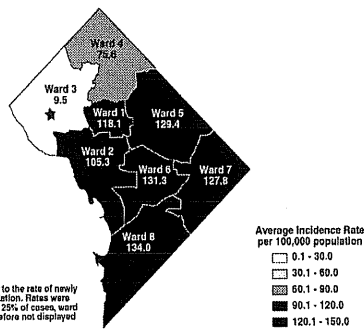
Test and Treat Concept

- Infected patients who are unaware of their status – more likely to engage in high risk behavior
- Risk of HIV transmission directly relates to amount of circulating HIV in the plasma & in genital tract
- Effective combination ART can significantly reduce HIV RNA
- Therefore, reduction in community viral load (CVL) may reduce “community HIV transmission”

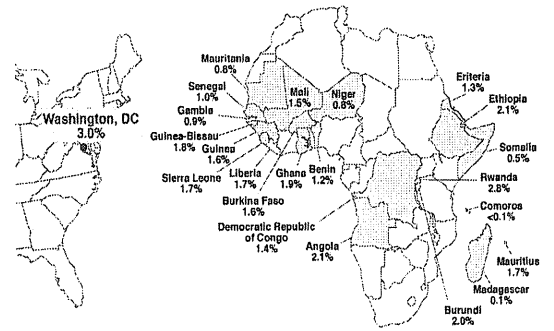
Lessons Learned from San Francisco - Decrease in HIV incidence following Reduction in CVL



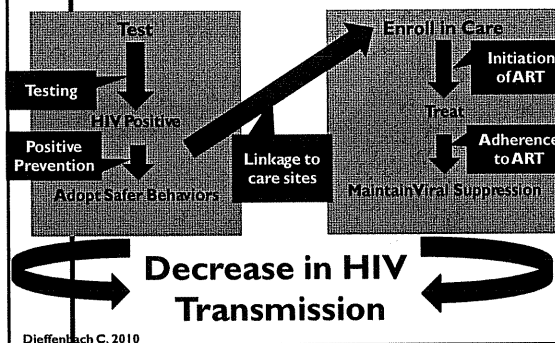
Average Annual Rate of AIDS Cases by Ward, Washington, DC 2001-2006



The HIV Prevalence Rate in Washington DC is Higher than in 22 Sub-Saharan African Countries



HPTN 065: TLC-Plus Study



Pharmacologic Strategies to Prevent HIV Acquisition

ART for HIV (-) High Risk Individuals

- **Post-Exposure Prophylaxis (PEP)**
Occupational Exposure
Sexual Exposure
- **Pre-Exposure Prophylaxis (PrEP)**
Putting the ownership on the high risk uninfected

Pharmacologic Strategies for HIV-Negative Individuals to Prevent HIV Acquisition

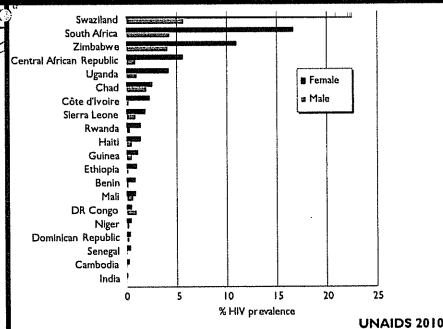
| | |
|------------------------------|---|
| WHO? | <ul style="list-style-type: none"> • High risk MSM & Transgender females • Commercial Sex Workers • Women in Countries with high rate of heterosexual transmission • Others ? |
| WHEN? | <ul style="list-style-type: none"> • Daily • Intermittent, Episodic (or "event driven") |
| HOW? | <ul style="list-style-type: none"> • Oral Antiretroviral Therapy • Local Application – Microbicide, Vaginal Ring, Injectable? |
| Other Considerations! | <ul style="list-style-type: none"> • Efficacy • Cost • Implementation |

Properties of ART Most Suitable for Prevention

- Relatively safe when given to a large population
- Long half-life
- Ease of administration
- Effective as treatment
- Low rate of resistance in the community
- Relatively inexpensive



HIV prevalence (%) among 15–24 years old, by sex, selected countries, 2005–2007



Topical Microbicides

- Female controlled intervention – local vaginal or anal application
- Several prior microbicides failed to show efficacy – nonoxynol-9, Pro2000

Ideal Properties for Drugs used as Microbicides

- Active against HIV
- No adverse effect to mucosal membrane
- Will not promote acquisition of other sexually transmitted infections

CAPRISA 004 – Tenofovir (TDF) 1% gel as Microbicide

[Abdool Karim Q, et al, Science Exp 2010]

| | |
|-------------------------------|--|
| Study Design | 2-arm, double-blind, randomized, placebo-controlled trial |
| Setting | 1 rural and 1 urban clinic in KwaZulu Natal, South Africa, HIV incidence 11.2% & 15.6% respectively |
| Subjects | HIV (-), sexually active (by vaginal intercourse) females, age 18-40 yr, non-pregnant, using a non-barrier form of contraception |
| Key Exclusion Criteria | Enrolment in other trials; CrCl < 50 mL/min; evidence of genital deep epithelial disruption |

CAPRISA 004 – TDF1% gel as Microbicide

[Abdool Karim Q, et al, Science Exp 2010]

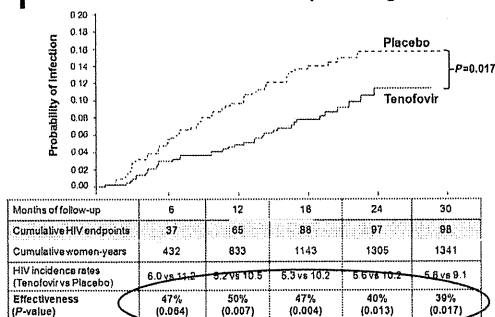
| | |
|----------------------------|--|
| Dosing Strategy | Insert one pre-filled applicator within 12 hrs before and repeat within 12 hrs after vaginal sexual intercourse, no more than 2 applications q24h |
| Other Interventions | •Comprehensive service – extensive counseling on HIV risk reduction, condom use, STI treatment, reproductive services •Use of TDF gel – held during pregnancy |
| Follow-up | •Monthly visits for HIV & pregnancy testing & counseling, adherence assessment. •Quarterly – HBV, HSV •S.Cr. – performed at month 3, 12, 24 |
| Study Period | March 2007 – March 2010 |

CAPRISA 004 – Results

Abdool Karim Q, et al, Science Exp 2010]

- 889 (611 rural, 278 urban) women
- 445 TDF, 444 Placebo, balanced in baseline characteristics
- Rural women – younger, poorer, less lifetime partners, lower condom use, lower HSV-2 prevalence
- Injectable contraception – commonly used
- Median follow-up 18 months

Fig. 2 Kaplan-Meier estimates of cumulative probability of HIV infection in the tenofovir and placebo gel arms.



Q Abdool Karim et al. Science 2010;320:1168-1174

Published by AAAS

Science

CAPRISA 004 Results

- High adherence (>80%) – associated with lower HIV incidence in TDF vs. Placebo group (54% effective, p=0.025)
- High TDF-DP conc. in cervicovaginal fluid – effective against both HIV & HSV-2
- Adverse effects – similar in both arms –diarrhea (TDF > placebo)
- No TDF-associated mutations seen in HIV-infected women
- Side benefit – 51% reduction in HSV infection

Lessons Learned, Remaining Questions, & Implication

- TDF 1% gel may be effective if adherent
- Small sample size – Can these results be replicated in other settings?
- Is the 2-dose strategy necessary?
- Despite extensive counseling & frequent follow-up, the HIV incidence is still very high
- Implementation of such intervention in the real world will be difficult

Other studies/modalities underway

Vaginal ring

- Dapivirine
- Dapivirine + Maraviroc


Long acting injectables


- Rilpivirine – monthly injection

Combination oral ART

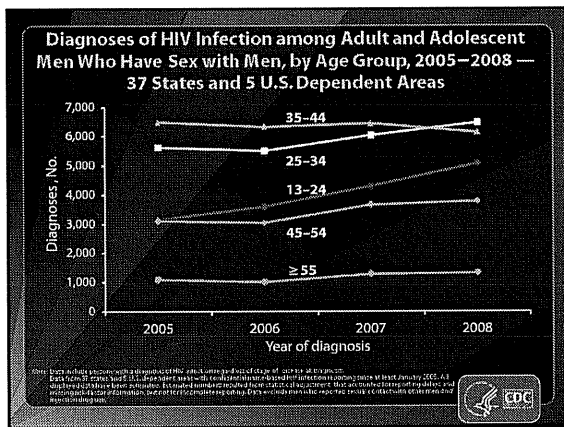
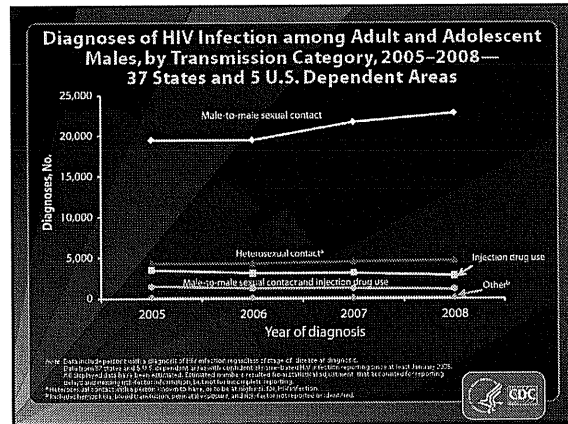
- Oral maraviroc +/- TDF/FTC

Daily Oral TDF/FTC as PrEP – Success & Failure





- High Risk MSM & Transgender Female
- 42% Efficacy
- High Risk Heterosexual Females from Africa
- Study stopped due to fertility



iPrEx Study – Rationale of Study Design [Grant RM, et al. NEJM 2010]

| | |
|-------------------------------|---|
| Animal Model | Mice & non-human primate studies – demonstrated efficacy of tenofovir (TDF) + emtricitabine (FTC) to protect against SIV acquisition (better than either alone) |
| Timing of Intervention | Given before and after exposure – important for maximum protective benefit |
| Choice of ART | Relatively safe; once-daily therapy |
| Study Population | High risk of HIV acquisition – therefore, high risk MSM and transgender females were chosen |

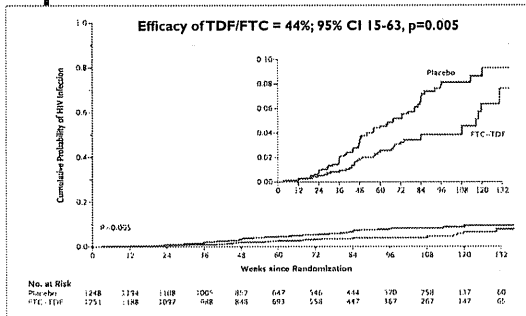
iPrEx Study [Grant RM, et al. NEJM 2010]

| | |
|------------------------|---|
| Study Design | Double-blind, randomized, placebo-controlled trial of TDF300/FTC200 vs. Placebo once daily |
| Countries | Brazil, Ecuador, Peru, South Africa, Thailand, US |
| Subjects | • HIV seronegative, ≥ 18 yo, male at birth • High risk sexual exposure with men • HBV screening, if susceptible, vaccinate |
| Study follow-up | • Every 4 weeks – HIV testing & counseling, drug refill, pill count, adherence counseling, condoms • At least every 12 weeks – Chemistry, CBC, physical exam, high risk history, STI screening |

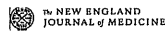
iPrEx Study Results [Grant RM, et al. NEJM 2010]

- 2,499 randomized:
 - 1,251 (TDF/FTC); 1,248 (placebo)
- 70% < 30 year old
- 83% from South America
- Only 10% from US (San Francisco, Boston)
- Median of 18 sexual partners in the past 12 weeks
- 13% (+) syphilis serology; 37% (+) HSV
- Median follow-up = 1.2 yr (max. 2.8 yr)

Results: Time to HIV Infection (Modified Intention-to-Treat Population).



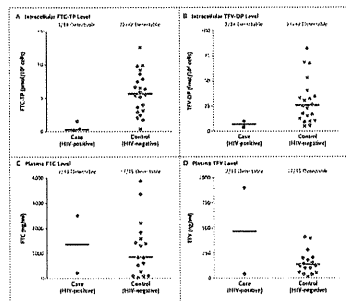
Grant RM et al. N Engl J Med 2010;363:2587-2597.



iPrEx – HIV-infection (Grant R, CROI 2011)

- Updated data - 131 infected: 48-TDF/FTC, 83- placebo (efficacy 42%, p=0.005)
- 10 subjects tested (+) at f/u, but later found to have detectable HIV RNA at enrollment – indicating acute HIV infection at screening
 - 2 in TDF/FTC, 8 in placebo
 - Both of the TDF/FTC patients had selected FTC-resistant mutations

Levels of Study-Drug Components in Blood of Subjects Receiving FTC-TDF, According to HIV Status.



Grant RM et al. N Engl J Med 2010;363:2587-2597.



iPrEx Results - Summary

- TDF/FTC given daily to high risk MSM – resulted in 42% reduction in HIV acquisition over a median of 1.8 yr f/u
- Subjects were followed monthly for HIV testing and prevention counseling
- TDF/FTC was well tolerated, lower bone mineral density in the TDF/FTC arm
- HIV acquisition – highly assoc. w/ non-adherent
- Testing with HIV antibody only missed 10 subjects with acute HIV infection

iPrEx – from study to practice?

| For | Against |
|-------------------------|--|
| • 42% efficacy in iPrEx | • only one RCT w/ only 10% of subjects from US |
| • relatively safe | • \$12,000 per year – who will pay for this? |
| • once daily dosing | • monthly HIV testing & STI counseling – not practical |
| | • Screening HIV Ab test – may miss acute infection & risk resistance |
| | • Risk of non-adherence, pill sharing, intermittent therapy |
| | • Unknown long term toxicities |



- TDF/FTC vs. Placebo - Trial began in 2009, enrolling high risk women in Kenya, South Africa, and Tanzania
- Overall HIV prevalence 21%
- Screened 3,752 women, 1,951 enrolled
- Data up till Feb 2011 – 56 new HIV cases identified – equal # of cases in each group
- April 18, 2011 - Interim review of Independent Data Monitoring Committee – recommended stopping the study because of futility

Trial Results
FEM-PrEP Pre-Exposure Prophylaxis for HIV

Why did TDF/FTC fail to prevent HIV transmission in high risk heterosexual women?

- Adherence?
- Differential penetration of TDF/FTC in rectal mucosa vs. vaginal mucosa ?
- Genetic or other reasons ?
- Will another ART combination work ?

Other Ongoing Oral PrEP Studies

- Oral TDF - in Injection Drug Users
- Oral TDF/FTC – in African discordant couples
- VOICE Study – oral TDF/FTC vs. oral TDF vs. Vaginal TDF daily
- Intermittent or “event-driven” PrEP

Summary

- Despite the success of ART in improving survival, majority of HIV-infected patients are not on therapy, therefore, serve as the source of further transmission
- Some prevention strategies are effective, if used consistently, obviously, this is not the case
- Testing, treating, and linkage to HIV care – can be a key method for transmission reduction

Summary (2)

Pre-exposure prophylaxis in high risk population –

- TDF 1% gel as Vaginal Microbicide –
 - 39% efficacious in high risk females in Africa
- Daily oral TDF/FTC –
 - 42% efficacious in high risk MSM & transgender females
 - No benefit in high risk females in Africa

Like Treating HIV Infected Patients, Many Issues Remain Concerning PrEP

- Adherence
- Cost
- Behavioral Modification
- Resistance
- Adverse Effects
- Follow-up HIV testing
- Health Disparity
- Implementation and Integration

Integrated HIV Prevention Strategies – The Only Way to Success

The diagram consists of four overlapping circles. The top-left circle is labeled 'Behavioral Modification'. The top-right circle is labeled 'Vaccine'. The bottom-left circle is labeled 'Biomedical'. The bottom-right circle is labeled 'ART as Prevention'. A black ribbon icon is located to the left of the title.