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**Immune profile at HIV infection diagnosis: evolution in the French Alps area over the last 20 years**

**Profile immunologique au diagnostic de VIH : évolution dans les Alpes françaises sur les 20 dernières années**

Romain GUENEAU<sup>1,2,3</sup>, Sylvie DUFRESNE<sup>1,2,3</sup>, Amélie VALRAN<sup>1,2,4</sup>, Cécile JANSSEN<sup>1,4</sup>, Pascale LECLERCQ<sup>1,2,3</sup>, Olivier EPAULARD<sup>1,2,3</sup>

1 – Comité Régional de Coordination de la Lutte contre le VIH de l'Arc Alpin, Grenoble, France

2 – Fédération d'Infectiologie Multidisciplinaire de l'Arc Alpin, Université Grenoble Alpes, France

3 – Service de maladies infectieuses, Centre Hospitalier Universitaire Grenoble Alpes

4 – Service de maladies infectieuses, Centre Hospitalier Annecy-Genevois, Annecy, France

**Mots clés :** VIH ; diagnostic ; HSH ; taux de lymphocytes

**Keywords:** HIV; diagnosis; MSM; lymphocyte count

## **Abstract**

**Objectives.** Health of HIV-infected people relies on early antiretroviral therapy, *i.e.* early diagnosis. We aimed to determine whether the characteristics at HIV diagnosis in two French medical centers changed over the last 20 years.

**Patients and methods.** All individuals diagnosed with HIV infection in Grenoble University Hospital (n=814) and Annecy Hospital (n=246) between 1997 and 2015 were included. We collected age, country of birth, mode of transmission, CD4 T cell count, CD4/CD8 ratio, and HIV viral load.

**Results.** Among the 1,060 patients (mean age  $37.4 \pm 11$  years, 70.2% of men), 42.5% were men having sex with men (MSM); 65.2% were born in France, and 24.4% were born in Africa. Mean CD4 T cell count at diagnosis was  $396 \pm 288/\text{mm}^3$  and was stable over the study period when considering all patients; when considering the MSM group, a significant increase over time was observed with a mean increase of  $7.3 \text{ CD4}/\text{mm}^3$  per year ( $p < 0.001$ ). A higher CD4 count at diagnosis was observed after 2005 ( $400 \pm 289$  vs  $468 \pm 271/\text{mm}^3$ ,  $p = 0.005$ ). The proportion of MSM patients with a CD4 count  $< 200/\text{mm}^3$  at diagnosis was lower after 2005 (14.7% after 2005 and 25.6% before,  $p = 0.028$ ) This was not observed in heterosexual patients born in Africa or not.

**Conclusion.** In the MSM population, CD4 count at diagnosis is higher after 2005, suggesting that screening campaigns have become more efficient. This was not observed in other populations, who should be better targeted in future strategies.

## **INTRODUCTION**

The number of HIV infection diagnoses in France in 2016 was 6,003 [1]. French guidelines [2] emphasized the importance of early diagnosis as a priority to reduce the epidemic. At an individual level, late diagnosis of HIV infection is associated with increased mortality (any cause), even in the absence of AIDS-defining diseases [3], and it has been shown that an early diagnosis is also cost-effective [4]. At a community level, the incidence of HIV infection is driven, among other factors, by the prevalence of infected people unaware of their status (“hidden epidemic”) [5]: the longer the time to diagnosis, the higher the number of potential secondary cases. Several studies highlighted the partial failure of the screening campaign in France, even though more than 5,000,000 blood tests are performed annually [6,7].

The effectiveness of the screening policy may be evaluated by the proportion of early vs late diagnoses [7]. Thus, we aimed to describe the characteristics of people living with HIV/AIDS (PLWHA) at the time of diagnosis in two major centers of the French Alps area, and to analyze whether these characteristics changed over the last 20 years.

## **POPULATION AND METHOD**

We conducted an epidemiological, multicentric, and retrospective study and reviewed the files of PLWHA at Grenoble University Hospital (2,200 beds) and Annecy Hospital (1,450 beds).

The study population was made of all patients who had been referred for an HIV diagnosis at these two centers between January 1, 1997 and December 31, 2015, and for whom relevant data was available. We used the DOMEVIH® software, commonly used for the follow-up of HIV-infected subjects, to extract the date of diagnosis (first positive HIV serology), the

country of birth, and the following clinical and biological variables at diagnosis: age; mode of contamination; CD4+ T lymphocyte count, and CD8+ T lymphocyte count (allowing the computation of the CD4/CD8 ratio); and plasma HIV viral load. We considered all viral load values  $\leq 6$  log, as this was considered the test threshold value before 2006.

The date of diagnosis was defined by the first positive HIV serology, or the first detection of HIV RNA in plasma in case of primary infection. Subjects with a CD4+ T cell count  $< 200/\text{mm}^3$  were classified as “late diagnosis”, subjects with a CD4+ T cell count  $> 200/\text{mm}^3$  and  $< 500/\text{mm}^3$  were classified as “intermediate diagnosis”, and subjects with a CD4+ T cell count  $> 500/\text{mm}^3$  were classified as “early diagnosis”. The CD4/CD8 ratio was also evaluated, as it is a surrogate for immune activation associated with the risk of non-AIDS events [8].

After the first data extraction, all files were checked individually as follows:

- in case of missing data (*e.g.*, no CD4+ T cell count) at diagnosis, we checked the DOMEVIH files and hospital files manually to retrieve data over the three months following diagnosis; if not found, they were considered as “missing data”;

- in case of date discrepancy between the notification of HIV infection diagnosis and the first available blood test (*e.g.*, CD4 count), a maximum gap of three months was tolerated; otherwise the case was excluded.

PLWHA who were already diagnosed (and sometimes treated) before being referred to the two study hospitals were not included in the study.

The main transmission groups were analyzed: men having sex with men (MSM); heterosexual (women or men) not born in Africa (HeNBA); heterosexual (women or men) born in Africa (HeBA).

The normality of the distribution was tested with a Shapiro-Wilk test; we observed that the distribution of values was not following the normal curve, except for the viral load,

prohibiting the use of parametric tests. CD4 count, CD4/CD8 ratio, and viral load changes over time as a continuous variable was analyzed using Spearman's correlation test. We also analyzed the evolution of CD4 count between various periods (1997-1999; 2000-2002; 2003-2005; 2006-2008; 2009-2011; 2012-2015) using a Kruskal-Wallis test, associated with a non-parametric trend test. The proportion of subjects with a late diagnosis or an early diagnosis before 2006 and from 2006 onwards was analyzed using the Chi<sup>2</sup> test. The correlation between age at diagnosis and CD4 count was analyzed using Spearman's correlation test.

## **RESULTS**

From January 1997 to December 2015, 1,427 new cases of HIV infection were recorded in the DOMEVIH database in Grenoble and Annecy:

- 902 were diagnosed at Grenoble Hospital; among those, 88 were excluded because of non-exploitable data or missing data, or because they were not newly diagnosed with HIV infection;
- 525 were diagnosed at Annecy Hospital; among those, 279 were excluded because of non-exploitable data, or because they were not newly diagnosed with HIV infection.

The mean diagnosis rate was 76 patients per year (47.5 diagnoses per year in Grenoble and 27.6 per year in Annecy).

### **Population**

Patients had been infected by heterosexual intercourse (44.6%), male homosexual intercourse (37.0%), IV drug use (3.0%), blood infusion (0.8%), or other/unknown (14.6%).

Patients were born in 65 different countries; 691 (65.2%) were born in France, 259 (24.4%)

were born in Africa (35 countries), and the remaining patients were born in Europe (4.4%), America (1.1%), or in an unknown country (3.9%).

Characteristics of patients at diagnosis are detailed in Table 1.

#### Age at diagnosis

Age at diagnosis did not significantly vary over time for these various subgroups except for HeNBA, in whom a slight increase in age was observed ( $Rho=0.18$ ,  $p=0.012$ ).

#### CD4+ T cell count

When considering time as a continuous variable, the CD4 count at diagnosis was not modified over time in the HeNBA subgroup ( $p=0.76$ ) and the HeBA subgroup ( $p=0.9$ ). It was also not modified when considering separately men and women. Conversely, a significant increase was observed over time in the CD4+ T cell count at diagnosis in the MSM subgroup ( $Rho=0.18$ ,  $p<0.001$ ), with a mean increase of 7.3 CD4/mm<sup>3</sup> per year.

When considering time as a discrete variable (comparison of six time periods), CD4 count at diagnosis did not change in the general population ( $p=0.66$ ), nor did it change in the HeNBA ( $p=0.15$ ) and HBA ( $p=0.45$ ) subgroups. It was also not modified when considering separately men and women. Conversely, a significant increase was observed over time in the MSM subgroup ( $p=0.029$ ) (Figure 1), associated with a positive trend test ( $p<0.001$ ).

We then only considered two time periods: before 2005 and after 2005. Overall, the proportion of patients with CD4+ T cell count  $<200/\text{mm}^3$  at diagnosis was significantly higher before 2005 (28.3% vs 22.6%,  $p=0.037$ ). This difference was neither significant in the HeNBA group (31.2% vs 25.7%,  $p=0.36$ ) nor in the HeBA group (32.9% vs 28.1%,  $p=0.60$ ), but it was statistically significant in the MSM group (25.6% vs 14.7%;  $p=0.01$ ) (Figure 2). The proportion

of patients with a CD4+ T cell count  $>500/\text{mm}^3$  among the general population was not statistically different before and after 2005 (30.7% versus 32.5%;  $p=0.57$ ), neither in the HeNBA group (34.4% versus 36.1%;  $p=0.85$ ), the HeBA group (20.7% versus 24.0%;  $p=0.74$ ), nor the MSM group (31.0% versus 39.7%;  $p=0.091$ ).

A negative correlation was observed between age and CD4 count at diagnosis in the general population ( $\text{Rho}=-0.204$ ;  $p<0.001$ ) and in MSM ( $\text{Rho}=-0.212$ ;  $p<0.001$ ), HNBA women ( $\text{Rho}=-0.285$ ;  $p=0.002$ ) and HNBA men ( $\text{Rho}=-0.212$ ;  $p=0.0053$ ), which was absent in the HeBA group ( $p=0.98$ ).

#### CD4/CD8 ratio

A modest increase in CD4/CD8 ratio ( $\text{Rho}=0.08$ ,  $p=0.022$ ) was observed over the study period. In the subgroup analysis, this increase was only observed in the MSM group ( $\text{Rho}=0.17$ ,  $p=0.018$ ).

The proportion of patients with CD4/CD8 ratio  $<0.5$  at diagnosis was significantly higher before 2005 (63.4% vs 55.4%,  $p=0.035$ ). It was significantly higher before 2005 in the HeNBA group (66.7% vs 52.3%,  $p=0.025$ ) but not in the MSM group (62.5 % vs 51.0%,  $p=0.080$ ) or the HeBA group (67.7% vs 56.5%,  $p=0.22$ ).

#### Viral load

The median viral load at diagnosis was 4.77 log copies/ml [4.15;5.39]. No evolution of the viral load at diagnosis was observed over time ( $p=0.088$ ). The median viral load in the various subgroups was 4.8 [IQT: 4.02; 5.38] for HeNBA, 4.8 [IQT: 4.27; 5.39] for MSM, and 4.7 [IQT: 3.98; 5.17] for HeBA.



## **DISCUSSION**

We aimed to determine the immune profile of patients at HIV diagnosis in our area (French Alps) over the last 20 years, to explore the effectiveness of screening campaigns.

We observed a significant change in the proportion of late diagnoses in the general population (CD4+ T cell count  $<200/\text{mm}^3$ ) before and after 2005, but no evolution of the CD4+ T cell count over the years. In a study performed in Paris, France, [9] comparing the profile at diagnosis between 2003 and 2012, no evolution was observed in the general population (22.3% in 2003 and 26.3% in 2012,  $p=0.4$ ). However, the two areas may not be comparable as the proportion of PLWHA born in France was 33.1% in this study versus 63.8% in our study. In two nationwide French studies respectively conducted from 1996 to 2002 [10] and from 2003 to 2011 [11], the proportion of late diagnoses was 33.1% in the first and 28.1% in the second, even though those proportions are higher than in our study. Conversely, in a study [12] conducted in Barcelona, Spain, an increased proportion of late diagnoses (defined as CD4 count  $<350/\text{mm}^3$ ) was observed between 2001-2003 and 2004-2005 (it was not confirmed in the 2006-2009 period); in this study the proportion of patients with CD4 count  $<200/\text{mm}^3$  was lower than in our study (12.7% over the study period vs 25.4% in our study). In a study conducted in North America [13], overall improvement was observed in the median CD4 count at diagnosis between the years 1997 and 2007 (256 vs  $317/\text{mm}^3$ ). This improvement was more important in the MSM subgroup, as in our population, and in the Latino subgroup; mean improvement of the CD4 count was 5 cells/ $\text{mm}^3$  per year in MSM, close to what was observed in our study ( $7.3$  cells/ $\text{mm}^3$ ).

A 2013 systematic review [14] compiling the data of 44 studies from high-income countries (18 in the United States and 11 in the United Kingdom) reported a non-significant increase in

CD4 count at diagnosis (+1.5 cells/mm<sup>3</sup> per year). No decrease was observed in the proportion of late diagnoses (CD4 count <200/mm<sup>3</sup> or AIDS-defining disease) over the 1991-2011 period. This data should be considered with caution as the study period included very different periods of the HIV epidemic.

The CD4 count increased in the MSM subgroup of our area over time, and the proportion of late diagnoses was statistically lower as of 2006 in this subgroup, as compared to before 2005. This suggests that screening for HIV improved over the years in this group of patients. The decreased proportion of late diagnoses in the MSM population over the same period was also observed at the national level in France, as 29% of MSM were diagnosed at AIDS stage in 2005 versus 19% in 2015 [1,15]. This trend can also be observed when comparing the data of two nationwide epidemiological studies, with a proportion of late diagnoses of 27.6% between 1996 and 2002 [10] and 19.6% between 2003 and 2011 [11]. This difference between the MSM and other groups may be due to prevention programs specifically targeting MSM as they are known to be at high risk of transmission [16]. This is increasingly underlined in the national recommendations for HIV screening since 2006 [15,17,18], and has been reinforced in the most recent French guidelines mentioning that MSM should be tested every three months in case of risky sexual behavior. A recent French study of 2,938 MSM infected between 2011 and 2014, estimated that the median time to diagnosis was 2.7 years [IQ: 0.5-5.0] [19]. Time to diagnosis was longer in other groups. Future screening campaigns should therefore be improved and strategies such as community testing or self-testing should be further developed [20].

No improvement was observed in the immune profile at HIV diagnosis of patients born in Africa over the study period. At the French national level, the proportion of late diagnoses between 2003 and 2011 was 41.2% in men and 34.2% in women among sub-Saharan

migrants [11]. This well-defined high-risk population is targeted by tailored screening programs when arriving in France [21]. Many of them are already infected when they arrive in France, which might explain the incompressible time to diagnosis. However, frequent transmissions on the French territory have been documented [22]. Access to health services may also be impaired by administrative and judiciary policies related with their migrant status; indeed, people may avoid medical facilities out of fear of deportation. A recent French study reported that African-born patients experienced the highest level of discrimination [23], which may impair early diagnosis.

Late diagnosis was associated with older age at diagnosis among the general population as well as in the MSM and HNBA groups, as previously reported [24]. We did not observe any evolution in terms of age at diagnosis over the study period that may explain the CD4 count trend at diagnosis, except in the HNBA group.

Viral load at diagnosis was stable over the study period in our study. Viral load is obviously not a marker of late diagnosis as the evolution of the viral load during the course of HIV infection has a three-phase curve (intense replication resulting in high viral load during the primary infection, progressively decreasing over the first year; stable replication during the latency period; and increase during the AIDS phase) [25].

A significant increase in CD4/CD8 ratio was observed among the general population, suggesting that time to diagnosis improved over the study period. The CD4/CD8 ratio is a reliable marker of HIV-induced immune activation [26]; a low CD4/CD8 ratio is associated with a higher risk of consequences of the immune activation deleterious effects, especially cardio-vascular complications, and a higher case fatality rate [27]. A weaker response to treatment has also been reported in this situation [28]. A screening program should

therefore aim to diagnose PLWHA when the CD4/CD8 ratio is not deeply altered. Our results may reflect that screening procedures have been optimized, allowing for earlier diagnosis.

The retrospective analysis of data recording is one of the limitations of the present study. It might explain missing data, especially the CD4/CD8 ratio. Another limitation is the small size of some subgroups – especially IV drug users – preventing statistical analysis. It might also have been interesting to analyze other variables such as the context of diagnosis (primary care consultation, spontaneous attendance at the free and anonymous screening center, screening campaign organized by advocacy groups) or the socio-demographic status to evaluate which part of the screening strategy was associated with early diagnosis.

This study reports the profile of patients at HIV diagnosis in the French Alps area over the last 20 years. Time to diagnosis has been substantially improved in MSM unlike other populations. Further progress should be made in the screening strategy addressed to African-born patients and heterosexuals born in France. Although new effective tools such as pre-exposure prophylaxis [29] are available, early diagnosis leading to a treatment-as-prevention strategy remains a pillar that should not be forgotten.

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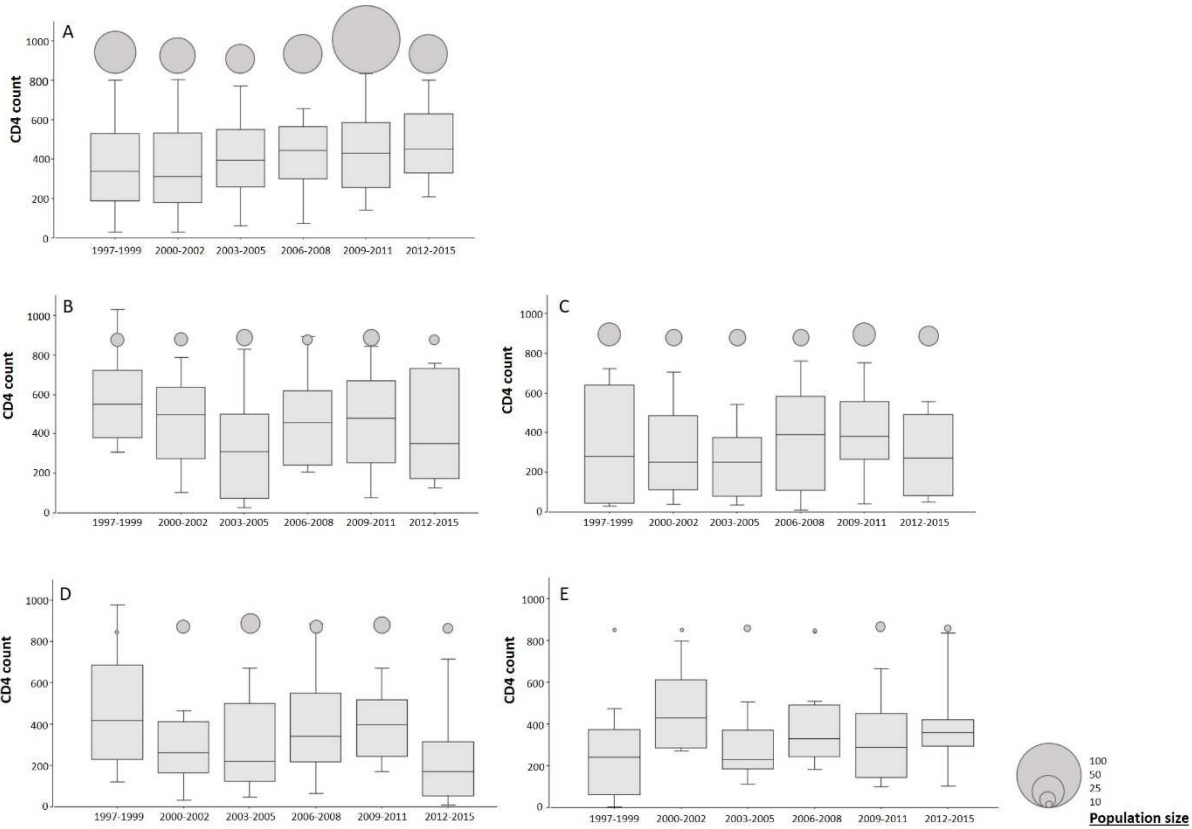
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**Figure 1** CD4+ T cell count at diagnosis over time. The circles above the boxes reflect the number of patients diagnosed in each time period (A, MSM; B and C, HeNBA (respectively women and men); D and E, HeBA (respectively women and men))

**Figure 1.** Taux de CD4 au diagnostic dans le temps. Les cercles au-dessus des boîtes représentent le nombre de patients par période de temps (A : homme ayant des relations sexuelles avec des hommes ; B et C : hétérosexuel(le)s né(e)s hors Afrique (respectivement femmes et hommes) ; D et E : hétérosexuel(le)s né(e)s en Afrique (respectivement femmes et hommes))



MSM: men who have sex with men

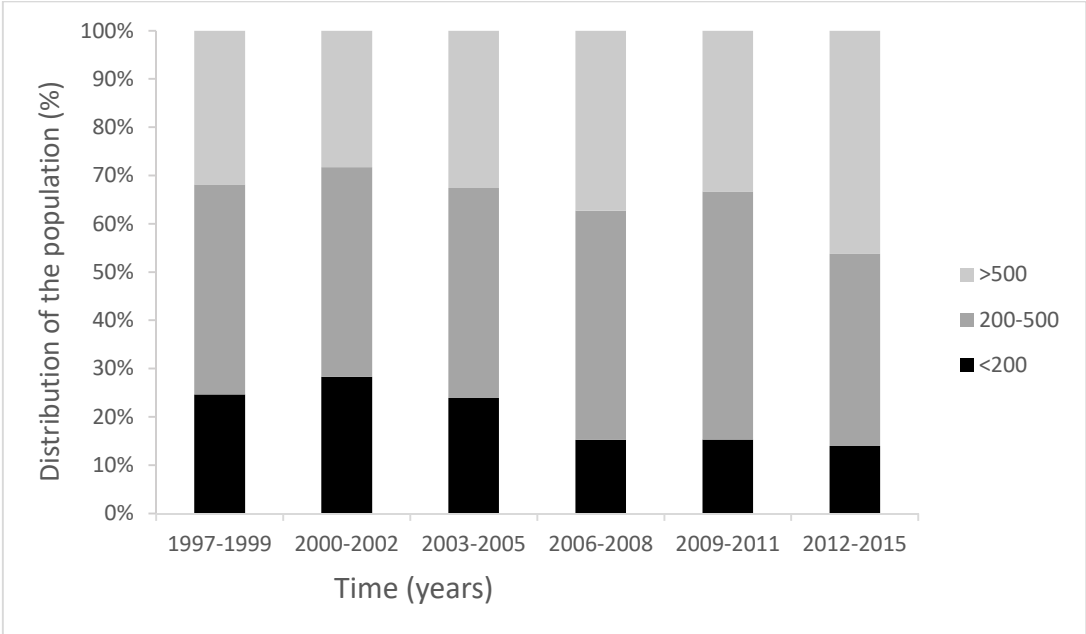
HeNBA: heterosexual not born in Africa

HeBA: heterosexual born in Africa



**Figure 2.** Proportion of MSM with CD4 <200, 200-500, and >500/mm<sup>3</sup> at diagnosis

**Figure 2.** Proportion de patients HSH avec un taux de CD4 au diagnostic < 200, 200-500 et > 500/mm<sup>3</sup>



**Table 1.** Features of the various subgroups at HIV diagnosis. Values are expressed as median and interquartile.

**Tableau 1.** Caractéristiques des différents sous-groupes au moment du diagnostic VIH. Les valeurs sont exprimées en médiane et interquartiles.

	Total	Heterosexual				MSM
		born in Africa		not born in Africa		
		Male	Female	Male	Female	
<b>Gender</b>						
<b>N (count)</b>	1,060	56	122	178	118	392
<b>Age (year)</b>	36 [29;45]	36 [28;41]	31 [26;37]	43.5 [34;52]	36 [28;45]	36 [28;43]
<b>CD4 count (cell/mm<sup>3</sup>)</b>	360 [199;540]	292 [190;440]	285 [170;466]	305 [90;530]	460 [234;630]	420 [259;574]
<b>Viral load (log copies/ml)</b>	4.8 [4.2;5.5]	4.7 [4.2;5.6]	4.7 [4;5.4]	5.0 [4.2;5.6]	4.5 [3.8;5.1]	4.8 [4.3;5.5]
<b>CD4/CD8 ratio</b>	0.44 [0.22;0.68]	0.45 [0.22 ; 0.64]	0.50 [0.23;0.63]	0.37 [0.14;0.64]	0.50 [0.3;0.77]	0.47 [0.24;0.70]

MSM: men who have sex with men