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

1. C. Sommen et al. (2009). In : *Stat Med* 28.
2. L. Marty et al. (2018). In : *J Int AIDS Soc* 21.3.
3. C. Sommen et al. (2011). In : *Biometrics* 67.2.
4. S. Le Vu et al. (2010). In : *The Lancet, Infectious Diseases* 10.10.

HIV diagnoses surveillance data

- 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 $k = 1, ..., 10$:

$$\begin{cases} y_{2004} = \lambda_{2004} \\ y_{2004-k} \sim Poisson(y_{2004-k+1} \times 1.07) \end{cases}$$

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 $y_i \sim Poisson(\lambda_i)$ with λ_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% pear year

5. L. MARTY et al. (2018). In : *J Int AIDS Soc* 21.3.

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 [6] :
  - 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

6. M. S. JAMIL et al. (2017). In : *Lancet HIV* 4.6.

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] $F_{AIDS}(t) = 1 - \exp -(0.0215t)^{2.516}$ with a median of 10 years.

7. C. SOMMEN et al. (2009). In : *Stat Med* 28.
8. R. BROOKMEYER et al. (1989). In : *Stat Med* 8.1.

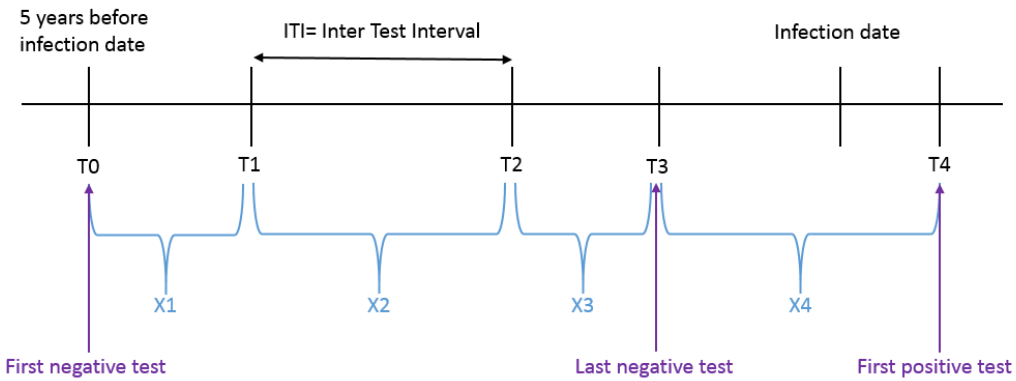
Simulation design : diagnosis date (2)

- 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].

9. C. Sommen et al. (2009). In : *Stat Med* 28.
10. J. M. Karon et al. (2008). In : *Stat Med* 27.23.
11. Q. An et al. (2017). In : *Am J Prev Med* 53.3.
12. R. Song et al. (2005). In : *Commun Stat Theory Methods* 34.8.

Simulation design : diagnosis date (3)

Figure 1 : Renewal process for regular testers



- $X \sim exp(\frac{1}{\mu})$ with μ the mean of time between last negative test and first positive test, for regular testers with a positive recent infection test at the diagnosis [13].
- In the HIV mandatory notification $\mu = 9.23$ months, so the renewal process $X \sim exp(\frac{1}{\mu} = 0.11)$.

13. R. SONG et al. (2005). In : *Commun Stat Theory Methods* 34.8.

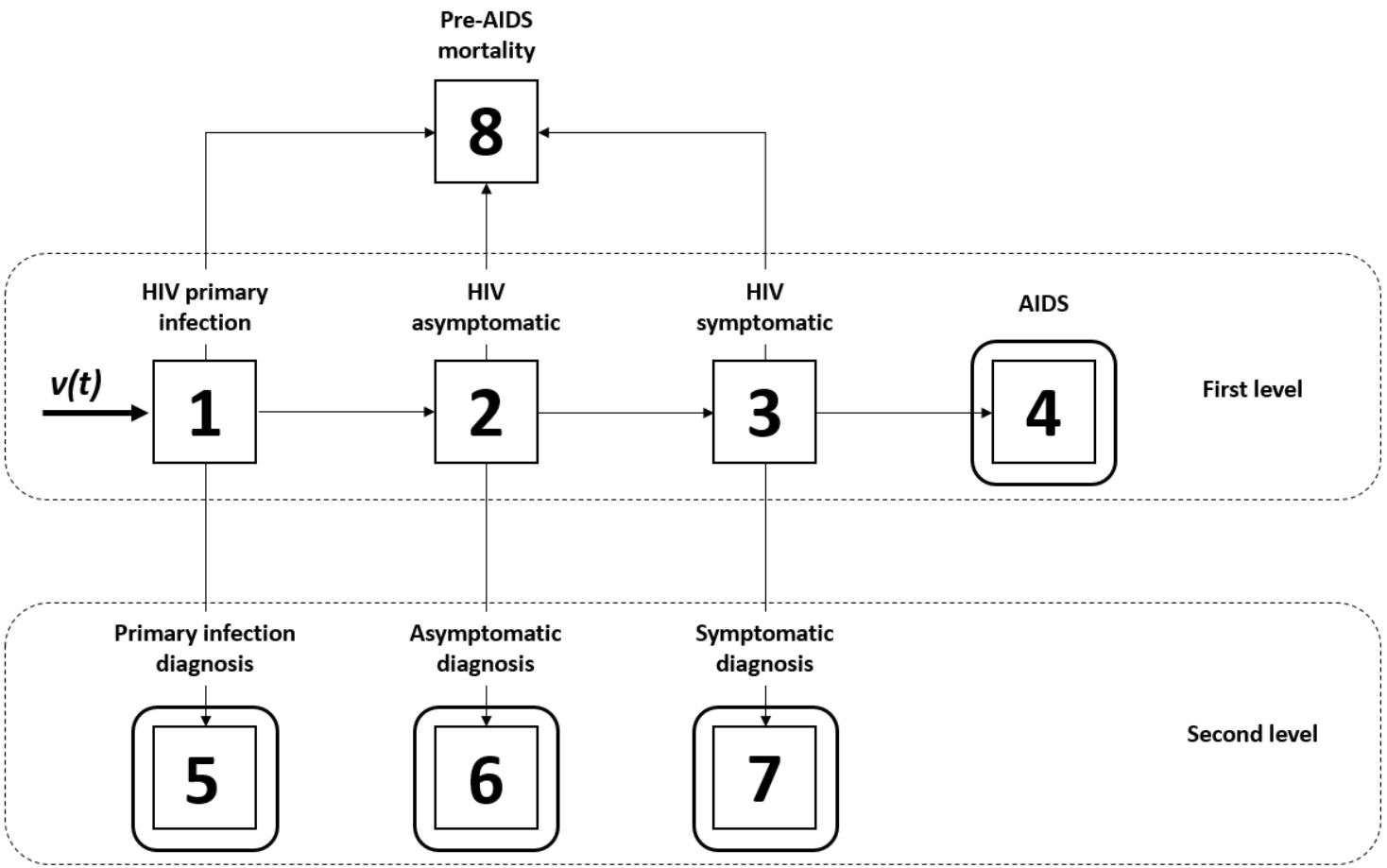
Simulation design : summarize

- We know the theorical 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.[14], we can then write the expected number of individuals in states 1 to 8 at the time t_i with the vector $E_i = (E_{i,l}), l = 1, ..., 8$, by the relation of recurrence according to P_i and H_i :

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

- $H_i = \left(h_i = \int_{t_{i-1}}^{t_i} \nu(x)\mathrm{d}x, 0, 0, 0, 0, 0, 0, 0 \right)^T$
- $P_i = (\alpha_{k,l}^i)$ where $\alpha_{k,l}^i$ is the transition probabilities of state k to state l between t_{i-1} and t_i with $k, l = 1, 2, ..., 8$:
  - Homogeneous markov model : P_i is no time dependant
  - Non-homogeneous markov model, P_i is time dependant

14. O. O. Aalen et al. (2007). In : *Stat Med* 16.19.

Likelihood of the model (2)

- Expected number of new positive HIV diagnoses in the week $T_i, i = 1, ..., K$ is expressed by :
  - $e_i^4 = E_{i-1,3}\alpha_{3,4}$ the expected number of individuals entering in AIDS stage (state 4) in week T_i
  - $e_i^5 = E_{i-1,1}\alpha_{1,5}$ the expected number of individuals entering in primo-infection stage (state 5) in week T_i
  - $e_i^6 = E_{i-1,2}\alpha_{2,6}$ the expected number of individuals entering in asymptomatic stage (state 6) in week T_i
  - $e_i^7 = E_{i-1,3}\alpha_{3,7}$ 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 :

$$L = \prod_{i=H}^{K} \prod_{j=4}^{7} (e_i^j)^{n_i^j} exp(-e_i^j)$$

- Smooth curve, no negative values and low local variations
- The penalized likelihood is : [15] [16]

$$pl = \log(L) - \lambda \int \nu''(u)^2 \mathrm{d}u$$

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

15. I.J. GOOD et al. (1980). In : *Journal of the American Statistical Association* 75.369.
16. P. JOLY et al. (1998). In : *Biometrics* 54.

Penalized likelihood (2)

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

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

- For a fixed value of λ 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
- λ is by a cross-validation approximation and then injected in the penalized likelihood for maximisation with Marquardt algorith [18]

17. P. JOLY et al. (1998). In : *Biometrics* 54.
18. D. MARQUARDT (1963). In : *SIAM Journal on Applied Mathematics* 11.

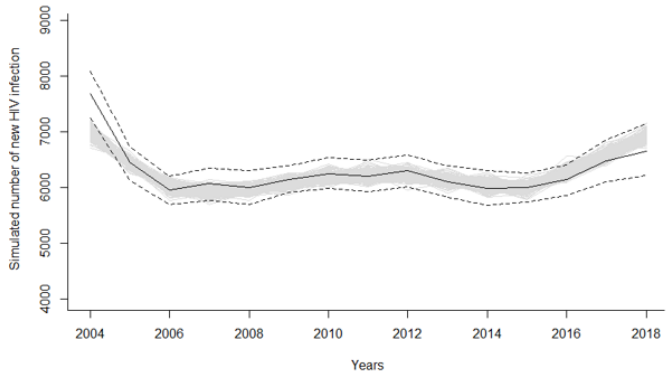
Simulation results

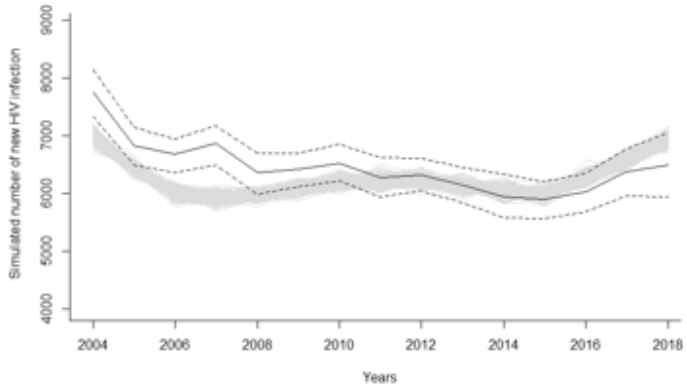
Simulation results

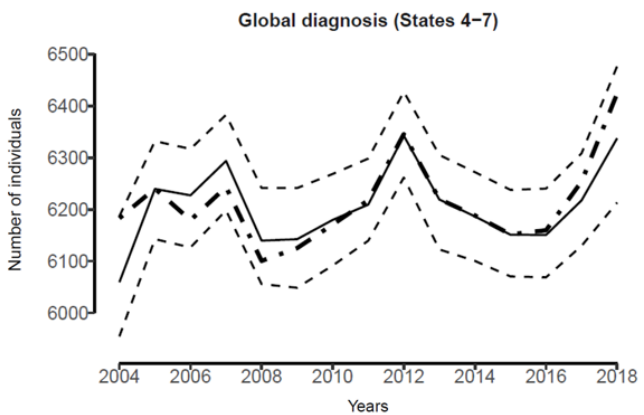
- Results presented after were obtained from 200 simulations
- We present results obtained from the increasing trend for the last 3 years
- On the left we presented results with homogeneous Markov model : only one transition probabilities matrix for the period 2004-2018 (3 transition probabilities)
- 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)

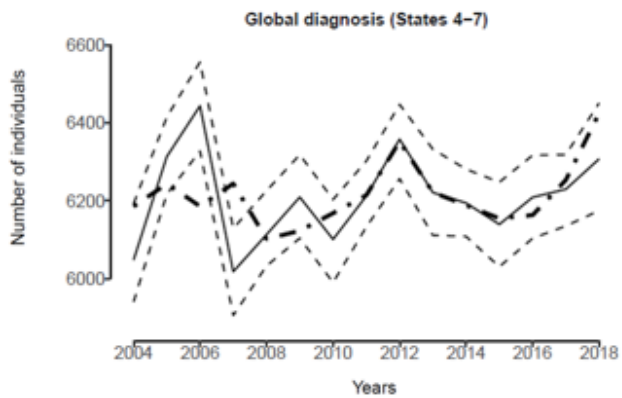
Incidence and global diagnosis

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



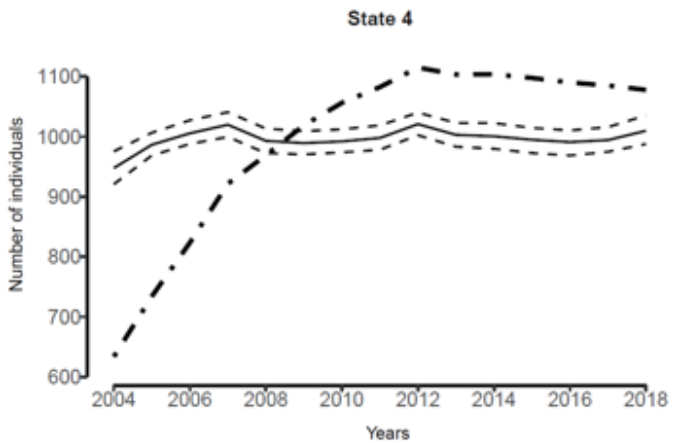


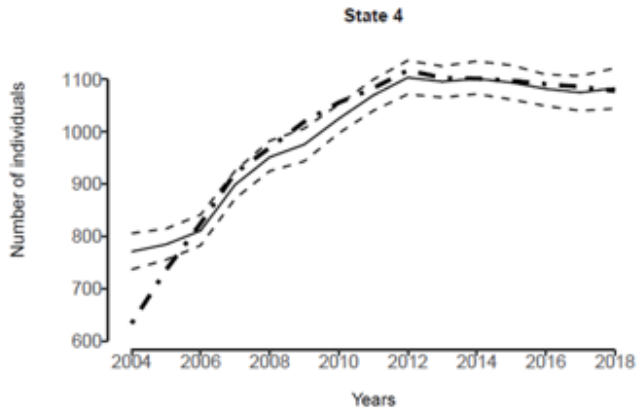


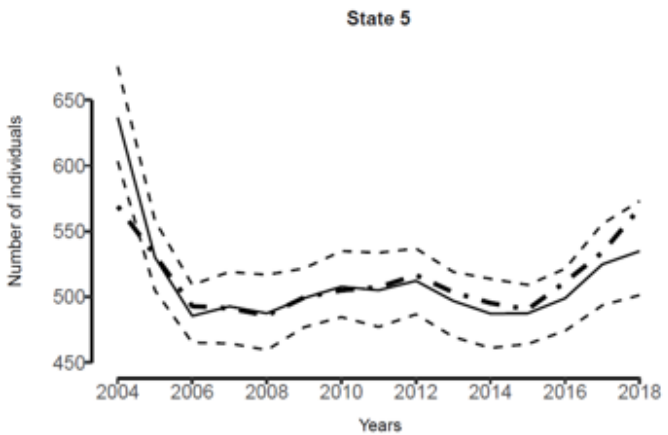


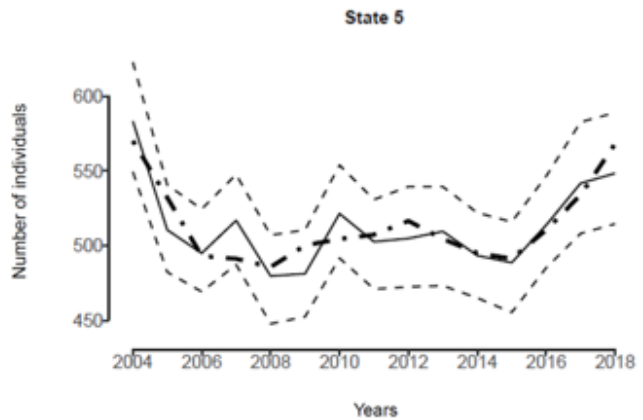
Estimated diagnosis for state 4 and state 5

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



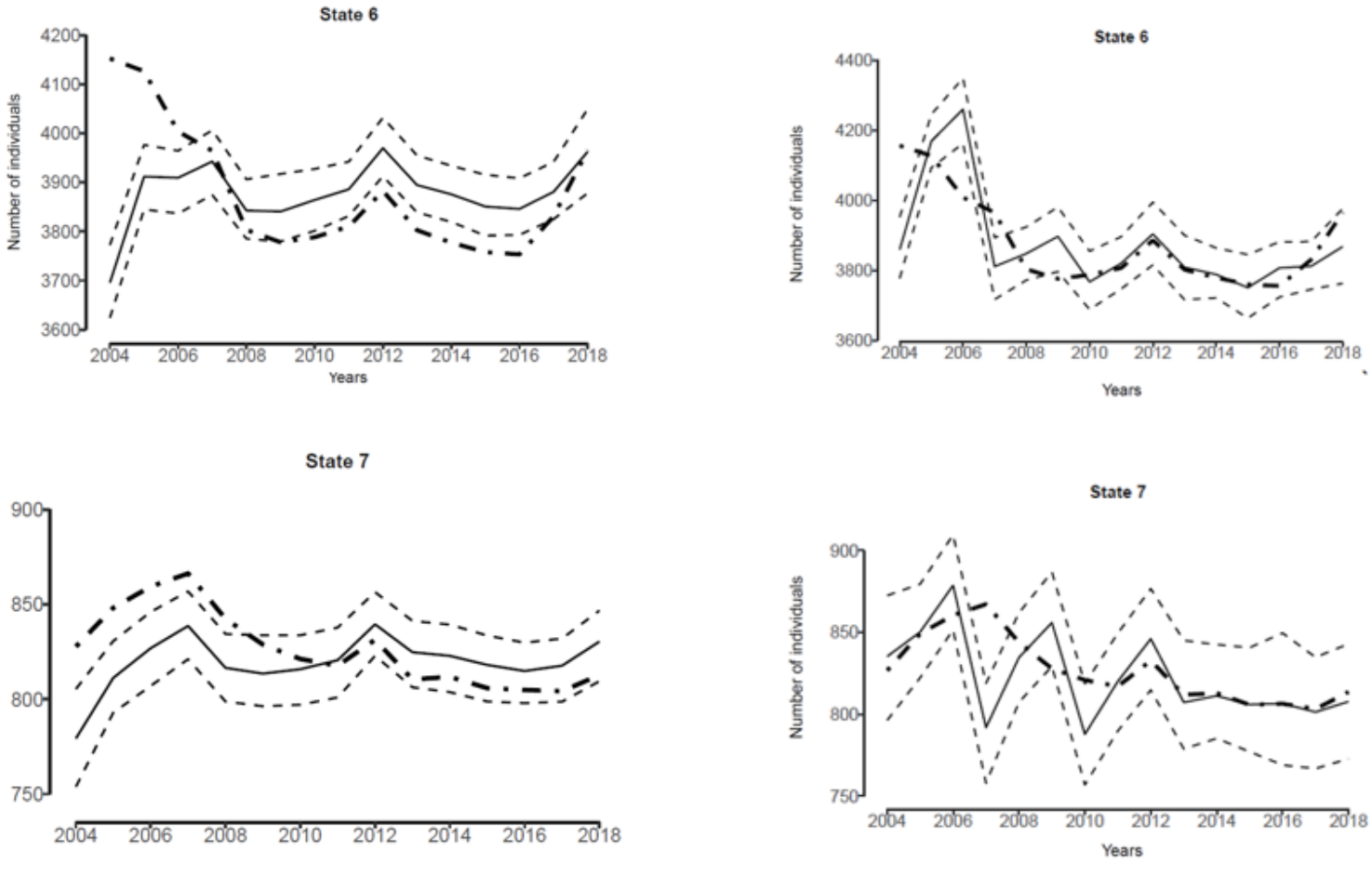






Estimated diagnosis for state 6 and state 7

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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