Combination Strategies for HIV Prevention

Thomas C. Quinn MD, MSc
Associate Director for International Research, NIAID
Director of Global Health, Johns Hopkins University

32 Years of AIDS
68 Million People Infected
34 Million Living with HIV
34 Million Deaths
Global Prevalence of HIV infection: 34 Million
Incidence 2.5 Million; 1.7 Million Deaths

Adult prevalence %
- 15.0% − 39.0%
- 5.0% − 15.0%
- 1.0% − 5.0%
- 0.5% − 1.0%
- 0.1% − 0.5%
- 0.0% − 0.1%
- not available

The HIV epidemic in 2012: 34.2 million infected

2.5 million new infections per year

19 million: will need ARVs in future

9.7 million treated

5.5 million need treatment, but have no access

1.7 million deaths per year

Source: UNAIDS 2012: “Together we will end AIDS”
The HIV epidemic in 2016: 40 million infected

![Pie chart showing the distribution of HIV treatment and need for ARVs.]

- 23 million will need ARVs
- 15 million treated
- 12 million need treatment, but have no access

Positive RCTs of HIV Prevention Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Circumcision (MC)</td>
<td>Orange Farm, S.A.</td>
<td>60% (32%-76%)</td>
</tr>
<tr>
<td></td>
<td>Rakai, Uganda</td>
<td>57% (25%-76%)</td>
</tr>
<tr>
<td></td>
<td>Kisumu, Kenya</td>
<td>53% (22%-72%)</td>
</tr>
<tr>
<td>Treatment as Prevention (TasP)</td>
<td>HPTN 052</td>
<td>96% (73%-99%)</td>
</tr>
<tr>
<td>Pre-Exposure Prophylaxis (PrEP)**</td>
<td>CAPRISA 004 (TDF Topical)</td>
<td>39% (6%-60%)</td>
</tr>
<tr>
<td></td>
<td>iPrEx (TDF/FTC Oral, MSM)</td>
<td>44% (15%-63%)</td>
</tr>
<tr>
<td></td>
<td>Partners PrEP (TDF Oral)</td>
<td>62% (34%-78%)</td>
</tr>
<tr>
<td></td>
<td>Partners PrEP (TDF/FTC Oral)</td>
<td>73% (49%-85%)</td>
</tr>
<tr>
<td></td>
<td>CDC (TDF/FTC Oral)</td>
<td>63% (22%-83%)</td>
</tr>
</tbody>
</table>

*1 vaccine and 1 STI trial omitted due to conflicting evidence (STI) and infeasibility (vaccine).
**3 Negative Arms (FEM-PrEP (FTC/TDF); TDF pill and gel arms of VOICE)
Combination HIV Prevention

AIDS Free Generation = Prevention of Mother to Child Transmission of HIV
Biological Factors affecting Perinatal Transmission of HIV

Maternal

Placental

Fetal

Duration of Ruptured Membranes

C-Section

HIV-1 RNA

ART Rx

Breast Feeding

ART Rx

Stage 3 (AIDS) Classifications among Perinatally Infected Persons, 1985–2011—United States and 6 Dependent Areas

Year of diagnosis

Diagnoses, No.

Aged <13 years

Aged ≥13 years

Note: All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
Coverage of antiretroviral medicine for preventing mother-to-child transmission: most effective regimens, low- and middle-income countries, by region, 2011

Source: UNAIDS. Together we will end AIDS 2012

HIV Sexual Transmission
Treatment as Prevention in Rakai

- Impact of antiretroviral therapy on HIV transmission among 250 HIV discordant couples in Rakai, 2004-2009

- 42 HIV transmissions occurred among 218 couples not on ART over 459.4 person years, incidence: 9.2/100 py (95% CI 6.59-12.36)

- No HIV transmissions occurred among the 32 couples in whom the index partner was on ART over 53.6 py (>90% efficacy; \( p = 0.0097 \))

- No perinatal transmissions since introduction of ARVs to pregnant women

Reynolds, Quinn et al, AIDS, 2010
HPTN 052 Study: Key Finding

1,763 sero-discordant couples (97% heterosexual) HIV infected partners: 890 men, 873 women

39 HIV Transmissions

28 linked HIV transmissions
11 unlinked

Immediate ART:
1 transmission

Deferred ART:
27 transmissions

96% Protection

Effect of ART coverage on rate of new HIV infections in a rural South African population

For every 10% increase in coverage there is a 17% decrease in individual risk

Proportion of all HIV-infected people receiving ART (CD4 ≤ 200)

Source: Tanser F et al. Science Feb 22, 2013
Increase in Life Expectancy following ARV Introduction

Could widespread use of combination antiretroviral therapy eradicate HIV epidemics?

J X Velasco-Hernández, H B Geraehdeun, and S M Blower

Modelling the effect of combination antiretroviral treatments on HIV incidence

Matthew G. Law, Garrett Prestage, Andrew Grulich, Paul Van de Ven, and Susan Kippax

Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M. Gwinnich, Charles F. Gils, Christopher Dye, Kevin M. De Cock, Brian G. Williams

A Mathematical Model of Comprehensive Test-and-Treat Services and HIV Incidence among Men Who Have Sex with Men in the United States

Stephen W. Sorensen, Stephanie L. Sansom, John T. Brooks, Gary Marks, Elizabeth M. Begier, Kate Buchacz, Elizabeth A. DiNenno, Jonathan H. Mermin, Peter H. Kilmarx
### Combination HIV Prevention

- **Treatment as prevention**
- **PrEP**
- **PMTCT**
- **STI treatment**
- **Male circumcision**
- **Microbicides**
- **Testing/counseling**
- **Education**
- **Drug/alcohol treatment**
- **Condoms**
- **Harm reduction**
- **Blood screening**

### Number of People Receiving Antiretrovirals in Low- and Middle-Income Countries

- 840,000 AIDS-related deaths were averted by ART in 2011

**Source:** UNAIDS. 7/2012
WHO 2013: Updated Treatment Guidelines for Adults, Adolescents, and Children

- **Expanded ART eligibility**
  - Treatment initiation threshold: CD4+ ≤ 500 cells/mm³
  - Prioritize severe or advanced HIV or CD4+ ≤ 350 cells/mm³

- **Viral load testing preferred for monitoring ART**

- **Preferred initial regimen:** fixed-dose TDF + 3TC (or FTC) + EFV
  - Discontinue use of d4T due to toxicity


---

**Proportion of HIV-Infected Individuals in the United States at Each Stage of Care**

<table>
<thead>
<tr>
<th>Stage of Care</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
<td>80%</td>
</tr>
<tr>
<td>HIV-diagnosed</td>
<td>72%</td>
</tr>
<tr>
<td>Linked to HIV care</td>
<td>62%</td>
</tr>
<tr>
<td>Retained in HIV care</td>
<td>41%</td>
</tr>
<tr>
<td>On antiretroviral therapy</td>
<td>36%</td>
</tr>
<tr>
<td>Suppressed viral load (&lt;200 copies/ml)</td>
<td>28%</td>
</tr>
</tbody>
</table>

Source: CDC. 11/2011
Key areas for optimization in the cascade

• Expand, simplify and diversify HIV testing
• Offer concrete interventions in the pre-ART window
• Use simple and better drugs for first- and second-line
• Provide diagnostic tests and monitoring tools at point-of-care
• Innovate service delivery to enhance adherence and retention

HIV Care Cascade: Local Influence
King County, Washington vs US

King County estimates account for in- and out-migration of persons living with HIV/AIDS.
Linkage to care: CD4/HIV-1 RNA report or confirming a completed medical appointment.
HIV Acquisition among Male Partners of HIV + Female Partners By Circumcision Status In Rakai

40/137 uncircumcised men (16.7/100 py) vs. 0/50 of circumcised men became infected after two+ years (p = 0.004).

Quinn et al NEJM 2000
Medical Male Circumcision

Adult Male Circumcision Provides Long-Lasting Protection Against HIV Infection in Rakai, Uganda

Cumulative Probability of HIV Infection

73% Effectiveness

Gray et al. *AIDS*, 2012

A.S. Fauci/NIAID
Effective prevention interventions have not been brought to scale

Goal:
~ 20 million by 2016

Total MCs through 2011:
~1.35 million, 6.5% of target

Male circumcisions performed annually in 14 priority countries in eastern and southern Africa

Source: WHO

Combination HIV Prevention

Treatment as prevention
PMTCT
STI treatment
Male circumcision
Microbicides
PrEP
Testing/counseling
Education
Drug/alcohol treatment
Condoms
Harm reduction
Blood screening

A.S. Fauci/NIAID
Oral PrEP: Mixed Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM – iPrEx (Americas, Thailand, SA)</td>
<td>42%</td>
</tr>
<tr>
<td>Heterosexual discordant couples –</td>
<td>75%</td>
</tr>
<tr>
<td>Partners PrEP (Kenya, Uganda)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women – TDF2</td>
<td>62%</td>
</tr>
<tr>
<td>(Botswana)</td>
<td></td>
</tr>
<tr>
<td>Women – FEM-PrEP (Kenya, SA, Tanzania)</td>
<td>0%</td>
</tr>
<tr>
<td>Women – VOICE (SA, Uganda, Zimbabwe)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Plasma Tenofovir Detection in Random Cohort Sample

- FTC/TDF
- TDF
- Tenofovir 1% Gel

Level of TFV detection
\geq 0.3 \text{ ng/ml}
PrEP (like ART) works when taken

<table>
<thead>
<tr>
<th></th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP FTC/TDF arm</td>
<td>81%</td>
<td>75%</td>
</tr>
<tr>
<td>TDF2</td>
<td>79%</td>
<td>62%</td>
</tr>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>26%</td>
<td>6%</td>
</tr>
<tr>
<td>VOICE</td>
<td>20%</td>
<td>0%</td>
</tr>
</tbody>
</table>

There is a clear dose-response between evidence of PrEP use & efficacy

Grant et al N Engl J Med 2010

PrEP (like ART) works when taken

There is a clear dose-response between evidence of PrEP use & efficacy

Efficacy increases with better adherence

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>49%</td>
</tr>
<tr>
<td>&gt;67%</td>
<td>54%</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>58%</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>68%</td>
</tr>
<tr>
<td>&gt;95%</td>
<td>72%</td>
</tr>
<tr>
<td>&gt;97.5%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Martin M for Bangkok Tenofovir Study, IAS, 2013
Total HIV-1 Transmission Events: 38

- **ASPIRE** ~3500 women in Malawi, South Africa, Uganda, Zambia, and Zimbabwe
- **The Ring Study (IPM 027)** ~1,650 women in South Africa, Rwanda, and Malawi

HPTN 052: Lots of “Uncoupled” Transmissions

- Linked Transmissions: 29
- Unlinked Transmissions: 9

Immediate Arm: 1
Delayed Arm: 28

Up to 30%-50% of new infections in couples occur outside the primary relationship (Campbell et al PLoS One 2011; Hughes et al. J Infect Dis 2011; Grabowski et al CROI 2013)
Estimated proportion of transmission in 2011 in cohabiting couples caused by extra-couple intercourse, by Country

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesotho</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swaziland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimbabwe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion of transmission

Bellan SE et al Lancet 2013

Transmission Dynamics in Rakai

- Geospatial relationship of HIV cases (n=1,786)
  - GPS household location
  - Sexual partnership data
  - Viral genetic relatedness

Grabowski, CROI 2013
Transmission Dynamics in Rakai

- 39% of transmissions occurred in stable household partnerships
- 20% unknown sources
- 40% were from known extra-household contacts
  - 62% of these were non-stable partners from outside the community.

- Significant amount of viral introductions
- Localized key populations (fishermen, FSW etc) may have major effect on regional HIV transmission

Grabowski, CROI 2013

Mobility of Fishing Villagers

- Lwamaggwa 12%
- Buyamba 10%
- Kibale-Rakai 13%
- Katana 12%
- Lwanda 11%
- Kališizo 15%
- Kabira 14%
- Kyotera 16%
- Kasasa-Sanje 14%
- Kakuuto 20%
- Kasensero 40%

To Masaka and Kampala
TasP not associated with reductions in HIV incidence among MSM in UK

- 40,000 HIV+ UK MSM
  - 26% undiagnosed
  - 80% of diagnosed MSM on ART (84% with CD4>350)

Access to & retention in care >95% from 2001-2010

**BUT** HIV incidence still climbing because

- Risk behavior and increasing STIs
- Low annual testing (only 15 – 25%) among MSM ages 15-59
- Undiagnosed 60%-80% transmissions
  - 62% of undiagnosed infective (VL >1500 copies/ml)
  - 34-60% transmissions due to primary HIV infection in first few months of infection

**Early Syphilis Incidence per 100,000 Among MSM by HIV Status, King County, WA 1997-2012**

- In 2011, 4.1% of all HIV+ MSM were diagnosed with early syphilis
- Syphilis rate in HIV+ MSM was >17x higher than in HIV- MSM

Golden M unpublished data
Combination Prevention
Multiple disciplines and approaches

Future Effects of Combination Prevention

Cremin I, et al AIDS 2013
### Prevention with Positives

- HIV testing, linkage to care and prevention services
- Antiretroviral therapy
- Retention in care and adherence
- Partner services
- Risk reduction interventions and condoms
- STD screening and treatment
- Perinatal transmission interventions

### Prevention with Negatives

- Condom distribution
- Behavioral risk reduction interventions and condoms
- Pre-exposure prophylaxis (PrEP)
- Microbicides
- STD screening and treatment
- Post-exposure prophylaxis

### Not focused on HIV status

- Social mobilization
- Condom availability
- Substance use, mental health, and social support

### What’s different about these approaches?

- Focuses on **packages of interventions**, and the synergies and antagonisms across interventions
- Considers the **combination**, differential uptake and sustainability of interventions
- Includes interventions that modify **social determinants** of morbidity
- **Includes planning**, modeling and research into “required and achievable coverage” or reach of interventions
- Prioritizes evaluation and **operational research** on implementation of interventions
- Considers issues of **resource expansion**, advocacy, and mobilization
Conclusions

• Global progress on scale-up of ART has been extraordinary and the target of 15 million can be reached by 2015 with the right resources

• Further scale-up must address disparities and inequities (countries, key populations)

• Countries face strategic choices and should take advantage of new opportunities of treatment and prevention (early ART, TasP, PrEP) in combination

• ARVs for treatment and prevention are a powerful tool towards ending the HIV epidemic, but only if adherence to medication and behavioral change are emphasized.

Acknowledgments

LIR
Tony Fauci
Steve Reynolds
Oliver Laeyendecker
Andrew Redd
Aleisha Collingsworth-Streng
Sarah Wendel
Andrew Longosz
Samantha Conroy
Kevin Newell

Rakai
David Serwadda
Nelson Sewankambo
Fred Wabwire-Mangen
Tom Lutalo
Fred Nalugoda
Godfrey Kigozi
Noah Kiwanuka
Ronald Galiwango

RML
Craig Martens
Stacy Ricklefs
Steve Porcella

Johns Hopkins
Ron Gray
Maria Wawer
Aaron Tobian
Jordyn Manucci
Kate Grabowski
Caroline Mullins
Xianrong Kong
Ben Amour

DIR
Kathy Zoon
Karyl Barron
Mark Pineda
Joe Shott