Increased incidence of Sexually Transmitted Diseases (STD) in the recent years: data from the ICONA cohort.

A Cingolani[1*], S Zona[2], E Girardi[3], A Cozzi-Lepri[4], L Monno[5], E Quiros Roldan[6], G Guaraldi[2], A Antinori[7], A d'Arminio Monforte[8], S Marcotullio[9] for *the Community Oriented Study Group* of The Icona Foundation Study Group

[1]Dep of Public Health, Infectious Diseases, Catholic University, Roma, Italy; [2] Clinic Infectious Diseases, Univerisy of Modena and Reggio Emilia, Modena, Italy; [3] Dep of Epidemiology and [7] Clinical Department, National Institute for Infectious Diseases "L.Spallanzani", Roma, Italy; [4] Department of Infection and Population Health. Division of Population Health, UCL Medical School, Royal Free Campus, London, United Kingdom; [5] Insitute of Infectious Diseases, University of Bari, Bari, Italy;[6] Insitute of Infectious Diseases, University of Brescia, Brescia, Italy; [8] Clinic of Infectious and Tropical Diseases, Dept. of Medicine, Surgery and Dentistry, San Paolo University Hospital Milan, Milano, Italy, 9 Nadir Foundation Onlus, Roma, Italy

* a.cingolani@rm.unicatt.it

Background: Aims of this analysis were to identify temporal trends in the incidence of sexually transmitted diseases (STDs) in a cohort of HIV+ 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. STD incidence rates (IR) were calculated and stratified by calendar periods. Predictors of STDs were identified by Poisson regression model with sandwich estimates for standard errors.
Results: Data from 9,168 participants were analyzed (median age 37.3 (range: 18-81), 74% male, 30% MSM). Over 46,736 PYFU, 996 episodes of STDs were observed (crude IR = 21.3/1,000 PYFU, 95% CI: 20.0-22.6). By multivariable Poisson regression analysis, MSM (rate ratio (RR) 3.03, 95%CI 2.52–3.64 vs. heterosexuals), calendar period (RR 1.67, 95% C.I. 1.42–1.97, in 2008-2012 vs. 1998-2002), HIV-RNA>50 c/ml (RR 1.44 , 95%CI 1.19–1.74 vs. HIV-RNA ≤50c/ml) and a current CD4+ cell count<100/mmc (RR 4.66, 95%CI 3.69–5.89, p<0.001 vs. CD4+ cell count>500) were associated with increased risk of STDs. In contrast, older age (RR=0.82 per 10 years older, 95%CI 0.77–0.89) and to be currently on ART (RR 0.38, 95%CI 0.33–0.45) compared to be ART-naïve people and on 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 young population, MSM and people currently not receiving ART

1. INTRODUCTION

The role of fully suppressive cART in reducing the transmission of HIV infection to HIV-negative partner has been well established (1). Nevertheless, some local genital factors such as bacterial or viral infections, namely Sexually Transmitted Diseases (STDs), can increase the shedding of HIV in semen, leading to an increase of HIV transmission (2).

This aspect has been well demonstrated in people not assuming cART, whereas little is known whether the same increase risk is applicable to people on fully-suppressive cART. It has been recently demonstrated that effective cART does not completely reduce the risk of HIV transmission in sexually active men who have sex with other men (MSM) with concomitant STD (3). Thus it has been recently hipothesized that the persistent risky behaviours may reduce the beneficial effect of cART on the incidence of HIV infection (4), to study the incidence and determinants of STD may help to increase knowledgment regarding risky behaviours.

A previous analysis whitin ICONA cohort demonstrated that the use of highly active antiretroviral therapy (cART) was not associated with a higher risk of newly acquired HBV and syphilis, and that suppressive cART was associated with a lower risk of HBsAg seroconversion (5). Nevertheless, a comprehensive approach considering all STI has never been assessed.

Specific objectives were to analyze temporal trend of any incident STI, according with plasma HIV-RNA level in the entire period of cohort observation, to evaluate factors associated with a new diagnosis of STI in patients according with level of HIV-RNA and to analyze the role of ART on the onset of STI during time.

2. PATIENTS & METHODS

All HIV-infected patients enrolled in the Icona Foundation Cohort Study from 1997 were included in the present analysis.

STD is defined at the occurrence of any of the following conditions: any-stage syphilis (primary, secondary, latent, tertiary, and unspecified), HPV-related diseases, urethritis (gonococcal, non-gonococcal), HSV-related genital ulcers, any genital ulcer disease not otherwise specified, vaginitis (trichomonas, bacteric, not specified), HBV, HCV, HAV (see statistical methods for details regarding inclusion of hepatitis).

Data on STD are available at enrolment and they are updated at the occurrence of any clinical event or, in their absence, at least every 6 months.

STDs incidence rate (IR) were calculated according to current plasma viral load level (HIV-RNA≤50 c/ml, HIR-RNA> 50 c/ml) and calendar period (1998-2002, 2003-2007, 2008-2012).

Predictors of STD occurrence were estimated using Poisson regression. Sandwich estimates were used when people had more than one event.

Two different regression analyses were done: 1) Excluding acute hepatitis in IVDU. 2) Excluding all cases of acute hepatitis.

As covariates will be used demographical, epidemiological and clinically relevant variables recorded in the database, namely: age (strafied as 18-30 year old, 31-40, 41-50, 51-60 and >60 year old), gender, risk behaviour for HIV transmission (heterosexual, MSM, intravenous drug users, other risks), educational level (primary, secondary school, college, and university), ethnicity; current CD4 cell count (<100, 101-350, 351-500, and >500 cells/uL), ART status (ART-naïve, on ART, on treatment interruption at STD diagnosis).

3. RESULTS
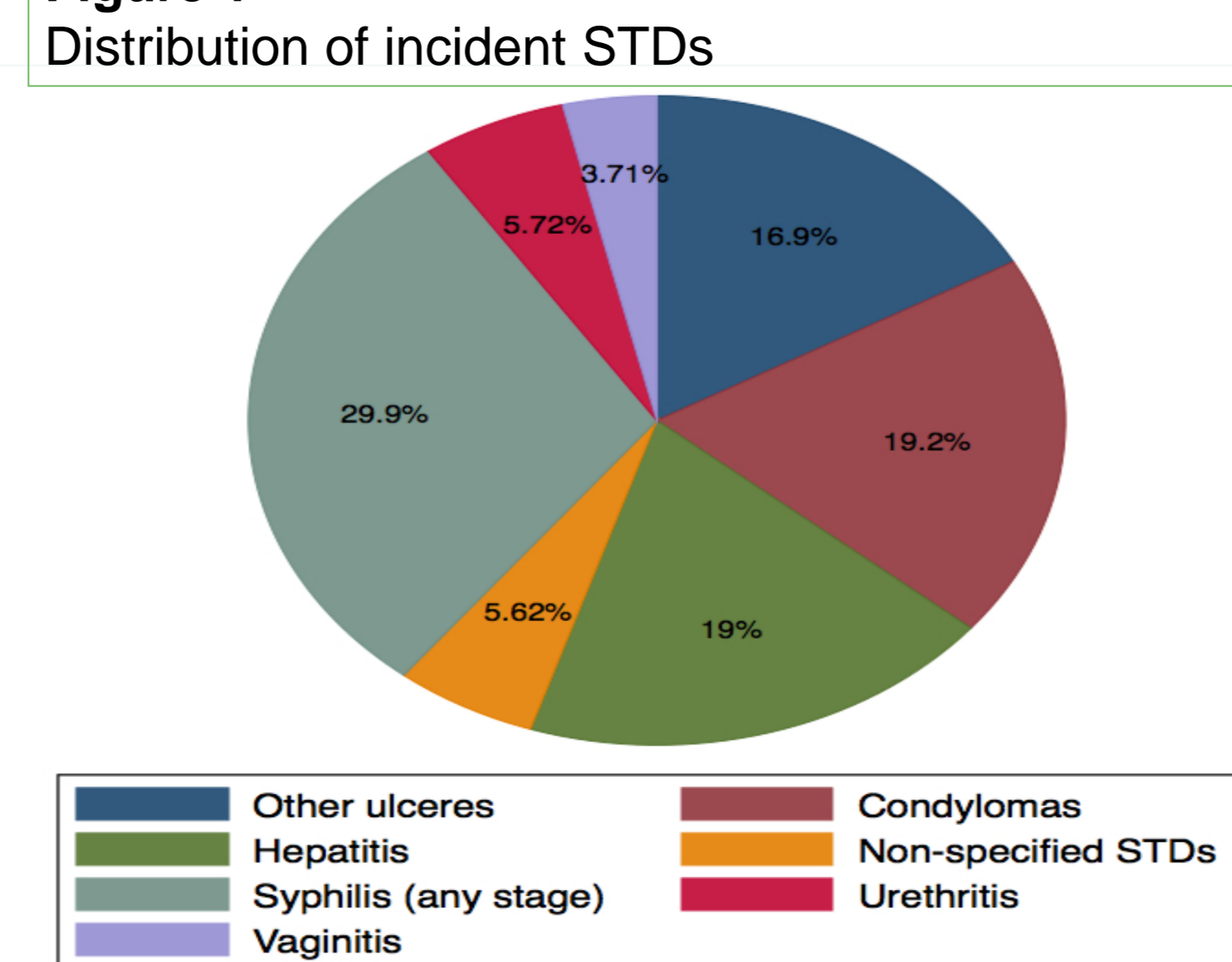
Data of 9,168 pts were analysed. 2355 were women (25.7%). Over 46,736 PYFU, 996 episodes of STD were observed (crude IR 21.3/1,000 PYFU)
Mean age at first visit 37.3 (SD 9.3)
74% were male. 31% were MSM, 39% heterosexuals, 25% IDU, 6% other risk.
3327 pts were enrolled in 1998-2002, 1273 in 2003-2007, 4568 in 2008-2012.
Median (IQR) CD4/mmc and HIV-RNA/ml at STD: 433 (251-600) and 10,900 (200-63,000). 400 (40%) episodes occurred while people were on ART (IR 12.8/31297 PYFU), 534 (53%) in naive patients (IR 44.6/11961 PYFU).
48 pts (0.5%) presented more than 1 episode of incident STD.

Table 1 Incident rates (IR) according to population characteristics.

	All patients			Naive patients			Patients on cART			Treatment interruption		
	N events	PYFU	IR (95% C.I.)	N events	PYFU	IR (95% C.I.)	N events	PYFU	IR (95% C.I.)	N events	PYFU	IR (95% C.I.)
Women	204	13912	14.66 (12.72-16.82)	95	3652	26.01 (21.04-31.80)	90	8901	10.11 (8.13-12.42)	19	1358	13.99 (8.42-21.85)
Men	792	32824	24.13 (22.48-25.87)	434	8309	52.23 (47.43-57.38)	310	22396	13.84 (12.34-15.47)	43	2119	20.29 (14.68-27.33)
Age												
18-30	181	3982	45.45 (39.07-52.58)	127	1709	74.31 (61.95-88.42)	47	2039	23.05 (16.93-30.65)	7	234	29.91 (12.03-61.63)
31-40	441	18421	23.94 (21.76-26.28)	224	5577	40.16 (35.07-45.78)	184	11377	16.17 (13.92-18.68)	33	1467	22.49 (15.48-31.59)
41-50	276	16992	16.24 (14.38-18.27)	146	3616	40.37 (34.09-47.48)	116	11994	9.67 (7.99-11.60)	14	1382	10.13 (5.54-16.99)
51-70	93	7012	13.26 (10.70-16.25)	35	1018	34.38 (23.95-47.81)	50	5613	8.91 (6.61-11.74)	8	381	21.00 (9.06-41.37)
>70	5	329	15.19 (4.93-35.46)	2	41	48.78 (5.91-176.21)	3	274	10.95 (2.25-31.99)	0	13	0
HIV transmission route												
Hetero	22	18557	15.73 (13.98-17.64)	155	4146	37.39 (31.73-43.75)	114	13095	8.70 (7.18-10.45)	23	1317	17.47 (11.07-26.20)
MSM	561	10843	51.73 (47.54-56.20)	321	3105	103.38 (92.4-115.3)	212	7213	29.39 (25.56-33.62)	28	525	53.33 (35.44-77.08)
IDU	87	14926	5.83 (4.66-7.19)	31	4238	7.31 (4.97-10.38)	47	9158	5.13 (3.77-6.82)	9	1531	5.88 (2.69-11.16)
other	56	2410	23.23 (17.55-30.17)	27	473	57.08 (37.62-83.05)	27	1831	14.74 (9.71-21.45)	2	106	18.94 (2.28-68.16)
Period of STD												
1998-2002	272	15745	17.27 (15.28-19.45)	138	5202	26.53 (22.29-31.34)	114	9392	12.4 (10.01-14.58)	20	1150	17.39 (10.62-26.86)
2003-2007	269	15399	17.46 (15.44-19.68)	112	3509	31.92 (26.28-38.40)	125	10178	12.28 (10.22-14.63)	32	1712	18.69 (12.78-26.38)
2008-2012	455	15592	29.18 (26.56-31.99)	284	3251	87.36 (77.49-98.13)	161	11726	13.73 (11.69-16.02)	10	615	16.26 (7.80-29.90)
CD4 at STD												
>500	457	24789	18.43 (16.78-20.20)	247	6208	39.78 (34.98-45.07)	186	17366	10.72 (9.24-12.38)	24	1235	19.43 (12.45-28.91)
351-500	203	10765	18.86 (16.35-21.64)	109	3179	34.28 (28.15-41.36)	81	6726	12.04 (9.56-14.97)	13	860	15.11 (8.05-25.85)
101-350	247	9832	25.12 (22.08-28.46)	124	2304	53.82 (44.76-64.17)	105	6462	16.25 (13.29-19.67)	18	1066	16.88 (10.01-26.68)
<100	89	1350	65.92 (52.94-81.13)	54	270	200 (150.24-260.95)	28	764	36.65 (24.35-52.97)	7	316	22.15 (8.90-45.64)
HIV-RNA at STD												
<50	174	16289	10.68 (9.15-12.39)	5	587	8.52 (2.76-19.88)	168	15551	10.80 (9.23-12.56)	1	151	6.62 (0.17-36.90)
>50	822	30446	27.00 (25.18-28.91)	524	11374	46.50 (42.63-50.65)	232	15746	14.73 (12.90-16.75)	61	3327	18.33 (14.02-23.55)
Years of HIV												
<10	860	28932	29.72 (27.77-31.78)	495	8004	61.84 (56.51-67.54)	321	19159	16.75 (14.97-18.69)	44	1770	24.86 (18.06-33.37)
11-20	122	14956	8.16 (6.77-9.74)	36	3422	10.52 (7.37-14.56)	70	10006	6.99 (5.45-8.84)	16	1528	10.47 (5.98-17.00)
>20	11	2680	4.10 (2.05-7.34)	2	473	4.23 (0.51-15.27)	7	2028	3.45 (1.39-7.11)	2	179	11.17 (1.35-40.36)
missing	3	168	18.86 (3.68-52.18)	1	63	15.87 (0.40-88.44)	2	104	19.23 (2.32-69.46)	0	1	0

Figure 1
Distribution of incident STDs

Other ulcers — Condylomas
Hepatitis — Non-specified STDs
Syphilis (any stage) — Urethritis
Vaginitis

Figure 2
Incidence of specific STDs

STD	Incidence rate/1000 PYFU	95%CI
Any stage syphilis	3.95	3.59-4.35
HPV	1.96	1.71-2.24
Acute viral hepatitis	1.72	1.49-1.99
HAV	0.19	0.09-0.36
HBV	6.54	5.83-7.32
HCV	3.74	3.21-4.34
HSV	0.81	0.65-0.99
Gonococcal uretritis	0.46	0.35-0.61
Non gonococcal uretritis	0.47	0.36-0.62
Other genital ulcers	0.11	0.06-0.19

Figure 2
Multivariable Poisson regression analysis for factors associated with incident STDs (analysis performed excluding new onset of hepatitis in IVDU; similar results were observed excluding all cases of hepatitis)
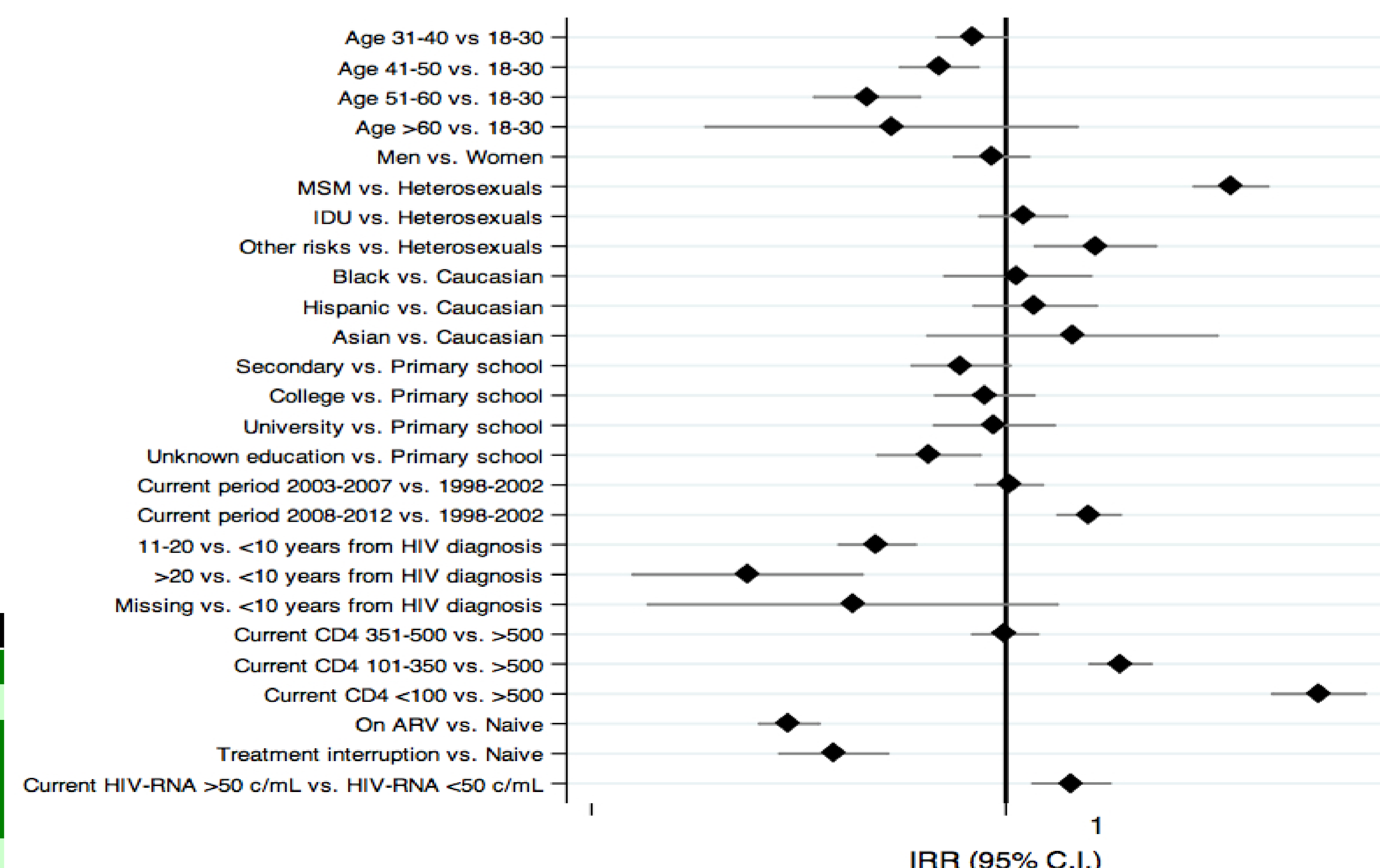

IRR (95% C.I.)

4. DISCUSSION

- Risk of acquiring a new STD has been increasing over the years of observation whitin the ICONA cohort
- The use of ART reduce the risk of acquiring STD (as a proxy of whether a person is regularly seen for care)
- Highly tailored interventions (focused on young people, MSM, people with low CD4+ cell count, those with low schooling and those recently diagnosed with HIV) - involving Community groups and/or specific experts for every field - to prevent STDs and potential further spread of HIV infection should be considered.
- The biological role of virological suppression in reducing the risk of STD could not be derived from our results

REFERENCES

1.Cohen MS, Chen YQ, McCauley M. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505.
2.Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis.Sex Transm Dis. 2008 Nov;35(11):946-59
3.Politch JA, Mayer KH, Welles SL, et al. Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men. AIDS 2012; 26:1535-1543.
4.Phillips AN, Cambiano V, Nakagawa F, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic.Plos One 2013; 8:55312
5.P. Cicconi, A. Cozzi-lepri, G. Orlando, et al. . Recent Acquired STD and the Use of HAART in the Italian Cohort of Naive for Antiretrovirals (I.Co.N.A): Analysis of the Incidence of Newly Acquired Hepatitis B Infection and Syphilis. Infection 2008: 36:46-53