IMPLEMENTATION OF U=U IN REAL LIFE IN ITALY: RESULTS FROM THE ICONA COHORT

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BACKGROUND

✓ Since the end of '80s, several studies have investigated the role of a detectable p24 antigen or viral load in the transmission of HIV. In 1994, an Italian study [1], demonstrated how patients who were treated with zidovudine had a reduced rate of transmission to their female partner.

✓ In 2008 The Swiss Cohort statement wrote that "an HIV-infected individual without additional sexual transmitted disease (STD) and on an anti-retroviral therapy (ART) with completely suppressed viremia is sexually non-infectious" [2].

✓ More recently, in 2011, a large randomized trial (HPTN-052) showed with striking evidence that early ART is able to dramatically reduce HIV linked transmissions by 96% [3].

✓ Moreover, between 2010 and 2019 two large observational studies (Partner and Opposites Attract) showed no linked HIV transmission in serodiscordant couples when the HIV-infected partner is undetectable [4-6].

✓ Based on the scientific evidence, the Prevention Access Campaign, launched the Undetectable = Untransmittable (U = U) initiative in 2016.

AIMS

✓ In a population of people living with HIV (PLWH) enrolled in a clinical cohort on stable U=U status in 2010, we aimed to estimate the proportion of time in which this status was maintained over time.

✓ We also aimed to identify factors associated with the risk of losing the U=U status.

METHODS

✓ We included participants in the ICONA cohort who had reached an established U=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 after June, 01 2010.

✓ The outcome variable was a proportion reflecting the number of days of follow-up (PDFU) spent with a viral load (VL) >200 copies/mL, relative to the total number of PDFU, calculated for individual participants. We computed this outcome using consecutive VL pairs, using the method proposed by Marks et al (Figure 1).

✓ In addition, this proportion was also used to define a binary endpoint for individual participants: losing the U=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. Alternative endpoints, less dependent on participants' length of follow-up, were examined which led to similar results (data not shown).

✓ Main characteristics of the participants at baseline were compared between those who remained or lost the U=U status using chi-square or Kruskal-Wallis test, as appropriate, to test for significant dif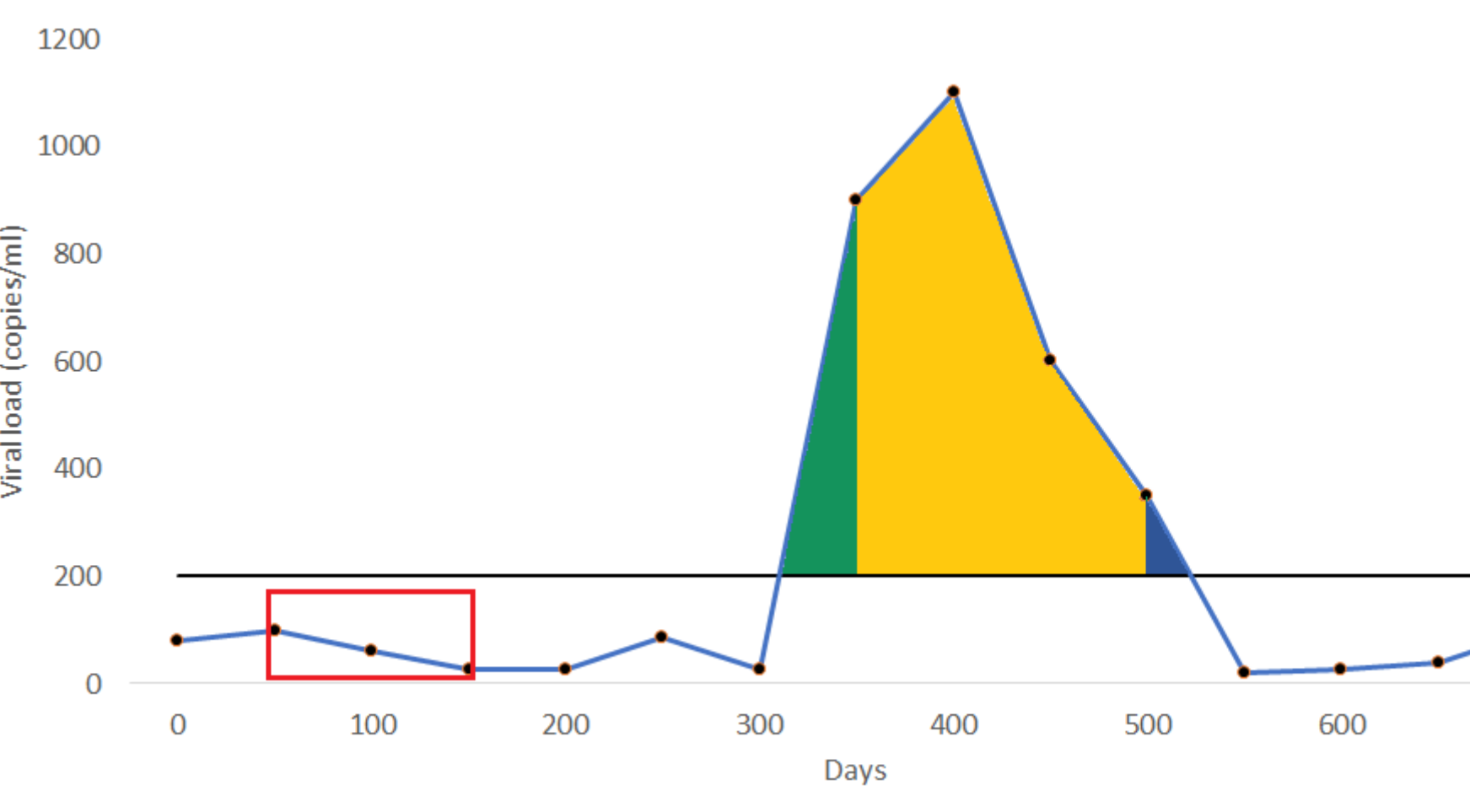ferences between groups (Table 1). A multivariable logistic regression analysis was also performed to identify factors independently associated with the risk of losing the U=U status. All factors which were considered a priori to be important predictors, on the basis of the literature or other axiomatic knowledge, have been included in the multivariable model, regardless of the p-value in the unadjusted comparison.

Figure 1 Estimating PDFU with VL > or ≤200 cp/ml for a hypothetical participant. If both VL measurements of a pair were ≤200 copies/mL copies/ml (red square), then all intervening PDFU were considered to have been ≤200 copies/ml. If both measurements of a pair were >200 copies/ml VL (orange area) , then all intervening PDFU were considered to have been >200 copies/ml. If the first VL in the pair was above 200 copies/ml, and the second was ≤200 copies/ml (blue area), or vice versa (green area), we used a straight-line approximation to estimate viral loads between measurements.

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RESULTS

✓ 8,241 PLWH were included in the study for a total of 12,670,888 PDFU. Median age was 39 (IQR 31,47), 20% were female. The majority of participants have acquired HIV infection trough sexual contacts (45.9% MSM and 38.5% heterosexuals). During follow-up 617 patients have spent ≤ 90% of the time with a VL ≤ 200 copies/ml, losing the U=U status.

✓ Main participants' characteristics are summarized in the table 1.

Table 1. Participants' characteristics.

	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(%)	87 (1.1%)	26 (4.2%)	205 (2.7%)	0.027
Smoking, n(%)	231 (2.8%)	253 (41.0%)	2686 (35.2%)	0.004
CVD diagnosis, n(%)	2939 (35.7%)	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+	344 (3.9%)	65 (10.5%)	259 (3.4%)	

*Median (IQR); **Chi-square or Kruskal-Wallis 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.

✓ The median of VL measurements was 9 (IQR: 4-15) and the median time with VL>200 cp/ml was 47.3 days (IQR: 46.3-47.9).

✓ At individual level, 617 participants (7.5%) spent <90% of PDFU with a VL<=200 copies/mL and were classified as losing their initial U=U status over time.

✓ At univariate analysis, when comparing PLWH with U=U status ≤90% (n=617) to those with >90% (n=7624) of time were more frequently female (p<0.001), PWID (p<0.001), foreign born (p<0.001). They had less frequently a college or university degree (p<0.001) and were more frequently unemployed (p<0.001). The also had a previous AIDS diagnosis (p=0.008), an hepatitis coinfection (p<0.001), lower current and nadir CD4 count (p<0.001), higher peak median viral load (p<0.001) and longer time from HIV diagnosis (p=0.002). They showed a longer time from HIV diagnosis and follow up time and had more frequently 1-3 or >3 virological failures (VFs), p<0.001.

✓ During the entire follow-up (2011-2019), 96.9% of the PDFU observed were spent with a VL ≤200 cp/ml. Thus, only 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 next years, especially after 2016 (Figure 2).
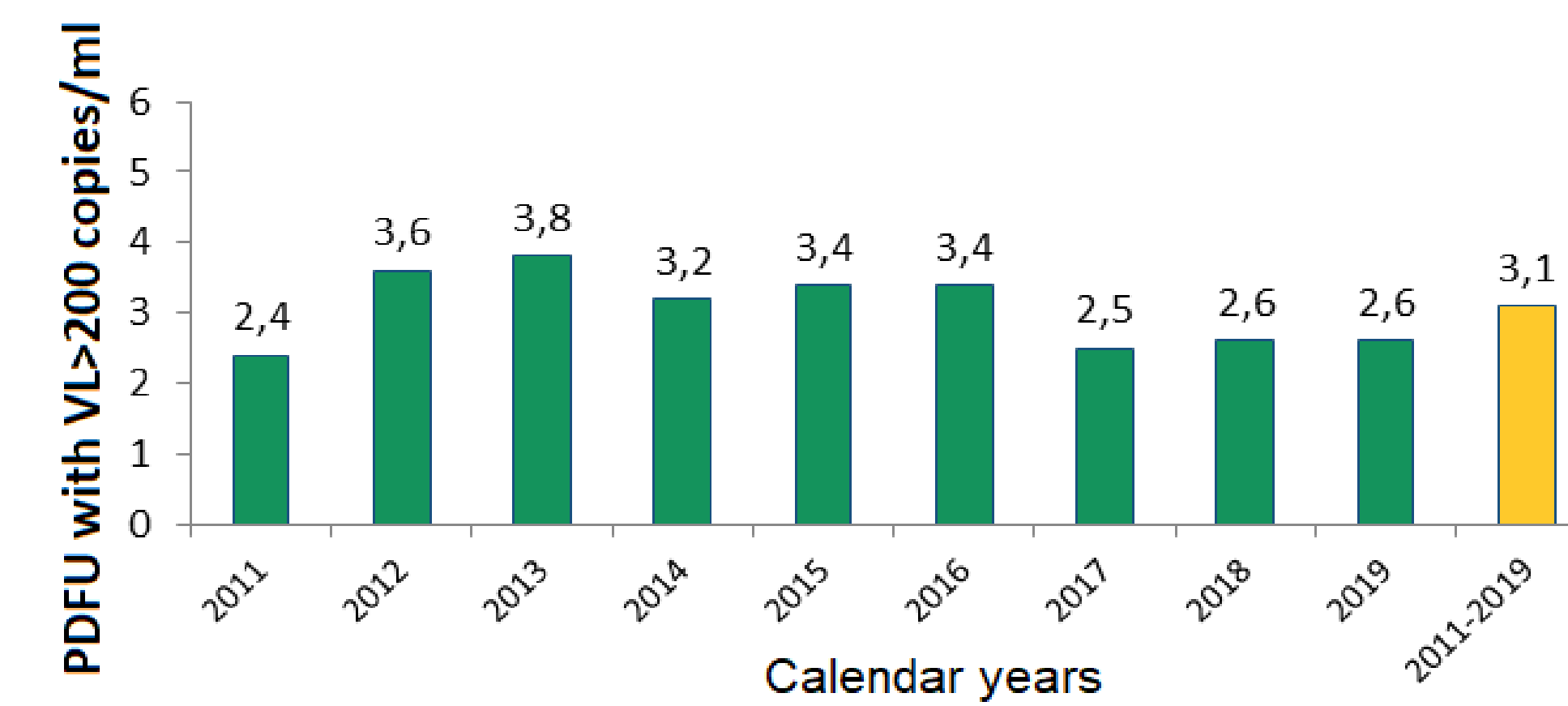

Figure 2. Person day follow up (PDFU) with VL >200 copies/ml by calendar year of follow-up.

✓ 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>3 previous virological failures (6.3%).

✓ No differences were present when comparing patients with a age between 18-45 and ≥46 years (Table 2).

Table 2. Distribution of PDFU according to time spent in VL categories and risk factors

	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

✓ At multivariate unadjusted logistic regression analysis female gender, being PWID, foreign born and unemployed were independent predictors of losing U=U status. Having had 1-3 and, with higher Odds ratio, more than 3 previous virological failures were also associated with a significant risk of losing U=U status. The same variables were also confirmed as significant predictors of losing U=U status at the adjusted analysis.

✓ Unadjusted and adjusted Odds ratios of losing U=U status from fitting the logistic regression model are shown in Table 3.

Table 3. Multivariate logistic regression estimates of factors associated with losing U=U status.

	Unadjusted		Adjusted*		
Factor	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Type III p-value
Gender					
Female vs. Male	2.26 (1.89, 2.69)	<.001	1.55 (1.20, 2.00)	<.001	
Mode of HIV Transmission					<.001
PWID vs. MSM	3.68 (2.86, 4.72)	<.001	2.50 (1.80, 3.46)	<.001	
PWID vs. Heterosexual	2.09 (1.72, 2.54)	<.001	1.43 (1.10, 1.87)	0.009	
PWID vs. Other/Unknown	1.77 (1.24, 2.53)	0.002	1.67 (1.07, 2.60)	0.017	
Nationality					
Foreign-born vs Italian	1.36 (1.14, 1.63)	<.001	1.42 (1.12, 1.80)	0.004	
Employment, n (%)					<.001
Unemployed vs. Employed	2.14 (1.70, 2.70)	<.001	1.46 (1.13, 1.89)	0.004	
Previous virological failure, n					<.001
1-3 vs. 0	2.02 (1.50, 2.73)	<.001	1.84 (1.22, 2.76)	0.003	
>3 vs. 0	3.52 (2.64, 4.69)	<.001	2.85 (1.84, 4.44)	<.001	

*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 STDs. PWID: people who inject drugs; MSM: men who have sex with men.

STRENGHTS AND LIMITATIONS

✓ Our study has some strengths an limitations. The first include the huge number of PLWH enrolled and the diversity of the population which include males, females and all risk categories including PWID. The latter include the arbitrary choice of the cut-off for the time spent with <200 copies/mL (>or ≤90%) and the different number of visits (and VL) per year for each patient.

CONCLUSIONS

✓ Our population of PLWH meeting the definition of U=U at December 2010 maintained this status for 97% of the following 10 years of observation and the proportion showed a trend for a further increase in recent years.

✓ We also identified a small subset of more fragile individuals, including females, PWID, unemployed and foreign-born, at higher risk of not maintaining the U=U status.

✓ In these populations, greater efforts and focused interventions seem useful to further reduce the occurring of (although infrequently observed) periods with a VL>200 cp/ml.

✓ Taken together our results from a "real life" setting reinforce the validity of the U=U message in real world settings and the promotion of related campaigns.

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