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

Abba B. Gumel,
Department of Mathematics,
University of Manitoba , Winnipeg, Manitoba, Canada.

DIMACS-SACEMA-AIMS Meeting; Stellenbosch, South Africa, June 25, 2007.

UNIVERSITY OF MANITOBA

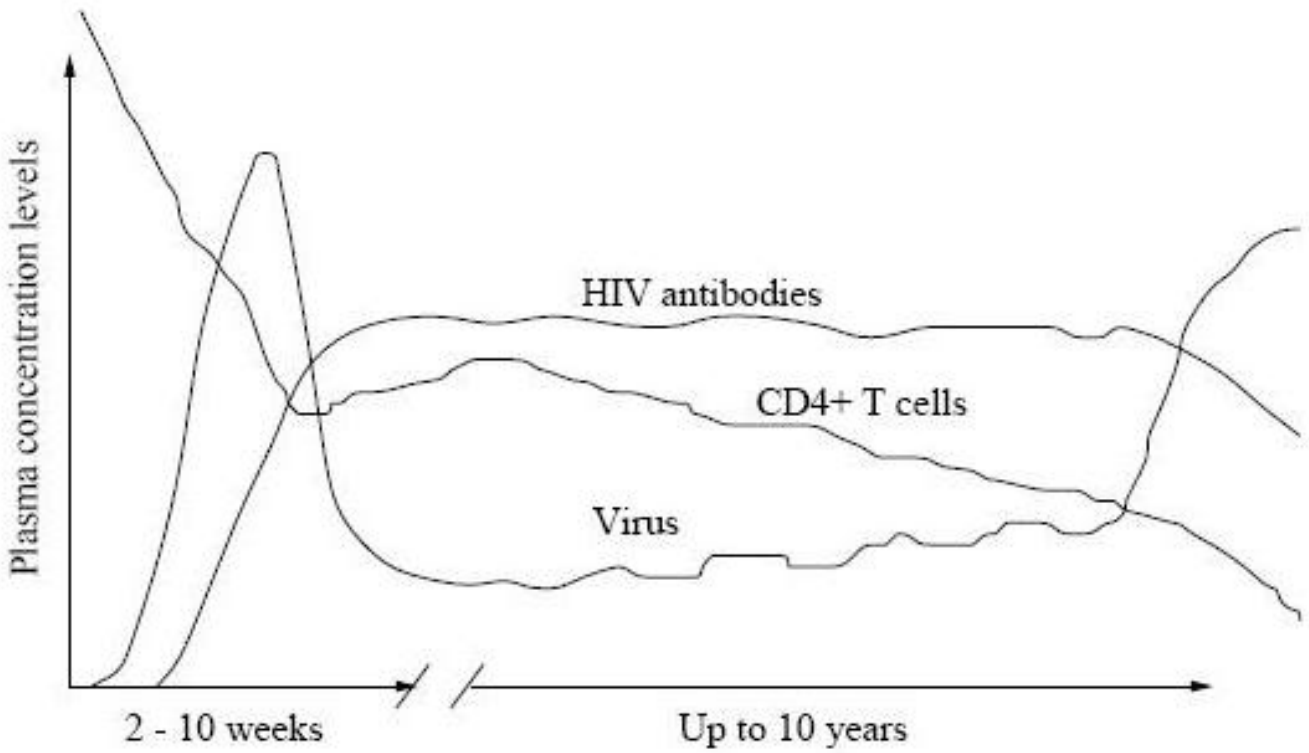
Outline

- **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

- **Human Immunodeficiency Virus (HIV): causative agent of Acquired Immune Deficiency Syndrome (AIDS). First appeared in 1980s;**
- **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



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

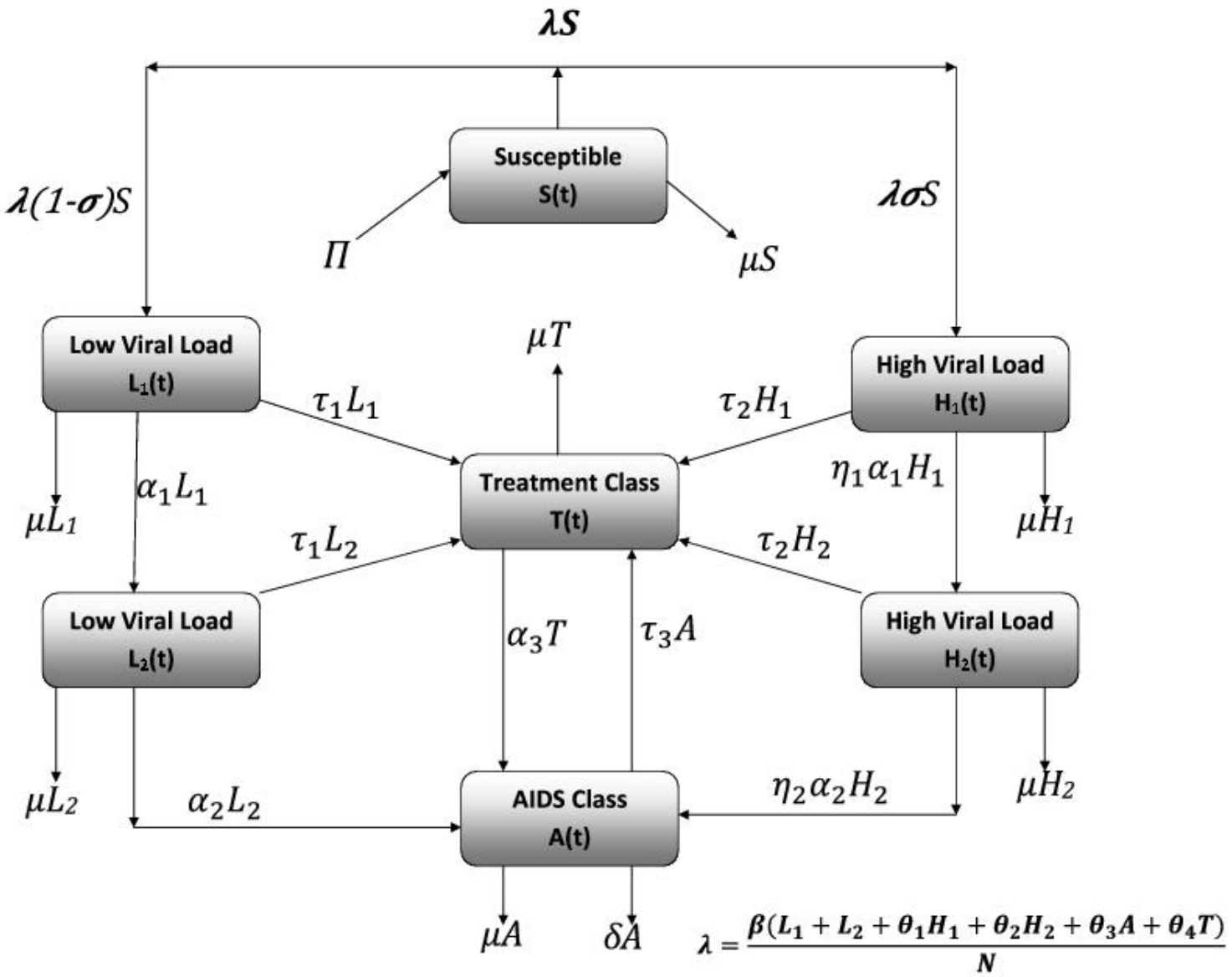
(i) **Universal:**

- **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



Viral-load Dependent Treatment Model With Multiple Infection Stages (Sharomi and Gumel, Bull. Math. Biol., 2007)

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

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

Dynamical Features

Theorem

The disease-free equilibrium of the DISPT model is globally-asymptotically stable if $\mathcal{R}_T < 1$.

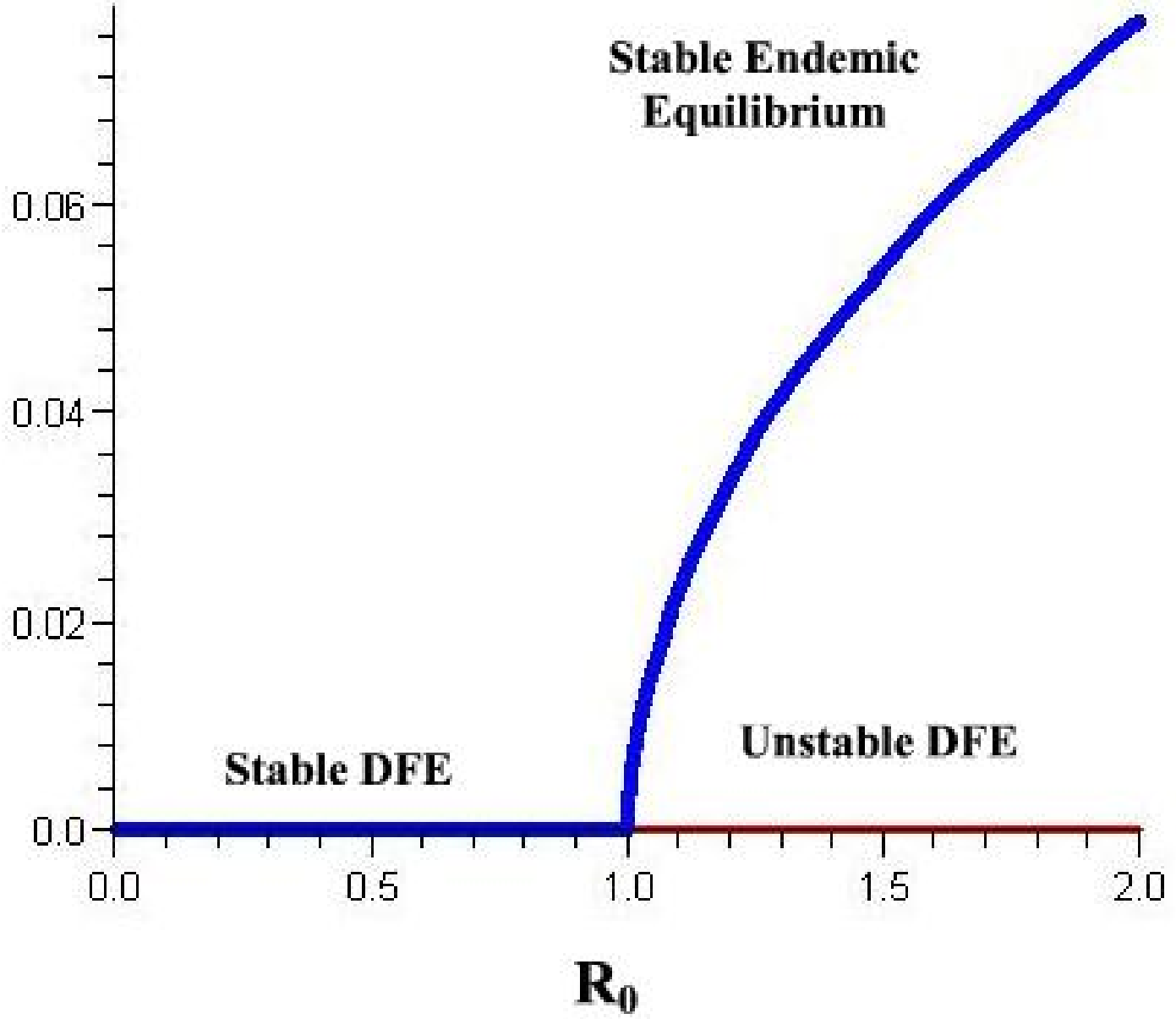
Proof based on using a Lyapunov function ($p_i > 0$):

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

Theorem

Model has a unique locally-stable endemic equilibrium whenever $\mathcal{R}_T > 1$

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

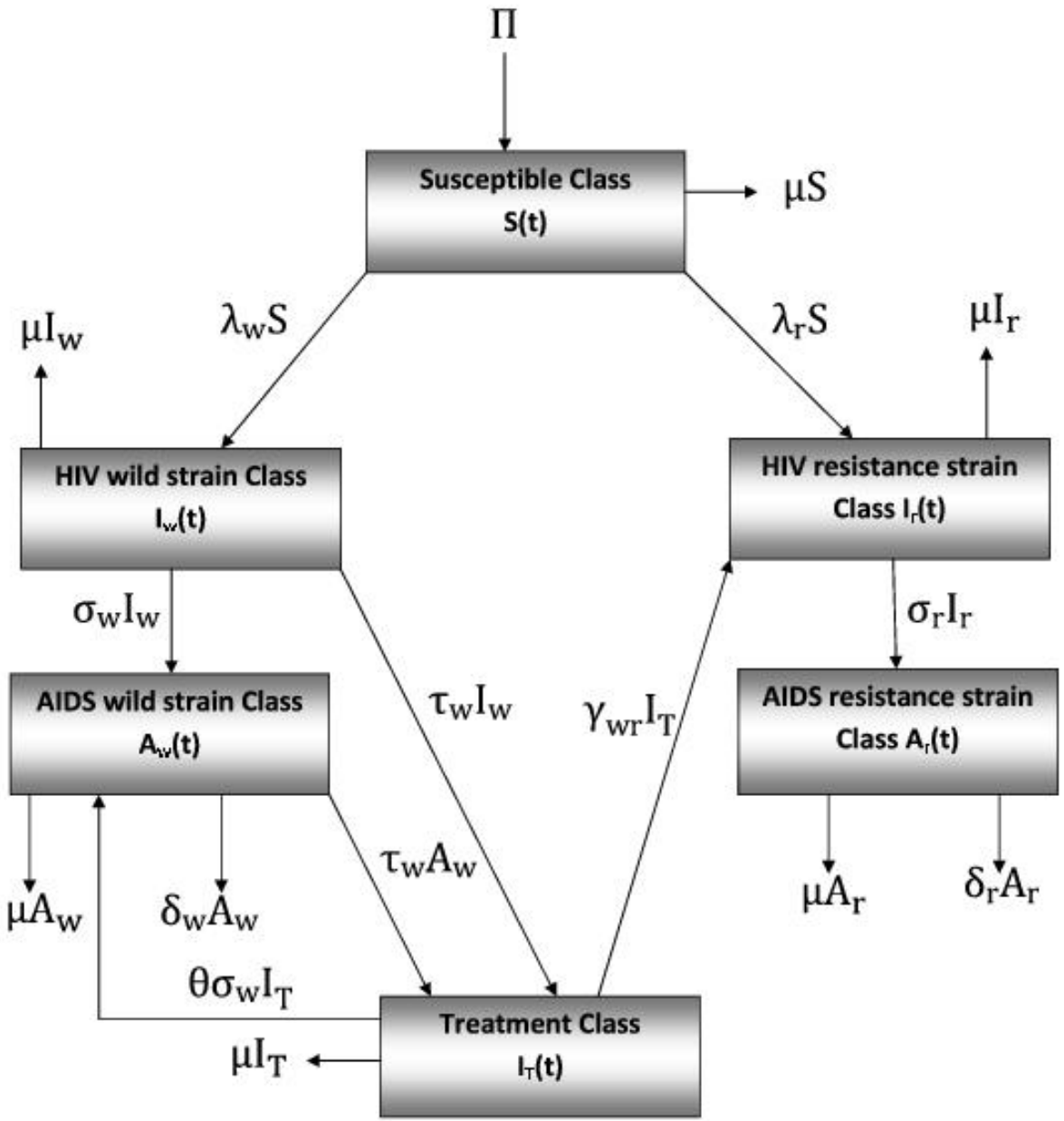
Drawbacks of ARVs: emergence and spread of ARV-resistant strains.

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

$$\frac{dS}{dt} = \Pi - \frac{\beta(I_w + \eta_w A_w + \eta_T I_T)S}{N} - \frac{\beta(I_r + \eta_r A_r)S}{N} - \mu S,$$

$$\frac{dI_w}{dt} = \frac{\beta(I_w + \eta_w A_w + \eta_T I_T)S}{N} - (\mu + \sigma_w + \tau_w)I_w,$$

$$\frac{dI_r}{dt} = \frac{\beta(I_r + \eta_r A_r)S}{N} - (\mu + \sigma_r)I_r + \gamma_{wr} I_T,$$

$$\frac{dA_w}{dt} = \sigma_w I_w - (\tau_w + \mu + \delta_w)A_w + \theta\sigma_w I_T,$$

$$\frac{dA_r}{dt} = \sigma_r I_r - (\mu + \delta_r)A_r,$$

$$\frac{dI_T}{dt} = \tau_w I_w + \tau_w A_w - (\mu + \gamma_{wr} + \theta\sigma_w)I_T.$$

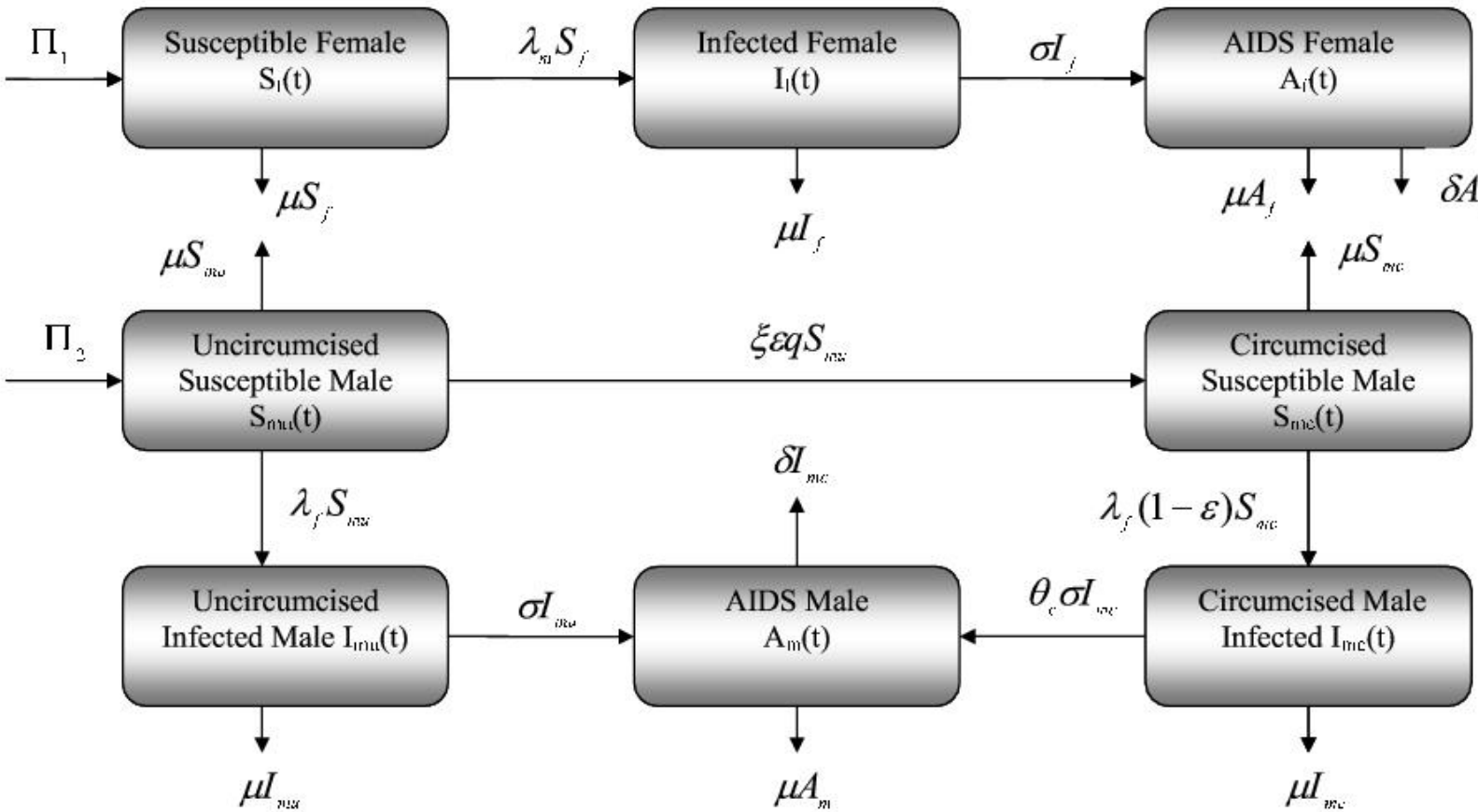
Summary of Dynamical Features of Multi-Strain Model

	Treatment-free model	Treatment model
$\mathcal{R}_w^t < \mathcal{R}_r^t < 1$	**both strains die out**	**both strains die out**
$\mathcal{R}_w^t < 1 < \mathcal{R}_r^t$	**resistant strain dominates**	**resistant strain domina**
$\mathcal{R}_r^t < 1 < \mathcal{R}_w^t$	**wild strain dominates**	**low endemicity co-existence equilibriu**
$\mathcal{R}_w^t = \mathcal{R}_r^t = 1$	**both strains die out**	**both strains die out**
$\mathcal{R}_w^t = \mathcal{R}_r^t > 1$	**continuum of endemic equilibria**	**resistant strain domina**
$\mathcal{R}_w^t > \mathcal{R}_r^t > 1$	**wild strain dominates**	**high endemicity co-existence equilibriu**
$\mathcal{R}_r^t > \mathcal{R}_w^t > 1$	**resistant strain dominates**	**resistant strain domina**

Modeling the Impact of Male Circumcision

- **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**
  - **Preliminary modeling work by Brian G. Williams, James Lloyd-Smith, E. Gouws, C. Hankins, Wayne Getz, John Hargrove, I. de Zoysa, C. Dye and B. Auvert (Plos Medicine 2006)**

Flow Diagram



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

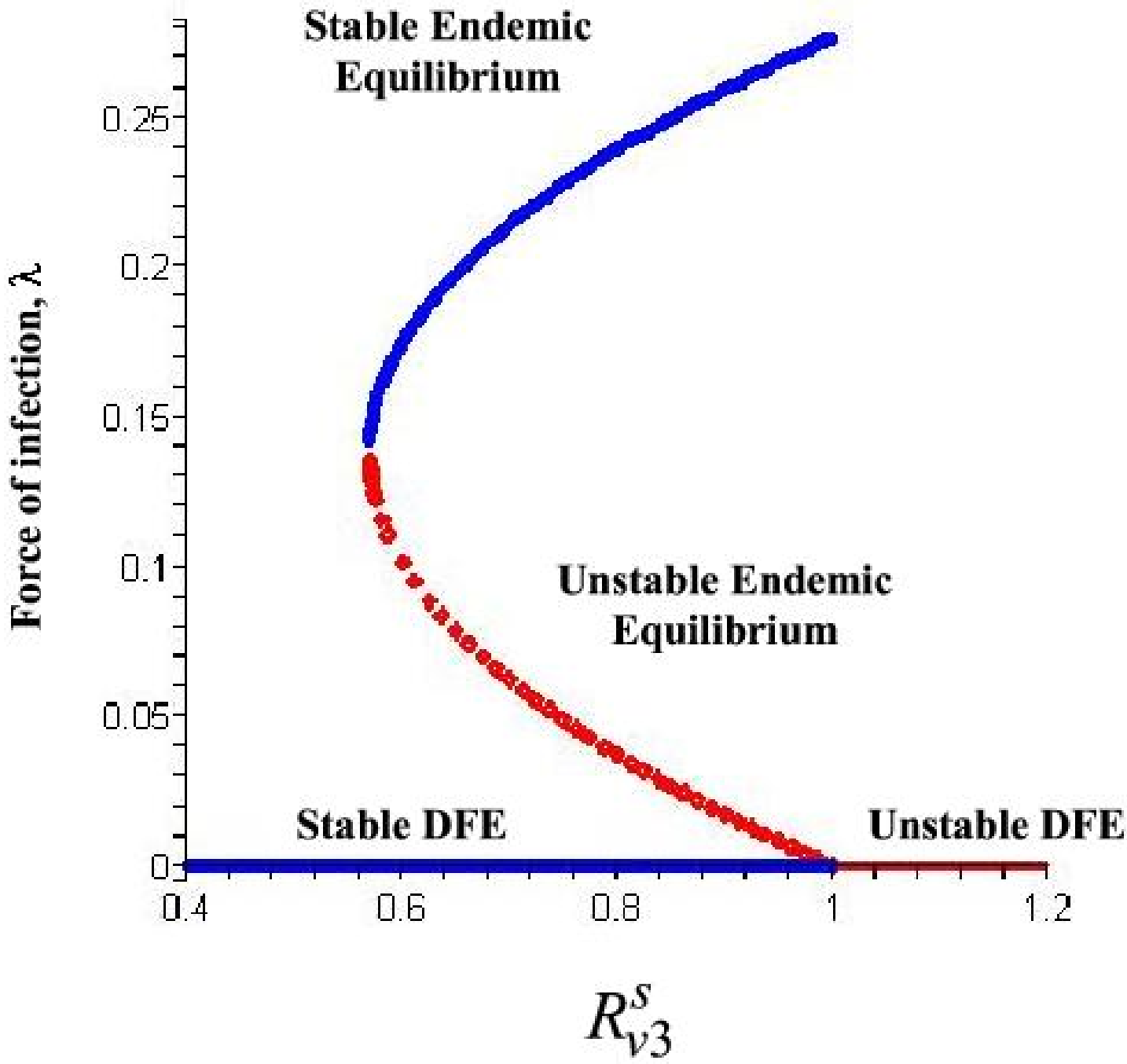
$$
\begin{aligned}
\dot{S}_f &= \Pi_1 - \lambda_m S_f - \mu S_f \\
\dot{S}_{mu} &= \Pi_2 - \lambda_f S_{mu} - \xi q \epsilon S_{mu} - \mu S_{mu} \\
\dot{S}_{mc} &= \Pi_3 + \xi q \epsilon S_{mu} - \lambda_f (1-\epsilon) S_{mc} - \mu S_{mc} \\
\dot{I}_f &= \lambda_m S_f - \sigma I_f - \mu I_f \\
\dot{I}_{mu}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

$$
\lambda_f = \frac{\beta_f (I_f + \eta A_f)}{N_f} \quad \text{and} \quad \lambda_m = \frac{\beta_m (I_{mu} + I_{mc} + \eta A_m)}{N_m},
$$

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 (ϕ). 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

$$
\begin{aligned}
\dot{S}_f &= \Pi_1 - \lambda_m(1-\nu c)S_f - \mu S_f \\
\dot{S}_{mu} &= \Pi_2 - \lambda_f(1-\nu c)S_{mu} - \xi q \epsilon S_{mu} - \mu S_{mu} \\
\dot{S}_{mc} &= \Pi_3 + \xi q \epsilon S_{mu} - \lambda_f(1-\nu c)(1-\epsilon)S_{mc} - \mu S_{mc} \\
\dot{I}_f &= \lambda_m(1-\nu c)S_f - \sigma I_f - \tau_1 I_f - \mu I_f \\
\dot{I}_{mu} &= \lambda_f(1-\nu c)S_{mu} - \sigma I_{mu} - \tau_1 I_{mu} - \mu I_{mu} \\
\dot{I}_{mc} &= \lambda_f(1-\nu c)(1-\epsilon)S_{mc} - \sigma I_{mc} - \tau_1 I_{mc} - \mu I_{mc} \\
\dot{A}_f &= \sigma I_f + \theta_t \sigma T_f - \delta A_f - \tau_2 A_f - \mu A_f \\
\dot{A}_m &= \sigma I_{mu} + \sigma I_{mc} + \theta_t \sigma T_m - \tau_2 A_m - \delta A_m - \mu A_m \\
\dot{T}_f &= \tau_1 I_f + \tau_2 A_f - \theta_t \sigma T_f - \mu T_f \\
\dot{T}_m &= \tau_1 (I_{mu} + I_{mc}) + \tau_2 A_m - \theta_t \sigma T_m - \mu T_m
\end{aligned}
$$

$$
\lambda_f = \frac{\beta_f (I_f + \eta A_f + \eta_f T_f)}{N_f}; \quad \lambda_m = \frac{\beta_m (I_{mu} + I_{mc} + \eta A_m + \eta_m T_m)}{N_m}.
$$

Fig. 2A: circumcision coverage (50%); condom (compliance (60%); efficacy 60%); ARVs

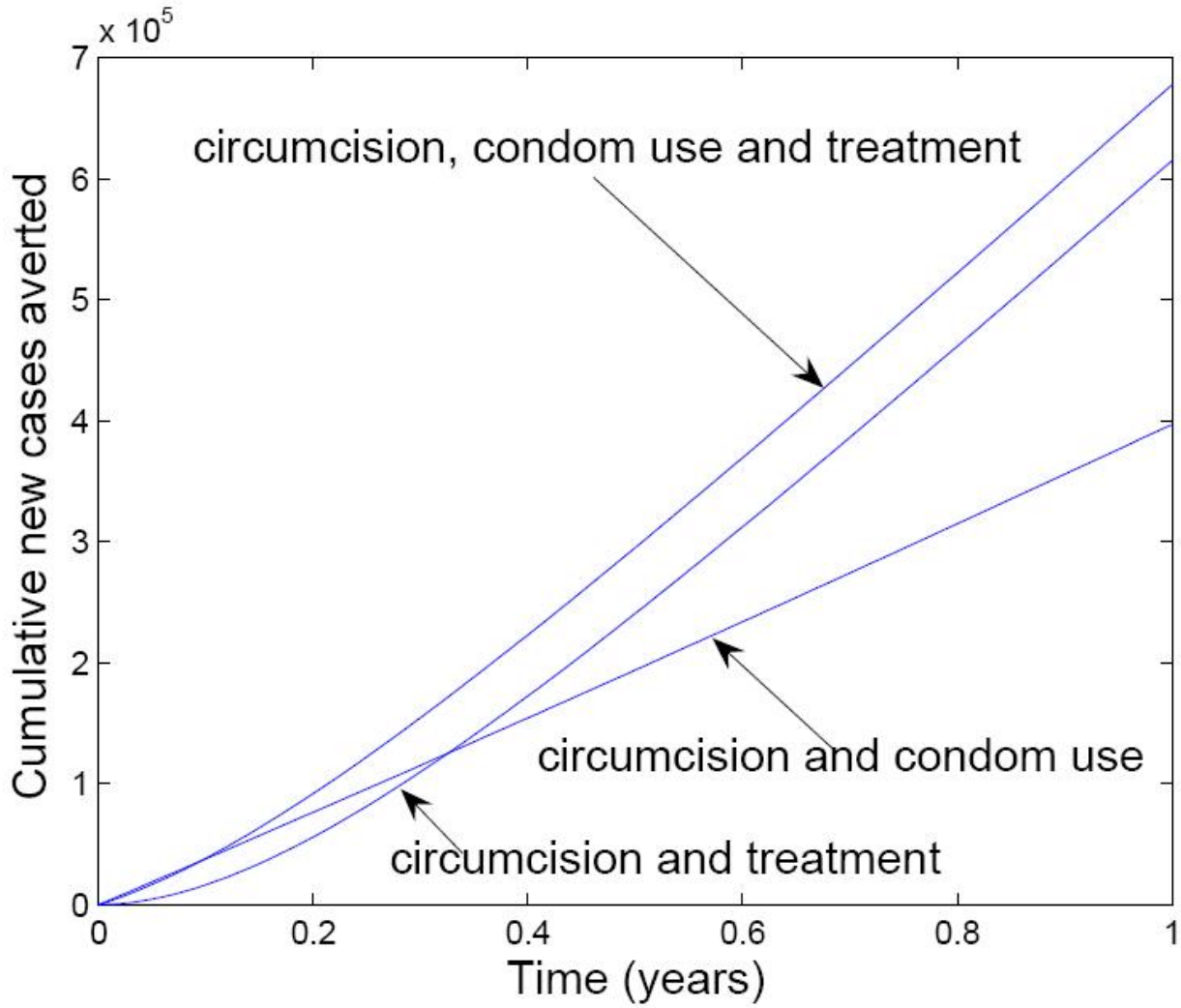


Fig. 2B: circumcision coverage (50%); condom (compliance (100%); efficacy 60%); ARVs

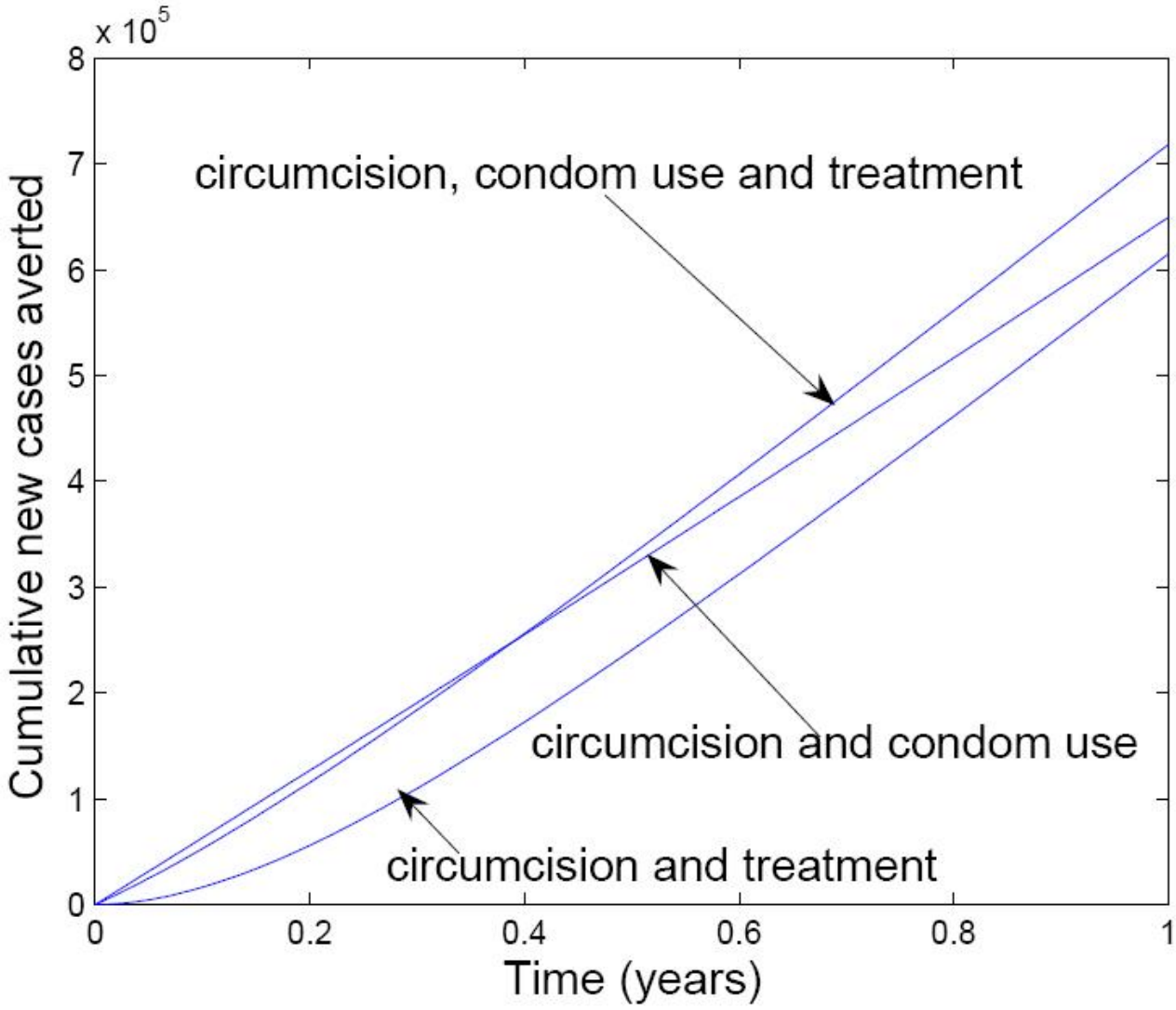


Fig. 2C: circumcision coverage (50%); condom (compliance (60%); efficacy 60%); no ARVs

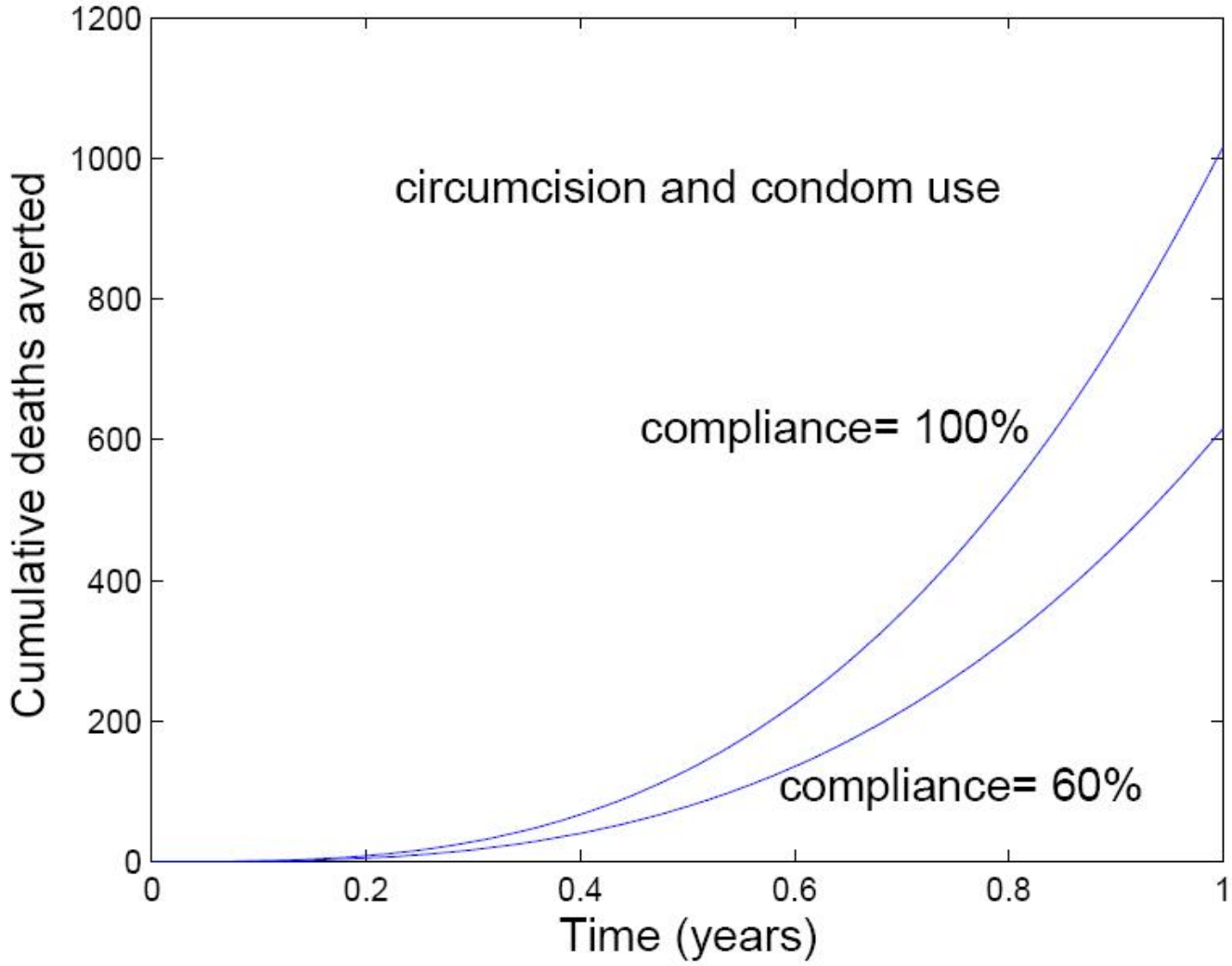


Fig. 2D: circumcision coverage (50%);no condoms; with ARVs

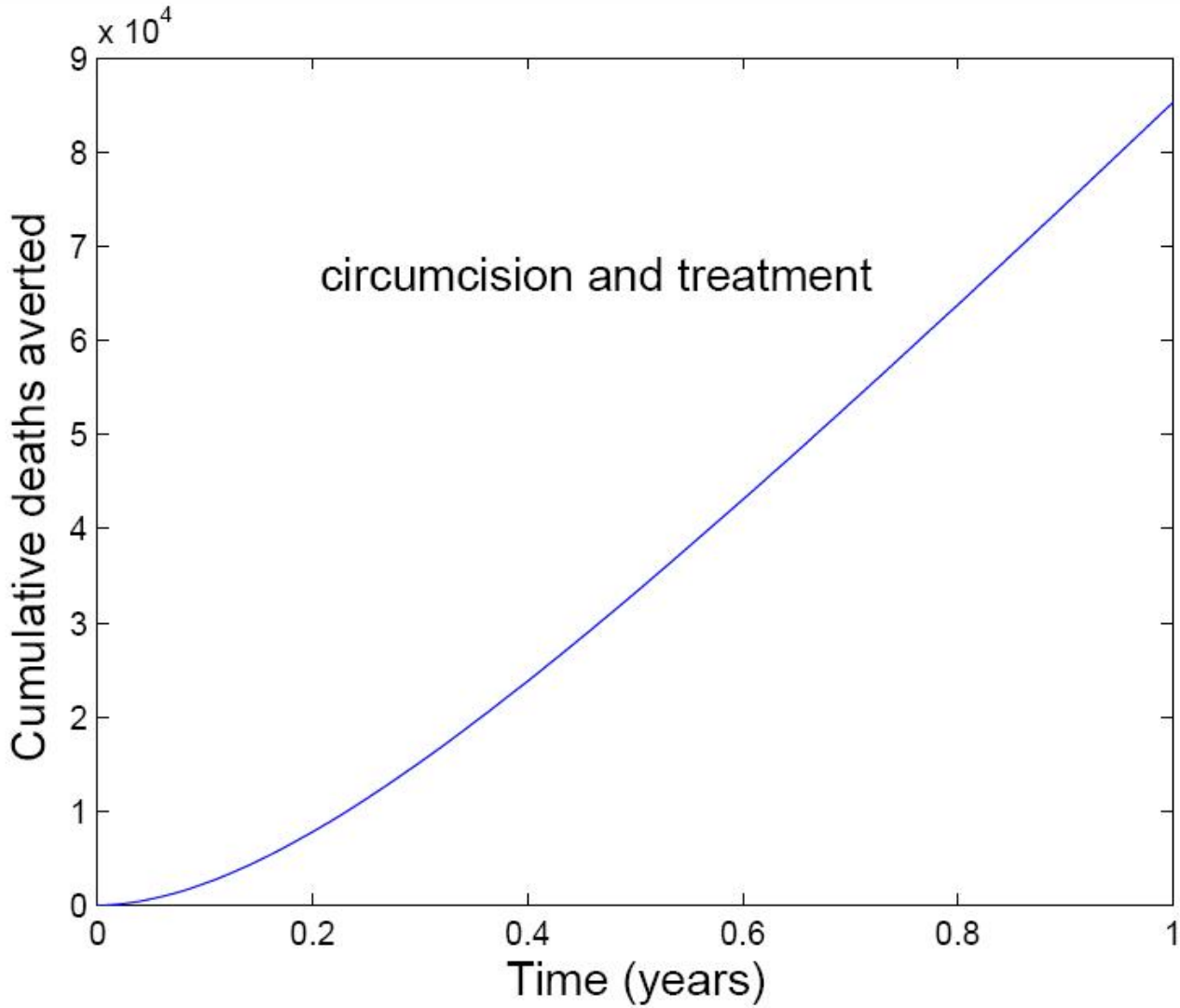
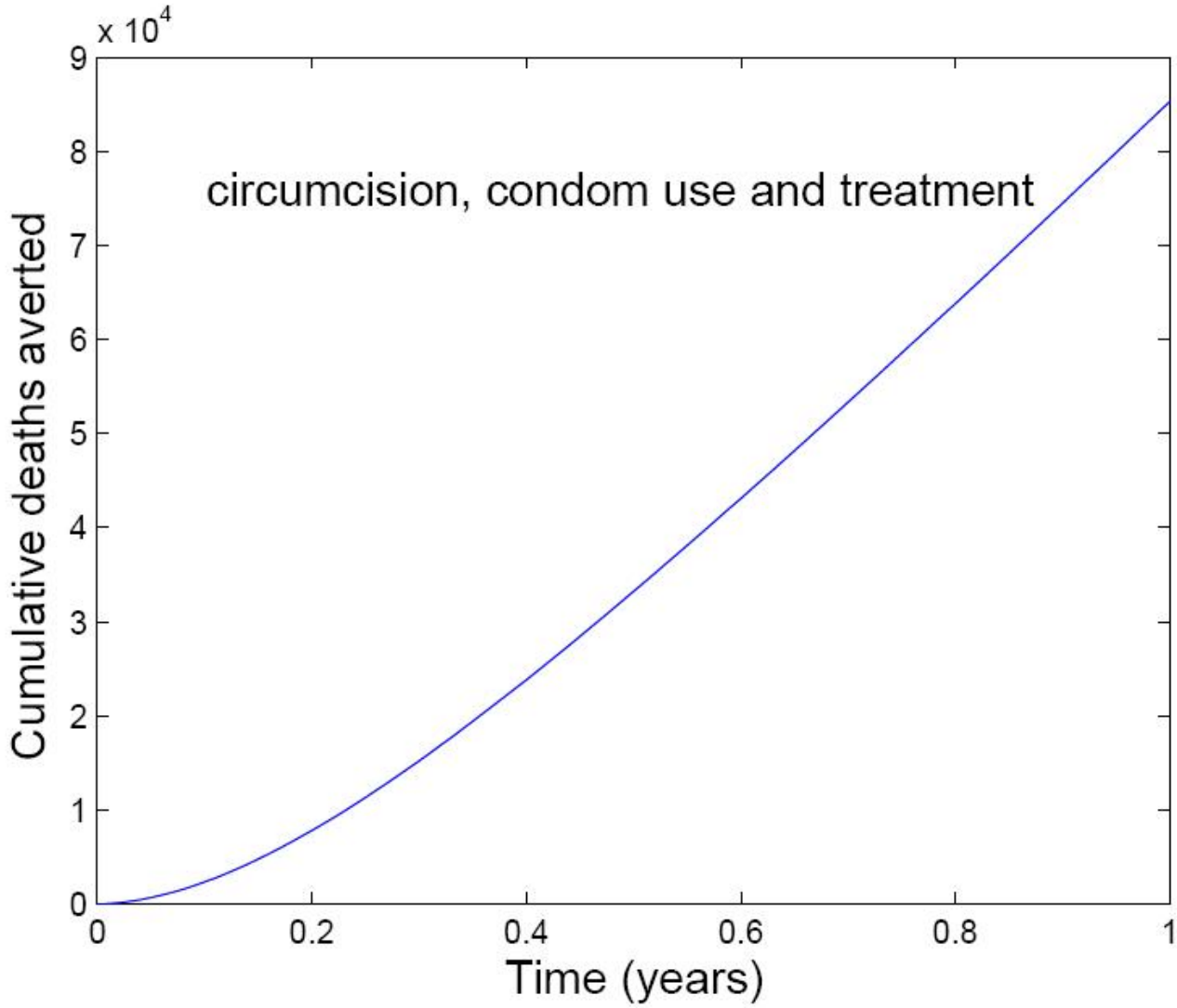


Fig. 2E: circumcision coverage (50%); condoms (60% compliance; 60% efficacy); with ARVs



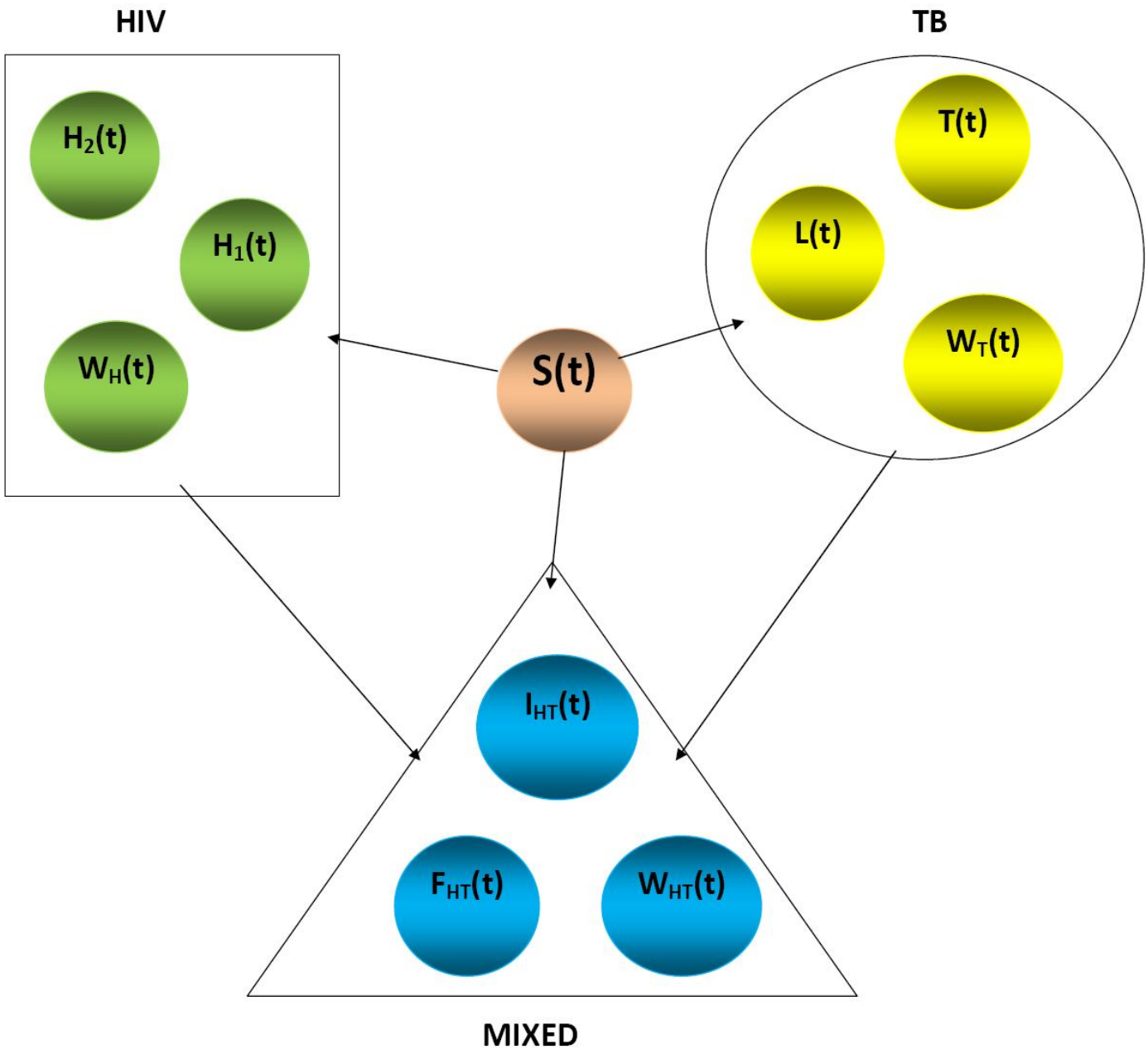
HIV/TB Dynamics

- **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;**

HIV/TB Dynamics Ctd.

- **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



Mathematical Model of HIV/TB Dynamics

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

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

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

$$\dot{L} = f_1 \lambda_T S + q_2 \lambda_{HT} S + \rho W_T - \frac{\beta_T (1-\epsilon_L) \eta L T}{N} - \lambda_H L - \lambda_{HT} L - (\mu + \alpha) L$$

$$\dot{T} = (1 - f_1) \lambda_T S + q_3 \lambda_{HT} S + \frac{\beta_T (1-\epsilon_L) \eta L T}{N} + \alpha L - \lambda_H T - \lambda_{HT} T - (\mu + \delta_T + \tau_3) T$$

HIV/TB Model ctd.

$$\begin{aligned}
\dot{\mathbf{I}}_{\mathbf{HT}} &= (\mathbf{1}-\mathbf{q_1}-\mathbf{q_2}-\mathbf{q_3})\lambda_{\mathbf{HT}}\mathbf{S}+\lambda_{\mathbf{H}}\mathbf{L}+\lambda_{\mathbf{T}}(\mathbf{H_1}+\mathbf{H_2}) \\
&\quad +\lambda_{\mathbf{H}}\mathbf{T}+\lambda_{\mathbf{HT}}(\mathbf{H_1}+\mathbf{H_2}+\mathbf{L}+\mathbf{T})-(\mu+\sigma+\tau_{\mathbf{H}}+\tau_{\mathbf{T}})\mathbf{I}_{\mathbf{HT}} \\
\dot{\mathbf{F}}_{\mathbf{HT}} &= \sigma\mathbf{I}_{\mathbf{HT}}+\theta_{\mathbf{HT}}\sigma\mathbf{W}_{\mathbf{HT}}-(\mu+\delta_{\mathbf{HT}}+\tau_{\mathbf{HT}})\mathbf{F}_{\mathbf{HT}} \\
\dot{\mathbf{W}}_{\mathbf{H}} &= \tau_1\mathbf{H_1}+\tau_2\mathbf{H_2}-(\mu+\theta_{\mathbf{t}}\sigma)\mathbf{W}_{\mathbf{H}} \\
\dot{\mathbf{W}}_{\mathbf{T}} &= \tau_3\mathbf{T}-(\mu+\rho)\mathbf{W}_{\mathbf{T}} \\
\dot{\mathbf{W}}_{\mathbf{HT}} &= \tau_{\mathbf{H}}\mathbf{I}_{\mathbf{HT}}+\tau_{\mathbf{T}}\mathbf{I}_{\mathbf{HT}}+\tau_{\mathbf{HT}}\mathbf{F}_{\mathbf{HT}}-(\mu+\theta_{\mathbf{HT}}\sigma)\mathbf{W}_{\mathbf{HT}}
\end{aligned}$$

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**

Relevant Books

(i) **Mathematical Studies on Human Disease Dynamics: Emerging Paradigms and Challenges. Contemporary Mathematics Series, American Mathematical Society. Volume 410, 386, 2006.**

Abba B. Gumel (Editor-in-Chief)
Carlos-Castillo-Chavez (Editor)
Ronald E. Mickens (Editor)
Dominic P. Clemence (Editor)

(ii) **Optimal Control Applied to Biological Models. Suzanne Lenhart. Chapman and Hall/CRC Mathematical and Computational Biology.**

Acknowledgements

(a) **Sponsors:**

- **MITACS,NSERC, CIHR, Health Canada,**
- **NSF-DIMACS program on Infectious Disease Modelling in Africa (AIMS, DIMACS, SACEMA)**

(b) **Collaborators:**

(i) **C. Podder, J. Ehiemua and O. Sharomi (Graduate Students), E.H. Elbasha (Merck Inc., USA), J. Watmough (New Brunswick)**

(ii) **Related HIV Projects: C. Bowman (Inst. for Biodiagnostics), British Columbia Centre for Disease Control, C. MCCluskey (Wilfrid Laurier), Z. Mukandivare (Zimbabwe), P. van den Driessche (Victoria), B. Song (Montclair), C. Struchiner (Brazil)**