TnT – Understanding the impact on HIV: what we know and what we need to know

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Plan

• How to measure indirect effects?
  – From efficacy to effectiveness
• Sensitivity of predictions to efficacy and behaviour change & case study
• The role of acute infection
• Conclusions
Efficacy & effectiveness

VCT/behaviour
Reduced concurrency
Male circumcision
ART therapy
ART PrEP, PEP

<table>
<thead>
<tr>
<th>Not yet available</th>
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<tr>
<td>Vaccines</td>
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<td>Microbicides</td>
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Bacterial STIs
HSV
Co-infections

Estimates of EFFICACY exist for each of these

(Almost) no direct estimates of EFFECTIVENESS exist

Attribution in combination
Difficulty in separating effect from secular trends
Effectiveness is measured over many years

Modelling can be used to explore different scenarios
Law of increasing returns

![Graph showing the relationship between HIV prevalence and the Basic Reproductive Number, R0.](image-url)
How to account for multiple exposures?

protected

Some time later...
Joint interventions:
Consider both interventions separately

![Graph showing the relationship between Basic Reproductive Number (R0) and HIV Prevalence (%). Points [A] and [B] are marked on the graph.](image-url)
Epidemiological synergy

HIV Prevalence (%) vs Basic Reproductive Number, R0

[A] and [B] indicate points of synergy.
Testing the TnT model

Untreated HIV +ve

- Do nothing
- Standard care
- Universal

On treatment

- Universal
- Standard care

Assumptions
- Testing once per year
- 99% reduction in infectiousness
- High take-up rates
- High adherence, low failure (Malawi)

Model structure
- 2 Simple model structures, needs testing
- Empirical approach to ‘sexual mixing’
- Does not address logistical constraints
- No model or statistical uncertainty

Granich et al – Lancet 2009
Many questions

- Logistics, acceptability, ethics
- When to treat? – Do we need to treat acute HIV?
- Does ARV treatment *fully* block transmission?
- How strong is the link between viral load & transmission?
- How does a population respond to universal ART?
- How sensitive are the results to different assumptions
- Drug resistance?
- Even within assumptions, is it optimal use of resources?
Meta-analysis of efficacy

Efficacy of 92% (67%-98%)

Attia et al – AIDS 2009
Effect of varying efficacy of ARV (1)

\[ \lambda = \lambda_0 \exp\left(-\alpha P^n\right) \]

Model adapted from Granich et al, Lancet 2009
Effect of varying efficacy of ARV (2)

\[ \lambda = \lambda_0 \exp\left(-\alpha P_{\text{treat}}^n\right) \]

Model adapted from Granich et al, Lancet 2009
Changes in risk behaviour (1)

\[ \lambda = \lambda_0 \exp(-\alpha P^n) \]

Model adapted from Granich et al, Lancet 2009
Changes in risk behaviour (2)

\[ \lambda = \lambda_0 \exp\left(-\alpha P_{\text{treat}}^n\right) \]

Model adapted from Granich et al, Lancet 2009
Effect of varying efficacy of ARV (3)

\[ \lambda = \text{constant} \]

Model adapted from Granich et al, Lancet 2009
More sensitivity analysis

Comparing 90% and 99% efficacy, and different duration of survival on ART
1. Population with little variation in risk and random mixing.

2. Population with strong variation in risk and partly restricted mixing

(dots shows same intervention – 80% coverage of ART initiation within 1 year of infection)
Lines show isoclines in reduction in incidence in these populations.
From Dodd, Garnett and Hallett – AIDS in press
Even more sensitivity analysis

‘Voluntary universal testing and treatment is unlikely to lead to HIV elimination: a modeling analysis’

B.G. Wagner and S. Blower, Nature Preprints 2009
Population response to treatment

• Assuming ART blocks transmission, how does population respond?
• Case study: resurgent European epidemics
• Cautious extrapolations, but lessons can be learnt
• Monitor effect of intensified diagnosis & treatment policies

Bezemer et al AIDS 2008, and Epidemics to appear
Situation in European MSM

Surveillance on HIV MSM diagnoses from HIV Monitoring Foundation, HPA
Robert Koch Institute, Swiss Federal Gov’t
Ecological study – MSM in Netherlands

HIV amongst MSM infected in the Netherlands – Bezemer et al AIDS 2008
Estimated parameters

Bezemer et al AIDS 2008 and Epidemics in press
Hypothetical Scenarios

Important to contrast with British Columbia – Montaner results

No antiretroviral therapy:
- 5080 new diagnoses since 1995
- 9996 new diagnoses since 1995 (up 97%)

No Behaviour Change:
- 5996 new diagnoses since 1995
- 4272 diagnoses since 1995 (down 16%)
Epi context: Stages of infection

10^7 10^6 10^5 10^4 10^3 10^2 10 1

Primary/ Acute

Viral load

DIAGNOSIS

SAFE SEX & ARVs

Asymptomatic

Pre-AIDS, AIDS

~weeks/months 2-12 years 2-3 years
Outlook in European MSM

• Analysis suggests ART and behaviour change amongst untreated individuals have offset each other
  – Huge benefit, but epidemic growth
• Monitor over next few years, Time to diagnosis has been falling
  – Potential to test TnT in setting with good infrastructure
• Alternative explanations:
  – ART ineffective at blocking transmission (<90%)
  – Increases in infectiousness (STIs, evolution...).
Parameters from Rakai discordant study

Random mixing (high risk subpopulation)

Serial monogamy

Concurrent partnerships??

Hollingsworth, Anderson & Fraser, J Infect Dis 2008
Acutes in generalized epidemic

- From doubling time of the epidemic (or growth rate, $r$), and generation time (time from infection to onwards transmission), can estimate $R_0$

$$R_0 = \frac{1}{\int \omega(r) \exp(-rt) dt}$$

Acutes in generalized epidemic (2)

Doubling time 1.22 years, growth rate $r=0.56$ per year
Acutes in generalized epidemic (4)

\[ R_0 = \frac{(1 + rd_{\text{acute}})(1 + rd_{\text{set}})(1 + rd_{\text{aids}})}{f_{\text{acute}}(1 + rd_{\text{set}})(1 + rd_{\text{aids}}) + f_{\text{set}}(1 + rd_{\text{aids}}) + f_{\text{aids}}} \]

An epidemic dominated by acute infection is easier to control.
When to intervene?

- In generalised epidemics, with serial monogamy, standard diagnosis may be very effective.
- In high risk populations, may need to diagnose acute infections.
- Role of (clusters of) concurrent long-term relationships needs to be studied further, need more data and more maths.
  - (Morris & Kretzchmar 1997, Halperin & Epstein)
Conclusions

• Expect the unexpected in extrapolating efficacy to population effectiveness (herd effects, synergies, redundancies)
• WHO TnT model sensitive to efficacy assumptions, and encodes strong behaviour change assumptions
• No consensus yet between different model structures, but other models may be less sensitive to assumptions
• Better understanding of varying epidemiological context
  – Are there ‘bridging scenarios’ with high role of acutes in generalised epidemic?
  – Need detailed simulations and plausible rules of thumb
• Integrative statistical framework for incorporating disparate sources of data and new evidence (e.g. SMC-ABC)
Conclusions (2)

• Some other TnT models suggest conclusions may be more robust than an analysis of Granich et al suggests

• Need an understanding of the interplay between efficacy of ART and behavioural dis-inhibition in WHOLE at risk population
Acknowledgments

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Tom Quinn
Oliver Laeyendecker
The End
Does treatment block transmission?

- So far: dependence on stage of infection, and viral load.
- Does ART effectively block transmission?
- Direct evidence, in couples, is limited (N<600).
- Recent evidence from couples in Uganda, Zambia & Rwanda add to the evidence (CROI ’08 and ‘09).
- HPTN-052 will, in time, provide more evidence (N=1,750).
HIV amongst MSM infected in the Netherlands – Bezemer et al AIDS 2008
Hypothetical Scenarios

- No Behaviour Change: 5080 new diagnoses since 1995
- No antiretroviral therapy: 9996 new diagnoses since 1995 (up 97%)
- No ART, No Behaviour Change: 4272 diagnoses since 1995 (down 16%)

Bezemer et al, POSTER 1019; Van Sighem et al, POSTER 1020
Outlook in European MSM

• Analysis suggests ART and behaviour change amongst untreated individuals have offset each other.

• Monitor over next few years, Time to diagnosis has been falling

• Alternative explanations:
  – ART ineffective at blocking transmission (<90%)
  – Increases in infectiousness (STIs, evolution...)
Viral load set-point (with aside)

- No advantage (long-term) in targeting high VL
- Has virus evolved to maximize transmission?
- Most common viral loads, most infectious
- Tested idea of transmissible viral factors by comparing viral loads in 54 transmitting couples in Rakai, Uganda.
- Explains $R^2=27\%$ of VL variability (Hollingsworth et al, Poster 496)

Fraser et al, PNAS 2008
Transmission rate & viral load set-point

Caution when extrapolating this to very low viral loads
(Wilson et al, Lancet 2008)

Fraser et al, PNAS 2008
Discordant couples studies

Stratified by risk factors:
- Viral load
- STI
- Circumcision
- Acute infection
- ART

Discordant couple:

The low viral load paradigm

Garcia et al, NEJM 1999
The low viral load paradigm

No transmitters with low viral load

Fidel et al, AIDS Res Human Retr 2000 (ZAMBIA)
Variable viral load set-point

No transmitters with low viral load
Many non-transmitters with high viral load

Fideli et al, AIDS Res Human Retr 2000
Transmission potential

Fraser et al, PNAS 2008
Baggaley et al AIDS 2009
The low viral load paradigm

*Blips, Adherence, Treatment Failures, Mode of Transmission, Mucosal/Genital VL*

- Antiretroviral therapy
- Low peripheral blood viral loads
- Low rates of transmission

Need direct assessment

*Powers et al, Lancet Infect Dis 2008*
Transmission rate & viral load set-point

Caution when extrapolating this to very low viral loads
(Wilson et al, Lancet 2008)

Fraser et al PNAS 2008
Predictions: CD4 count at diagnosis

Data

Model
When to intervene?

Serial monogamy – frequent partner change (right axis)
Random mixing – high risk group (left axis)

Cumulative # people infected

Years since infection

Intervention

Hollingsworth, Anderson & Fraser, J Infect Dis 2008 - Garnett & Baggaley, Lancet 2009
Measures of efficacy, on transmission

Prevention acts on transmission
Efficacy, and a transmission chain

Protecting one individual has indirect protective effects on others

Effectiveness > Efficacy

<100% Efficacy can lead to 100% Effectiveness

(the HERD effect)
How to account for multiple exposures?

protected

Some time later...
Population level analysis

1. No protection
2. Some protection
3. Full protection

Cluster randomised trial
Mathematical models
Joint interventions:
Consider both interventions separately

![Graph showing HIV prevalence vs. Basic Reproductive Number, R0]