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ORIGINAL RESEARCH

Consequences of HIV/Syphilis Co-Infection on HIV Viral Load and Immune Response to Antiretroviral Therapy

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Introduction: Although syphilis is a frequent co-infection in patients with human immunodeficiency virus (HIV) infection, the influence of syphilis on immune response and virologic failure in HIV-infected patients following initiation of antiretroviral therapy (ART) is not well-defined.

Methods: A retrospective study was conducted at Tianjin Second People's Hospital to evaluate the prevalence of syphilis and immune status in 4171 ART-naïve patients. The study included patients who initiated ART between August 2009 and June 2019.

Results: The prevalence of syphilis was 40.1% in all ART-naïve patients and 42.5% in ART-naïve men who have sex with men. HIV/syphilis co-infection was associated with higher virologic failure (odds ratio (95% confidence interval): 1.30 (1.04, 1.63)). Patients with HIV/syphilis co-infection had lower median $CD4^+$ T cell counts and CD4/CD8 ratios at baseline. After initiation of ART, patients co-infected with HIV/syphilis had smaller increases in $CD4^+$ T cell counts and CD4/CD8 ratios than patients infected only with HIV. The rate of recurrence of syphilis or reinfection was 9% (n = 128) during seven years of ART.

Conclusion: HIV/syphilis co-infection had a negative impact on immune recovery and antiretroviral effectiveness. RPR titer and HIV viral load should be monitored in patients co-infected with HIV/syphilis, especially in patients with high RPR titers.

Keywords: HIV/syphilis, co-infection, antiretroviral therapy, virologic failure, CD4 response

Introduction

Syphilis, a sexually transmitted infection caused by the bacterium *Treponema pallidum*, is frequently encountered amongst human immunodeficiency virus (HIV)-infected individuals. The prevalence of co-infection with HIV and syphilis varies from 8% to 25%,[1,2] depending on the prevalence of both infections within the community and the group of patients studied. In China, the prevalence of HIV and syphilis among men who have sex with men (MSM) was recently shown to be higher than that in heterosexual men (about 6.5% and 11.2%, respectively).[3] Although homosexual transmission has been recorded as the major route of transmission of HIV in Tianjin,[4] there is no information about the prevalence of syphilis among HIV-infected patients, especially among HIV-infected MSM.

HIV/syphilis co-infection is considered to be a dangerous combination[5] since HIV makes failure of syphilis treatment more likely[6] and co-infection leads to more profound neurocognitive impairment.[7] Although active antiretroviral therapy (ART)

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allows successful management of HIV infection and enhances the lives of people living with HIV/AIDS (PLWHA), the consequent downregulation of innate and acquired immune responses to syphilis may increase susceptibility to infection.[8] Reciprocally, syphilis enhances the likelihood of HIV transmission[9] since it can negatively impact the immune system, and has been shown to increase HIV viral loads and reduce $CD4^+$ T cell counts in PLWHA receiving ART.[10–14] The relationship between HIV/syphilis co-infection and treatment responses after initiation of ART has not been fully investigated. Thus, the aim of this study was to evaluate the impact of syphilis on the virologic (HIV viral load) and immunologic (CD4 counts, CD4/CD8 ratio) parameters of PLWHA, before and after initiation of ART.

Methods

Study Population

The study was conducted at Tianjin Second People's Hospital, China, which, since August 1999, has been a designated hospital for the treatment of HIV. The study methodology conformed to the Declaration of Helsinki and was approved by the ethics committee of Tianjin Second People's Hospital. HIV positive patients initiating ART in 2009 and followed up until June 2019 were considered for inclusion in the study. After authorization by the ethics committee (Approval no. 2019-7), available patient data were provided from electronic medical records by the hospital and the need for informed consent was waived.

From the available data, we collected information about 4171 patients who initiated ART from 2009 and were followed up until 2019. After applying exclusion criteria, incomplete information (ie, individuals without examinations for syphilis before antiretroviral treatment initiation, n = 347) were excluded. Indeed, to investigate the consequences of HIV/syphilis coinfection on HIV viral load and immune response to antiretroviral therapy, 3829 PLWHA were followed up after the initiation of ART. $CD4^+$ lymphocyte counts and viral loads were determined according to clinical protocols: assessments were initially performed 6-monthly, then yearly or twice per year after the first year on ART from 2009. The exclusion criteria included fatalities (n = 59) and syphilis diagnosed after ART initiation (n = 92). Of the remaining 3678 patients initiating ART who were included in the study, 2164 had only HIV infection and 1514 were co-infected with syphilis. A flow chart showing patient characteristics and selection is provided in Figure 1A.

Follow-Up

As shown in Figure 2A, two patients were infected with only HIV in 2009, and one of whom was removed from the analysis due to the diagnosis of syphilis after ART initiation, and the other was deceased. In 2010, 10 patients with mono-HIV infections were included, of whom, three patients were removed from the analysis due to the diagnosis of syphilis after ART initiation, two were deceased, and five began ART after July 2010. Thus, no data from participants with mono-HIV infections were included in 9-year follow-up analysis. Similarly, no such data were used for the 8-year follow-up analyses for the same reasons. As a result, patients were followed up with for up to 7 years.

Definition

HIV virologic failure was defined as two consecutive measurements with HIV RNA > 200 copies/mL after six months of ART.[15] Recurrent syphilis or reinfection were identified by a 4-fold increase in antibodies in a Rapid Plasma Reagin (RPR) test,[16] following a previously documented successful course of treatment for syphilis and were evaluated by a specialist in sexually transmitted infections.

Data Collection

Retrospective data, including demographic and clinical/laboratory characteristics, were collected from medical records. Variables included age, sex, HIV transmission route, co-infection with hepatitis B virus (HBV), co-infection with hepatitis C virus (HCV), HIV stage as defined by the World Health Organization (WHO),[17] HIV-1 viral load and body mass index (BMI). $CD4^+$ T cell count was stratified as <50 cells/μ l, 50–200 cells/μL and >200 cells/μ l.[18] HIV viral load at baseline was not included in the medical records, and therefore, based on WHO clinical criteria for HIV disease in adults and adolescents, subjects were classified into stage I, stage II, stage III and stage IV infection.[17] BMI was stratified as underweight (<18.5 kg/m^2), normal weight (18.5–24 kg/m^2) and overweight and obesity (>24.0 kg/m^2).[19,20]

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 software (SPSS, Chicago, IL, USA) and GraphPad 7 (GraphPad Software, La Jolla, CA, USA). Because of skewed statistical distributions, numerical data are presented as medians with interquartile ranges; categorical variables are presented as percentages. Differences between two groups were analyzed

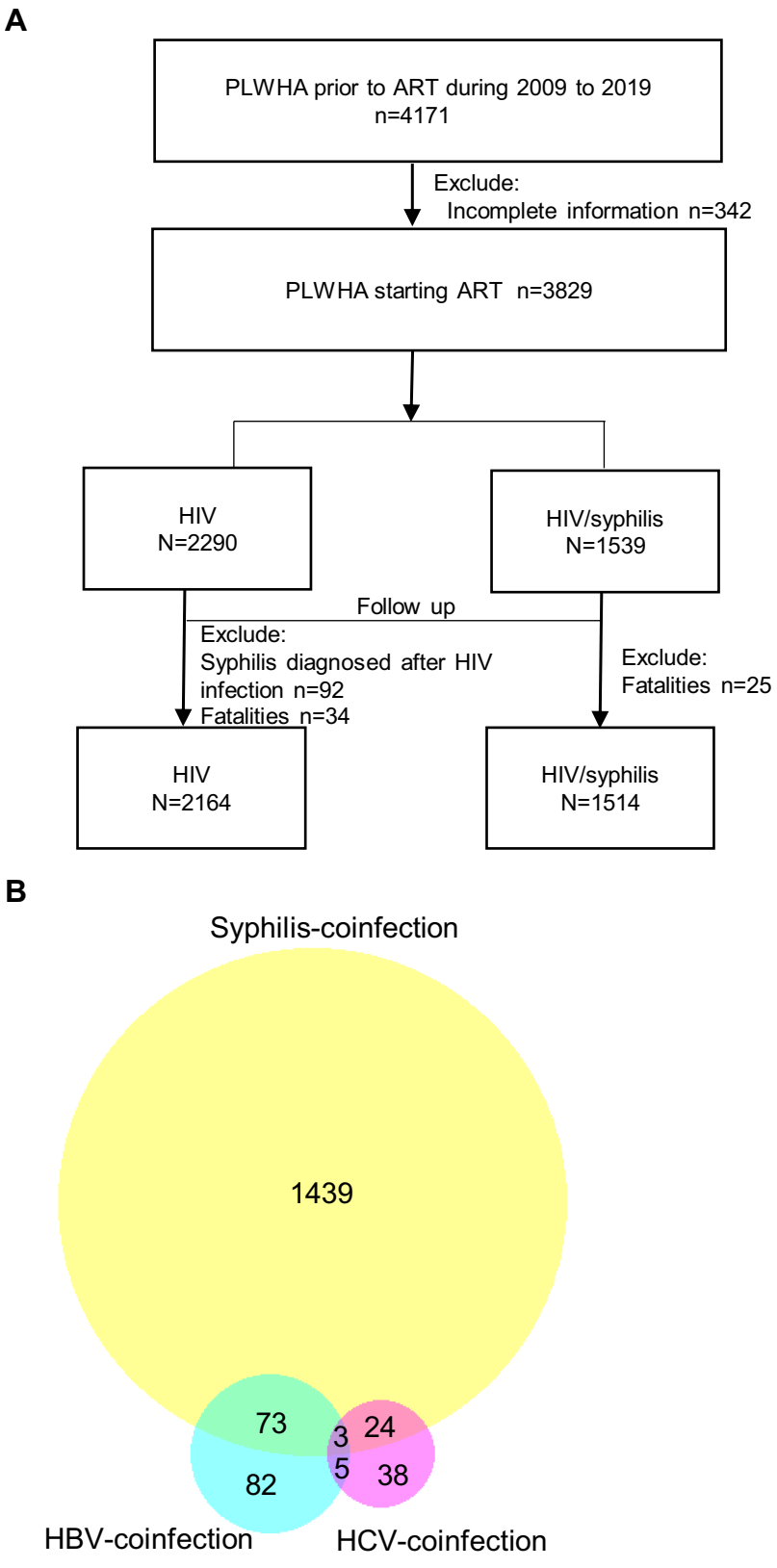

Figure 1 (**A**) Flow chart showing patient characteristics and selection; (**B**) Venn diagram showing co-infections in PLWHA.

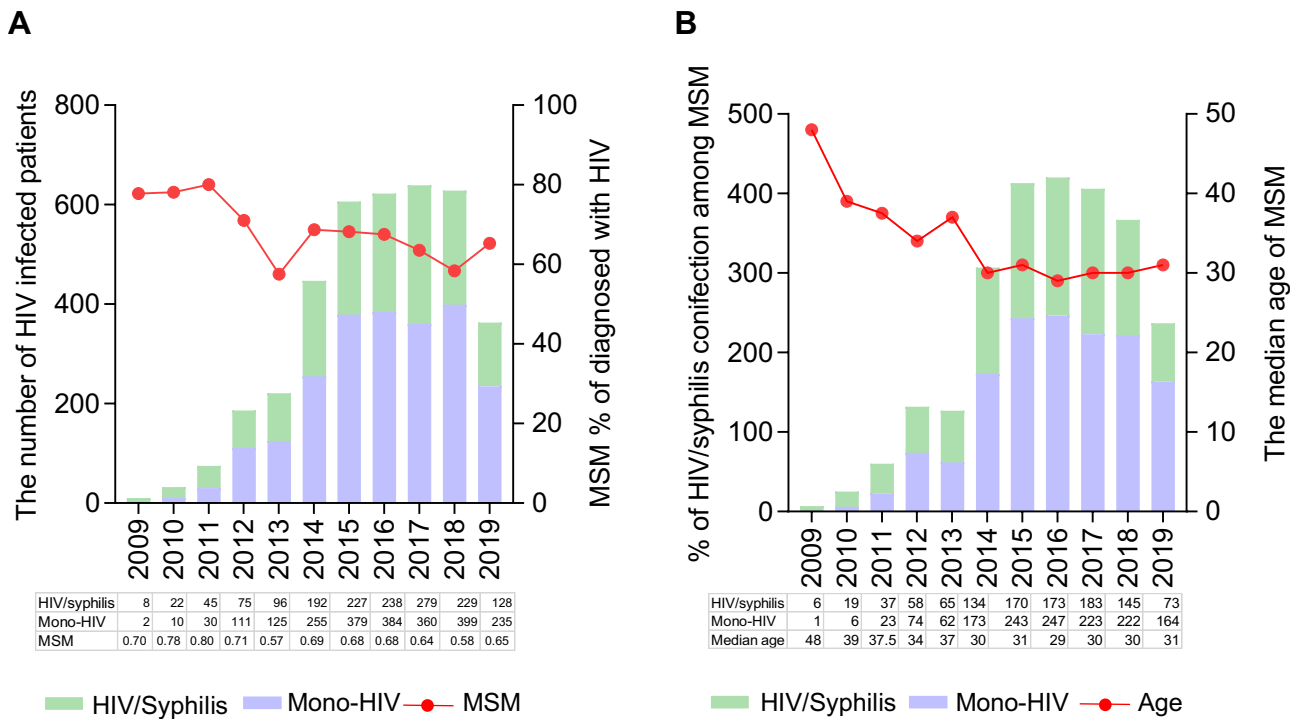

Figure 2 (**A**) Percentage of syphilis-positive cases and numbers of MSM among HIV-infected patients per year; (**B**) Annual syphilis rates and age in MSM with HIV infection.

using the Mann–Whitney *U*-test (nonparametric). Repeated measurements of $CD4^+$ T cell counts, $CD8^+$ T cell counts and CD4/CD8 ratios during follow-up were modeled using linear mixed effects models, with a random subject effect. Binary logistic regression models were used to evaluate risk factors associated with virologic failure during seven years of ART. Kaplan–Meier curves were computed for this cohort. Log rank testing was carried out to evaluate differences in cumulative virologic failure in HIV-infected patients, with or without co-infection with syphilis. Demographic variables (sex, age), clinical/laboratory characteristics ($CD4^+$ T cell count, HIV stage, co-infection with syphilis, co-infection with HBV and co-infection with HCV) and the combination of antiretroviral regimens were included to investigate risk factors of virologic failure, regardless of their significance between groups at baseline. A p-value < 0.05 was considered to be statistically significant.

Results

Demographic and Clinical Characteristics, and Prevalence of Syphilis in HIV Infected Patients Prior to ART

A total of 3829 individuals were included in the study, 1539 (40.2%) of whom were co-infected with syphilis before initiation of ART (Figure 1A). The distribution of co-infection with syphilis, HBV and HCV at baseline is shown in Figure 1B. The median age of the study participants was 32 years, the ratio of men to women was 18.5:1, the median BMI was 22.2 (interquartile range [IQR], 20.1, 24.5) kg/m2 and the median CD4+ T cell count was estimated to be 268 (IQR, 145, 392) cells/μL. Same-sex relationships were the main route of transmission and accounted for 65.3% of all cases. Most of the participants (83.1%, 3182/3829) had stage II HIV-1 infection, based on WHO criteria. Patients who were co-infected with syphilis were older (median age 34 vs 31 years, $p < 0.001$) and more likely to be male (98.2% vs 92.8%, $p < 0.001$) than patients infected only with HIV. HIV/syphilis co-infection was also associated with lower $CD4^+$ T cell counts (258 vs 276, $p = 0.01$) and lower CD4/CD8 ratios (0.22 vs 0.25, $p < 0.001$) (Table 1). The proportion of cases of HIV/syphilis co-infection decreased from 80% to 30% during the follow-up period of the study (2009 to 2019), although the homosexual transmission route remained steady at around 50–70% (Figure 2A). Both the fraction of MSM co-infected with HIV/syphilis and the median age of MSM fell from 2009 to 2019 (Figure 2B).

Table 1 Characterization of PLWHA Prior to ART

Characteristics	Total (n=3829)	Mono-Infected HIV (n=2290)	HIV/Syphilis (n=1539)	*P* values
Age (Year)	32 (26, 44)	31 (25, 42)	34 (28, 46)	<0.001
Male	3637 (95%)	2126 (92.8%)	1511 (98.2%)	<0.001
HBV co-infection	162 (4.2%)	87 (3.8%)	75 (4.9%)	0.11
HCV co-infection	70 (1.8%)	43 (1.9%)	27 (1.8%)	0.78
BMI (kg/m^2)	22.2 (20.1, 24.5)	22.2 (20.1, 24.5)	22.3 (20.2, 24.6)	0.53
Infection route				<0.001
Heterosexual	716 (18.7%)	475(20.7%)	241 (15.7%)	
Homosexual	2501 (65.3%)	1438 (62.8%)	1063 (69.1%)	
Other	612 (16%)	377 (16.5%)	235 (15.3%)	
HIV stage				0.09
I	363 (9.5%)	205 (9%)	158 (10.3%)	
II	3182 (83.1%)	1930 (84.3%)	1252 (81.4%)	
III	151 (3.9%)	79 (3.4%)	72 (4.7%)	
IV	133 (3.5%)	76 (3.3%)	57 (3.7%)	
Laboratory data				
CD4 (cells/μL)	268 (145, 392)	276 (151, 396)	258 (140, 378)	0.01
CD8 (cells/μL)	1038 (693, 1458)	1028 (680, 1441)	1059 (707, 1477)	0.17
CD4/CD8 ratio	0.24 (0.14, 0.37)	0.25 (0.14, 0.38)	0.22 (0.13, 0.35)	<0.001
ART drugs				0.27
IN based	175 (4.6%)	112 (4.9)	63 (4.1%)	
PI based	494 (12.9%)	306 (13.4%)	188 (12.2%)	
NNRTI based	3160 (82.5%)	1872 (81.7%)	1288 (83.7%)	

Note: Evaluation of median based on Q2 (Q1–Q3).
Abbreviations: PLWHA, patients living with HIV/AIDS; IN, integrase inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; ART, antiretroviral therapy.

HIV/Syphilis Co-Infected Individuals Have Higher Risk of Virologic Failure During ART

In the HIV/syphilis group, 63 patients received INR-based ART drugs, 188 received PI-based ART drugs, and 1288 received NNRI-based ART drugs. No significant differences were found between HIV/syphilis coinfection and HIV mono infection.

The effect of syphilis on virologic response to ART was assessed by plotting Kaplan–Meier survival curves (Figure 3). Log rank testing showed a significant difference between patients infected only with HIV-1 and patients co-infected with HIV/syphilis ($p = 0.005$).

The multivariate logistic regression model showed that HIV/HCV co-infection (adjusted odds ratio (AOR): 2.34, 95% confidence interval (CI): 1.25–2.11, $p = 0.01$), age (AOR: 1.01, 95% CI: 1.00–1.02, $p = 0.046$), HIV/syphilis co-infection (AOR: 1.30, 95% CI: 1.04–1.63, $p = 0.02$), HIV-1 stage III–IV (AOR: 1.89, 95% CI: 1.31–2.74, $p < 0.001$) and CD4$^+$ T cells counts <50 cells/μL (AOR1.89, 95% CI: 1.31–2.02, $p = 0.001$) were associated with increased virologic failure in Chinese HIV-1 infected patients (Table 2).

HIV/Syphilis Co-Infected Individuals Have Poorer Immune Recovery During ART

CD4 is the main immunologic marker of HIV/AIDS progression and the CD4/CD8 ratio is considered to be a marker for the risk of non-AIDS diseases.[21] At baseline, HIV/syphilis co-infected subjects had, on average, slightly lower CD4$^+$ T cell counts and lower CD4/CD8 ratios ($p = 0.01$ and $p < 0.001$, respectively, Table 1). Before initiation of ART, CD8$^+$ T cell counts were higher in HIV/syphilis co-infected patients than in patients infected with only

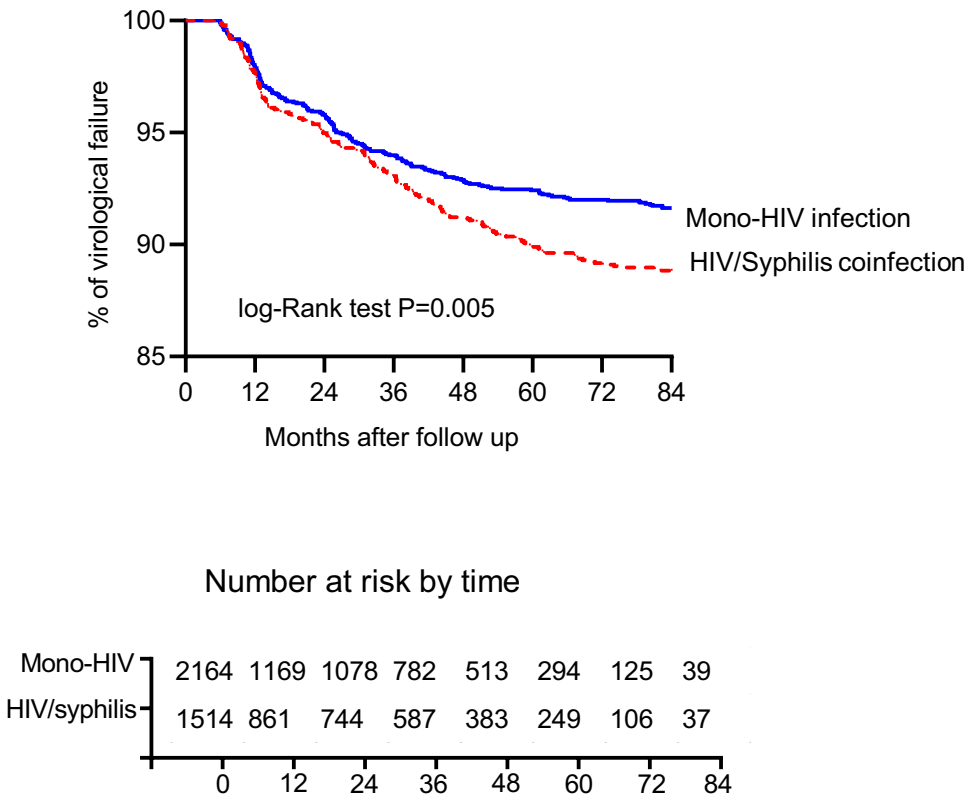

Figure 3 Seven-year virologic failure curves of HIV infected patients with or without syphilis.

HIV, but the difference was not statistically significant (p = 0.17, Table 1). Individuals co-infected with HIV/syphilis had significantly slower recovery of $CD4^+$ T cells and CD4/CD8 ratio compared with patients infected with only HIV (Figure 4), and the differences were significant after adjusting for baseline $CD4^+$ T cell counts and other baseline covariates in the regression analyses (Table 3).

Recurrence of Syphilis or Reinfection During Seven-Year Follow-Up

The impact of recurrence or reinfection of syphilis on immune recovery and virologic failure during HIV treatment was also investigated. A total of 1423 patients were included in the analysis. Episodes of recurrence or reinfection with syphilis were estimated to be 9% (n = 128) during the study period, and of which, at baseline, the proportion was 23.8% (31 cases) in patients with RPR titers >1:32, which is significantly higher compared to 10.75% (57 cases) in patients with RPR titers 1:2–1:16 groups, and 6% (40 cases) in patients with RPR titers <1:2 ($p < 0.01$) (Figure 5A). This indicated that high RPR titers at baseline were associated with a higher incidence of recurrence of syphilis or reinfection. $CD4^+$ T cell counts and CD4/CD8 ratios during the one-year periods before or after diagnosis in HIV/syphilis co-infection, and with or without the recurrence or reinfection with syphilis, are shown in Figure 5B and C. The difference between the two groups was not significant.

Discussion

In the present study, we found that individuals co-infected with HIV/syphilis before initiation of ART had a higher probability of virologic failure and smaller increases in $CD4^+$ T cell count and CD4/CD8 ratios during seven years of ART, compared with individuals infected only with HIV. Higher RPR titers were associated with recurrence or reinfection with syphilis.

Syphilis is known to have a negative impact on immune recovery during HIV infection[11] and our results are consistent with previous studies. As well as the change in $CD4^+$ T cell counts, we observed, for the first time, that CD4/CD8 ratios were reduced in these individuals at baseline and after seven years of ART. The CD4/CD8 ratio is a strong marker of immune activation and immune senescence,[22,23] and a lower CD4/CD8 ratio is also

Table 2 Risk Factors for Virologic Failure in PLWHA During Seven Years of ART

Variables at Baseline	df	Univariate Analysis OR (95% CI)	*p* value	Multivariate Analysis OR (95% CI)	*p* value
Age	1	1.01 (1.00, 1.02)	0.02	1.01 (1.00, 1.02)	0.046
HCV coinfection	1				
No		Ref	–	Ref	–
Yes		2.74 (1.43, 5.24)	0.02	2.34 (1.25, 2.11)	0.01
$CD4^+$T cell counts	2		0.001		0.004
≥200		Ref	–	Ref	–
50–199		1.42 (0.99, 2.04)	0.06	1.37 (0.96, 1.97)	0.08
<50		1.63 (1.25, 2.12)	0.001	1.89 (1.31, 2.74)	0.001
Syphilis	1				
No		Ref	–	Ref	–
Yes		1.28 (1.02, 1.61)	0.03	1.30 (1.04, 1.63)	0.02
WHO stage	1				
I–II		Ref	–	Ref	–
III–IV		1.91 (1.32, 2.76)	0.001	1.89 (1.31, 2.74)	0.001
ART drugs	2		0.20		0.11
PI based		Ref	–	Ref	–
IN based		1.27 (0.90, 1.82)	0.18	1.29 (0.90, 1.84)	0.16
NNRTI based		0.76 (0.37, 2.76)	0.45	0.73 (0.36, 1.52)	0.40
HBV co-infection	1				
No		Ref	–		
Yes		0.79 (0.44, 1.44)	0.45		
Sex	1				
Female		Ref	–		
Male		1.04 (0.59, 1.85)	0.89		

Abbreviations: IN, integrase inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; ART, antiretroviral therapy; OR, odd ratio.

considered to indicate the presence of residual HIV viremia in virologically suppressed patients.[24,25] Taken together, these findings allow us to speculate that co-infection with syphilis contributes to poor immune recovery and subsequently increases the likelihood of virologic failure.

An interesting finding of the present study is the higher probability of virologic failure in HIV/syphilis co-infected patients than in patients infected only with HIV during the seven-year ART follow-up period. To the best of our knowledge, this is the first evidence linking HIV/syphilis co-infection to virologic failure. Co-infection with syphilis could enhance HIV replication by increasing activation of host immune cells, altering the secretion of cytokines, including TNF-α, and upregulating transcription factors, such as nuclear factor kappa beta.[26]

It has been shown that higher RPR titers are associated with an effective immunological response, leading to more effective elimination of *T. pallidum*.[27] Previous studies have also shown that high RPR titers are associated with a good response to treatment for syphilis.[28] In HIV-infected individuals, however, RPR titers >1:32 have also been associated with laboratory-defined neurosyphilis.[29] In the present study, we demonstrated a correlation between high RPR titers (>1:32) and recurrence or reinfection with syphilis. Further research is needed to investigate the incidence of neurosyphilis in recurrent syphilis and following reinfection. These results underline the importance of monitoring RPR titers in PLWHA co-infected with syphilis, even if these individuals have a good response to treatment, and this should be recognized by clinicians.

Since ART became widely available, the evidence that undetectable HIV equals non-transmissible HIV has spread, and the prevalence of HIV/syphilis co-infection has been significantly increased by the reduced use of condoms.[8] Syphilis seroprevalence in individuals

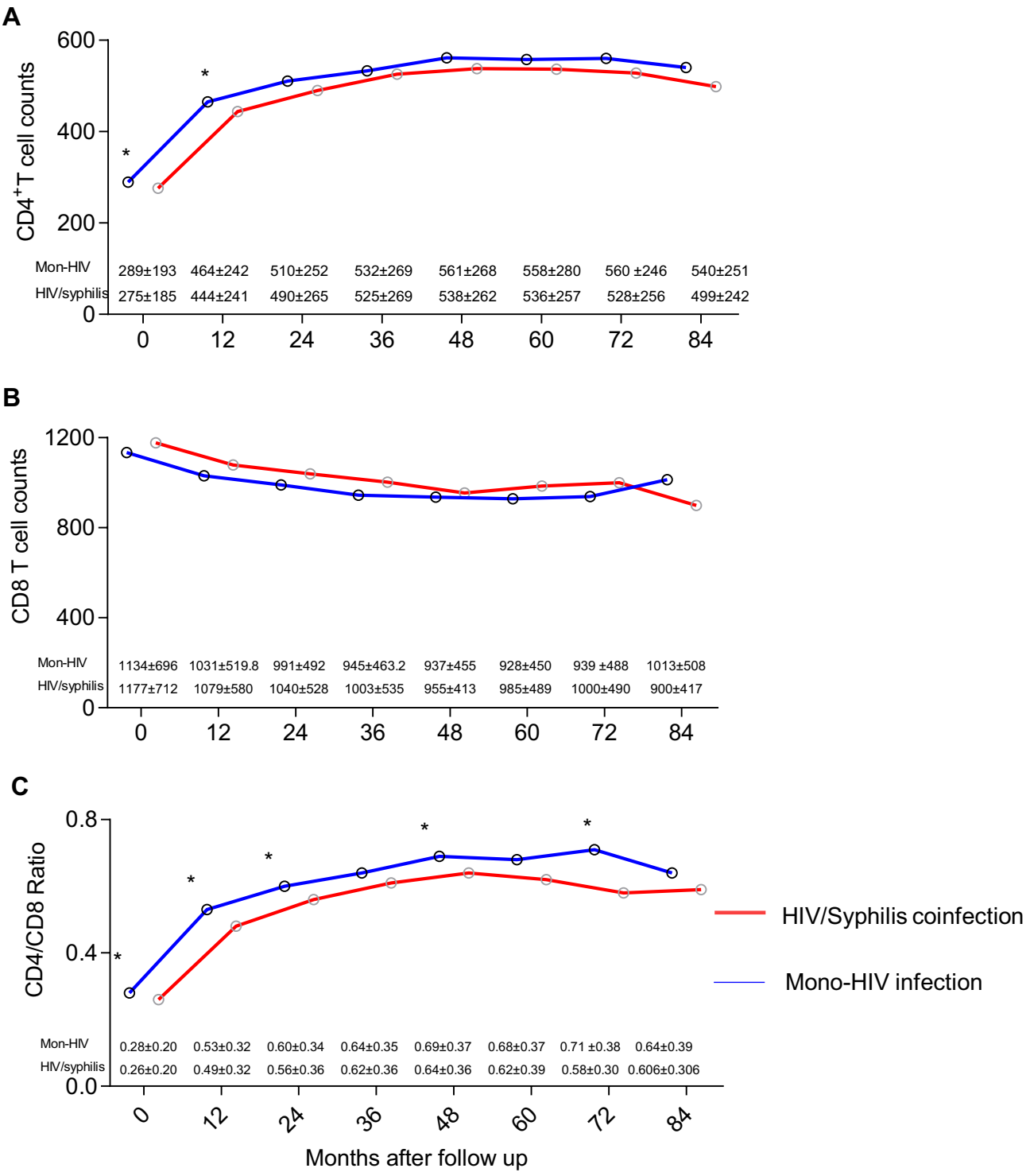

Figure 4 Trends of mean (**A**) $CD4^+$ T cell counts, (**B**) $CD8^+$ T cell counts and (**C**) CD4/CD8 ratio, during seven-year ART follow-up according to syphilis status. *$p < 0.05$.

Table 3 Multivariable/Adjusted Models for Mean Differences in $CD4^+$ T Cell Counts, $CD8^+$ T Cell Counts and CD4/CD8 Ratios During Seven-Year ART Follow-Up

Variables	CD4		CD8		CD4/CD8	
	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value	Estimate (95% CI)	*p* value
Intercept	301.61 (275.05, 328.17)	<0.001	968.8 (904.69, 1032.93)	<0.001	0.39 (0.35, 0.42)	<0.001
Syphilis/HIV co-infection at baseline	−12.61 (−22.57, −2.66)	0.01	38.05 (14.10, 62.01)	0.02	−0.03 (−0.05, −0.02)	<0.001
HCV co-infection at baseline	−47.08 (−82.29, −11.87)	0.01	−30.1 (−83.55, 23.29)	0.27	−0.06 (−0.11, −0.01)	0.02
HBV co-infection at baseline	9.98 (−12.50, 32.45)	0.38	−30.12 (−83.54, 23.29)	0.27	0.02 (−0.01, 0.05)	0.21
Male	7.20 (−15.79 30.20)	0.61	119.66 (64.78, 174.53)	0.001	−0.05 (−0.08, 0.02)	0.04
ART drugs						
IN based	−46.61 (−84.95, −8.28)	<0.001	223.35 (121.23, 325.46)	<0.001	−0.12 (−0.18, −0.06)	<0.001
NNRTI based	−42.92 (−58.46, −27.38)	0.02	−90.46 (−128.48, −52.45)	<0.001	−0.01 (−0.03, −0.02)	0.58
PI based	0		0		0	
Baseline $CD4^+$T cell counts	0.86 (0.86, 0.91)	<0.001	−0.10 (−0.17, −0.02)	0.005	0.03 (0.05, 0.02)	<0.001

Abbreviations: IN, integrase inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; ART, anti-retroviral therapy.

diagnosed with HIV has been reported to range from 5.2% to 25%.[30–33] In the present study, at baseline, syphilis infection among PLWHA accounted for 40.2% of total infections. The reason for the higher prevalence was related to the higher proportion of MSM in PLWHA. It has previously been reported that HIV-infected MSM are at an increased risk of contracting syphilis. A survey carried out in 14 cities throughout China reported that the prevalence of syphilis was 6.7% in MSM adults,[34] which was lower than that reported in Tianjin[35] (11%, 2016). A total of 11.4% of HIV-infected MSMs with confirmed syphilis was reported in Guangzhou, China.[36] Homosexual transmission was the main route of HIV infection in Tianjin, and the higher proportion of MSMs with unfixed sex partner may be responsible for the higher rate of HIV/syphilis coinfection. In the present study, at baseline, syphilis infections among HIV-infected MSM accounted for 65.3% of the total HIV infected individuals. The proportion of co-infected MSM decreased from 80% to 30% from 2009 to 2019, which was inconsistent with a previous study.[1,33,35,37–39] Effective education in the correct use of latex condoms may be responsible for this phenomenon.

This study had several limitations. First, retrospective studies are subject to innate bias. Second, the study was carried out in a single health center and the conclusions drawn from this study may not be fully representative of what would be seen throughout China. Our findings should, therefore, be confirmed by further studies. Third, HIV viral load at baseline was not included in the medical records and we could not exclude the effect of baseline viral load on immune response. Fourth, HCV and HBV seroconversion after ART initiation were not recorded, and thus, the effect of such seroconversion was not considered. Fifth, assessments of viral load were performed yearly or twice per year during the follow-up period, and is a weakness that could not be addressed as it is the protocol used in our hospital. Sixth, this is the only study that analyzed factors associated with changes in HIV viral loads and CD4 cell count during ART in HIV/syphilis coinfected patients. Further studies of the effects of genital ulcers on HIV-1 transmission and HCV, HBV seroconversion on the immunology and virology of PLWHA are warranted.

Conclusions

In conclusion, this study reveals the relationship between HIV/syphilis co-infection and responses to ART during a seven-year follow-up period. The higher virologic failure rate in co-infected patients argues for close monitoring of ART treatment effects and HIV disease progression in this population, especially in reinfected patients or patients with recurrent infection. The attenuated immunologic responses seen here support earlier initiation of ART in HIV/syphilis co-infected patients to optimize their in-treatment $CD4^+$ T cell counts. RPR titers should also be monitored in HIV/syphilis co-infected patients, especially in patients with high RPR titers, even if these individuals respond well to treatment for syphilis. Further research is needed to determine whether early treatment of syphilis in

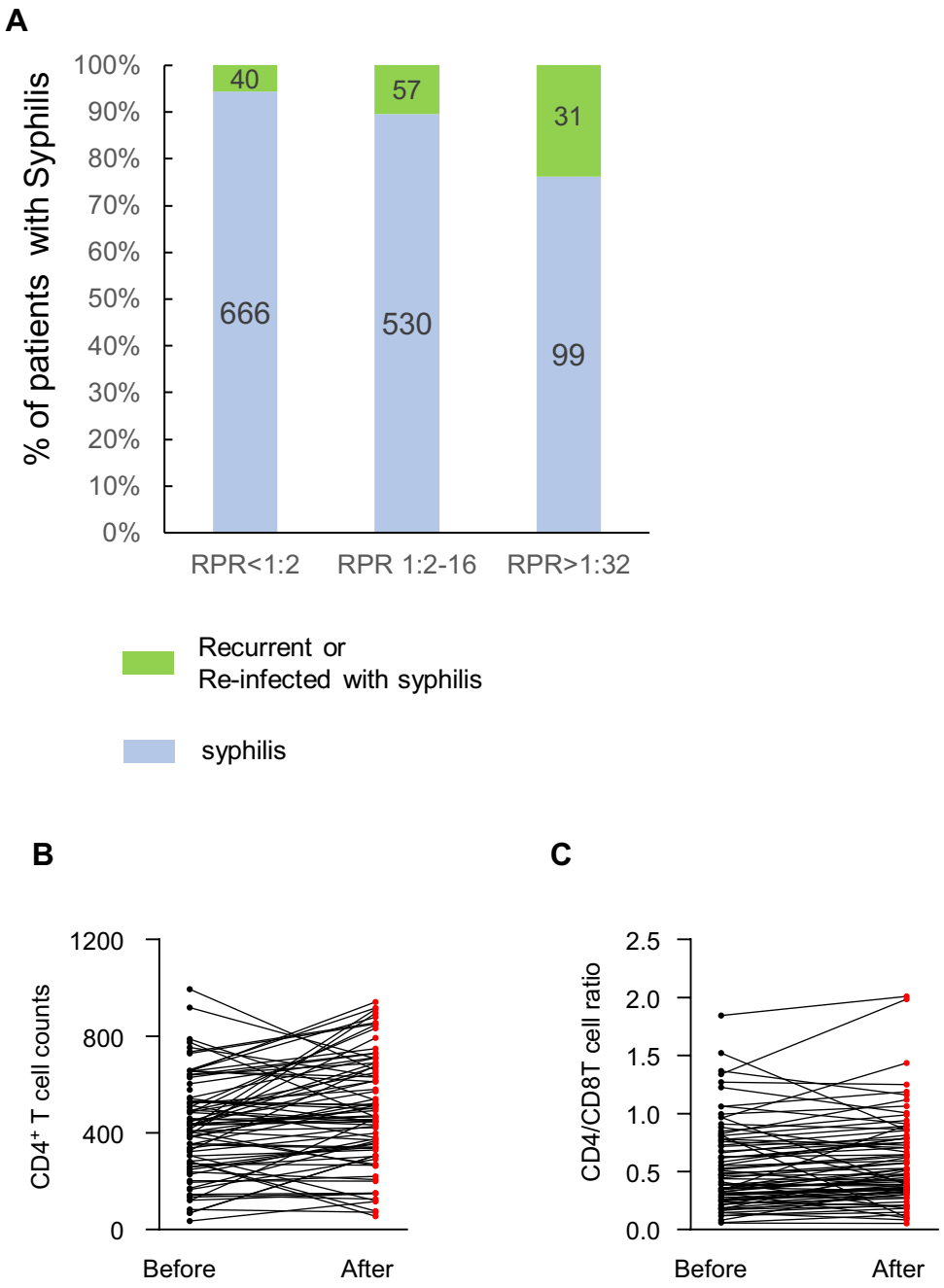

Figure 5 (**A**) RPR titers at baseline in recurrent syphilis or reinfection patients; (**B**) $CD4^+$ T cell counts during the one-year periods before or after the diagnosis of recurrent syphilis or reinfection in patients receiving ART; (**C**) CD4/CD8 ratios during the one-year periods before or after recurrent syphilis or reinfection diagnosis in patients receiving ART.

HIV/syphilis co-infected patients would be associated with improved responses to ART and better clinical outcomes.

Abbreviations

HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ART, anti-retroviral therapy; MSM, men who have sex with men; HR, hazard ratio; RPR, rapid plasma reagin; BMI, body mass index; PLWHA, people living with HIV/AIDS, STI, sexually transmitted infection, AOR, adjusted odds ratio, OIS, opportunistic infections.

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Disclosure

All authors agreed to publication of this article and declare no conflicts of interest.

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