Clinical Manifestations of Early Syphilis in People Living With HIV and AIDS. A Review

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Abstract

Background: Syphilis and HIV-infection both are serious global health and social problem. These infectious diseases are both systemic diseases with many clinical and epidemiological features. Coexistence of these diseases is not rare in clinical practice. This is not surprising due to the same route of transmission. During the last 5 years we observe an increase in a manifest forms of early syphilis. HIV/AIDS may influence clinical course of syphilis. So, natural history of syphilis in people living with HIV and AIDS (PLWHA) has certain clinical features. Clinical manifestations of early syphilis are sometimes a clue for diagnosis of HIV/AIDS. But generally clinical manifestations of PS and SS in HIV-positive individuals sometimes may not differ from those in HIV-negative, i.e. syphilis itself with or without any clinical features (latent syphilis) may be a key for the diagnosis of HIV/AIDS. Thus persons with any clinical forms, manifestations and stages of syphilis should be screened for HIV/AIDS. HIV/AIDS is not treatable but it is manageable. However, early diagnosis of HIV/AIDS as well as syphilis is a great importance because we can manage former (to take under control the virus by antiretroviral therapy (ART)) and treat the last one to increase the quality of life, to prevent progression of disease to late-stage and transmission to healthy people. Finally, lifestyle change (high risk behavior avoidance) is one of the most important and effective ways to prevent sexually transmitted diseases (STD), including HIV/AIDS and syphilis. The aim of this review was to provide updated information on clinical manifestation of syphilis in PLWHA. The article is accompanied by several original clinical images.

Introduction

Syphilis and HIV-infection both are serious systemic diseases with many clinical and epidemiological features. Coexistence of these diseases is not rare in clinical practice, especially among individuals from certain risk groups, e.g. persons, who practice unprotec-ted sexual intercourse, MSM, transgender persons, sex business workers, people undergoing medical and non-medical parenteral manipulations (invasive medical procedures, surgery, people who inject drugs (PWID), tattoo etc.), prisoners, etc. Moreover, they are at relatively high risk of HIV/AIDS in areas with any prevalence of this infection. This is not

surprising due to the same route of transmission. Asymptomatic clinical course, which may last for a long period of time is characteristic for either early latent syphilis and HIV-infection. Persons with latent forms of infectious diseases are more common a source of infection, so they are more dangerous in the context of epidemiology.

Epidemiology

HIV continues to be a major global public health issue, having claimed more than 32 million lives so far. There were approximately 37.9 million people living with HIV at the end of 2018 with 1.7 million people becoming newly infected in 2018 globally. Key populations and their sexual partners accounted over half of all new infections (an estimated 54%) for the first time in 2018 [1].

In the late 1990s, the prevalence of syphilis plummeted in many countries with endemic syphilis, largely thought to be due to the introduction of syndromic management for STIs [2,3], behavioral changes, and the effect of AIDS mortality disrupting sexual networks [4,5,6]. However, since the introduction of antiretroviral therapy (ART), rates of syphilis have increased, especially among men who have sex with men (MSM), perhaps due to the reconstruction of sexual networks and increased frequency of sexual contact [7,8].

In Europe, there were 28,701 cases of early syphilis reported in 2015, yielding a rate of 6.0 per 100,000 inhabitants [9]. One of the most important factors affecting syphilis transmission is the practice of condomless anal sex (CAS) [10]. Other factors, such as drug consumption, internet use for sexual cont acts, and sex in group have also been reported [11].

If untreated both HIV/AIDS and syphilis lead to significant morbidity. The prognosis in patients with untreated HIV infection is poor, with an overall mortality rate of more than 90%. The average time from infection to death is 8-10 years, although individual variability ranges from less than 1 year to long-term nonprogression [12]. According to World Health Organization (WHO) data in 2018, 770 000 people died from HIV-related causes globally [1]. Syphilis is also a serious global health and social problem. However, adults now

rarely die from syphilis. Increases in infections in the late 1980s did not lead to an increase in adult syphilis deaths. But at the same time congenital syphilis deaths still increase when syphilis increases among women [13]. That is why screening of asymptomatic individuals from high risk behavior groups is crucial. The same sexual route of transmission of these infectious diseases emphasizes that patients with syphilis should be screened for HIV-coinfection and conversely people living with HIV and AIDS (PLWHA) must be screened for syphilis. In our clinical practice we usually screen PLWHA for the presence of syphilis at the time of HIV/AIDS diagnosis and then annually, according to local existing clinical practice guidelines. It is important to take into consideration that any patient with syphilis even after successful treatment, may still be at certain risk of reinfection (repeated syphilis). So retesting or more frequent testing may be appropriate in some clinical conditions. At the same time clinicians must take into account the so-called window period phenomena when testing for HIV. It is defined as a period of time from the transmission of HIV to detection of anti-HIV in the serum (3 weeks – 12 months, 3 months on average). So retesting may be an appropriate approach while screening for HIV/AIDS performed.

Screening Strategy

HIV co-infection has been demonstrated to be strongly associated with syphilis [10, 14]. Several studies revealed improved detection of syphilis among MSM or HIV positive men who are screened every 3 months vs. 6 or 12 months screening strategy [15,16,17,18]. So increasing the frequency of syphilis screening strategy may be expedient in cases with ongoing high risk behavior, including PLWHA. *Avoundjian T*, et al. revealed that increasing HIV testing among partners of syphilis case patients could increase HIV case finding [19]. In a cohort of women engaged in HIV care in the southern United States, detection of chlamydia, gonorrhea, and syphilis was infrequent but trichomoniasis was common. Many women screened for STD were low risk and universal testing strategies warrant evaluation [20].

Interaction Between Treponema Pallidum And HIV

Syphilis influences natural history and epidemiology of HIV/AIDS. Several studies demonstrate different degree of CD4 cells count decrease and HIV viral load (HIV-VL) increase which may last for different period of time, in the state of syphilis/HIV co-infection [**21, 22**]. Usually this effect resolve after infection is cured. So syphilis may facilitate transmission of HIV even in patients receiving antiretroviral therapy (ART) and with a HIV-VL of less than 500 copies/ml. [**21**]. How these transient changes affect the overall course of the HIV disease or the risk for syphilis transmission remains unknown [**23**]. It is important to keep in mind that such otherwise unexplained CD4 cell count and HIV-VL changes in PLWHA may be an indicator of T. pallidum infection. That is why clinicians should perform an appropriate laboratory tests to rule out early syphilis.

Given that primary syphilis (PS) facilitates both the transmission and the acquisition of HIV infection [**24,25,26,27**], expansion of the HIV epidemic within the MSM population is a concern. However, to date, there is no clear evidence of increased spread of HIV infection [**28**].

Clinical Manifestations of Early Syphilis In PLWHA

Primary syphilis manifestations in PLWHA

During the last 5 years we observe an increase in a manifest forms of early syphilis. Clinical manifestations of syphilis are sometimes a clue for diagnosis of HIV/AIDS. HIV/AIDS may influence clinical course of syphilis. The aim of this review was to provide updated information on clinical manifestation of syphilis in PLWHA.

There are several differences between clinical manifestations of syphilis in pts with and without HIV co-infection. PS in PLWHA may present with >1 chancre (up to 70% of patients). In addition to quantity lesions may be larger and deeper [**29,30**]. Furthermore, several chancres may persist in PLWHA with secondary syphilis (SS) [**30**]. But the presence of several chancres may be as a result of repeating infection in either HIV-positive or HIV-negative pts. Generally clinical manife

stations of PS and SS in HIV-positive individuals sometimes may not differ from those in HIV-negative one.

Secondary Syphilis Manifestations in PLWHA

SS is most common clinical stage of syphilis in PLWHA [**30,31**]. It also has some distinguishing features. Many unusual clinical manifestations of SS in PLWHA described in the literature.

• Persons with repeat infections were more likely to have had secondary or early latent syphilis and be infected with human immunodeficiency virus compared with those having 1 episode of infection [**32**].

• Among patients with first episodes of syphilis, patients positive for HIV who had secondary syphilis were more likely to present with persistent chancres [**30**]

• In our clinical practice we observed PLWHA with simultaneous existence of different syphilis stages in the same pt (**Figure 1**), (**Figures 2a and b**), (**Figure 3**), (**Figures 4a and b**). According to the literature approximately one-fourth of PLWHA present with concomitant lesions of both primary and secondary stages of syphilis at the time of diagnosis [**29,30**].

• Ecthyma as clinical manifestation of SS - syphilitic ecthyma (**Figure. 4a**).

• Erythema multiforme like lesions [**33,34**].

• A secondary syphilis rash with pruritic scaly target lesions [**35**].

• Erythematous pink-red oval macules and papules 1-2 cm in size distributed on scalp, face, trunk, and arms. A few papules contained fine collarettes of scale (**Figure 1**) [**36**].

• Secondary syphilis presenting as a corymbiform syphilide [**37**].

• SS with pulmonary involvement [**38**].

Oral Mucosa İnvolvement of SS in PLWHA

Velia Ramírez-Amador et al. studied oral secondary syphilis lesions in 20 male patients. Oral lesions were the first clinical sign of syphilis in 80% of cases. Mucous patch was the most common oral manifestation - 85.5%,

Figure 1. Secondary syphilis in HIV-positive person

Figures 2 a and b a. Palmar involvement in secondary syphilis (HIV-positive person) **b**. Plantar involvement in secondary syphilis (the same HIV-positive person)

followed by shallow ulcers - 10% and macular lesions - 1,5%. They came to conclusion that due to the recent rise in HIV-syphilis co-infection, dental and medical practitioners should consider secondary syphilis in the differential diagnosis of oral lesions, particularly in HIV-infected patients [**39**].

Lues Maligna and HIV/AIDS

Although atypical and aggressive presentations of syphilis occur more frequently among HIV-infected patients, these represent a very small minority of the cases [**40**]. At the same time overwhelming majority of cases of aggressive clinical presentation of secondary syphilis, so-called lues maligna (malignant syphilis or ulceronodular syphilis, LM) had been described in PLWHA [**41,42,43,44**]. So, *Sands M* et al., found that 12 cases of LM (including their pt) were reported in the literature from 1989 to1994, of those 12 cases, 11 occurred in patients who either were infected with HIV or were at high risk for HIV infection [**41**]. In addition, even late publications demonstrate that in overwhelming majority of them HIV co-infection took place. And besides some authors suppose that untreated HIV-1 infection is one of the clues to the diagnosis of LM [**44**]. In fact, before the HIV-1 epidemic only 14 cases of LM has been reported in the literature 1900s through the early 1980s [**45,41**]. LM in HIV-positive pt first described by *Shulkin D.* et al. in 1988 [**46**]. Based to own clinical practice and all of these descriptions we can suppose that in the context of concomitant HIV infection

syphilis clinical course may have more aggressive course including LM. So, it is important to keep in mind LM when PLWHA present with nodulo-ulcerative skin lesions. Such aggressive clinical course of syphilis take place most probably due to immuno-suppression.

Clinical manifestations of LM (most aggressive form of secondary syphilis) in PLWHA

• Nodulo-ulcerative and erythrodermic secondary syphilis (LM) (*Tambe S* et al. 2019) [**47**].

• Widespread noduloulcerative and two vesiculonecrotic lesions (LM) [**42**].

• Large painful gummatous ulcers in the groin and lower back [**43**].

• LM in PLWHA with ocular involvement *Pleimes M*, et al., 2009 [**48**].

Ocular Syphilis in PLWHA

An increased frequency of ocular disease is another clinical feature of syphilis in PLWHA. *Cope AB.* et al., revealed that syphilis patients with HIV were nearly twice as likely to report OS symptoms as were patients without documented HIV. HIV-related immuno-deficiency possibly increases the risk of OS development in co-infected patients [**49**]. It is important to take into consideration that non-treponemal tests may be negative in HIV-infected patients with ocular syphilis (OS). OS remains an important clinical manifestation that can lead to initial HIV diag-

Figure 3. Condylomata lata in secondary syphilis (HIV-positive person)

Figures 4 a, b and c a. Syphilitic ecthyma (SS manifestation) in HIV-positive person **b**. Three painless chancres in different stages of development in HIV-positive person with primary syphilis (the same patient) **c.** Three painless chancres in different stages of development in HIV-positive person with primary syphilis (close-up)

nosis [**50**]. The study of ocular syphilis in North Carolina performed *Oliver SE* et al., demonstrated that increase OS from 2014 to 2015. This may be due to increased recognition of ocular manifestations, or a true increase OS. Many OS patients experienced vision loss; however, most improved post-treatment [**51**]. Non-treponemal tests may be negative in HIV-infected patients with ocular syphilis. Ocular syphilis (OS) may develop in pts with LM [**48**].

Treatment of Syphilis in PLWHA

Data on syphilis treatment success are controversial. So, according *Long CM* et al. HIV infection did not affect syphilis treatment success rates [**52**]. But Malone JL concluded that standard penicillin regimens, including high-dose intravenous penicillin, transiently lowered serum VDRL titers in nearly all cases, but were sometimes inadequate in preventing serologic and clinical relapse in patients infected with HIV type-1, especially among those with secondary syphilis and reactive CSF VDRL titers. Careful long-term follow-up is essential, and repeated courses of therapy may be needed for patients infected with HIV type-1 who have syphilis [**53**]. In fact, LM as most serious clinical variant of syphilis in PLWHA demonstrate dramatic response to antibiotic therapy [**54,44,42**]. We successfully treat early syphilis with standard treatment methods when co-infected with HIV in our clinical practice in overwhelming majority of cases.

Prophylaxis

A pilot study of daily doxycycline prophylaxis for bacterial STIs among HIV-infected MSM found that daily doxycycline users had reduced incidence of syphilis infections [**55**]. A larger randomized control study of on-demand post-exposure prophylaxis with doxycycline among MSM that were not infected with HIV

found that doxycycline use after sexual activity "post-exposure" reduced the incidence of syphilis infections [**56**]. Prior studies on periodic presumptive treatment of syphilis among sex workers have produced mixed findings [**57**].

Among population diagnosed as having primary and secondary syphilis, 1 in 6 MSM and 1 in 16 persons co-infected with gonorrhea were subsequently diagnosed as having HIV during 36 months of follow-up. These findings have implications for HIV screening and recruitment as priority preexposure prophylaxis (PrEP) candidates [**58**].

In addition, local health care providers should offer PrEP to MSM diagnosed with syphilis or gonorrhea and to non-MSM with a previous gonorrhea diagnosis at time of a syphilis or gonorrhea diagnosis. The high proportion and short time to an HIV diagnosis among MSM after a syphilis or gonorrhea diagnosis suggest immediate PrEP initiation [**59**].

Conclusion

HIV co-infection has been demonstrated to be strongly associated with syphilis [**10,14**]. This is not surprising due to the same route of transmission. MSM are at highest risk of HIV/AIDS, syphilis and their co-infection acquisition.

Natural history of syphilis in PLWHA has certain clinical features. But generally clinical manifestations of PS and SS in HIV-positive individuals sometimes may not differ from those in HIV-negative, i.e. syphilis itself (latent syphilis) is a key for the diagnosis of HIV/AIDS. So persons with any clinical forms, manifestations and stages of syphilis should be screened for HIV/AIDS.

Accurate screening tests are available to identify syphilis infection in populations at increased risk [**60**]. It is important to take into consideration that any person with syphilis even after successful treatment, may still be at certain risk of reinfection (repeat syphilis). So retesting or more frequent testing may be appropriate in some clinical conditions. At the same time clinicians must take into account the so-called window period phenomena when testing for HIV. It is defined as a period of time from the transmission of HIV to detection of anti-HIV in the serum (3 weeks – 12 months, 3 months on average). So retesting

may be an appropriate approach while screening for HIV/AIDS performed.

HIV/AIDS is not treatable but it is manageable. However, early diagnosis of HIV/AIDS as well as syphilis is a great importance because we can manage former (to take under control the virus by ART) and treat the last one to increase the quality of life, to prevent progression of disease to late-stage and transmission to healthy people. So according to WHO Between 2000 and 2018, new HIV infections fell by 37%, and HIV-related deaths fell by 45% with 13.6 million lives saved due to ART in the same period. This achievement was the result of great efforts by national HIV programmes supported by civil society and a range of development partners [**1**].

Finally, lifestyle change (high risk behavior avoidance) is one of the most important and effective ways to prevent STD, including HIV/AIDS and syphilis.

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