

## The Effects of Syphilis Infection on CD4 Counts and HIV-1 RNA Viral Loads in Blood: A Cohort Study Among MSM with HIV Infection in Sanglah Hospital Bali-Indonesia

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**Background:** Men who have sex with men (MSM), particularly those with HIV infection, are at high risk for contracting syphilis. However, little is known about the effect of syphilis on HIV-1 RNA and CD4 count among HIV infected MSM. **Methods:** MSM were enrolled into the MSM-VCT study cohort at Sanglah Hospital in Bali between June 22<sup>nd</sup> 2011 to February 13<sup>rd</sup> 2012. All participants had anti-HIV test and VDRL test at baseline, with TPHA confirmation for reactive VDRL results. Plasma HIV-1 RNA levels and CD4 counts were measured at baseline and month 6 visits. T-test or non-parametric Mann-Whitney test were used to compare changes in CD4 counts and HIV-1 RNA levels between those with and without syphilis. To analyze difference of baseline and 6 month visit in each group, we used paired students t-test. **Results:** HIV positive MSM with syphilis co-infection had significantly higher mean baseline CD4 count than those without syphilis (P=0.017). No difference was seen for median baseline plasma HIV-1 RNA between HIV positive MSM with and without syphilis (P=0.885). Mean change in CD4 count from baseline to month 6 was similar between HIV positive MSM with syphilis (n=11) and without syphilis (n=20) (P=0.860). Similarly, no significant difference in median HIV-1 RNA change was identified between those with (n=8) and without syphilis (n=11) (P=1.000). **Conclusions:** HIV positive MSM with syphilis co-infection had higher CD4 cell counts. However, syphilis influences the changes of CD4 cell count and HIV-1 RNA 6 months after HIV diagnosis, but not statistically significance.

**Keywords:** MSM, HIV, Syphilis; HIV-1 RNA, CD4 count

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### INTRODUCTION

Syphilis and HIV both are infectious diseases that transmitted sexually. Men sex men (MSM) is a group that is very vulnerable to infection that sexually contagious. Nowadays, syphilis infection often found and tend to increase especially in MSM with HIV infection.<sup>1-3</sup>

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The interaction between syphilis and HIV is not fully understood.<sup>2</sup> Syphilis causes disruption of epithelial barrier and genital mucosa, facilitates sexual transmission of HIV.<sup>4</sup> Whereas the effect of syphilis on HIV-1 RNA viral load (VL) and CD4 in HIV patient is not fully understood until now.<sup>5-11</sup> Several studies about the effect of syphilis in HIV has been done in a group of HIV patient in general, but still only few of reports about the effect of syphilis in VL and CD4 level in a group of MSM with HIV positive. The following reported a cohort study to gain knowledge about the effect of syphilis in alteration of viral load and CD4 count in MSM with HIV plasma.

## MATERIALS AND METHODS

We conducted MSM-VCT cohort study in Nusa Indah VCT Sanglah Hospital in Bali between June 22<sup>nd</sup> 2011 to February 13<sup>rd</sup> 2012. Men aged 18 years old or older with a history of anal sex with men recruited in the study. Participants were excluded if they have a history of health problems or psychiatric disorder that affects the ability to receive an explanation about informed consent. Study has been approved by the institutional review board of *Kerti Praja* Foundation with ethical clearance No 027/IRB-YKP/2011. All of participants received informed consent. At baseline, participants filled out written demographic and risk behavior data questionnaires, syphilis serology test and anti-HIV test. Risk behavior data including report of debut anal sex, number of sexual partners in last 1 month, anal receptive in last 1 month, using of condoms in last 1 month and circumcision. Additional data on current CD4 count, plasma HIV RNA in HIV positive were collected from participants. HIV diagnosis is made based on the results of the reactive 3 method of anti-HIV test. While the syphilis diagnosis is made based on results of tests VDRL and TPHA reactive. All participants were positive for syphilis treated with Benzatine Pencillin 2.4 million IU in a single intramuscular. Antiretroviral therapy (ART) was initiated for HIV-positive MSM who had CD4 count below 350 cells/mm<sup>3</sup>. Plasma HIV-1 RNA levels and CD4 counts were measured at baseline and month 6 visits among those who were HIV-positive.

## Specimen Collection

Anti HIV test conducted with 3 rapid test methods that are different, VIKIA ® HIV 1/2, HIV 1 & 2 Antibody Rapid Test Oncoprobe and HIV INTEC ½ rapid test. The measurements of HIV plasma viral load with PCR using amplicor HIV-1 monitor Test version 1.5 kit, (Roche; US: 83135, ART: 11 1775 0, P/N: 21117750 123) in a range of level: 400 – 750.000 copy/ml. Whereas CD4 test conducted by immunofluorescent flowcytometry methods: BD FACSCCount CD4 reagents. VDRL serology test using Syphilis toluidine red untreated serum test (TRUST). TPHA test using rapid serological, immunochromatographic assay for detection of antibodies to syphilis antigen in human serum or plasma (intec Advanced Quality One Step Syphilis (TP) test strip KEMENKES RI AKL 20303805175).

## Statistical Analysis

We used the Chi square test for assessing categorical associations of demographic and behavioral characteristics between HIV positive MSM with and without syphilis. To assess the influence of syphilis on HIV plasma VL and CD4, we compare changes in CD4 counts and HIV-1 RNA levels from baseline to month 6 by using T-test or non-parametric Mann-Whitney test, respectively between those with and without syphilis. To analyze difference of baseline and 6 month visit in each group, we used paired students t-test. A P value is considered significant at 0.05. The statistical analysis was performed with SPSS, version 15.0 for windows (SPSS, Chicago, IL).

Table 1. Baseline characteristics of HIV positive MSM with and without syphilis

Characteristic	Total	Syphilis positive	Syphilis negative	P-value
Age (years), mean ± SD	N= 49 33.36 ± 7.153	N= 14 35.93 ± 6.391	N= 35 32.31 ± 7.124	0.106
Debut anal sex (years), mean ± SD	N= 45 17.32 ± 5.112	N=13 19.54 ± 5.710	N= 32 16.66 ± 4.79	0.091
Numbers of sexual partners, median	N= 48 3.5	N=13 6	N=35 3	0.722
Anal receptive				
- Yes, n(%)	40	13 (92.85%)	27 (77.14%)	0.415
- No, n(%)	9	1 (7.15%)	8 (32.86%)	
Condom use				
- No, n(%)	7	1 (7.15%)	6 (17.14%)	0.489
- Sometimes, n(%)	16	6 (42.85%)	10 (28.57%)	
- Always, n(%)	26	7 (50%)	19 (54.28%)	
Circumcision				
- Yes, n(%)	28	10 (71.42%)	18 (51.42%)	0.338
- No, n(%)	21	4	17 (48.57%)	
Antiretroviral Treatment	15	3 (21.42%)	12 (35.28%)	0.502
Mean (±SD) CD4 baseline (cells/mm <sup>3</sup> )	304.31 ± 163.00	426.71 ± 177.98	305.74 ± 145.24	<b>p=0.017</b>
Median HIV-1 RNA (copy/mL)	22572 (400 - 750000)	20078.50 (400-750000)	28343 (400-750000)	p=0.885

## RESULTS

### Participants Characteristics

There were 89 MSM enrolled, 49 HIV positive MSM and 40 HIV negative MSM. Syphilis were diagnosed in 4 (10%) HIV negative MSM and 14 (28.57%) HIV positive MSM at baseline. There was no significant difference in mean of age and risk behavior: debut anal sex, number of sexual partners, anal receptive, using of condoms and circumcision between HIV positive MSM with and without syphilis infection at baseline. Mean CD4 level at baseline significantly higher in MSM with HIV positive compared to MSM without HIV.

### Influence of Syphilis on Plasma HIV RNA Levels and CD4 Cell Count

After follow up for 6 months, it appears that in the HIV patient with syphilis, the difference in viral load reduction after 6 months is lower than the patient without syphilis. Also appears that difference in increase of average level of CD4 after 6 months in HIV patient with syphilis is lower than patient without syphilis, although this is statistically meaningless. (Table 2)

Meanwhile, analyze in each group in HIV positive MSM with syphilis and without syphilis with paired student's or wilcoxon test at baseline and 6 months follow up. Baseline level of HIV-1 RNA and at 6 months in HIV positive with syphilis (n=8) and without syphilis (n=11) was [20078 (400-750000) vs. 1240 (400-57368), z=-1.52, P=0.128]; [28343 (400-750000) vs. 8958 (400-76768), z=-0.80, P=0.424] respectively. Baseline CD4 level and at 6

months in HIV positive with syphilis (n=11) and without syphilis (n=20) was (426.71 ± 177.98 vs. 449 ± 213.53, t=0.92, P=0.381); (305.74 ± 145.24 vs. 307.80 ± 112.36, t = 2.03, P=0.057) respectively (Table 3).

## DISCUSSION

In this study we found the prevalence of syphilis overall among MSM is 22%, almost same like the study in Jakarta which is 19.3%.<sup>2</sup> Meanwhile in MSM patient with HIV positive, in this study we found that the prevalence of syphilis (28.57%), almost same like the study in Thailand (27.1%),<sup>3</sup> higher than the study in China (2.7%).<sup>1</sup>

Several studies found that syphilis has effect in decreasing CD4 level and increasing VL,<sup>5-9</sup> although other study found that the effect is getting better after receiving syphilis therapy and ART,<sup>8-10</sup> and don't have the influence in the progression of HIV infection.<sup>11</sup> On the other side, it's said that syphilis don't have the effect in immunologic and virologic changes in HIV patient.<sup>12</sup>

In this study, all syphilis cases received benzatin penicillin 2.4 million IU IM therapy and received ART in HIV infection with or without syphilis in a level of CD4 < 350 cell/ul. Several studies reported that syphilis therapy and ART will improve changing level of CD4 and viral load.<sup>8-10</sup> In this study, it is found that an increase of CD4 level and decrease of VL in syphilis group is lower than a group without syphilis, although this is statistically meaningless.

Table 2. HIV-RNA Levels and CD4 Cell Count at Baseline and 6 month follow up

Parameter	Syphilis positive	Syphilis negative	P-value
Δ HIV-RNA (copy/ml), Median (IQR)	- 6823.50 (-199626 to 128770)	-21819.50 (-483068 to 70981)	<b>1.000</b>
Δ CD4 (sel/mm <sup>3</sup> ), Mean ± SD	30.63 ± 110.95	37.50 ± 82.68	p=0.860

‡Indicates no. of patients with (-) a decrease in measurements

Table 3. CD4 Cell Count and HIV-RNA Levels at Baseline and 6 month follow up

	Syphilis positive Mean ± SD or median (IQR)	Syphilis negative Mean ± SD or median (IQR)	P-value**
CD4 baseline (sel/mm <sup>3</sup> ), (N)	N= 14 426.71 ± 177.98	N= 35 305.74 ± 145.24	<b>0.017</b>
CD4 at 6 months (sel/mm <sup>3</sup> ), (N)	N= 11 449 ± 213.53	N=20 307.80 ± 112.37	0.062
<b>P-value*</b>	0.381	0.057	
HIV-RNA baseline (copy/ml), (N)	N=14 20078.50 (400-750000)	N=35 28343 (400-750000)	0.885
HIV-RNA at 6 months (copy/ml), (N)	N=8 1240 (400-57368)	N=11 8958 (400-76768)	0.472
<b>P-value*</b>	0.128	0.424	

\*P-value from paired student's t or wilcoxon analysis

\*\*P-value from independent student's t or mann-whitney analysis between group

There are several limitations in this study that cause failure to see some changes in VL and CD4 in a subgroup analysis because of the small number of sample, high loss to follow up in 6 months and long range of time to do another test of VL and CD4.

## CONCLUSION

The prevalence of syphilis in group MSM with HIV in Bali is really high. Syphilis influences the alteration of viral load and CD4 count in blood eventhough statistically meaningless. Screening and therapy of syphilis needs to be integrated in a HIV in MSM prevention and treatment program.

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