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Increased repeat syphilis among HIV-infected patients

A nationwide population-based cohort study in Taiwan

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Abstract

Among human immunodeficiency virus (HIV)–infected individuals, syphilis is an important sexually transmitted infection (STI), and repeat infections are common. Identifying risk factors for delineating the trends in repeat syphilis are essential for STI and HIV prevention.

This study is to investigate the dynamic of the syphilis epidemic among HIV-infected patients and to identify the risk factors associated with repeat syphilis.

A population-based cohort design was used to analyze claim data between January 2000 and December 2010 using the Taiwan National Health Insurance Research Database. The Poisson regression test was used to identify risk factors for repeat syphilis.

Of 13,239 HIV-infected patients, annual syphilis screen tests have been performed in 4,907 (37.1%) of these patients. Syphilis has been diagnosed in 956 (19.5%) patients, and 524 (10.7%) had repeat syphilis. The annual trend in repeat syphilis showed a significant increase in the study period ($\beta = 0.23$, $P < .001$). Younger age (adjusted incidence rate ratio [aIRR] 1.43; 95% CI 1.11–1.86), male gender (aIRR 11.14, 95% CI 4.16–29.79), a history of STIs (aIRR 1.39, 95% CI 1.21–1.59) were independently associated with repeat syphilis. The retention in HIV care and adherence to antiretroviral therapy ≥85% ([aIRR] 0.77, 95% CI 0.61–0.98; $P < .001$) were associated with a reduced risk of repeat syphilis.

The incidence of repeat syphilis increased during 11 years of follow-up. The screening of syphilis for early diagnosis and retention in HIV care with medication adherence should be encouraged to minimize the risk of repeat syphilis in the targeted population.

Abbreviations: aIRR = adjusted incidence rate ratio, ART = antiretroviral-therapy, CDC = Centre of Diseases Control, HIV = human immunodeficiency virus, ICD-9-CM = International Classification of Diseases, 9th revision, clinical modification, MSM = men who have sex with men, NHIRD = national health insurance research database, RPR = rapid plasma regain, STIs = sexually transmitted infections, TPHA = treponema pallidum hemagglutination assay.

Keywords: antiretroviral therapy, human immunodeficiency virus, incidence, repeat syphilis, Taiwan

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Concurrent sexually transmitted infections (STIs) in human immunodeficiency virus (HIV)–infected patients are common, either at the time of HIV diagnosis or thereafter.[1,2] Individuals with active STIs are more susceptible to HIV infection, and in HIV-infected patients concurrent STIs increase viral concentrations of HIV in genital tracts, leading to an increased transmission potential.[3] Therefore, early diagnosis, effective treatment of STIs, and the reduction of risky behaviors are important strategies for preventing HIV transmission.[2–4]

Syphilis is a common STIs in HIV-infected patients.[5] The interaction between HIV and syphilis is important in both sentinel surveillance and clinical treatment of both infections.[5] Among men who have sex with men (MSM) population, HIV infection has been shown to be strongly associated with syphilis infections with a prevalence rate of as high as 20%.[6] Moreover, the occurrence of syphilis in HIV-infected patients is an indication of behaviors increasing the likelihood of HIV transmission.[5,7] A substantial number of HIV-infected individuals remain sexually active and acquire STIs.[8] Syphilis might be particularly important in the early stages of a localized HIV epidemic, when people with risky sexual behaviors are most likely to become infected.[9] In the real world, there were few men diagnosed with primary syphilis, suggestive of possible missed opportunities for early diagnosis and longer periods of infectiousness.[7]

HIV-infected patients with repeat syphilis might bear a disproportionate burden of both syphilis and HIV infection.[7] Because repeat syphilis can be an indicator of continued engagement in behaviors associated with acquisition and transmission of HIV and other STIs.[7] HIV-infected patients with repeat syphilis should be prioritized for comprehensive interventions to prevent future syphilis and HIV infections and to mitigate the spread of both diseases.[2,7] Targeted syphilis detection and treatment should have a central role in HIV prevention in these emerging epidemics.[9,10]

In parallel with treatment, the use of antiretroviral drugs as a prevention tool has been a focus from the beginning of the antiretroviral-therapy (ART) era.[11] In theory, the widespread use of ART could lead to a reduction in the rate of HIV transmission in the entire population and contribute to the control of the HIV pandemic.[12,13] It is controversial whether receiving ART influences syphilis incidence or whether immunologic improvement through ART is related to the incidence of syphilis in HIV-infected patients.[14–16]

As ART uptake among HIV-infected populations increases, monitoring population changes in syphilis epidemiology and identifying individuals most at risk will become increasingly important for informing effective and focused syphilis prevention. Our objectives are to investigate the dynamic of the syphilis epidemic among HIV-infected patients at the national level and to identify the risk factors associated with repeat syphilis.

2. Methods

2.1. Data source

A population-based cohort study was conducted using the National Health Insurance Research Database (NHIRD), which has been established and collected data on all ambulatory care (including outpatient services) and inpatient medical claims from the enrollees since 1995. It covers 99% of medical utilization of 2.3 million people in Taiwan.

The study protocol was approved by the institutional review board of National Cheng Kung University Hospital (NCKUH No. B-BR-104–117). The encrypted database in this analysis was obtained from the Taiwan NHIRD, which contained all HIV outpatient care claims in the patients with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code of 042 or V08, from January 1, 2000 through December 31, 2010. A maximum of 3 leading diagnoses and procedures, details on a participant's date of medical visit, pharmacy refill record, antiretroviral drug code numbers and prescription dates, laboratory items, and basic socio-demographic information, including sex, date of birth, insurance area, and insurance monthly salary, can be obtained. However, the NHIRD database was limited by the nature of its retrospective design and data sources, and important clinical or laboratory parameters were not available, such as CD4 counts, HIV viral loads, or information on sexual behaviors.

2.2. Cohort of HIV-infected patients

From the NHIRD database, a total of 16,402 HIV-infected patients with a principal diagnosis of HIV infection (ICD-CM-9 code 042 or V08) visiting ambulatory care facilities were confirmed using code 91, which referred to HIV cases that were reported for reimbursement by the Taiwan Centre of Diseases Control (CDC). Tests of goodness-of-fit between our study HIV population and the annual syphilis incidence, we limited the analysis to 4907 patients with annual syphilis screen tests (ICD-CM-9 code, 12001C for rapid plasma regain, RPR; 12018C for Treponema pallidum hemagglutination assay, TPHA) after HIV diagnosis. Subgroup analyses were performed for 1243 patients with a single syphilis test every year to evaluate the association between ART and repeat syphilis (Fig. 1).

2.3. Definition of study endpoints

Syphilis is a reportable illness in Taiwan health care system. A syphilis episode refers to a syphilis test in conjunction with

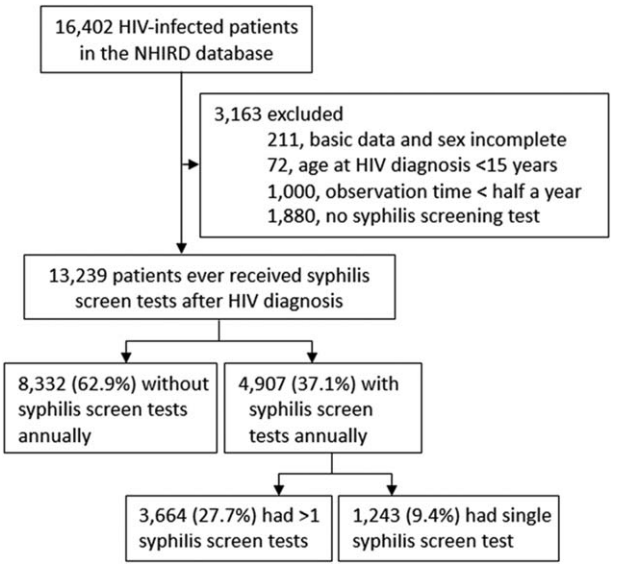


Figure 1. The flow chart of the study cohort in the present study.

ICD-CM-9 codes related to primary, secondary or latent syphilis (091–097) treated by currently recommended antibiotics for syphilis, such as benzathine penicillin G, doxycycline, tetracycline, or ceftriaxone. The primary dependent variable is repeat syphilis, which is defined as the second episode of treated syphilis with at least 12 months apart from the first episode.[14] Only the episodes of syphilis after the diagnosis of HIV are counted.

2.4. Covariates

The information regarding the potential confounding factors was retrieved from the claim data, including age at HIV diagnosis, year of HIV diagnosis, sex, geographic area, monthly income, occupation, opioid dependence (ICD-CM-9: 3040, 3055, 3047), and history of sexual transmitted infections (STIs) (including syphilis, genital warts, gonorrhea, trichomoniasis, or chlamydia infection) that was identified before HIV diagnosis, and frequency of syphilis screening test after HIV diagnosis. Their occupation was categorized as the group I (civil servants, teachers, employees of governmental or private business, professionals, or technicians), II (people without particular employers, self-employed, or seamen), III (farmers or fishermen), and IV (low-income families supported by social welfare or veterans).[15] The retention in HIV care was defined as having 2 or more outpatient visits separated by ≥ 90 days during a calendar year.[16] According to each individual's pharmacy refill records, the receipt of ART was defined as exposure to ART before the first episode of syphilis after HIV diagnosis. The patterns of ART use were classified into 2 groups: adherence (≥ 85%) and non-adherence.[15]

2.5. Data analysis

In the study cohort, we categorized HIV-infected patients as 3 groups: no syphilis, single syphilis, and repeat syphilis. The ANOVA with Tukey's post hoc test was used for categorical variables and the Kruskal–Wallis test for continuous variables. The annual syphilis incidence was calculated by the annual number of HIV-infected patients with syphilis as the numerator (inclusion of the episodes occurring at least 12 months apart) and the annual number of those with HIV infection as the denominator, over the 11-year study period. The annual incidence of repeat syphilis was derived from the annual number of the HIV-infected patients with repeat syphilis as the numerator. The Poisson regression model was used to test for the differences between the predicted and observed number of repeat syphilis, after adjusting for the variables significantly related to repeat syphilis after HIV diagnosis in the prior univariate analyses. In order to prevent the index event bias on the association between risk factors and recurrence of an event,[17] we further limit our analyses to 1480 patients with syphilis to verify the association of ART and the risk of repeat syphilis. In the subgroup analysis for the patients with annual single syphilis tests, *Kaplan–Meier test was used to assess the association* between ART and repeat syphilis. All analyses were performed with the 9.3 SAS statistical package.

3. Results

3.1. Demographic characteristic

A total of 13,239 people received 1 or more syphilis test (s) after the diagnosis of HIV infection between 2000 and 2010, resulting in an average annual study rate of 47.8% with the range of 37.7% to 66.5%. Of them, 4907 (37.1%) had syphilis tests annually. Demographic and clinical characteristics of patients with and without annual syphilis tests were summarized at Table 1.

Table 1

Comparisons of 13,239 HIV-infected patients with or without annual syphilis screening tests in Taiwan between 2000 and 2010.

	Annual syphilis screening tests		
Variables	No (n = 8332; 62.9%)	Yes (n = 4907; 37.1%)	*P* value
Age at HIV diagnosis (year)			<.001
15–24	1302 (15.6)	1070 (21.8)	
25–34	3783 (45.4)	2235 (45.6)	
35–44	2214 (26.6)	1103 (22.5)	
≥45	1033 (12.4)	449 (10.2)	
Median (range)	32.4 (15.2–81.8)	30.6 (15.0–82.7)	<.001
Sex			<.001
Male	7537 (90.5)	4587 (93.5)	
Female	795 (9.5)	320 (6.5)	
Year of HIV diagnosis			<.001
2000–2003	2806 (33.7)	479 (9.8)	
2004–2006	4036 (48.4)	1026 (20.9)	
2007–2010	1490 (17.9)	3402 (69.3)	
Geographic area			<.001
Taipei	1718 (20.6)	1554 (31.7)	
Northern	2536 (30.4)	1681 (34.3)	
Central	14355 (17.2)	488 (9.9)	
Southern	2493 (29.9)	1116 (22.7)	
Eastern	150 (1.8)	68 (1.4)	
Monthly income (NT$)			<.001
≧17,280	4701 (56.4)	2361 (48.1)	
17,281–26,400	2012 (24.2)	1252 (25.5)	
26,401–43,900	1001 (12.0)	808 (16.5)	
<43,901	618 (7.4)	486 (9.9)	
Occupation			<.001
I	2667 (32.1)	2306 (47.0)	
II	1323 (15.9)	825 (16.8)	
III	555 (6.7)	166 (3.4)	
IV	3777 (45.3)	1610 (32.8)	
Opioid dependence			<.001
No	6619 (79.4)	4323 (88.1)	
Yes	1713 (20.6)	584 (11.9)	
History of STIs			<.001
No	7784 (93.4)	3944 (80.4)	
Yes	548 (6.6)	963 (19.6)	
Retention in HIV care			<.001
No	5513 (66.2)	2550 (52.0)	
Yes	2819 (33.8)	2357 (48.0)	
Receipt of ART			<.001
No	3496 (42.0)	2339 (47.7)	
Yes	4836 (58.0)	2568 (52.3)	
Pattern of ART use (n = 7404)			<.001
Non-adherence	3716 (76.8)	1539 (59.9)	
Adherence (≥85%)	1120 (23.2)	1029 (40.1)	

ART = anti-retroviral therapy, STIs = sexually transmitted infections.

3.2. Trend in the incidence of syphilis after HIV diagnosis

Among 4907 HIV-infected patients with annual syphilis tests, 956 (19.5%) had a single episode of syphilis, and 524 (10.7%) repeat syphilis. The lapse between the time of HIV diagnosis and the first episode of syphilis was 5.3 months (range: 0–

Table 2

Characteristics of 4907 HIV-infected patients with annual syphilis screen tests in Taiwan between 2000 and 2010.

Variables	Syphilis infection			*P* value [a]
	No, n = 3427 (69.8%)	Single, n = 956 (19.5%)	Repeat, n = 524 (10.7%)	
Age at HIV diagnosis (yr)				<.001
15–24	692 (20.2)	262 (27.4)	116 (22.1)	
25–34	1499 (43.7)	451 (47.2)	285 (54.4)	
35–44	833 (24.3)	180 (18.8)	90 (17.2)	
≥45	403 (11.8)	63 (6.6)	33 (6.3)	
Median (range)	31.3 (15.0–82.7)	28.8 (16.1–72.7)	29.1 (17.0–67.3)	<.001
Sex				<.001
Male	3119 (91.0)	946 (99.0)	522 (99.6)	
Female	308 (9.0)	10 (1.1)	2 (0.4)	
Year of HIV diagnosis				<.001
2000–2003	187 (5.5)	107 (11.2)	185 (35.3)	
2004–2006	635 (18.5)	219 (22.9)	172 (32.8)	
2007–2010	2605 (76.0)	630 (65.9)	167 (31.9)	
Geographic area				<.001
Taipei	953 (27.8)	346 (36.2)	255 (48.7)	
Northern	1202 (35.1)	310 (32.4)	169 (32.3)	
Central	345 (10.1)	101 (10.6)	42 (8.0)	
Southern	876 (25.6)	189 (20.0)	51 (9.7)	
Eastern	51 (1.5)	10 (1.1)	7 (1.3)	
Monthly income (NT$)				<.001
≧17,280	1738 (50.7)	419 (43.8)	204 (38.9)	
17,281–26,400	877 (25.6)	241 (25.2)	134 (25.6)	
26,401-43,900	508 (14.8)	203 (21.2)	97 (18.5)	
<43,901	304 (8.9)	93 (9.7)	89 (17.0)	
Occupation				<.001
I	1467 (42.8)	525 (54.9)	314 (59.9)	
II	615 (18.0)	160 (16.7)	50 (9.5)	
III	146 (4.3)	14 (1.5)	6 (1.2)	
IV	1199 (35.0)	257 (26.9)	154 (29.4)	
Opioid dependence				<.001
No	2856 (83.5)	938 (98.1)	523 (99.8)	
Yes	565 (16.5)	18 (1.9)	1 (0.2)	
History of STIs				<.001
No	2882 (84.1)	669 (70.0)	393 (75.0)	
Yes	545 (15.9)	287 (30.0)	131 (25.0)	
No. of syphilis screening after HIV diagnosis (mean, range)	5.2 (1–46)	7.6 (1–33)	12.8 (1–34)	<.001
Retention in HIV care				<.001
No	1854 (54.1)	471 (49.3)	225 (42.9)	
Yes	1573 (45.9)	485 (50.7)	299 (57.1)	
Receipt of ART [b]				<.001
No	1373 (40.0)	652 (68.2)	314 (59.9)	
Yes	2054 (60.0)	304 (31.8)	210 (40.1)	
Pattern of ART use (n = 2568)				<.001
Non-adherence	1178 (57.3)	204 (67.1)	157 (74.8)	
Adherence (≥85%)	876 (42.7)	100 (32.9)	53 (24.2)	

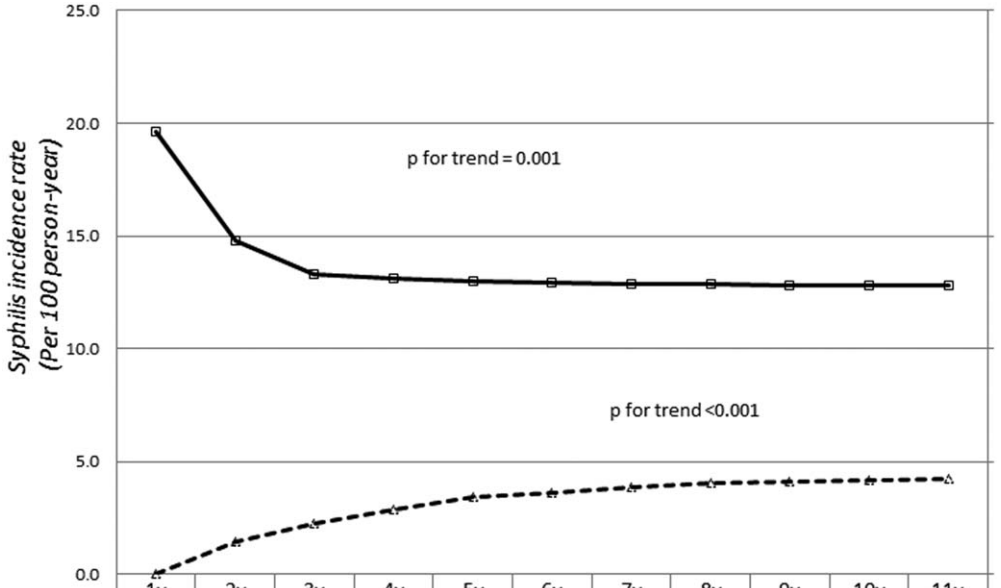
ART = anti-retroviral therapy, OI = opportunistic infection, PYs = person years, STIs = sexually transmitted infections.

[a] *P* value for $\chi 2$ and Kruskal–Wallis test.

[b] Exclude ART after syphilis diagnosis.

125.5 months) and 24.8 months (range: 12.0–116.2 months) between the first and second episode of syphilis. Those with repeat syphilis were more likely to be younger (<35 years: 76.5% *vs* 53.9%), male (99.6% *vs* 91.0%), diagnosed with HIV infection in the 2000–2003 year period (35.3% *vs* 5.5%), residence in urbanized cities (Taipei area: 48.7% *vs* 27.8%), and paid by a high monthly salary (17.0% *vs* 8.9%) than those without syphilis. Moreover, they were less likely to be opioid-dependent (0.2% *vs* 16.5%), receiving ART (40.1% *vs* 60.0%), or adherence to ART (24.2% *vs* 42.7%), but were more likely to have a history of STIs (25.0% *vs* 15.9%), to be retained in HIV care (57.1% *vs* 45.9%), or to receive syphilis screening tests (mean: 12.8 *vs* 5.2 times), as shown in Table 2.

There was a decreasing trend in syphilis incidences among 4907 HIV-infected patients from the first year through the 11th year after HIV diagnosis (β = -0.01, P = .001). Furthermore, there was an increasing trend in annual incidences of repeat syphilis over 11 years (β = 0.08, P < .001). The incidence of repeat syphilis after HIV diagnosis was 1.5 per 100 patient-years (95% confident interval [CI] 0.4–2.6) in the second year and 4.3 per 100 patient-years (95% CI 1.4–7.2) in the 11th year after diagnosis (Fig. 2).



	1y	2y	3y	4y	5y	6y	7y	8y	9y	10y	11y
Syphilis incidence rate	19.7	14.8	13.3	13.1	13.0	12.9	12.9	12.9	12.8	12.8	12.8
Repeat syphilis incidence rate	0.0	1.5	2.2	2.9	3.4	3.7	3.9	4.1	4.1	4.2	4.3
Syphilis episode (n)	962	1333	1584	1809	1934	2022	2087	2145	2173	2201	2222
Repeat syphilis episode (n)	0	133	266	397	511	572	626	676	699	722	742

Figure 2. Trends in the incidence of syphilis and repeat syphilis among HIV-infected persons with annual syphilis screen tests in Taiwan from the first year through the 11th year since human immunodeficiency virus diagnosis.

3.3. Factors associated with repeat syphilis among HIV-infected patients

In the multiple Poisson regression analysis, model 1 showed that the following characteristics were associated with repeat syphilis: younger age at time of HIV diagnosis (adjusted incidence rate ratio [aIRR] 1.43; 95% CI 1.11–1.86), male gender (aIRR 11.14, 95% CI 4.16–29.79), HIV infection diagnosed between 2004 and 2006 (aIRR 1.30, 95% CI 1.11–1.53), residence in Taipei area (aIRR 2.30, 95% CI 1.87–2.83), a history of STIs (aIRR 1.39, 95% CI 1.21–1.59), more syphilis screen tests (aIRR 1.09, 95% CI 1.07–1.10), individuals without particular employers, self-employed, or seamen (occupation II) (aIRR 0.62, 95% CI 0.47–0.80), non-opioid dependence (aIRR 0.01, 95% CI 0.00–0.04), and receipt of ART (aIRR 0.30, 95% CI 0.27–0.34) (Table 3). We further examined the effects of adherence to ART on the risk of repeat syphilis. Of the patients with ART, model 2 showed that an adherence rate ≥85% was associated with a lower risk of repeat syphilis after adjusting for confounding variables (aIRR 0.77, 95% CI 0.61–0.98; $P < .001$) (Table 3). Model 3 limited the analysis for 1480 patients ever having syphilis to avoid the index event bias. Patients with receipt of ART were associated with reduce the risk of repeat syphilis after controlling for confounding variables (aIRR 0.86, 95% CI 0.79–0.95; $P = .002$) (Table 3). We further adjusted the frequencies of syphilis testing on the diagnosis of repeat syphilis. In the subgroup analysis of 1243 HIV-infected patients with annual single syphilis testing, the Kaplan–Meier method showed that those with ART had a lower risk of repeat syphilis (hazard ratio, 0.14; 95% CI 0.03–0.62, $P = .01$) (Fig. 3).

4. Discussion

Our study showed that the syphilis incidence after diagnosis with HIV remained high, 30.2%, when compared with a previous report.[18] Rather, the overall trend in repeat syphilis showed a significant increase across 11 years of observation, which is consistent with other reports of repeat syphilis.[7,19] Recent studies have summarized point prevalence data of STIs among HIV-infected populations[15,18] and identified risk factors associated with STIs after HIV diagnosis.[20] The major STI studied is syphilis, with a median prevalence of 9.5%.[18] One long-term study reported a syphilis prevalence at the timing of HIV diagnosis of approximately 6% and a subsequent incidence of 1.3 cases per 100 patient-years of follow-up.[21] However, comparisons of repeat syphilis incidences across studies are problematic due to the heterogeneity in study population (all individuals or only MSM), case definition (early syphilis or only primary syphilis), and time frame for repeat infection (within 1 year, within 2 years, or ever). A longitudinal research approach to the analysis of repeat syphilis would facilitate cross-study comparisons.[22]

In contrast with increasing reported syphilis incidence from 1998 to 2008 in Arizona among HIV-infection by Skinner and colleagues (2014),[23] our study found the syphilis incidence decreased significantly in HIV-infected persons with time since HIV diagnosis, particular after the first year it has a sharp decline. We suppose it might be related to recommendations given by the Taiwan Center of Disease Control, which suggests that all patients with STIs should undergo HIV screening. This could result in syphilis patients being identified with co-occurring

Table 3

Multivariate Poisson analysis of the factors associated with repeated syphilis among 4907 HIV-infected persons with annual syphilis screen tests.

Variables	Incidence rate ratio	95% CI		*P* value	Adjusted incidence rate ratio	95% CI		*P* value
		Lower	Upper			Lower	Upper	
Model 1								
Age at HIV diagnosis (yr)								
15–24	1.98	1.54	2.55	<.001	1.43	1.11	1.86	.01
25–34	1.96	1.55	2.49	<.001	1.37	1.08	1.75	.01
35–44	1.22	0.94	1.59	.13	1.09	0.84	1.42	.52
≥45	Reference			Reference				
Sex			<0.001			<0.001		
Male	25.06	9.39	66.87		11.14	4.16	29.79	
Female	Reference			Reference				
Year of HIV diagnosis								
2000–2003	2.75	2.40	3.15	<.001	0.88	0.70	1.11	.27
2004–2006	1.90	1.65	2.20	<.001	1.30	1.11	1.53	.001
2007–2010	Reference			Reference				
Geographic area								
Taipei	3.08	2.54	3.74	<.001	2.30	1.87	2.83	<.001
Northern	1.99	1.62	2.43	<.001	2.19	1.78	2.70	<.001
Central	2.30	1.77	2.99	<.001	2.10	1.60	2.75	<.001
Southern	1.66	0.99	2.80	.06	1.13	0.67	1.91	.65
Eastern	Reference			Reference				
Monthly income (NT$)								
≧17,280	Reference			Reference				
17,281–26,400	1.21	1.05	1.39	.01	1.24	1.00	1.55	.05
26,401–43900	1.30	1.11	1.53	<.001	0.93	0.74	1.18	.55
<43,901	1.76	1.51	2.06	<.001	1.16	0.91	1.47	.23
Occupation								
I	1.43	1.26	1.61	<.001	0.91	0.73	1.13	.39
II	0.70	0.57	0.86	<.001	0.62	0.47	0.80	<.001
III	0.39	0.23	0.65	<.001	0.50	0.28	0.88	.02
IV	Reference		Reference					
Opioid dependence				<.001			<0.001	
No	Reference				Reference			
Yes	0.01	0.00	0.04		0.01	0.00	0.05	
History of STIs				<.01				<.001
No	Reference			Reference				
Yes	1.72	1.51	1.96		1.39	1.21	1.59	
Frequency of syphilis screening after HIV diagnosis	1.07	1.06	1.07	<.001	1.09	1.07	1.10	<.001
Retention in HIV care				<.001				.56
No	Reference			Reference				
Yes	1.24	1.11	1.38		1.04	0.92	1.16	
Receipt of ART therapy				<.001				<.001
No	Reference			Reference				
Yes	0.44	0.39	0.49		0.30	0.26	0.34	
Model 2[a]								
Pattern of ART use (n=2568)				<.001				.03
Non-adherence	Reference			Reference				
Adherence (≥85%)	0.54	0.43	0.66		0.77	0.61	0.98	
Model 3[b]								
Receipt of ART therapy (n=1480)			<0.001				0.002	
No	Reference				Reference			
Yes	0.69	0.63	0.75		0.86	0.79	0.95	

ART = antiretroviral therapy, CI = confidence interval, STIs = sexually transmitted infections.

[a] Model 2 limited analysis for 2568 patients with ART use and adjusted age at HIV diagnosis, sex, geographic area, monthly income, occupation, drug dependence, history of STIs, HIV diagnosis year, frequency of syphilis screen tests after HIV diagnosis, and retention in HIV care.

[b] Model 3 limited analysis for 1480 patients with syphilis and adjusted age at HIV diagnosis, sex, geographic area, monthly income, occupation, drug dependence, history of STIs, HIV diagnosis year, frequency of syphilis screen tests after HIV diagnosis, and retention in HIV care.

diagnoses of HIV.[24] After 1 year of HIV diagnosis, the incidence of syphilis remained low and decreased slightly. This may be attributable to the implementation of case management program,[25] the case management approach to retain patients in HIV care, and counsel provided to patients on safe sex practices.[26] However, we found that the trends of repeat syphilis increased with the length of HIV diagnosis. In addition to the increased trend, recurrent syphilis infections occurred to 10.7% of HIV-infected persons. That is, there is a certain proportion of HIV patients who repeatedly acquired syphilis

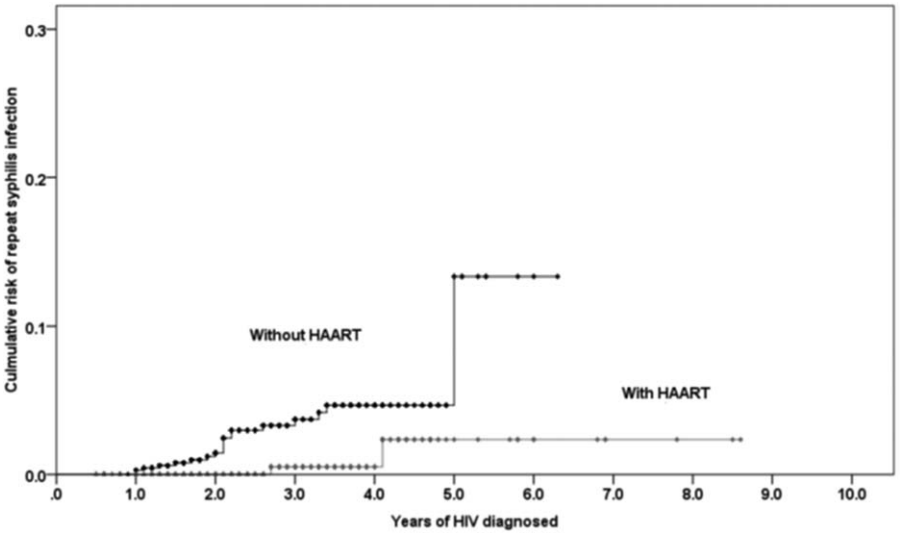


Figure 3. Kaplan–Meier survival analysis estimated cumulative risk of repeat syphilis among HIV-infected persons with (n = 544) or without (n = 699) anti-retroviral therapy with annual single syphilis screening test ($P = .01$).

infections, particularly in those with characteristics of being a younger male adult, residing in an urban city, being less likely to have a particular job, and having past STIs. This finding was consistent with a large epidemiology study, which showed that a total of 13.6% of adolescents and adults in Campinas presented more than 1 syphilis infection.[27] Our study suggests that health care providers could play important roles in consultation and education to keep patients with specific demographics in the health care system to decrease the risk of syphilis occurrence.

Treatment as prevention has been a focus of HIV prevention.[11,28] The clinical role of ART on prevention of STIs other than HIV infection is pondered. Although ART has been associated with a lower incidence of STIs, including syphilis,[29] the association between ART and repeat syphilis in HIV-infected patients remained controversial.[10,19,30–32] Our national data demonstrated that retention in HIV care with ART adherence rate of ≥ 85% were associated with a lower risk of repeat syphilis. The immunorestoration resulting from ART could lead to a decreased biological susceptibility to syphilis acquisition or transmission.[33] An alternate behavioral hypothesis for the impact of ART on syphilis incidence is that individuals with ART are a population that is more likely to adhere to medical and behavior modification advices, and less likely to engage in risky sexual behavior.[14] Moreover, ART could reduce the serological failure rate[14] and the time to achieve serological responses to syphilis treatment.[34] In Taiwan, HIV-infected patients could easily access to free ART since 1997, and since 2007 a national integrated case management program was launched to reduce risky behaviors in AIDS referral hospitals.[25,29] Other than antiviral agents, integration of program of assessment of ART adherence, health education and counseling of STIs prevention were provided by clinician and HIV case manager is important strategy for control of syphilis.[25,26] Previous studies have demonstrated that risky behaviors among HIV-infected patients will decrease when linked to and retained in primary care[35] and with clinician-delivered intervention.[16,25]

It is not surprising that the history of STIs and frequent syphilis screen tests are associated with repeat syphilis. The CDC guidelines advise at least annual routine syphilis testing for sexually active HIV-infected persons[36] because the incidence of asymptomatic syphilis, which can be detected only through routine serology testing, is high.[37] A repeated history of STIs after the diagnosis of HIV infection was an independent predictor for active STIs.[2] These findings demonstrate that STIs frequently occurred even in patients aware of their HIV-infected status[2,38] and highlight the need to continue behavioral interventions and periodic screenings for new STIs among HIV-infected individuals with STIs.[2,39] Because HIV-infected patients are more likely to be retained in medical care than HIV-negative persons, the former might be more likely to be screened for syphilis, which increases the chance of identifying repeat syphilis.[40] Our results also underscore the importance of current recommendations for routine and frequent syphilis screen tests in sexually active HIV-infected patients, particularly if they ever had syphilis.[36]

With the structural nature of the NHIRD, the present work had some study limitations. First, the diagnosis of syphilis was based on the case registry. However, to avoid the inaccuracies of administrative coding of clinical diagnosis, only the episodes with corresponding antimicrobial therapy were included. Second, the syphilis episodes were based on clinical diagnosis. HIV-infected patients may have more episodes of asymptomatic syphilis, if the frequency of syphilis tests increased, and it is likely that our data represent an underestimation of the syphilis incidence in the risky cohort. Finally, the study was limited by the administrative nature of the database and the absence of numeric data of laboratory tests (such as CD4 counts and viral load) and the details of sexual behaviors. The interaction of immunosuppression or viral suppression and the incidence of repeat syphilis cannot be evaluated.

In conclusion, in this population-based study using national data, the incidence of repeat syphilis among HIV-infected individuals increased during 11 years of follow-up. Routine screening for syphilis for early diagnosis and retention in HIV care with adherence to ART should be encouraged to minimize the risk of repeat syphilis in the targeted population.

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Author contributions

Y.C.C., N.Y.L., W.C.K., and N.Y.K. participated in the study design. C.Y.L. and Y.C.C. participated in the data analysis. N.Y.L., Y.C.C., H.Y.L., N.Y.K., and W.C.K. participated in the interpretation of the results. N.Y.L., Y.C.C., and N.Y.K wrote the manuscript.

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