Syphilis infection markers among HIV positive individuals in the Mexico City HIV/AIDS Program

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Abstract

Objective. The aim of this study is to evaluate the prevalence of *T. pallidum* infection markers in HIV-positive individuals receiving highly active antiretroviral therapy (ART) in the Mexico City HIV/AIDS Program, as well as predictive characteristics. **Materials and methods.** The reverse serologic algorithm method was used for the *T. pallidum* diagnosis, and applied to 2 383 HIV-positive individuals. Sociodemographic characteristics, sexual practices, previous syphilis diagnosis, and length of antiretroviral treatment, were evaluated. Variables significantly associated with syphilis markers were analyzed using a logistic regression model. **Results.** Prevalence of "active or resolved" and "probable active" infection markers were 44.2 and 28.8%, respectively. Predictive factors were: *Clínica Especializada Condesa Iztapalapa* (CECI), previous syphilis diagnosis, men in who have sex with men (MSM), and receptive sex practices. **Conclusions.** The prevalence of *T. pallidum* infection markers was the highest ever reported in Mexico, and was related to specific sexual practices as well as previous syphilis diagnosis, elements which require preventive measures in the Mexico City HIV/AIDS Program.

Keywords: HIV; syphilis; men; sexual behavior; Mexico City

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Resumen

Objetivo. Evaluar las prevalencias de marcadores de infección por *T. pallidum* en personas que viven con VIH y reciben tratamiento antirretroviral en el Programa de VIH/SIDA de la Ciudad de México, así como sus características asociadas. **Material y métodos.** Se siguió el método del algoritmo reverso para el diagnóstico de *T. pallidum* aplicado a 2 383 individuos VIH positivos, quienes contestaron un cuestionario sobre características sociodemográficas, prácticas sexuales, diagnóstico previo de sífilis y tiempo de tratamiento antirretroviral. Las variables significativamente asociadas con los marcadores de sífilis se analizaron mediante un modelo de regresión logística. **Resultados.** Las prevalencias de marcadores de infección "activa o resuelta" y "probablemente activa" fueron 44.2 y 28.8%, respectivamente. Las características asociadas con los marcadores fueron Clínica Especializada Condesa Iztapalapa (CECI), diagnóstico previo de infección por sífilis, hombres que tienen sexo con hombres (HSH) y prácticas sexuales receptivas. **Conclusiones.** Las prevalencias de marcadores de infección por *T. pallidum* fueron altas y estuvieron relacionadas con prácticas sexuales específicas y con el diagnóstico previo de sífilis, características que requieren medidas preventivas dentro del programa.

Palabras clave: VIH; sífilis; hombres; prácticas sexuales; Ciudad de México

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Syphilis has reemerged as a growing risk to global public health, particularly in persons living with HIV.[1] This resurgence has been noted principally in men who have sex with men (MSM), although it has also affected other groups with high frequencies of HIV infection such as female sex workers, intravenous drug users, and also those with heterosexual practices.[2-9]

The incidence of syphilis has also been shown to increase proportionally with the duration of antiretroviral therapy (ART) in those infected with HIV. This observation has led to the recommendation of early detection of syphilis in patients receiving ART, in function with the time in which they have been in treatment.[10] Furthermore, various authors have noted an increased frequency of syphilis reinfection in HIV carriers, particularly in MSM who could be playing an important role in syphilis transmission.[11-14]

Syphilis is diagnosed through serological testing and the presence of clinical manifestations. Generally, when tests are applied to confirm clinical findings or for screening purposes, the first used is the nontreponemal test (rapid plasma regain [RPR] or venereal disease research laboratory [VDRL]) whose positive results must be confirmed with a subsequent treponemal test (ex. FTA-ABS).[15] The advent of rapid treponemal test kits has allowed the algorithm for syphilis diagnosis to be reversed; that is, the first test applied may be treponemal, and positive results may then be corroborated with a nontreponemal test.[16]

In the *Clínica Especializada Condesa* (CEC), which operates the Mexico City HIV/AIDS Program, integral detection of HIV/STI testing which includes syphilis has been implemented since 2009, using the reverse algorithm.* Due to the large number of clinic users who test positive for syphilis it was found to be critical to establish a continual monitoring program for syphilis in ART patients.[17,18,‡,§] To this end, rapid treponemal tests were applied and positive results were further subjected to RPR test in two different laboratories, one in CEC and one in *Clínica Especializada Condesa Iztapalapa* (CECI). Then a protocol was established which guarantees the use of the standardized and reproducible test method in all clinic users.

This study aims to establish the beginnings of an incidence cohort of syphilis in ART patients, realizing a base evaluation of the presence of *T. pallidum* infection markers in HIV carriers who receive ART in the Mexico City HIV/AIDS Program. It also analyzes the relationship between prevalence of these pathological conditions with sociodemographic factors, sexual practices, previous syphilis or gonorrhea diagnosis, and length of ART in the study population.

Materials and methods

Study population

The CEC is the site of the Center for Prevention and Integral Attention for HIV/AIDS of the Federal District (Mexico City) whose contributions to public policy include implementation of the Mexico City HIV/AIDS Program.[19] A cohort was constructed of HIV-positive patients who received antiretroviral therapy. The cohort was expanded to also include HIV-positive patients who receive HIV treatment at the CECI, which is part of the same Mexico City HIV/AIDS Program.

Research ethics

The protocol of the present study was evaluated and approved by the Committees of Research and Ethics of the National Institute of Public Health of Mexico, reference number CI: 1499, October 30, 2017.

Study design and duration

The present study involved the formation of a cohort of HIV-positive patients, in whom it is attempted to estimate the basal prevalence of syphilis infection. Between March and July, 2018, 2 383 individuals were included in this cohort: 2 011 from the CEC, and 372 from the CECI.

Participant selection and questionnaire

A convenience sample was carried out. Upon arrival at the CEC or the CECI to receive ART, patients were invited to participate in the study. Those who accepted participation signed an informed consent and answered a questionnaire which inquired about their sociodemographic characteristics such as age, gender, marital

* Juárez-Figueroa L, Iracheta P, Conde-Glez C, Bautista-Arredondo S, González-Rodríguez A. Validation of a treponemic antibodies automated test for Syphilis detection among inmates of Mexico City. Abstract #P3-S6.01 presented in the 19th Biennial Conference of the International Society for Sexually Transmitted Diseases Research (ISSTDR), July 10-13, 2011; Quebec, Canada (poster request lajfigueroa@gmail.com).

‡ Juárez-Figueroa L, Arellano J, Iracheta P, González A. Toward "real time" HIV/STI diagnosis in the HIV/AIDS Program of Mexico City. Abstract presentation in AIDS 2010, XVIII International AIDS Conference, 2010 18-23 July; Vienna, Austria (poster request lajfigueroa@gmail.com).

§ Juárez-Figueroa L, González-Rodríguez A, Casillas J, Rodríguez-Nolasco E, Iracheta P. Faster and integral HIV diagnosis among MSM in the HIV/AIDS Program of Mexico City (HIVPMC): Necessary but not sufficient. Abstract presentation in AIDS 2012, XIX International AIDS Conference, 2012, 22-27 July; Washington, DC (poster request lajfigueroa@gmail.com).

status, education level, birthplace, place of residence, and occupation. The following sexual practices were also evaluated: age at first sexual relation, scale of activity heterosexual-homosexual,[20] sexual exchanges for money of goods, previous payment for sexual acts, intravenous drug use, and insertive or receptive practices. The questionnaire then inquired about any previous diagnosis of syphilis or gonorrhea, as well as duration of time with known HIV infection and duration of adherence to ART. A non-response rate was of 40%.

Laboratory processes and diagnoses

During March of 2018, before including patients in the syphilis incidence cohort, the performance of the non-treponemal test RPR (Licon) was compared with that of VDRL. The procedures for analysis, registration, and reporting were standardized across both laboratories. In order to evaluate the performance of the two test methods, a panel of 105 treponemal antibody positive samples was tested with non-treponemal VDRL and RPR. tests. Results of the comparison of RPR versus VDRL demonstrated a correlation coefficient of 0.95 (p<0.001), a Rho of Spearman of 0.96 (p<0.001), and intra-class correlation coefficients of 0.95 (p<0.001).

For detection of *T. pallidum* infection markers, the reverse algorithm method was used through a rapid treponemal test for TP antibodies (Neogene-Syphilis Interbiol), in which positive results went on to be tested with the nontreponemal test of RPR with titles (Licon RPR). A positive result in the treponemal test indicates the presence of syphilis, but does not determine if the infection is recent or whether it has been treated previously;[16] for this reason, positive results are defined as "active or resolved". However, a positive result in both the treponemal and nontreponemal test implicates the presence of active syphilis even though it may include recently treated cases in which the antibody levels may remain high.[16] For this reason, in the present study positive results obtained by the reverse algorithm method are defined as "probable active" infection. To confirm this classification, the first 879 study participants from the CEC were analyzed who received a clinical diagnosis of syphilis according to their CEC records as well as titers of the RPR test. On the same clinical basis, different categories of syphilis were defined such as "syphilis under treatment", "syphilis treated and cured" and "syphilis reinfection under treatment".

Plan of analysis

A descriptive analysis was performed for individual characteristics of the participants, including sociodemographic traits, sexual habits, history of syphilis and gonorrhea infection, and the duration of any ART. The statistical test of independence was used to evaluate the relation between dependent (syphilis markers) and independent variables. Odds ratio was calculated in all variables significantly associated to syphilis markers and also were analyzed performing a multivariate logistical regression model using the method *enter*. The SPSS software (version 19) was utilized to perform the statistical analysis. Furthermore, an analysis was undertaken of the RPR test titers of the first 879 CEC clinically studied participants of which showed positive results through the reverse algorithm method.

Results

A total of 2 386 individuals were studied, with an average age of 36.9 years (SD: 10.6), largely male (96.6%) and the rest transsexual, predominantly single (70.5%), an average age of first sexual relation at 16.9 years (SD: 3.8), over half with higher education or technical certification (54.5%), high proportion were MSM (90.8%), nearly one-third with previous syphilis diagnosis, (30.9%), a portion with previous gonorrhea diagnosis (13.9%), and over half originating from Mexico City (59.8%). The prevalence of "active or resolved" or "probable active" infection markers was 44.2% (1 053/2 383) and 28.8%

Table I

TITRATION DISTRIBUTION OF RPR TEST BY THE THREE PRINCIPLE CATEGORIES OF SYPHILIS DIAGNOSIS WITHIN THE FIRST 879 CLINICALLY STUDIED INDIVIDUALS IN THE CEC. CITY OF MEXICO, 2018

Titrations of RPR test	*Syphilis, under treatment n (%)*	*Syphilis, treated and cured n (%)*	*Syphilis reinfection, under treatment n (%)*
1:1	2 (3.1)	26 (25.2)	0
1:2	7 (10.8)	59 (57.3)	3 (3.3)
1:4	17 (26.21)	15 (14.6)	9 (10.0)
1:8	10 (15.4)	1 (1.0)	13 (14.4)
1:16	7 (10.8)	1 (1.0)	19 (21.1)
1:32	8 (12.3)	1 (1.0)	18 (20.0)
1:64	5 (7.7)	0	13 (14.4)
1:128	6 (9.2)	0	10 (11.1)
1:256	3 (4.6)	0	3 (3.3)
1:512	0	0	2 (2.2)
Total	65 (100)	103 (100)	90 (100)

RPR: rapid plasma regain
CEC: *Clínica Especializada Condesa*

(686/2 383), respectively. The distribution of positive titers results of the RPR test in the analysis of the 879 clinically studied CEC participants is shown in table I. Of a total of 272 positive cases determined by the reverse algorithm method, 258 (94.8%) were concentrated within three categories of clinical care: a) treated syphilis in follow-up (23.8%), b) treated and cured syphilis (37.8%), and c) syphilis reinfection in follow-up (33.1%).

Results of the bivariate analysis showed a significant association between "active or resolved" and "probable active" syphilis infection with marital status, previous syphilis diagnosis, hetero-homosexual practices, and insertive-receptive practices. "Active or resolved" infection was also associated with the type of clinic in which interviews were undertaken, as well as with sexual exchanges for money or goods. No relation was found between syphilis markers and age, education level, gender of the individual, birthplace, age of first sexual relation, having paid for sexual relations, intravenous drug use, or duration of ART (table II).

After controlling for age in the logistical regression model, the predictive variables of "active or resolved" infection were: CECI (OR=1.6, CI95%: 1.2-2.0), previous syphilis diagnosis (OR=14.2, CI95%: 11.2-18.2); MSM (OR=2.8, CI95%: 1.8-4.2); and receptive sexual practices (OR=1.3, CI95%: 1.0-1.7). For "probable active" infection markers, predictive factors were found to be: previous syphilis diagnosis (OR=7.0, CI95%: 5.7-8.6); MSM (OR=2.3, CI95%: 1.4-3.8); and receptive sex practices (OR=1.6, CI95%: 1.2-2.1) (table III).

Table II
Bivariated analysis of "active or resolved" and "probable active" syphilis infection marquers and related characteristics of HIV-positive individuals attended through the Mexico City HIV/AIDS Program

Characteristics	*n*	*Prevalence*	*OR*	*CI95%*	*n*	*Prevalence*	*OR*	*CI95%*
Clinic								
Condesa	2 011	43.2	1.3	1.0-1.6*				
Iztapalapa	372	49.7						
Marital status								
Married	203	36.0	1.4	1.1-1.9*	203	21.7	1.5	1.1-2.1*
Other‡	2 179	45.0			2 179	29.5		
Syphilis§								
No	1 640	26.2	15.4	12.2-19.3#	1 640	15.4	7.9	6.5-9.7#
Yes	732	84.6			732	59.2		
Gonorrhea&								
No	1 980	42.5	1.7	1.3-2.2#				
Yes	314	55.7						
Sexual practices								
Hetero	217	18.0	4.0	2.8-5.7#	217	9.2	4.3	2.7-6.9#
MSM	2 162	46.8			2162	30.7		
Sex&								
No	2 087	43.1	1.4	1.1-1.8*				
Yes	294	52.0						
Insertive sex practices								
No	1 504	39.0	1.7	1.4-2.0≠	1 504	24.6	1.7	1.4-2.0#
Yes	878	53.1			878	36.0		
Receptive sex practices								
No	1 565	37.4	2.2	1.8-2.6#	1 565	22.5	2.4	1.9-2.8#
Yes	812	56.8			812	40.8		

* $p < 0.05$
‡ Single, separated, divorced, widowed
§ Previous diagnosis of syphilis
# Previous diagnosis of gonorrhea
& Sex in exchange for money
≠ $p < 0.001$
HIV: human immunodeficiency virus
AIDS: acquired immunodeficiency symdrome
MSM: men who have sex with men

Table III
Adjusted odds ratio of "active or resolved" and "probable active" syphilis infection marquers and related characteristics of HIV-positive individuals attended through the Mexico City HIV/AIDS Program, 2018

Characteristics	*OR*	*CI95%*	*P value*	*OR*	*CI95%*	*P value*
Age	1.01	1.00-1.02	0.04	0.9	0.8-1.9	0.15
Clinic Iztapalapa	1.6	1.2-2.0	0.002			
Marital status Other*	1.2	0.8-1.8	0.18	1.3	0.8-1.9	0.15
Syphilis Previous diagnosis	14.2	11.2-18.2	<0.001	7.0	5.7-8.6	<0.001
Gonorrea Previous diagnosis	0.8	0.6-1.1	0.23			
Sex practices MSM	2.8	1.8-4.2	<0.001	2.3	1.4-3.8	0.001
Sex‡ Yes	1.1	0.8-1.6	0.41			
Incertive sex practices Yes	1.2	0.9-1.6	0.12	1.0	0.8-1.3	0.80
Receptive sex practices Yes	1.3	1.0-1.7	0.01	1.6	1.2-2.1	<0.001

* Single, separated, divorced, widowed
‡ Sex in exchange for money
HIV: human immunodeficiency virus
AIDS: acquired immunodeficiency syndrome
MSM: men who have sex with men

Discussion

Since the second decade of the century, growing numbers of syphilis infection have been reported in Mexico in individuals with high-risk sexual practices such as male sex workers (MSW) and MSM. For example, in 2014 a high frequency of active syphilis infection was reported in 21% of MSW, in whom frequency of HIV infection was also high at 35%.[21] In a similar study in 2015, prevalence of treponemal antibodies in HIV-positive patients was at 25%, rising to 30% in MSM.[22]

In this context the present study chose to include individuals undergoing ART in whom a high prevalence of treponemal antibodies (44.2%) were encountered: higher than numbers previously reported by Mata-Marín and colleagues[22] in MSM carriers of HIV. The treponemal test method identifies those individuals with history of syphilis treatment, or untreated or incompletely treated syphilis,[11] situations in which a high proportion of study subjects found themselves.

Secondary application of the nontreponemal test, in accordance with the reverse algorithm procedure for syphilis diagnosis, showed that the prevalence of "probable active" cases was 28.8%, with respect to the total population studied. This frequency was higher in the present study than in the 21% previously found for MSW in Mexico,[21] as well as of the 21% frequency in MSM HIV-positives in Japan.[23] These high frequencies of "active or resolved" and "probable active" infection suggest that the population under study has a high level of interaction between individuals infected with syphilis and susceptible to the infection in HIV-positive patients, as has been previously reported particularly among MSM HIV-positives according to a meta-analysis with results from 11 European countries.[24]

The results of this study highlight the importance of syphilis monitoring by the Mexico City HIV / AIDS Program. For example, while in the present study a 28.8% rate of probable active syphilis was found, the statistics corresponding with a total of 19 350 men, 7 427 women, and 320 transsexuals who realized HIV testing at the CEC during the year of 2018 were 10.24, 2.1, and 15.31%, respectively. Nonetheless, the prevalence of probable active syphilis in HIV-positive men (n=3 243), women (n=176), and transsexuals (n=54) in the same time period were 25.5, 6.8, and 29.6%, respectively.* These numbers demonstrate that the groups with greater prevalence of

* HIV / AIDS Program of Mexico City. Results of The Condesa Specialized Laboratory (umpublished data).

probable active syphilis in the CEC and CECI are men and transsexual who are HIV-positive.

The results of the RPR test titers presented in table I justify the methods used in this study to define probable active syphilis infection. It has been documented that antibody titrations of the nontreponemal test may correlate to the activity of the syphilis infection and may therefore be used to follow up on the response to treatment. A four-fold change (ex. 1:16 to 1:4 or 1:8 to 1:32) in titrations of two results of nontreponemal tests using the same serological test can serve to judge the effects of the syphilis treatment.[11,15] Distribution of titers in the first clinical category of "under treatment" syphilis in this study suggest that initiation of syphilis treatment is recent, and therefore cases of high dilution titrations still exist, while in the second clinical category of "treated and cured" syphilis the results of titrations are concentrated in low values of dilution. In the third clinical category of "reinfection of syphilis under treatment" it was clearly shown that the percentage distribution of the titers rose along with the rise in test dilution, suggesting the presence of syphilis infection activity.

In terms of risk factors, the present study showed that there was a significant upward trend in the risk of probable active syphilis infection in MSM, taken as a reference group those with heterosexual practices. Furthermore, this study showed a significant relationship between the prevalence of probable active syphilis and receptive sex practices, showing that the male HIV-positive population with the highest frequency of probable active syphilis in this study is that which identifies as MSM according to Kinsey and collagues classification of male sex practices.[20] Along these lines, it has been reported that one of the predictive factors associated with coinfection of HIV and syphilis in males with exclusively homosexual practices are insertive-receptive practices[25] and also that the highest rates of syphilis infection in HIV-positive males are presented in MSM.[24] In Mexico, the risk of HIV infection in men is significantly higher among males with homosexual as well as insertive-receptive practices in accordance with a pioneer study on the subject.[26]

The strongest predictive factor associated with probable active syphilis infection in the present study was previous syphilis diagnosis. These results suggest a high rate of syphilis reinfection in the population under study, and are consistent with reports in the literature of previous syphilis diagnosis and presence of reinfection by *T. pallidum* found predominantly in HIV-positive MSM.[27,28] Furthermore, 33.1% of the cases evaluated in their clinical stage (table I) were classified as "reinfection of syphilis under treatment," which supports the hypothesis of a high rate of syphilis reinfection for the population under study.

The lack of evaluative components regarding condom use or number of sexual partners represents one of the most important limitations of the present work. In addition, the hypothesis relating the frequency of syphilis infection and longer duration of ART in HIV-positive individuals could not be tested.

Conclusions

The application of the reverse diagnosis of syphilis in the context of the Mexico City HIV / AIDS Program showed that the prevalence of "active or resolved" and "probable active" syphilis infection is the highest observed in Mexico among HIV-positive individuals. Although the syphilis detection program is currently operating in both clinics in which the present study was realized, the CEC and the CECI, preventive strategies should be established which are focused towards the sexual practices significantly associated with both infection markers in order to reduce prevalence as well as the reinfection pattern observed in this population.

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Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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