Time spent with viral load≤200 copies/mL in a cohort of people with HIV seen for care in Italy during the U=U prevention campaign era

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Abstract

Objective: Zero risk of linked HIV transmission in sero-discordant couples when the HIV-infected partner had viral load (VL) <200 copies/mL ('U status') was found in observational studies. We aimed at estimating the proportion of time in which 'U status' was maintained and identifying factors associated with the risk of losing it.

Design: Observational cohort study.

Methods: We included participants in the ICONA cohort who had reached an established 'U status' (VL≤200 copies/mL for >6 months) as of December 2010. The outcome was the number of person-days of follow up (PDFU) above a VL>200 copies/ml, relative to the total number of PDFU observed. A logistic regression model was used to identify factors independently associated with the risk of losing 'U status'.

Results: 8,241 persons living with HIV were included in the analysis who contributed 12,670,888 PDFU. Of these, 1,648 (20%) were female, 768 (9%) were people who inject drugs (PWID), and 2,066 (25%) were foreing-born. The median of VL measurements was 9 (IQR: 4-15). Overall, only 3.1% of PDFU were observed when VL was >200 copies/mL. The proportion of PDFU with VL>200 cp/ml was higher than average in females (5.3%), unemployed (5.4%), PWID (4.7%), and in people with>3 previous virologic failures (6.3%). These variables were significant predictors of losing 'U status' in the multivariable logistic regression.

Conclusions: Our results reinforce the validity of the U=U message in real-world setting. However, we identified subsets of our study population at higher risk of losing the 'U status' for whom additional efforts are needed.

Introduction

Since the end of the 1980s, several studies have investigated the association between HIV replication, as measured by plasma HIV-RNA or p24 antigen, and the risk of sexual transmission of HIV.[1–6] In 1994, an Italian study demonstrated how patients treated with zidovudine had a reduced transmission rate to their female partners.[7]

After the introduction combination Antiretroviral Therapy (cART), several investigators hypothesized that treatments could decrease the risk of sexual HIV transmission and that a person with an undetectable HIV-RNA may not transmit the virus.[8]

In 2008, the Swiss National AIDS Commission published a document stating that "an HIV-infected individual without additional sexually transmitted disease (STD) and on cART with completely suppressed viremia is sexually non-infectious".[9] In a meta-analysis published in 2009, Attia et al. suggested that there was no direct evidence that the HIV sexual transmission risk in serodiscordant couples was zero. Therefore, the definition of a transmission threshold was questionable or needed to be lower than previously believed.[10] However, in this metanalysis, no case of sexual transmission was observed in people with an HIV-RNA<400 cp/ml while on cART, despite the fact that the confidence interval (CI) for the zero rate was wide.

The HIV Prevention Trials Network (HPTN) developed a randomized, and controlled trial (HPTN052), enrolling 1,750 sero-discordant couples. The purpose of this trial was to determine whether cART can prevent HIV sexual transmission in serodiscordant couples who started treatment immediately vs. couples who delayed treatment start. At the end of the follow-up, no HIV transmission was registered among couples, provided the HIV-positive partner had an undetectable (HIV-RNA<200 cp/ml) viral load. Although no cases of HIV sexual transmission was reported in HPTN052, the CI was still too large (0-0.26) to be used to support the "zero risk statement".[11]

After HPTN052, three observational studies, Partner1, Partner2, and Opposites Attract showed no cases of HIV transmission among both heterosexuals and men who have sex with men (MSM) sero-discordant couples.[12–14] In 2019, a systematic review including data on over 4,000 couple-years of follow-up was analyzed by Vernazza.[15] A combined HIV sexual transmission risk of 0.00 (CI 0.00 – 0.07), while the HIV-positive person was virally suppressed, was estimated.

In February 2016, after that Partner 1 results were first published, the Prevention Access Campaign launched the Undetectable=Untransmittable (U=U) slogan. Since then, more than 750 organizations worldwide, including the World Health Organization), took part in the U=U campaign. Even if these data have been enthusiastically approved by the community and by most scientists, several others have expressed concerns, mainly related to the persistence of undetectable viral load (VL) over time. The frequency of VL determination to be sure that the undetectability lasts over time is still debated.

Although the absence of risk of transmission in the presence of viral suppression is well established in clinical trials and observational studies, there is little information on how long a VL≤200 cp/ml can be maintained in persons under routine clinical care. The present study aims to estimate, in a target population of people with HIV (PWH) seen for care in Italy who achieved a stable

"undetectable (U) status', the proportion of time in which such status was maintained over follow-up and to identify factors associated with the risk of eventually losing the 'U status'.

Methods

The Icona Foundation Study is an Italian cohort of patients with HIV that followed the original ICONA study.[16] We included participants in the ICONA cohort who had achieved a stable 'U status' (VL≤200 copies/mL for >6 months); entry in the analysis was set at the time of the first of two consecutive viral load ≤200 copies/mL experienced on ART after June 01, 2010 (baseline) until July 31, 2019. All patients signed consent forms to participate in the Icona Foundation Study in their local participating clinical sites. The research study protocol has been approved by local institutional review boards.

The number of person days of follow-up (PDFU) spent above or below a threshold were calculated for individual participants using consecutive VL pairs and the method proposed by Marks et al. (Figure 1).[17] In detail, if both VL measurements of a consecutive pair were >200 copies/ml, then all intervening PDFU were considered to have been >200 copies/ml (grey area in Figure 1). If both VL measurements of a pair were ≤200 copies/mL copies/ml, all intervening PDFU were considered ≤200 copies/ml (square A in Figure 1). If the first VL in the pair was ≤200 copies/ml and the second was above 200 copies/ml (square B), or vice versa (square C), we used a straight-line approximation to estimate viral loads between measurements.

The primary outcome was then defined at the population level as the proportion of PDFU spent with a VL >200 copies/ml, relative to the total number of PDFU

In addition, this same proportion was also used to define a binary endpoint for individual participants: losing the 'U status' over follow-up (yes/no). This was defined through the arbitrary cut-off of 10%, i.e., if the proportion of PDFU for a person over the whole observation period was >10%, it was defined as having lost such a status (Figure 1).
The main characteristics of the participants at baseline were compared between those who remained or lost the 'U status' using chi-square or Mann-Whitney U test, as appropriate. A multivariable logistic regression analysis was also performed to identify factors independently associated with the risk of losing the 'U status'. All factors considered *a priori* to be significant predictors, based on the literature or other axiomatic knowledge, have been included in the multivariable model, regardless of the *p*-value in the unadjusted comparison. Key exposure factors were defined as follows: a history of virological failure was a binary variable classified as 'Yes' if the participant had experienced before baseline at least 4 months with an HIV-RNA>500 copies/mL while receiving ART, 'No' otherwise; hepatitis co-infection was defined based on the results of serology test); all clinical diagnoses of STDs before baseline was counted. Finally, we considered both the most recent CD4+ count prior to baseline (within 6 months of this date) and the CD4+ count nadir.

Alternative endpoints, less dependent on participants' length of follow-up, were examined. In one of these analyses, losing the 'U status' was defined as experiencing at least three months with a VL>200 copies/mL.

After removing participants whose HIV-RNA monitoring was less frequent than twice a year, we have also performed a sensitivity analysis, which is the average monitoring frequency by the protocol in the cohort.

Results

Out of all PWH enrolled in the Icona cohort, 8,241 subjects were included in this analysis. Of these, 1,648 (20%) were female, and the foreign-born were 2,066 (25.1%).
Concerning the modality for acquiring HIV infection, 768 (9.3%) were people who inject drugs (PWID), 3,786 (45.9%) MSM, and 3,176 (38.5%) heterosexuals.
Four-hundred and six (4.9%) subjects have had AIDS-defining events before baseline. The median age at baseline was 39 (IQR 31-47) years, with a median of CD4+ count of 545 (IQR 400-722) cells/mm^3. The majority of participants (7,488; 90.9%) have never had a history of virological failure (VF) before baseline. However, 429 (5.2%) PWH had previously experienced a number of VF between one and three, and 324 (3.9%) had more than three VFs.
The median of VL measurements over the study period was nine (IQR 4-15), and the median time with VL>200 cp/ml was 47.3 days (IQR 46.3-47.9). Thus, HIV-RNA was collected at least twice a year (average 2.5 times per year), which is the monitoring frequency by the cohort protocol. The main baseline patients' characteristics have been summarized in Table 1.
Overall, 617 participants (7.5%) spent <90% of PDFU with a VL≤200 copies/mL and were classified as losing their initial 'U status' over time**.** Approximately 65% of participants showed less than 2 values >200 copies/mL over follow-up, and 30% of the participants experienced a single sustained episode, and approximately an additional 7% experienced two or more episodes (Supplemental Figure 1).

At univariable analysis (Table 1), when comparing PWH who did not retain the 'U status' over time (n=617) with those who did (n=7,624), the first were more frequently female (p<0.001), PWID (p<0.001), and foreign-born (p<0.001). They were also less likely to have achieved a college or university degree (p<0.001) and were more frequently unemployed (p<0.001).

Regarding HIV-related characteristics, PWH who had not retained the 'U status' overtime had also been more frequently previously diagnosed with AIDS (p=0.008), less likely having a co-infection (p<0.001), showed lower current and nadir CD4+ count (p<0.001), higher peak median viral load (p<0.001).Furthermore, they showed a longer time from HIV diagnosis to baseline (p=0.002)., had been followed up for longer, and were more likely to have previously experienced one or more episodes of VF (p<0.001)..

In order to identify factors independently associated with the outcome, a multivariable logistic regression has been performed. In this unadjusted analysis, female gender, being PWID, foreign-born, low educational level, and unemployed, were independent predictors of losing 'U status'. Having previously experienced at least one VF episode was also associated with a significantly higher risk of losing 'U status'. The same variables were also confirmed as significant predictors of losing 'U status' after controlling for age, AIDS diagnosis, HBsAg/HCV status, duration of ART, anchor drug used, geographical region, diabetes, smoking, use of statins/lowering blood pressure drugs, glucose, and prior STDs. Unadjusted and adjusted Odds ratios of losing 'U status' from fitting the logistic regression model are shown in Figure 2. The adjusted odds ratio (aOR) for the main independent predictors were 1.55 (95%CI 1.20-2.00) comparing females vs. males, 2.50 (95%CI 1.80-3.46), and 1.43 (95%CI 1.10-1.87) comparing PWID vs. MSM and heterosexuals, respectively. Being foreign-born had aOR of 1.42 (95%CI 1.12-1.80) vs. Italians, and 1.46 (95%CI

1.13-1.89) comparing unemployed vs. employed. Previous VF (>3) had an aOR of 2.85 (95%CI 1.84-4.44). When we used the alternative endpoint of at least three months with a VL>200, results were similar (Supplemental Table 1S). The magnitude of these associations was similar after restricting the analysis to participants with HIV-RNA monitoring of at least 2 measures/year (Supplemental Figure 2).

When using the PDFU as the statistical unit instead of the number of PWH, a total of 12,670,888 PDFU were counted over the entire observation period (2011-2019). Of these, 96.9% of PDFU were spent with a VL ≤200 cp/ml. Thus, only the remaining 3.1% of PDFU were observed when VL was >200 copies/mL. The highest proportion of time spent with a VL>200 cp/ml was observed in 2013, with a progressive decrease in the following years, especially after 2016 (Figure 3). Of note, in a sensitivity analysis restricted to people with HIV-RNA monitoring of at least 2 measures/year, the percentage of PDFU >200 copies/mL was even lower at 2.5% (650/25,663).

The proportion of PDFU with VL>200 cp/ml was significantly higher than average in females (5.3%), foreign-born (5.4%) unemployed (5.4%), PWID (4.7%), and in people with more than three previous VFs (6.3%). There was no evidence of a difference in proportions when comparing patients with ages between 18-45 and ≥46 years (Table 2).

Discussion

The Prevention Access Campaign (PAC) launched the slogan "Undetectable=Untransmittable" or "U=U" in 2016. PAC officially started this U=U prevention campaign after the publication of two studies, HPTN052 and Partner1 [11,12]. The subsequent publication of the other two studies, Partner 2, and Opposites Attract studies [13–14], encouraged even more people to support the U=U message campaign. In these four studies, no cases of sexual transmission were registered when the HIV-positive partner had an HIV viral load under 200 copies/mL.

However, in HPTN052 and Partner 1, the serodiscordant couples were both heterosexual and MSM. On the contrary, in Partner 2 and Opposites Attract, only MSM couples were included. In none of the four studies, data about PWID and foreign-born were available. Furthermore, information on whether participants have had an AIDS-defining disease or precedent virological failure were not recorded. Although there is no strong reason to think that results would have been different in different target populations, strictly speaking, the quantitative results seen in these studies do not apply to these different case-mix populations.

Our analysis using the data of a cohort of PWH seen for care in Italy evaluated, for the first time, the probability of retaining an HIV-RNA≤200 copies/mL (the 'U status') over a long period during the U=U prevention campaign era.

We found that in our population of PWH the 'U status' was maintained, on average, for 97% of the following ten years of observation, and the proportion of PDFU spent in the 'U status' showed a trend for an increase in recent years. Although a causal link cannot be established and we cannot ascribe these results to the correct receipt of the U=U message, because of very high rates of viral suppression, this data reassuringly suggests that U=U is an appropriate message to communicate to help decrease stigma and increase motivation to remain virally suppressed. Of note, although the risk of transmission was not evaluated in the analysis, our study population included MSM,

heterosexual women, and men, as well as PWID and foreign-born, subpopulations which were underrepresented in other studies.

Furthermore, when fitting a multivariable logistic regression analysis, female gender, being PWID, foreign-born, and unemployed, were all independently associated with the risk of losing 'U status'.

Looking at each of these factors in detail, we found that females have lost the 'U status' more frequently than males (5.3% vs. 2.4%). The role of female gender as a risk factor associated with VF risk is debated in the literature.[18] A meta-analysis of RCT showed no difference in the probability of reaching a virological success by gender.[19] However, in a real-life observational cohort, after controlling for other variables, females resulted at increased risk of delayed ART initiation and therapy discontinuation, even if no differences in response rates to the first year of ART were shown.[20]

Foreign nationality has already been associated with an increased risk of VF. Saracino et al., in the same cohort analysed here, showed that the incidence rate of VF was higher in foreign-born (15.5 per 100 person-years) compared to Italian-born (8.9 per 100 person-years).[21]. More recently, Reyes-Urueña et al. showed that foreign-born had a significantly lower proportion of patients under follow-up with viral suppression compared with Spanish-born (82.9% vs. 87.2%).[22] Furthermore, PWH originating from Latin America or the Caribbean showed a significantly increased risk (OR 6.59; 95%CI 2.08-20.92) of VF compared to those born in the Netherlands in the Athena cohort.[23]

The use of injection drugs was the most significant risk factor in losing 'U status' in our analysis. It has been previously associated with low adherence levels to cART, risk of treatment discontinuation, and VF. In the Swiss HIV cohort, Weber et al. conducted a study on 6,529 participants who were followed up for a total of 31,215 person-years.[24] They showed that drug use lowered cART adherence, increased cART change rates, and cART interruptions and that VF was more frequent among PWID. In the EuroSIDA cohort, PWID in East Central and Eastern Europe were around half as likely as MSM to have a suppressed viral load on ART (aOR 0.52; 95%CI 0.25–1.06).[25] Furthermore, a longitudinal study conducted in the United States has shown that only 10.2% of PWID had sustained virologic suppression (HIV-RNA<400 cp/ml) during a median follow-up of 8.7 years.[26]

PWH with poor education and those who were unemployed showed, in our analysis, a significant risk in losing the 'U status', compared, respectively, to PWH with advanced education and those employed. Many other studies demonstrated how these social determinants play a crucial role in response to antiretroviral therapy. D'Almeida et al. aimed that the unemployed, compared with the employed, had a lower sustained virological suppression (aOR= 0.6).[27] Saracino et al. showed in 8,023 PWH that the unemployed and people with lower education had a higher 1-year risk of first-line ART discontinuation.[20] The COHERE study found that virological response was significantly related to the degree of education (67% in PWH without completed basic vs. 87% with tertiary education).[28] Socio-economic factors are seldom collected in HIV cohort studies, so this is one of our analysis strengths.

When considering virological and immunologic characteristics, losing 'U status' in our cohort was most frequently observed in PWH with a high peak viral load and in those with a CD4+ count ≤200 cells/mm^3. In a cohort study with 5,766 PWH, Armenia et al. demonstrated how people with a high viremia had a high probability of experiencing a virological rebound with an HIV-RNA > 200

copies/ml.[29] The role of CD4+ count as a predictor of VF is controversial. In the HPTN052 study, Eshleman et al. found that PWH with a high CD4+ cell count before starting cART have an increased VF risk.[30] On the contrary, in their meta-analysis, Skowron et al. found that baseline CD4+ cell count was a critical predictor of virologic suppression.[31] More recently, Stirrup et al. evidenced how a lower CD4+ cell baseline is a predictor of VF with drug resistance in the UK CHIC study.[32] Some of these discrepancies are likely to be due to the study design. For example, the CD4+ count measured at the time of viral suppression (like in our analysis) is likely to be a predictor of subsequent risk of viral rebound as it reflects adherence to ART received before baseline.

Previous VFs remained a significant predictor of losing 'U status' by multivariable model in our analysis. Moreover, PWH, who never experienced a VF, spent significantly lower PDFU with VL>200 cp/ml (2.9%) when compared to those who have had one to three (4.4%) and more than three previous episodes of VF (6.3%). These results were in accordance with previous observations from a number of other studies. Rusconi et al. showed how the risk of VFs was decreasing in the last year; despite that, the risk associated with viral rebound according to the previous history of virological failure remained constant over time.[33] In the same study, other factors independently associated with a lower risk of VF were Italian origin, a longer history of virological suppression, and maximum level of education achieved (those with a university degree having the lowest risk). Similar results were obtained by Reekie et al., who showed that the rate of virological failure was significantly related to the number of viral rebounds the patient had experienced in the EUROSIDA cohort.[34]

Our study has some limitations. Firstly, it can be argued that the definition of losing the 'U status' based on 10% of PDFU spent with a VL>200 copies/mL is arbitrary and highly dependent on the duration of follow-up. Indeed the longer the follow-up, the greater the chance to reach this endpoint. However, when we used the alternative endpoint of 5% of PDFU and of >3 months with a VL>200 copies/mL, the results were similar.

Secondly, the frequency of viral load measurements is likely to vary from patient to patient, which could have affected the calculation of the PDFU. Specifically, PDFU could be more accurate for people with more frequent measures, although because we used a 'most recent value carried forward' approach, we believe that any bias is probably negligible. Also, we performed a sensitivity analysis in a subset of the cohort of participants whose HIV-RNA was monitored at least twice/year, and the results were again similar. If anything, the estimate of 3.1% of PDFU spent in the 'U status' is an under-estimate of what happened to the average person who is stably in care in our clinics.

Thirdly, considering that our study is a retrospective analysis and no data about HIV-negative partners was available, we could not assess whether HIV sexual transmissions in PWH who have lost the 'U status' have occurred. Similarly, we identified factors associated with losing the 'U status', not the risk of HIV sexual transmission, and we are assuming that by reducing the proportion of people leaving the 'U status', we could achieve less new infections.

Last but not least, adherence is a key unmeasured confounder in all these analyses, and failing to control for adherence could have biased the magnitude and significance of some of the associations described.

With evidence coming from both clinical trials and observational studies supporting these efforts, clinicians should correctly communicate the U=U prevention message to the PWH.[11–14] However, a recent international survey found that only 77% of infectious disease specialists and 42% of primary care physicians communicated the message to patients when informing them of their undetectable viral load level.[35].

Conclusion

Our data show an ecological correlation between the introduction of the U=U campaign and a scenario of unfrequent episodes of VL>200 copies/mL over a long period of time with a further trend toward a decrease after the launch of the campaign. U=U is an essential but straightforward campaign founded on scientific evidence. It has already successfully influenced public opinion, reducing the stigma in PWH and consequently improving their quality of life.
Nevertheless, our and previous studies also show that more efforts need to be made to encourage clinicians to introduce this message during routine visits. Our data are useful to identify subpopulations (e.g., females and foreign-born) who may particularly benefit from targeted interventions.

Competing interests

G Madeddu reports personal fees from Gilead Sciences, personal fees from Janssen, personal fees from Merck Sharp and Dohme, personal fees from ViiV, outside the submitted work; FM reports grants and personal fees from ViiV, grants and personal fees from Gilead, personal fees from MSD, grants and personal fees from Jannsen, outside the submitted work; RG reports personal fees from ViiV, personal fees from Merck, grants from Gilead, outside the submitted work; AS reports grants from GILEAD, outside the submitted work; ADM reports grants, personal fees and non-financial support from Gilead Sciences, personal fees from Janssen-Cilag, personal fees from Merck, personal fees and non-financial support from ViiV Healthcare, outside the submitted work; AA reports grants, personal fees and non-financial support from Gilead Sciences, grants and personal fees from Janssen-Cilag, personal fees from Merck, grants, personal fees and non-financial support from ViiV Healthcare, outside the submitted work; EG reports personal fees from ViiV, personal fees from Gilead, grants from Gilead, grants from Mylan, personal fees from Mylan, personal fees from Angelini, outside the submitted work; ADV, ACL, AC CFP and G Marchetti have nothing to disclose.

Authors contribution:

GM, ADV, ACL, ADM, AA, and EG conceived the study. ACL performed the statistical analyses. ADV, AC, FM, CFP, RG, GM, and AS contributed to the patients' enrolment and data collection. GM, AD, ACL, ADM, AA, and EG wrote the first version of the manuscript. All authors reviewed the manuscript, provided critical scientific revisions, and approved the final version of the manuscript.

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Figures

Figure 1. Estimating PDFU with VL > or ≤ 200 cp/ml for a hypothetical participant. If both viral load (VL) measurements of a pair were ≤ 200 copies/mL copies/ml (square A), then all intervening person days of follow-up (PDFU) were considered to have been ≤200 copies/ml. The grey area represents the PDFU >200 copies/ml. If both measurements of a pair were >200 copies/ml VL, then all intervening PDFU were considered to have been >200 copies/ml. If the first VL in the pair was ≤200 copies/ml and the second was above 200 copies/ml (square B), or vice versa (square C), we used a straight-line approximation to estimate viral loads between measurements.

Figure 2. Forrest Plot of multivariable logistic regression estimates of factors associated with losing 'U status'. Multivariable model includes all variables selected by backward selection that were retained with a p-value less than 0.3 level. Also adjusted for age, AIDS diagnosis, HBsAg/HCV status, duration of ART, anchor drug used, geographical region, diabetes, smoking, use of statins/lowering blood pressure drugs, glucose, and prior sexual transmitted diseases. PWID: people who inject drugs; MSM: men who have sex with men; VF: virological failure.

Figure 3. Person days of follow up (PDFU) with VL >200 copies/ml by calendar year of follow-up. The grey area represents the PDFU with HIV-RNA >200 copies/ml

Supplemental Material

Supplemental Table 1. Odds Ratio of U=U status (≤3 months with VL>200) from fitting a logistic regression

Supplemental Figure 1. Spaghetti plot of individual participants' HIV-RNA trajectory (selected subset of people with ≥2 episodes of sustained HIV-RNA>200 copies/mL).

Supplemental Figure 2. Adjusted OR from fitting a logistic regression model restricted to the subset of participants with ≥2 HIV-RNA measures/year

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Table 1. Characteristics of 8241 patients meeting the definition of U status (i.e. a HIV-RNA≤200 copies/mL) in the ICONA cohort

	Total	≤ 90% time	>90% time	p-value*
	N= 8241	N= 617	N= 7624	
Female, n (%)	1648 (20.0%)	212 (34.4%)	1436 (18.8%)	<.001
Age§, years	39 (31, 47)	39 (32, 47)	39 (30, 47)	0.435
Mode of HIV Transmission, n(%)				<.001
PWID	768 (9.3%)	115 (18.6%)	653 (8.6%)	
MSM	3786 (45.9%)	173 (28.0%)	3613 (47.4%)	
Heterosexual contacts	3176 (38.5%)	289 (46.8%)	2887 (37.9%)	
Foreign-born, n (%)	2066 (25.1%)	190 (30.8%)	1876 (24.6%)	<.001
Education, n(%)				<.001

Primary school	426 (5.2%)	59 (9.6%)	367 (4.8%)	
Secondary school	1629 (19.8%)	164 (26.6%)	1465 (19.2%)	
College	2579 (31.3%)	161 (26.1%)	2418 (31.7%)	
University	1019 (12.4%)	45 (7.3%)	974 (12.8%)	
Employment, n(%)				<.001
Unemployed	952 (14.0%)	123 (23.5%)	829 (13.2%)	
Employed	3488 (51.4%)	226 (43.2%)	3262 (52.0%)	
Self-employed	1187 (17.5%)	69 (13.2%)	1118 (17.8%)	
HbsAg +, n (%)	108 (1.3%)	8 (1.3%)	100 (1.3%)	0.716
HCVAb +, n (%)	905 (11.0%)	128 (20.7%)	777 (10.2%)	<.001
Diabetes, n(%)	231 (2.8%)	26 (4.2%)	205 (2.7%)	0.027
Smoking, n(%)	2939 (35.7%)	253 (41.0%)	2686 (35.2%)	0.004
CVD diagnosis, n(%)	87 (1.1%)	13 (2.1%)	74 (1.0%)	0.008
Prior STDs	1862 (22.6%)	144 (23.3%)	1725 (22.6%)	<.001
AIDS diagnosis, n(%)	1009 (12.2%)	110 (17.8%)	899 (11.8%)	<.001
CD4+ count[§], cells/mmc	532 (356, 730)	507 (302, 698)	534 (361, 733)	<.001
CD4+ count nadir, cells/mmc	300 (162, 436)	264 (119, 403)	302 (166, 438)	<.001
CD8 count[§], cells/mmc	878 (633, 1198)	900 (661, 1244)	874 (632, 1195)	0.111
Peak viral load in follow-up[§], log10 copies/mL	4.52 (3.67, 5.12)	4.81 (4.16, 5.35)	4.49 (3.63, 5.11)	<.001

CD4+ count ≤200 cells/mmc**, n(%)**	824 (10.0%)	94 (15.2%)	730 (9.6%)	<.001
Time from HIV diagnosis[§] **months**	15 (7, 65)	31 (9, 115)	14 (7, 61)	<.001
Follow-up time[§]**, months**	45 (21, 78)	58 (30, 82)	44 (20, 78)	<.001
No previous VF, n(%)				<.001
1-3	429 (5.2%)	54 (8.8%)	375 (4.9%)	
3+	324 (3.9%)	65 (10.5%)	259 (3.4%)	

[§]Median (IQR); *Chi-square or Mann-Whitney U test as appropriate; PWID: people who inject drug; MSM: man who have sex with men; CVD: cardiovascular disease; STDs: sexual transmitted diseases; VF: virologic failure; ART: antiretroviral therapy.

Table 2. Distribution of person days of follow-up according to time spent in viral load categories and risk factors.

Variables	**HIV-RNA category (copies/mL)**			
	≤ 200	**>200**	**% >200**	**p-value**
Gender				<.001
Male	26856	671.8	2.4	
Female	7034	393.2	5.3	
Age				0.091
46+	12345	361.0	2.8	
18-45	21371	698.5	3.2	
Mode of HIV transmission				<.001

MSM	14529	259.4	1.8	
Heterosexuals	13629	480.1	3.4	
PWID	1972	97.9	4.7	
Foreign-born				<.001
No	28835	777.2	2.6	
Yes	5055	287.7	5.4	
Employment				<.001
Self-employed	5306	126.5	2.3	
Employed	15847	443.6	2.7	
Unemployed	3449	198.1	5.4	
No. previous VF				<.001
0	29262	809.6	2.7	
1-3	2644	122.7	4.4	
>3	1985	132.6	6.3	

PWID: people who inject drug; MSM: man who have sex with men; VF: virologic failure.