HIV Viral Transmission Kinetics: Lessons from Rakai

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Rakai, Uganda

- Epicenter of HIV epidemic in Uganda (Serwadda Lancet 1985)
- HIV prevalence 35% in trading centers in 1988
- RCCS started in 1994
- ART available in 2004 (PEPFAR), now 2000 on HAART
- Annual Household survey 12,000 to 15,000 subjects / year
- Blood samples on > 60,000 different individuals
- Identified ~1500 HIV seroconverters
Structure of the Rakai Health Sciences Program

Human Subjects Review Boards (Uganda, US), Community Advisory Board

Observational Research (Qualitative/Quantitative)
- ARV effects in the community on HIV epidemiology and behaviors
- HIV epidemic trends
- Behaviors
- Circumcision and HIV
- Hormonal contraception and HIV
- Condoms and HIV/STDs
- VCT impact
- Coercion/violence, alcohol and HIV
- Ethics research
- Demographic of HIV (mortality, fertility, marital stability, orphanhood)
- HIV vaccine preparedness

Randomized Trials
- STD control for HIV prevention
- STD control to improve pregnancy outcomes
- Male circumcision for HIV/STD prevention in men
- Male circumcision: safety and effects in HIV+ men, women and the community
- HSV 2 suppression

Operations Research
- Nevirapine pMTCT
- Cervical cancer/HPV
- VCT
- Family planning
- Adolescent health

Rakai Community Cohort Study

Basic science
- HIV subtypes
- HIV genomics
- Immunology
- Microbiology

Molecular epidemiology
- HIV transmission dynamics
- Resistance to ARV drugs
- HSV-2, HHV-8, Malaria/TB
- STDs

Time trend analyses
- HIV/STD incidence and prevalence
- Behaviors
- Morbidity, mortality, fertility

Clinical care
- OIs
- ARVs
- STD treatment
- General health care
- Provision of safe circumcision

Training
- Uganda
- USA
Viral load Predicts Heterosexual and Perinatal Transmission

**Figure 1.** Mean (+SE) Rate of Heterosexual Transmission of HIV-1 among 415 Couples, According to the Sex and the Serum HIV-1 RNA Level of the HIV-1-Positive Partner.

At baseline, among the 415 couples, 228 male partners and 187 female partners were HIV-1-positive. The limit of detection of the assay was 400 HIV-1 RNA copies per milliliter. For partners with fewer than 400 HIV-1 RNA copies per milliliter, there were zero transmissions.

Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda

- **No Genital Ulcer Disease**
- **Genital Ulcer Disease**

Source: Gray et al., *Lancet* 2001;257:1149
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, 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 transmissions

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

Source: Tanser F et al. Science Feb22, 2013
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; Gray et al AIDS 2000
Randomised controlled trials of male circumcision to reduce HIV infection

Rakai, Uganda
Gray et. al. (2007) Lancet; 657 – 66

Kisumu, Kenya
Bailey et. al. (2007) Lancet; 643 – 56

Orange Farm, South Africa
Auvert et. al. (2005) PLoS Med; e298
Medical Male Circumcision
Adult Male Circumcision Provides Long-Lasting Protection Against HIV Infection in Rakai, Uganda

73% Effectiveness

HR=0.27 (95%CI 0.16-0.44)

Gray et al. AIDS, 2012
## Protective Efficacy of MC for STIs

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>FEMALE PARTNERS</th>
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<tbody>
<tr>
<td></td>
<td><strong>GUD</strong></td>
<td><strong>GUD</strong></td>
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<tr>
<td>•</td>
<td>RR = 0.53 (0.43-0.64)</td>
<td>RR = 0.78 (0.63-0.97)</td>
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<tr>
<td>•</td>
<td><strong>HSV-2</strong></td>
<td><strong>Trichomonas</strong></td>
</tr>
<tr>
<td>•</td>
<td>RR = 0.72 (0.56-0.92)</td>
<td>RR = 0.52 (0.05-0.98)</td>
</tr>
<tr>
<td>•</td>
<td><strong>Pro-inflam anaerobes</strong></td>
<td><strong>Severe BV</strong></td>
</tr>
<tr>
<td>•</td>
<td>RR = 0.28 (P=0.014)</td>
<td>RR = 0.39 (0.24-0.64)</td>
</tr>
<tr>
<td>•</td>
<td><strong>HPV</strong></td>
<td><strong>HPV</strong></td>
</tr>
<tr>
<td>•</td>
<td>RR = 0.65 (0.46-0.90)</td>
<td>RR = 0.72 (0.60-0.85)</td>
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</tbody>
</table>

HSV-2 infection enhances HIV acquisition due to increased inflammation. HIV and HSV-2 dual infection have an inverse effect on CD4 cell density, but a synergistic effect on CD8 cell density in the foreskin.

Redd et al, JID 2011
Timing and Kinetics of Mucosal Transmission
HIV transmission per coital act by stage of infection

Transmission per 1,000 coital acts

Months after index partner seroconversion

Incident infections

Latent infections

AIDS

Wawer et al. *JID* 2005
Transmission Pairs

HIV Status by Year

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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Male Partner</td>
<td>+</td>
<td>n/a</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Female Partner</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Prevalent partner sequence similarity to infecting strain of incident partner

Year difference of prevalent partner sample compared to incident partner's time point of infection

Proportion Divergent

0.04

0.03

0.02

0.01

0.00

-3

-2

-1

0

Redd et al JID 2012
Genetic bottleneck during transmission of HIV

Transmission

Re-emergence of viral diversity

Diverse virus population in chronically infected "donor"

As HIV Diverges from the Founder to the Chronically Replicating Virus It Accumulates N-linked Glycosylation Sites

Sagar M, et al. JID 2009
Impact of HIV Subtype on Transmission and Disease Progression

<table>
<thead>
<tr>
<th>HIV-1 subtype</th>
<th>Adjusted RR* (95%CI)</th>
<th>Trans/Total</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>1.98 (1.17 – 3.34)</td>
<td>15 / 31</td>
</tr>
<tr>
<td>D</td>
<td>1 (referent)</td>
<td>59 / 194</td>
</tr>
</tbody>
</table>

*Covariates included age, GUD, condom use, male circumcision, sex frequency, stage of infection and viral load

Kiwanuka et al *AIDS* 2009

Subtype on Progression

![Graph showing the impact of HIV subtype on disease progression.](image)

Log rank p=0.038

Subtype on Transmission

Kiwanuka et al *JID* 2009

Population Subtype Change

Conroy et al *AIDS& Hum Ret* 2010
Transmission Dynamics in Rakai

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

Grabowski et al, 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 et al, CROI 2013
Mobility of Fishing Villagers

- Lake Victoria
- Lake Kijjanebola
- Highway
- Paved road
- All weather Murran
- Tracks
- Swamp

- Lwamaggwa 12%
- Buyamba 10%
- Kibale- Rakai 13%
- Lwanda 11%
- Katana 12%
- Kalisizo 15%
- Kasasa-Sanje 14%
- Kabira 14%
- KaKuuto 20%
- Kasensero 40%

To Masaka and Kampala

- Tanzania
- Masaka
- Farming village
- Per-urban village
- Fishing village

Map showing the mobility of fishing villagers to Masaka and Kampala.
Combination Prevention
Multiple disciplines and approaches

- Biomedical Interventions
- HIV/STI Testing & Linkage to Care
- Individual & Small Group Interventions
- Community Interventions
- Structural Interventions

Combination prevention

Adapted from Coates Lancet; 2008
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