Natural experiment of syphilis treatment with doxycycline or benzathine penicillin in HIV-infected patients

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Background: Although doxycycline is widely used as an alternative to benzathine penicillin for the treatment of early and late latent syphilis, data on serological response following treatment with doxycycline among HIV-infected patients are limited.

Methods: In this study, we analysed serological response to syphilis treatment with doxycycline among HIV-infected patients treated during a benzathine penicillin shortage period and compared with treatment response among patients treated with benzathine penicillin. Cases with neurosyphilis and those treated with suboptimal doses or with concurrent medications in association with benzathine penicillin or doxycycline were excluded.

Results: Fifty patients treated with doxycycline from September 2014 to December 2016 were compared with 115 patients treated with benzathine penicillin for early, late latent or latent syphilis of unknown duration. Patients treated with doxycycline were slightly older [(median 49 years old, 95% confidence interval (95% CI) 43–56] than those in the penicillin group (median 44 years old, 95% CI 37–50; $P = 0.007$). Groups had no statistically significant differences regarding sex, HIV suppression under treatment and syphilis stages. Serological response to treatment, defined as a nonreagent Venereal Disease Research Laboratory (VDRL) or at least a four-fold reduction in VDRL titres measured 6–12 months after treatment, was seen in 72% (95% CI 58–84) of patients treated with doxycycline and 70% (95% CI 60–78) of patients treated with penicillin ($P = 0.753$).

Conclusion: We found no statistically significant differences in serological response to treatment with doxycycline or benzathine penicillin among HIV-infected patients with early, late latent or latent syphilis of unknown duration. Our findings suggest that doxycycline is an acceptable treatment to HIV-infected patients with nontertiary stages of syphilis.

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Introduction

Syphilis is a public health issue across the world, with estimated incidence of 42.5 cases/100 000 individuals in Brazil and 8.7 cases/100 000 in the USA in 2016 [1]. Although syphilis incidence in the USA and Western Europe declined after the introduction of penicillin treatment in the 1940s [2], a substantial resurgence in syphilis has been observed in the 21st century and, in 2016, syphilis cases increased by 74.0% compared with 2012.

Penicillin has been used as the first-line treatment for all forms of syphilis. However, penicillin shortage has been recently reported in many countries [3,4], highlighting the need for effective alternative treatment options. In addition, for patients presenting penicillin allergy or other contraindications, alternative treatment options are needed.

For HIV-infected patients, the evidence for syphilis treatment with nonpenicillin regimens is limited, and serological failure, defined as failure to achieve a nonreagent Venereal Disease Research Laboratory (VDRL) or at least a four-fold reduction in VDRL titres measured 6–12 months after treatment, occurs more frequently than among HIV-uninfected persons [5–7]. Two studies addressing syphilis treatment response suggested that the efficacy for serological cure is similar for doxycycline and benzathine penicillin, ranging from 64% to 85% [5,6,8].

In this natural experiment conducted in an HIV outpatient clinic in Sao Paulo, Brazil, we compared serological response with syphilis treatment with doxycycline or benzathine penicillin during a period of penicillin shortage.

Materials and methods

We conducted a retrospective cohort study at the HIV/AIDS outpatient clinic, Hospital das Clinicas, University of Sao Paulo Medical School.

All patients with HIV-syphilis coinfection treated with doxycycline or benzathine penicillin between September 2014 and December 2016 were identified using institutional records of medication prescription. Cases with neurosyphilis and those treated with suboptimal doses or with other medications (ceftriaxone, azitromicin, tetraciclin) were excluded.

Syphilis stages

Syphilis stages were defined on the basis of information collected from medical charts and laboratory reports. Primary syphilis were characterized by genital ulcers; secondary syphilis by maculopapular mucocutaneous lesions (associated with a positive result in the treponemal test or any increase in VDRL titre); early latent syphilis was defined by seroconversion in the treponemal test or any increase in VDRL titre detected within less than 1 year without clinical manifestations; and late latent syphilis was defined by asymptomatic seroreactivity (positive result in the treponemal test and any increase in VDRL titre) persisting for more than 1 year without a description of treatment in the medical chart since initial diagnosis. We defined those cases with asymptomatic seroreactivity as latent syphilis of unknown duration without a prior documented VDRL test report. Patients with an increase in VDRL titres for whom the timing of VDRL rise could not be determined (i.e. prior measurement more than 1 year before the current measurement) were also defined as latent syphilis of unknown duration.

Treatment

Benzathine penicillin treatment was considered appropriate when including at least one 2 400 00 IU intramuscular dose of benzathine penicillin for early stages or three weekly 2 400 00 IU intramuscular doses for late latent/unknown duration stages. For doxycycline, treatment with at least 100 mg twice daily for 14 days for early stages and at least 100 mg twice daily for 28 days for late latent/unknown duration stages was considered for the analysis.

Outcomes/serological cure

Serological response (cure) was defined as a nonreagent VDRL or at least a four-fold reduction in titres measured 6–12 months posttreatment [9].

Statistical methods

Demographic and clinical characteristics were described using frequencies, percentages, medians and interquartile ranges (IQRs). We described the proportion of patients with serological cure and their respective 95% confidence intervals (95% CIs).

Comparisons between groups treated with doxycycline or benzathine penicillin were performed using chi-square or Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for numeric variables. The independent effect of doxycycline treatment compared with benzathine penicillin was analysed using a multivariate logistic model adjusted for potential confounders. We used the statistical software Stata 13.1 (StataCorp LP, StataCorp College Station, Texas, USA) with a two-tailed alpha error of 0.05 in all analyses.

Ethical aspects

The study was approved by the institutional Ethics Committee with exemption from formal informed consent. All individual identifiable information were maintained in secured cabinets and electronic files.

Results

Baseline characteristics of study participants

From September 2014 to December 2016, 293 patients were included for initial analysis and 128 patients were excluded: 46 patients had no VDRL titres measured 6–12 months after treatment; 28 patients used antibiotics for nonsyphilis conditions; 20 patients had incomplete data; eight received more than one course of treatment during the assessed period; two were HIV-seronegative; two had neurosyphilis, 10 had incomplete treatment and 12 had no initial increase in VDRL titre (Fig. 1).

We included 165 patients, 50 (30%) treated with doxycycline and 115 (70%) with benzathine penicillin. Demographic and clinical characteristics are described in Table 1. Patients treated with doxycycline were slightly older (median 49 years old, 95% CI 43–53). Groups were similar regarding all remaining demographic characteristics. Most patients were male ($n = 164$, 99%). Median time since HIV diagnosis was 15 years (IQR 8–19 years), similar in both groups. Overall, 95% were under antiretroviral therapy, 83% had undetectable HIV viral load and median T $CD4^+$ cell count was 600 cells/μl (IQR 451–745). Participants treated with doxycycline had lower median T $CD4^+$ cell counts compared with those treated with benzathine penicillin (542, 95% CI 391–683 versus 617, 95% CI 469–769, $P = 0.036$).

Most patients in both groups had a previous diagnosis of syphilis (79%). Early and latent syphilis of unknown duration were the most frequently observed stages in this population (55% and 32%, respectively). We also observed a wide variation of VDRL titres, with no statistically significant difference between the groups (Table 1).

Serologic response to treatment with doxycycline or benzathine penicillin

Overall, serological response to treatment, defined as a nonreagent VDRL or a $\geq$ 4-fold reduction in VDRL titres measured 6–12 months after treatment, was seen in 116 patients (70%; 95% CI 63–77). We found no statistically significant difference in treatment response between the groups; serological response to treatment was seen in 80 patients treated with benzathine penicillin (70%; 95% CI 60–78) and 36 patients treated with doxycycline (72%; 95% CI 58–84; $P = 0.753$). In the multivariate analysis adjusted for age and T $CD4^+$ count, doxycycline was associated with 1.12 times the probability of serological treatment response compared with penicillin (95% CI 0.52–2.40, $P = 0.771$).

Discussion

In this natural experiment, we compared serological response to syphilis treatment with doxycycline or benzathine penicillin among patients followed in a HIV outpatient clinic in Sao Paulo, Brazil. We observed similar proportions of serological response in patients treated with doxycycline ($n = 50$, 72%) and those treated with benzathine penicillin ($n = 115$, 70%), suggesting

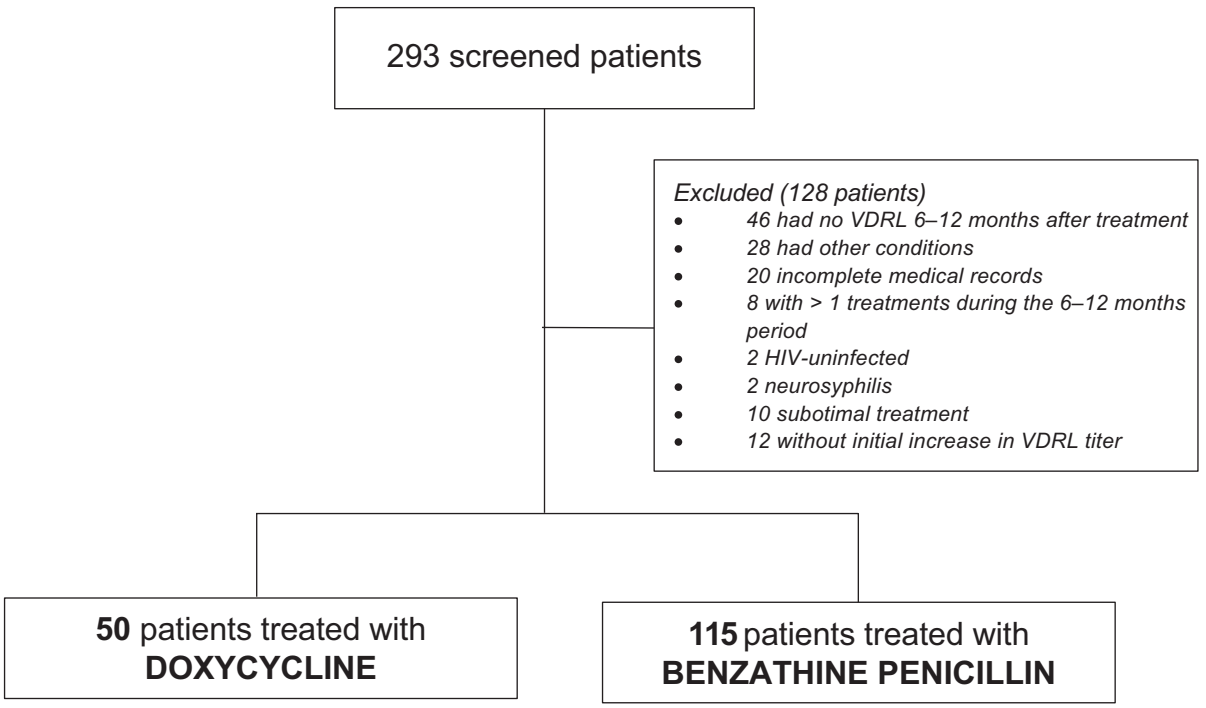

Fig. 1. Screening and selection for the study.

Table 1. Baseline characteristics of study participants, overall and by treatment.

	All participants $N=165$	Treated with penicillin $N=115$	Treated with doxycycline $N=50$	P
Age	45 (40–52)	44 (37–50)	49 (43–56)	**0.007**
Male sex (%)	164 (99)	114 (99)	50 (100)	1.000
Education[b]				0.110
Elementary/Middle	34 (25)	19 (20)	15 (37)	
High school	58 (42)	44 (46)	14 (34)	
University education	45 (33)	33 (34)	12 (29)	
MSM[c]	136 (88)	94 (89)	42 (86)	0.720
Years since HIV diagnosis	15 (8–19)	15 (8–18)	16 (12–20)	0.226
Under ART	155 (95)	109 (95)	46 (96)	1.000
$CD4^+$ cell count (cells/μl)	600 (451–745)	617 (469–769)	542 (391–683)	**0.036**
Undetectable HIV viral load[a]	137 (83)	96 (83)	41 (82)	0.816
Prior syphilis diagnosis[d]	124 (79)	87 (78)	37 (82)	0.527
Syphilis stage				0.920
Primary 1	4 (2)	3 (3)	1 (2)	
Secondary 2	7 (4)	4 (3)	3 (6)	
Early latent 3	91 (55)	65 (57)	26 (52)	
Late latent 4	11 (7)	8 (7)	3 (6)	
Unknown latent 5	52 (32)	35 (30)	17 (34)	
VDRL titre				0.936
≤1/4	15 (9)	10 (9)	5 (10)	
1/8–1/32	68 (41)	46 (40)	22 (44)	
1/64–1/256	74 (45)	53 (46)	21 (42)	
≥1/512	8 (5)	6 (5)	2 (4)	

Numeric variables as presented as medians and interquartile ranges. Significant values ($P<0.05$) are shown in bold.
[a]Lower limit of HIV viral load detection = 40 copies/ml.
[b]Information missing for 28 patients.
[c]Information missing for 10 patients.
[d]Information missing for eight patients.

doxycycline may be used as an alternative treatment for syphilis in patients coinfected with HIV.

There is limited evidence on serological response following syphilis treatment with nonpenicillin regimens. A meta-analysis published in 2017 compared the efficacy of different regimens for the treatment of early syphilis stages [10]. Encompassing 2049 patients, the meta-analysis showed no statistically significant difference in serological response between penicillin and the alternative treatment regimens.

The medical literature is even more restricted in studies addressing HIV-infected patients. In a multicentre observational study conducted in Taiwan, similar serological response was observed at 12 months after treatment with doxycycline (65.9%) and penicillin (68.3%, $P=0.075$) [6]. These results are consistent with the rates described in our study and also with those described by Cousins *et al.* [8] among HIV-infected patients in the UK.

In another study assessing serological response to syphilis treatment in HIV-infected patients conducted in Denmark [11], failure at 12 months was observed in 15% of patients treated with doxycycline and 17% of those treated with penicillin. In this study, although patients in the doxycycline group had higher T $CD4^+$ counts and were more frequently under antiretroviral treatment, propensity-score adjusted odds ratios showed no statistically significant difference in serological failure between groups. Compared with this study, our patients had lower serological response rates, which could be partly explained by differences in the time point of serological response assessment; HIV-coinfected patients may present a slower decay in VDRL titres than HIV-uninfected individuals, with higher serological cure outcomes within 24 months after treatment [11]. In addition, in our study, we could not distinguish between true treatment failure and reinfection. Indeed, 80% of our cohort had previous syphilis diagnosis, indicating high levels of re-exposure.

Our study had a few limitations. Due to retrospective, medical records based data collection, many cases had missing information on clinical characteristics and VDRL titres during posttreatment follow-up and had to be excluded. Our posttreatment definition follow-up time was short, precluding outcome assessment more than 12 months after treatment.

Our design using a cohort study in the context of a natural experiment is more robust than traditional observational studies, which are potentially under higher influence of indication bias for the assessment of doxycycline efficacy compared with benzathine penicillin. However, as some penicillin was still available in our clinic during the shortage period, we cannot rule out that penicillin

treatment was preferably indicated for patients with a higher risk of treatment failure. We compared baseline characteristics between groups and found no statistically significant differences in demographic or clinical characteristics, except for older age and lower T $CD4^+$ cell counts in doxycycline group, and adjusted analysis reassured our results. We can further rule out the occurrence of any indication bias in our cohort assuming that standard treatment with penicillin would have been preferably prescribed for older patients with lower T $CD4^+$ cell counts, while the opposite was observed. In addition, exposure to treatment with benzathine penicillin or doxycycline was determined by institutional records of prescription and withdrawal at the pharmacy's electronic system, not addressing actual adherence to treatment.

Finally, it is plausible that adherence to doxycycline was lower than estimated due to unsupervised administration and considerable gastrointestinal side effects. However, considering this possible misclassification of doxycycline use, we estimate that if only patients with adequate adherence had been included, the percentage of patients treated with doxycycline with serological cure would be even higher, supporting that doxycycline is an acceptable alternative treatment in HIV-infected patients with syphilis.

Importantly, patients with neurosyphilis have been excluded from this analysis. For most patients with neurosyphilis and any contraindication to receive penicillin or during penicillin shortage, ceftriaxone has been used as a preferred alternative treatment regimen. Studies addressing the efficacy of nonpenicillin regimens for the treatment of neurosyphilis are also needed.

Conclusion

In this cohort study outlined as a natural experiment comparing serological response to syphilis treatment with benzathine penicillin or doxycycline among HIV-infected patients, we found similar serological cure rates at 6–12 months after treatment.

Our findings are relevant for clinical conditions that represent absolute or relative contraindication to the use of benzathine penicillin. In addition, our findings are useful in the context of penicillin shortage, which has proven to be a growing problem in several countries [4].

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Conflicts of interest

None declared.

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