Multi-state Markovian model for estimating HIV incidence from French surveillance data: a simulation study

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Introduction
Context

- Epidemic still active and difficult to control:
  - Approximately 6,500 HIV-positive discoveries per year, stable since 10 years
  - Seropositivity findings mainly among MSM (44%) and foreign-born heterosexuals (39%)
  - Higher rates in French overseas territories and Ile-de-France
  - Population not knowing their HIV status at high risk of transmission
  - Measures to reduce transmission: condoms, preventive treatments (PreP), screening and rapid treatment
Objectives

Need to estimate and consolidate 3 epidemiological indicators:

- Number of people newly infected with HIV
- Number of people who do not know their HIV status
- The distribution of the time between infection and diagnosis
Existing methods for estimating HIV incidence in France from HIV mandatory notification

- Back calculation (INSERM U1136 and ISPED)\(^1\)\(^2\):
  - Use of historical data from clinical stage to diagnosis
  - Joint estimation of the incidence, the distribution of time between infection and diagnosis, and the seropositive population not knowing its status

- Methods from the recent infection test (SpF and ISPED)\(^3\)\(^4\):
  - Use of HIV serological markers TM and V3
  - Estimated only HIV incidence

HIV mandatory notification and virological surveillance:

- Since 2003 at Santé Publique France
- Sociodemographic characteristics
- Mode of contamination, reason for screening, clinical stage, history of HIV tests, date of possible contamination
- For the most recent years: CD4, antiretroviral treatments, viral load
- Virological surveillance: markers of recent infection to distinguish between recently infected and those who have been infected for longer
Simulation design
Simulation design : HIV incidence (1994-2018)

1) 1994-2003 : We generated the number of new HIV infection cases according to the following recurrence relation for $k = 1, \ldots, 10$ :

\[
\begin{align*}
    y_{2004} &= \lambda_{2004} \\
    y_{2004-k} &\sim \text{Poisson}(y_{2004-k+1} \times 1.07)
\end{align*}
\]

2) 2004-2015 : For each year $i$, we generated the number of new HIV infection cases, noted $y_i$, according to a Poisson distribution such as $y_i \sim \text{Poisson}(\lambda_i)$ with $\lambda_i$ the number of new HIV infection cases from previous study 5.

3) 2016-2018 : numbers of new HIV infection cases were simulated according to 3 different variation rates over the period : $-5\%$ per year, $0\%$ per year and $+5\%$ per year.

Simulation design: clinical stage at diagnosis date

- In the HIV mandatory notification, at time of diagnosis, a clinical stage for HIV is assigned to the individual by a medical doctor: primo-infection (PI), asymptomatic (ASY), symptomatic (SYM)) or AIDS

- This distribution does not really vary over time in the HIV mandatory notification, we chose the mean distribution over the period: 8.3% of HIV primo-infection, 61.6% of HIV asymptomatic, 13% of HIV symptomatic and 17.1% of AIDS

- For each individual, a clinical stage was assigned randomly, under the constraint of respecting this distribution
Simulation design : testing behaviours

- Simulated HIV test dates depend on the frequency of testing among diagnosed individuals. Indeed, individuals have different HIV testing behaviours and we distinguished regular testers from non-regular testers.

- The proportion of regular testers in the HIV mandatory notification was stable since 2004, we chose the mean distribution of 23% using the following definition:
  - Regular tester: last negative HIV test in 2 years before his positive test date
  - Non regular tester: last negative HIV test more than 2 years before his positive test date

- Primo infection, symptomatic and AIDS: 100% non regular testers

- Asymptomatic: 23% regular testers and 77% non regular testers

Simulation design: diagnosis date (1)

For primo infection stage, symptomatic stage and AIDS stage:

- Primo-infection stage: time from infection to diagnosis was assumed to be uniform between 2 weeks and 6 weeks.
- Symptomatic stage: duration from infection to diagnosis was generated according to a cumulative distribution \( F_{SYM}(t) \) obtained from previous study\(^7\) giving a median of 4.3 years.
- AIDS stage: the AIDS incubation was generated according to a Weibull distribution\(^8\) \[ F_{AIDS}(t) = 1 - \exp\left(-0.0215t\right)^{2.516} \] with a median of 10 years.

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Simulation design : diagnosis date (2)

☐ For asymptomatic stage :

- For non regular testers : duration from infection to diagnosis was generated according to a cumulative distribution $F_{ASYM}(t)$ obtained from previous study\(^9\) giving a median of 2.3 years.

- For regular testers : duration between infection and diagnosis was generated according to a renewal process\(^10\)\(^11\)\(^12\).

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Simulation design : diagnosis date (3)

Figure 1: Renewal process for regular testers

- $X \sim \text{exp}\left(\frac{1}{\mu}\right)$ with $\mu$ the mean of time between last negative test and first positive test, for regular testers with a positive recent infection test at the diagnosis\textsuperscript{13}.

- In the HIV mandatory notification $\mu = 9.23$ months, so the renewal process $X \sim \text{exp}(\frac{1}{\mu} = 0.11)$.

\textsuperscript{13} R. Song et al. (2005). In : Commun Stat Theory Methods 34.8.
Simulation design : summarize

- We know the theoretical incidence

- For each individual, we know:
  - His clinical stage at diagnosis
  - His diagnosis date
  - His infection date
  - His testing behaviours
Multi-state Markov model
Multi-state Markov model

Figure 2: Multi-state Markov model describing the progression of HIV infection.
Likelihood of the model (1)

- Poisson process in discrete time
- Using the same approach as in Aalen et Al.\textsuperscript{14}, we can then write the expected number of individuals in states 1 to 8 at the time $t_i$ with the vector $E_i = (E_{i,l})$, $l = 1, \ldots, 8$, by the relation of recurrence according to $P_i$ and $H_i$:

$$\begin{cases} E_0 = H_0 \\ E_i = P_i^T E_{i-1} + H_i, \, i = 1, 2, \ldots, K \end{cases}$$

- $H_i = \left( h_i = \int_{t_{i-1}}^{t_i} \nu(x)dx, 0, 0, 0, 0, 0, 0, 0 \right)^T$

- $P_i = (\alpha_{k,l}^i)$ where $\alpha_{k,l}^i$ is the transition probabilities of state $k$ to state $l$ between $t_{i-1}$ and $t_i$ with $k, l = 1, 2, \ldots, 8$:
  - Homogeneous markov model: $P_i$ is no time dependant
  - Non-homogeneous markov model, $P_i$ is time dependant

Expected number of new positive HIV diagnoses in the week $T_i, i = 1, ..., K$ is expressed by:

- $e^4_i = E_{i-1,3}\alpha_{3,4}$ the expected number of individuals entering in AIDS stage (state 4) in week $T_i$
- $e^5_i = E_{i-1,1}\alpha_{1,5}$ the expected number of individuals entering in primo-infection stage (state 5) in week $T_i$
- $e^6_i = E_{i-1,2}\alpha_{2,6}$ the expected number of individuals entering in asymptomatic stage (state 6) in week $T_i$
- $e^7_i = E_{i-1,3}\alpha_{3,7}$ the expected number of individuals entering in symptomatic stage (state 7) in week $T_i$
Penalized likelihood (1)

□ The likelihood of the model can be expressed as follow :

\[ L = \prod_{i=H}^{K} \prod_{j=4}^{7} (e_{ij}^i)^{n_j^i} \exp(-e_{ij}^i) \]

□ Smooth curve, no negative values and low local variations

□ The penalized likelihood is :

\[ pl = \log(L) - \lambda \int \nu''(u)^2 du \]

□ Parameters to be estimated are \( \alpha_{1,5} = (\alpha_{1,5}^1, \alpha_{1,5}^2, \ldots, \alpha_{1,5}^K) \), \( \alpha_{2,6} = (\alpha_{2,6}^1, \alpha_{2,6}^2, \ldots, \alpha_{2,6}^K) \), \( \alpha_{3,7} = (\alpha_{3,7}^1, \alpha_{3,7}^2, \ldots, \alpha_{3,7}^K) \) and \( \nu(.) \).

Penalized likelihood (2)

- $\nu(.)$ is approximated by a base of $M$-splines Cubic functions of order 4 $^{17}$:

$$\tilde{\nu}(.) = \sum_{j=1}^{Q+2} \theta_j M_j(.)$$

- For a fixed value of $\lambda$ we try to estimate the vector of parameters $\hat{\Theta}_\lambda = (\hat{\theta}, \hat{\alpha}_{1,5}, \hat{\alpha}_{2,6}, \hat{\alpha}_{3,7})$ which maximizes the penalized log-likelihood

- $\lambda$ is by a cross-validation approximation and then injected in the penalized likelihood for maximisation with Marquardt algorithm $^{18}$

Simulation results
Simulation results

- Results presented after were obtained from 200 simulations.
- We present results obtained from the increasing trend for the last 3 years.
- On the left we presented results with homogeneous Markov model: only one transition probabilities matrix for the period 2004-2018 (3 transition probabilities).
- On the right we presented results with non-homogeneous Markov model. We defined 5 times periods of 3 years: 5 transition probabilities matrix for the period 2004-2018 (15 transition probabilities).
Incidences and global diagnosis

Figure 3: Estimated incidence and global diagnosis. Homogeneous period at left and non-homogeneous period by 3 years at right.
Estimated diagnosis for state 4 and state 5

Figure 4: Estimated number of diagnosis. Homogeneous period at left and non-homogeneous period by 3 years at right.
Estimated diagnosis for state 6 and state 7

Figure 5: Estimated number of diagnosis. Homogeneous period at left and non homogeneous period by 3 years at right.
Discussion
Discussion and perspective

- The model presented here is a new useful tool for estimating the incidence of HIV infection using all informations from the clinical stages of French data.

- Need to consolidate the simulation

- The model will then be expanded to include biomarkers of recent infection and take into account any relevant information provided by mandatory reporting of HIV.

Perspective : Application of the method in the HIV mandatory notification database :

- Global estimation of the incidence
- Estimation of the incidence by transmission groups
- Estimation of the incidence by geographical area
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**SONG, R. et al. (2005).** « Distribution of renewal variables when renewal process reaches a special event ». In : *Commun Stat Theory Methods* 34.8, p. 1813-1819.