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

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Abstract

Objective: To estimate the incidence of newly acquired syphilis (n-syphilis) and hepatitis B infection (n-hepatitis B) in I.Co.N.A. and to evaluate the impact of HAART, calendar date and risk group.

Methods: Cohort study: Incidence was calculated by person–years analyses. Poisson regression was used for the multivariate model.

Results: The rate of n-syphilis was 23.4/1,000 PYFU and it increased over time; HIV transmission risk was the most important predictor: men who have sex with men (MSM) had a considerable higher risk (RR 5.92, 95% CI 2.95–12.13 vs IDU/exIDU, $p < 0.0001$). The rate of n-hepatitis B was 12.2/1,000 PYFU; it declined in recent years and halved per 10 years age. Patients with HIV-RNA < 500 copies/ml had a 60% reduced risk of n-hepatitis B if they were treated with HAART compared with not treated individuals.

Conclusions: In our population, the use of HAART was not associated with a higher risk of newly acquired sexually transmitted diseases (STD). Suppressive HAART was associated with a lower risk of HbsAg seroconversion. Incidence of n-hepatitis B has recently been declining possibly due to herd immunity provided by vaccination policies. The risk of acquiring n-syphilis has increased over time and it is higher in the population of MSM compared with other categories of HIV exposure.

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Introduction

Several studies suggest that an increase in the incidence of sexually transmitted diseases (STD) has occurred in industrialized countries in recent years, especially among men who have sex with men (MSM). This increase appears to parallel an increase in sexual behaviors at risk that were recorded during the same time period in a number of behavioral surveys [1–5].

A possible explanation for this increase is that the introduction of highly active antiretroviral therapy (HAART) may have encouraged a more optimistic attitude toward the risk of acquiring HIV infection. HIV-uninfected people may perceive the disease as less severe and may not be concerned about infection; on the other hand, patients treated with HAART may feel that they are not likely to transmit HIV [6–12].

Conflicting results [12–16] are provided by studies analyzing the association between HAART and sexual behaviors. Other factors, which have been operating at population level in concomitance with the introduction of HAART, may have a role in increasing the rate of sexual practices at risk. These include: sex-seeking on Internet, the higher opportunity of meeting sexual partners in

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saunas or backrooms, decision to use condom only based on HIV serostatus of the sexual partner and also a sort of accustoming to the risk of infection after many years of the AIDS epidemic [14, 15].

Our aim in this study was to calculate the incidence rate of newly acquired syphilis (n-syphilis) and newly acquired hepatitis B infection (n-hepatitis B) in a prospective cohort of HIV-infected individuals. In this population, these events were considered as crude surrogate markers of recent unsafe sexual exposure in general, bearing in mind that both syphilis and hepatitis B may also be transmitted by sexual practices which are considered as relatively safe in terms of HIV transmission (i.e., oral sex). Our main objective was to investigate whether the rate of acquiring these STD was different in untreated patients, patients on effective and not effective treatment with HAART in order to consider also the impact of effective HAART on susceptibility for n-syphilis and n-hepatitis B.

Methods

The I.Co.N.A. Study

The Italian Cohort of Naive for Antiretrovirals (I.Co.N.A.) is a multi-centre prospective observational study, of HIV-1-positive persons, which began in 1997. Patients eligible for inclusion in the cohort are those who, for whatever reason, are naive to antiretrovirals at the time of enrollment. Demographic, pre-enrollment, clinical and laboratory data, information on antiretroviral and non-antiretroviral therapies including start, stop date and reason for stopping are collected for all participants and recorded online [17]. A local monitor is responsible for the consistency of the data entered online and the data source (patient record).

Data on the following STD are available at enrollment and they are updated at the occurrence of any clinical event or, in their absence, at least every 6 months: genital ulcer disease, lymphogranuloma venereum, chancroid, herpetic ulcers, non-herpetic ulcers, urethritis (gonococcal, non-gonococcal), vaginitis (candida, trichomonas, bacteric, and unspecified), condylomata acuminata (genital, anal, and others), syphilis (primary, secondary, latent, tertiary, and unspecified). Serologic treponemal test (Treponema Pallidum Hemagglutination Assay: TPHA), and serologic tests for HBV (HBsAg and HBsAb) are part of the 6 months routine screening available for all the patients and corresponding to the clinical visits. Details of the cohort have been published elsewhere [18].

Population Selected for Newly Acquired Syphilis (n-Syphilis) and Definition of Endpoint

All patients with negative TPHA at enrollment were considered eligible. Since we aimed to identify seroconverters, only patients with at least two available determinations of TPHA were included. Included patients and the entire cohort were compared in terms of demographical and clinical characteristics at enrollment. The Chi square test and Wilcoxon test for independent samples were performed.

A case of n-syphilis was defined as the occurrence of a positive TPHA serologic test following an initial TPHA-negative test. The date of n-syphilis was calculated as the date of seroconversion to TPHA (defined at the median time between the date of last negative and the first positive test) or the date of symptoms for symptomatic patients, whichever occurred first.

Population Selected for n-Hepatitis B and Definition of Endpoint

All non-intravenous drug users (IDU) patients who were HBsAg/HBsAb-negative at enrollment, were considered to be eligible. We excluded IDU to consider subjects who were likely to acquire HBV infection through sexual contacts only. HBV testing is routinely conducted in I.Co.N.A.; however, less than two tests were available for some eligible patients and they were excluded from the analyses. Included patients and the entire cohort were compared in terms of demographical and clinical characteristics at enrollment. The Chi-square test and Wilcoxon test for independent samples were performed.

A case of n-hepatitis B was defined as a positive HBsAg in patients previously tested HBsAg-negative. The date of n-hepatitis B was calculated as the date of occurrence of symptoms or the date of asymptomatic seroconversion (defined at the median time between the date of last negative and the first positive HBsAg), whichever occurred first.

Analysis of Incidence Over Follow-up

Two person-years analyses were conducted to study the incidence of n-syphilis and n-hepatitis B. For both analyses, we studied the time to the occurrence of the first event. Person–years at risk were calculated from date of recruitment in I.Co.N.A. until the last available follow-up, or development of the STD, whichever occurred first. Incidence rates of first STD were calculated according to whether the patients were currently taking HAART (patients not taking HAART were those who for whatever reason were not taking therapy including those who were on treatment interruption), current CD4 (fitted as binary covariate using the cut-off of 200 cells/μl) and viral load (fitted as binary covariate using the cut-off of 500 cps/ml), current calendar year, and demographics. In the analysis of incidence of n-syphilis, we also adjusted for the current use of clarithromycin or azithromycin, antimicrobials active against *T. pallidum*. Standard Poisson regressions were used for the multivariate analysis to identify the predictors for the development of n-syphilis and n-hepatitis B. These models included the same covariates listed above; in addition, we tested for the presence of interaction between the use of HAART and viral load to study whether the impact of HAART on the risk of acute STD was different according to the level of viral suppression.

Antiretroviral drugs such as lamivudine, emtricitabine, and tenofovir have been shown to be effective against HBV [27–29]. To test whether the use of a HAART regimen containing effective drugs against HBV was associated with different estimates another model was performed: it included a covariate that indicated whether the patient was not receiving therapy, on a lamivudine/emtricitabine/tenofovir-containing HAART (a regimen containing at least three antiretroviral drugs), on a lamivudine/emtricitabine/tenofovir-containing ART (a regimen containing less than three antiretroviral drugs), a lamivudine/emtricitabine/tenofovir-sparing HAART or a lamivudine/emtricitabine/ tenofovir-sparing ART.

Results

Incidence of n-Syphilis

Patients included in the analysis of incidence of n-syphilis (n = 1,744) did not show clinically significant differences in immuno-virological characteristics compared with the entire cohort (n = 5,765). A slightly higher proportion of included patients were European (96.5% of the included

vs 94.41% of the entire cohort, p = 0.0006) and got infected with HIV by intravenous drug abuse (42.09% of the included vs 39.06% of the entire cohort, p = 0.0249). A higher percentage of the patients we included was enrolled in I.Co.N.A. in the year 1997 (58.66% vs 45.29% of the excluded; p < 0.0001) (Table 1).

The overall rate of n-syphilis was 85 cases per 2,295 person–years, 23.4 per 1,000 person–years of follow-up (PYFU; 95% CI 18.91–28.92). New syphilis incidence rate appeared to increase over time, rising from 11.3 per 1,000 PYFU (95% CI 3.63–34.91) in 1997, to 21.3 per 1,000 PYFU (95% CI 15.31–29.69) in 1998–2000, and 27.2 per 1,000 PYFU (95% CI 20.45–36.23) after year 2000 (test for trend p = 0.003).

From all groups MSM had the highest risk of n-syphilis (absolute incidence rate 74.9 per 1,000 PYFU [95% CI 55.9–100.3]). Patients with a university degree (69.5 per 1,000 PYFU; 95% CI 37.4–129.1) were at high risk of acquiring n-syphilis; patients with CD4 cell counts < 200 cell/μl (38.6 per 1,000 PYFU, 95% CI 22.9–65.2) and patients who had experienced an STD before enrollment (31.2 per 1,000 PYFU, 95% CI 18.8–51.8) were at medium risk. The incidence rate calculated when patients were receiving HAART was low (28.7 per 1,000 PYFU; 95% CI 21.5–38.4), and was even lower over the period in which patients were not receiving HAART (19.34 per 1,000 PYFU; 95% CI 14.18–26.36).

The most significant independent variable associated with the outcome was HIV transmission risk: the risk among MSM was 6.17 higher compared with the risk of IDU/exIDU (95% CI 3.03–12.58 p < 0.0001). Patients receiving HAART appeared to have slightly higher risk of n-syphilis than patients currently not receiving HAART (Adjusted Rate Ratio [ARR] = 1.32; 95% CI 0.72–2.42) but this result was not statistically significant (p = 0.36) (Table 2). No interaction was observed between HAART and viral load. (p-value for the interaction: p = 0.59).

There was likewise no evidence for a significant association between the risk of n-syphilis and the exposure to HAART (ARR 1.66; 95% CI 0.75–3.79 vs not receiving HAART), current undetectable HIV-RNA (ARR 0.63; 95% CI 0.29–1.35 vs detectable HIV-RNA), current CD4 ≤ 200 cells/μl (ARR 1.02; 95% CI 0.34–3.07 vs CD4 > 200 cells/μl), education level (high school ARR 1.54; 95% CI 0.36–6.58 and university ARR1.66; 95% CI 0.33–8.23 vs primary school) and use of clarithromycin/azithromycin (ARR 1.16; 95% CI 0.59–2.27) in the group with transmission risk MSM when analysed separately. Again, no interaction was observed between HAART and viral load (p-value for the interaction: p = 0.72).

Table 1
Background characteristics of the entire I.Co.N.A. cohort and the patients selected for the analyses of incidence of acute HB and syphilis.

Characteristics	I.Co.N.A. (n = 5,765)	Acute HB analysis (n = 1,037)	p*	Syphilis analysis (n = 1,744)	p**
Sex					
Female (n, %)	1,726 (29.94)	428 (41.27)	< 0.0001	529 (30.33)	0.7316
Mode of HIV transmission					
IDU/ex IDU (n, %)	2,252 (39.06)	–	–	734 (42.09)	0.0249
Homosexual (n, %)	1,112 (19.29)	273 (26.33)	< 0.0001	312 (17.89)	0.1829
Heterosexual (n, %)	2,052 (35.59)	675 (65.09)	< 0.0001	625 (35.84)	0.8154
Other/unknown (n, %)	349 (6.05)	89 (8.58)	0.0023	73 (4.19)	0.0001
Citizenship					
EU (n, %)	5,443 (94.41)	965 (93.06)	0.0784	1,683 (96.50)	0.0006
Education level					
Primary (n, %)	552 (9.57)	102 (12.11)	0.1660	156 (12.41)	0.1629
High (n, %)	3,097 (53.72)	660 (80.10)	0.9568	1,005 (81.44)	0.3295
University (n, %)	217 (3.76)	62 (7.52)	0.0341	73 (5.92)	0.6803
Year of enrolment					
1997 (n, %)	2,610 (45.29)	490 (47.25)	0.309	1,023 (58.66)	< 0.0001
1998–1999 (n, %)	1,315 (22.81)	254 (24.49)	0.209	411 (23.82)	0.4564
After 2000(n, %)	2,030 (35.21)	293 (28.25)	0.026	310 (17.78)	< 0.0001
STD at enrolment					
Yes (n, %)	716 (12.42)	112 (10.8)	0.132	204 (11.7)	0.3916
Age (years, IQR)	35 (31–40)	35 (30–41)	0.103	35 (32–39)	0.3505
Baseline CD4 (cell/mmc, IQR)	426 (220–614)	411 (220–603)	0.119	445 (261–624)	0.0197
Baseline VL (cp/ml, IQR)	4.32 (3.52–4.99)	4.34 (3.60–5.01)	0.199	4.22 (3.46–4.89)	0.0048

*p value for the difference between I.Co.N.A. and the group eligible for the acute HB analysis; **p value for the difference between I.Co.N.A. and the group eligible for the acute syphilis analysis

Table 2
Absolute crude rates of incidence of n-syphilis and adjusted rate ratios from fitting a multivariable Poisson regression.

Factor	New syphilis	Person/years	Rate per 1,000 pys (95% CI)	Adjusted RR (95% CI)	p
Age					
Per 10 years				1.17 (0.89–1.53)	0.25
Sex					
Male	75	2,486	30.17 (24.06–37.83)	1.00	
Female	10	1,149	8.71 (12.73–16.18)	0.46 (0.16–1.29)	0.14
Mode of HIV transmission					
IDU/exIDU	17	1,571	10.82 (6.73–17.40)	1.00	
MSM	45	601	74.86 (55.89–100.26)	6.17 (3.03–12.58)	< 0.0001
Heterosexual	15	1,336	11.23 (6.77–18.62)	0.83 (0.32–2.16)	0.71
Other/Unknown	8	126	63.49 (31.65–126.96)	3.65 (1.23–10.82)	0.02
Citizenship					
EU	81	3,522	23.00 (18.50–28.60)	1.00	
Not EU	4	113	35.35 (13.27–94.18)	1.25 (0.36–4.33)	0.71
Education level					
Primary	10	305	33.79 (17.65–60.95)	1.00	
High school	45	2,165	21.09 (15.74–28.24)	0.64 (0.30–1.33)	0.23
University	10	146	69.45 (37.37–129.08)	0.95 (0.36–2.45)	0.91
STDs at enrolment					
No	70	3,154	22.19 (17.56–28.05)	1.00	
Yes	15	481	31.21 (18.81–51.76)	1.21 (0.64–2.31)	0.54
Current use of clarythromicin/azithromicin					
Off	60	2,822	21.23 (16.55–27.45)	1.00	
On	25	819	30.50 (20.61–45.14)	0.99 (0.57–1.72)	0.97
Current use of HAART					
Off	40	2,069	19.34 (14.18–26.36)	1.00	
On	45	1,566	28.73 (21.45–38.44)	1.32 (0.72–2.42)	0.36
Current CD4					
> 200 cells/μl	71	3,272	21.70 (17.19–27.38)	1.00	
≤ 200 cells/μl	14	362	38.64 (22.88–65.24)	1.37 (0.61–3.05)	0.44
Current HIV-RNA					
> 500 copies/ml	48	2,100	22.86 (17.47–33.28)	1.00	
≤ 500 copies/ml	37	1,535	24.11 (17.22–33.33)	1.18 (0.47–2.93)	0.71
Current year of the event					
1997	3	266	11.26 (3.63–34.91)	1	
1998–1999	35	1,642	21.32 (15.31–29.69)	1.73 (0.40–7.41)	0.45
After 2000	47	1,727	27.22 (20.45–36.23)	2.57 (0.61–10.86)	0.19
Total	85	3,635	23.39 (18.91–28.92)		

Incidence of n-Hepatitis B

Baseline HBsAg and HbsAb determinations were available for 5,765 patients: 387 (7%) HBsAg positive and 1,671 (29%) HBsAb positive were excluded from the analysis. Compared with HBsAg/HBsAb negative patients, HBsAb/HBsAg positives at baseline (n = 2,058) were more frequently males (76% vs 66%; < 0.0001), infected with HIV by intravenous drug abuse (50% vs 33%; < 0.0001), and with a previous history of STD (20% vs 8%; p < 0.0001). Other 1,030 patients were excluded because of IDU, and 1,448 because of less than two HBsAg determinations to be available.

Included patients (n = 1,037) were comparable with the entire cohort with respect to immuno-virological status and the prevalence of STD reported at enrollment. Patients who had been enrolled in I.Co.N.A. in recent years were less likely to be included: 28.2% of the study population was enrolled during year 1997 vs 35.2% of the entire cohort (p < 0.02) (Table 1); 599 (57.8%) patients included in the analysis of incidence of n-hepatitis B have been also included in the analysis of incidence of n-syphilis.

The overall rate of n-hepatitis B was 28 cases per 2,295 person–years, i.e. 12.2 per 1,000 PYFU (95% CI 8.42–17.67).

During year 1997 the risk of acquiring n-hepatitis B appeared to be very high: seven cases of n-hepatitis B in 116 PYFU, for a crude incidence rate of 60.1 per 1,000 PYFU (95% CI 28.7–126.1). During years 2000–2001, we observed a low incidence (9.25 per 1,000 PYFU –95% CI

4.41–19.39) and a very low incidence (3.60 per 1,000 PYFU 95% CI 0.9–14.4) after year 2001. Patients receiving HAART with undetectable HIV viremia seemed to be at a low risk (5.64 per 1,000 PYFU 95% CI 2.35–13.54). The crude risk of n-hepatitis B was high for patients receiving HAART with a detectable viral load (20.9 95% CI 10.4–41.7).

In the multivariate model, viral load and HAART were not associated with the risk of n-hepatitis B. Among patients with viral load > 500 copies/ml, those currently receiving HAART had an increased risk of HB compared with those currently not receiving HAART (ARR 1.39 95% CI 0.49–3.91). Among those with a viral load ≤ 500 copies/ml the use of HAART was associated with a reduced risk (ARR 0.40 vs not receiving HAART, 95% CI 0.08–1.87) after having adjusted for other potential confounders. The p-values for the interaction were p = 0.06 in the univariable and p = 0.17 in the adjusted model. When we examined the effect of antiretrovirals which are active against both HIV and HBV, we observed that the risk of the patients on lamivudine/ emtricitabine/tenofovir-containing regimens or on lamivudine/emtricitabine/tenofovir-containing HAART, seemed to be lower compared to the patients on lamivudine/emtricitabine/tenofovir sparing HAART (respectively, ARR 0.60 95% CI 0.09–3.83, p = 0.59 and ARR 0.65 95% CI 0.76–2.51, p = 0.54); however none of these differences were statistically significant. The risk of n-hepatitis B was significantly lower in more recent years: compared to 1997 the risk of n-hepatitis B was 0.22 (95% CI 0.07–0.65, p = 0.005) in 1998–1999, 0.20 (95% CI 0.06–0.63 p = 0.006) in 2000–2001 and 0.08 (95% CI 0.01–0.41, p = 0.002) after year 2001. Age was also found to be an independent predictor: the risk of n-hepatitis B seemed to be halved per 10 years age (ARR 0.54; 95% CI 0.30–0.98 p = 0.004; Table 3).

Discussion

Most of the studies conducted to determine the effect of HAART and patients' beliefs on sexual behavior [6–16] were based on questionnaires supplied to patients. We considered a different approach evaluating the onset of newly acquired pathologies as indicators of high-risk sexual behavior among HIV individuals. We chose syphilis and newly acquired hepatitis because they can be detected by specific, routinely conducted and standardized serologic tests. Excluding from our analysis all the patients with a positive treponemal test at enrollment we were not able to see any possible re-exposure (detectable by VDRL or RPR). Furthermore, the definition we used for n-syphilis would miss serofast persons previously infected and treated for syphilis, and those seronegative, but actually infected as in the case of a person diagnosed in the primary stage of the disease.

Moreover, the population selected for the analysis of incidence of n-syphilis only partially represented the entire cohort (Table 1). All these limitations may have led to an underestimation of the incidence of n-syphilis and limit the generalization of our findings. Even with these limitations, our results agree with other studies showing an increasing incidence of syphilis in recent years in both HIV positive and HIV negative populations especially among MSM [1–5]. In our cohort, the mode of HIV exposure was the strongest predictor of syphilis (MSM seemed to have a significant sixfold increased risk compared to IDUs). We did not observe any increasing trend in the incidence of n-hepatitis B; in contrast we estimated a dramatically decreasing rate from 1997 to year 2001 and after. Again, the generalization of our results may be limited by the fact that the population selected for the analysis of incidence of n-hepatitis B only partially represents the entire cohort (Table 1).

Decreasing trends with similar magnitude, however, have been described by other authors [19–21] and they may be related to the massive vaccination policy: in Italy selective HBV vaccination of individuals from high-risk groups (e.g., health care workers, household contacts with chronically infected people, intravenous drug users, persons being evaluated for STD, babies born to HBsAg carrier mothers, etc.) was initiated on regional scale in 1983, universal vaccination of all infants and 12-year-old adolescents became mandatory on national scale in 1991 and more recently immunization became recommended among HIV positive individuals, according to international guidelines [22–24]. HBsAb/ HBsAg seroepidemiological studies on Italian population showed that the prevalence of patients exposed to HBV tended to increase with older age [25, 26]. Two peaks in the age bands approximately between 15 and 24 years (because vaccinated) and between 50 and 60 years for males, and 60 and 70 for females (because exposed to the virus) result immune against HBV, providing that the herd immunity may explain the declining incidence by age.

Another possible explanation for the decreasing incidence of newly acquired HBV infection according to age is that older individuals might be at lower risk of sexual exposure due to declining partner numbers, particularly when heterosexually infected.

Furthermore, in chronic HBV carriers co-infected with HIV, HAART combination treatments also decrease HB viral load and transmission risk (e.g. lamivudine, tenofovir, and emtricitabine) [27–29].

Although we were not able to study the relationship between the use of HAART and related optimistic beliefs, we believe that our results are useful to help understand whether patients receiving HAART should be considered at higher risk of STD. We observed that the use of HAART was associated with an increased risk of n-hepatitis B in patients with a VL > 500 but not in those with a VL < 500, although not significantly so; nevertheless, the large difference in the magnitude of the effect

Table 3
Absolute crude rates of incidence of acute HB and adjusted rate ratios from fitting a multivariable Poisson regression.

Factor	Acute HB	Person/years	Rate per 1,000 pys (95% CI)	Adjusted RR (95% CI)	p
Age					
Per 10 years				0.54 (0.30–0.98)	0.04
Sex					
Male	16	1,334	12.00 (7.35–19.58)	1.00	
Female	12	962	12.48 (7.09–21.98)	0.84 (0.28–2.52)	0.75
Mode of HIV transmission					
MSM	10	579	17.28 (9.30–32.12)	1.00	
Heterosexual	16	1,544	10.36 (6.35–16.92)	0.56 (0.18–1.74)	0.32
Other/unknown	2	173	11.58 (2.90–46.29)	0.84 (0.17–4.17)	0.83
Citizenship					
EU	26	2,164	12.01 (8.18–17.65)	1.00	
Not EU	2	131	15.26 (3.82–61.01)	0.49 (0.05–4.10)	0.51
Education level					
Primary	3	217	13.80 (4.45–42.80)	1.00	
High school	19	1,509	12.59 (8.03–19.74)	0.67 (0.18–2.47)	0.55
University	2	138	14.48 (3.72–57.88)	0.72 (0.11–4.63)	0.73
STDs at enrolment					
No	3	2,055	12.07 (8.22–18.01)	1.00	
Yes	25	241	12.47 (4.02–38.66)	0.92 (0.26–3.18)	0.89
Current use of HAART					
Off HAART	15	1,025	14.63 (8.82–24.27)	1.00	
On HAART $\leq$ 500 copies/ml	5	887	5.64 (2.35–13.54)	0.39 (0.08–1.85)	0.17
On HAART > 500 copies/ml	8	383	20.88 (10.44–41.76)	1.43 (0.50–4.03)	0.17
Current CD4					
> 200 cells/μl	25	2,048	12.21 (8.25–18.06)	1.00	
$\leq$ 200 cells/μl	3	247	12.14 (3.92–37.65)	1.13 (0.30–4.21)	0.85
Current year of the event					
1997	7	116	60.13 (28.66–126.12)	1.00	
1998–1999	12	867	13.85 (7.86–24.38)	0.22 (0.07–0.65)	0.005
2000–2001	7	757	9.25 (4.41–19.39)	0.20 (0.06–0.63)	0.006
After 2001	2	555	3.60 (0.90–14.41)	0.08 (0.01–0.41)	0.002
Total	28	2,295	12.20 (8.42–17.67)		

(pointing in opposite directions) suggests that the lack of statistical significance was probably due to limited power. Thus, it is unlikely that this increased risk could be explained by higher level of optimism related to the use of HAART.

As to the occurrence of n-syphilis no differences were observed in the risk of acquiring n-syphilis according to the level of plasma viremia. Comparable results were obtained from analyzing the group with transmission risk MSM separately. We had no information regarding all antimicrobials active against syphilis taken by our patients, but our results were controlled for the use of clarithromycin and azithromycin against MAC (Table 2).

Data on sexual risk-taking behaviors such as unprotected anal intercourse, number of sexual partnerships, condom use behavior were not collected in our cohort, and this may represent a confounder that is not accounted for in the study. Our findings suggest that effective treatment with HAART seemed to provide some protection against n-hepatitis B, at least in patients with undetectable viral load, but not against n-syphilis. The reasons behind this are unclear, but we hypothesize that the protection HAART offers against n-hepatitis B can be ascribed to a biological rather than a behavioral mechanism. First of all, HAART-mediated immune reconstitution may play a role against n-hepatitis B. It has been described that intra-hepatic HBV-specific $CD8^+$ T cells are required for rapid viral clearance during n-hepatitis BV infection [30]; *Lascar* et al. [31] have recently demonstrated that HAART seems to induce immune-reconstitution of HBV-specific $CD8^+$ T and $CD4^+$ T cell responses despite the presence of drugs with an anti-HBV activity in the regimen. We can therefore speculate that the lower rate of HBsAg seroconversion observed in our patients with suppressed viral load on HAART, could be a consequence of HAART-mediated immune reconstitution. Furthermore, the role of anti HIV-drugs which are also strong inhibitors of HBV replication should be considered. In particular, lamivudine seems to be effective as

prophylaxis against hepatic complications in renal transplant HBsAg$^+$ recipients [27, 28] and to prevent HBV recurrence after liver transplantation in patients with chronic hepatitis B [29]. Longer exposure to lamivudine seems to be associated with lower death rates in HBV/HIV co-infected individuals (Puoti et al. AVT, in press). Our results, however, did not show a clear effect of lamivudine/emtricitabine/tenofovir containing regimens in the reduction of risk of n-hepatitis B.

Taking into account that both the analyses of incidence were conducted on selected populations that only partly represented our cohort (Table 1), that we had no comparison group available for similar analyses, and all the limitations mentioned above, we can conclude that overall, new STD acquisition in HIV infected persons in this cohort was not associated with receiving HAART when compared with persons not receiving HAART. Furthermore, suppressive HAART seemed to be protective against HBsAg seroconversion, and further studies are needed to clarify the reasons for this protection. The incidence of n-hepatitis B has been dramatically declining in our cohort in recent years, possibly due to herd immunity provided by mass vaccination policy. As indicated by the international guidelines, all HIV infected patients still susceptible for HBV should be vaccinated especially those on effective HAART treatment which may help to improve the immunological response to vaccination. As in other countries, the risk of acquiring n-syphilis increased over time and is higher in the population of MSM compared to other categories of HIV exposure. The increasing incidence of newly acquired syphilis in HIV patients, especially in HIV-positive MSM would also call for improved STI prevention programmes for people living with HIV, whether on or off HAART.

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Appendix: I.CO.N.A. Study Group

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