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Syphilis and HIV co-infection: excellent response to multiple doses of benzathine penicillin

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Abstract

Background: The number of new syphilis diagnoses in Slovenia is steadily increasing, especially among HIV-infected men who have sex with men (MSM). We studied the effect of penicillin for treating syphilis in HIV co-infected patients and risk factors for treatment failure. The primary endpoint was response to therapy (fourfold reduction of VDRL at month 12).
Methods: Three hundred forty-two paper records were reviewed and MSM with positive VDRL and/or TPHA and serological follow up of at least 12 months were enrolled in the survey.
Results: Incidence of syphilis increased from 1.2% (2005) and 2.9% (2007) to 6.4% (2009) and 3.8% (2011, until July). Two hundred sixty-one (76.3%) were MSM and 102 (29.8%) were co-infected; 53.9% had primary/secondary syphilis, 37.3% latent syphilis, and 8.8% neurosyphilis. Patients with primary/secondary/latent syphilis were treated with three doses of benzathine penicillin (2.4 MU i.m.). Treatment was successful in 92.2%. With respect to risk factors, there was no difference between the "success" and "failure" group. Twenty-six patients (25.5%) had re-infections.
Conclusions: The rate of cure in our study population was excellent, probably due to a low degree of immunosuppression and a three-dose benzathine penicillin regimen.

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Introduction

Syphilis and HIV infection have been observed to facilitate the acquisition of one another and are in epidemiological synergy (1, 2). In recent years, the incidence of syphilis among men who have sex with men (MSM) has increased rapidly, especially among HIV-infected MSM (3–8). This has been attributed to an increase in sexual risk behavior (9–11) and to decreased mortality associated with Highly Active Antiretroviral Therapy (HAART) (12, 13).

HIV co-infected patients may experience more syphilis treatment failure than patients with syphilis mono-infection (14). However there is little information about factors influencing syphilis treatment failure in HIV co-infected patients. The aim of our nationwide study was to analyze the effect of penicillin for treating syphilis in HIV co-infected patients and risk factors for treatment failure among adult HIV-positive individuals in Slovenia. The primary endpoint was response to therapy; a fourfold reduction of VDRL titers at month 12 after treatment was considered to be adequate.

Methods

This study was approved by the National Medical Ethics Committee of the Republic of Slovenia (NMEC).

Study group

Three hundred forty-two paper records of adult HIV-infected patients were reviewed. In Slovenia, VDRL and TPHA titers are used for primary screening, and patients with positive tests and no prior treatment are considered to have newly diagnosed syphilis. MSM patients with positive VDRL and/or TPHA tests and serological follow up of at least 12 months were enrolled in the survey. All patients with primary/secondary/latent syphilis were treated with three doses of benzathine penicillin (2.4 MU, i.m.).

Variables

We collected data on demographics, route of transmission, co-infections with hepatitis B or C, smoking, parameters of the immune status (viral load (VL), CD4 T cell counts, stage of HIV infection according to the Centers for Disease Control and Prevention (CDC stage), and treatment with HAART), and stage of syphilis at diagnosis. Serologic data (VDRL/RPR, TPHA, and FTA IgG tests) at diagnosis and during follow-up (6, 12, and 24 months after treatment) were also obtained. VDRL/RPR titers were assessed and categorized into "success" (fourfold decrease in VDRL/RPR titers at month 12 after treatment) and "failure" (no fourfold decrease in VDRL/RPR titers 12 months after treatment). VL was evaluated as a dichotomous variable (≥ 40 copies/mL or < 40 copies/mL). Treatment with HAART was evaluated as affirmative if the patient had been treated for at least 6 months; otherwise it was evaluated as negative.

Statistical analysis

For analysis, descriptive statistics with the chi square test, Mann–Whitney test, Kruskal–Wallis test, and logistic regression were used, using SPSS 21.0 (SPSS, Chicago, IL, USA). Using logistic regression, we assessed associations between syphilis treatment failure and the following outcomes: treatment with HAART, smoking, and CDC stage C. $P < 0.05$ was considered statistically significant. From this analysis we excluded patients that had negative VDRL/RPR titers at the beginning of follow-up at our Clinic for Infectious Diseases and Febrile Illnesses (n = 17) and patients without follow-up 12 months after treatment of syphilis (n = 8) because we could not assess the success of syphilis treatment.

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Results

The first patient in Slovenia with syphilis and HIV co-infection was diagnosed in 1987. Before 2005 we found only six additional cases. After that, the incidence of syphilis among our HIV-positive population increased progressively from four (1.2%) cases (2005) and 10 (2.9%) cases (2007) to 22 (6.4%) cases (2009) and 13 (3.8%) cases (first half of 2011). Out of 342 HIV-infected patients, 261 (76.3%) were MSM and 102 (29.8%) also had syphilis; of these, 40.2% (n = 41) were diagnosed simultaneously, 50.0% (n = 51) had a new diagnosis of syphilis, and 9.8% (n = 10) had a prior infection. The average age of our patients was 40.9 years; median per-patient follow-up was 5 years.

Fifty-five patients (53.9%) had primary/secondary syphilis, 38 patients (37.3%) had latent syphilis, and nine patients (8.8%) had neurosyphilis. Patients with primary/secondary/latent syphilis were treated with three doses of benzathine penicillin (2.4 million units, i.m.). Seventy-seven patients (89.6%) had a fourfold decrease in VDRL/RPR test 12 months after treatment (successful treatment). Including those that were excluded from statistical analysis (studying risk factors for treatment failure), the treatment was successful in 92.2% (n = 94). The initial average CD4 T cell count was 427 cells/mL. Out of 102 patients, 26 (25.5%) had re-infections. According to statistical analysis, there was no significant difference between the "success" and "treatment failure" group (p > 0.05) (Table 1).

Multiple logistic regression included the factors HAART treatment, CDC stage, and smoking. None of them were significantly associated with treatment failure of syphilis (p > 0.05) (Table 2).

Table 1 | Characteristics of HIV and syphilis co-infected patients according to treatment response (n = 77)*. SD – standard deviation; HBV/HCV + – Infected with the virus of hepatitis B and/or hepatitis C; CDC – Centers for Disease Control and Prevention (Atlanta, GA, USA); CD4 – CD4 T cell count at the time of the diagnosis and treatment of syphilis; VL – HIV viral load at the time of the diagnosis and treatment of syphilis (number of copies of HIV-RNA/1 mL); HAART treatment – treatment with Highly Active Antiretroviral Therapy for a minimum of 6 months; re-infected – with a fourfold increase of VDRL / RPR test after successful treatment of syphilis.

Protocols	Treatment success after 12 months	Treatment failure after 12 months	P value
N of patients (%)	69 (89.6)	8 (10.4)	
Age (± SD)	40.75 (± 10.91)	41.25 (± 10.96)	0.682
Slovenians (%)	64 (92.8)	7 (87.5)	0.557
Smokers (%)	22 (44.9)	5 (83.3)	0.196
HBV/HCV + (%)	3 (4.3)	1 (12.5)	0.366
CDC stage C (%)	19 (27.9)	3 (37.5)	0.107
CD4 (± SD)	450.9 (± 308.6)	338.4 (± 250.9)	0.423
VL ≥ 40 copies/mL (%)	42 (61.8)	5 (62.5)	0.166
HAART treatment (%)	24 (34.8)	1 (12.5)	0.203
Syphilis stage	/	/	0.61
Primary/secondary (%)	45 (65.2)	2 (25.0)	
Latent (%)	19 (27.5)	4 (50.0)	
Neurosyphilis (%)	5 (7.3)	2 (25.0)	
VDRL/RPR at diagnosis (median)	64.0	48.0	0.679
TPHA at diagnosis (median)	2,560.0	3,200.0	0.827
IgG at diagnosis	1,280.0	2,560.0	0.627
Re-infected (%)	20 (29.0)	4 (50.0)	0.224

*Note that we studied treatment success in 102 patients, but only 77 were included in the presented statistical analysis for evaluating risk factors for treatment failure.

Discussion

Since the early 2000s, for the first time since the introduction of HAART, the number of newly diagnosed HIV infections in the developed world has increased considerably compared to previous years. The increase was largely restricted to MSM from larger cities. This has been attributed to a decrease in safe sex practices. Simultaneously the re-emergence of syphilis, especially among MSM, was observed worldwide and a significant proportion of patients have been found to be co-infected with HIV (3, 5, 6).

We found a significant rise in the incidence of syphilis in the Slovenian HIV-positive MSM population after 2004. By 2011, 29.8% of all HIV-positive patients had had syphilis. The majority (76.3%) of the HIV-positive population in our study are MSM. A recent Slovenian study has shown a deterioration of safe sexual behavior among MSM and sexual mixing among Slovenian MSM and MSM abroad (15). Sexual risk taking goes on after the diagnosis of HIV and/or syphilis in a sizeable proportion of our MSM population, a result of which is probably also the high rate of re-infections in our study (25.5%). This suggests that implementing more strenuous safe-sex education may be effective in lowering the HIV and syphilis burden, as stated in some studies (16, 17). The rate of successfully treated individuals in our cohort was surprisingly good, which was most probably due to the low degree of immunosuppression and more intensive treatment regimen for early syphilis. The latter has already been advised by some authors (18–20). According to statistical analysis of different variables, there was no significant difference between the "success" and "treatment failure" group (p > 0.05). Similar findings are reported in many similar studies with patients mostly receiving HAART treatment and with an intact immune system (21–25). In Slovenia, HIV-positive patients start their HAART regimen treatment immediately after HIV diagnosis. In our study we included in the group "treated with HAART" only patients that had been treated with HAART for at least 6 months. Many patients were diagnosed with syphilis and HIV coincidentally or syphilis preceded HIV diagnosis, which gives a false low estimation of the rate of HAART treated. According to the statistical analysis, there was also no association between syphilis stage and values of serological tests 12 months after treatment (p > 0.05). This differs from the results of other studies. Some studies found that an increased treatment failure rate among the HIV-positive population was connected with early syphilis stage (primary and/or secondary and/or early latent syphilis) (26–28).

An important strength of our study is the total coverage of patients with double infection due to the fact that all Slovenian HIV-positive patients are screened, treated, and followed up at one center. However, due to the small number of participants in some study groups, statistical analysis may have yielded unreliable results.

Our findings may serve to guide clinicians to intensify the treatment and follow-up of HIV-infected patients with syphilis because of the possibility of re-infection.

Table 2 | Multiple logistic regression of factors influencing treatment failure of syphilis. HAART treatment – treatment with Highly Active Antiretroviral Therapy for minimum of 6 months; CDC – Centers for Disease Control and Prevention (Atlanta, GA, USA).

Factor	Observed category	Reference category	Odds ratio	95% confidence interval	P value
HAART treatment	Yes	No	0.720	0.048–10.873	0.812
CDC stage	C	Non C	3.034	0.357–25.759	0.309
Smoking	Yes	No	4.007	0.276–58.168	0.309

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