Occurrence, risk factors, diagnosis and treatment of syphilis in the prospective observational Swiss HIV Cohort Study

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Background: Annual syphilis testing was reintroduced in the Swiss HIV Cohort Study (SHCS) in 2004. We prospectively studied occurrence, risk factors, clinical manifestations, diagnostic approaches and treatment of syphilis.

Methods: Over a period of 33 months, participants with positive test results for Treponema pallidum hemagglutination assay were studied using the SHCS database and an additional structured case report form.

Results: Of 7244 cohort participants, 909 (12.5%) had positive syphilis serology. Among these, 633 had previously been treated and had no current signs or symptoms of syphilis at time of testing. Of 218 patients with newly detected untreated syphilis, 20% reported genitooral contacts as only risk behavior and 60% were asymptomatic. Newly detected syphilis was more frequent among men who have sex with men (MSM) [adjusted odds ratio (OR) 2.8, $P < 0.001$], in persons reporting casual sexual partners (adjusted OR 2.8, $P < 0.001$) and in MSM of younger age ($P = 0.05$). Only 35% of recommended cerebrospinal fluid (CFS) examinations were performed. Neurosyphilis was diagnosed in four neurologically asymptomatic patients; all of them had a Venereal Disease Research Laboratory (VDRL) titer of 1:$\geq$32. Ninety-one percent of the patients responded to treatment with at least a four-fold decline in VDRL titer.

Conclusion: Syphilis remains an important coinfection in the SHCS justifying reintroduction of routine screening. Genitooral contact is a significant way of transmission and young MSM are at high risk for syphilis. Current guidelines to rule out neurosyphilis by CSF analysis are inconsistently followed in clinical practice. Serologic treatment response is above 90% in the era of combination antiretroviral therapy.

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Introduction

Reemergence of syphilis, especially among men who have sex with men (MSM), was observed in metropolitan areas in the United States and in western Europe in the new millennium [1–10]. Several studies showed that HIV-infection was associated with a higher risk for syphilis [11–13]. Unprotected anal intercourse was found to be an important route of syphilis transmission indicating a trend for increasing sexual risk behavior [12]. Additionally, a high proportion of persons with syphilis stated unprotected oral contacts as the only risk for transmission [6,7,14,15].

Diagnosis, course and optimal management of syphilis in HIV coinfected persons remain somewhat controversial. Reports, mostly from the era before the advent of combination antiretroviral therapy (ART), indicated a tendency for atypical and malignant presentation of syphilis. However, these observations were not substantiated by recent larger studies [16,17]. The frequency and clinical relevance of neurological involvement of syphilis in HIV-coinfected patients remains a subject of debate [18–20]. As a result, the diagnostic strategies suggested by the recently published Centers for Disease Control and Prevention (CDC) guidelines on opportunistic infections in HIV-positive adults currently include lumbar puncture for all patients with neurological symptoms and for HIV-infected persons with either late latent syphilis (>1 year duration) or latent syphilis of unknown duration [21,22].

Because of the steady decline of infection rates since the late 1980s, syphilis was removed from the lists of notifiable diseases in Switzerland in 1999. In the Swiss HIV Cohort Study (SHCS), routine screening for syphilis in HIV-positive patients was abandoned at the end of 1998 after an analysis had revealed that screening every 2 years had little impact in the context of the declining incidence at that time (unpublished data). However, the network of Swiss dermatology clinics observed an increase in rates of primary and secondary syphilis beginning in 2001 [23,24]. This observation, paralleled by the international epidemics, led to the reintroduction of systematic annual syphilis serology screening in the SHCS in 2004.

The aims of this prospective observational cohort study were to monitor the occurrence of syphilis in the SHCS after 2004, to identify risk factors for syphilis, to study the diagnostic work-up, and to evaluate treatment strategies in clinical practice.

Patients and methods

Swiss HIV Cohort Study

The SHCS (www.shcs.ch) is a nationwide prospective cohort study with ongoing enrolment of adult patients with HIV infection [25]. Information about the course and treatment of HIV infection, socioeconomic situation, sexual behavior including sexual intercourse with stable or casual partners and condom use is collected according to standardized criteria at enrolment and at follow-up visits every 6 months. All participants gave written informed consent and the study is approved by ethical committees of all participating centers.

Diagnostic and treatment algorithm

Before reinitiating routine testing for syphilis, treating physicians were provided with a standardized diagnostic and treatment algorithm (Supplemental Digital Content Figure 1, http://links.lww.com/QAD/A54). Specifically, the stage of infection was assessed according to history, clinical signs and symptoms (primary or secondary syphilis and suspected neurosyphilis) or time of syphilis seroconversion in the case of latent infection using the published definitions [21,22].

Syphilis testing and case report form

Annual syphilis testing was reintroduced in 2004. TPHA (Treponema pallidum hemagglutination assay) was used as screening test, positive results were considered indicative for prior exposure to *T. pallidum*. VDRL (Venereal Disease Research Laboratory) titers were assessed to determine disease activity and response to therapy. All patients with a positive TPHA (including VDRL negative persons) were assessed by their physicians using a case report form (CRF) for test results, clinical symptoms, diagnosis [primary syphilis, secondary syphilis, early latent syphilis, late latent syphilis (>1 year duration), latent infection of unknown duration and neurosyphilis] and presumed route of transmission (unprotected anal or vaginal intercourse, genitooral contact). The physicians decided on initiating further diagnostic steps and treatment strategy.

Data base

We used the SHCS database updated in February 2008 in addition to CRF results for analysis. For each patient, SHCS information collected during the last follow-up visit prior to the syphilis test was used, which took place, on average, 10 days before syphilis testing.

Sexual behavior

Information about sexual behavior including sex preference (MSM vs. heterosexual) was collected using information given during the last SHCS follow-up visit prior to syphilis testing. Patients who were sexually active with a stable partner and did not explicitly state to have sexual contacts with casual partners (including patients who refused to answer questions about casual contacts) were categorized as having sexual contacts with their stable partner only. Patients who stated to have casual partners were categorized as having casual partners regardless of their having a stable partner too. Inconsistent condom use was defined as condom use only sometimes or never with sexual contacts. Additional information on

mode of transmission (insertive, receptive, oral, anal contact) was gained through the CRF. Sex of sexual contacts was not specifically assessed, patients who self-described as MSM were considered to have sex with men, patients who self-described as heterosexual were considered to have sexual contacts with the opposite sex.

Treatment

Suggested treatment strategies are listed in Supplemental Digital Content Figure 1, http://links.lww.com/QAD/A54. All previously, untreated patients with a positive TPHA result were considered to be eligible for treatment according to their current clinical stage independent of VDRL results.

Statistical analysis

The proportion of patients with a positive TPHA result out of all patients who were tested over a period of 33 months between January 2004 and September 2006 was calculated. For descriptive analysis, tabulations were used and relevant differences between subgroups were assessed using nonparametrical tests (Wilcoxon-rank sum test for ordinal/numerical data and chi-squared test for categorical data). Unadjusted and adjusted ORs for explanatory variables were calculated using logistic regression models. All analyses were performed using Stata SE, version 10.0 (Stata Corp., College Station, Texas, USA).

Results

Patient flow and characteristics

A total of 7244 participants were tested for syphilis between January 2004 and September 2006 (Fig. 1). Repeated testing either in the course of annual routine screening or in the context of clinical symptoms was allowed. The numbers of patients with positive TPHA tests are shown in Fig. 1. A newly detected, previously untreated syphilis episode was found in 218 persons (3% of tested population).

Patient characteristics are shown in Table 1. Of 851 participants with a positive TPHA test result, 633 were adequately treated before January 2004 and did not show any clinical or laboratory signs of relapse or reinfection at the time of testing. The remaining 218 patients had newly detected syphilis without previous treatment for this episode. These patients were predominantly male and most had acquired HIV through MSM contacts. They were younger and time since HIV diagnosis was significantly shorter compared with previously treated and/or seronegative patients. The majority of these patients had no signs of advanced HIV disease and only 19% had a previous AIDS-defining event. Accordingly, fewer patients were on ART as compared with the other subgroups. A higher proportion of 81% was sexually active as compared with 60% in the previously treated

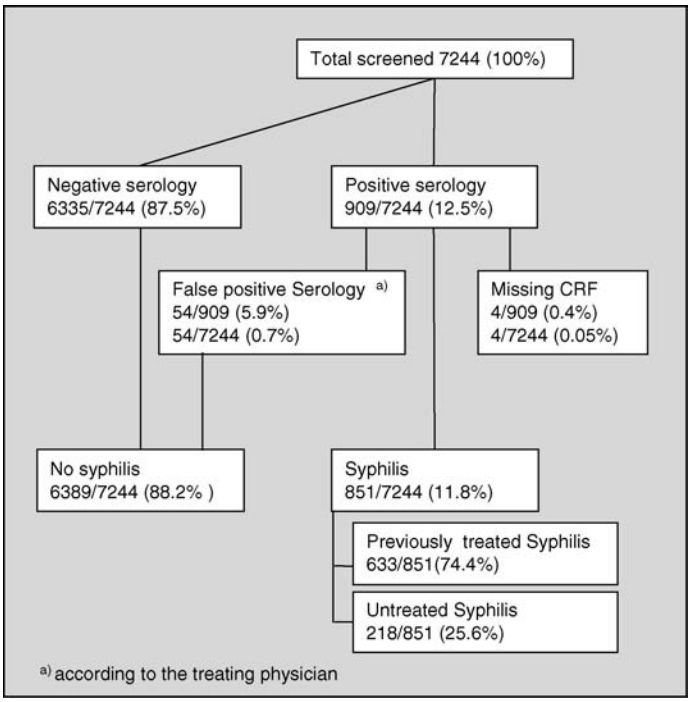


Fig. 1. Screening results: of 7244 screened individuals 909 had a positive syphilis serology. According to the treating physicians, 54 patients had false positive test results and they were included in the seronegative group, resulting in 6389 patients with no syphilis. For four patients with positive results no further information was available and they were excluded from analysis, resulting in 851 patients with syphilis, 633 of these had previously received adequate treatment and 218 patients had newly detected, previously untreated syphilis.

Table 1. Population characteristics.

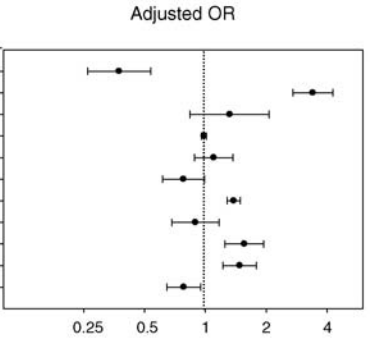
		Screened population		Negative syphilis serology		Positive syphilis serology[¶]		P^a	Positive syphilis serology				P^b	P^c
									Previously treated syphilis		Untreated syphilis			
		P_{50}	(P_{25}–P_{75})	P_{50}	(P_{25}–P_{75})	P_{50}	(P_{25}–P_{75})		P_{50}	(P_{25}–P_{75})	P_{50}	(P_{25}–P_{75})		
Age	42.2	(36.8–48.2)		41.8	(36.5–47.3)	46.8	(40.1–55.9)	<0.001	49.8	(41.9–57.8)	41.4	(35.2–45.9)	0.04	<0.001
CD4 cell count per μl	439	(301–618)		435	(300–618)	464	(315–614)	0.04	458	(308–600)	495	(347–650)	0.004	0.03
HIV years	9.0	(3.8–14.9)		8.9	(3.7–15.0)	9.5	(4.9–14.4)	0.07	10.1	(6.0–15.3)	6.7	(2.0–12.5)	<0.001	<0.001
		n	(%)	*n*	(%)	*n*	(%)		*n*	(%)	*n*	(%)		
Total		7244	(100)	6389	(100)	851	(100)		633	(100)	218	(100)		
Sex	Man	4983	(68.8)	4235	(66.3)	744	(87.4)	<0.001	554	(87.5)	190	(87.2)	<0.001	0.9
	Woman	2261	(31.2)	2154	(33.7)	107	(12.6)		79	(12.5)	28	(12.8)		
HIV risk	HET	2803	(38.7)	2629	(41.2)	174	(20.4)	<0.001	131	(20.7)	43	(19.7)	<0.001	0.4
	IDU	1497	(20.7)	1457	(22.8)	39	(4.6)		33	(5.2)	6	(2.8)		
	MSM	2650	(36.6)	2033	(31.8)	614	(72.2)		452	(71.4)	162	(74.3)		
	Other	294	(4.0)	270	(4.2)	24	(2.8)		17	(2.7)	7	(3.2)		
CDC stage	CDC A	3397	(46.9)	2970	(46.5)	424	(49.8)	0.1	291	(46.0)	133	(61.0)	<0.001	0.001
	CDC B	2034	(28.1)	1817	(28.4)	217	(25.5)		173	(27.3)	44	(20.2)		
	CDC C	1813	(25.0)	1602	(25.1)	210	(24.7)		169	(26.7)	41	(18.8)		
HIV–RNA <50 copies/ml	4547	(62.8)		4001	(62.6)	545	(64.0)	0.4	421	(66.5)	124	(56.8)	0.07	0.01
Triple ART	Yes	5254	(72.5)	4632	(72.5)	621	(73.0)	0.8	484	(76.5)	137	(62.8)	0.001	<0.001
Sexually active														
	Yes	4588	(63.3)	4028	(63.0)	556	(65.3)	0.2	380	(60.0)	176	(80.7)	<0.001	<0.001
If sexually active														
	Casual partners	1523	(33.2)	1193	(29.6)	327	(58.8)	<0.001	207	(54.5)	120	(68.2)	<0.001	0.002
Condom use with casual partners														
	Yes	1221	(80.2)	960	(80.5)	258	(78.9)	0.5	169	(81.6)	89	(74.2)	0.09	0.1

Population characteristics. HIV-risk: presumed risk for HIV transmission (HET= heterosexual, IDU= intravenuous drug abuse, MSM= men having sex with men). P_{50} indicates the median, P_{25}–P_{75} indicates the interquartile range for a given set of observations. [¶]: patients with false positive test results were excluded. *P*-values for significant differences among subgroups are indicated: p^a: comparing the subgroup with positive syphilis serology vs. the subgroup with negative syphilis serology; p^b: comparing the subgroup with untreated syphilis vs. the subgroups with negative syphilis serology and previously treated syphilis; p^c: comparing the subgroup with untreated syphilis vs. the subgroup with previously treated syphilis.

(a)

Factors predictive of having positive syphilis serology

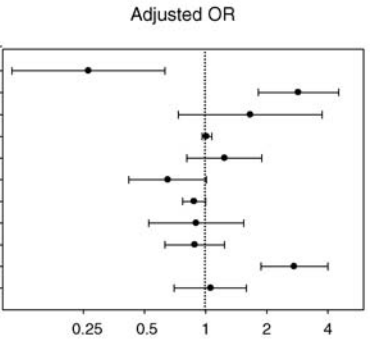
Variable	n^a(7240)	Unadjusted OR	(95% CI)	Adjusted OR	(95% CI)	*P*
IDU (compared to HET)	1496	0.40	(0.28 – 0.58)	0.37	(0.26 – 0.53)	<0.001
MSM (compared to HET)	2647	4.56	(3.80 – 5.45)	3.39	(2.70 – 4.26)	<0.001
OTHER (compared to HET)	294	1.34	(0.86 – 2.10)	1.29	(0.82 – 2.03)	0.267
CD4 count (100)	n.a.	1.01	(0.98 – 1.04)	0.99	(0.96 – 1.02)	0.438
RNA < 50 copies	4546	1.06	(0.91 – 1.23)	1.06	(0.85 – 1.32)	0.597
Receiving triple ART	5253	1.02	(0.87 – 1.20)	0.80	(0.63 – 1.02)	0.074
Age (quartiles)	n.a.	1.51	(1.41 – 1.62)	1.38	(1.28 – 1.48)	<0.001
Sex female compared to male	2261	0.28	(0.23 – 0.35)	0.90	(0.69 – 1.18)	0.467
HIV for more than 3 years	5749	1.46	(1.20 – 1.77)	1.58	(1.27 – 1.97)	<0.001
Casual partners	1520	2.72	(2.34 – 3.16)	1.53	(1.27 – 1.86)	<0.001
Sex with stable partner only	3064	0.46	(0.39 – 0.54)	0.77	(0.63 – 0.93)	0.007



(b)

Factors predictive of having untreated syphilis

Variable	n^b(7240)	Unadjusted OR	(95% CI)	Adjusted OR	(95% CI)	*P*
IDU (compared to HET)	1496	0.26	(0.11 – 0.61)	0.26	(0.11 – 0.62)	0.002
MSM (compared to HET)	2647	4.18	(2.98 – 5.88)	2.81	(1.79 – 4.43)	<0.001
OTHER (compared to HET)	294	1.57	(0.70 – 3.51)	1.66	(0.74 – 3.76)	0.222
CD4 count (100)	n.a.	1.05	(1.00 – 1.10)	1.02	(0.97 – 1.07)	0.515
RNA < 50 copies	4546	0.78	(0.59 – 1.02)	1.19	(0.77 – 1.83)	0.430
Receiving triple ART	5253	0.63	(0.48 – 0.83)	0.70	(0.45 – 1.09)	0.115
Age (quartiles)	n.a.	0.87	(0.77 – 0.98)	0.86	(0.76 – 0.98)	0.027
Sex female compared to male	2261	0.32	(0.21 – 0.47)	0.88	(0.52 – 1.50)	0.652
HIV for more than 3 years	5749	0.59	(0.44 – 0.79)	0.91	(0.65 – 1.27)	0.585
Casual partners	1520	4.92	(3.74 – 6.46)	2.89	(1.98 – 4.22)	<0.001
Sex with stable partner only	3064	0.46	(0.34 – 0.63)	1.04	(0.69 – 1.67)	0.846



(c)

Factors predictive of having untreated syphilis if MSM

Variable	n^c(2647)	Unadjusted OR	(95% CI)	Adjusted OR	(95% CI)	*P*
CD4 count (100)	n.a.	1.04	(0.98 – 1.10)	1.02	(0.96 – 1.08)	0.574
RNA < 50 copies	1645	0.85	(0.62 – 1.18)	1.37	(0.80 – 2.31)	0.248
Receiving triple ART	1892	0.68	(0.49 – 0.95)	0.67	(0.39 – 1.15)	0.146
Age (quartiles)	n.a.	0.74	(0.64 – 0.85)	0.79	(0.68 – 0.92)	0.003
HIV for more than 3 years	2054	0.74	(0.51 – 1.05)	1.12	(0.74 – 1.68)	0.595
Casual partners	1059	2.87	(2.06 – 4.00)	3.26	(2.02 – 5.26)	<0.001
Sex with stable partner only	824	0.64	(0.44 – 0.93)	1.40	(0.81 – 2.41)	0.232

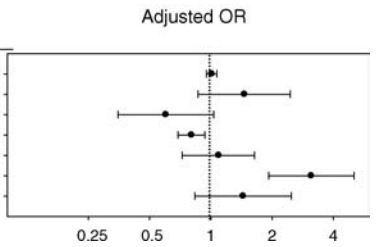


Fig. 2. Risk factors associated with syphilis infection. (a) Risk factors for having syphilis; (b) Risk factors for having untreated syphilis; (c) Risk factors for having untreated syphilis in the MSM subpopulation. Unadjusted and adjusted odds ratios are indicated, *P*-values are given for multivariate analysis. Presumed risk for HIV transmission: HET= heterosexual, IDU= intravenous drug abuse, MSM= men having sex with men. CD4 cell count 100: level of CD4 T cells/μl per 100 increase. RNA less than 50 copies RNA level below 50 copies/ml. Age (quartiles): age per quartile increase. *n*: number of participants with respective criterion in analyzed population (n^a n^b entire screened population with available case report form; n^c screened MSM population with available case report form). n.a.: not applicable.

group and 63% in the seronegative group. More than two-thirds stated to have casual sexual partners. Compared with the other subgroups, condom use with these contacts was slightly less common.

Factors associated with syphilis

MSM as presumed route of HIV transmission, higher age, and HIV diagnosis for more than 3 years prior to syphilis screening and having casual sex partners were all associated with positive TPHA results (Fig. 2a). HIV transmission through MSM contacts and having casual sex partners were predictive for a newly detected, untreated syphilis episode (Fig. 2b). Receiving ART showed a negative correlation with untreated syphilis in the univariable but not in multivariable analysis. Of 218 patients with untreated syphilis, 162 (74%) were MSM and risk factors for this subgroup were analyzed separately (Fig. 2c): Younger age and having sexual contacts with casual partners correlated with untreated syphilis in the MSM population.

Presumed route of syphilis transmission

Of 218 patients, 54 had acquired syphilis through anal, 42 patients through vaginal intercourse and 43 patients

Table 2. Mode of syphilis transmission according to sex, HIV-risk group and sexual behavior.

		Mode of syphilis transmission											
		Unknown		Oral-risk only		Anal-risk only		Vaginal-risk only		Genital and oral risk		Total	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	%
Total		31	(14.2)	43	(19.7)	54	(24.8)	42	(19.3)	48	(22.0)	218	(100)
Man		28	(14.7)	43	(22.6)	54	(28.4)	20	(10.5)	45	(23.7)	190	(100)
Woman		3	(10.7)	0	(0.00)	0	(0.00)	22	(78.6)	3	(10.7)	28	(100)
MSM		21	(13.0)	39	(24.1)	50	(30.9)	6	(3.7)	46	(28.4)	162	(100)
Casual partners	Yes	17	(14.2)	32	(26.7)	32	(26.7)	11	(9.2)	28	(23.3)	120	(100)
Consistent condom use with casual partners													
	No	3	(9.7)	6	(19.4)	13	(41.9)	2	(6.5)	7	(22.6)	31	(100)
	Yes	14	(15.7)	26	(29.2)	19	(21.4)	9	(10.1)	21	(23.6)	89	(100)

Most probable route of syphilis transmission. Unknown: no information given by patient and or physician. Oral risk only patients with exclusive genitooral contacts and no insertive or receptive genital intercourse. Anal risk receptive or insertive anal intercourse. Vaginal risk receptive or insertive vaginal intercourse. Genital and oral risk both genital intercourse and genitooral contacts.

through exclusive genitooral contacts (Table 2). Even though anal intercourse was the most important risk behavior among MSM (31%), 24% of these patients stated to have genitooral contacts exclusively. Of 89 persons with casual sex partners and condom use with all these contacts, 29% practiced genitooral contacts as only way of syphilis transmission.

Diagnosis, cerebrospinal fluid analysis

Overall 130 (60%) of 218 patients with untreated syphilis were asymptomatic and syphilis infection was detected through routine screening. The final diagnoses are shown in Table 3.

None of the four patients diagnosed with neurosyphilis by CSF analysis showed clinical signs of neurological alteration. One of these patients had symptoms of secondary syphilis, the other three persons were asymptomatic and the diagnosis was based on results of lumbar puncture. However, in all four patients an increased serum VDRL titer of 1:$\geq$32 was found in addition to positive TPHA tests as possible indicator for disease activity. The only patient who underwent CSF analysis because of neurological symptoms had a negative CSF result and was diagnosed with latent syphilis of unknown duration.

Table 3. Untreated syphilis: diagnosis and CSF analysis.

	Total		CSF analysis done	
Diagnosis				
	n	(%)	*n*	(%)
Primary syphilis	26	(11.9)	1	(3.9)
Secondary syphilis	50	(22.9)	3	(6.0)
Neurosyphilis[a]	4	(1.8)	4	(100.0)
Early latent syphilis	25	(11.5)	2	(8.0)
Latent infection (unknown duration)[b]	55	(25.2)	17	(30.9)
Late latent syphilis[b]	26	(11.9)	11	(42.3)
Reinfection[c]	32	(14.7)	5	(15.6)
Total	218	(100.0)	43	(19.7)

Diagnosis and CSF analysis in 218 patients with newly detected, untreated syphilis.
[a]None of the four patients diagnosed with neurosyphilis had neurologic symptoms at the time of CSF analysis, 1 patient had signs of secondary syphilis, the remaining three patients were asymptomatic.
[b]CSF analysis indicated according to guidelines.
[c]32 patients with reinfection: 22 asymptomatic, six signs of primary syphilis, four with signs of secondary syphilis. Of the five reinfected patients with CSF analysis four were asymptomatic and one had signs of secondary syphilis.

According to the diagnostic and treatment algorithm, CSF examination would have been indicated in 84 (38.5% of 218) asymptomatic patients with either late latent syphilis ($n = 26$) or syphilis infection of unknown duration ($n = 58$) but was performed in only 31 persons. Laboratory signs of neurosyphilis were found in three (9.7%) of those 31 persons tested. This corresponds to a 95% confidence interval (CI) of frequency of central nervous system (CNS) involvement in latent syphilis of 3–32%. Of 53 patients in whom CSF analysis was not performed, 43 had a VDRL titer of 1:$\leq$4 and in 31 of them the treating physician decided actively against lumbar puncture.

Treatment and treatment response

All previously untreated patients with a positive TPHA test were considered to be eligible for treatment of their current episode independent of VDRL test results. Patients with a VDRL titer of 1:$\leq$4 at baseline tended to be slightly older [median 43.4 years; interquartile range (IQR) 36.3–49.9] compared to patients with reactive VDRL tests (median 40.9 years; IQR 34.8–44.5) but were similar in other descriptive parameters. Most initiated treatment strategies (197 of 218, 90.3%) were adequate according to current standards [22]. However, 11 patients, all of them with either late latent infection or latent infection of unknown duration were not treated at all: One was lost to follow-up, two refused treatment and for the remaining eight patients with positive TPHA

serology, the treating physician declined treatment due to a nonreactive VDRL test. An additional five patients received inadequate treatment: Two patients with latent infection of unknown duration and two patients with late latent infection were treated with a single dose of 2.4 million units of benzathine penicillin only, and one patient diagnosed with early syphilis was treated with azithromycin, a regimen that is not encouraged due to the possibility of resistance of *T. pallidum*.

Interestingly, ceftriaxone 2 g/day i.v. (intravenously) for 14 days was used to treat three of four patients with neurosyphilis, a regimen that is probably effective but currently not recommended by guidelines, one patient diagnosed with neurosyphilis received penicillin G for 14 days.

Of the 207 patients treated for syphilis, 125 had a reactive VDRL titer at time of diagnosis and treatment responses were assessed for this subgroup: Most patients (105/125, 87%) showed an adequate treatment response at month 12, an additional five patients had a documented decline in VDRL titers at months 18. Over the course of 24 months, 114 of 125 patients (91%) showed an adequate treatment response with at least four-fold decline in VDRL titer.

Of the 11 'nonresponders' six had incomplete serological follow-up data, three patients were reinfected during the 24-months follow-up and two patients (one with primary and one with secondary syphilis) showed insufficient declines in VDRL titers despite adequate treatment.

Discussion

After introduction of routine syphilis screening in 2004, we found, in 12.5% of 7244 SHCS participants, a positive syphilis serology over the course of 33 months. TPHA titer was used for primary screening, and was considered to be indicative of prior exposure to *T. pallidum*. Patients with positive TPHA tests and no prior treatment were considered to have newly diagnosed syphilis. This strategy differs from practices in Anglo-Saxon countries where VDRL test is used for screening, but allows patients with presumed latent infection who are likely to have low or negative VDRL titers [26,27]. Of 218 patients with a newly detected and untreated syphilis episode, 130 (60.5%) were asymptomatic. Both the proportion of positive syphilis serology and the frequency of asymptomatic patients seem to justify reintroduction of routine screening.

The rate of positive syphilis serology among all MSM in the SHCS was 23%, and more than 70% of patients with positive syphilis serology were MSM. These findings confirm the reports on syphilis epidemics in metropolitan areas in the United States and in western Europe, showing an increase of syphilis rates predominantly in MSM communities, although infection rates among heterosexual women and men decreased [1–9].

The currently observed rise in rates of syphilis infections among HIV-positive MSM could represent a rebound due to increased sexual activity as a direct effect of ART associated reduction in morbidity [28]. Alternatively, it has been argued that ART could reduce the perceived risk for HIV transmission and lead to increased sexual risk taking [29–31]. However, we did not find evidence that receiving ART or having a suppressed viral load was associated with positive syphilis serology. In our study, it was not the treated population who more often acquired syphilis but the patients who were only recently diagnosed with HIV. These findings are in accordance with previous reports including one meta-analysis where no direct association between ART and sexual risk taking was found [32–34].

In Switzerland, the federal office of public health recently reported an increase of newly diagnosed HIV, attributable to a resurgence of sexual risk behavior among younger MSM, many of whom had a prior history of sexually transmitted diseases (STDs). In our study, patients with newly detected, untreated syphilis were younger with a shorter time since HIV diagnosis and a lower proportion of ART but a higher rate of casual sexual partners. Arguably, the association of a shorter time since HIV diagnosis (i.e. less than 3 years) with untreated syphilis might reflect a concurrent acquisition of HIV and syphilis and would also correspond to the observed rise in syphilis rates since 2000. Taken together, these findings support the hypothesis that sexual risk behavior is raising especially among younger MSM leading to an increased rate of transmission of STDs including HIV.

An important proportion of patients with newly detected syphilis stated oral contacts as only sexual risk factor during the time of syphilis transmission. This finding points to a misperception of oral sex as 'safe', which may to a certain degree apply for the risk of HIV transmission but not for many other STDs. Furthermore, syphilitic lesions at mucosal sites might propagate viral shedding and induce recruitment of inflammatory cells thereby allowing for HIV transmission via oral route [35]. As a consequence, efforts to discuss sexual risk behavior and routes of transmission, not only of HIV but also of other STDs, should be made early in the course of HIV counseling and more frequent risk-based screening might be warranted.

We also studied diagnostic and treatment strategies initiated by the treating physicians. One major concern in HIV patients coinfected with syphilis is the possibility of increased neurological involvement. During the initial dissemination in primary or secondary syphilis *T. pallidum* frequently invades the CNS in both HIV-coinfected and HIV-negative patients. In HIV-negative persons,

immunologic mechanisms seem to control early CNS involvement in most cases, reflected by the low incidence of neurologic relapse after treatment with benzathine penicillin despite its lack of bactericidal CNS concentrations. The frequency and clinical relevance of neurologic involvement in HIV-coinfected patients remains a subject of debate. In a multicenter, randomized, double-blind trial, Rolfs *et al.* [18] found a lower rate of serologic response in HIV-coinfected patients treated for early syphilis but clinical treatment failure or development of neurosyphilis was similarly rare in both HIV-negative and HIV-positive persons independent of adding high-dose amoxicillin and probenecid to standard treatment for early syphilis. Somewhat contrary, Marra *et al.* [19,20] found an increased risk for neurosyphilis in HIV-coinfected patients with a rapid plasma reagin (RPR) titer of 1:>32 or a CD4 T-cell count of less than 350 cells/μl. Furthermore, HIV-coinfected patients were less likely to normalize CSF–VDRL reactivity after treatment for neurosyphilis compared with HIV-negative persons.

In accordance with current guidelines, we proposed CSF examination in all patients with neurologic symptoms, late latent syphilis or latent infection of unknown duration [22]. However, lumbar puncture was performed in only 31 of these 84 patients. In four patients without neurological signs evidence for neurosyphilis was found in CSF, all of those had a VDRL titer of 1:≥32. For 31 of the remaining 53 patients, the treating physician decided against CSF analysis, all of these patients had a VDRL titer of 1:<4. Of note, two recent publications argue towards performing CSF puncture in neurologically asymptomatic patients only in case of high VDRL titers [36,37], in concordance with the findings of Marra *et al.* [19].

Even though treatment was adequate in 207 of 218 patients, there is room for improvement. Although all the patients are followed in specialized infectious diseases services, 11 patients did not receive treatment at all and five patients were inadequately treated.

Treatment success is usually assessed by monitoring the decline in VDRL titers, a four-fold reduction at month 12 after treatment is considered to be adequate. In our population of 218 newly diagnosed patients, only 125 (58%) had VDRL titers of 1:>4 at the time of diagnosis and treatment response was assessed in this subgroup; adequate response was found in 114 of 125 patients over a period of 24 months, two patients showed real treatment failure despite adequate therapy. Taken together, these results demonstrate a good serological treatment response comparable to HIV-negative syphilis-infected patients similar to recently published findings of a large series in the era of combination ART [38].

Our study has several limitations. No statement about syphilis incidence rate in the SHCS can be made as the time of infection remains unknown for patients with late latent infection, latent infection of unknown duration and patients with previously treated syphilis. The presented rate of newly detected syphilis might overestimate the actual frequency as a result of the catch-up strategy after abandoning routine screening for 5 years. However, analysis of yearly rates of newly detected, previously untreated syphilis for the years 2004–2006 showed an increase of rates over time rather than a decrease, probably reflecting a rise of over-all syphilis incidence. The sexual behavior analyzed in the context of syphilis acquisition reflects the answers given at the last follow-up visit prior to syphilis screening and depicts the sexual behavior during the 6 months prior to this visit. As the time of transmission remains unknown for patients with late latent infection or latent infection of unknown duration, the sexual behavior at the time of infection might differ from the statements used for our analysis. However, analysis of answers given at five consecutive follow-up visits over a period of 2 years revealed no significant variation, implicating that sexual behavior did not significantly change over time. Finally, the low incidence of proven neurosyphilis in our study may be partly attributable to the low number of CSF examinations performed in patients with latent infection and might not adequately depict the occurrence of neurosyphilis in a HIV-coinfected population.

Conclusion

In summary, our study shows that syphilis remains an important coinfection in the SHCS. A relevant proportion of persons with newly detected syphilis were asymptomatic at the time of testing, justifying the reintroduction of routine screening as opposed to testing guided by clinical symptoms only. The affected population consisted predominantly of MSM, and among them younger persons with a shorter duration of HIV infection and a tendency for sexual risk behavior were at risk for newly acquiring syphilis. Importantly, 20% of patients with newly detected syphilis stated genitooral contacts as their only risk at the time of syphilis infection, pointing to a relevant misconception of oral sex as safe practice, and providing incentive for further preventive interventions. Treatment guidelines were incompletely followed; only a minor part of the indicated lumbar punctures were performed and some treatment strategies were inadequate according to current standards. In contrast to interventional studies, our findings might reflect current clinical practice. We are confident that identification and discussion of suboptimal management within our survey helped to improve clinical performance in the network of the SHCS, including performing lumbar puncture when warranted. On the contrary, one of the most frequent observed deviations from the predefined algorithm may be justified. According to new clinical findings, lumbar puncture may not be needed in patients with late latent syphilis and negative VDRL test [36] but clearly should be performed in those with a high-VDRL titer.

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M.C.T. and H.F. designed the study with important contributions of R.W. and M.Z., were responsible for data analysis and drafted and finalized the manuscript. M.C.T., H.F., R.W., L.T.T., M.C., L.E., P.S., E.B. were responsible for patient enrolment and CRF gathering at their sites. A.B.C. received the CRFs centrally and was responsible for building up the database. All coauthors revised the manuscript and read and approved the final version.

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