Prevalence Of Syphilis, Neurosyphilis And Associated Factors In a Cross-Sectional Analysis Of HIV Infected Patients Attending Bugando Medical Centre Mwanza Tanzania

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Abstract

Background: HIV-syphilis co-infection is a combination that enhances rapid progression of early syphilis or late latent syphilis to neurosyphilis and can cause catastrophic neurological complications. In studies in Mwanza, syphilis affects ~8% of healthy outpatients, and older studies have suggested that up to 23.5% of HIV-syphilis co-infected patients also have neurosyphilis. The study aimed at determining the prevalence of syphilis, neurosyphilis and associated factors among HIV infected patients attending Bugando Medical Center.

Methods: This was a cross sectional study in which HIV infected patients who were hospitalized or attending the outpatient Care and Treatment Clinic (CTC) were interviewed using structured questionnaire and screened for syphilis using serum *Treponema Pallidum* hemagglutination assay (TPHA). We included all HIV-infected persons aged 18 years and above who consented. Blood was also taken for CD4+ T cells and viral load. Those who were found to have syphilis underwent neurological examination for any neurologic deficit and offered lumbar puncture.

Results: The prevalence of syphilis in HIV infected patients was found to be 9.6%. The majority of these were female (72.5%) and median age was 42 years [interquartile range, 32-50]. Most patients were on ART (99.4%).The majority of participants with syphilis (89.2%) reported not knowing that they had syphilis, and had not previously been treated. One hundred forty one participants with syphilis had neurological examinations performed, 4 of whom had abnormal findings that necessitated that they undergo lumbar puncture. One of these had confirmed neurosyphilis.

Conclusion: The high prevalence of syphilis in HIV infected patients indicates that there is a need to increase efforts in targeting this population to reduce sexually transmitted infections. Screening for syphilis should be done for all HIV patients given the high prevalence of the infection and the risk that aggressive forms of neurosyphilis can occur despite recovery of CD4+Tcell counts in untreated syphilis.

Background

Syphilis is still a global health problem causing substantially high morbidity despite availability of potentially effective preventive measures and relatively effective, cheap treatment options. It is estimated that about 10 million infected each year worldwide with a global prevalence of about 0.5%.In Sub Saharan the burden has dropped from 6% to around 1% in the past 50 years (1, 2).In Tanzania the prevalence of syphilis ranges from 2.5% to 8% in available studies (3, 4).In Sub Saharan Africa the most affected are heterosexual individuals (5).

HIV-*Treponema pallidum* co-infection represents an important problem with serious clinical implications. The genital ulcers in syphilis infection facilitate acquisition of HIV. The genital ulcers are usually attended by inflammatory cells and expression of HIV co-receptors that enable the virus to infect the cell and establish initial HIV infection in the genital mucosa(6). Additionally the presence of syphilis among HIV patients increases the HIV viral load (7). HIV-positive *Treponema pallidum* co-positive individuals tend to

develop neurosyphilis more frequently as compared to HIV negative syphilis positive individuals(6). HIV infection has also been associated with syphilis treatment failure when a normal dose of Benzathine penicillin positive is used (9).

Of note the prevalence of neurosyphilis in untreated early syphilis among HIV positive patients was reported be as high as 23.5% in a previous study done in Spain (13). Likewise 24.6% of HIV positive patients were reported to have neurosyphilis in a study done in Canada. In addition it was also indicated that development of neurosyphilis was significantly associated CD4 less than 500 cells/µland uncontrolled viremia(14). Despite the magnitude of the problem and its associated factors among HIV positive patients in Tanzania is scarce. Hence the study was designed to determine the prevalence of syphilis neurosyphilis and associated factors among HIV positive patients at Bugando Medical Centre in order to improve screening, diagnosis and treatment.

Methods

The study was conducted at Bugando Medical Centre's medical department. Bugando Medical Centre is one of four zonal hospitals in Tanzania; it serves a catchment population of about 15 million people with a bed capacity of about 900. HIV care and treatment services are part and parcel of outpatients' activities. Bugando HIV clinic was started 2004 operating on weekdays as a zonal referral center. The centre cares for all patients diagnosed from within the hospital and those sent from catchment facilities. In addition to opportunistic infections, all newly diagnosed patients with HIV are routinely screened for Hepatitis B &C and Syphilis. In the first three months of 2017 about 448 newly diagnosed HIV patients were screened for syphilis and 36 of them tested positive for VDRL. Currently screening for neurosyphilis is not done in our setting where more than 15,000 HIV positive patients are served by the center and more than 5000 patients are active on ART.

This was an observational cross-sectional hospital based study. The study involved all HIV positive adult patients who were admitted to the Bugando Medical Centre, medical wards and those seen at CTC.All HIV positive patients 18 years and above attending Bugando Medical Centre HIV clinic or admitted in the medical wards and who consented for the study and tested positive for *T. pallidum* in the three months prior to study initiation or during the study period were included. We excluded all HIV negative patients.

Convenience sampling method was used to all HIV-positive patients admitted to the hospital or being seen at the CTC.A minimum sample size of 138 patients was calculated by Kish Leslie formula (1965) Using estimated prevalence of neurosyphilis among HIV positive patients of 10% (13,14). The tools and investigations that were used included a questionnaire, Fundoscopic examination, tuning fork, patella hammer, cotton wool, pin prick, mini mental status chart, syringes and needles, treponemal test TPHA Kit, VDRL kit, CD4+ machine, viral load machine, EDTA bottles, reagents for CSF culture, cytology and biochemistry, lumbar puncture gauge 22 needles, computer, scientific calculator, plain papers, pens and pencils.

Participants were interviewed using structured questionnaire for those consented to be enrolled in the study. Blood was drawn by trained personnel at antecubital fossa 5 milliter put in EDTA bottles and tested for *Treponema pallidum* antibodies by *Treponema Pallidum* Hemagglutination Assay (TPHA) and for CD4 count and viral load. A qualitative determination by reagent made in Spain by Chronolab systems S.L, Travessia Prat de la Riba was used for diagnosis of syphilis. Participants with positive results underwent a thorough neurological examination including cognitive assessment, fundoscopic examination and subjective audiometry (Weber and Rinne tests). These patients were also examined for sensory, motor, gait and balance. Participants with neurologic features were offered lumbar puncture by competent personnel. Neurosyphilis was defined according to CDC criteria, serum treponemal test TPHA positive plus neurological features plus CSF-VDRL positive and /or 20 WBC/micolitre or more without unexplained other cause(15).Patients discovered to have syphilis and neurosyphilis were referred to their attending physician where they were offered treatment as per CDC guidelines for treatment of neurosyphilis which recommends first line treatment as IV benzyl penicillin 18 to 24 MU divided in 3 to 4 MU every 4 hours for 10 to 14 days or second line is procaine penicillin G 2.4MU daily with probenecid 500mg 4hourly for 10 to 14 days, the European guideline recommends also use of ceftriaxone 1 to 2 g per day for 10 to 14 days. Patients were followed up for 30 days since the day of treatment to assess clinical outcome after treatment(8,15).

Data were collected using a coded questionnaire and entered into Microsoft Excel. Data were analyzed using STATA version 13(College Station, Texas). All continuous variables were summarized as medians with interquartile ranges, while categorical variables were summarized as proportions or percentages using chi-squared. Univariable followed by multivariable logistic regression analysis were used to determine factors associated with syphilis. Any factor with a p-value of <0.3 on univariable logistic regression analysis was included in the multivariable model. A p-value less than 0.05 was also considered to be statistically significant in the final model.

Results

In this study a total of 1748 participants were screened for syphilis. Of all the study participants 167(9.6%) were found to be serum TPHA positive. More than half, 1008 (57%) of the studied participants had enrolment CD4 count of >350 cells/uL and 1333 (76.3%)had viral load of less than 50 copies /ml.Details of the 167 members of the study population who were TPHA positive are found in Table 1. Females comprised a large number with positive serum TPHA 121 (72.5%): participants aged 40- 64 years were the majority (100/167, 59.9%). The age distribution of the *T.pallidum* seropositive group was significantly higher than the THPA negative group. The TPHA positive group also had more monogamously married people. The TPHA positive group also had significantly more people with only primary education. Vendors constituted a bigger group of occupation 104(62.3) among those who were *T.pallidum* seropositive.

In 167 participants, 18 (10.8%) reported to have previous history of syphilis and among them 12(66.7%) reported prior history of treatment with penicillin doses, 10(83.3%) had 3 penicillin injection doses and

2(16.7%) had single dose. Participants who reported prior history of chancre were 14(8.4%) majority reported single genital lesion 10 (71.4%).In nine participants (64.3%) the chancre had occurred in the past year. Very few 3(1.8%) participants had reported painless rashes on palm and sole and all did not have treatment. All except for one participant were on ART (166, 99.4%).

Details of the patients who underwent neurological examination are shown in Table 3. Participants who had seropositive for *T.pallidum* and managed turn up for results and the neurological examination were 141. Most of participants (138, 97.9%) had no cognitive impairment while one had mild and two had severe impairment. Only two participants (1.5%) had blurred vision, and after further examination one was found have a cataract in the left eye and the other had corneal ulcer. Both of these patients were managed by the ophthalmologist accordingly. No features of syphilis of the eye were noted. Most of patients were on ART, and the majority had been on ART more than 2 years (111, 66.5%).Few patients 3(1.8%) were on ART less than six months. A large number (130, 77.8%) of those with seropositive for *T.pallidum* had a suppressed viral load of less than 50copies/ml and only a small number of participants (10, 6%) had viral load of 1000 copies/ul.More participants had CD4+T cells above 350 cells/uL (94, 56.3%).

Two patients were noted to have confusion (1.5%) of whom one had fever as well (0.7%) both of them were bedbound and it was difficult to assess gait. No participant was noted to have sight loss, uveitis, or Argyll-Robertson pupil. Two of the participants were noted to have hearing loss. One had right-sided sensorineural hearing loss and all other neurological features were normal. The other had reduced cognition and thus it was difficult to assess the type of hearing loss. The bed bound patient did not have Romberg or vibration sense test done. All the other patients had negative Romberg's test and normal vibration sense. All had normal reflexes.

There were four participants with seropositive for *T. pallidum* with neurological abnormalities who underwent lumbar puncture after consent. One (25%) patient was CSF –VDRL positive and had CSF-WBC <5 cells/uL. Three patients (75%) had negative CSF –VDRL and CSF-WBC <5 cells/ul.In the univariable logistic regression analysis several factors were statistically significantly associated with seropositivity for *T.pallidum* including older age group of 65–85 (Odds ratio (OR) 2.37[95% CI, 1.10–5.09], p = 0.027), being widowed (OR 1.88 [1.50–3.90], p = 0.013) and polygamy (OR 9.77, [2.15–46.16], p = 0.003),.prior history of genital chancre (OR 3.93, [2.07–7.44], p<0.001). Previous history of syphilis (OR 5.34 [95% CI, 2.95–9.65], P-value <0.001).On multivariable logistic regression analysis, only polygamy (OR 8.51 [1.71–42.37], p = 0.009) and previous history of syphilis (OR 3.5[1.75–7.01], p<0.001) remained independently associated with syphilis co infection.

In the study among 141 HIV-positive patients who were seropositive for *T.pallidum* were assessed for neurological features. Of these, four participants were found to have neurological manifestations that could have been consistent with syphilis. Given their positive serum for *T.pallidum* status, these patients were counseled and offered lumbar puncture.

One patient among four had neurosyphilis confirmed with CSF- VDRL positive while CSF –WBC<5.The other three patients did not meet the criteria of neurosyphilis in HIV patients according to CDC recommendation. The table 5 below shows the details of CSF finding after lumbar puncture in the four patients who underwent lumbar puncture.

Discussion

In total HIV positive patients167 (9.6%) of the studied patients were seropositive for *T.pallidum.* This finding was similar to a prevalence rate of 10.0% reported in a study done in Uganda by Mboowa *et al* (11). It was as well similar to finding from a an Ethiopian study where 30 (9.8%) out of 306 HIV positive patients were found to be positive for seropositive for T.pallidum(10). This study showed lower Seroprevalence as compared to study done in Ghana by Mamoojee where 45(14.8%) out of 284 HIV positive participants and higher than study done in Rwanda by Mutagoma 20 (4.8%) out 482 HIV positive participant.

People who reported being married to one person were significantly more frequently seropositive for *T.pallidum* (56.3% versus 53.5% in the TPHA negative).This finding was similar to study results in Uganda and Ethiopia, and was presumed to be because of concurrency of partners. Specifically, Kenyon *et al* reported that male partner concurrency in which men had an average of five concurrent partners was significantly associated with high prevalence of syphilis (46). People who were TPHA positive were significantly more likely to have only a primary education, perhaps suggesting that they may have lacked knowledge on preventive measures against sexually-transmitted infections. This finding was contrary to the study done in Ethiopia in which having a secondary education was associated with TPHA positivity. Employed persons were less likely to have seropositive *T.pallidum* for is perhaps due to a reduced network of partners. Only 10% of patients who were seropositive for *T.pallidum* reported previous history syphilis. Syphilis is not screened routinely among people living with HIV or thought to be unimportant problem. Similarly high rates of undiagnosed syphilis have been reported from the Ethiopia study. For those who had syphilis, only two-thirds (67.7%) received treatment. The majority received three intramuscular penicillin doses according to CDC recommendation, as also reported by Katz and colleagues (47).

Most patients who were seropositive for *T.pallidum* had CD4+ T cells above 350 cells/uL (56.3%) and viral load levels less than 50 copies/mL (77.8%). We did not find an association between CD4 counts or viral loads. This might be because most of the patients in our study were on ART and in a latent stage of syphilis. Our results contrast with the study in the US by Kate *et al* which showed syphilis reduces CD4+ T cells and increases viral load (7), particularly in those with secondary syphilis on ART and those with syphilis not on ART. This study also showed that the majority of participants who were seropositive for *T.pallidum* reported no prior history of genital lesion (97.1%), possibly due to the painless lesions of syphilis that might go unnoticed primary stages. A study in Spain similarly found that few patients who were seropositive for*T.pallidum* reported a past genital lesion (13).

Among the 141 participants who were serum TPHA positive and returned to the clinic for neurological assessment, 3 participants had cognitive impairment. One of those with cognitive impairment had also hearing loss. The second patient had hearing loss alone with no other symptoms. The third patient had fever, headache, and altered mental status. The patients were also assessed for any sign of meningeal irritation but no one was positive. In addition, eye examinations identified no patient with typical features of ophthalmic syphilis. Patients were also examined for gait, unilateral weakness, and sensory modalities and were all found to be normal. This was contrasting to the study done US by Katz *et al* which had found 12 patients with neurosyphilis 4,of whom had eye problems, 3 altered mental status and five had unilateral weakness(47). Of note, a major difference between the Tanzania and the US study is that not all US patients were on ART, whereas all but one of the Tanzanian study patients were on ART.

Among the 141 screened by examination, only 4 (2.8%) had neurological symptoms necessitating lumbar puncture to assess for neurosyphilis. This was in accordance with expert guidelines recommending lumbar punctures not in all seropositive for *T.pallidum* plus HIV-positive patients, but only in those with neurological manifestation (8,15,48). In our study among the 4 participants with syphilis who underwent lumbar puncture one was confirmed to have neurosyphilis. That person had no prior history of syphilis and was not on ART. TheCD4+ T cell count was 412 cells/uL. The patient was treated with daily intravenous ceftriaxone per the CDC guideline but died after 3 days in the ward after rapid neurologic deterioration. This patient might have suffered from the meningoencephalitis form of neurosyphilis which has fast progression with poor prognosis in HIV positive patients. This form of neurosyphilis was seen in one case study in an HIV-positive patient who presented with abnormal behavior (49). In HIV positive patients might have normal CD4+ T cells with altered function increasing the risk of syphilitic meningoencephalitis this was observed in a study Mark *et al(*50). Likewise in study done by Marra *et al* in US found 16 neurosyphilis patients with only CSF-VDRL among 50 patient with neurosyphilis (51). By contrast, in the study done in Spain by Alverez *et al,* all patients who had a diagnosis of neurosyphilis presented with mild headache, had no prior history of treatment, and improved after therapy (13). The three patients who were negative for neurosyphilis, all were on ART and reported no history of prior treatment for syphilis. This may have occurred because ART use reduces the chances of having neurosyphilis to be equal to that of HIV-unpositive people with syphilis (43).

In our study we found a prevalence of neurosyphilis of only 0.7% of all who were examined for neurologic features. This prevalence was surprisingly low given the findings of other studies that have suggested the prevalence could be as high as 25%. This low prevalence may be due either to ART use in most patients, or possibly having been previously treated with antibiotics, for a different indication, that have activity against *Treponema pallidum.* Our findings on neurosyphilis fit with a systemic review of neurosyphilis in Africa by Mark *et al(*52), which found only two patients with meningitis (3.3%).Another study done in Brazil by Jacquelline *et al* had showed to be 1% among HIV positive patient with neurologic features(53). In contrast, a study by Borden *et al* showed that 23.5% seropositive for *T.pallidum* patients who were not on ART had neurosyphilis. (13). Therefore, our study documents an important and encouraging finding that rates of neurosyphilis are lower in our setting than previously reported. This may be due to the

expanding use of ART and also to the use of antibiotics, some of which may be excess but may serve inadvertently to treat seropositive for *T.pallidum* patients and prevent neurosyphilis.

Our study had some limitations It was difficult to know if patients were previously treated for syphilis with other agents which active for syphilis like ceftriaxone or doxycycline because of the lack of electronic data keeping. In our study we excluded patients without neurologic features for lumbar puncture hence we may have missed asymptomatic neurosyphilis. We were not able to determine whether a patient may have had seroreversion of syphilis as the reagent used was only qualitative and usually stays positive for life. Risk factor for neurosyphilis could not be determined due very small number. HIV-positive patients with neurosyphilis may die rapidly and this cross-sectional study would not have found those patients

Conclusions

In conclusion we found seropositivity for *T.pallidum* in HIV positive participants the was high (9.6%) in which one out of ten people was affected and a very low prevalence of neurosyphilis (0.7%. This argues for the need of STI screening especially syphilis with specific focus on HIV positive patients. Factors associated with neurosyphilis could not be determined because of low prevalence. Factors associated with syphilis were being polygamist, low level of education. High percentage of untreated syphilis among HIV-positive patients of 89.2%.Only 10.8% of HIV-positive patients who had syphilis were aware of their diagnosis, which highlights the importance of prioritizing screening and treatment. Cases of neurosyphilis were (0.7%), likely due to the activity of antibiotics that are frequently given to HIV-positive patients for other indications but have activity against syphilis like doxycycline, ceftriaxone, azithromycin. Based on the fact that only 10.8% of people living with HIV identified to have syphilis co infection were treated for syphilis, we recommend that screening for syphilis for all HIV positive individuals, those with untreated syphilis to receive three doses of penicillin and those with neurological manifestation to be treated by benzyl penicillin or ceftriaxone according to National Standard treatment guidelines or CDC recommendation to reduce the risk of progression to neurosyphilis. Screening and treating syphilis in all HIV positive patient should be routinely done as the disease can present as fulminant meningoencephalitis which is usually fatal with rapid deterioration. HIV positive patients with neurological manifestation neurosyphilis should be considered as one of diagnosis. We also recommend having further study done to HIV positive patients with seropositive for *T.pallidum* admitted to hospital with neurologic manifestation for neurosyphilis.

Declarations

Abbreviations:

ART = Antiretroviral therapy; BMC = Bugando Medical Centre; CDC = Center for Disease Control; CD4 = Cluster differention; CREC = CUHAS /BMC Joint Ethics and Review Committee; CSF = Cerebarospinal fluid; CTC = Care and treatment clinics; CUHAS = Catholic University of Health and Allied Sciences; HIV =

Human immunodeficiency Virus; TPHA = Treponema pallidum Haemoglutination Assay; VDRL = Veneral disease research laboratory; WBC = White blood cell

Ethics approval and consent to participate:

Ethical clearance was obtained from the CUHAS /BMC Joint Ethics and Review Committee with certificate number CREC/242/2017. Written informed consent was obtained from each patient or patient's next of kin for those unable to consent for themselves. Patient found to have syphilis and neurosyphilis were sent to clinician for a free treatment for syphilis. Results were communicated to the treating physician immediately and a copy of the results was placed in the patient's file.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests in this section.

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Authors: contributions:

SK and PM reviewing the manuscripts. EM examined patient who had suspected to have syphilis of the eyes. BM did all the laboratory work for diagnosis of syphilis and syphilis. All authors read and approved the final manuscript

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Tables

Due to technical limitations, Tables 1 - 5 are only available for download from the Supplementary Files section.

Figures

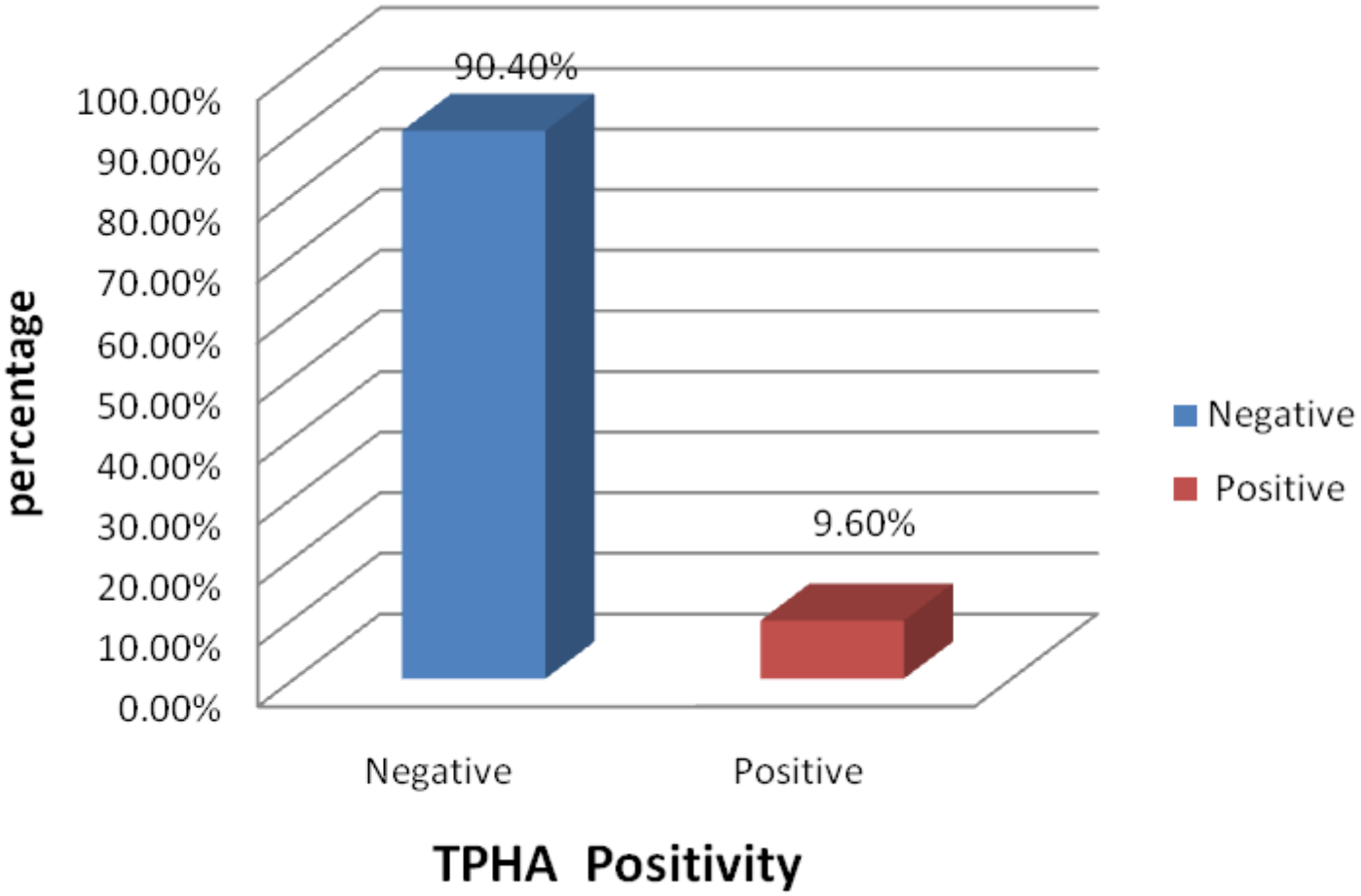

Figure 1

Prevalence of syphilis among 1748 study participants

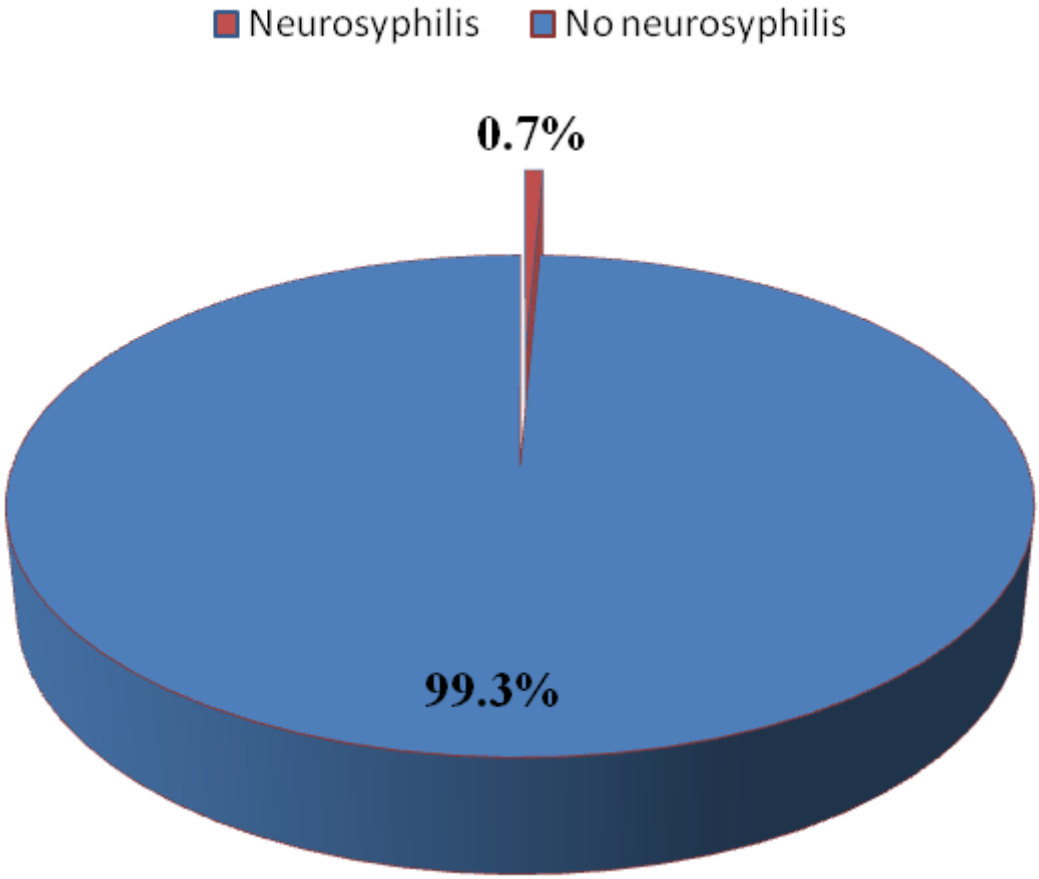

Figure 2

Prevalence of Neurosyphilis among 141 HIV-positive patients in Mwanza Tanzania

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