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ORIGINAL ARTICLE

Clinical and epidemiological characteristics of patients with early syphilis from three academic centres in Poland, Germany and Ireland: initial findings from the POETS study

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ABSTRACT

Objectives Syphilis recognition in HIV-positive patients has important implications. Initial data from this study, established in June 2012 to better understand the natural history of syphilis and treatment response, examine the characteristics of patients including sexual behaviour, rates of concurrent sexually transmitted infections (STI) and type of treatment given.

Methods Patients were recruited from Ireland, Poland and Germany. Data gathered included demographics, method of syphilis acquisition, stage of syphilis infection, HIV status, nadir and current CD4 counts and HIV viral suppression rates. Data were then subanalysed into HIV-positive and HIV-negative groups.

Results Of 175 patients recruited, 68% were HIV-positive and 86.3% were men who have sex with men. Most HIV-positive patients presented with secondary syphilis (55.7% vs 13.2%) (p=0.0001) while the majority of HIV-negative patients had primary syphilis noted at the time of recruitment (47.2% vs18.9%, p=0.0002). Approximately half of all patients had a HIV RNA viral load <40 copies/mL (55%). Previous syphilis infection occurred more frequently in HIV-positive than HIV-negative patients (p=0.0001). Concurrent STIs at the time of syphilis diagnosis were found in 26.8%, of whom 31 (25.4%) were HIV-positive (p=0.64). HIVpositive patients received doxycycline more frequently than their HIV-negative counterparts (33.6% vs 1.9%, p=0.0001) while HIV-negative patients were treated with long-acting penicillin in 88.7% of cases vs 58% of HIV-positive patients (p=0.0002).

Conclusions A 40% rate of unsuppressed viraemia, high levels of STIs and varying treatment regimens represent a public health risk for Europe, suggesting the model of sexual healthcare delivery in HIV-positive patients requires further evaluation.

INTRODUCTION



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Syphilis is a sexually transmitted infection (STI) caused by the spirochete *Treponema pallidum*. It has a long and rich history with cases of treponemal infection being documented in pre-Columbus Europe, Africa and Asia.¹

Following the Second World War, with increased access to penicillin and better public health policies addressing venereal diseases, the rates of syphilis infection dropped substantially in high-income settings.² However, since the turn of the 21st century, the incidence of syphilis has risen globally.^{3–6} Ireland, Poland and Germany have also followed this trend with reported cases of syphilis in 2012 of 518, 963 and 4410, respectively, with the majority occurring among men who have sex with men (MSMs).^{3–5 7}

This increased incidence is a result of widely differing underlying factors that include economic, social and technological factors,⁸ along with migratory and stigma-related issues.⁹ ¹⁰The rise has occurred most dramatically among MSMs, and syphilis now disproportionately affects people who HIV-positive, particularly HIV-positive are MSMs.^{11–14} The reasons for this are complex and manifold; the increased incidence cannot simply be explained by a rise in HIV infections alone since many countries with rising rates of syphilis infections have not seen a corresponding rise in HIV incidence.¹⁵ Changes in social norms and sexual behaviours including a greater rate of high-risk sex with a high turnover of sex partners, use of the internet to meet sex partners, serosorting (choosing a partner based on their HIV status), the use of recreational drugs,¹⁶ to heighten sexual experiences (eg, crystal methamphetamine), and a perception that oral sex is the safest option to prevent HIV acquisition¹⁷ have all likely contributed to the epidemic.

Early reports in the literature referred to HIV affecting the natural history of syphilis, but that is no longer thought to be the case. Some differences remain, however, between syphilis when it presents in the HIV-positive population compared with the HIV-negative population. Higher rates of asymptomatic primary infection, greater rates of chancres occurring in the secondary stage and overall much higher rates of patients presenting with secondary syphilis have all been documented.¹⁶ ^{18–20} There may also be greater numbers of chancres that are deeper in appearance and, finally, individuals with syphilis may present with or progress to neurological signs and symptoms more frequently.²⁰

Syphilis facilitates the transmission and acquisition of HIV in a number of ways. At the time of primary infection, mucosal breaks in the skin due to anogenital ulceration cause loss of the skin's natural defence mechanism.¹⁹ Within these ulcers, syphilitic-infected macrophages undergo CCR5 receptor expression as a result of syphilitic surface lipoprotein stimulation. These CCR5-induced cells then act as a reservoir for macrotrophic CCR5-positive HIV virions to attack.²¹ The systemic secondary stage is marked by a potent cellular response causing increased numbers of activated CD4+ cells to circulate, which likely increase the transmission of HIV. Syphilis also alters the natural history of the HIV infection as HIV viral load rises and CD4 cell counts drops at the time of infection.²² ²³

To date, there have been few prospective randomised clinical trials examining the treatment of syphilis particularly in HIV-positive persons. One study revealed that clinical treatment failures were rare among both HIV-positive and HIV-negative persons but that serological failures were more common in those with HIV infection. The authors of this study concluded, however, that treatment was adequate regardless of HIV status.²⁴ A recent systematic review examining the treatment of syphilis in HIV-infected subjects found there was no known optimal antibiotic regimen for those who were coinfected with syphilis and HIV,²⁵ with most sites choosing parenteral forms of penicillin, oral doxycycline, azithromycin or ceftriaxone.

Comprehensive guidelines exist in different jurisdictions for the management of syphilis,^{26–28} all of which make special reference to HIV coinfected patients in whom it is advised to treat as per HIV-negative patients.

The prospective observational European study of the natural history and treatment of syphilis in HIV-positive and HIV-negative individuals (POETS) study was primarily designed to assess the natural history of syphilis infection along with treatment response in HIV-positive versus HIV-negative persons. It is anticipated that this would inform future guidelines. In this paper, we provide a summary of the patients recruited to the study, and associations found between lifestyle, sexual behaviour and other clinical factors such as their HIV status, viral suppression rates and staging of syphilis infection.

METHODS

A prospective multicentre cohort study was conducted examining all patients newly diagnosed with syphilis infection attending three tertiary referral university hospitals in Ireland, Poland and Germany. Included individuals could be HIV-positive or HIV-negative.

In Ireland, patients were recruited from a combined genitourinary medicine and infectious disease clinic where a mix of HIV-positive and general STI patients attend. Ten doctors provided care for the Irish cohort.

In Germany and Poland, patients were recruited from an academic HIV/infectious disease outpatient clinic and treated by five providers, respectively.

Demographic data were gathered including information on age, sexual orientation, country of birth, HIV status, whether or not the individual had a partner, and if this partner was aware of the person's HIV or syphilis diagnosis. The type of sexual activity that had led to the individual's diagnosis of syphilis, whether or not they had visited a bar, nightclub or a sex on premises venue, used the services of a commercial sex worker or consumed alcohol and/or illicit drugs was ascertained. The number and type of past STIs and the presence of a concurrent STI was noted.

Syphilis was diagnosed using a combination of treponemal tests and non-treponemal tests.

Treponemal tests included fluorescent treponemal antibody absorbed, *T. pallidum* particle agglutination and immunoglobulin G to *T. pallidum* as detected by enzyme immunoassay.

Non-treponemal tests included the Venereal Disease Research Laboratory test or the rapid plasma regain test.

Dark field microscopy was used in conjunction with these tests in a number of cases of syphilis with chancres present.

Syphilis infection was staged according to primary, secondary, latent (early or late) and tertiary. The presence of chancres, rash, lymphadenopathy and any cardiac and neurological signs was recorded. In addition, any neurological symptoms or penicillin allergies were documented. For those with HIV infection, length of time since HIV diagnosis, nadir CD4 count, current CD4 count, viral load and highly active antiretroviral therapy regimen were detailed. Finally, syphilis therapy was recorded.

A full STI screen was performed at baseline as per standard of care for MSMs. This included rectal, pharyngeal and urethral combined nucleic acid amplification test for chlamydia and gonorrhoea. HIV, hepatitis A, B, C and syphilis serology were also taken.

A swab for syphilis PCR, macrolide resistance and genotyping was taken from any primary ulcer site for future analysis.

Blood was taken for syphilis PCR, macrolide resistance and genotyping for patients presenting with secondary syphilis for future analysis.

Statistical methods

Comparisons between study participants in the three different countries and between those who were HIV-positive and HIV-negative were performed using χ^2 test for categorical variables or Mann–Whitney U test for continuous variables. All analyses were performed using SAS V.9.13, and a p value <0.05 was considered to be statistically significant.

RESULTS

To date, the study has recruited 175 patients, 122 (69.7%) of whom were HIV-positive and 53 (30.3%) of whom were HIV-negative. Almost all were men (170/175, 97.1%), of whom 151 (86.3%) were homosexual/bisexual and 22 (12.6%) heterosexual. Although most patients reported being born in one of the participating countries (Ireland, Poland or Germany), 39 (22.3%) reported other countries of birth (table 1). All were resident in the local country at the time of presentation.

The way in which patients met future sex partners varied between the three sites as did their alcohol and recreational drug consumption. The presence of a partner, along with the partner's awareness of the patient's HIV status and syphilis coinfection, also differed (table 1).

Among the HIV-positive patients, viral suppression rates ranged from 48.0% to 73.3%. There was some degree of difference in terms of nadir CD4 count between Ireland, Poland and Germany, but the median CD4 counts at the time of syphilis diagnosis were well matched (table 2).

The 122 HIV-positive men in the study had a median age of 35 years compared with 31 years for the 53 HIV-negative patients (p=0.05).

Overall, 75 (42.9%) individuals presented with secondary syphilis, 68 (55.7%) of the HIV-positive group and 7 (13.2%) of the HIV-negative group (p=0.0001). Among those with secondary syphilis, a rash was present in 33 (48.5%) of the HIV-positive group versus 4 (57.1%) of the HIV-negative group (p=0.71).

Overall, 50 (28.6%) individuals presented with primary syphilis, 23 (18.9%) of the HIV-positive group and 27 (50.9%) of the HIV-negative group (p=0.0001). Among those with primary syphilis, a chancre was present in 12 (52.2%) HIV-positive patients vs 15 (55.6%) HIV-negative patients (p=1.002). Also, 8 (6.6%) HIV-positive patients were classified

	Ireland	Per cent	Poland	Per cent	Germany	Per cent
Number of patients	85	100.0	73	100.0	17	100.0
Gender						
Male	81	95.3	72	98.6	17	100.0
Female	4	4.7	1	1.4	0	0
Age (years)						
Median (range)	35 (19–77)		34 (23–68)		35 (21–56)	
Country of birth						
National	49	57.7	72	98.6	15	88.2
Other European	20	23.5	1	1.4	0	0
Africa	3	3.6	0	0	0	0
South America	10	11.8	0	0	0	0
North America	1	0	0	0	0	0
Asia	2	2.4	0	0	0	0
Middle East	0	0	0	0	1	5.9
Sexual orientation						
Homosexual/bisexual	73	85.9	63	86.3	15	88.2
Heterosexual	12	14.1	9	12.3	1	5.9
Not stated	0	0	1	1.4	1	5.9
HIV status						
Negative	50	58.8	0	0	3	17.7
Positive	35	41.2	73	100.0	14	82.4
Current partner	34	40.0	8	11.0	7	50.0
Partner aware of Treponema pallidum	21	61.8	1	12.5	8	57.1
Partner aware of HIV*	33	94.0	8	100.0	10	76.9
Mode of meeting partners						
Internet	42	49.4	0	Not stated	10	58.8
Clubs/bars	48	56.5	64	87.7	3	17.7
Sex on premises venues (sauna, sex cinema)	22	25.9	0	0	1	5.9
Commercial sex workers	7	8.2	1	1.4	0	0
Alcohol use around time of sex	59	69.4	62	84.9	7	41.2
Illicit oral/nasal 'party' drugs use						
Ecstasy, ketamine, GBH'G', cocaine	33	38.8	6	8.2	4	23.5

 Table 1
 Demographic comparison between Ireland, Poland and Germany and differences across the three sites in the use of the internet, commercial sex workers, sex on premises venues and alcohol and recreational drugs

*Refers to the partners of HIV-positive patients (n=35).

as having early latent syphilis compared with 6 (11.3%) HIV-negative patients (p=0.36) while 16 (13.1%) HIV-positive patients had late latent disease compared with 9 (17.0%) HIV-negative patients (p=0.66).

With regards to sexual behaviours and STIs, the HIV-positive group was found to be engaging in more anal-insertive and anal-receptive sex compared with their HIV-negative counterparts. There were also high rates of concurrent STIs in both groups with a significant proportion of HIV-positive patients being diagnosed with acute hepatitis B and C virus. A past history of syphilis infection was more common in the HIV-positive group (table 3).

Table 2	Viral suppression rates and CD4 counts in HIV-positive		
patients across three sites			

HIV-positive	Ireland (n=35)	Poland (n=73)	Germany (n=14)
Virologically suppressed <39 copies/mL	22/30 (73.3%)	35/73 (48.0%)	7/12 (58.3%)
Current CD4 (10 ⁶ /L), median (range)	570 (64 to 986)	460 (6 to 1214)	544 (120 to 1220)
Nadir CD4 (10 ⁶ /L), median (range)	306 (64 to 907)	308 (6 to 1051)	200 (15 to 610)

Within the HIV-positive group, 64 of the 115 patients with a viral load measurement (55.7%) had a suppressed viral load (<39 copies/mL). Rates of reported oral sex, anal-insertive and anal-receptive sex and vaginal intercourse did not differ significantly between those with suppressed or non-suppressed viral loads (data not shown).

Treatment varied across the three sites (p<0.0001); a longacting penicillin formulation was administered in 46.3%, 19.4% and 6% of cases in Ireland, Poland and Germany, respectively. Doxycycline was given in 1.7%, 21% and 1.7% of cases, ceftriaxone in 0%, 2.3% and 1.1% and azithromycin in 0%, 0.6% and 0.6% of cases, respectively.

In total, 71/122 (58%) HIV-positive patients received a longacting penicillin formulation compared with 47/53 (88.7%) HIV-negative patients (p=0.0002). Forty-one (33.6%) HIV-positive patients received doxycycline compared with only one (1.9%) of the HIV-negative group (p=0.0001). Two (1.6%) HIV-positive patients were treated with azithromycin (p=1.0) while six (4.9%) received ceftriaxone (p=0.18).

DISCUSSION

Our study recruited broadly similar patient groups from all three sites in terms of age, sexual orientation and gender. Most were men, either homosexual or bisexual in orientation with a

Table 3	Comparison of age, sexual orientation, sexual practices
and past	history of sexually transmitted infections (STIs) between
HIV-posit	ive and HIV-negative groups

	HIV-negative	HIV-positive	
Patient	(N=53)	(N=122)	p Value
Age (years), median (range)	31 (19 to 62)	35 (19 to 77)	0.05
Homosexual	36 (67.9)	96 (78.7)	
Bisexual	8 (15.1)	11 (9.0)	
Heterosexual	9 (17.0)	13 (10.7)	
Oral sex	48 (90.6)	113 (92.6)	0.87
Anal-insertive sex	30 (56.6)	95 (77.9)	0.007
Anal-receptive sex	24 (45.3)	97 (79.9)	0.0001
Vaginal sex	13 (26.0)	21 (17.4)	0.28
Fisting	3 (5.7)	3 (2.5)	0.37
Concurrent STIs	16 (30.2)	31 (25.4)	0.64
Anogenital warts	4 (7.6)	8 (6.6)	0.76
Chlamydia	7 (13.2)	7 (5.7)	0.13
Non-specific urethritis	1 (1.9)	0 (0)	0.30
Gonorrhoea	5 (9.4)	20 (16.4)	0.33
Herpes	1 (1.9)	3 (2.5)	1.00
Acute hepatitis C	0 (0)	7 (5.7)	0.10
Infectious hepatitis B	1 (1.9)	8 (6.6)	0.28
Acute hepatitis C+ Infectious hepatitis B	1 (1.9)	15 (12.3)	0.04
Past history of STIs	20 (37.7)	64 (52.2)	0.1
Past syphilis infection	4 (7.6)	54 (44.3)	0.0001

median age of 34 years, with a wide variation in country of birth. This population is therefore reflective of a young, mobile population, acknowledged to be the group presently at the greatest risk of STI acquisition, particularly syphilis.² ¹¹ ¹⁴

Social factors, including the way in which our patients met future sex partners, were examined with variations seen between the Western European and Eastern European sites. Alcohol use at the time of presumed syphilis acquisition was high with rates of 69.4%, 84.9% and 41.2% in Ireland, Poland and Germany, respectively, with illicit oral/nasal recreational drug use also reported frequently with rates of 38.8%, 8.2% and 23.5%, respectively. We recognise that some of the differences between the sites are likely explained by response bias in terms of social desirability and stigma-related issues, but clearly social differences do exist between the three sites.

In terms of clinical presentation, only one in five of the HIV-positive patients had primary syphilis compared with almost half of the HIV-negative group (p=0.0002). We did not identify atypical syphilitic ulcers as noted in other clinical reports.¹⁸ This is in keeping with previous findings that primary syphilis may be symptomless in HIV-positive patients.²⁰ Around half of the HIV-positive patients presented with secondary syphilis compared with only 13% of the HIV-negative patients, consistent with previous studies.¹⁶ ¹⁹ ²⁹

As expected, the rates of oral sex between the HIV-positive and HIV-negative groups were similar at 90.6% vs 92.6%, although anal-insertive rates were higher among the HIV-positive patients (77.9% vs 56.6%, p=0.007) with anal-receptive rates of 79.9% and 45.3% (p=0.0001). When we further subdivided the group into those patients who had an HIV viral load <39 copies/mL and those with a viral load >40 copies/mL, we found no statistical differences between the rates of any types of sex, with high rates of all sexual activities (anal-insertive/anal-receptive and vaginal intercourse) across both groups. While it is of concern that there was a

significantly greater amount of anal-insertive and anal-receptive sex among our HIV-positive patients, it is perhaps of greater concern that the virally non-suppressed patients did not appear to modify their sexual behaviour according to their viral load status. This has clear implications for healthcare providers in terms of delivering safe sex messages and risk reduction strategies to our HIV-positive patients. Interestingly, the levels of partner awareness regarding the recruited patients syphilis and HIV status indicated patients were more likely to have disclosed their HIV status rather than their syphilis infection to a current partner. This indicates that there may be a disconnect between the level of knowledge of increased transmissibility of HIV in the presence of another STI.

A high rate of concurrent STIs at the time of syphilis diagnosis was found in both HIV-positive and HIV-negative patients. Although no individual STI was found to be more common in the HIV-positive group, there was a significantly higher frequency of acute/infectious hepatitis C and B in those with HIV infection. A past history of STIs was noted in half of HIV-positive patients compared with 37% of HIV-negative patients, although it was noteworthy that a previous syphilis infection had occurred more frequently in the HIV-positive patients (p=0.0001).

Although much data exist³⁰⁻³² regarding the treatment of syphilis, there are few studies that have compared the outcomes of treatment of HIV-positive and HIV-negative individuals, particularly with oral antibiotics compared with parenteral forms of penicillins.^{24 33} A number of trials comparing the use of tetracyclines or macrolides versus long-acting penicillin have also shown to be equivalent,^{31 32} and, initially, azithromycin as a large single dose was thought to be a promising alternative. This was favoured due to the cumbersome and painful long-acting parenteral penicillins and clearance rates were good.³⁰ However, the ever-growing epidemic of macrolide resistance around the world has prevented its recommended use.³⁴⁻³⁶ Interestingly, the most commonly referenced guidelines^{26 27 28} all recommend parenteral penicillin as first-line treatment for HIV-positive and HIV-negative patients with syphilis; however, second-line and third-line therapy in HIV-positive patients remains contentious.. Despite this, we found that only 58% of HIV-positive patients received a long-acting penicillin formulation compared with almost 90% of HIV-negative patients. In fact, the HIV-positive patients were more likely to receive oral doxycycline than the HIV-negative group. Reassuringly, only two HIV-positive patients received azithromycin while six received ceftriaxone. The administration of parental penicillin is dependent on the availability of on-site treatment clinic rooms and nursing staff, which may have been a factor favouring the use of oral tetracyclines in the context of an exclusive HIV service compared with a combined sexual health and HIV service.

The authors acknowledge a number of limitations that must be taken into consideration when analysing these data. First, as patients were recruited in a convenience sampling manner, with a relatively small German cohort, the findings may not be generalisable to all HIV-positive and HIV-negative MSMs in their respective countries. Second, the authors recognise that there may be bias in the results treatment administered due to a centre effect. Finally, this study was not designed to collect information about the probable route of transmission of infectious hepatitis B and C and partner serosorting, all of which may have provided useful information.

Despite these limitations, this prospective study recruited patients from both Eastern and Western Europe, the majority of whom were HIV-positive. The clinics chosen represent an accurate picture of where the majority of HIV-positive patients receive care in their respective countries and all three are

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specialist HIV sites. Follow-up treatment results in this study will undoubtedly inform future treatment guidelines of syphilis in HIV-positive patients.

European MSMs and, in particular, HIV-positive MSMs carry a disproportionate burden of STIs including syphilis infection and reinfection. There are a number of reasons for this, including social, economic and migratory, but what remains unclear is whether or not this increased incidence is reflective of an immunological susceptibility or whether this is due to increased treponemal exposure secondary to risky sexual behaviour. Good evidence exists that syphilis and HIV coinfection can affect a person's own disease trajectory (ie, viral load escapes and CD4 count drops)^{22–23} not to mention the risk of onward HIV transmission. Our study found a notable rate of concurrent STIs, 40% uncontrolled HIV vireamia and little apparent behaviour modification, regardless of viral load.

Targeted sexual healthcare in HIV-positive patients is vital, and the model of combined sexual health and HIV clinics needs further evaluation to optimise the assessment and management of these patients. We feel this has important implications for education and prevention strategies both for patients, their partners and their healthcare providers.

Key messages

- Syphilis infection continues to rise in Western and Eastern Europe, with men who have sex with men (MSMs), and in particular HIV-positive MSMs being disproportionately affected.
- This cohort of HIV-positive MSMs had significant high-risk sexual activity regardless of their viral load status and experienced high rates of concurrent sexually transmitted infections.
- ► HIV-positive MSMs were more likely to present with secondary syphilis and more likely to receive oral doxycycline than their HIV-negative counterparts.
- Treatment varied across all three sites despite the current guidelines on management of syphilis.

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Contributors FM and GF conceived the study. The original research protocol was written jointly by SOD and FM. DR, SOD, ET and PS were responsible for execution of the study. DR has written the manuscript, recruited the patients from Ireland and coordinated the three sites including the gathering together of all data. PS recruited patients in Poland and created the database. EFB recruited patients in Poland and maintained the database. CSab performed the statistical analysis and revised the manuscript. ET recruited patients in Germany and created and maintained the database. SS and CS recruited patients in Ireland. SOD created the database, recruited patients and maintained the data. AH was in charge of the study at the Infectious Disease Hospital in Warsaw. GF was in charge of the study in the

investigator and in charge of the study in Ireland. All authors had full access to the data in the study, and read, revised and approved the final manuscript.

Competing interests None.

Ethics approval Tallaght Hospital/St. James's Hospital Joint Research Ethics Committee, Dublin, Ireland. The ethical approval granted covered all three sites with additional ethical approval granted for the German cohort, allowing them to exchange pseudonymised data to multilateral projects.

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