



Pharmacologic Strategies in HIV Prevention: Small Steps Toward HIV Control

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Disclosures

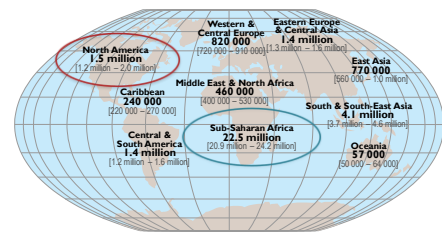
- Financial Conflict of Interest: None
- Unapproved Use of Drugs:
 - Tenofovir as Microbicide
 - Tenofovir and Tenofovir/Emtricitabine as Pre-Exposure Prophylaxis
 - Maraviroc as Microbicide

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

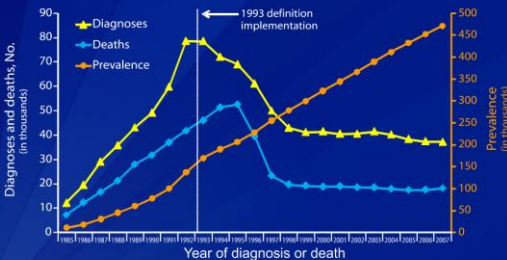
Adults and children estimated to be living with HIV - 2009



Total: 33.3 million [31.4 million - 35.3 million]

Source: WHO/UNAIDS 2011

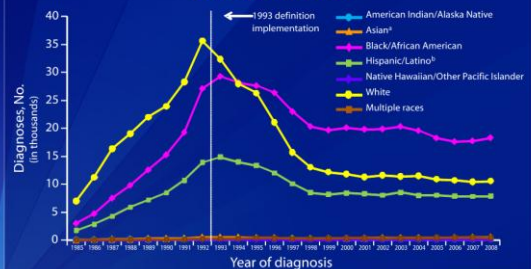
AIDS Diagnoses, Deaths, and Persons Living with AIDS, 1985-2007—United States and Dependent Areas



Note: All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.



AIDS Diagnoses among Adults and Adolescents, by Race/Ethnicity, 1985-2008—United States and Dependent Areas



Note: All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.

* Includes American Indian/Alaska Native, Asian, and Native Hawaiian/Other Pacific Islander.

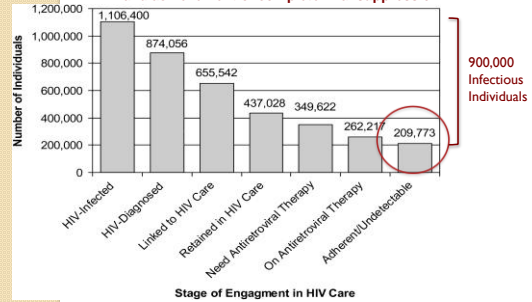
* Hispanic/Latino can be of any race.



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

The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to full engagement in care, receipt of antiretroviral therapy, and achievement of complete viral suppression.

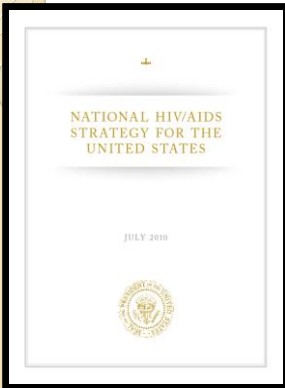


Gardner E M et al. Clin Infect Dis. 2011;52:793-800
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Clinical Infectious Diseases

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)



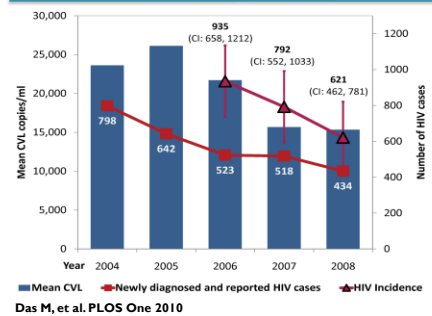
“Treatment as Prevention” - not a new concept, successes reported in –

- **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

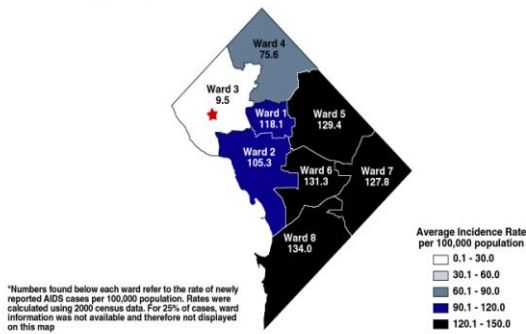
Test and Treat Concept

- 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”

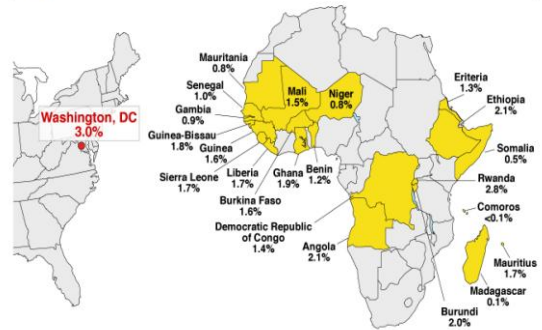
Lessons Learned from San Francisco - Decrease in HIV incidence following Reduction in CVL



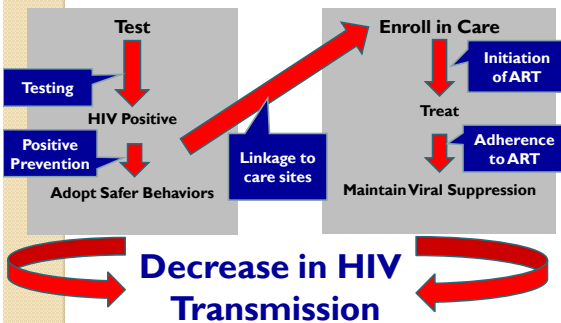
Average Annual Rate of AIDS Cases by Ward, Washington, DC 2001-2006



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

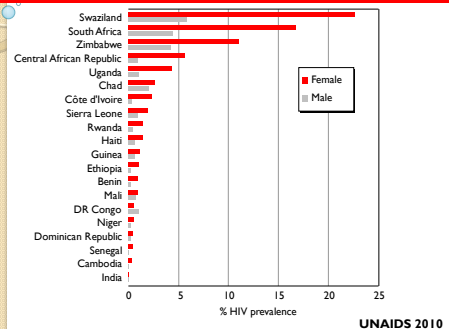
WHO ?	<ul style="list-style-type: none"> • High risk MSM & Transgender females • Commercial Sex Workers • Women in Countries with high rate of heterosexual transmission • Others ?
WHEN ?	<ul style="list-style-type: none"> • Daily • Intermittent, Episodic (or "event driven")
HOW ?	<ul style="list-style-type: 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 [Abdoal 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]

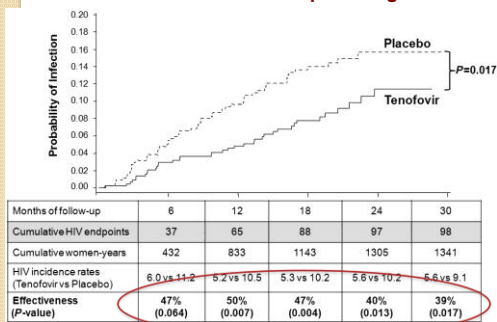
Dosing Strategy	Insert one pre-filled applicator within 12 hrs before and repeat within 12 hrs after vaginal sexual intercourse; no more than 2 applications q24h
Other Interventions	•Comprehensive service – extensive counseling on HIV risk reduction, condom use, STI treatment, reproductive services •Use 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.



© Abdool Karim et al. Science 2010;329:1168-1174

Science
Direct

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

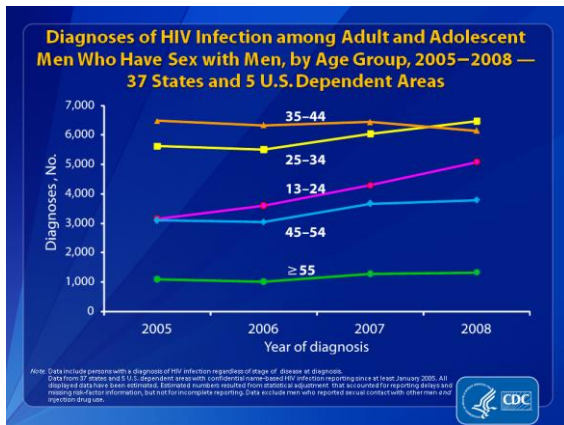
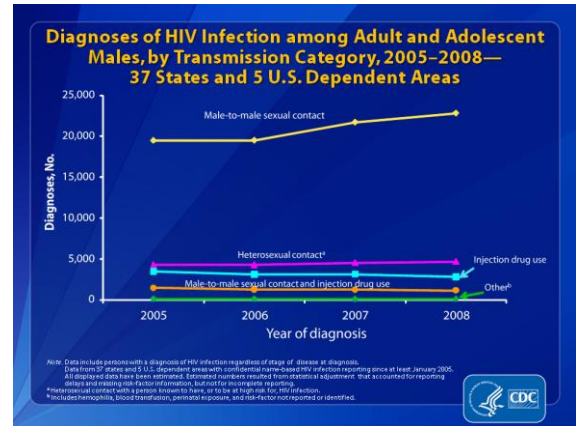
Combination oral ART

- 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

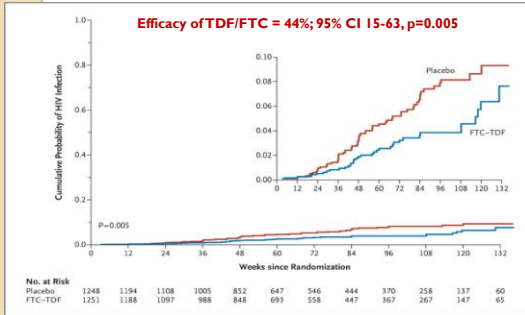
iPrEx Study [Grant RM, et al. NEJM 2010]

Study Design	Double-blind, randomized, placebo-controlled trial of TDF300/FTC200 vs. Placebo once daily
Countries	Brazil, Ecuador, Peru, South Africa, Thailand, US
Subjects	<ul style="list-style-type: none"> • HIV seronegative, ≥ 18 yo, male at birth • High risk sexual exposure with men • HBV screening, if susceptible, vaccinate
Study follow-up	<ul style="list-style-type: none"> • 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

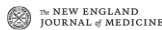
iPrEx Study Results [Grant RM, et al. NEJM 2010]

- 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).



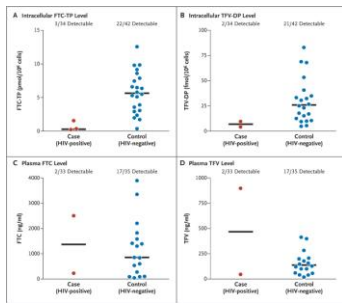
Grant RM et al. N Engl J Med 2010;363:2587-2599.



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;363:2587-2599.



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 fertility



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

