

High Incidence, Re-Infections, and Active Syphilis in Populations Attending A Specialized HIV Clinic in Mexico, A Dynamic Cohort Study.

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Abstract

Background. Syphilis has reemerged in many vulnerable groups around the world. The objective of the current study was to determine the prevalence and incidence of syphilis among people who attended a specialized HIV clinic in Mexico from 2011-2015.

Methods. Databases from the laboratory were analyzed and four groups were formed: people seeking HIV-1 voluntary counseling and testing (VCT), people in prison (PPr), people living with HIV (PLWH) and patients from primary care clinics (others). Syphilis diagnosis was made using the reverse algorithm; antibody titers were examined to determine the stage of infection. Baseline data was analyzed, and with follow-up information, a retrospective dynamic cohort was formed. Factors associated with seroprevalence of syphilis and active syphilis were evaluated by the chi-square test. Moreover, risk factors for the incidence of syphilis were described.

Results. A total of 81,863 baseline individuals were analyzed. Syphilis seroprevalence was 9.9% in VCT, 8.2% in PPr, 37.0% in PLWH, and 8.7% in others; the prevalence of active syphilis was 1.7-13.1%. A total of 11,124 people were followed-up; the incidence (cases per 100 years people) was 3.5 among VCT and 16.0 among PLWH; moreover, the frequency of re-infections was 11.1-24.4%. Men, transgender, persons between 20-39 years old, and individuals with a history of HIV or hepatitis B had a higher risk of syphilis.

Conclusions. Several vulnerable groups have exhibited a reemergence of syphilis, with high prevalence of active syphilis, high incidence, and re-infections. Persons living with HIV had the highest risk.

Background

The World Health Organization (WHO) estimated the number of new cases of syphilis in 2012 at 5.6 million; it increased to 6 million in 2016. In the latter year, the incidence was 1.7 cases per thousand women and 1.6 cases per thousand men. Globally, the syphilis prevalence was 3.2% among female sex worker (FSW) and 6.0% among men who have sex with men (MSM). The WHO set the goal to reduce the incidence of *Treponema pallidum* by 90%, with a focus on priority groups: MSM, FSW, and intravenous drug users (IDUs).^{1,2}

Syphilis has increased in different parts of the world. Between 2013 and 2017, the number of cases per 100,000 inhabitants in the U.S. increased from 5.5 to 9.5.³ The European Economic Community reported an increase from 4.7 cases to 6.1 cases per 100,000 inhabitants between 2012 and 2016.⁴ In Mexico, an increase in syphilis was documented among young men, focused in Mexico City.⁵ Syphilis is important because of the number of cases as well as the higher risk to acquire and transmit HIV. Moreover, syphilis and HIV coinfection negatively modifies both diseases.⁶

The Clinica Especializada Condesa (CEC) in Mexico City is the institution that serves the largest number of people seeking HIV testing, as well as people living with HIV. The CEC also performs test for other sexually transmitted infections (STI), hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis. The

objective of the current study was to determine the prevalence, incidence, and risk factors of infection by *T. pallidum* among populations attending the CEC from 2011–2015.

Methods

A database was elaborated with the variables year, internal number, population type, sex, age, HIV by chemiluminescent microparticle immunoassay (CMIA), HIV rapid test 1, HIV rapid test 2, HIV Western blot, *T. pallidum* by CMIA, *T. Pallidum* rapid test, venereal disease research laboratory (VDRL) titer, HVB antigen detection, and HCV antibodies detection. Syphilis was detected using the reverse algorithm. This method starts with a treponemal test to later perform the VDRL. Some authors have mentioned that in the absence of clinical data, the antibody titer can be used to determine the stages of syphilis, as active syphilis (titer $\geq 1:8$), latent syphilis (titer 1:1–1:4) and cured syphilis (VDRL negative, positive treponemal test).^{7,8} The attending population was classified into four groups: (1) people seeking HIV-1 voluntary counseling and testing (VCT), (2) people living with HIV (PLWH), (3) people in prison (PPr), and (4) others, people from others clinics, principally primary care clinics. The CEC sends patients with syphilis to their primary care clinics for treatment, only PLWH without social security attended CEC. The present study was approved by the ethics committee of the National Institute of Public Health from Mexico. The database had identification keys, we did not have access to the names of the participants.

From the baseline information, frequency analysis stratified by population group was performed, and chi-square (χ^2) tests were used to evaluate the differences. Subsequently, a bivariate analysis was performed to determine associated variables, both to the seroprevalence of syphilis and the presence of active syphilis. The trend test was used for the year and age variables, considering the four population groups.

A retrospective dynamic cohort was elaborated with individuals that had two syphilis tests with at least four months between measurements and incidence densities was calculated using person years (py). During follow-up, syphilis was considered cured if the antibody titer decreased until negative or if the antibody concentration decreased four times or more. Syphilis re-infection was defined when it was cured at baseline and the titer was $\geq 1:1$ during follow-up or if antibody titer increased four times or more. Persistent infection was considered if the antibody titer remained similar (± 2 times).⁹ Incidence rate ratios (IRR) were calculated with 95% confidence intervals (CI), and a cumulative incidence curve was constructed using the Kaplan-Meier method. A p-value < 0.01 was considered statistically significant. Statistical analysis was performed using the SPSS program.

Results

Basal. A total of 129,613 blood/serum samples were processed in the CEC laboratory between 2011 to 2015. In 2011, there were 17,589 samples, and in 2015, there were 37,342. Results for syphilis detection were from 95,732 samples, of which 81,863 people attended at least once; 78.1% were VCT, 9.9% PPr, 2.2% PLWH, and 9.8% others. Table 1 shows the demographic characteristics and laboratory results of the four analyzed populations. In all groups, there was an increase in the number of samples analyzed

over the years, with the exception of PPr that presented the greatest number of samples during 2012–2013. Men were the majority in all groups, from 63.3% among others to 85.5% among PLWH. The highest percentage of transgender was in the PLWH group. PLWH had the highest average age at 34.6 years, and VCT were the youngest on average (29.0 years). One-in-five VCT individuals were HIV positive; 3.8% of PPr individuals were HIV positive. Among PLWH, 4.9% had HBV antigens and 2.9% had antibodies against HCV.

Table 1

Demographic and clinical characteristics in populations attending a specialized HIV clinic in Mexico.

	VCT N = 63,916	PDL N = 8,083	PLWH N = 1,808	Others N = 8,056	p
	%	%	%	%	
Year					
2011	8.9	16.1	18.8	13.3	< 0.001
2012	19.3	25.3	24.5	17.5	
2013	21.9	22.3	19.1	24.5	
2014	23.4	17.3	14.8	23.3	
2015	26.5	19.0	22.8	21.5	
Sex					
Female	34.3	31.8	11.9	36.6	< 0.001
Male	64.3	67.2	85.5	63.3	
Transsexual	1.3	1.0	2.6	0.1	
Age (years)					
≤ 9	1.1	0.1	-	7.9	< 0.001
10–19	11.7	2.4	2.0	19.2	
20–29	49.9	33.7	32.2	28.7	
30–39	22.0	37.9	36.8	19.8	
40–49	9.9	18.8	21.7	12.4	
50–59	3.9	5.9	6.1	6.8	
≥ 60	1.5	1.3	1.1	5.1	
HIV test					
Negative	81.4	91.0	-	86.0	< 0.001
Positive	18.6	3.8	100	7.2	
Not done	-	5.2	-	6.7	
HBV test					

VCT: People seeking HIV-1 voluntary counseling and testing; PPr: people in prison; PLWH: people living with HIV; Others: patients from primary care clinics. Bold: p < 0.01 statistically significant.

	VCT N = 63,916	PDL N = 8,083	PLWH N = 1,808	Others N = 8,056	p
Negative	89.1	74.2	77.3	83.9	< 0.001
Positive	0.9	0.9	4.9	0.6	
Not done	10.0	24.9	17.8	15.5	
HCV test					
Negative	95.4	81.5	81.7	86.0	< 0.001
Positive	0.9	3.1	2.9	1.4	
Not done	3.6	15.4	15.4	12.6	
VCT: People seeking HIV-1 voluntary counseling and testing; PPr: people in prison; PLWH: people living with HIV; Others: patients from primary care clinics. Bold: p < 0.01 statistically significant.					

The seroprevalence of syphilis was 8.2% (95% CI 7.6–8.8) among PPr, 8.7% (95% CI 8.1–9.3) among others, 9.9% (95% CI 9.7–10.1) in the VCT population, and 37.0% (95% CI 34.8–39.2) among PLWH. Figure 1 shows the seroprevalence of syphilis and active syphilis. Almost 40% of people with antibodies showed a cured infection, except among PLWH, in which the percentage was 32.4%. The VCT and PLWH populations had the highest seroprevalence of active syphilis, with 3.6 and 13.1%, respectively.

The seroprevalence of syphilis decreased over time in the CVT and PPr groups ($p < 0.001$). The transgender population had the highest seroprevalence; it was higher among the PPr followed by PLWH, with more than 40% in both cases ($p < 0.001$). At an older age, the seroprevalence of syphilis increased in the four analyzed population groups ($p < 0.001$). Individuals with other STIs (HIV, HBV, or HCV) had a higher association with the seroprevalence of syphilis ($p < 0.05$; Table 2, left).

When analyzing the frequency of active syphilis, there was a decrease during the study period in the VCT group. In contrast, active syphilis increased among PLWH during the analyzed period. Women presented the lowest proportion of active syphilis in the four groups; the highest frequency of active syphilis was in transgender and men living with HIV: 17.0% and 14.2%, respectively ($p < 0.001$). People aged 20–29 and 30–39 years had the highest frequency of active syphilis in the VCT group. A history of STIs was associated with a higher frequency of active syphilis in the entire population (Table 2, right).

Table 2
Seroprevalence of *T. pallidum* and active syphilis in populations attending a specialized HIV clinic in Mexico.

	Seroprevalence <i>T. pallidum</i>				Active syphilis			
	VCT	PPr	PLWH	Others	VCT	PPr	PLWH	Others
Year								
2011	13.2	9.9	37.5	2.0	4.7	1.8	4.7	2.0
2012	9.7	7.7	38.8	2.5	3.6	1.4	13.5	2.5
2013	9.5	9.2	33.0	2.0	3.4	1.8	15.7	2.0
2014	9.2	8.9	38.4	1.9	3.1	1.6	14.6	1.9
2015	9.9	5.9	37.0	2.4	3.8	1.9	16.2	2.4
Trend p	<0.001	0.005	0.812	0.700	<0.001	0.775	<0.001	0.700
Sex								
Female	1.7	7.2	14.9	2.3	0.4	0.8	3.7	2.3
Male	14.1	8.2	39.9	2.1	5.3	1.9	14.2	2.1
transsexual	18.9	43.9	42.6	0.0	5.0	13.4	17.0	0.0
p	<0.001	<0.001	<0.001	0.720	<0.001	<0.001	<0.001	0.720
Age (years)								
≤ 9	0.7	33.3	–	0.9	0.0	0.0	–	0.9
10–19	3.0	5.7	13.9	1.6	1.8	2.6	13.9	1.6
20–29	9.0	7.5	29.0	2.8	4.0	2.1	14.8	2.8
30–39	13.5	8.1	39.9	1.6	4.6	1.5	13.5	1.6
40–49	12.9	8.4	42.0	2.6	3.1	1.1	11.5	2.6
50–59	13.1	10.2	48.6	2.5	2.1	1.5	9.0	2.5
≥ 60	18.2	22.3	52.6	2.7	1.4	2.9	0.0	2.7
p trend	<0.001	<0.001	<0.001	0.021	<0.001	0.217	0.223	0.021
HIV test								
Negative	5.1	6.5	—	0.8	1.8	1.2	—	0.8

Seroprevalence of antibodies against *T. pallidum*. VCT: People seeking HIV-1 voluntary counseling and testing; PPr: people in prison; PLWH: people living with HIV; Others: patients from others clinics. Active syphilis, titers ≥ 1:8 in non-treponemic tests. Bold: p < 0.01 statistically significant

	Seroprevalence <i>T. pallidum</i>				Active syphilis			
Positive	30.8	29.4	37.0	7.9	11.4	10.7	13.1	7.9
p	< 0.001	< 0.001	—	< 0.001	< 0.001	< 0.001	—	< 0.001
HBV test								
Negative	9.9	7.9	34.0	1.3	3.6	1.8	11.3	1.3
Positive	41.9	34.3	49.4	13.3	17.2	10.0	21.3	13.3
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
HCV test								
Negative	9.9	7.8	32.8	1.4	3.6	1.9	11.5	1.4
Positive	26.6	12.6	53.8	3.6	9.5	1.6	19.2	3.6
p	< 0.001	0.003	< 0.001	< 0.001	< 0.001	0.030	< 0.001	< 0.001
Seroprevalence of antibodies against <i>T. pallidum</i> . VCT: People seeking HIV-1 voluntary counseling and testing; PPr: people in prison; PLWH: people living with HIV; Others: patients from others clinics. Active syphilis, titers $\geq 1:8$ in non-treponemal tests. Bold: $p < 0.01$ statistically significant								

Dynamic Retrospective Cohort. There were samples from 11,124 individuals with a baseline syphilis outcome and at least one additional visit to the CEC, the median time between visits was 10.6 months (interval interquartil 6.0–18.0). Figure 2 shows that from baseline, 10,844 people were negative for the treponemal test and 283 were positive. During follow-up of negative samples, 413 positive samples were detected in the second measurement. Considering the non-treponemal test at baseline and second measurement, 59.6% had a cured infection, 13.6% had re-infection, and 26.8% had persistent infection among the VCT group; 29.6% had a cured infection, 11.1% re-infection, and 59.3% persistent infection among PPr; 56.1% had cured infection, 24.4% re-infection, and 19.5% persistent infection among PLWH; 50.0% had cured infection, 21.4% re-infection and 28.6% persistent infection in the others group. Considering all groups, 49.4% of persons with persistent syphilis infection had twelve months or more between the two measurements (treatment failure); among people without HIV this percentage was 41.9% (26/62) and among people living with HIV it was 73.7% (14/19), this difference was statistically significant ($p = 0.019$).

The highest incidence of syphilis was found in the PLWH group, with 16.0 cases per 100 py (95% CI 12.6–20.3), followed by the VCT population, with 3.5 cases (95% CI 3.1–3.8), PPr group with 0.95 cases (95% CI 0.5–1.7), and finally others with 0.86 cases (95% CI 0.3–2.6). Among the PLWH, at 39.67 months (95% CI 30.91–48.41), 50% of the population acquired syphilis, a value that was lower compared to VCT individuals (52.5 months; 95% CI 48.51–56.5). This difference was statistically significant ($p < 0.001$; Log

Rank; Fig. 3). For the other groups, it was impossible to calculate the infection time due to the sample size and the low proportion of positive cases.

Table 3 shows the incidence rate ratio for syphilis. Notably, the incidence increased in relation to the calendar year, but this change was not statistically significant. Men and transgender had an incidence of 4.6 cases per 100 py and had a 9-times greater risk to have syphilis compared to women. The 20–29 and 30–39 year age groups had the highest incidence of *T. pallidum* infection, with 3.9 and 3.4 cases per 100 py, respectively. These groups also had twice the risk of infection compared to individuals over 50 years old. People with a history of HIV infection had an incidence of 12.2 cases per 100 py, those with a history of HBV infection had an incidence of 11.4 cases, and individuals with HCV infection showed 1.7 cases per 100 py.

Table 3
Incidence and risk factors for *T. pallidum* infection in populations attending a specialized HIV clinic in Mexico.

	Cases/years follow-up	Incidence per 100 py*	IRR**
Year			
2015	10/309	3.23	1.03 (0.47–2.02)
2014	70/1,867	3.75	1.20 (0.84–1.70)
2013	126/3,288	3.83	1.22 (0.90–1.67)
2012	140/4,238	3.30	1.05 (0.78–1.43)
2011	67/2,137	3.14	1.0
Sex			
Male	386/8,411	4.59	8.68 (5.35–15.06)
Transgender	10/213	4.69	8.88 (3.64–20.54)
Female	17/3,217	0.53	1.0
Age (years)			
≤ 9	0/51	–	
10–19	31/956	3.24	1.82 (0.79–4.91)
20–29	244/6,267	3.89	2.19 (1.05–5.51)
30–39	99/2,951	3.35	1.89 (0.88–4.82)
40–49	31/1,120	2.77	1.56 (0.67–4.19)
≥ 50	7/394	1.78	1
HIV basal test			
Positive	113/923	12.24	4.42 (3.53–5.51)
Negative	298/10,767	2.77	1.0
HBV basal test			
Positive	9/78	11.54	3.21 (1.46–6.17)
Negative	343/9,554	3.59	1.0
HCV basal test			
Positive	2/114	1.75	0.5 (0.1–1.82)
Negative	386/11,009	3.51	1.0

*py: persons years of follow-up; bold: statistically significant. **IRR: Incidence rate ratio

Discussion

The prevalence of syphilis in the groups that attended the CEC is high (8.2% among PPr to 37.0% among PLWH) compared to other vulnerable populations such female sex workers (14.2%),¹⁰ people in prison (2.0%),¹¹ and MSM (9.5%, 14.8%, and 30% in 2014, 2016, and 2017, respectively).¹² Likewise, the prevalence detected at the CEC is higher than groups such as pregnant women (0.26%), blood donors (1.4%), and the general population (3.1%).¹³⁻¹⁵

The highest seroprevalence of syphilis and active syphilis was among men and transgender people. It is possible that a high proportion of men attending the CEC are MSM, a group in which the HIV epidemic in Mexico is concentrated.¹⁵ In the case of men, the high frequency and incidence of active syphilis could be related to sexual practices, unprotected anal sex, a large number of sexual partners, and/or casual relationships. The transgender population had different vulnerabilities, namely being sex workers, unfavorable economic conditions, and/or stigma and discrimination.¹⁶

The highest frequency of active syphilis, as well as the highest incidence of syphilis, was found in 20-39-year-old individuals. These data are consistent with the worldwide trend, which shows that the largest number of new STI cases occur in the young population.³ Thus, it is necessary to focus syphilis prevention and diagnosis programs in these groups. The presence of other STIs is a risk factor for acquisition and transmission of *T. pallidum*, as shown with HIV and HBV but not HCV (whose main route of transmission is parenteral rather than sexual). People living with HIV have a suppressed immune system, and this suppression increases their susceptibility to other STIs such as syphilis.¹⁷ People with HIV-syphilis coinfection have a higher risk of neurological complications, which may be more frequent, progress faster, and present atypical signs. These individuals may also have treatment failure or present serofast (individuals without syphilis but higher antibodies titers).¹⁸ On the other hand, syphilitic lesions increase the risk of acquiring and transmitting HIV; persons with syphilis have a 4-fold greater risk of acquiring HIV.¹⁹ This value is similar to current study among people attending the CEC.

The higher prevalence and incidence of syphilis among PLWH may be by the individual risk perception and their social networks.²⁰ From the onset of antiretroviral treatment, the number of deaths decreased and life expectancy improved. Consequently, some PLWH continued with risky sexual behaviors, such as sex without a condom, anal sex, occasional sexual partners, concurrent sexual partners, and/or alcohol and illegal drug use.²¹

A high percentage of people had persistent infection, that is, they maintained similar levels of antibodies during the study period. Failures in syphilis treatment have been documented from 3% among people without HIV to 17% among PLWH.²² Furthermore, among PLWH, the antibody titers take longer to decrease (serofast patients) up to 25% of population.²³ The CEC prescribes the treatment for syphilis;

however, it is unknown if people receive the treatment, as most of the participants are sent to their family medical clinic for follow-up. Only the PLWH without social security are followed in the CEC.

There are few studies on the incidence of syphilis in Mexico. Among FSW, it was 4.31 cases, and among their stable sexual partners, it was 3.64 cases per 100 py.²⁴ In current study, the VCT group had a similar incidence, 3.4 cases. However, the highest incidence was among the PLWH, with 16 cases per 100 py. The syphilis incidence was higher than detected in other countries, including Italy (1.94), Singapore (6.21), and Australia (5.47 per 100 py), all among PLWH.^{23,25,26} It was similar to the very high incidence of syphilis reported in Argentina (14.9 cases per 100 py).²⁷ In addition to the high incidence, there was a high percentage of syphilis re-infection. In other countries, this re-infection has been reported and appears to be a risk factor for re-infection, being asymptomatic, living with HIV, being a MSM, and failure in case follow-up.²⁸

In relation to limitations of current study, did not include sociodemographic, sexual behavior, and clinical information about participants; it was difficult to know if all patients received the adequate treatment and follow up because there is no epidemiological surveillance information about others clinics; the prevalence of active infection without clinical information may be overestimating the prevalence especially among PLWH that presents serofast; and there was a potential selection bias in the dynamic cohort, due to the small number of cases with follow up.

Conclusion

Different vulnerable groups showed high prevalence of active syphilis, high incidence, and re-infections. The results confirm that it is necessary to allocate more resources for the detection, treatment and monitoring of syphilis cases, as established by WHO, which prioritizes three STIs: human papillomavirus, *Neisseria gonorrhoeae*, and *T. pallidum*, the latter with objectives of eliminating congenital syphilis and controlling syphilis in specific populations.²⁹ The strategy should be focused specifically among vulnerable groups, such as FSW, IDUs, MSM, and transgender women.³⁰

Abbreviations

People seeking HIV-1 voluntary counseling and testing: VCT

People in prison: PPr

People living with HIV: PLWH

World Health Organization: WHO

Female sex worker: FSW

Men who have sex with men: MSM

Intravenous drug users: IDUs

Clinica Especializada Condesa: CEC

Sexually transmitted infections: STI

Hepatitis B Virus: HBV

Hepatitis C Virus: HCV

Chemiluminescent microparticle immunoassay: CMIA

Venereal disease research laboratory: VDRL

chi-square: χ^2

person years: py

Incidence rate ratios: IRR

Confidence intervals: CI

Declarations

- **Ethics approval and consent to participate.** The participants signed an informed consent letter. The study was approved by the ethics committee of the National Institute of Public Health
- **Consent for publication.** Not applicable
- **Availability of data and materials.** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- **Competing interests.** The authors declare that they have no competing interests
- **Funding.** Not funding
- **Authors' contributions.** Construct the dataset and statistical analyses. VRG. Laboratory analyses about syphilis, VHB, VHC and HIV. GCS Revised the dataset about laboratory results. AGR coordinate the laboratory analyses and the basic information about the assistant to "Clinica Especializada Condesa". AHO. Write the manuscript and analyzed the information. MOP Revised the paper. MASA Write the manuscript, statistical analyses and analyzed the information.
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- **Authors' information.** Not applicable

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Figures

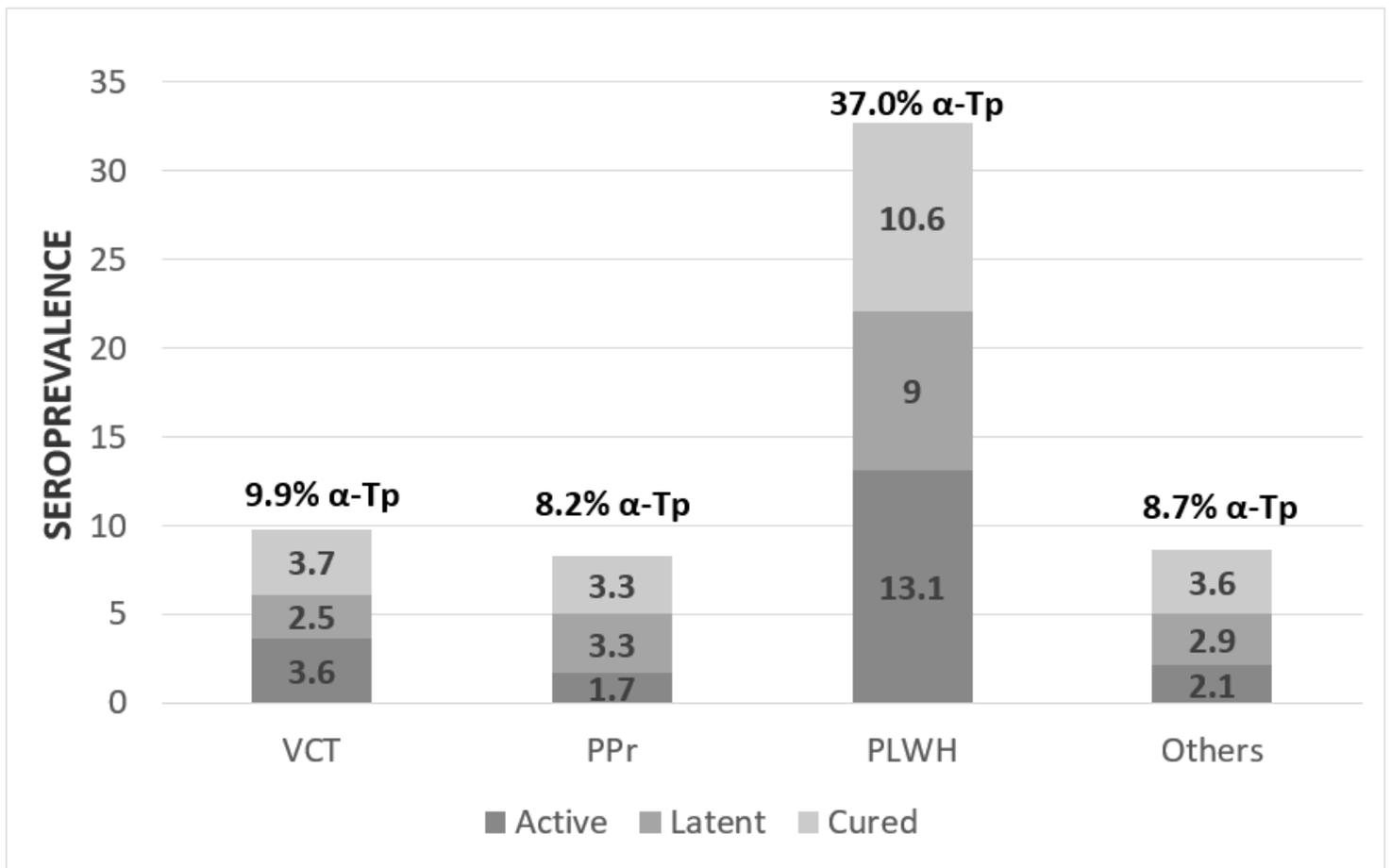


Figure 1

Seroprevalence of *T. pallidum* and active syphilis in populations attending a specialized HIV clinic in Mexico. α -Tp: antibodies against *T. pallidum*. Antibodies titers was not performed in 0.2% of people seeking HIV-1 voluntary counseling and testing (VCT), in 0.04% of people in prison (PPr), in 4.5% of people living with HIV (PLWH) and in 0.1% others.

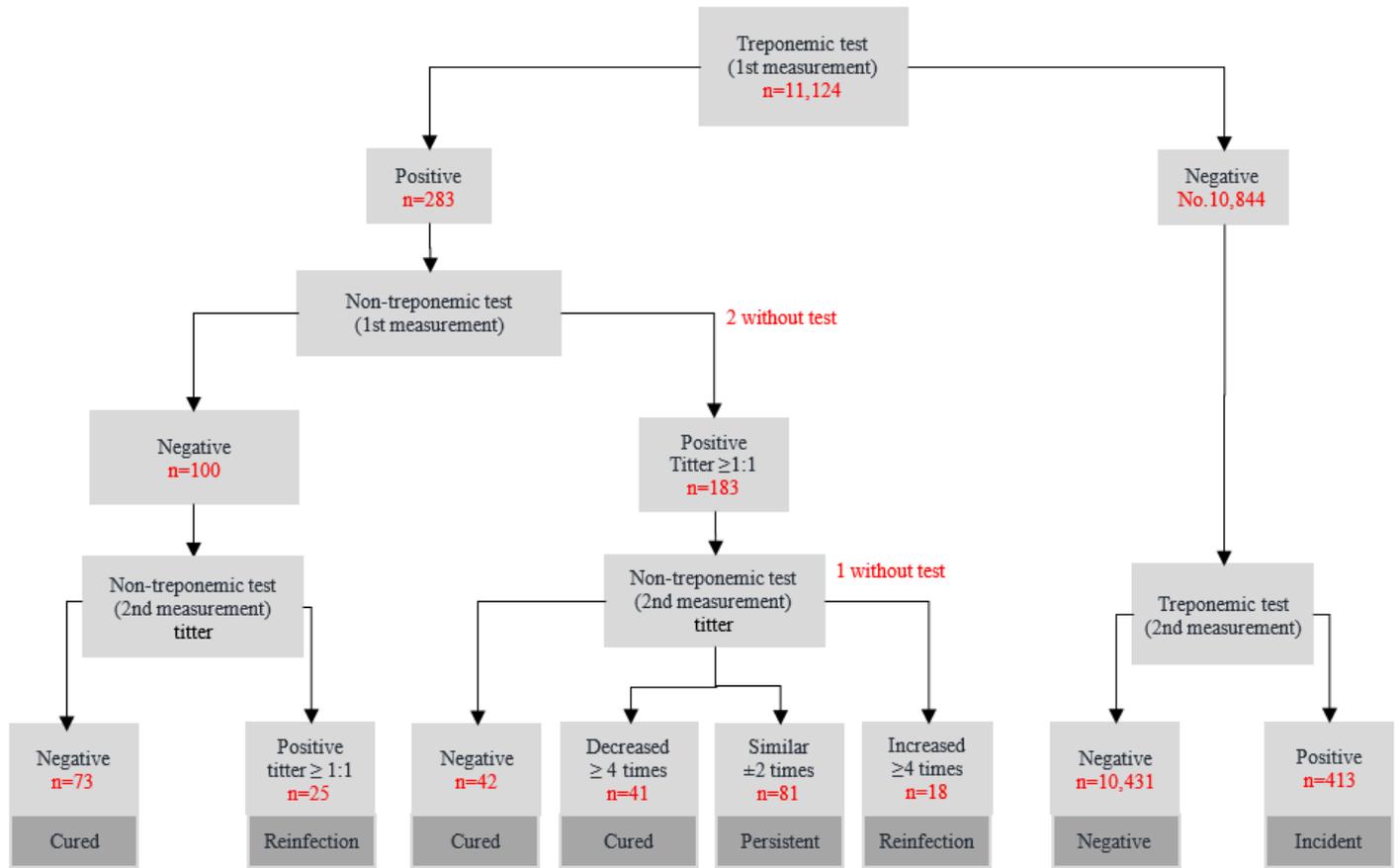


Figure 2

Retrospective dynamic cohort in populations attending a specialized HIV clinic in Mexico.

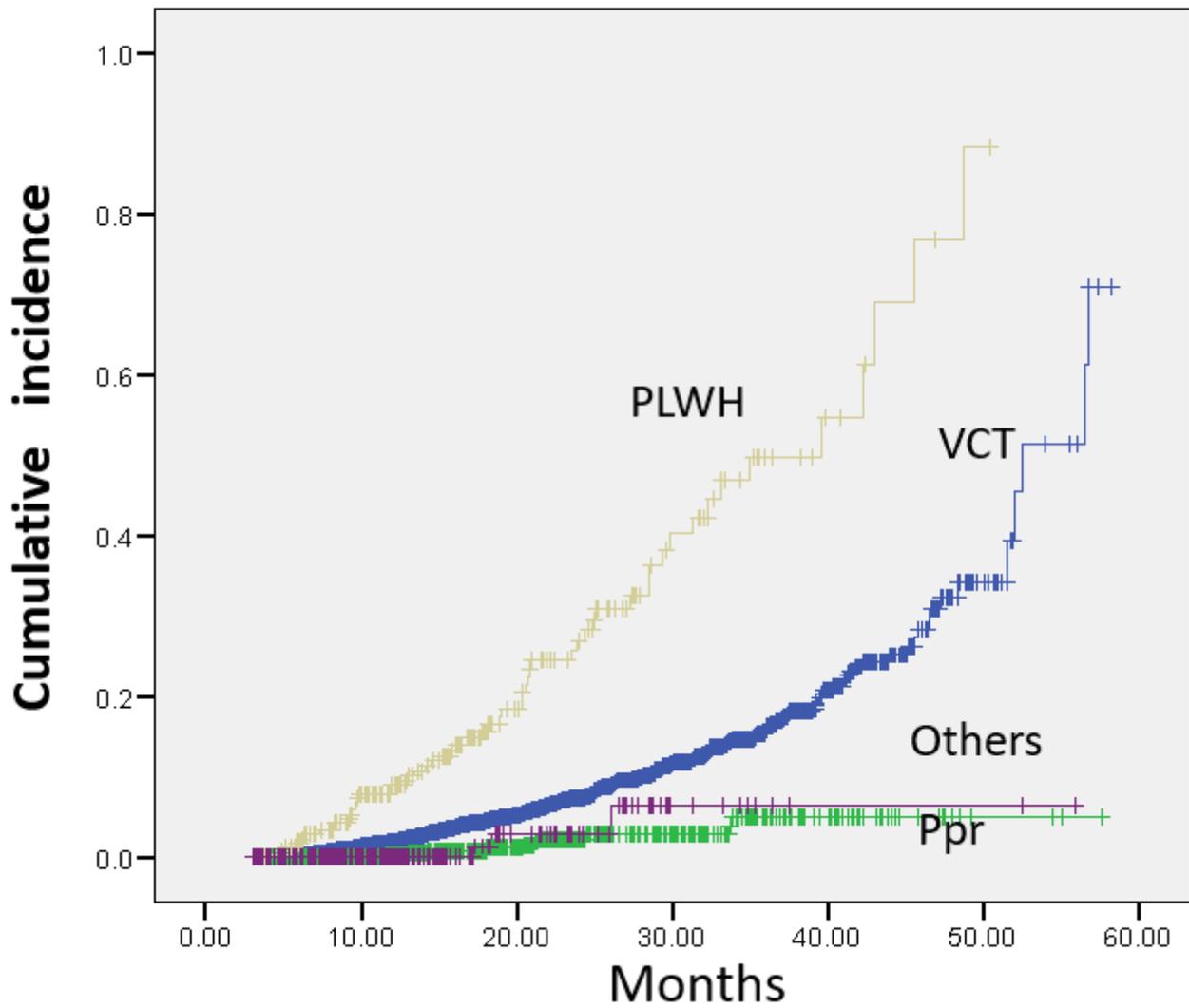


Figure 3

Cumulative incidence of *T. pallidum* in populations attending a specialized HIV clinic in Mexico. VCT: People seeking HIV-1 voluntary counseling and testing; PPr: people in prison; PLWH: people living with HIV; Others: patients from others clinics.