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## **Treatment as prevention enrolling at least 75% of individuals on ART will be needed to significantly reduce HIV prevalence in a HIV cohort**

Helene Jeulin, Eliette Jeanmaire, John Murray, Brice Malve, Marie André, Hugues Melliez, Jean-Philippe Lanoix, Laurent Hustache-Mathieu, Marialuisa Partisani, François Goehringer, et al.

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1 **Title page.**

2 **Treatment as Prevention enrolling at least 75 percent of individuals on ART will be**  
3 **needed to significantly reduce HIV prevalence in a HIV cohort**

4 *Running head: Enrolling 75% of untreated individuals on ART to reduce HIV diagnoses and*  
5 *prevalence by 2021*

6 Authors: H el ene Jeulin<sup>1\*</sup> P.D. PhD, Eliette Jeanmaire<sup>2\*</sup> M.D., John M Murray<sup>3,4</sup> PhD, Brice Malve<sup>1</sup>  
7 P.D., Marie Andr e<sup>2</sup> M.D., Hugues Melliez<sup>5</sup> M.D., Jean-Philippe Lanoix<sup>6</sup> M.D., Laurent Hustache-  
8 Mathieu<sup>7</sup> M.D., Marialuisa Partisani<sup>8</sup> M.D., Fran ois Goehringer<sup>2</sup> M.D., Thierry May<sup>2</sup> M.D. PhD,  
9 Evelyne Schvoerer<sup>1</sup> M.D. PhD

10 \*Both authors equally contributed to the work

11 <sup>1</sup> Laboratoire de Virologie, H opital Brabois, CHRU de Nancy, Vandoeuvre-les-Nancy, France  
12 et LCPME (Laboratoire de Chimie Physique et Microbiologie pour les Mat riaux et  
13 l'Environnement), UMR 7564, Facult  de Pharmacie, Nancy F-54000, France

14 <sup>2</sup> Service de Maladies Infectieuses et Tropicales, H opital Brabois, CHRU de Nancy,  
15 Vandoeuvre-les-Nancy, France

16 <sup>3</sup> School of Mathematics and Statistics, UNSW Sydney, NSW 2052, Australia

17 <sup>4</sup> Cancer Research Division, Cancer Council NSW, Woolloomooloo, NSW 2021, Australia

18 <sup>5</sup> Service de Maladies Infectieuses et Tropicales, H opital Guy Chatiliez, CH Tourcoing,  
19 Tourcoing, France

20 <sup>6</sup> Service de Maladies Infectieuses et Tropicales, CHU Amiens, Amiens, France

21 <sup>7</sup> Service de Maladies Infectieuses, H opital Jean Minjot, CHRU de Besan on, Besan on, France

22 <sup>8</sup> HIV Infection care Center, H opitaux Universitaires Strasbourg, Strasbourg, France

23 Corresponding author:  
24 Pr Evelyne Schvoerer  
25 Tel. +33383155269  
26 Fax 333831573474  
27 Email [e.schvoerer@chru-nancy.fr](mailto:e.schvoerer@chru-nancy.fr)  
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30 **Abstract (250 words)**

31 Background. "Treatment as Prevention" (TasP) aims to reduce new HIV infections through  
32 higher enrolment on suppressive antiretroviral therapy (ART).

33 Objectives. We studied the current epidemic and possible impact of TasP in a French HIV  
34 cohort including MSM and migrant subjects.

35 Study design. Socio-demographic, clinical and laboratory variables were collected during the  
36 follow-up of 6995 HIV-infected patients. The numbers of individuals living with HIV in each year  
37 were estimated from diagnoses up to that year minus recorded deaths. Patients were classified  
38 according to gender, transmission mode, country of birth and treatment status.

39 Results. The cohort includes 6995 individuals diagnosed from 1985 to 2015, of whom 72% were  
40 men. Unprotected sexual intercourse was the main mode of transmission. Women were more  
41 likely to be migrants (45% versus 13%), whereas men were more likely to have been born in  
42 France (52% versus 27%). Diagnoses were more correlated with untreated than treated  
43 prevalence in each group. MSM diagnoses was strongly correlated to untreated prevalence  
44 whatever the country of birth ( $p < 0.0001$ ). However, heterosexual diagnoses were better  
45 correlated with prevalence within individual country groups ( $b = 0.29$  female diagnoses/year per  
46 untreated male born in France, compared to  $b = 0.73$  for foreigners). Using these transmission  
47 rates, mathematical modelling estimated that enrolling 75% of untreated individuals per year  
48 would decrease diagnoses ten-fold by 2021.

49 Conclusions. Enrolling at least 75% of individuals on ART is necessary to substantially impact  
50 numbers of new HIV infections in this cohort. Treatment as prevention will actually be effective  
51 to reduce HIV prevalence.

52

53 Keywords: Treatment as prevention, antiretroviral therapy, HIV prevalence

54

55 **Background**

56 In recent years, the data on reducing the risk of HIV transmission from treated individuals, have  
57 resulted in a new place for antiretroviral therapy (ART) in prevention strategies (1,2). "Treatment  
58 as Prevention" (TasP) in combination with "Test and Treat" provide both individual and  
59 collective benefits reducing the risk of HIV transmission and acquisition (3). HIV viral load is the  
60 main predictor of the risk of HIV-1 heterosexual transmission (2,4, 5). By lowering a  
61 community's viral load (CVL), TasP can contribute to decrease new HIV infections within a  
62 community as observed in San Francisco (6). This was also proven in Northern and Eastern  
63 France, between 2005 and 2010 (7).

64 The extent to which TasP could contribute to eradication of HIV infection in France is a key  
65 issue. Several mathematical models have been used to estimate the long-term impact of these  
66 strategies. Granich et al. demonstrated that annual screening with immediate treatment in  
67 heterosexual men in South Africa would reduce HIV incidence within 10 years (8).

68 More recently, the impact of TasP on estimated future HIV prevalence and incidence was  
69 evaluated in a high income country setting, Australia. Clinical and biological data were used to  
70 predict the number and age distribution of MSM living with HIV in the future. Simulation of  
71 increasing ART usage estimated that 90% ART enrollment could reduce HIV prevalence (9).

72 **Objectives**

73 The present study investigated the current context and the prediction of the evolution for HIV  
74 infection in a French cohort against the backdrop of TasP and Test and Treat, with the  
75 complication that HIV infected patients are quite heterogeneous in France, including MSM and  
76 migrant populations.

77

## 78 Study design

79 This study was performed on a cohort of French HIV-infected patients. It was a multicentric  
80 study. Socio-demographic variables, clinic and laboratory data were collected in an electronic  
81 medical database (Nadis® - available for the patients cohort since 2005) during the follow-up of  
82 HIV-infected patients and were extracted for a descriptive analysis. Data from patients  
83 previously monitored (since 1985) were implemented when the database was created. The  
84 diagnosis refers to new infections or unknown older infection and was obtained either by  
85 symptomatic suspicion, or by periodic screening or during medical care.

86 Data were recorded for sex, each mode of transmission, country of birth and treatment status.  
87 The number of people living with HIV each year was estimated from diagnoses up to that year,  
88 minus background mortality as well as AIDS deaths (Figure 1A). HIV diagnoses from the  
89 database were grouped by exposure group  $g$  (restricted, to MSM, heterosexual men, and  
90 women, plus the country of birth: France, Other or unknown NR), 5-year age group  $a$ , and year  
91 of diagnosis  $i$ . Other groups were excluded due to the small size of the compartment.

92 The number of HIV infected individuals alive at year  $i + 1$  for the age group  $a$  and exposure  
93 group  $g$ ,  $H(i + 1, a, g)$ , was assumed equal to the number alive at year  $i$  minus those who died  
94 from AIDS in year  $i$ ,  $A(i, a, g)$ , or from non-AIDS causes at rate  $\mu(a, g)$ , plus those newly  
95 diagnosed  $I(i, a, g)$ . Because we group individuals into 5-year age groups, we assume 1/5<sup>th</sup> will  
96 age into the next age group each year. This gives the formula

$$97 \quad H(i + 1, a, g) = \frac{1}{5} [1 - \mu(a - 1, g)] (H(i, a - 1, g) - A(i, a - 1, g)) + \frac{4}{5} [1 - \mu(a, g)] (H(i, a, g) - A(i, a, g))$$
$$98 \quad \quad \quad + I(i, a, g)$$

99 Correlations between numbers of HIV diagnoses and the estimated number of individuals living  
100 with HIV in each year, determined for exposure groups, were calculated and these correlations  
101 used to predict future HIV incidence, with HIV prevalence being updated through the formula  
102 above.

103

## 104 **Results**

### 105 **Men were diagnosed later with lower CD4**

106 The cohort included 6995 individuals of whom 72% were men (Table 1). The cohort is  
107 diversified, including 44% of MSM and 45% of patients with heterosexual exposure. Only 44%  
108 of patients were known to be born in France, and 22% were foreigner, for the majority African  
109 (Table 2).

110 At diagnosis, men were statistically older (mean 37.5 (11.0 standard deviation (sd)) versus 34.6  
111 (11.6 sd) years,  $p < 0.0001$ ). Overall, CD4 count at diagnosis decreased with age, at the rate of  
112 3.76 cells/ $\mu$ L with each year of age ( $p = 1.26 \times 10^{-31}$ ), (Table 3). However CD4 count at  
113 diagnosis did not differ by gender (median 401 for men vs 379 for women, Figure 1B). People  
114 aged 40 or older were more likely to have a CD4 count  $< 100$  cells /  $\text{mm}^3$  at diagnosis (Figure  
115 1BC) ( $p < 0.0001$ ) with these more likely to be men (14% versus 11% in women) ( $p = 0.002$ ).

116

### 117 **Unprotected sexual intercourse as the main mode of transmission**

118 Unprotected sexual intercourse was the main mode of transmission, 87% for women and 89%  
119 for men with 61% of MSM transmissions. Women were more likely to be migrants (45% versus  
120 13%). Most of the MSM were born in France (59.34%), while only 33.64% of other patients were  
121 born in France. Individuals born in foreign countries ('Other') tended to show CD4  $< 300$   
122 cells/ $\text{mm}^3$  at diagnosis (46% versus 31% for those born in France).

### 123 **Estimated prevalence**

124 By incorporating diagnoses, deaths due to AIDS and other causes, and ageing of previously  
125 diagnosed individuals each year (see Methods), we could estimate the number and age

126 distribution of men and women living with HIV infection (Figure 1D). The relative decline in  
127 diagnoses over recent years, combined with ageing and associated increased death rates, has  
128 resulted in a stabilization of HIV prevalence in each gender, if not a slight decrease for women.

### 129 **HIV diagnoses were highly correlated with prevalence of untreated patients**

130 As might be expected numbers of Female and non-MSM Male diagnoses within each year were  
131 strongly correlated ( $p < 0.0001$ ,  $b = 0.78$  MSF/Female diagnoses). Numbers of diagnoses in each  
132 year were also correlated with estimated prevalence from the likely infecting group, with the  
133 correlations generally stronger with untreated compared to treated prevalence. Furthermore,  
134 diagnoses were also strongly correlated with estimated untreated prevalence when restricted to  
135 either France or Other (Figure 2). Female HIV diagnoses were correlated to numbers of men  
136 who acquired HIV through heterosexual transmission and where each were born in France  
137 ( $b = 0.29$ ) or elsewhere (Other  $b = 0.73$ ). Similarly strong correlations were obtained between non-  
138 MSM Male diagnoses and female untreated prevalence (France  $b = 0.36$ , Other  $b = 0.19$ ), as well  
139 as for MSM diagnoses and untreated MSM prevalence (France  $b = 0.32$ , Other  $b = 0.62$ ) (Figure  
140 2).

141 Enrolling 75% of untreated individuals per year would decrease HIV diagnoses. Our method of  
142 estimating treated and untreated prevalence year-by-year (separated into exposure groups and  
143 countries of origin), and the correlations between untreated prevalence and diagnoses in each  
144 year, allowed us to predict the future evolution of HIV prevalence and diagnoses. For example,  
145 the rate of  $b = 0.29$  female diagnoses in each year per estimated untreated non-MSM Male for  
146 country of origin France, suggested on average 0.29 women will become infected each year for  
147 each Male who is untreated at the beginning of that year (Sensitivity to these values was based  
148 on randomly drawing from the 95% confidence intervals) for these  $b$  values. Starting from  
149 prevalence estimates at the beginning of 2016 and the estimated number not enrolled on ART,  
150 we estimated numbers of new diagnoses in each of the exposure groups and by country of

151 origin in that year, through the rates determined between diagnoses and untreated prevalence  
152 (Figure 2). The age of individuals was not incorporated in these predictions so the annual death  
153 rate (0.89%) was determined from the Mortalite 2010 survey of deaths in patients with  
154 immunovirological success in France (10). Since the NR correlations were poor and numbers  
155 smaller than the other groups, the NR diagnoses for heterosexual transmission were  
156 proportionately distributed to the France and Other countries of origin. MSM diagnoses were  
157 more strongly correlated when combining all countries so future MSM predictions assumed a  
158 rate of 0.23 infections per year per untreated MSM. We assumed that once enrolled on ART  
159 individuals stayed on therapy.

160 A fraction  $T$  of these untreated individuals were then assumed enrolled on ART while the  
161 diagnoses in that year were added to the untreated cohort. Prevalence numbers were updated  
162 with diagnoses and death, and the process repeated each year.

163 Using these transmission rates, the mathematical modelling estimated that enrolling  $T \geq 35\%$  of  
164 untreated individuals per year onto ART, and adding them to the surviving 85% treated group of  
165 men and women living with HIV in 2015, was required to reduce future HIV diagnoses (Figure  
166 3A). Enrolling 75% of untreated individuals per year would decrease diagnoses by ten-fold by  
167 2021; prevalence in 2021 would be 10% lower than with 35% ART enrollment (Figure 3B). If the  
168 transmission rates for each Exposure type/Country/gender with a 75% enrollment rate are  
169 sampled from their 95% confidence intervals, we obtain the estimates of change in diagnoses  
170 and prevalence shown in Figure 3C.

171 The enrolment of untreated individuals on ART needs to be at least 40% per year if 90% of  
172 diagnosed individuals have to be treated by 2030. Given the larger average rate at which men  
173 infect women versus women infect men and the assumption that incident infections are  
174 untreated in their first year, women are slower to reach 90% treated compared to men. MSM

175 has an estimated per-act probability of acquiring HIV depending on insertive or receptive anal  
176 intercourse (11,12). The risk of MSM HIV infection is thus difficult to evaluate.

177

## 178 **Discussion**

179 In this study conducted in France, we determined that HIV infection incidence was more likely  
180 correlated with prevalence of untreated rather than treated patients in each group. Mathematical  
181 modelling predicted that enrolling 75% of untreated individuals on ART per year (TasP) would  
182 decrease incidence 10-fold in 2021 compared to an incidence of 310 new cases in 2015, even if  
183 the cohort is quite heterogeneous. We assumed that newly infected patients would not start  
184 ART within the first year. Since new diagnoses are expected to spread uniformly over the year,  
185 this means that on average new infections would be untreated for at least 6 months. Because of  
186 this and the estimated higher rates of transmission from males to females versus females to  
187 males, women are slower to reach 90% coverage than men, and their new diagnoses fail to  
188 decrease as quickly.

189 A recent study estimated that, among MSM, 3.4% of the new HIV cases would have been  
190 prevented by early initiation of ART, 7% by a 50% increased diagnosis rate, 11.5% by  
191 introducing Prep, and 18% by associated PreP and test and treat (13). In another agent-based  
192 simulation model including data on MSM, TasP would prevent 27.1% of infections (14). These  
193 population model-based strategies emphasize the role of ART in the combined strategies of HIV  
194 prevention.

195 In United Kingdom it was estimated that both increased testing and earlier ART are needed in  
196 order that men HIV prevalence to be less in 2030 than 2015. An incidence below 1/1000 will  
197 require 90% of virally suppressed HIV infected-MSM (15). Another mathematical model was  
198 developed to assess the benefit of coupling ART and PrEP. The authors concluded that  
199 combined PrEP and ART offers the best potential for substantial new HIV infection reduction

200 and that high adherence is a key to effectiveness. Elsewhere the model showed that an  
201 increase in the number of misdiagnosed infected individuals on PrEP, that generates PrEP drug  
202 resistance, could be a key driver of HIV infection spread (16). PrEP was authorized in France in  
203 2015 and consequently was not evaluated

204 For this study, exhaustive data on viral genotypes distribution are not available. In France, over  
205 1996 to 2006, the proportion of patients harboring HIV-1 non-B virus increased with time, from  
206 10% to 25.5% (17). In a representative sampling of our present cohort, a study from 2013 (18)  
207 found a majority of B subtypes (57.1%) and CRF02AG recombinant form (22.3%). We can  
208 assume that the genotypes distribution is different between MSM and migrants group. In 2007-  
209 2012 in France, the prevalence of non-B strains increased in heterosexuals and concomitantly  
210 decreased in MSM (19). Genotypic resistance tests performed at the time of primary infection  
211 and/or treatment initiation decrease the impact of genotypes or transmitted drug resistance on  
212 TASP efficacy.

213 By 2020, the 90/90/90 WHO recommendations aimed that 73% of HIV infected patients  
214 worldwide should be controlled for viral load. In Europe, this target is inconsistently reached  
215 varying to countries. In France it reached 85-91-97 in 2018 (20), meaning that reducing HIV  
216 prevalence is feasible according to our prevision. In other European countries the proportion  
217 diagnosed of people ranged from 38% to 98%, the proportion on ART ranged from 27% to 96%,  
218 and viral suppression rates ranged from 32% to 97%. The overall continuum of care is higher in  
219 western than in central regions and is much lower in eastern regions. In western countries, the  
220 lowest percentage on ART was in Southern Europe i.e. 61.9% (21). In Central and Eastern  
221 Europe the median of patients linked to care and treated was 31,5% (22), well below the WHO  
222 targets and the projection of our model. Moreover, within the same country, the continuum of  
223 care also varied according to the subgroups(23) as observed in our cohort.

224 Even within the same country and the same subgroup, HIV transmitters are not homogenous  
225 populations and transmission dynamics in HIV is very complex depending on viral load, number  
226 of transmission events and transmission efficacy (2,24). This is concordant with our study that  
227 displayed different results depending on the gender and the mode of sexual transmission.

228 There are some limitations to our study. First, this study may include bias related to missing  
229 data (i.e. country of origin). Indeed, the Nadis database was available since 2005 and previous  
230 data related to patient follow-up have been implemented retrospectively. Because we did not  
231 include age in predictions, we used the death rate of Goehringer et al. of 0.89% per year in  
232 future prevalence estimations, which was a higher death rate than the mean death rate from  
233 these patients over the last 5 years (of approximately 0.26% per year) (10,25). Regardless of  
234 which of these rates we used, HIV prevalence was expected to increase in the future, despite  
235 eliminating new infections with increased ART, because these averaged death rates are low.  
236 Finally, no assessment of the undiagnosed group of patients was included in the model, and so  
237 diagnoses are used as representative of the size of new infections. This will introduce a time  
238 delay in our calculations in terms of being able to impact infections relative to diagnoses. New  
239 diagnoses that arose from persons infected in another country or region and movement  
240 between countries may explain the very high rate of heterosexual transmissions from men to  
241 women ( $b=0.73$ ) versus women to men ( $b=0.19$ ) for individuals born outside of France.

242

243 In conclusion, HIV eradication is a challenge that will require several complementary strategies,  
244 TasP being one of them. In this French cohort, the population is quite heterogeneous, with two  
245 major populations, MSM born in France and heterosexual men and women mostly foreigner.  
246 These factors complicate the process of reducing HIV incidence. In spite of these limitations,  
247 our mathematical modelling estimated that enrolling 75% of untreated individuals per year would  
248 decrease diagnoses by ten-fold by 2021 and will help to control the HIV epidemic by limiting

249 incidence. Obviously, this approach has to be combined with other preventive and curative  
250 methods against HIV infection.

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327

328 Table 1. Description of the HIV patient's cohort (n = 6995)

329

	n=	%
<b>Gender</b>		
Male	5012	71.65
Female	1983	28.35
<b>Exposure</b>		
other/undetermined	532	7.61
Male homosexual contact	3080	44.03
Accidental exposition to blood	14	0.20
Receipt of blood/tissue	47	0.67
Haemophilia/coagulation disorder	13	0.19
Mother-to-child transmission	19	0.27
Intravenous drug user	154	2.20
Heterosexual contact	3136	44.83
<b>Country of birth</b>		
France	3153	45.08
Other <i>including</i>	1564	22.36
Africa	1249	79.86
South america	21	1.34
North america	46	2.94
Europe	145	9.27
Asia	100	6.39
Oceania	3	0.19
NR	2278	32.57

330 Table 2. Country of origin of African migrants and distribution by gender.

331

	n=	%	(female ; male)
Africa	1249		
CAMEROUN	280	22.42	(229 ; 51)
CONGO (REPUBLIQUE DU)	122	9.77	(80 ; 42)
COTE D'IVOIRE	119	9.53	(85 ; 34)
REPUBLIQUE CENTRAFRICAINE	63	5.04	(41 ; 22)
SENEGAL	61	4.88	(18 ; 43)
CONGO (RDC, ex Zaïre)	60	4.80	(35 ; 25)
GUINEE	55	4.40	(27 ; 28)
TOGO	52	4.16	(41 ; 11)
Other	437	34.99	

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344 Table 3. CD4+ T cell counts (/mm<sup>3</sup>) versus age at diagnosis in the HIV cohort (n = 6995)

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	<100	100s	200s	300s	400s	500s	600s	700s	800s	900s	1000+
0-15	2	2	0	2	3	3	0	1	0	1	4
16-29	132	147	241	335	333	294	202	171	66	63	103
30-39	308	265	312	347	356	258	177	118	89	62	68
40-49	265	151	205	211	191	184	127	65	56	42	43
50-59	144	117	88	108	79	64	34	32	24	11	50
60-69	43	26	31	27	25	9	7	15	3	7	3
70+	12	7	8	1	4	3	1	2	0	0	0

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351 **Figure captions.**

352 Figure 1: A) Diagram of the statistical model. B) Number of HIV diagnoses in each year by  
353 CD4+ T cell count at diagnosis. C) Distribution of CD4 count at diagnosis within each age  
354 group. D) Estimated HIV prevalence separated by age in each year.

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356 Figure 2: Correlations between diagnoses (y-axis) and estimated untreated prevalence of the  
357 likely infecting group (x-axis), restricted by recorded country of origin. Filled markers show data  
358 for the first 20 years (1985 to 2004).

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360 Figure 3: Evolution of HIV diagnoses and prevalence from 2016 to 2026 in a French cohort if A)  
361 35% of untreated individuals are enrolled on ART each year, or B) 75% of untreated individuals  
362 are enrolled on ART each year. C) Sensitivity analysis to estimated trends in the incidence and  
363 prevalence of HIV infection, by transmission rate for each type exposure type/Country/gender  
364 with a 75% enrollment rate (dynamics for mean transmission parameters shown in red).

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Figure 1.

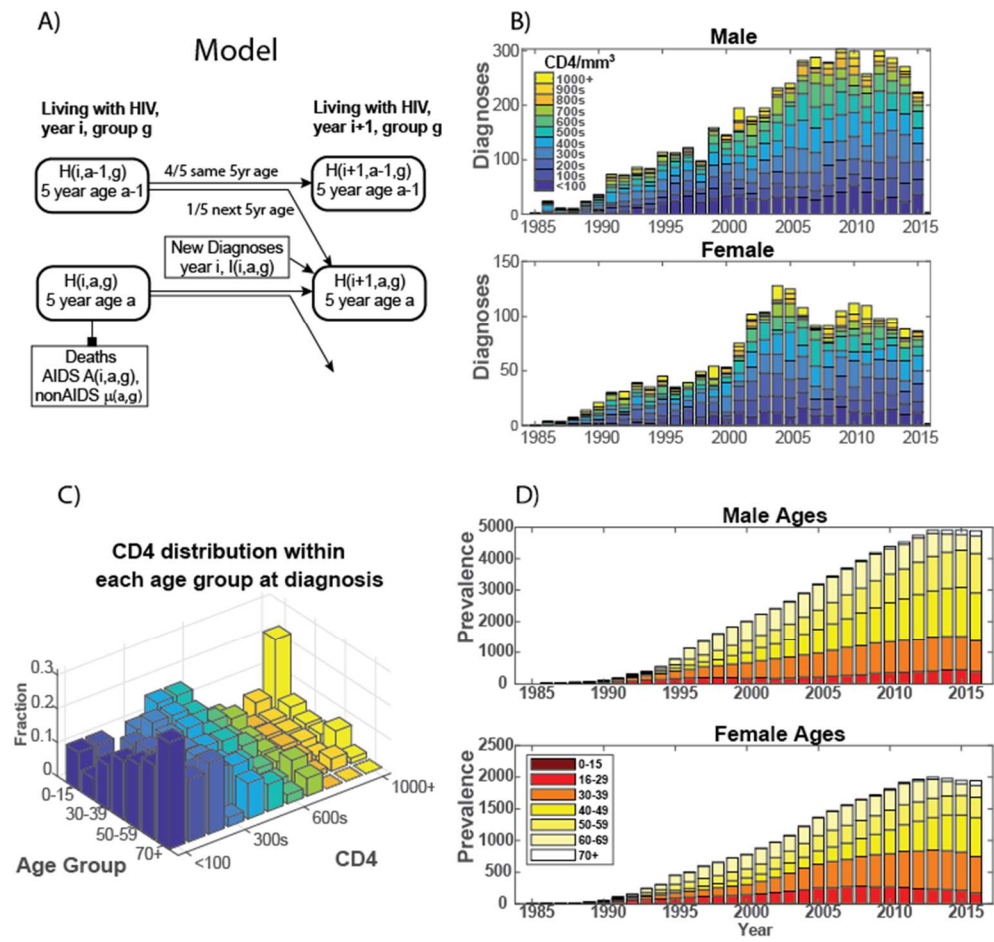


Figure 2.

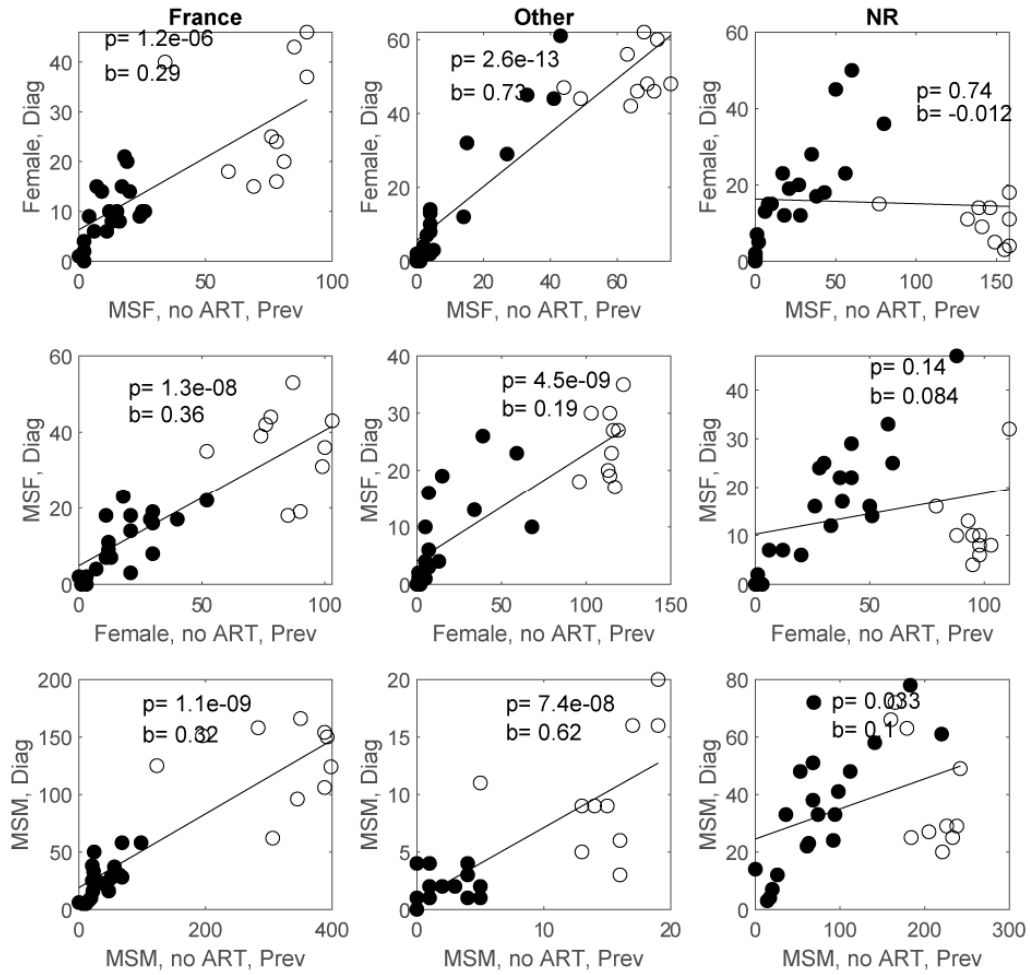


Figure 3.

