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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

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ABSTRACT

Background: "Treatment as Prevention" (TasP) aims to reduce new HIV infections through higher enrolment on suppressive antiretroviral therapy (ART).
Objectives: We studied the current epidemic and possible impact of TasP in a French HIV cohort including MSM and migrant subjects.
Study design: Socio-demographic, clinical and laboratory variables were collected during the follow-up of 6995 HIV-infected patients. The numbers of individuals living with HIV in each year were estimated from diagnoses up to that year minus recorded deaths. Patients were classified according to gender, transmission mode, country of birth and treatment status.
Results: The cohort includes 6995 individuals diagnosed from 1985 to 2015, of whom 72% were men. Unprotected sexual intercourse was the main mode of transmission. Women were more likely to be migrants (45% versus 13%), whereas men were more likely to have been born in France (52% versus 27%). Diagnoses were more correlated with untreated than treated prevalence in each group. MSM diagnoses was strongly correlated to untreated prevalence whatever the country of birth ($p < 0.0001$). However, heterosexual diagnoses were better correlated with prevalence within individual country groups ($b = 0.29$ female diagnoses/year per untreated male born in France, compared to $b = 0.73$ for foreigners). Using these transmission rates, mathematical modelling estimated that enrolling 75% of untreated individuals per year would decrease diagnoses tenfold by 2021.
Conclusions: Enrolling at least 75% of individuals on ART is necessary to substantially impact numbers of new HIV infections in this cohort. Treatment as prevention will actually be effective to reduce HIV prevalence.

1. Background

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

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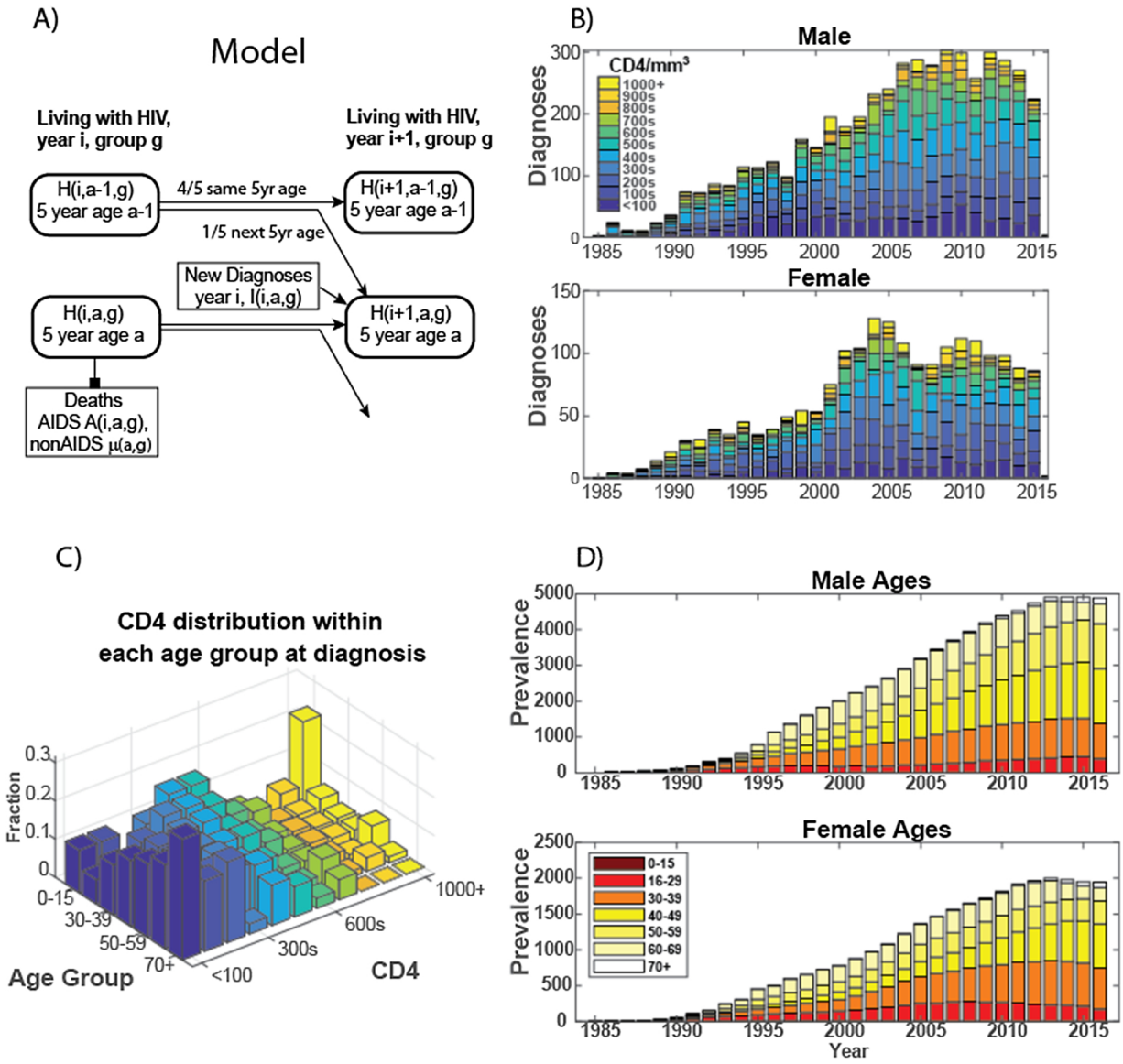

Fig. 1. A) Diagram of the statistical model. B) Number of HIV diagnoses in each year by CD4 + T cell count at diagnosis. C) Distribution of CD4 count at diagnosis within each age group. D) Estimated HIV prevalence separated by age in each year.

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

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

2. Objectives

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

3. Study design

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

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

The number of HIV infected individuals alive at year $i + 1$ for the age group a and exposure group g, $H(i + 1, a, g)$, was assumed equal to

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

	n=	%
Gender		
Male	5012	71.65
Female	1983	28.35
Exposure		
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
Country of birth		
France	3153	45.08
Other *including*	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

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

	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	

the number alive at year i minus those who died from AIDS in year i, $A(i, a, g)$, or from non-AIDS causes at rate $\mu(a, g)$, plus those newly diagnosed $I(i, a, g)$. Because we group individuals into 5-year age groups, we assume $1/5^{th}$ will age into the next age group each year. This gives the formula

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

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

4. Results

4.1. Men were diagnosed later with lower CD4

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

At diagnosis, men were statistically older (mean 37.5 (11.0 standard deviation (sd)) versus 34.6 (11.6 sd) years, $p < 0.0001$). Overall, CD4 count at diagnosis decreased with age, at the rate of 3.76 cells/μL with each year of age ($p < 0.0001$), (Table 3). However CD4 count at diagnosis did not differ by gender (median 401 for men vs 379 for women, Fig. 1B). People aged 40 years old or older were more likely to have a CD4 count <100 cells / mm^3 at diagnosis (Fig. 1C) ($p < 0.0001$) with these more likely to be men (14% versus 11% in women) ($p = 0.002$).

4.2. Unprotected sexual intercourse as the main mode of transmission

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

4.3. Estimated prevalence

By incorporating diagnoses, deaths due to AIDS and other causes, and ageing of previously diagnosed individuals each year (see Methods), we could estimate the number and age distribution of men and women living with HIV infection (Fig. 1D). The relative decline in diagnoses over recent years, combined with ageing and associated increased death rates, has resulted in a stabilization of HIV prevalence in each gender, if not a slight decrease for women.

4.4. HIV diagnoses were highly correlated with prevalence of untreated patients

As might be expected numbers of Female and non-MSM Male diagnoses within each year were strongly correlated ($p < 0.0001$, $b = 0.78$ MSF/Female diagnoses). Numbers of diagnoses in each year were also correlated with estimated prevalence from the likely infecting group, with the correlations generally stronger with untreated compared to treated prevalence. Furthermore, diagnoses were also strongly correlated with estimated untreated prevalence when restricted to either France or Other (Fig. 2). Female HIV diagnoses were correlated to numbers of men who acquired HIV through heterosexual transmission and where each were born in France ($b = 0.29$) or elsewhere (Other $b = 0.73$). Similarly strong correlations were obtained between non-MSM Male diagnoses and female untreated prevalence (France

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

	<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

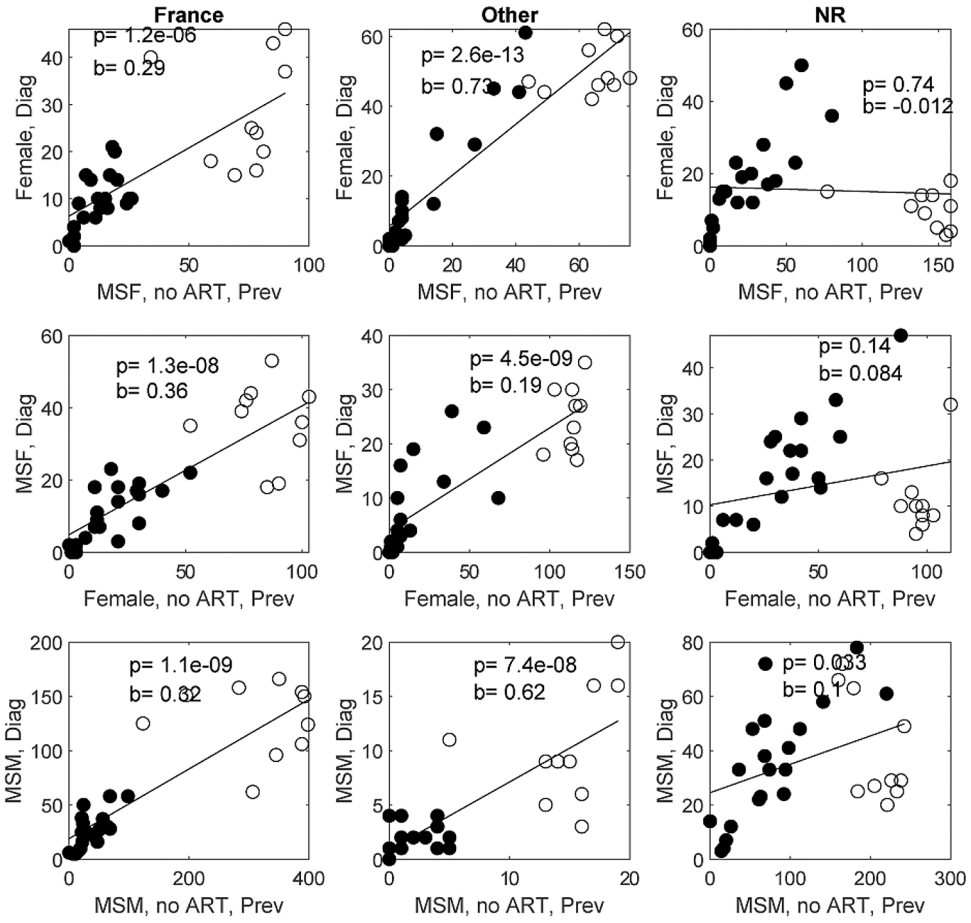

Fig. 2. Correlations between diagnoses (y-axis) and estimated untreated prevalence of the likely infecting group (x-axis), restricted by recorded country of origin. Filled markers show data for the first 20 years (1985–2004).

b = 0.36, Other b = 0.19), as well as for MSM diagnoses and untreated MSM prevalence (France b = 0.32, Other b = 0.62) (Fig. 2).

Enrolling 75% of untreated individuals per year would decrease HIV diagnoses. Our method of estimating treated and untreated prevalence year-by-year (separated into exposure groups and countries of origin), and the correlations between untreated prevalence and diagnoses in each year, allowed us to predict the future evolution of HIV prevalence and diagnoses. For example, the rate of b = 0.29 female diagnoses in each year per estimated untreated non-MSM Male for country of origin France, suggested on average 0.29 women will become infected each year for each Male who is untreated at the beginning of that year (Sensitivity to these values was based on randomly drawing from the 95% confidence intervals) for these b values. Starting from prevalence estimates at the beginning of 2016 and the estimated number not enrolled on ART, we estimated numbers of new diagnoses in each of the exposure groups and by country of origin in that year, through the rates determined between diagnoses and untreated prevalence (Fig. 2). The age of individuals was not incorporated in these predictions so the annual death rate (0.89%) was determined from the Mortalite 2010 survey of deaths in patients with immunovirological success in France [10]. Since the NR correlations were poor and numbers smaller than the other groups, the NR diagnoses for heterosexual transmission were proportionately distributed to the France and Other countries of origin. MSM diagnoses were more strongly correlated when combining all countries so future MSM predictions assumed a rate of 0.23 infections per year per untreated MSM. We assumed that once enrolled on ART individuals stayed on therapy.

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

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

The enrolment of untreated individuals on ART needs to be at least 40% per year if 90% of diagnosed individuals have to be treated by 2030. Given the larger average rate at which men infect women versus women infect men and the assumption that incident infections are untreated in their first year, women are slower to reach 90% treated compared to men. MSM has an estimated per-act probability of acquiring HIV depending on insertive or receptive anal intercourse [11,12]. The risk of MSM HIV infection is thus difficult to evaluate.

5. Discussion

In this study conducted in France, we determined that HIV infection incidence was more likely correlated with prevalence of untreated rather than treated patients in each group. Mathematical modelling predicted that enrolling 75% of untreated individuals on ART per year (TasP) would decrease incidence 10-fold in 2021 compared to an

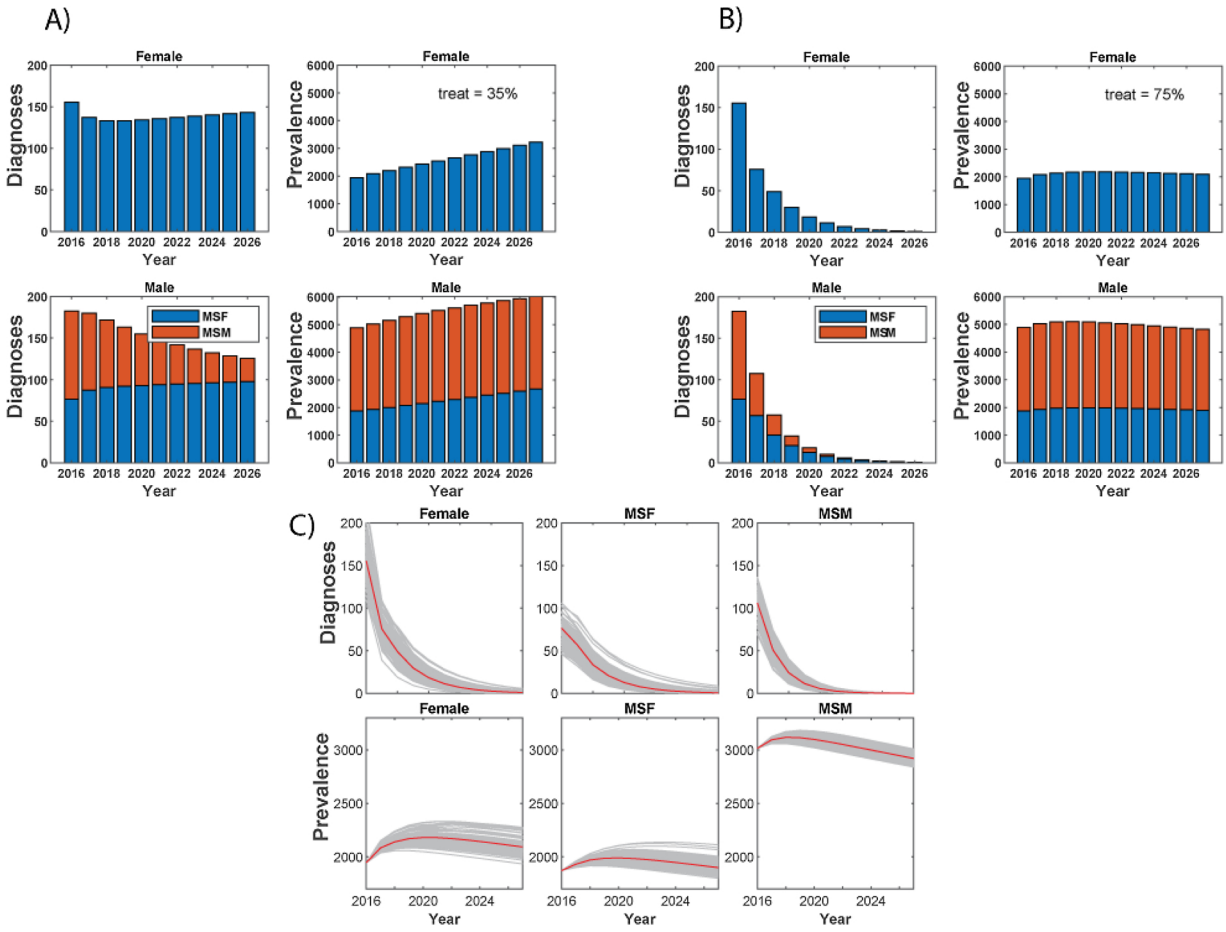

Fig. 3. Estimated evolution of HIV diagnoses and prevalence from 2016 to 2026 in a French cohort if A) 35% of untreated individuals are enrolled on ART each year, or B) 75% of untreated individuals are enrolled on ART each year. C) Sensitivity analysis to estimated trends in the incidence and prevalence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

incidence of 310 new cases in 2015, even if the cohort is quite heterogeneous. We assumed that newly infected patients would not start ART within the first year. Since new diagnoses are expected to spread uniformly over the year, this means that on average new infections would be untreated for at least 6 months. Because of this and the estimated higher rates of transmission from males to females versus females to males, women are slower to reach 90% coverage than men, and their new diagnoses fail to decrease as quickly.

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

In United Kingdom it was estimated that both increased testing and earlier ART are needed in order that men HIV prevalence to be less in 2030 than 2015. An incidence below 1/1000 will require 90% of virally suppressed HIV infected-MSM [15]. Another mathematical model was developed to assess the benefit of coupling ART and PrEP. The authors concluded that combined PrEP and ART offers the best potential for substantial new HIV infection reduction and that high adherence is a key to effectiveness. Elsewhere the model showed that an increase in the number of misdiagnosed infected individuals on PrEP, that generates PrEP drug resistance, could be a key driver of HIV infection spread [16]. PrEP was authorized in France in 2015 and consequently was not evaluated

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

By 2020, the 90/90/90 WHO recommendations aimed that 73% of HIV infected patients worldwide should be controlled for viral load. In Europe, this target is inconsistently reached varying to countries. In France it reached 85-91-97 in 2018 [20], meaning that reducing HIV prevalence is feasible according to our prevision. In other European countries the proportion diagnosed of people ranged from 38% to 98%, the proportion on ART ranged from 27% to 96%, and viral suppression rates ranged from 32% to 97%. The overall continuum of care is higher in western than in central regions and is much lower in eastern regions. In western countries, the lowest percentage on ART was in Southern Europe i.e. 61.9% [21]. In Central and Eastern Europe the median of patients linked to care and treated was 315% [22], well below the WHO targets and the projection of our model. Moreover, within the same country, the continuum of care also varied according to the subgroups [23] as observed in our cohort.

Even within the same country and the same subgroup, HIV transmitters are not homogenous populations and transmission dynamics in

HIV is very complex depending on viral load, number of transmission events and transmission efficacy [2,24]. This is concordant with our study that displayed different results depending on the gender and the mode of sexual transmission.

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

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

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CRediT authorship contribution statement

Hélène Jeulin: Methodology, Validation, Writing - original draft, Writing - review & editing. **Eliette Jeanmaire:** Methodology, Investigation, Validation, Writing - original draft, Writing - review & editing. **John M. Murray:** Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing. **Brice Malve:** Resources. **Marie André:** Resources. **Hugues Melliez:** Resources. **Jean-Philippe Lanoix:** Resources. **Laurent Hustache-Mathieu:** Resources. **Marialuisa Partisani:** Resources. **François Goehringer:** Resources. **Thierry May:** Supervision. **Evelyne Schvoerer:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None of the authors declare a conflict of interest.

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