# A New Method for Estimating HIV Incidence Using Public Health Surveillance and Viral Genetic Data

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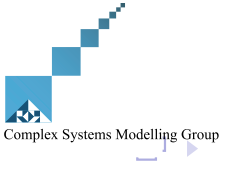


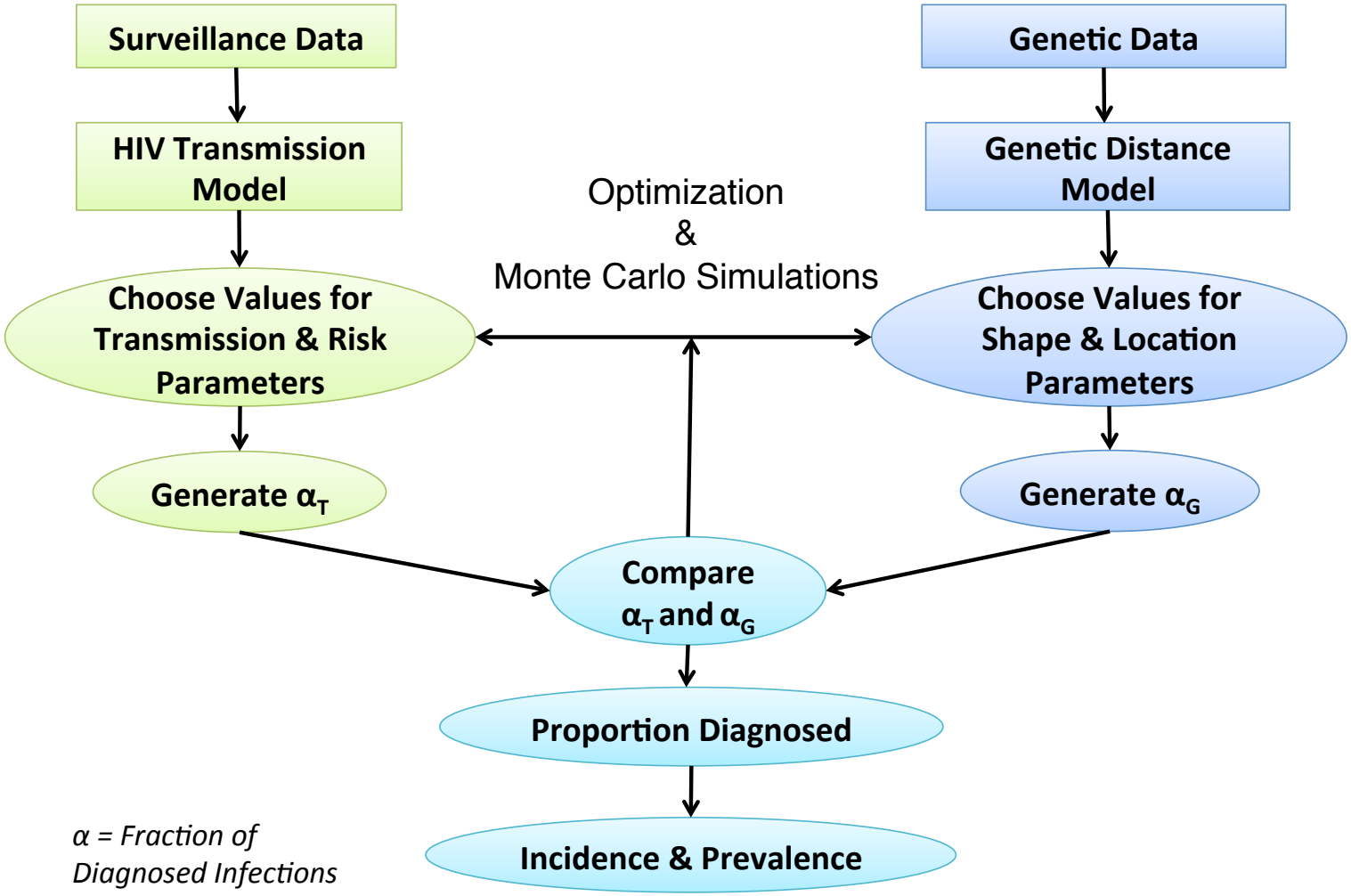

# HIV Incidence

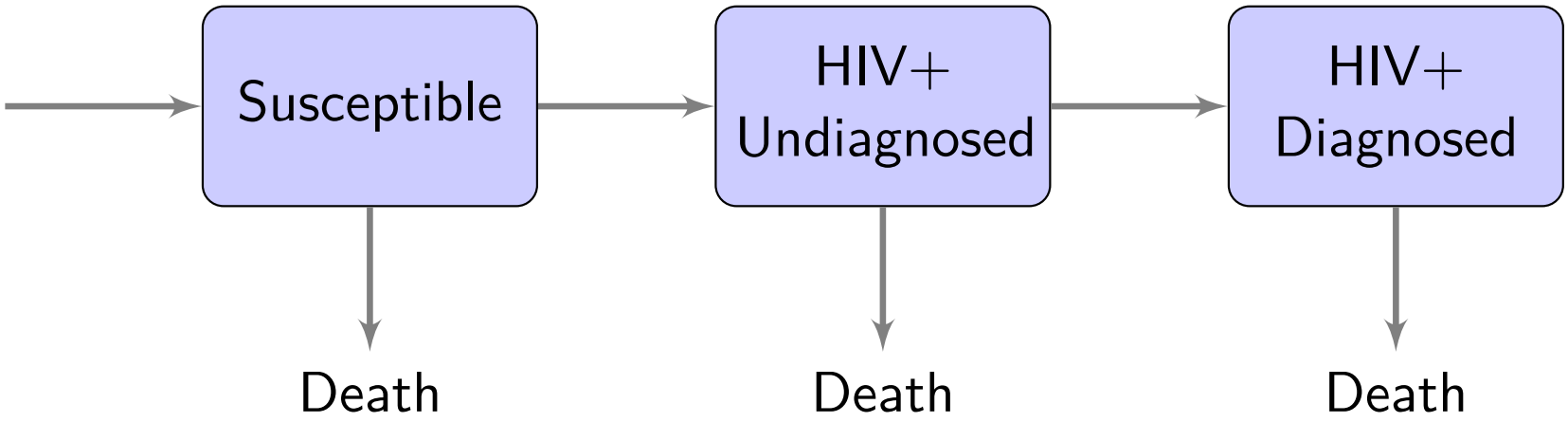
- Important indicator for the success of public health programs.
- Difficult to measure, because people infected with HIV may be asymptomatic for as long as 8 years.
- Currently estimated using back-calculation methods or longitudinal cohort studies.
- Our goal is to develop a method for estimating HIV incidence from *existing* public health and medical data.

# Data Sources
## British Columbia

- Reconciled Ministry of Health, BC Centre for Disease Control, and BC-CfE Drug Treatment Program data on new HIV diagnoses, mortality, immigration, and emigration.
- Drug treatment program data on number of patients receiving HAART and number virally suppressed.
- BC-CfE viral genetic data from genotypic drug resistance tests.

# Algorithm


Surveillance Data
HIV Transmission Model
Choose Values for Transmission & Risk Parameters
Generate $\alpha_T$
Optimization & Monte Carlo Simulations
Genetic Data
Genetic Distance Model
Choose Values for Shape & Location Parameters
Generate $\alpha_G$
Compare $\alpha_T$ and $\alpha_G$
Proportion Diagnosed
Incidence & Prevalence
$\alpha$ = Fraction of Diagnosed Infections




- The change in the number of prevalent HIV cases is the result of HIV+ individuals being added and removed from the population.
- New HIV infections are generated by transmission from both diagnosed and undiagnosed HIV+ individuals.
- HIV+ individuals are removed from the population through death — both AIDS related and other causes.

The number of HIV+ individuals $N$ is given by

$$\frac{dN}{dt} = e(1-\alpha_T)N + p_b\, p_h\, e\alpha_T\, N - d(1-\alpha_T)N - D + F_d + F_u$$

$\alpha_T$ = fraction of the HIV+ subpopulation that is diagnosed

$e$ = number of new HIV infections generated by each undiagnosed HIV+ individual per unit time

$p_b$ = factor by which the undiagnosed transmission rate is reduced after diagnosis

$1 - p_h$ = diagnosed fraction of HIV+ subpopulation who are on HAART and virally suppressed

$d$ = per person all cause death rate for individuals with undiagnosed HIV infection

$D$ = all cause death rate for individuals with diagnosed HIV infection

$F_u$ = net immigration for undiagnosed HIV+ individuals

$F_d$ = net immigration for diagnosed HIV+ individuals

The fraction diagnosed of the HIV+ subpopulation is given by

$$\frac{d\alpha_T}{dt} = \alpha_T^2 \left( \left( 1 - p_b \left( 1 - h_{\text{eff}} \frac{H}{M} \right) \right) e - d - \frac{F_d + F_u - D}{M} \right) + \alpha_T \left( d - e + \frac{F_d + T - D}{M} \right)$$

$H$ = number of diagnosed on HAART

$h_{\text{eff}}$ = fraction virally suppressed on HAART

$M$ = number of people known to be living with HIV/AIDS

$T$ = rate of new HIV diagnosis

The equation for $\alpha_T$ has the form of the Bernoulli differential equation:

$$\frac{d\alpha_T}{dt} + p(t)\,\alpha_T(t) = q(t)\,\alpha_T^2(t)$$

Can be solved by integrating factors.

However, $p(t)$ and $q(t)$ are only known as data time series.

- The differential equation for $\alpha_T$ is solved numerically using Euler's method.
- It has three free parameters:

$e$ = number of new HIV infections generated by each HIV+ individual per unit time

$p_b$ = factor by which the undiagnosed transmission rate is reduced after diagnosis

$\alpha_0$ = value of $\alpha_T$ at an arbitrary "initial" or reference time $t_0$

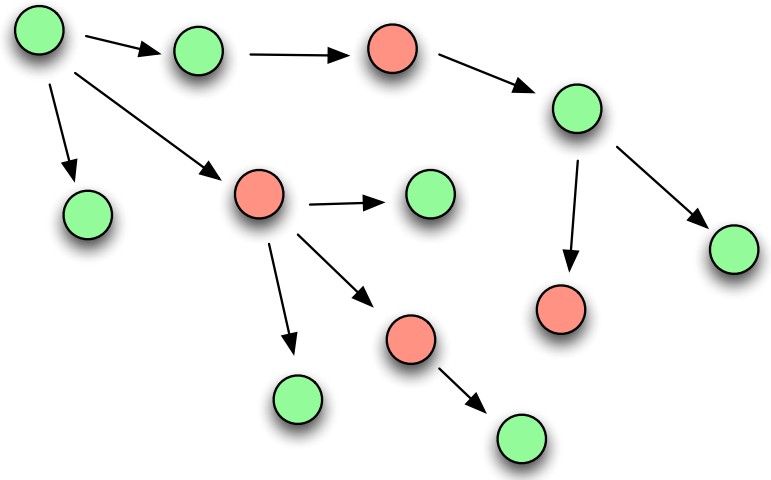
# Genetic Distance Model

## Overview

- Utilises viral RNA sequence data from genotypic drug resistance tests, which are done for every new diagnosis.
- HIV evolves continually and its genetic sequence diverges from a given ancestor with each transmission.
- As the fraction diagnosed increases it becomes more likely that a sequence and its closes ancestor are both in the genetic database.

# Genetic Distance Model
## Transmission Network

Genetic distance computations using genotypic drug resistance data can be used to construct the HIV transmission network.



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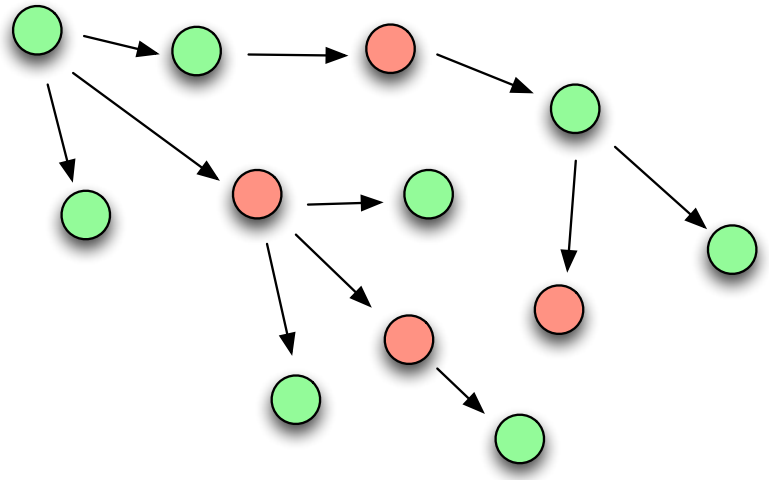
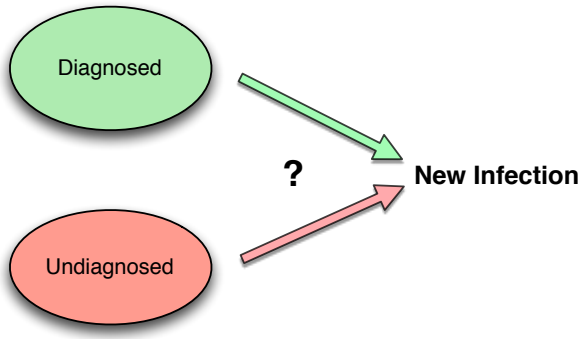


Constructing the transmission network for a large population is very computationally expensive.

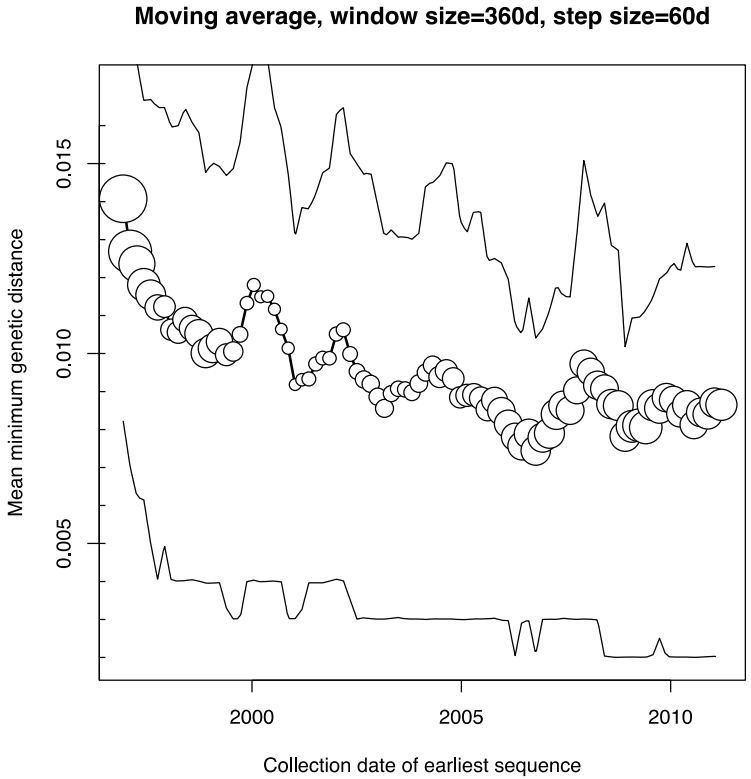
**Do we really need to construct the network?**



# Genetic Distance Model
## Population Genetic Distance

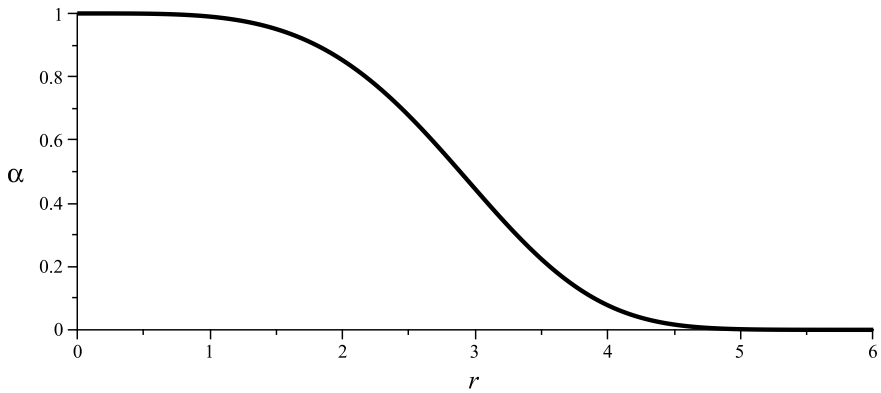
$$r(t) = \underset{\substack{i \text{ at} \\ \text{time } t}}{\text{ave}} \left[ \min_{\substack{j \text{ at time} \\ \tau < t}} g(i,j) \right]$$

where $g(i,j)$ is the Tamura-Nei genetic distance between virus $i$ and virus $j$.




K. Tamura and M. Nei, *Mol Biol Evol*, **10** (1993).

The fraction diagnosed as a function of the population genetic distance has the form of a decreasing function from 1 to 0.




This family of functions is modelled by

$$\alpha_G(r) = e^{-cr^k}$$

where $c > 0$ and $k > 0$ are free parameters.

# Optimisation and Monte Carlo Simulations

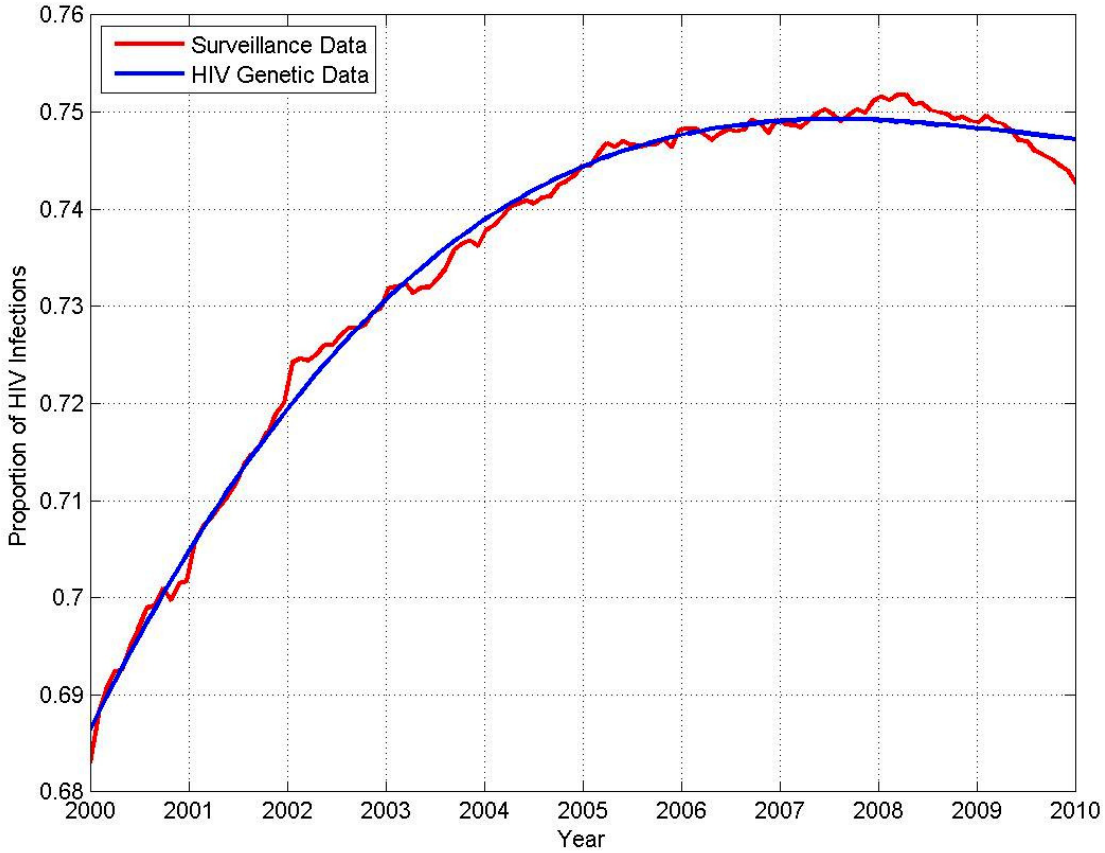
Tabu search is used to find the values of the 5 parameters $e$, $p_b$, $\alpha_0$, $c$, and $k$ that minimise the objective function

$$F(\alpha_0, e, p_b, c, k) = \sum_i \frac{\left(\alpha_T(\alpha_0, e, p_b; t_i) - \alpha_G(c, k; t_i)\right)^2}{\alpha'_G(t_i)} .$$

A bias is introduced into the solution for $\alpha_T$ by the choice of reference time $t_0$. A Monte Carlo simulation is done in which the optimisation is repeated for randomly chosen $t_0$.

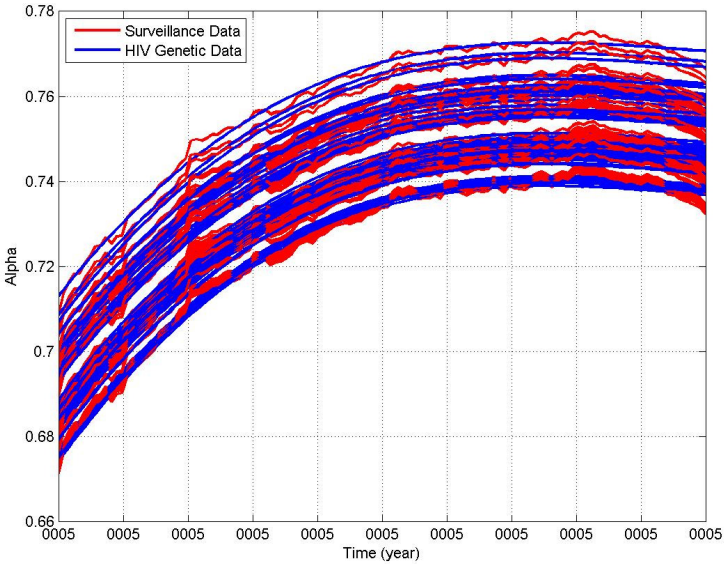
The results of the Monte Carlo are used to calculate $\alpha$, HIV prevalence, and HIV incidence. The empirical distribution of Monte Carlo results is used to calculate confidence intervals.

A single tabu search result for the fraction diagnosed from the transmission model $\alpha_T$ to a spline-smoothing of the fraction diagnosed from the genetic distance model $\alpha_G$.

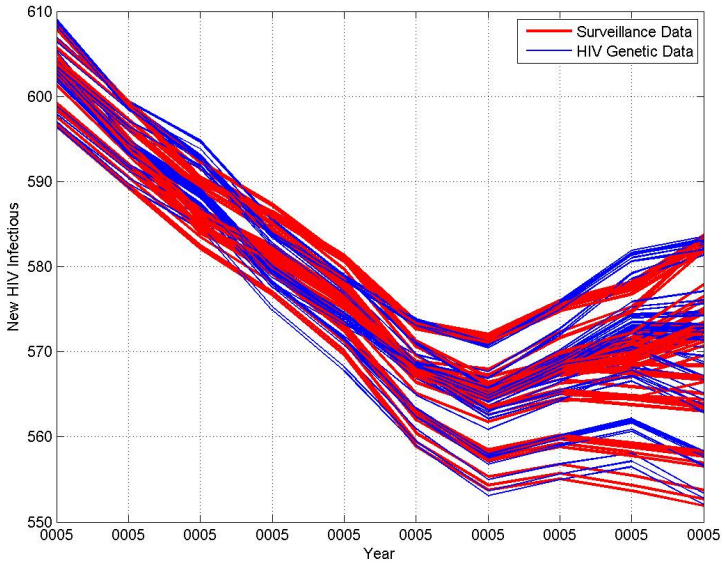


# Monte Carlo Simulations

Results of the Monte Carlo simulation for 71 tabu search optimisations with randomly chosen reference times $t_0$ for the transmission model.



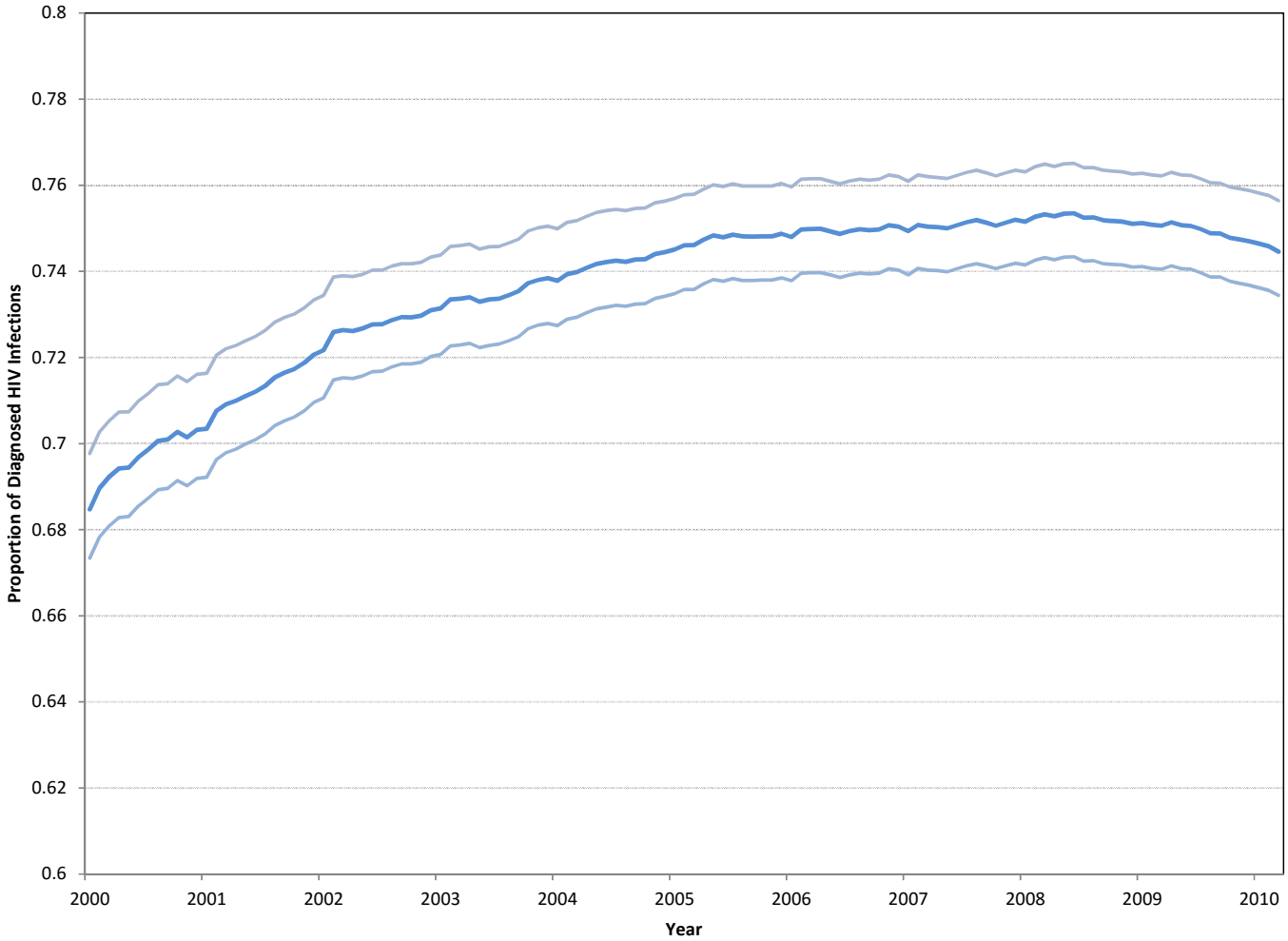

Fraction Diagnosed




HIV Incidence

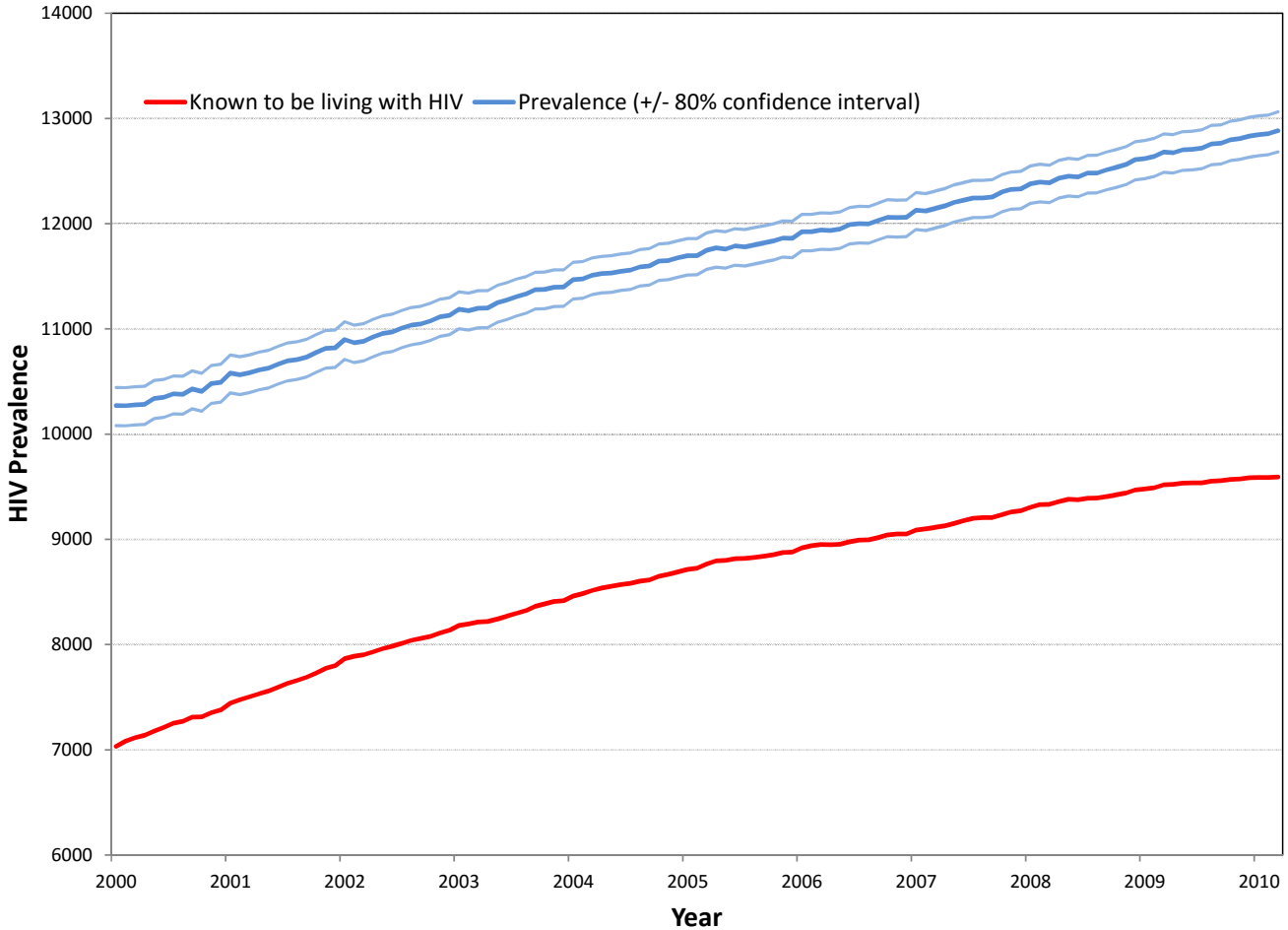
# Diagnosed Fraction of HIV+ Subpopulation
## British Columbia

Model results for the fraction of the HIV+ subpopulation in British Columbia that was diagnosed from 2000 to 2010.



# HIV Prevalence
## British Columbia

Comparison of model results for HIV prevalence in British Columbia to the number of people known to be living with HIV/AIDS.



# HIV Incidence

HIV incidence may be obtained from the model results for $\alpha$, the fraction diagnosed, using the equation

$$I = Me\left(\frac{1}{\alpha} - 1 + p_b\left(1 - h_{\text{eff}}\frac{H}{M}\right)\right)$$

where

$M$ = number of people known to be living with HIV/AIDS

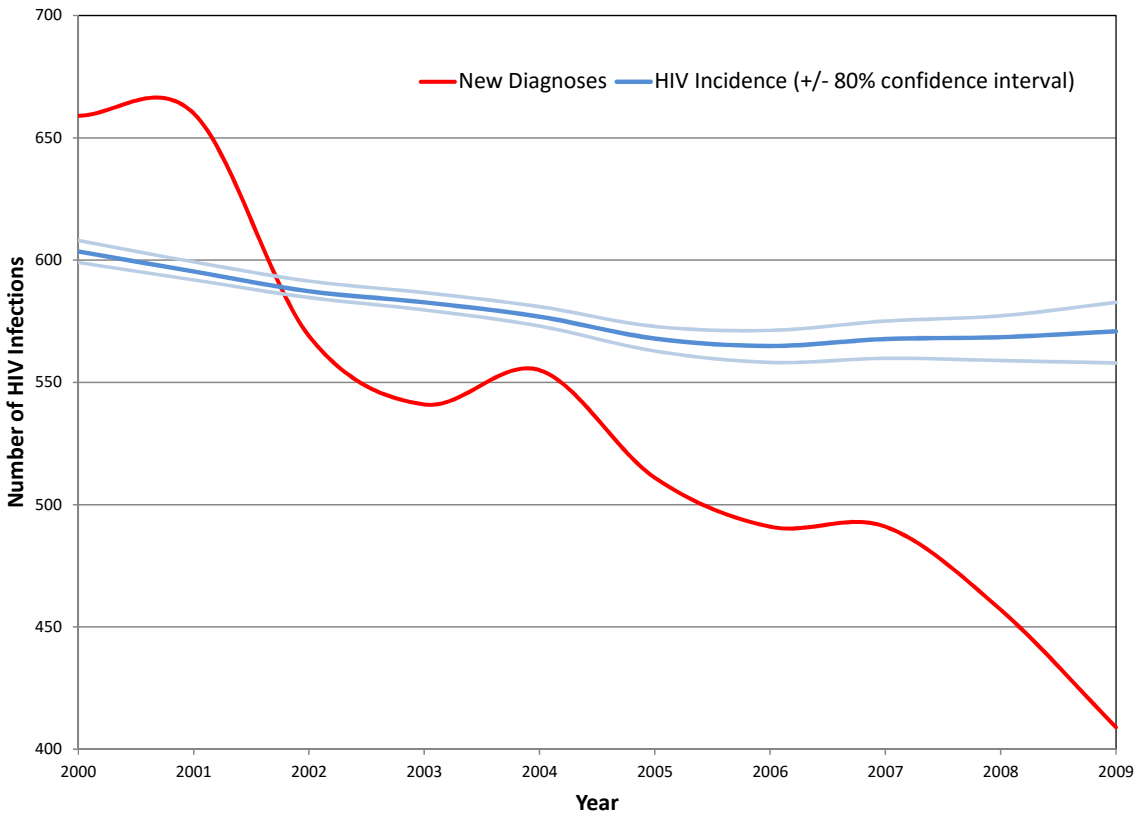
$p_b$ = factor by which the undiagnosed transmission rate is reduced after diagnosis

$h_{\text{eff}}$ = fraction virally suppressed on HAART

$H$ = number of diagnosed on HAART

# HIV Incidence
## British Columbia

Comparison of model results for HIV incidence in British Columbia to the number of new diagnoses.



# Validation

| Parameter | Estimate from Model | Estimate from Literature | Reference |
|---|---|---|---|
| Proportion diagnosed in 2002 | 0.80 | 0.76 | PHAC 2006 |
| Proportion diagnosed in 2005 | 0.82 | 0.79 | PHAC 2006 |
| Proportion diagnosed in 2008 | 0.83 | 0.81 | PHAC 2008 |
| Reduction in transmission due to behaviour change after diagnosis ($p_b$) | 0.45 | 0.29 | Marks, et al., AIDS, 2006 |
| Transmission rate for undiagnosed ($e$) | 0.11 | 0.069 | Marks, et al., AIDS, 2006 |
| HIV incidence in 2005 | 548 | 320 - 620 | BCCDC 2010 |
| HIV incidence in 2008 | 538 | 280 - 540 | BCCDC 2010 |
| HIV prevalence in 2005 | 10,560 | 10,350 (8,300 – 12,400) | BCCDC 2010 |
| HIV prevalence in 2008 | 11,108 | 11,400 (9,300 – 13,500) | BCCDC 2010 |

# Future Work

- Analyse more recent data from British Columbia
  - STOP HIV/AIDS programme data
- Time-dependent model parameters
  - requires sufficient data
- Apply to other jurisdictions
- Compare to other methods for estimating HIV incidence
  - retrospective cohort studies
    - often focused on specific risk groups
  - incidence assays

# Thank You

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