Modeling Transmission Dynamics of HIV/AIDS: Some Results & Challenges

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Outline

- Introduction
- Modelling Control Strategies
  - ARVs
  - Male Circumcision
  - Imperfect Prophylactic Vaccine
- Modelling HIV Co-infection
  - HIV-TB
  - HIV-Malaria
- Conclusions and Current Challenges
HIV: Facts and Figures


- Modes of Transmission: sexual, needle-sharing, blood transfusion, vertical etc;

- Global Statistics:
  - Accounts for $\approx$ 20 million deaths;
  - 34-46 million people live with HIV; 30% unaware of infection status.

- Inflicts severe public health & socio-economic burden.
  - Economic burden due to HIV-related death or disability in 50 countries (US, Russia, 5 in Asia, 8 in Latin America, and 35 in sub-Saharan Africa) during 1992–2000 estimated at $25 billion (Fleck, 2004).
Typical Course of HIV Disease

- Plasma concentration levels
  - HIV antibodies
  - CD4+ T cells
  - Virus

Timeline:
- 2 - 10 weeks
- Up to 10 years
Control Mechanisms

(i) Therapeutic: Anti-retroviral Drugs (ARVs)
- Drawback: resistance development (spread of resistant HIV);
- Not widely accessible in some resource-poor nations with high HIV prevalence;

(ii) Preventive:
- Abstinence;
- “Be faithful”;
- Correct and consistent use of condoms;
- Education and counseling about safer sex practices;
- Voluntary testing, screening of blood products and use of sterilized needles;
- Use of a vaccine;
- Male circumcision.
Modeling the Impact of ARVs

- Anti-retroviral drugs (ARVs), particularly HAART, have had dramatic impact in curtailing HIV burden;
  
  ▶ use of ARVs, over long periods of time, reduces the viral loads in HIV-infected individuals to non-detectable levels
  
  ▶ reduce infectiousness; extends life and quality of life

- ARVs not widely accessible globally
Implementation Strategies of ARVs

(i) Universal:
- ARVs administered to all infected individuals
- popularly used (success story in Brazil)
- could lead to emergence and transmission of ARV-resistant HIV

(ii) Targeted (viral-load or CD4-dependent):
- treat only those with low CD4 count (< 200 cells/ml) (individuals with such low CD4 count are at pre-AIDS or AIDS stage; high viral loads);
- strategy justified by the results of randomized controlled trials (provide strong evidence of improved survival and reduced progression)
- minimize probability of resistance development and ARV-related side effects and toxicity
- part of new control guidelines in USA, Canada, Botswana etc.
Flow Diagram for DISP ARV Model

\[
\begin{align*}
\dot{S} &= \Pi - \lambda S - \mu S, \\
\dot{L}_1 &= (1 - \sigma)\lambda S - (\mu + \alpha_1 + \tau_1)L_1, \\
\dot{L}_2 &= \alpha_1 L_1 - (\mu + \alpha_2 + \tau_1)L_2, \\
\dot{H}_1 &= \sigma \lambda S - (\mu + \eta_1 \alpha_1 + \tau_2)H_1, \\
\dot{H}_2 &= \eta_1 \alpha_1 H_1 - (\mu + \eta_2 \alpha_2 + \tau_2)H_2, \\
\dot{A} &= \alpha_2 L_2 + \eta_2 \alpha_2 H_2 + \alpha_3 T - (\mu + \delta + \tau_3)A, \\
\dot{T} &= \tau_1 (L_1 + L_2) + \tau_2 (H_1 + H_2) + \tau_3 A - (\mu + \alpha_3)T,
\end{align*}
\]

\[
\lambda = \beta \frac{(L_1 + L_2 + \theta_1 H_1 + \theta_2 H_2 + \theta_3 A + \theta_4 T)}{N}.
\]
Dynamical Features

**Theorem**

The disease-free equilibrium of the DISPT model is globally-asymptotically stable if $R_T < 1$.

Proof based on using a Lyapunov function $(p_i > 0)$:

$$
\mathcal{F} = p_1 L_1 + p_2 L_2 + p_3 H_1 + p_4 H_2 + p_5 A + p_6 T,
$$

**Theorem**

Model has a unique locally-stable endemic equilibrium whenever $R_T > 1$.
Forward Bifurcation Diagram
Simulation Results

(i) Universal strategy gives highest reduction in number of cases;

(ii) Low viral load strategy accounts for the highest mortality;

(iii) For low treatment rates (low ARV supplies), high viral load and the AIDS-only strategies avert more deaths than any of the remaining strategies;

(iv) For high treatment rates, the universal strategy averts more deaths than any of the other strategies.

(v) In terms of reduction of new cases, the strategies are listed in descending order of significance as follows: universal, high viral load, AIDS-only and low viral load strategies;
ARV Model with Two Strains

Drawbacks of ARVs: emergence and spread of ARV-resistant strains.

Reasons:
- Incomplete compliance to the specified ARV regimen;
- Primary infection of susceptible individuals with the resistant strain;
- Biological factors.

Motivation: what is the impact of the emergence and transmission of HIV resistant strain on HIV control?
Mathematical Model: Flow Diagram
The Model

\[
\frac{dS}{dt} = \Pi - \frac{\beta (I_w + \eta w A_w + \eta_T I_T) S}{N} - \frac{\beta (I_r + \eta r A_r) S}{N} - \mu S,
\]

\[
\frac{dI_w}{dt} = \frac{\beta (I_w + \eta w A_w + \eta_T I_T) S}{N} - (\mu + \sigma w + \tau w) I_w,
\]

\[
\frac{dI_r}{dt} = \frac{\beta (I_r + \eta r A_r) S}{N} - (\mu + \sigma r) I_r + \gamma w r I_T,
\]

\[
\frac{dA_w}{dt} = \sigma w I_w - (\tau w + \mu + \delta w) A_w + \theta \sigma w I_T,
\]

\[
\frac{dA_r}{dt} = \sigma r I_r - (\mu + \delta r) A_r,
\]

\[
\frac{dI_T}{dt} = \tau w I_w + \tau w A_w - (\mu + \gamma w r + \theta \sigma w) I_T.
\]
# Summary of Dynamical Features of Multi-Strain Model

<table>
<thead>
<tr>
<th>( R_t^w )</th>
<th>Treatment-free model</th>
<th>Treatment model</th>
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</thead>
<tbody>
<tr>
<td>( R_t^r &gt; 1 )</td>
<td>both strains die out</td>
<td>both strains die out</td>
</tr>
<tr>
<td>( R_t^r &gt; 1 )</td>
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<tr>
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<td>both strains die out</td>
<td>both strains die out</td>
</tr>
<tr>
<td>( R_t^w = R_t^r &gt; 1 )</td>
<td>continuum of endemic equilibria</td>
<td>resistant strain dominates</td>
</tr>
<tr>
<td>( R_t^r &gt; R_t^w &gt; 1 )</td>
<td>wild strain dominates</td>
<td>high endemicity</td>
</tr>
<tr>
<td>( R_t^r &gt; R_t^w &gt; 1 )</td>
<td>resistant strain dominates</td>
<td>resistant strain dominates</td>
</tr>
</tbody>
</table>
Motivation: Randomized controlled trial shows that male circumcision reduces 60% of women-to-men HIV transmission (Aubert et al.)

- Removal of foreskin reduces the susceptibility of men to sexually-transmitted infections

Two more randomized trials on-going;

AIM: Use modeling to evaluate the potential impact of MC

Flow Diagram
Mathematical model (Podder, Sharomi, Gumel, Moses. BMB 2007)

\[
\begin{align*}
\dot{S}_f &= \Pi_1 - \lambda_m S_f - \mu S_f \\
\dot{S}_{mu} &= \Pi_2 - \lambda_f S_{mu} - \xi q \epsilon S_{mu} - \mu S_{mu} \\
\dot{S}_{mc} &= \Pi_3 + \xi q \epsilon S_{mu} - \lambda_f (1 - \epsilon) S_{mc} - \mu S_{mc} \\
\dot{I}_f &= \lambda_m S_f - \sigma I_f - \mu I_f \\
\dot{I}_{mu} &= \lambda_f S_{mu} - \sigma I_{mu} - \mu I_{mu} \\
\dot{I}_{mc} &= \lambda_f (1 - \epsilon) S_{mc} - \sigma I_{mc} - \mu I_{mc} \\
\dot{A}_f &= \sigma I_f - \delta A_f - \mu A_f \\
\dot{A}_m &= \sigma I_{mu} + \sigma I_{mc} - \delta A_m - \mu A_m \\
\end{align*}
\]

\[
\lambda_f = \frac{\beta_f (I_f + \eta A_f)}{N_f} \quad \text{and} \quad \lambda_m = \frac{\beta_m (I_{mu} + I_{mc} + \eta A_m)}{N_m}.
\]
Dynamical Features: Impact of Circumcision

Theorem

*The circumcision model exhibits backward bifurcation.*
Simulations

Data from South Africa (Williams et al., UNAIDS).
Simulation Results

(i) Impact of MC in reducing disease burden is dependent on the sign of a certain quantity known as the circumcision impact factor ($\phi$). MC will have positive impact if $\phi > 0$, no impact if $\phi = 0$, and will have negative impact if $\phi < 0$;

(ii) MC could avert 150,000 new cases and 9,4000 deaths in South Africa in a year (figures agree with the estimates in Williams et al.);

(iii) Using the estimate of circumcision efficacy (of 60%), at least 60% MC coverage is needed to curb HIV spread in South Africa using MC alone;

(iv) Further significant reductions in disease burden will be achieved if MC offers therapeutic benefits (such as reducing transmissibility amongst infected circumcised males).
Extended Model: Treatment and Condoms

\[
\begin{align*}
\dot{S}_f &= \Pi_1 - \lambda_m(1 - \nu c)S_f - \mu S_f \\
\dot{S}_{mu} &= \Pi_2 - \lambda_f(1 - \nu c)S_{mu} - \xi q\epsilon S_{mu} - \mu S_{mu} \\
\dot{S}_{mc} &= \Pi_3 + \xi q\epsilon S_{mu} - \lambda_f(1 - \nu c)(1 - \epsilon)S_{mc} - \mu S_{mc} \\
\dot{l}_f &= \lambda_m(1 - \nu c)S_f - \sigma l_f - \tau_1 l_f - \mu l_f \\
\dot{l}_{mu} &= \lambda_f(1 - \nu c)S_{mu} - \sigma l_{mu} - \tau_1 l_{mu} - \mu l_{mu} \\
\dot{l}_{mc} &= \lambda_f(1 - \nu c)(1 - \epsilon)S_{mc} - \sigma l_{mc} - \tau_1 l_{mc} - \mu l_{mc} \\
\dot{A}_f &= \sigma l_f + \theta_t\sigma T_f - \delta A_f - \tau_2 A_f - \mu A_f \\
\dot{A}_m &= \sigma l_{mu} + \sigma l_{mc} + \theta_t\sigma T_m - \tau_2 A_m - \delta A_m - \mu A_m \\
\dot{T}_f &= \tau_1 l_f + \tau_2 A_f - \theta_t\sigma T_f - \mu T_f \\
\dot{T}_m &= \tau_1 (l_{mu} + l_{mc}) + \tau_2 A_m - \theta_t\sigma T_m - \mu T_m \\
\lambda_f &= \frac{\beta_f(l_f + \eta A_f + \eta_f T_f)}{N_f}, \quad \lambda_m = \frac{\beta_m(l_{mu} + l_{mc} + \eta A_m + \eta_m T_m)}{N_m}.
\end{align*}
\]
Fig. 2A: circumcision coverage (50%); condom (compliance (60%); efficacy 60%); ARVs
Fig. 2B: circumcision coverage (50%); condom (compliance (100%); efficacy 60%); ARVs
Fig. 2C: circumcision coverage (50%); condom (compliance (60%); efficacy 60%); no ARVs
Fig. 2D: circumcision coverage (50%); no condoms; with ARVs

circumcision and treatment

Cumulative deaths averted

Time (years)
Fig. 2E: circumcision coverage (50%); condoms (60% compliance; 60% efficacy); with ARVs
HIV/TB Dynamics

- HIV and TB exhibit synergistic interaction: each accelerates the progression of the other.
  
  ▶ HIV pandemic plays a major role in the resurgence of TB (resulting in increased morbidity and mortality worldwide);
  
  ▶ HIV fuels progression to active disease in people infected with TB (increases recurrence of TB, both due to endogenous reactivation and exogenous re-infection)

- TB incidence on the rise in some African countries;
TB affects at least 2 billion people (one-third of the world’s population) and is the second greatest contributor of adult mortality amongst infectious diseases (2 million deaths a year worldwide);

Approximately 8% of global TB cases is attributable to HIV infection (60% of HIV cases in India had TB).

Largest number of TB cases occurs in South-East Asia
  ▶ rising incidence in Sub-Saharan Africa and Eastern Europe

Treatment:
  ▶ HAART for HIV
  ▶ drug therapy such as DOTS (directly observed treatment short course). DOTS cures TB in 95% of cases.
Flow diagram

HIV

- $H_2(t)$
- $H_1(t)$
- $W_H(t)$

TB

- $T(t)$
- $L(t)$
- $W_T(t)$

S(t)

$S(t)$ connects to both HIV and TB compartments.

$S(t)$ leads to $I_{HT}(t)$, $F_{HT}(t)$, and $W_{HT}(t)$.

$I_{HT}(t)$, $F_{HT}(t)$, and $W_{HT}(t)$ are part of the mixed compartment, "MIXED".
Mathematical Model of HIV/TB Dynamics

\[ \dot{S} = \pi - \lambda_H S - \lambda_T S - \lambda_{HT} S - \mu S \]

\[ \dot{H}_1 = \lambda_H S + q_1 \lambda_{HT} S - \lambda_T H_1 - \lambda_{HT} H_1 - (\mu + \sigma + \tau_1) H_1 \]

\[ \dot{H}_2 = \sigma H_1 + \theta_t \sigma W_H - \lambda_T H_2 - \lambda_{HT} H_2 - (\mu + \delta_a + \tau_2) H_2 \]

\[ \dot{L} = f_1 \lambda_T S + q_2 \lambda_{HT} S + \rho W_T - \frac{\beta_T (1 - \epsilon_L) \eta_{LT}}{N} - \lambda_H L - \lambda_{HT} L - (\mu + \alpha) L \]

\[ \dot{T} = (1 - f_1) \lambda_T S + q_3 \lambda_{HT} S + \frac{\beta_T (1 - \epsilon_L) \eta_{LT}}{N} + \alpha L - \lambda_H T - \lambda_{HT} T - (\mu + \delta_T + \tau_3) T \]
HIV/TB Model ctd.

\[ \dot{I}_{HT} = (1 - q_1 - q_2 - q_3) \lambda_{HT} S + \lambda_{H} L + \lambda_{T} (H_1 + H_2) + \lambda_{HT} (H_1 + H_2 + L + T) - (\mu + \sigma + \tau_{H} + \tau_{T}) I_{HT} \]

\[ \dot{F}_{HT} = \sigma I_{HT} + \theta_{HT} \sigma W_{HT} - (\mu + \delta_{HT} + \tau_{HT}) F_{HT} \]

\[ \dot{W}_{H} = \tau_{1} H_1 + \tau_{2} H_2 - (\mu + \theta_{t} \sigma) W_{H} \]

\[ \dot{W}_{T} = \tau_{3} T - (\mu + \rho) W_{T} \]

\[ \dot{W}_{HT} = \tau_{H} I_{HT} + \tau_{T} I_{HT} + \tau_{HT} F_{HT} - (\mu + \theta_{HT} \sigma) W_{HT} \]
Dynamical Features

- HIV-only model exhibits global forward bifurcation at $R_H = 1$; model with co-infection-only also displays such;

- TB model allows for exogenous re-infection and endogenous re-activation;

- TB-only model undergoes backward bifurcation (shown using Centre Manifold theory);

- TB-only model exhibits global forward bifurcation in the absence of exogenous reinfection;

- Full HIV-TB model undergoes backward bifurcation.
Simulations

(i) Treating any of the two diseases offers indirect positive benefit;

(ii) Treating individuals with TB or HIV only results in more cases of TB prevented than HIV;

(iii) The universal treatment of individuals infected with both diseases is more beneficial compared to the treatment of individuals infected with a single disease.
HIV-Malaria Interaction

- HIV increases the risk of malaria infection and accelerates development of clinical symptoms;

- Malaria induces HIV-1 replication *in vitro* and *in vivo*
  - cellular-based immune responses to HIV and malaria
  - when HIV-infected individuals are attacked by malaria, their body immune system weakens significantly, creating a conducive environment for HIV replication

- symbiotic HIV-malaria relationship is a double blow to Sub-Saharan Africa region because of the high prevalence of HIV/AIDS and incidence of malaria
Model Equations (Mukandavire, Gumel, Tchuenche, Garira, JMB)

\[ S'_H = \Lambda_H + \phi_1 I_M - \lambda_H S_H - \lambda_M S_H - \mu_H S_H, \]
\[ E'_M = \lambda_M S_H - \lambda_H E_M - (\gamma_H + \mu_H) E_M, \]
\[ I'_M = \gamma_H E_M - \sigma \lambda_H I_M - (\mu_H + \delta_M + \phi_1) I_M, \]
\[ I'_H = \lambda_H S_H + \phi_2 I_{HM} - \vartheta \lambda_M I_H - (\mu_H + \kappa) I_H, \]
\[ E'_{HM} = \lambda_H E_M + \vartheta \lambda_M I_H - (\epsilon \gamma_H + \mu_H) E_{HM}, \]
\[ I'_{HM} = \sigma \lambda_H I_M + \epsilon \gamma_H E_{HM} - (\mu_H + \tau \delta_M + \phi_2 + \xi \kappa) I_{HM}, \]
\[ A'_H = \kappa I_H + \phi_3 A_{HM} - \vartheta \lambda_M A_H - (\mu_H + \delta_H) A_H, \]
\[ E'_{AM} = \vartheta \lambda_M A_H - (\epsilon \gamma_H + \mu_H) E_{AM}. \]
Equations ctd.

\[ A'_{HM} = \xi \kappa I_{HM} + \epsilon \gamma_H E_{AM} - (\mu_H + \phi_3 + \tau \delta_M + \psi \delta_H)A_{HM}, \]

\[ S'_V = \Lambda_V - \lambda_V S_V - \mu_V S_V, \]

\[ E'_V = \lambda_V S_V - (\gamma_V + \mu_V)E_V, \]

\[ I'_V = \gamma_V E_V - \mu_V I_V, \]

\[ \lambda_H = \frac{\beta_H \{ I_H + \eta_{HM} (E_{HM} + \theta_{HM} I_{HM}) + Q \}}{N_H} \]

\[ Q = \eta_A [A_H + \eta_{HM} (E_{AM} + \theta_{HM} A_{HM})] \]

\[ \lambda_M = \beta_M b_M \frac{I_V}{N_H}, \]
Numerical Results

(i) model undergoes malaria-induced backward bifurcation;

(ii) model has a locally-asymptotically stable disease-free equilibrium when its reproductive threshold is less than unity, and unstable if the threshold exceeds unity;

(iii) two diseases will co-exist whenever their reproduction numbers exceed unity.
Some Challenges

(a) ARVs:
   - Optimal distribution
   - Minimizing risk of emergence and transmission of resistant strains
   - When to treat and what strain to treat?
   - Needs of individual vs society

(b) Male circumcision:
   - is adult male circumcision really practicable?
   - who oversees this?
   - possible increase in risky behaviour amongst circumcised men
   - randomized controlled trials politically sensitive (John Hargrove, June 25, 2007)
   - since a “perfect vaccine” is highly unlikely, should efforts be focussed on MC?
Challenges ctd.

(c) HIV Co-infection:

- should resources be targeted against the “other” pathogen?
- role of testing: should individuals diagnosed with one be tested for the others?

(d) Mathematical and statistical (relatively large models):

- global dynamics
- data quality: parameter estimates
- uncertainty and sensitivity analysis
- optimization issues
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