Reassessment of HIV-1 Acute Phase Infectivity

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Conclusion: HIV-1 acute infectivity has been substantially overestimated.
Outline

1. Relevance: Treatment as Prevention (TasP)

2. Measuring excess infectivity with $\text{EHM}_{\text{acute}}$

3. Literature review of past estimates

4. Re-estimation of $\text{EHM}_{\text{acute}}$ from viral load

5. Re-estimation of $\text{EHM}_{\text{acute}}$ from the Rakai cohort
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Treatment as Prevention (TasP)

Treated HIV-infected individuals transmit 96% less than untreated HIV-infected individuals

Cohen et al. (2011). *NEJM*. 
Treatment as Prevention (TasP)

model fit to South African data

adapted from Granich et al. (2009). Lancet.
Treatment as Prevention (TasP)

adapted from Granich et al. (2009). Lancet.
Universal Testing and Treatment

adapted from Granich et al. (2009). Lancet.

cluster randomized controlled trials underway
Will “Test and Treat” work?

- Logistics
- Uptake and adherence
- Drug Resistance
- Early Transmission

How much transmission happens before diagnosis and treatment?
What proportion of transmission occurs early?
What proportion of transmission occurs early?

\[
\frac{\text{biological infectivity}}{\times} \frac{\text{sexual contacts with susceptible partners}}{=} \text{rate of new infections generated}
\]
What proportion of transmission occurs early?

\[ \text{biological infectivity} \times \text{sexual contacts with susceptible partners} = \text{rate of new infections generated} \]

\[ \text{acute phase} \rightarrow \text{chronic phase} \]

\[ \text{time since infection} \]

?
What proportion of transmission occurs early?

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What proportion of transmission occurs early?

\[
\text{rate of new infections generated} = \left( \text{biological infectivity} \right) \times \left( \text{sexual contacts with susceptible partners} \right)
\]
What proportion of transmission occurs early?

\[
\begin{align*}
\text{(biological infectivity)} \times \\
\text{(sexual contacts with susceptible partners)}
\end{align*}
\]

\[=\]

rate of new infections generated

\[time\ since\ infection\]

\[acute\ phase\]

\[chronic\ phase\]

behavioral volatility

high concurrency

serial monogamy

?
What proportion of transmission occurs early?

\[ \frac{\text{biological infectivity}}{\text{sexual contacts with susceptible partners}} = \text{rate of new infections generated} \]
What proportion of transmission occurs early?

\[
\text{(biological infectivity)} \times \text{(sexual contacts with } \text{susceptible partners)} = \text{rate of new infections generated}
\]

? 

- acute phase
- chronic phase
- behavioral volatility
- high concurrency
- serial monogamy

\[\text{AF}_{\text{early}} \quad \text{infections missed by TasP} \]

tested, treated, virally suppressed

time since infection
Estimates of $AF_{\text{early}}$: proportion of transmission < 1 yr post-infection

Cohen et al. (2011). *NEJM.*
What proportion of transmission occurs early?

\[
\text{rate of new infections generated} = \text{(biological infectivity)} \times \text{(sexual contacts with susceptible partners)}
\]

- Acute phase
- Chronic phase
- Behavioral volatility
- High concurrency
- Serial monogamy

???

\[\text{AF}_{\text{early}} \quad \text{infections missed by TasP}\]

- Tested, treated, virally suppressed

Time since infection
What proportion of transmission occurs early?

Here, we focus only on biological infectivity.
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What affects biological infectivity?

\[
\text{(viral load)} \times \text{(per virion infectivity)}
\]
What affects biological infectivity?

\[
\text{biological infectivity} = \text{acute phase} \times \left\{ \begin{array}{l}
\text{viral load} \\
\text{per virion infectivity}
\end{array} \right\}
\]
What affects biological infectivity?

Maybe recently transmitted virus is more infectious?

Evidence from macaque-SIV

Ma et al. (2009). *Virology*. 
What affects biological infectivity?

Maybe recently transmitted virus is more infectious?

Evidence from macaque-SIV
Ma et al. (2009). *Virology*. 
What affects biological infectivity?

Assume constant strain infectivity for now.
Infectivity-Viral Load Relationship

2.5X infectivity / log10 viral load

hazard
(per 100 person–years)

viral load
(HIV RNA copies/ml)
Let’s take the average viral load trajectory

Viral Load
(log10 cp/ml)

days post-infection

Let’s take the average viral load trajectory
Determining a biological infectivity profile

All previous studies assumed discrete phases...
Determining a biological infectivity profile

All previous studies assumed discrete phases...

2.5X infectivity
log10 viral load
Determining a biological infectivity profile

All previous studies assumed discrete phases...

![Graph showing HIV RNA levels over time](graph1.png)

- HIV RNA (copies/ml)
  - Days since first RNA positive

![Graph showing relative hazard over time](graph2.png)

- Relative hazard (versus chronic phase)
  - Days since first RNA positive
  - Hazard-months
Determining a biological infectivity profile

![Graph showing HIV RNA levels and relative hazard over time.](image)

- HIV RNA (copies/ml)
- Days since first RNA positive

- Excess hazard-months attributable to acute phase
  
  \[ EHM_{\text{acute}} = (9-1) \times 3.1 \]
Determining a biological infectivity profile

- **HIV RNA (copies/ml)**
  - Days since first RNA positive:
    - 0
    - 50
    - 100
    - 150

- **Relative hazard (versus chronic phase)**
  - Days since first RNA positive:
    - 0
    - 50
    - 100
    - 150

- Excess hazard-months attributable to acute phase:
  - $EHM_{acute} = 25$
compare to 120 hazard-months during 10 years of infection

$EHM_{\text{acute}} = 25$
$\text{EHM}_{\text{acute}}$

25 compare to 120 hazard-months during 10 years of infection

comparable across different acute phase durations
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Estimating $\text{EHM}_{\text{acute}}$ Indirectly

- Viral load trajectories

- Fast epidemic growth explainable by
  - early transmission

Variation in $\text{EHM}_{\text{acute}}$ Estimates

Compare to 120 chronic phase hazard-months
Variation in $\text{EHM}_{\text{acute}}$ Estimates

Compare to 120 chronic phase hazard-months

(1) Jacquez et al. 1994
(2) Pinkerton and Abramson 1996
(3) Koopman et al. 1997
(4) Kretzschmar & Dietz 1998

Based on epidemic curve

$\text{EHM}_{\text{acute}}$
Variation in $EHM_{\text{acute}}$ Estimates

Compare to 120 chronic phase hazard-months
Variation in $EHM_{\text{acute}}$ Estimates

Directly measured once by the Rakai Community Cohort Study, Uganda

Compare to 120 chronic phase hazard-months
Variation in $EHM_{\text{acute}}$ Estimates

Directly measured once by the Rakai Community Cohort Study, Uganda

Most commonly cited estimates

$EHM_{\text{acute}} = 35$ and $71$

Compare to 120 chronic phase hazard-months
Why reevaluate $\text{EHM}_{\text{acute}}$ estimates?

- Viral Load
  
  Continuous trajectory instead of discrete phases

- Rakai Retrospective Cohort Study

  Biases due to (1) unmodeled heterogeneity
  (2) study design
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Determining a biological infectivity profile

Continuous trajectory to avoid overestimation

Graph 1: HIV RNA (copies/ml) vs. days since first RNA positive

Graph 2: Relative hazard (versus chronic phase) vs. days since first RNA positive
Determining a biological infectivity profile
Determining a biological infectivity profile

- **Graph 1:**
  - **Y-axis:** HIV RNA (copies/ml)
  - **X-axis:** Days since first RNA positive
  - **Trend:** Initial peak followed by a decline

- **Graph 2:**
  - **Y-axis:** Relative hazard (versus chronic phase)
  - **X-axis:** Days since first RNA positive
  - **Legend:** Excess hazard-months attributable to acute phase = 5.6 (95% CI: 3.3–9.1)
Variation in $\text{EHM}_{\text{acute}}$ Estimates

excess hazard-months attributable to acute phase = 5.6 (95% CI: 3.3–9.1)

Based on:
- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetcs

Our estimate: 5.6
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Direct Measurement of Acute Infectivity

- Identify recently infected individuals
- Observe rate at which they infect sexual partners
  - Must be switching between partners
  - Moral imperative to intervene

Very challenging and only done once!
In a prospective population cohort study 1994-1999 retrospectively identified 235 stable couples observed serodiscordant at least once

*Do individuals infect their partners at different rates early vs. later in infection?*

Wawer et al. (2005). *Journal of Infectious Disease.*
The Rakai Retrospective Cohort Study

- seronegative partner
- seropositive partner
- censored (loss to follow-up, couple dissolution, or study end)

chronic

prevalent

months of follow-up
The Rakai Retrospective Cohort Study

- **Prevalent**
- **Chronic**

- **Seronegative partner**
- **Seropositive partner**
- ? Censored (loss to follow-up, couple dissolution, or study end)

![Diagram showing follow-up months with seronegative and seropositive partners, and chronic cases.](image-url)
The Rakai Retrospective Cohort Study

Acute

Incident

Chronic

Prevalent

36/161 seroconverted

- Seronegative partner
- Seropositive partner
- ? Censored (loss to follow-up, couple dissolution, or study end)

Months of follow-up

0 10 20 30 40
The Rakai Retrospective Cohort Study

Suggestive of HIGH acute infectivity

- Acute:
  - 13/23 seroconverted
  - Seronegative partner
  - Seropositive partner
  - ? censored (loss to follow-up, couple dissolution, or study end)

- Chronic:
  - 36/161 seroconverted

months of follow-up
The Rakai Retrospective Cohort Study

Suggestive of HIGH acute infectivity

$$\text{EHM}_{\text{acute}} = 35 \text{ to } 71 \text{ depending on analysis}$$
Concluded acute infectivity >>> expected based on viral load

$EHM_{acute} = 35$ to $71$ depending on analysis
Heterogeneity in Transmission Rates

- Host genetics (e.g. CCR5)
- Circumcision
- Viral load of infected partner
- Viral genotype of infected partner
- Coital Rate
- Intercourse type (anal, dry, vaginal)
- Condom usage
- STIs
- Coinfections
- Nutrition
Bias 1: Unmodeled Heterogeneity

“Naïve” Couples. Some are high risk

Persistently serodiscordant. Selected to be low risk
Bias 1: Unmodeled Heterogeneity

Average risk acutely infected partners

Low risk chronically infected partners

Unmodeled heterogeneity might bias EHM_{acute} upwards
Bias 2: Inclusion Criteria

HIGH acute infectivity

incident

prevalent

13/23 seroconverted

36/161 seroconverted

? censored (loss to follow-up, couple dissolution, or study end)

months of follow-up
Bias 2: Inclusion Criteria

HIGH acute infectivity

LOW acute infectivity

incident

[Diagram showing incidence with arrows indicating transition from seronegative to seropositive partners.]

13/23 seroconverted

? censored (loss to follow-up, couple dissolution, or study end)

prevalent

[Diagram showing prevalence with arrows indicating transition from seronegative to seropositive partners.]

36/161 seroconverted

0 10 20 30 40

months of follow-up
Bias 2: Inclusion Criteria

HIGH acute infectivity

LOW acute infectivity

Accidentally excluded couples suggestive of low infectivity
Simulating Rakai Transmission & Observation

1. Simulate transmission in couples cohort
2. Replicate Rakai study design
3. Apply published analyses to simulated data.

Input \( EHM_{\text{acute}} \)

Estimated \( EHM_{\text{acute}} \)
Couple Transmission Model

example relationship history

Couple Transmission Model

Couple Transmission Model

- Premarital transmission
- Extramarital transmission
- Marital transmission

Stage-dependent transmission

RH\textsuperscript{stage}
Couple Transmission Model

Heterogeneity

\[ Z_{M,i} \sim \text{logNormal}(1, \sigma_{\text{hazard}}) \]
Simulating Rakai Transmission & Observation

1. Simulate transmission in couples cohort
2. Replicate Rakai study design
3. Apply published analyses to simulated data.

Estimated EHM_{acute}
Simulating Rakai Transmission & Observation

Bias Analysis

Estimates = Input Parameters ?
If not, what drives bias?

Estimation with ABC-SMC
What inputs generate data like the actual Rakai data?
Bias Analysis

Adjusted Poisson Regression  Unadjusted Survival Model

estimated EHM_{acute}  input EHM_{acute}
Bias Analysis

Adjusted Poisson Regression

Unadjusted Survival Model

estimated EHM\textsubscript{acute}

input EHM\textsubscript{acute}

upwards biased
downwards biased

upwards biased
downwards biased
Bias Analysis

Adjusted Poisson Regression

Unadjusted Survival Model

estimated $\text{EHM}_{\text{acute}}$

input $\text{EHM}_{\text{acute}}$
Variation in $EHM_{\text{acute}}$ Estimates

Most commonly cited estimates

$EHM_{\text{acute}} = 35$ and $71$

Based on:
- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics

Our estimate

$EHM_{\text{acute}}$
Variation in $\text{EHM}_{\text{acute}}$ Estimates

Most commonly cited estimates

$\text{EHM}_{\text{acute}} = 35$ and $71$

Bias-adjusted $8.4$ $\text{EHM}_{\text{acute}}$
Viral load & Rakai estimates reconciled by adjusting for biases.
Early proportion of transmission $AF_{\text{early?}}$
What about \( \text{AF}_{\text{early}} \)?

Our estimates

\[ \text{EHM}_{\text{acute}} \]

based on

- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics
Conclusions

• Acute infectivity *not* significantly greater than expected by viral load-infectivity relationship

• Both EHM_{acute} estimates <<< previous estimates

• Role of early transmission likely overestimated

• Acute HIV less likely to undermine TasP

**Simulation of study design & observation to identify biases**
• Simulation of transmission and study design/analysis

• Arose from GA Tech Modeling Conference in Jan 2015

• In collaboration with CDC (Lopman, Gambhir, Vaccine Team)

• Ethical & statistical merits of Stepped Wedge vs RCT

• EVD incidence declining & spatiotemporally variable
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Title: Reassessment of HIV-1 Acute Phase Infectivity

Attribution:

Code: https://github.com/sbellan61/AcuteRetroSim

For further information or slides in Microsoft Powerpoint please contact Steve Bellan (steve.bellan@gmail.com).