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Repeated Syphilis Episodes in HIV-Infected Men Who Have Sex With Men: A Multicenter Prospective Cohort Study on Risk Factors and the Potential Role of Syphilis Immunity

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Background. Syphilis is re-emerging globally in general and HIV-infected populations, and repeated syphilis episodes may play a central role in syphilis transmission among core groups. Besides sexual behavioral factors, little is known about determinants of repeated syphilis episodes in HIV-infected individuals—including the potential impact of preceding syphilis episodes on subsequent syphilis risk.

Methods. In the prospective Swiss HIV cohort study, with routine syphilis testing since 2004, we analyzed HIV-infected men who have sex with men (MSM). Our primary outcome was first and repeated syphilis episodes. We used univariable and multivariable Andersen-Gill models to evaluate risk factors for first and repeated incident syphilis episodes.

Results. Within the 14-year observation period, we included 2513 HIV-infected MSM with an initially negative syphilis test. In the univariable and multivariable analysis, the number of prior syphilis episodes (adjusted hazard ratio [aHR] per 1-episode increase, 1.15; 95% confidence interval [CI], 1.01–1.31), having occasional sexual partners with or without condomless anal sex (aHR, 4.99; 95% CI, 4.08–6.11; and aHR, 2.54; 95% CI, 2.10–3.07), and being currently on antiretroviral therapy (aHR, 1.62; 95% CI, 1.21–2.16) were associated with incident syphilis.

Conclusions. In HIV-infected MSM, we observed no indication of decreased syphilis risk with repeated syphilis episodes. The extent of sexual risk behavior over time was the strongest risk factor for repeated syphilis episodes. The observed association of antiretroviral therapy with repeated syphilis episodes warrants further immunological and epidemiological investigation.

Keywords. HIV; immunity; repeated infection; risk factor; syphilis.

Syphilis is re-emerging globally in general and HIV-infected populations as a major threat to individual and public health [1, 2]. Syphilis can be easily transmitted—often in asymptomatic stages—and may lead to independent syphilis outbreaks and sustained epidemics [1, 3]. Repeated syphilis episodes may

play a central role in syphilis transmission dynamics among so-called core groups and high-volume repeaters [4, 5]; however, besides sexual behavioral aspects, little is known about risk factors for repeated syphilis episodes in HIV-infected individuals. It has been speculated that repeated syphilis episodes induce or boost a host immune reaction, which may ultimately decrease the likelihood of acquiring further syphilis episodes [1, 6]. In HIV-infected populations, however, epidemiological data on the potential impact of syphilis immunity and other factors such as antiretroviral therapy (ART) on the occurrence of repeated syphilis episodes are scarce [7]. This information may help to improve targeted syphilis prevention strategies for high-risk individuals and to guide current syphilis vaccine developments [8].

In HIV-infected men who have sex with men (MSM), we aimed to identify risk factors for incident syphilis and in particular for repeated syphilis episodes. We especially wanted to

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assess whether syphilis risk is associated with the number of preceding syphilis episodes.

METHODS

Swiss HIV Cohort Study

The Swiss HIV Cohort Study (SHCS; www.shcs.ch) is a nationwide, prospective multicenter cohort study with semi-annual visits and blood collections—having enrolled >20 000 HIV-infected adults living in Switzerland since 1988 [9]. The SHCS is representative of the HIV epidemic in Switzerland and covers around 80% of new HIV infections in Switzerland since 1996 [9, 10]. The data collection is coded, and a written informed consent is required before study inclusion. In the SHCS, a standardized protocol is used for data collection. Sociodemographic, behavioral, and clinical data are recorded at study entry, and several laboratory tests are routinely performed at registration [9]. Clinical, treatment, and laboratory information (eg, cluster of differentiation 4 [CD4] cell counts, HIV viral load) are recorded twice per year during follow-up visits. Behavioral information, such as condom use, type of partners (occasional and/or stable), alcohol use, and drug use in the last 6 months are self-reported during follow-up visits. Additional interim laboratory evaluations are recorded, if available.

The SHCS is registered on the Swiss National Science Foundation longitudinal platform (www.snf.ch/en/funding/programmes/longitudinal-studies) and is accepted by the responsible ethical committees in Switzerland (www.shcs.ch/206-ethic-committee-approval-and-informed-consent).

Participants

We restricted our study population within the SHCS to MSM, who account for >80% of syphilis episodes and are disproportionately burdened by syphilis [2, 11, 12]. We included MSM who had their first nontreponemal and treponemal syphilis test—with a negative result—performed after January 1, 2004, and who had at least 2 consecutive syphilis tests recorded in the database. The observation period ended on January 1, 2018.

Syphilis Testing and Outcome Measures

Syphilis testing in the SHCS includes both concurrent nontreponemal and treponemal assays [10, 11]: The nontreponemal assay comprises either the Venereal Diseases Research Laboratory (VDRL) test or the rapid plasma reagin (RPR) test; the treponemal assay involves a *Treponema pallidum* particle agglutination/*Treponema pallidum* hemagglutination (TPPA/TPHA), Liaison (CLIA), Architect (CMIA) test, or a IgG/IgM immunoassay (ElecSys Syphilis immunoassay). Since the restart of routine syphilis testing in the SHCS in 2004, MSM have been tested for syphilis annually, whereas other individuals are tested for syphilis once every 2 years. Additionally, individual syphilis tests at the discretion of treating physicians (eg, in case of suspicion of active infection) are recorded in the SHCS.

Our primary outcome was incident syphilis episodes (first and repeated episodes): We defined repeated syphilis episodes as a reported positive nontreponemal and treponemal test following a syphilis episode and subsequent ≥ 4 -fold titer reduction or negativity in nontreponemal testing and a consecutive ≥ 4 -fold titer increase with a titer value of at least 8 in nontreponemal testing. We defined first syphilis episodes as a reported positive nontreponemal and treponemal test in individuals with a negative first treponemal test within the study period. As we could not infer the infection date precisely and due to short time intervals between negative and positive syphilis tests, we used the date of positive nontreponemal and treponemal testing as the infection date estimate.

Data Analysis

To identify risk factors for incident syphilis episodes and to account for recurrent events, we fitted univariable and multivariable semiparametric Anderson-Gill models—an extension of the Cox proportional-hazard model, with static and time-updated covariables, as described previously [13].

Based on previous reports, an explorative analysis, and clinical opinion, we evaluated the following independent variables in the univariable and multivariable analysis [10]: year of birth, ethnicity (white or nonwhite), education level at baseline (with or without continuing education after high school), year of HIV infection, and year of syphilis testing; furthermore, we evaluated the following time-updated variables, which represent the individuals' behavior in the previous 6 months; that is, alcohol use (with or without consumption of alcohol more than once a month), smoking status (with or without smoking of >1 cigarette per day), recreational use of intravenous and/or nonintravenous drugs (with or without use of recreational drugs), CD4 cell count, HIV viral load, ART (on or off ART), and sexual risk behavior (MSM with no occasional partners, MSM with occasional partners but no condomless anal intercourse, or MSM with occasional partners having condomless anal intercourse). In the final multivariable model, we excluded recreational drug use and alcohol consumption, as these variables were largely missing for the years 2004 to 2007; we included both variables in a sensitivity analysis (Supplementary Figure 1). In addition, we did not include HIV viral load in the final multivariable model due to potential collinearity with CD4 cell count and ART. Continuous variables were categorized in cases of evidence of departure from linearity. We performed an additional sensitivity analysis using a marginal-mean model (Supplementary Figure 2). We used complete-case analyses in all survival models.

In the final multivariable model, the proportional hazards assumption was met (Supplementary Figure 3), and respective deviance residuals to examine influential observations are reported in Supplementary Figure 4. We performed all analyses in R, version 3.5.0 (R Foundation for Statistical Computing,

Vienna, Austria). We used the `coxph` function from the `survival` package in R to fit the Anderson-Gill models and the `survminer` package for model diagnostics.

RESULTS

Within the 14-year observation period, 2513 HIV-infected MSM with an initially negative syphilis test formed the study population at risk (Figure 1). Of these 2513 individuals, 657 (26.1%) had at least 1 syphilis episode and 144 (5.7%) had at least 2 syphilis episodes; 42 (1.7%) MSM had 3 or more syphilis episodes (Table 1). Overall, MSM with an initially negative syphilis test were followed up for 15 002 person-years before they were lost to follow-up or had a first syphilis episode; similarly, MSM who had a first syphilis episode were followed up for a total of 2184 person-years.

Crude incidence rates of repeated syphilis episodes in MSM increased with the number of previous syphilis episodes—ranging from 66 episodes per 1000 person-years in MSM with 1 previous episode to 538 episodes per 1000 person-years in MSM with 6 previous episodes (Table 1). Overall, the median syphilis

testing rate was 1.30 tests per person-year; we describe time trends in syphilis testing in Supplementary Figure 5. Compared with MSM with ≤ 1 prior syphilis episode, individuals with repeated syphilis episodes were younger and more frequently had an occasional partner and exposure to condomless anal intercourse with an occasional partner.

The cumulative probability of an incident syphilis episode increased with the number of previous syphilis episodes (Figure 2). In the univariable analysis, the number of prior syphilis episodes (crude hazard ratio [HR] per 1-episode increase, 1.51; 95% confidence interval [CI], 1.35–1.7), having occasional sexual partners with or without condomless anal sex (crude HR, 5.59; 95% CI, 4.63–6.74; and crude HR, 2.58; 95% CI, 2.14–3.12), and being currently on ART (crude HR, 1.62; 95% CI, 1.22–2.14) depicted the strongest association with subsequent incident syphilis episodes (Figure 3). In the multivariable analysis, the number of prior syphilis episodes (adjusted HR per 1-episode increase, 1.15; 95% CI, 1.01–1.31), having occasional sexual partners with or without condomless anal sex (adjusted HR, 4.99; 95% CI, 4.08–6.11; and adjusted HR, 2.54; 95% CI, 2.10–3.07), and being currently on ART (adjusted HR, 1.62;

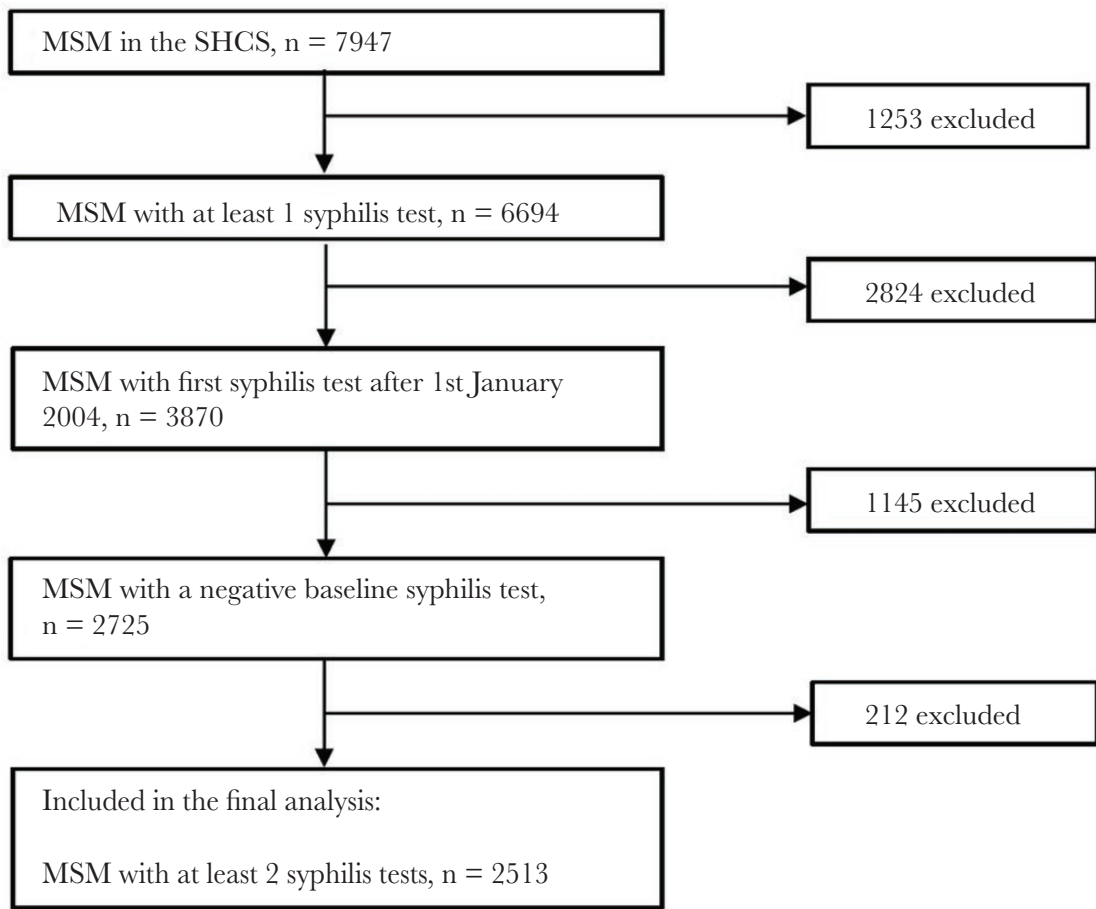


Figure 1. Study population. Abbreviations: MSM, men who have sex with men; SHCS, Swiss HIV Cohort Study.

Table 1. Characteristics of the Study Population

	No. Previous Syphilis Episodes								Overall
	0	1	2	3	4	5	6	7	
MSM, No. (%) ^a	2513 (100)	657 (26.1)	144 (5.7)	42 (1.7)	13 (0.5)	4 (0.2)	1 (0.04)	1 (0.04)	2513
Total person-years of follow-up	15 002.4	2184.1	359.7	80.6	17.7	5.0	1.9	1.9	17 653.1
Incidence rate of syphilis per 1000 person-years (CI)	44 (41–47)	66 (56–78)	117 (86–158)	161 (94–278)	226 (85–602)	202 (28–1431)	538 (–)	–	49 (46–52)
Median syphilis testing rate per person-year (IQR)	1.24 (1.04–1.59)	1.79 (1.35–2.38)	2.11 (1.58–3.12)	2.69 (1.85–3.32)	3.37 (2.37–3.67)	3.55 (2.92–4.02)	2.15 (–)	2.15 (–)	1.30 (1.08–1.68)
White ethnicity, No. (%) ^b	2239 (89)	583 (89)	129 (90)	38 (90)	11 (85)	4 (100)	1 (100)	1 (100)	2239 (89)
Median year of birth (IQR)	1971 (1964–1979)	1972 (1965–1979)	1972 (1965–1977)	1972 (1965–1978)	1973 (1968–1976)	1966 (1959–1974)	1977 (–)	1977 (–)	1971 (1964–1979)
Median age at HIV infection (IQR)	35 (29–43)	35 (29–41)	33 (29–40)	33 (29–41)	33 (29–41)	46 (37–49)	28 (–)	28 (–)	35 (29–43)
Continuing education after high school, No. (%) ^b	1259 (50)	334 (51)	66 (46)	23 (55)	8 (62)	3 (75)	1 (100)	1 (100)	1259 (50)
Median nadir CD4 (IQR)	367 (251–505)	561 (424–725)	541 (425–678)	552 (459–761)	522 (427–744)	528 (407–654)	539 (–)	542 (–)	362 (248–495)
Ever used a recreational drug, No. (%) ^{b,c}	673 (27)	227 (35)	58 (40)	20 (48)	4 (31)	2 (50)	1 (100)	1 (100)	778 (31)
Alcohol consumption more than once a month for at least 6 mo during the entire follow-up, No. (%) ^b	2178 (87)	556 (85)	132 (92)	37 (88)	12 (92)	4 (100)	1 (100)	1 (100)	2254 (90)
Current smoker, No. (%) ^b	1285 (51)	301 (46)	65 (45)	19 (45)	6 (46)	1 (25)	0 (0)	0 (0)	1321 (52)
Ever had an occasional partner, No. (%) ^b	1885 (75)	554 (84)	126 (88)	39 (93)	12 (92)	4 (100)	1	1 (100)	1941 (77)
Ever had condomless anal intercourse with an occasional partner, No. (%) ^b	1028 (41)	364 (55)	99 (69)	30 (71)	8 (62)	3 (75)	1 (100)	1 (100)	1168 (46)

Abbreviations: CD4, cluster of differentiation 4; CI, confidence interval; IQR, interquartile range; MSM, men who have sex with men.

^aPercentage of total individuals at risk with no prior syphilis episodes.^bColumn percentages.^cRecreational drug use was defined as intravenous or nonintravenous use of drugs for recreational purposes.

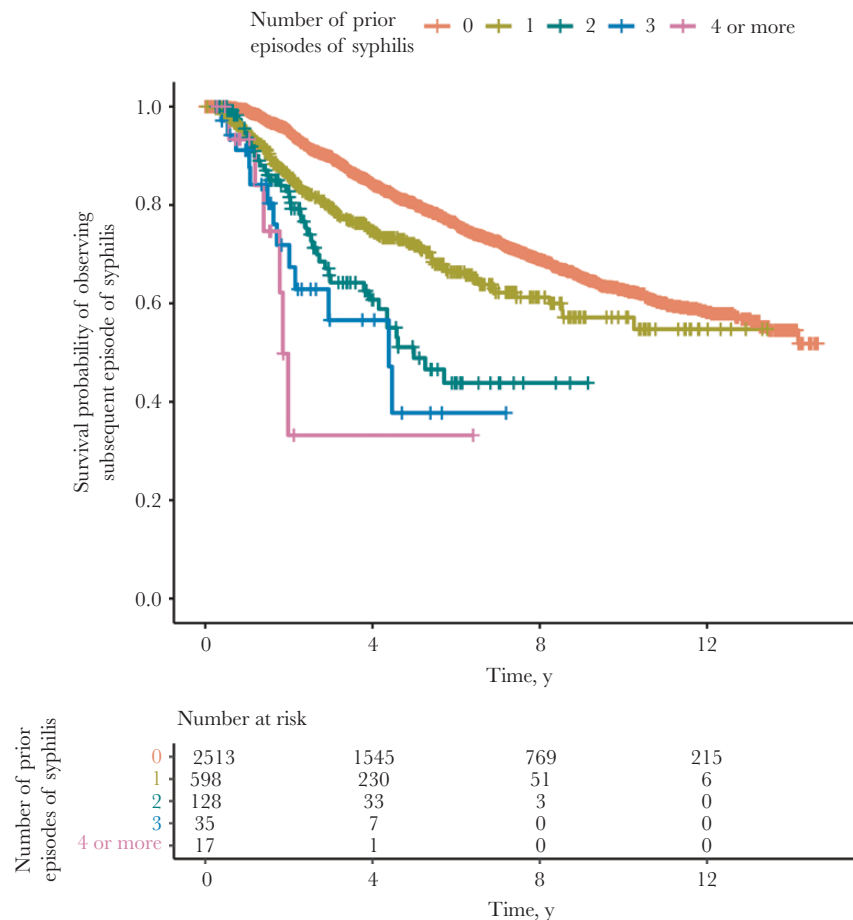


Figure 2. Repeated syphilis episodes in HIV-infected men who have sex with men; Kaplan-Meier estimates. Time is depicted since the previous syphilis episode, or since inclusion in the study in cases of absent previous syphilis episode.

95% CI, 1.21–2.16) remained associated with the occurrence of incident syphilis episodes. These findings were robust in the sensitivity analyses (Supplementary Figures 1 and 2).

DISCUSSION

In the SHCS, we observed a high rate of syphilis among HIV-infected MSM with previous syphilis episodes, which may be explained largely by the sexual risk behavior and the high background risk of syphilis among MSM populations [2, 12]. We identified several risk factors for the occurrence of syphilis episodes in MSM, which are in line with previous studies investigating risk factors for first incident syphilis episodes among HIV-infected individuals and specifically among HIV-infected MSM [2, 14]. However, insufficient adjustment for changing sexual risk behavior might have led to residual confounding in some studies, and repeated syphilis episodes were often not modeled longitudinally [14, 15].

Previous studies have reported that repeated syphilis episodes may be less symptomatic and that the plasma cytokine and VDRL/RPR titer responses differ between individuals with initial

and repeated syphilis episodes [16, 17]. Other studies found no difference in the clinical presentation of patients with initial and repeated syphilis episodes [15, 18, 19]. Interestingly, we observed no evidence of a decreased syphilis risk among HIV-infected MSM with repeated syphilis episodes; however, we cannot examine with the present study whether a partial attenuation, that is, less symptomatic repeated syphilis episodes, could be possible: Detailed clinical information on respective symptoms and signs was not collected in the SHCS database. In the present study, per 1-unit increase in the number of previous syphilis episodes, there was some evidence of a marginal positive association with the occurrence of subsequent syphilis episodes. The respective 95% CI of the adjusted HR ranged from 1.01 to 1.31. In the sensitivity analysis, the corresponding 95% CI of the adjusted effect estimate ranged from 0.99 to 1.34, with little (nonsignificant) evidence of an association between the number of syphilis episodes and the occurrence of subsequent syphilis episodes (Figure 3; Supplementary Figure 2). However, these 2 point estimates are largely consistent, as the respective effect sizes for previous syphilis episodes are comparable. Nevertheless, a causal, positive association between the number of preceding syphilis episodes and

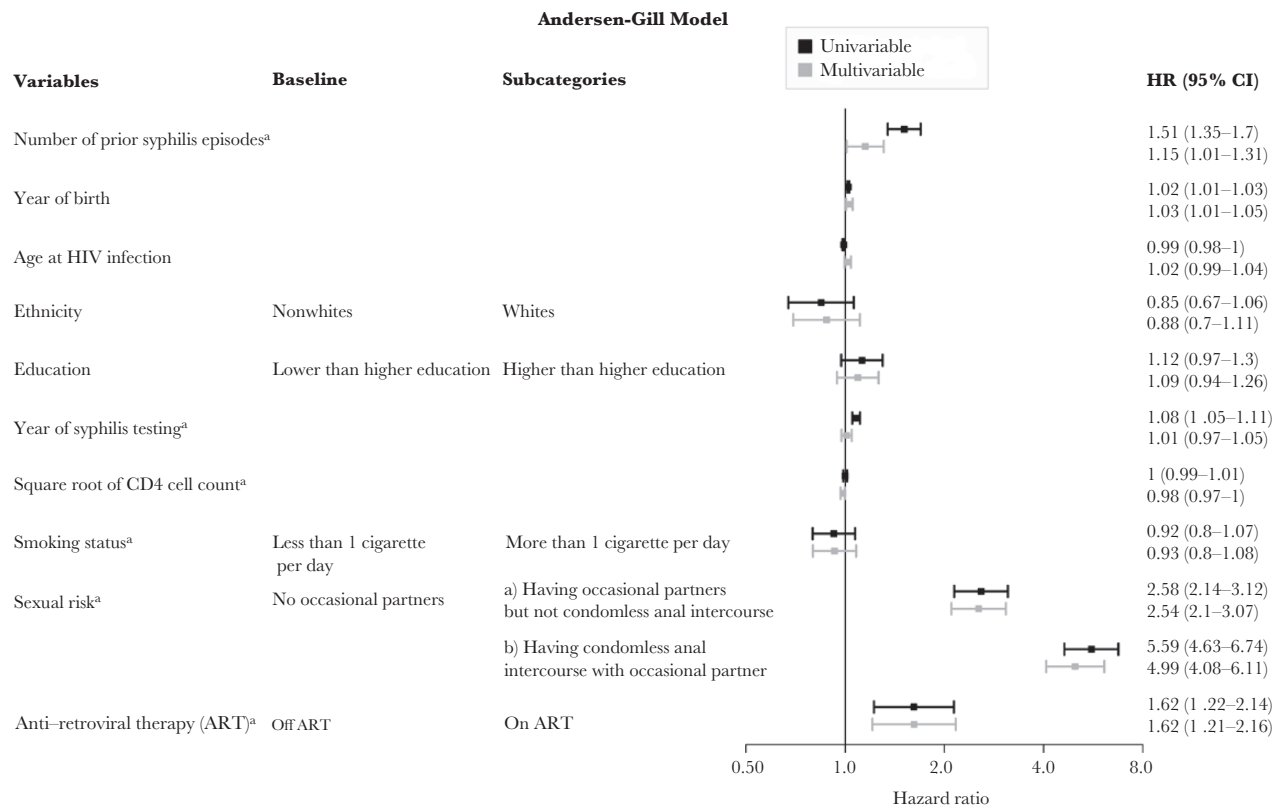


Figure 3. Risk factors for repeated syphilis episodes in HIV-infected men who have sex with men; Andersen-Gill model estimates. All effect estimates are expressed per 1-unit increase if no categories are stated. ^aTime-updated variables. Abbreviations: ART, antiretroviral therapy; CD4, cluster of differentiation 4; CI, confidence interval; HR, hazard ratio.

the risk for consecutive syphilis episodes is unlikely but necessitates further immunological investigation. The small potential effect of previous syphilis episodes may be explained by residual and/or unmeasured confounding effects in high-risk individuals (eg, frequency of unprotected anal sex, number of occasional partners), which are not collected in the SHCS. Still, our finding is in accordance with a previous study performed among MSM in HIV care in Ontario, Canada, which reported a 3-fold increased rate of syphilis in individuals with a past syphilis diagnosis [20]. In line with this study, our cohort was restricted to HIV-infected MSM in order to account for potential confounding effects of seroadaptive or serosorting behavior (ie, choosing sex partners based on HIV status), which may facilitate syphilis transmission among MSM [21].

In our individual-level analysis, the observation period was too short to examine potential long-term cycles in syphilis incidence. It has been speculated that repeated syphilis episodes induce or boost a host immune reaction, which may ultimately decrease the propensity of acquiring further syphilis episodes and which may have an impact of syphilis transmission dynamics at the population level [4, 16]. In contrast to gonorrhea, Grassly et al. showed in an ecological modeling study that syphilis epidemics may represent a rare example of endogenous oscillation in syphilis incidence with an 8–11-year period that is

predicted by the natural dynamics of syphilis infection and the associated partially protective immunity [6]. However, the hypothesis of endogenous cycling has been questioned [22].

In HIV-infected individuals, preliminary results from cohort studies, mathematical models, and reports have suggested that ART may be associated with increasing syphilis incidence due to changing sexual behavior and a multitude of effects of ART on the innate and adaptive immune system [7, 23–25]. The findings of the present cohort study, in which we modeled repeated syphilis episodes, are consistent with these investigations and reports; however, it is still uncertain whether the ART–syphilis relationship is causal, due to potential residual and unmeasured confounding (especially for sexual risk behavior such as the frequency of sexual intercourse with occasional partners [24, 25]) and the likely effect of HIV and ART on false-positive RPR serologies [26].

Our study has limitations. First, our syphilis episode definitions are based on results of nontreponemal and treponemal syphilis tests, as repeated syphilis episodes are often asymptomatic and as data on syphilis symptoms/signs and treatments have not been collected systematically in the SHCS database. Second, some individuals may not have been counted as having a repeated syphilis episode (ie, false negatives) due to a serofast state (ie, nontreponemal titers neither increase nor decrease 4-fold) after treatment of a prior syphilis episode [27]. This may

have led to an underestimation of the true incidence of repeated syphilis episodes and may have negatively confounded the association between previous syphilis episodes and subsequent incident syphilis infections; thus, the observed positive association between previous syphilis and subsequent syphilis episodes may be stronger. Third, we cannot exclude the possibility of residual and unmeasured confounding; for instance, the frequency of sexual intercourse and the number of occasional sexual partners are not collected in the SHCS database. Fourth, our study findings may not be generalizable to other populations with different risk profiles and immunological responses to syphilis [28].

However, our study has major strengths. First, our analyses were based on a large prospective cohort study with standardized, routine syphilis testing. Second, we analyzed risk factors for incident syphilis episodes in a well-defined population over a very long observation period—with a high retention proportion among participants. Third, our statistical models accounted for recurrent events and changes in risk behavior over time; this allowed us to longitudinally estimate the impact of repeated syphilis episodes on consecutive syphilis risk.

CONCLUSIONS

In HIV-infected MSM, we observed no indication of decreased syphilis risk with repeated syphilis episodes. The extent of sexual risk behavior over time was the strongest risk factor for recurrent syphilis episodes. The observed association of ART with repeated syphilis episodes may not be causal and warrants further epidemiological and immunological investigation.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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