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Syphilis diagnosis and serological response to Benzathine Penicillin G among patients attending HIV clinics in N'Djaména, Chad

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ABSTRACT

Background: Syphilis is endemic in the Sub-Saharan zone and disproportionately affects at-risk populations such as men who have sex with men, sex workers and HIV infected individuals. In this study, we measure the impact of syphilis among people living with HIV in the Republic of Chad, where no data are currently available.
Method: Outpatients attending 2 HIV clinics in N'Djamena, Republic of Chad, were tested for syphilis. Subjects who tested positive for both non-treponemal (VDRL) and treponemal (TPHA) received a single dose of Benzathine Penicillin G, 2.4 MU. An additional VDRL test was performed 6 months after treatment to ensure appropriate serological response.
Results: Of 207 patients included, 29 (14%) tested positive for VDRL at the first visit, with moderate/low antibody titers (ranging from 1/2 to 1/8); 24 (82.6%) of these had treponemal immunization confirmed by TPHA test. Six months after Benzathine Penicillin treatment, 22/24 of the patients (91.6%) tested negative for VDRL, and 2 showed a 4-fold titer decline.
Conclusion: This first study in the Republic of Chad suggests that syphilis infection is frequent among people living with HIV in this country. Systematic screening of syphilis should be considered in this population.
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Background

According to the World Health Organization (WHO) and the European Centre for Disease Prevention and Control, there are approximately 6 million new cases of syphilis worldwide per year (WHO, 2018; ECDC, 2019). In Western Europe, China and the USA, a large increase in syphilis incidence has been observed over the last 10 years among key populations such as men who have sex with men (MSM) and female sex workers (FSW) (Ghanem et al., 2020; Harmon and Robertson, 2019; McNamara and Yingling, 2020). The number of cases has particularly increased in Europe, with an average increase of 70% between 2010 and 2017 (Spiteri et al., 2019). In the US, the numbers of cases reported to the Centers for Disease Control and Prevention increased by 81% from 2014 to 2018 (Ghanem et al., 2020). In low- and middle-income countries, syphilis has remained endemic. More than 12 million people are currently infected with syphilis worldwide, with the majority of these infections occurring in sub-Saharan Africa and Asia (Kojima and Klausner, 2018). Sub-Saharan Africa accounts for more than 60% of the global burden of maternal syphilis (Wijesooriya et al., 2016). According to the WHO, in 2014, 3.4% of the participants in prenatal care tested positive for syphilis in the Republic of Chad (WHO, 2014). The highest prevalence of syphilis among the FSW population was found in Africa (median prevalence of 13.2%) (WHO, 2018). Among the MSM population, the median global reported syphilis seroprevalence is around 6.0% (range 0%–36.7%), with the highest values reported in the South American zone 12.4% (range 0.8%–61.5%). In Africa, the median syphilis seroprevalence among MSM has been estimated at 2.3% (0.8%–2.9%), but less than

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10% of the countries from this zone reported syphilis prevalence data (WHO, 2018).

Syphilis is also linked to an increased risk of HIV transmission and vice versa (Cohen, 2006; Kalichman et al., 2011; Wu et al., 2020). There is a high rate of *Treponema pallidum* co-infection among people living with HIV infection because the 2 pathogens share common transmission routes and because syphilis infection, through local lesions, increases the risk of HIV acquisition and transmission (White, 2017). In addition to the increase in risky sexual behaviors among people living with HIV, the effects of HIV infection on immunity may also increase susceptibility to other sexually transmitted pathogens or increase progression of the associated disease (Abdul Wahab et al., 2013; Lynn and Lightman, 2004). In HIV patients, syphilis appears to progress more rapidly through its clinical stages, often having an atypical clinical presentation (Nnoruka and Ezeoke, 2005; Singh and Romanowski, 1999). Moreover, HIV infection seems to alter the natural history of syphilis. In the case of HIV co-infection, the progression of the disease to the neurological form is more frequent, faster and patients generally respond less well to conventional syphilis treatment (Flood et al., 1998; Wang et al., 2018).

In the Republic of Chad, HIV prevalence is estimated at 1.3% in the 15–49 age group according to the Joint United Nations Programme on HIV/AIDS (UNAIDS, 2018), but syphilis screening is not routinely performed in people living with HIV infection. To date, there are no data available on syphilis prevalence in HIV infected peoples living in the Republic of Chad. The objective of this study is to evaluate syphilis prevalence among people living with HIV in the Republic of Chad and to assess serological response to treatment.

Methods

Study design, participants, period and location of the study

This study is a cross-sectional observational study of people living with HIV/AIDS and was conducted in the city of N'Djamena, the Republic of Chad, over a period of 12 months (1 December 2017 to 1 December 2018). Participants were people living with HIV attending outpatient clinics in the General Hospital (HGRN - l'Hôpital Général de Référence Nationale) and the APMS Center (Psychological Support for AIDS Patients) having provided written informed consent. Exclusion criteria were persons over 65 and under 18 years of age and pregnant women. The study included 207 adult patients from 18 to 65 years old infected with HIV (137 females [66.2%] and 70 males [33.8%]). Patients' characteristics are presented in Table 1. Medical, socio-demographic and personal data were collected and kept in compliance with medical confidentiality. Patients who have signed a written informed consent are free to accept or refuse to answer the questionnaires. The study was approved by the Bioethics Committee of the Republic of Chad (407/PR/PM/MSRI/SG/CNBT/2017) performed in accordance with good clinical practice guidelines.

Laboratory methods and follow up

Four ml of venous blood was collected, centrifuged at 800 rpm for 10 min, aliquoted in cryotubes for immediate use, or stored at −80 °C for further analysis. The syphilis testing algorithm was based on screening using a nontreponemal assay followed by a confirmatory treponemal assay on reactive samples (traditional syphilis testing algorithm). All subjects included in the study were screened for syphilis using a non-treponemal VDRL test administered according to the manufacturer's recommendations (IMMUTREP® CARBON ANTIGEN, Omega Diagnostic LTD, United Kingdom). Reactive VDRL were followed by a *T. pallidum* Hemagglutinations Assay (TPHA) test administered according to the manufacturer's recommendations (IMMUTREP® TPHA, Omega Diagnostic LTD, United Kingdom) to confirm immunization against the pathogen. The VDRL test was performed on the same day as the sample was taken (first visit). TPHA was performed on sera demonstrating reactivity with VDRL (Figure 1).

Patients testing positive for both VDRL and TPHA received a single dose of Benzathine Penicillin G (BPG) 2.4 MU provided intramuscularly according to international recommendations (WHO, 2016; CDC, 2015). Therapeutic response was assessed 6

Table 1
Clinical and general characteristics of HIV-positive patients enrolled in the study.

	Total[a]	No syphillis[b]	Syphillis[b]	p-Value
Gender				
Female	137 (66.5%)	118 (86.1%)	19 (13.9%)	0.90
Male	69 (33.5%)	59 (85.5%)	10 (14.5%)	
Median age [IQR], years	33 [27; 40]	32 [26; 40]	34 [29; 40]	0.42
Religion				
Christian	105 (50.7%)	85 (81.0%)	20 (19.0%)	0.10
Muslim	100 (48.3%)	91 (91.0%)	9 (9.0%)	
Other	2 (1.0%)	2 (100.0%)	0	
Median number of children per women[c] [IQR]	1 [1;3]	1 [1;3]	2 [0;3]	0.78
Use of condoms				
Yes	13 (6.3%)	11 (84.6%)	2 (15.4%)	0.04
No	140 (67.6%)	115 (82.1%)	25 (17.9%)	0.82[d]
Not reported	54 (26.1%)	52 (96.3%)	2 (3.7%)	
Multiple and occasional partners				
Yes	55 (26.6%)	45 (81.8%)	10 (18.2%)	0.007
No	105 (50.7%)	86 (81.9%)	19 (18.1%)	0.98[d]
Not reported	47 (22.7%)	47 (100.0%)	0	
MSM	3 (4.3%)	2	1	
ART				
Yes	122 (58.9%)	104 (85.2%)	18 (14.7%)	0.01
No	41 (19.8%)	31 (75.6%)	10 (24.4%)	0.15[d]
Unknown	44 (21.3%)	43 (97.7%)	1 (2.3%)	

[a] Column-percentage.
[b] Row-percentage.
[c] For the 137 women in the sample.
[d] P-Value for the tests without the unknown category.

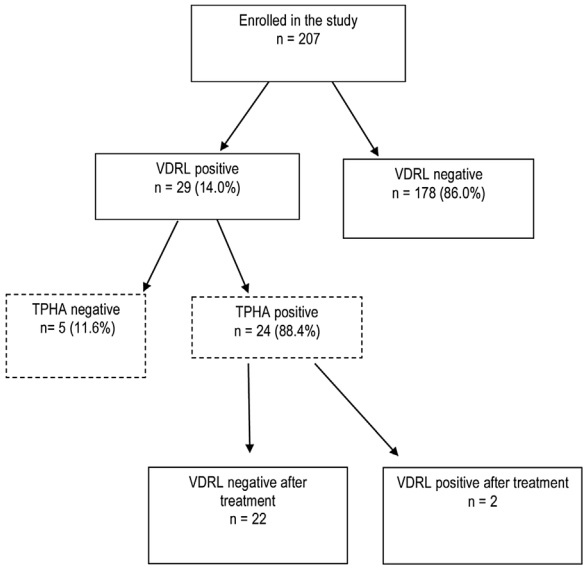

Figure 1. Overview of the study design, showing the enrollment and status of the patients.

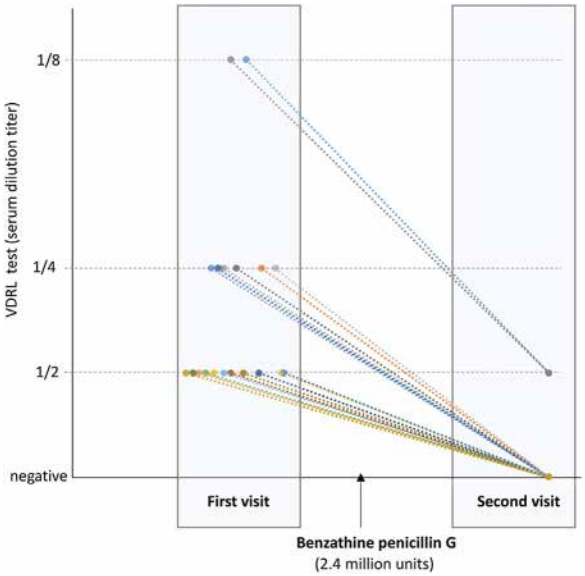

Figure 2. Evaluation of the efficacy of a single dose of penicillin G benzathine 2.4 million units 6 months after treatment by VDRL test.

months later (second visit) with an additional VDRL test. The satisfactory serological response in favor of a cure was defined as a reduction in VDRL titer of at least 4-fold (Ghanem et al., 2020). Patients with no or insufficient decrease of the VDRL titer received 3 additional doses of BPG 2.4 MU, 1 week apart. Further monitoring was conducted in accordance with standard patient management practices.

Data and statistical analysis

The data collected has been the subject of computerized processing in strict compliance with confidentiality and has been kept after anonymization. Characteristics of people were compared by syphilis status using the Chi-square test for categorical variables and Wilcoxon Mann–Whitney test for continuous variables. For variables with a large number of missing data, the comparison was made twice: with and without including missing as a specific category. We used Stata (version 14.0) for statistical analyses. A P value <0.05 was considered statistically significant. Preliminary study results have been communicated to patients and their treating physicians.

Results

Among the 207 patients enrolled in this study, 29 tested positive for the VDRL test, indicating a syphilis seroprevalence (95% CI) of 14% (7.2%–15.9%) (Table 1). VDRL serological titers were low or moderate, ranging from 1/2 to 1/8 (Figure 2). The presence of anti-treponemal antibodies was confirmed using TPHA. Among 29 VDRL-reactive patients, 24 (82.6%) tested positive by TPHA. No significant differences were found among gender, age or religion concerning serologic evidence of untreated syphilis. The prevalence of syphilis was significantly higher in patients who reported not being on antiretroviral treatment (24.5%), having multiple casual partners (18.2%), and not using condoms (17.9%) (Table 1). However, differences were observed only when the patients with unavailable data were included in the statistical analyses. All patients who tested reactive for VDRL with *T. pallidum* immunization confirmed by TPHA received a single dose of 2.4 MU PBG and were followed up 6 months later to ensure appropriate serological response. All patients with serological evidence of syphilis return to clinics 6 months after PBG administration. VDRL test became negative in 22 patients (91.7%) and showed a 4-fold decline in 2 cases, indicating that the treatment was effective (Figure 2).

Discussion

According to the WHO, the highest prevalences of syphilis and HIV are found in Africa and Asia, but epidemiological data are sorely lacking, particularly in sub-Saharan Africa. A 2011 systematic review of the literature from several regions of the world showed that the median prevalence of syphilis in HIV-infected patients was 9.5% (Kalichman et al., 2011). In this study, we found an overall syphilis seroprevalence of 14% among people in 2 HIV clinics from N'Djamena. Comparison is extremely difficult because limited studies on syphilis have been conducted in Africa, especially among specific populations. In Ethiopia, the mean prevalence of syphilis was found to be around 8.5% (9.8% and 7.3%) among people living with HIV (Eticha et al., 2013; Shimelis et al., 2015) and 11.4% in Cameroun (Zoufaly et al., 2012). Older studies conducted in Nigeria estimated the prevalence of syphilis among HIV-infected individuals to be between 2.1% and 14% (overall 6.5%) (Forbi et al., 2009; Uneke et al., 2006). The highest syphilis seroprevalence rate was reported in Dakar, Senegal (23.8%), but this was among the subpopulation of FSW who are more intensely exposed to sexually transmitted diseases (Laurent et al., 2003). In our study, the seroprevalence of syphilis was not significantly affected by gender, age or religious orientation. Serologic evidence of untreated syphilis was higher in patients who reported having multiple occasional sexual partners, not using condoms, or not receiving antiretroviral therapy. However, interpretation should be made with caution since missing data were more frequent when subjects did not return to a clinic for BPG 2.4 MU administration, and statistical significance is lost when patients who did not complete the standardized questionnaire are removed from the analysis.

In this study, we used the traditional syphilis testing algorithm with an initial screening with nontreponemal test, followed by a confirmatory treponemal test. The reverse testing algorithm, which first uses a treponemal test, has advantages (Dunseth

et al., 2017) and has been adopted in many guidelines (CDC, 2015; HAS, 2017; Kingston et al., 2016; WHO, 2016). However, in low-income countries, the traditional testing algorithm can be adopted because it requires less automation and begins with a rapid and inexpensive test.

BPG 2.4 MU remains the treatment of choice for all stages of syphilis with no resistance currently described. In our study, the serologic response was achieved 6 months after therapy and showed a 4-fold decline. Guidelines currently recommend that early syphilis—primary, secondary, and early latent syphilis—should be treated with a single dose of BPG 2.4 MU intramuscularly, regardless of the patient's HIV status (CDC, 2015; Clement et al., 2014; Kingston et al., 2016). However, it has been suggested that 3 doses might be more appropriate for people living with HIV (Workowski and Berman, 2010). Syphilis infection may be more atypical and severe in people living with HIV. In particular, early neurosyphilis, associated with a risk of long-term impairment of neurocognitive functions, is more frequent if left untreated (van Brussel and Landman, 2015; Clement et al., 2014). *T. pallidum* can be isolated in the cerebrospinal fluid of up to 40% of HIV infected people with early syphilis (Dunlop et al., 1979; Marra et al., 2004).

In conclusion, this first study in the Republic of Chad suggests that serologic evidence of untreated syphilis is frequent among people living with HIV. HIV and syphilis are clearly a bad combination; however, screening for syphilis is not part of the routine check-ups in the management of people living with HIV in Sub-Saharan Africa. People newly diagnosed with HIV and patients on antiretroviral therapy are not usually tested for syphilis in the absence of symptoms consistent with the disease. Coupled with increased public awareness of both syphilis and HIV, we emphasize the need for routine syphilis screening of HIV-infected patients in conjunction with improved diagnosis and treatment of syphilis.

Ethical approval

The study was approved by the Bioethics Committee of the Republic of Chad (407/PR/PM/MSRI/SG/CNBT/2017) and performed in accordance with good clinical practice guidelines.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abdul Wahab A, Rahman MM, Mohammad M, Hussin S. Case series of syphilis and HIV co-infections. Pak J Med Sci 2013;29:856–8, doi:http://dx.doi.org/10.12669/pjms.293.3346.

CDC. Sexually transmitted diseases treatment guidelines 2015. 2015. https://www.cdc.gov/std/tg2015/syphilis.htm.

Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA 2014;312:1905–17, doi:http://dx.doi.org/10.1001/jama.2014.13259.

Cohen MS. When people with HIV get syphilis: triple jeopardy. Sex Transm Dis 2006;33:.

Dunlop EM, Al-Egaily SS, Houang ET. Penicillin levels in blood and CSF achieved by treatment of syphilis. JAMA 1979;241:2538–40.

Dunseth CD, Ford BA, Krasowski MD. Traditional versus reverse syphilis algorithms: a comparison at a large academic medical center. Pract Lab Med 2017;8:52–9, doi:http://dx.doi.org/10.1016/j.plabm.2017.04.007.

ECDC. Syphilis and congenital syphilis in Europe: a review of epidemiological trends (2007–2018) and options for response. 2019. https://op.europa.eu/en/publication-detail/-/publication/0899df4e-3d93-11ea-ba6e-01aa75ed71a1/language-en.

Eticha BT, Sisay Z, Alemayehu A, Shimelis T. Seroprevalence of syphilis among HIV-infected individuals in Addis Ababa, Ethiopia: a hospital-based cross-sectional study. BMJ Open 2013;3:e002566, doi:http://dx.doi.org/10.1136/bmjopen-2013-002566.

Flood JM, Weinstock HS, Guroy ME, Bayne L, Simon RP, Bolan G. Neurosyphilis during the AIDS epidemic, San Francisco, 1985-1992. J Infect Dis 1998;177:931–40, doi:http://dx.doi.org/10.1086/515245.

Forbi JC, Pennap G, Obinyelaku A, Iperepolu O, Agwale S. Seroprevalence of syphilis among a cohort of HIV-infected subjects in North Central Nigeria. J Health Popul Nutr 2009;27:704–6, doi:http://dx.doi.org/10.3329/jhpn.v27i5.3782.

Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. N Engl J Med 2020;382:845–54, doi:http://dx.doi.org/10.1056/NEJMra1901593.

Harmon ED, Robertson EW. Syphilis: a growing concern. Nurse Pract 2019;44:21–8, doi:http://dx.doi.org/10.1097/01.NPR.0000558159.61349.cb.

HAS. Modification de la Nomenclature des actes de biologie médicale pour l'acte de suivi thérapeutique des patients infectés par *Treponema pallidum*. 2017. https://www.has-sante.fr/upload/docs/application/pdf/2017-03/dir3/argumentaire_-syphilis.pdf.

Kalichman SC, Pellowski J, Turner C. Prevalence of sexually transmitted co-infections in people living with HIV/AIDS: systematic review with implications for using HIV treatments for prevention. Sex Transm Infect 2011;87:183, doi:http://dx.doi.org/10.1136/sti.2010.047514.

Kingston M, French P, Higgins S, McQuillan O, Sukthankar A, Stott C, et al. UK national guidelines on the management of syphilis 2015. Int J STD AIDS 2016;27:421–46, doi:http://dx.doi.org/10.1177/0956462415624059.

Kojima N, Klausner JD. An update on the global epidemiology of syphilis. Curr Epidemiol Rep 2018;5:24–38, doi:http://dx.doi.org/10.1007/s40471-018-0138-z.

Laurent C, Seck K, Coumba N, Kane T, Samb N, Wade A, et al. Prevalence of HIV and other sexually transmitted infections, and risk behaviours in unregistered sex workers in Dakar, Senegal. AIDS 2003;17:1811–6, doi:http://dx.doi.org/10.1097/00002030-200308150-00010.

Lynn WA, Lightman S. Syphilis and HIV: a dangerous combination. Lancet Infect Dis 2004;4:456–66, doi:http://dx.doi.org/10.1016/S1473-3099(04)01061-8.

Marra CM, Maxwell CL, Smith SL, Lukehart SA, Rompalo AM, Eaton M, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis 2004;189:369–76, doi:http://dx.doi.org/10.1086/381227.

McNamara M, Yingling C. The reemergence of syphilis: clinical pearls for consideration. Nurs Clin North Am 2020;55:361–77, doi:http://dx.doi.org/10.1016/j.cnur.2020.06.009.

Nnoruka EN, Ezeoke ACJ. Evaluation of syphilis in patients with HIV infection in Nigeria. Trop Med Int Health 2005;10:58–64, doi:http://dx.doi.org/10.1111/j.1365-3156.2004.01344.x.

Shimelis T, Lemma K, Ambachew H, Tadesse E. Syphilis among people with HIV infection in southern Ethiopia: sero-prevalence and risk factors. BMC Infect Dis 2015;15:189, doi:http://dx.doi.org/10.1186/s12879-015-0919-7.

Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev 1999;12:187–209.

Spiteri G, Unemo M, Mårdh O, Amato-Gauci AJ. The resurgence of syphilis in high-income countries in the 2000s: a focus on Europe. Epidemiol Infect 2019;147:e143, doi:http://dx.doi.org/10.1017/S0950268819000281.

UNAIDS. CHAD UNAIDS. 2018. https://www.unaids.org/en/regionscountries/countries/chadUNAIDS.

Uneke C, Ogbu O, Alo M, Thaddeus A. Syphilis serology in HIV-positive and HIV-negative Nigerians: the public health significance. Online J Health Allied Sci 2006;5:.

van Brussel ASA, Landman GWD. Treatment of late-stage syphilis. JAMA 2015;313:968–9, doi:http://dx.doi.org/10.1001/jama.2015.0669.

Wang Z, Liu L, Shen Y-Z, Zhang R-F, Qi T-K, Tang Y, et al. The clinical and laboratory features of neurosyphilis in HIV-infected patients: a retrospective study in 92 patients. Medicine 2018;97:.

White Jr. AC. Treatment of early syphilis in HIV: what do we really know?. Clin Infect Dis 2017;64:765–6, doi:http://dx.doi.org/10.1093/cid/ciw866.

WHO. Syphilis in pregnancy: data by country. 2014. https://apps.who.int/gho/data/node.main.A1358STI?lang=en.

WHO. WHO guidelines for the treatment of *Treponema pallidum* (syphilis). 2016.

WHO. Report on global sexually transmitted infection surveillance. 2018. https://apps.who.int/iris/bitstream/handle/10665/277258/9789241565691-eng.pdf?ua=1.

Wijesooriya NS, Rochat RW, Kamb ML, Turlapati P, Temmerman M, Broutet N, et al. Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. Lancet Glob Health 2016;4:e525–33, doi:http://dx.doi.org/10.1016/S2214-109X(16)30135-8.

Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59:1–110 Centers for Disease Control and Prevention (CDC).

Wu MY, Gong HZ, Hu KR, Zheng H, Wan X, Li J. Effect of syphilis infection on HIV acquisition: a systematic review and meta-analysis. Sex Transm Infect 2020;1–9, doi:http://dx.doi.org/10.1136/sextrans-2020-054706.

Zoufaly A, Onyoh EF, Tih PM, Awasom CN, Feldt T. High prevalence of hepatitis B and syphilis co-infections among HIV patients initiating antiretroviral therapy in the north-west region of Cameroon. Int J STD AIDS 2012;23:435–8, doi:http://dx.doi.org/10.1258/ijsa.2011.011279.