

# Incidence and factors associated with the risk of sexually transmitted diseases in HIV-infected people seen for care in Italy: data from the Icona Foundation cohort

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## Objectives

The aims of this study were to identify temporal trends in the incidence of sexually transmitted diseases (STDs) in a cohort of HIV-infected people and to evaluate factors associated with the risk of a new STD diagnosis.

## Methods

All HIV-infected patients in the Icona Foundation Study cohort enrolled after 1998 were included in this study. STD incidence rates (IRs) were calculated and stratified by calendar period. Predictors of STDs were identified using a Poisson regression model with sandwich estimates for standard errors.

## Results

Data for 9168 participants were analysed [median age 37.3 (range 18–81) years; 74% male; 30% men who have sex with men (MSM)]. Over 46 736 person-years of follow-up (PYFU), 996 episodes of STDs were observed [crude IR 21.3/1000 PYFU; 95% confidence interval (CI) 20.0–22.6/1000 PYFU]. In multivariable Poisson regression analysis, MSM [rate ratio (RR) 3.03; 95% CI 2.52–3.64 versus heterosexuals], calendar period (RR 1.67; 95% CI 1.42–1.97 for 2008–2012 versus 1998–2002), HIV RNA > 50 HIV-1 RNA copies/mL (RR 1.44; 95% CI 1.19–1.74 versus HIV RNA ≤ 50 copies/mL) and a current CD4 count < 100 cells/μL (RR 4.66; 95% CI 3.69–5.89; *P* < 0.001 versus CD4 count > 500 cells/μL) were associated with an increased risk of STDs. In contrast, older age (RR 0.82 per 10 years older; 95% CI 0.77–0.89) and being currently on ART (RR 0.38; 95% CI 0.33–0.45) compared with being ART-naïve or on a treatment interruption were associated with a lower risk of developing STDs.

## Conclusions

An increase in the incidence of STDs was observed in more recent years. Interventions to prevent STDs and potential spread of HIV should target the younger population, MSM and people currently not receiving ART.

**Key words:** cohort, HIV, incidence, sexually transmitted diseases

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## Introduction

The role of fully suppressive combination antiretroviral therapy (cART) in reducing HIV transmission to HIV-negative partners is well established [1,2], and model simulations show that a policy based on timely identification and increased access to antiretroviral therapy may eventually lead to control of the HIV/AIDS epidemic [3]. However, the impact of ART on the spread of the epidemic has to date been at best limited, even in resource-rich countries, and it has been suggested that persistent risky behaviour, such as condom-less sex, may contribute to limit the beneficial effect of cART in reducing the incidence of HIV infection, at least in men who have sex with men (MSM) in the UK [4]. Concern has also been expressed that provision of ART may *per se* be associated with an increase in the rate of condom-less sex, as a result of so-called risk compensation, although a systematic review of available evidence did not support this hypothesis, but instead demonstrated that the probability of engaging in unprotected sex was associated with the belief that ART may prevent viral transmission, rather than with actual receipt of ART or viral suppression *per se* [5].

In this context, the analysis of the possible determinants of sexually transmitted diseases (STDs) among persons living with HIV may help to identify populations that are likely to engage in these risky behaviours. It has also been shown that STDs can increase the shedding of HIV in semen, leading to an increase of HIV transmission [6]. However, this phenomenon was demonstrated in people not receiving cART, and it remains largely unknown whether the same increase in the risk of STDs might be seen in people on fully suppressive cART. In addition, it has been recently demonstrated that effective cART does not completely reduce the risk of HIV transmission in sexually active MSM with concomitant STDs [7].

The Icona Foundation Study is an observational study enrolling HIV-infected patients naïve to ART over the period 1997–2014, and a previous analysis performed using the data from this cohort demonstrated that the use of cART was not associated with the risk of newly acquired hepatitis B virus (HBV) infection and syphilis, and that suppressive cART was associated with a lower risk of HBV surface antigen (HBsAg) seroconversion [8].

In the present analysis, we adopted a more comprehensive approach considering all incident STDs. Moreover, as it has been estimated that more than 85% of patients treated with cART in Italy are currently on fully suppressive cART and some of the patients in the cohort have now been followed up for over 15 years, we decided to perform this more comprehensive analysis focused on the role of current viral loads and extended to more recent years to

provide updated data that might be useful in planning STD prevention programmes aiming to reduce HIV transmission.

Specifically, we aimed to identify temporal trends in the incidence of STDs and to evaluate factors associated with the risk of a new diagnosis of an STD, with particular focus on the use of cART and the possible role of viral suppression.

## Methods

All HIV-infected patients enrolled in the Icona Foundation Study cohort from 1998 were included in our analysis. The Icona Foundation Study is an observational cohort study of HIV-infected individuals who are antiretroviral-naïve at the time of enrolment [9]. This cohort was set up in January 1997 and currently includes data on patients enrolled at 40 infectious disease units in Italy. Initiation and discontinuation dates of each antiretroviral drug, the HIV viral load and CD4 cell count at each clinical visit (every 4–6 months on average), and clinical HIV- and non-HIV-related events are recorded in the database. Data on STDs are available at enrolment and they are updated at the occurrence of any clinical event or, in their absence, at least every 6 months.

In this analysis, STD occurrence was defined at the date of clinical diagnosis of any of the following conditions: any-stage syphilis (primary, secondary, latent, tertiary or unspecified), human papilloma virus (HPV)-related diseases, urethritis (gonococcal or nongonococcal), herpes simplex virus (HSV)-related genital ulcers, any genital ulcer disease not otherwise specified, vaginitis (trichomonas, bacteric or not specified), or acute HBV, hepatitis A virus (HAV) or hepatitis C virus (HCV) infection. These conditions and not others were selected as they are routinely reported by clinicians enrolling patients in the cohort with reasonable accuracy. All episodes of STD counted as an event so that the same person could have contributed more than one event. Only true incident cases of STD were included as events, by considering only those that occurred at least 12 months after the date of enrolment in the cohort.

STD incidence rates (IRs) were calculated as the number of events divided by person-years of follow-up (PYFU). These rates were stratified according to a number of factors, including current plasma viral load (plasma HIV RNA < 50 HIV-1 RNA copies/mL versus > 50 copies/mL) and calendar period (1998–2002, 2003–2007 and 2008–2012). Other factors considered were age (stratified as 18–30, 31–40, 41–50, 51–60 and > 60 years old), gender, risk behaviour for HIV transmission [heterosexual, men who have sex with men (MSM), injecting drug user (IDU) and unknown/other], educational level (primary, secondary

school, college and university), ethnicity (Caucasian, black, Hispanic, Asian and other), current CD4 count (< 100, 101–350, 351–500 and > 500 cells/uL), ART status (ART-naïve, on ART and on treatment interruption at STD diagnosis). ART was defined as a regimen of at least one drug belonging to one of the three major historical drug classes [nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI)]. Independent predictors of STD occurrence were identified using a Poisson regression model. Sandwich estimates for the standard errors were used to control for the fact that some people might have contributed more than one event.

Because hepatitis is most frequently acquired via needle sharing rather than through sexual contacts, two sensitivity analyses were performed to assess the role of behavioural risks, (i) not counting as events all diagnoses of hepatitis and (ii) not counting as events the diagnoses of hepatitis that occurred in IDUs.

All individuals signed an informed consent form prior to enrolment and the study was approved by the Ethics Committee of each participating institution listed in the Appendix.

## Results

### Study population

A total of 9168 patients were included in the analysis 2355 (25.7%) of whom were women. The median age at enrolment was 37.3 years (range 18–81 years) and the median CD4 count was 387 cells/ $\mu$ L [interquartile range (IQR) 196–576 cells/ $\mu$ L]. Regarding risk behaviours, MSM represented 31.1% of the study population ( $n = 2850$ ), IDU 24.3% ( $n = 2226$ ) and heterosexual contact 38.4% ( $n = 3518$ ). A total of 3327 patients were enrolled in 1998–2002, 1273 in 2003–2007 and 4568 in 2008–2012. By definition, all patients were ART-naïve at enrolment but 70.8% of them started ART over the study period.

### Incidence of STDs

Over 46 736 PYFU, 996 diagnoses of STDs were reported in 945 patients [crude IR 21.3/1000 PYFU; 95% confidence interval (CI) 20.0–22.6/1000 PYFU]. Forty-eight patients (0.5%) contributed more than one episode of incident STD (45 patients with two episodes and three patients with three episodes).

Considering specific STDs, any-stage syphilis had a crude IR of 3.95/1000 PYFU (95% CI 3.59–4.35/1000 PYFU), HPV infection 1.96 (95% CI 1.71–2.24), acute viral hepatitis 1.72 (95% CI 1.49–1.99) [HAV 0.19 (95% CI 0.09–0.36), HBV 6.54 (95% CI 5.83–7.32), and HCV 3.74 (95% CI

3.21–4.34)], HSV infection 0.81 (95% CI 0.65–0.99), gonococcal urethritis 0.46 (95% CI 0.35–0.61), nongonococcal urethritis 0.47 (95% CI 0.36–0.62) and other genital ulcers 0.11 (95% CI 0.06–0.19).

As shown in Table 1, a higher IR of STDs was observed in men compared with women [24.1/1000 PYFU (95% CI 22.4–25.8/1000 PYFU) versus 14.6/1000 PYFU (95% CI 12.7–16.8/1000 PYFU), respectively] and in people aged 18–30 years compared with the other age strata [45.4/1000

**Table 1** Crude incidence of sexually transmitted diseases (STDs) in the whole population ( $n = 9168$ )

	Number of events	PYFU	IR (95% CI)
Women	204	13912	14.6 (12.7–16.8)
Men	792	32824	24.1 (22.4–25.8)
Age			
18–30 years	181	3982	45.4 (39.0–52.5)
31–40 years	441	18421	23.9 (21.7–26.2)
41–50 years	276	16992	16.2 (14.3–18.2)
51–70 years	93	7021	13.2 (10.7–16.2)
> 70 years	5	329	15.1 (4.9–35.4)
HIV transmission route			
Heterosexual	229	18557	15.7 (13.9–17.6)
MSM	561	10843	51.7 (47.5–56.2)
IDU	87	14926	5.8 (4.6–7.1)
Other	56	2410	23.2 (17.5–30.1)
Period of STDs			
1998–2002	272	15745	17.2 (15.2–19.4)
2003–2007	269	15399	17.4 (15.4–19.6)
2008–2012	455	15592	29.1 (26.5–31.9)
CD4 count at STD diagnosis			
> 500 cells/ $\mu$ L	457	24789	18.4 (16.7–20.2)
351–500 cells/ $\mu$ L	203	10765	18.8 (16.3–21.6)
101–350 cells/ $\mu$ L	247	9832	25.1 (22.0–28.4)
< 100 cells/ $\mu$ L	89	1350	65.9 (52.9–81.1)
HIV RNA at STD diagnosis			
< 50 copies/mL	174	16289	10.6 (9.1–12.3)
> 50 copies/mL	822	30446	27.0 (25.1–28.9)
Years since HIV diagnosis			
< 10 years	860	28932	29.7 (27.7–31.7)
11–20 years	122	14956	8.1 (6.7–9.7)
> 20 years	11	2680	4.1 (2.0–7.3)
Missing	3	168	18.8 (3.6–52.1)
Education			
Primary	79	4393	17.98 (14.2–22.4)
Secondary	248	16531	15.00 (13.2–17.0)
College	349	12855	27.15 (24.4–30.1)
University	113	2614	43.23 (35.6–52.0)
Missing	207	10343	20.01 (17.4–22.9)
Ethnicity			
Caucasian	909	44132	20.60 (19.3–22.0)
Afro-American	34	1364	24.93 (17.2–34.8)
Hispanic	45	968	46.50 (33.9–62.2)
Asian	8	217	36.91 (15.9–72.6)
ART status			
Naïve	534	11962	44.64 (40.9–48.6)
On ART	400	31297	12.78 (11.5–14.1)
On treatment interruption	62	3478	17.83 (13.6–22.8)

ART, antiretroviral therapy; CI, confidence interval; IDU, injecting drug use; IR, incidence rate; MSM, men who have sex with men; PYFU, person-years of follow-up.

PYFU (95% CI 39.0–52.5/1000 PYFU) versus 23.9 (95% CI 21.7–26.2) for 31–40 years, 16.2 (95% CI 14.3–18.2) for 41–50 years, 13.2 (95% CI 10.7–16.2) for 51–70 years and 15.1 (95% CI 4.9–35.4) for > 70 years].

More than half of all episodes of STDs (561 of 996) occurred among MSM, for whom the STD incidence was more than twice as high as that recorded in the other transmission groups [unadjusted rate ratio (RR) 3.29; 95% CI 2.85–3.79;  $P < 0.001$ ]. STD incidence increased in very recent years; in particular, the IR seemed to be stable over the period 2000–2008, with a marked increase observed after 2008 (unadjusted RR 1.69; 95% CI 2.85–3.79;  $P < 0.001$ ). Nevertheless, when the incidence in the different study periods was analysed separately for transmission categories (Fig. 1), MSM had the highest incidence in all time periods. Moreover, the difference in the risk of STDs between MSM and other transmission categories was not consistent over time periods (higher in more recent as opposed to less recent years), supporting the role of MSM in driving the increase in the STD incidence, especially in recent years ( $P$ -value of likelihood ratio test 0.002) (Fig. 1).

Four hundred episodes of STDs (40%) occurred while people were on ART (IR 12.8/31 297 PYFU), 534 (53%) in

ART-naïve patients (IR 44.6/11 961 PYFU) and 62 in those who had discontinued ART (IR 17.8/3478 PYFU). Patients in whom plasma HIV RNA was < 50 copies/mL had an STD incidence that was roughly one-third of that observed among patients with a detectable plasma HIV RNA [IR 10.6/1000 PYFU (95% CI 9.1–12.3/1000 PYFU) versus 27.0/1000 PYFU (95% CI 25.1–28.9/1000 PYFU), respectively; unadjusted RR 1.44; 95% CI 1.19–1.74;  $P < 0.001$ ].

As shown in Table 2, after adjusting for age, HIV transmission route, current calendar period, years from HIV diagnosis, current CD4 count and HIV RNA, and level of education, to be MSM (RR 3.03; 95% CI 2.52–3.64;  $P < 0.001$  compared with other routes of HIV transmission), to have a current CD4 count < 100 cells/ $\mu$ L (RR 4.66; 95% CI 3.69–5.89;  $P < 0.001$  compared with higher strata of CD4 count), to have uncontrolled plasma HIV RNA (RR 1.44; 95% CI 1.19–1.74;  $P < 0.001$  compared with viraemia < 50 copies/mL), and to be diagnosed with HIV infection in recent years (< 10 years ago versus > 10 years: RR 2.70; 95% CI 1.45–5.03;  $P = 0.002$ ) were all factors independently associated with the risk of acquiring an STD. Moreover, more recent calendar period (2008–2012) was also independently associated with an increased risk of

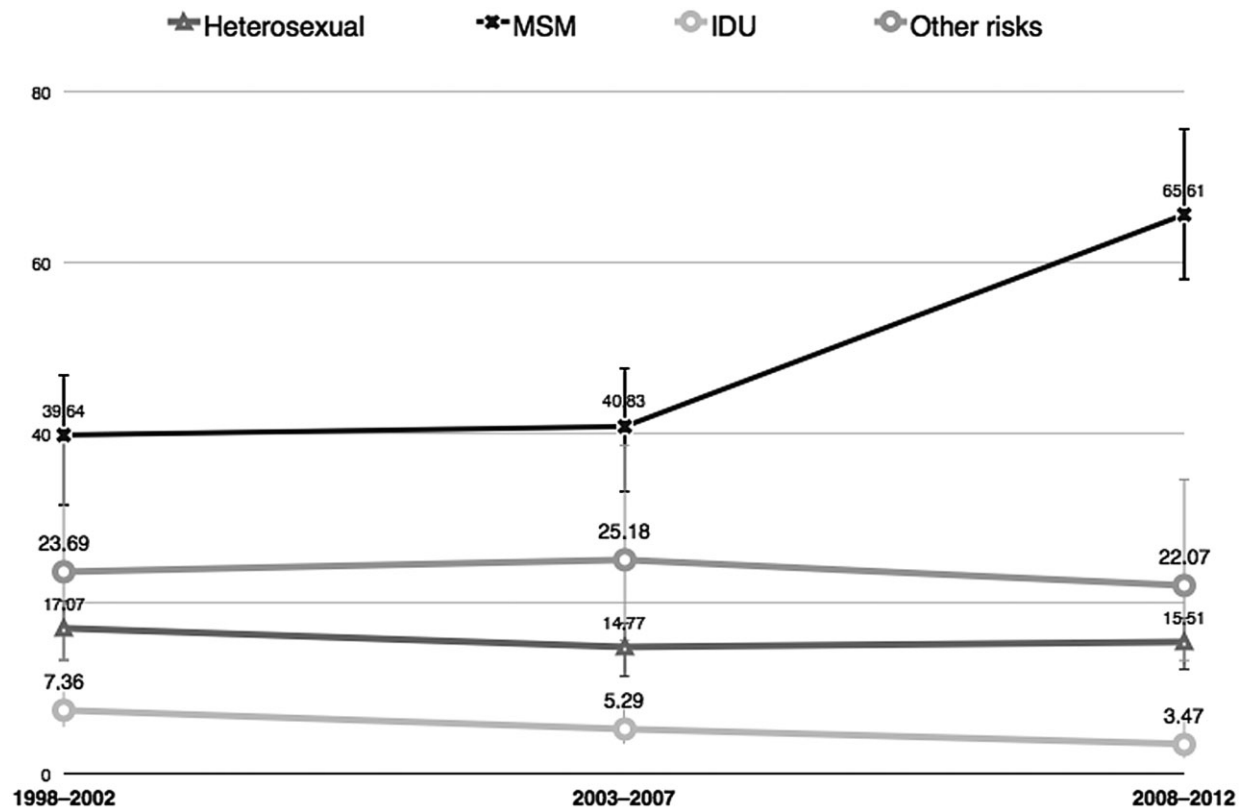


Fig. 1 Incidence rate for any sexually transmitted disease (STD) according to HIV transmission route in different periods of observation. IDU, injecting drug use; MSM, men who have sex with men.

**Table 2** Unadjusted and adjusted incidence rate ratios (IRRs) for developing sexually transmitted diseases (STDs) in the whole population

	Unadjusted IRR	95% CI	<i>P</i>	Adjusted IRR	95% CI	<i>P</i>
Women	1			1		
Men	1.64	1.41–1.92	< 0.001	0.88	0.72–1.09	0.21
Age						
18–30 years	1			1		
31–40 years	0.53	0.44–0.63	< 0.001	0.89	0.74–1.06	0.19
41–50 years	0.36	0.29–0.43	< 0.001	0.75	0.62–0.92	0.005
51–70 years	0.29	0.23–0.37	< 0.001	0.52	0.40–0.67	< 0.001
> 70 years	0.33	0.14–0.81	0.01	0.56	0.23–1.37	0.20
HIV transmission route						
Heterosexual	1			1		
MSM	3.23	2.85–3.79	< 0.001	3.03	2.52–3.64	< 0.001
IDU	0.82	0.68–0.98	0.030	0.51	0.39–0.66	< 0.001
Other	1.50	1.12–2.00	0.006	1.54	1.15–2.07	0.004
Period of STDs						
1998–2002	1			1		
2003–2007	1.01	0.85–1.19	0.89	1.16	0.98–1.38	0.08
2008–2012	1.69	1.45–1.96	< 0.001	1.67	1.42–1.97	< 0.001
CD4 count at STD diagnosis						
> 500 cells/ $\mu$ L	1			1		
351–500 cells/ $\mu$ L	1.02	0.86–1.21	0.78	0.94	0.79–1.11	0.45
101–350 cells/ $\mu$ L	1.36	1.16–1.59	< 0.001	1.63	1.39–1.91	< 0.001
< 100 cells/ $\mu$ L	3.57	2.85–4.48	< 0.001	4.66	3.69–5.89	< 0.001
HIV RNA at STD diagnosis						
< 50 copies/mL	1			1		
> 50 copies/mL	2.53	2.14–2.97	< 0.001	1.44	1.19–1.74	< 0.001
Years since HIV diagnosis						
> 20 years	1			1		
11–20 years	1.98	1.07–3.68	0.029	1.43	0.76–2.67	0.265
< 10 years	7.24	3.99–13.12	< 0.001	2.70	1.45–5.03	0.002
Missing	4.34	1.21–15.56	0.024	0.95	0.26–3.48	0.947
Education						
Primary	1			1		
Secondary	0.83	0.64–1.07	0.16	0.76	0.59–0.99	0.04
College	1.50	1.18–1.92	0.001	0.89	0.68–1.15	0.37
University	2.40	1.80–3.20	< 0.001	0.93	0.68–1.26	0.65
Missing	1.11	0.86–1.44	0.41	0.70	0.53–0.91	0.01
Ethnicity						
Caucasian	1			1		
Afro-American	1.21	0.85–1.70	0.27	1.00	0.70–1.43	0.98
Hispanic	2.25	1.67–3.04	< 0.001	1.07	0.79–1.46	0.62
Asian	1.79	0.89–2.67	0.10	1.34	0.66–2.70	0.40
ART status						
Naïve	1			1		
On ART	0.28	0.25–0.32	< 0.001	0.37	0.32–0.43	< 0.001
On treatment interruption	0.40	0.31–0.52	< 0.001	0.51	0.39–0.67	< 0.001

ART, antiretroviral therapy; CI, confidence interval; IDU, injecting drug use; MSM, men who have sex with men.

developing an STD (RR 1.67; 95% CI 1.42–1.97;  $P < 0.001$  compared with previous years of observation).

A significantly reduced risk of an STD was reported for people with a previous history of ART use (RR 0.38; 95% CI 0.33–0.45;  $P < 0.001$  compared with people who had never used ART) (Table 2). Nevertheless, when the current status of ART-experienced individuals was further classified as current use and temporary suspension, wide differences in terms of IR of STD were observed: 12.8/1000 PYFU in people currently receiving ART, 44.6/1000 PYFU in people who were ART-naïve, and 17.8/1000 PYFU for people on temporary ART interruption.

In terms of RRs, compared with ART-naïve patients, the RR for any STD was significantly lower for people currently receiving ART (RR 0.28; 95% CI 0.25–0.32;  $P < 0.001$ ) as well as for people previously exposed to ART, but currently on a temporary interruption (RR 0.40; 95% CI 0.31–0.52;  $P < 0.001$ ).

When we performed a multivariable analysis stratified by ART status (ART-naïve, on ART or on treatment interruption), the same associations found in the whole population (Table S1) were found among ART exposure categories for transmission route as well as for period of STD diagnosis.

Finally, to determine the possible impact of the exclusion of viral hepatitis from STDs for IDUs, we repeated the Poisson regression analysis after excluding viral hepatitis from the definition of an STD event. In this analysis, the association between transmission group and STD incidence was similar to that in the whole cohort: for MSM versus heterosexual, the incidence rate ratio (IRR) was 3.17 (95% CI 2.71–3.72;  $P < 0.001$ ), for IDU versus heterosexual, the IRR was 0.45 (95% CI 0.35–0.58;  $P < 0.001$ ), and for other risks versus heterosexual, the IRR was 1.44 (95% CI 1.04–2.00;  $P = 0.026$ ). Similar results were found in the second sensitivity analyses: for MSM versus heterosexual, the IRR was 3.29 (95% CI 2.85–3.78;  $P < 0.001$ ), for IDU versus heterosexual, the IRR was 0.37 (95% CI 0.29–0.47;  $P < 0.001$ ), and for other risks versus heterosexual, the IRR was 1.50 (95% CI 1.12–2.00;  $P = 0.006$ ).

## Discussion

The results of our analysis show that the risk of acquiring a new STD in HIV-infected individuals has been increasing over time. This is especially true in young people, in MSM, in people currently with a low CD4 count, in those recently diagnosed with HIV infection, and in patients currently not receiving ART. In particular, the increase in incidence observed in MSM compared with other HIV transmission groups seemed more marked in more recent calendar years. Similar data have been obtained in other cohorts enrolling subjects from sites located in other geographical areas [10].

This is certainly alarming, as the occurrence of a new STD has been generally reported to be deleterious for the health of people living with HIV, as a consequence of various mechanisms, such as an increased risk of HIV reinfection caused by either the disruption of mucosal barriers or the recruitment of activated CD4 cells to the genital tract, thereby increasing the pool of cells susceptible to HIV infection; moreover, proinflammatory cytokine release as a result of STDs may also facilitate HIV entry into cells and provide a perfect environment for its propagation [11,12]; and a significant acute decrease in CD4 count and increase in plasma HIV RNA have been reported during syphilis infection [13,14]. Moreover, although a correlation with an increased risk of HIV transmission has not been reported for all STDs, infection with some agents (herpes viruses, *Treponema pallidum*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae* and *Chlamidia*) has been shown to have an important impact on HIV shedding [15–18]. Of note, the most frequent STDs observed in our cohort were syphilis and HPV-related mucosal damage, which are both associated with an increased risk of HIV transmission [19].

In our analysis, the increased STD incidence in recent periods was significantly higher in MSM compared with

other transmission groups. This has also been widely reported [20–22] and it has been hypothesized to be related to several factors, such as the perception of a reduced risk of HIV transmission because of the availability of potent HIV treatment, the increasing use of erectile dysfunction agents which is known as a practice at highest risk of HIV acquisition or transmission [23], and the use of recreational drugs [24].

Moreover, the high prevalence of condom-less sex among the MSM community has been widely reported elsewhere: it was as high as 30% in US HIV-infected MSM [25], which is three-fold higher than that observed among HIV-uninfected MSM [26,27] and two-fold higher than that in HIV-infected men who have sex with women [28]. This fact could explain the spread of STDs among this group of individuals, in view of the protective role of condoms in preventing all STDs, not only HIV infection.

In a recently published analysis of HIV-infected patients in a cohort of MSM in Boston, a high prevalence of STDs and genital inflammation was reported, even in people on suppressive cART, and the presence of an STD/urethritis was independently identified as a predictor of seminal HIV detection, as well as of an increased likelihood of having unprotected anal sex with an HIV-infected partner [7].

The finding of a higher incidence of STDs in young people and in MSM is consistent with that reported in other cohorts in North America [10,29], and suggests that, in order to be maximally effective, specific intervention programmes for HIV prevention should be focused on young, recently diagnosed MSM, who might not have had sufficient health care contact to receive intensive prevention counselling.

Another key finding was that ART reduces the risk of acquiring an STD. It has been suggested that being on ART may represent a proxy for retention in care: people on ART are likely to be those with more stable follow-up, and those who receive more appropriate and efficacious prevention counselling or 'positive prevention' counselling regarding the risk of transmitting HIV infection and acquiring other STDs. 'Positive prevention' is defined as a set of strategies that help people living with HIV to live longer and healthier lives (1) by preserving their sexual and reproductive health and avoiding other STDs; (2) by delaying HIV disease progression; (3) by promoting shared responsibility to preserve their sexual health and reduce the risk of HIV transmission [30]. In contrast, people who remain untreated are typically seen for care less regularly as a result of either less clinical need or lower adherence to visits. Then, of course, there is the group of people who are untreated because they are not even aware of being infected, and these individuals are likely to be responsible for a large proportion of new infections [31]. An alternative hypothesis is that ART may have a protective role against

the acquisition of STDs via the reduction of plasma HIV RNA and consequently of genital HIV RNA concentrations [6].

This is a highly controversial issue. In the HIV Prevention Trial Network 052, in which a large reduction (96%) of HIV transmission to HIV-negative partners in people starting cART early [1] was reported, the observed prevalence of STDs was very low (5%), as also was the prevalence of homosexual couples (3%).

Several recent studies reported persistent seminal HIV RNA in people on ART despite viral suppression in plasma, with persistent risk of HIV transmission [32,33], suggesting the compartmentalization of HIV in the male tract. Nevertheless, more recently, the results of the PARTNER trial, in which more than 40% of couples were MSM, showed no episodes of HIV transmission in the discordant couples, even in the presence of a high prevalence of STDs [34].

Our study showed that patients currently on ART were at a reduced risk of STDs compared not only with those who had never started treatment but also with those who, after initiating ART in the past, were currently on a temporary treatment interruption. These results seem to favour the hypothesis that being on ART represents a proxy for retention in care; in fact, we found that ART has a protective role for STDs which cannot be explained solely by currently having a suppressed plasma viral load. Further analyses are needed to investigate whether a longer duration of viral suppression in plasma may lead to a lower risk of transmission by decreasing the level of HIV RNA in the genital tract or by other mechanisms that our current analysis could not explore. Also, the role of STDs in the risk of acquiring HIV infection could not be directly addressed in our analysis.

In conclusion, we observed a markedly increased incidence of STDs in HIV-infected individuals seen for care in Italy and identified a number of factors associated with this increased incidence. Our results should help in guiding a wide range of interventions aimed at preventing STDs and reducing the potential further spread of HIV infection through efforts to increase linkage and retention in care, and through interventions targeting youth and MSM, as well as people recently diagnosed with HIV infection and those with advanced HIV infection.

## Appendix: the ICONA Foundation Study Group

### Board of directors

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Table S1** Unadjusted and adjusted incidence risk of STD according to ARV status at STD.