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e da
INMI, Istituto Nazionale per le Malattie Infettive
ISS, Istituto Superiore di Sanità
AMCLI, Associazione Microbiologi Clinici Italiani
SIICA, Società Italiana di Immunologia, Immunologia
Clinica e Allergologia
SIMaST, Società Interdisciplinare per lo Studio delle
Malattie Sessualmente Trasmissibili
SITA, Società italiana per la Terapia Antinfettiva
SIV-ISV, Società Italiana di Virologia - Italian Society
for Virology
ANLAIDS, Associazione Nazionale per la lotta
all'AIDS
ARCIGAY, Associazione LGBT Italiana
ASA Onlus, Associazione Solidarietà AIDS Onlus
EpaC Onlus, Associazione EpaC Onlus
LILA, Lega Italiana per la lotta contro l'AIDS
MARIO MIELI, Circolo di Cultura Omosessuale
NADIR, Associazione Nadir Onlus
NPS Italia Onlus, Network Persone Sieropositive
PLUS, Persone LGBT Sieropositive onlus

effetti

ICAR

Impact of syphilis on the risk of HIV viral rebound in HIV positive patients under effective antiretroviral treatment: data from the ICONA cohort

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OC 33

Background

- In recent years a rise in sexual transmitted diseases (STDs) has been observed in HIV positive men who have sex with men

- Among STDs, syphilis has been associated to HIV-RNA increase combined with a temporary decline in CD4 T-cell count in patients not under antiretroviral treatment (ART)

- On the contrary, less convincing evidences are available in those under ART

Lang R et al BMC Infect Dis. 2018;18(1):125. Cingolani A, *HIV Med*. 2015;16(7):412–420. doi:10.1111/hiv.12226 Buchacz K, et al AIDS. 2004 Oct 21;18(15):2075-9 Jarzebowski W, et al; FHDH-ANRS CO4 Study Team. Arch Intern Med. 2012 Sep 10;172(16):1237-43. Grewal R, et al. J Acquir Immune Defic Syndr. 2019 Apr 15;80(5):585-589.

Research hypothesis and objectives

Hypothesis: Patients under effective antiretroviral treatment with syphilis infection could have an increased incidence of viral rebound in the period around syphilis infection

Outcomes were defined using the first HIV-RNA measure in the time window ranging between -2 and +6 months of the index date.

- The primary outcome will use the cut-off of >50 cp/mL to define rebound
- The secondary outcome will use the cut-off of >200 cp/mL to define rebound
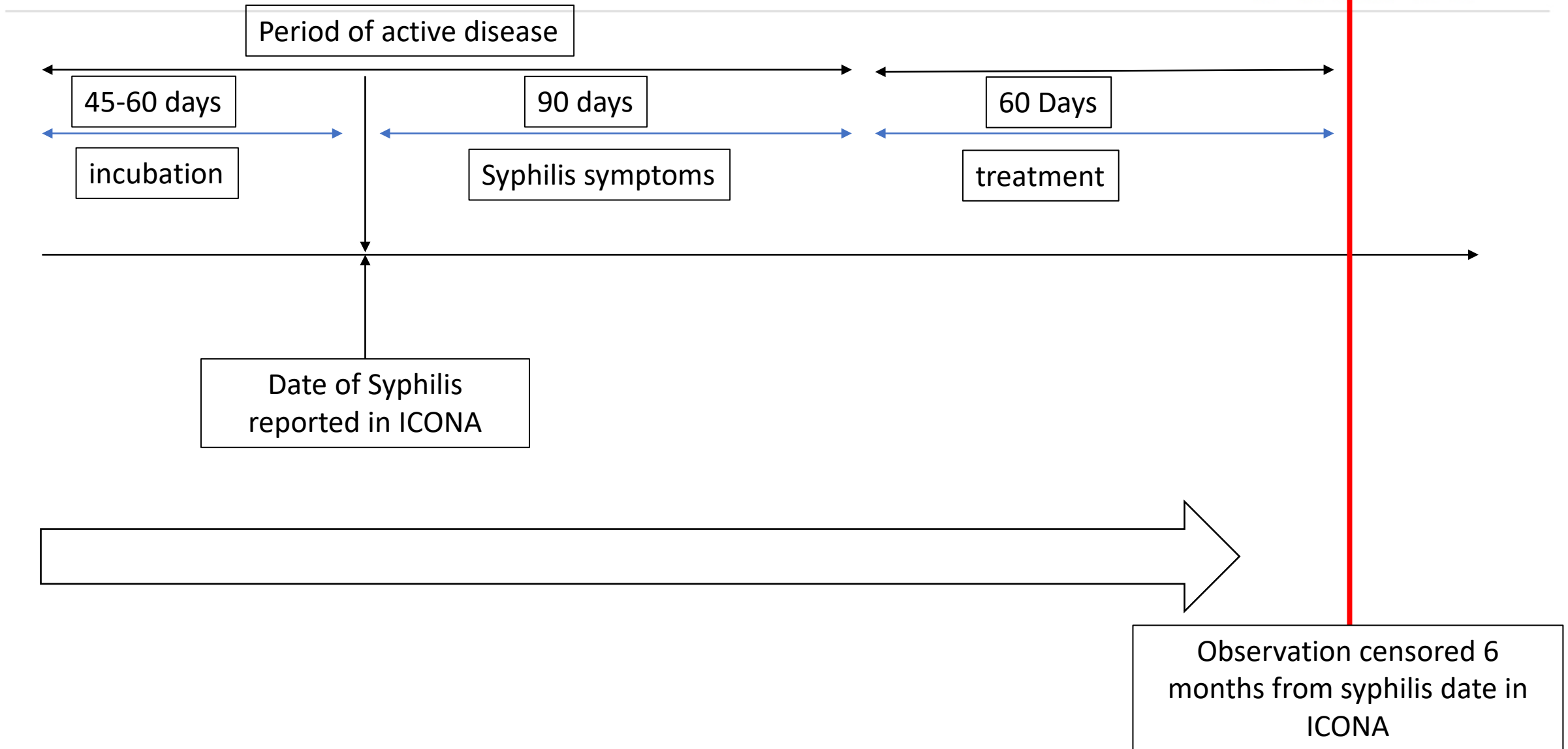
Materials and Methods

Study design: Retrospective observational study of prospectively collected data.

Population: All PLWH in the ICONA cohort (2009-2019) under ART with at least 2 consecutive HIV-RNA values ≤50 cp/mL before the date of syphilis diagnosis and at least one HIV-RNA determination after the syphilis event

Controls: A control group of PLWH without syphilis who after the same amount of time from enrolment of the syphilis case (index date) were free from syphilis will be matched for age, mode of HIV transmission and CD4 cell count at the enrolment in the ICONA cohort.

Materials and methods

Period of active disease

45-60 days

90 days

60 Days

incubation

Syphilis symptoms

treatment

Date of Syphilis reported in ICONA

Observation censored 6 months from syphilis date in ICONA

Statistical analysis

- An interrupted time series analysis (ITS) will be used to assess the trend of HIV-RNA in PLWH with syphilis.

- The association between syphilis infection and the protocol defined outcomes will be evaluated using logistic regression analysis.

- A multivariable logistic analysis will be used to adjust for potential confounders: previous AIDS, CD4 cell count, previous virological failure and time of virological suppression before the index date.

- Age, mode of transmission and CD4 cell count at ICONA enrolment will be controlled by matching.

Results

Characteristics	Cases	Controls	p-value*	Total
	N= 692	N= 933		N= 1625
Gender, n(%)			<.001	
Female	22 (3.2%)	102 (10.9%)		124 (7.6%)
Mode of HIV Transmission, n(%)			0.244	
IDU	26 (3.8%)	41 (4.4%)		67 (4.1%)
Homosexual contacts	535 (77.3%)	688 (73.7%)		1223 (75.3%)
Heterosexual contacts	108 (15.6%)	178 (19.1%)		286 (17.6%)
Other/Unknown	23 (3.3%)	26 (2.8%)		49 (3.0%)
Nationality, n(%)			0.017	
Not Italian	86 (12.4%)	82 (8.8%)		168 (10.3%)
AIDS diagnosis, n(%)			0.247	
Yes	78 (11.3%)	123 (13.2%)		201 (12.4%)
HBsAg, n(%)			0.471	
Negative	631 (91.2%)	866 (92.8%)		1497 (92.1%)
Positive	22 (3.2%)	23 (2.5%)		45 (2.8%)
Not tested	39 (5.6%)	44 (4.7%)		83 (5.1%)
HCVAb, n(%)			0.070	
Negative	619 (89.5%)	814 (87.2%)		1433 (88.2%)
Positive	69 (10.0%)	102 (10.9%)		171 (10.5%)
Not tested	4 (0.6%)	17 (1.8%)		21 (1.3%)
Calendar year of baseline**			0.074	
Median (IQR)	2015 (2012, 2017)	2015 (2012, 2017)		2015 (2012, 2017)
Median (IQR)	20108 (18862, 20875)	20272 (19179, 20868)		20205 (19012, 20868)

Characteristics	Cases	Controls	p-value*	Total
	N= 692	N= 933		N= 1625
Age, years			<.001	
Median (IQR)	42 (36, 50)	45 (38, 52)		44 (37, 51)
CD4 count, cells/mmc				
Median (IQR)	723 (583, 960)	756 (578, 951)		743 (582, 954)
CD4 count nadir, cells/mmc				
Median (IQR)	300 (200, 396)	279 (176, 378)		287 (182, 386)
CD8 count, cells/mmc				
Median (IQR)	833 (631, 1096)	826 (599, 1092)		830 (610, 1093)
CD4 count, n(%)			0.634	
<=200 cells/mmc	5 (0.7%)	5 (0.5%)		10 (0.6%)
Time from HIV diagnosis to baseline, months				
Median (IQR)	31 (16, 52)	37 (18, 62)		34 (17, 58)
Follow-up time, years				
Median (IQR)	2 (1, 4)	2 (1, 4)		2 (1, 4)
Time from HIV diagnosis to baseline, months				
Median (IQR)	70 (41, 116)	98 (63, 158)	<0.001	86 (52, 140)
Time of viral suppression before baseline, months				
Median (IQR)	30 (16, 51)	36 (18, 62)	<0.001	33.9 (17, 59)
*Chi-square or Kruskal-Wallis test as appropriate				

Results

Log RNA predictions from Interrupted Time Series Model
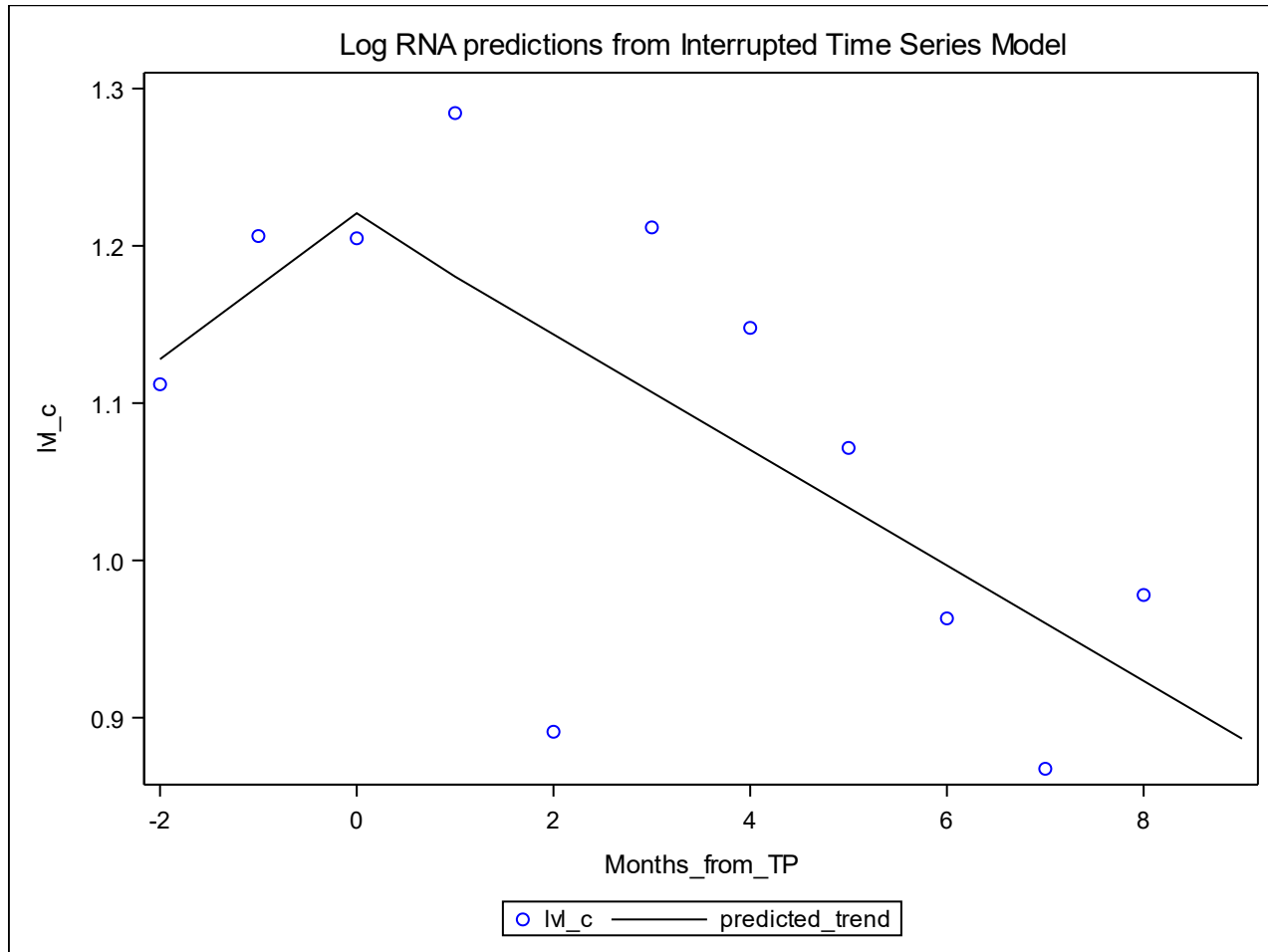
Period	HIV-RNA (log10 copies/mL)		
	Proportion <=50 copies/mL (Mean 95% CI)	ARIMA estimates (95% CI)	p-value*
2 Months prior to TP	1.11 (1.00, 1.23)	0.09 (-0.12, 0.30)	0.423
At TP	1.20 (1.01, 1.40)	-0.07 (-0.42, 0.29)	0.720
7 Months after TP	0.87 (0.74, 0.99)	-0.14 (-0.35, 0.07)	0.241
*ARIMA Wald test			

Logistic regression estimates of factors associated with the risk of a single VL>50 copies/mL

Factor	Unadjusted		Adjusted*		
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Type III p-value
Female vs. Male	2.27 (1.09, 4.74)	0.029	1.79 (0.80, 4.03)	0.156	
Mode of HIV Transmission					
PWID vs. MSM	4.60 (2.05, 10.36)	<.001			
PWID vs. Heterosexual	1.75 (0.93, 3.29)	0.084			
PWID vs. Other/Unknown	1.44 (0.34, 6.19)	0.620			
Not Italian vs. Italian	1.17 (0.52, 2.63)	0.695	1.01 (0.43, 2.38)	0.989	
AIDS Yes vs. No	1.72 (0.88, 3.37)	0.114	1.51 (0.72, 3.18)	0.279	
Age per 10 years older	1.28 (1.01, 1.62)	0.043			
CD4 count, cells/mmc at TP/index date					
per 100 lower	0.94 (0.86, 1.03)	0.214	0.98 (0.89, 1.08)	0.715	
CD8 count, cells/mmc at TP/index date					
per 100 higher	1.12 (1.07, 1.17)	<.001			
Previous VF					<.001
1-3 vs. 0	4.44 (2.42, 8.14)	<.001	4.81 (2.53, 9.14)	<.001	
3+ vs. 0	7.51 (3.79, 14.91)	<.001	6.55 (3.18, 13.49)	<.001	
Anchor HIV drug used					
PI/r vs. NNRTI	1.50 (0.87, 2.58)	0.140			
INSTI vs. NNRTI	0.43 (0.18, 1.02)	0.055			
Employment, n(%)					
Unemployed vs. Employed	1.12 (0.46, 2.71)	0.805			
Self-employed vs. Employed	1.16 (0.61, 2.22)	0.653			
Occasional vs. Employed	0.86 (0.11, 6.47)	0.881			
House work vs. Employed	0.99 (0.13, 7.50)	0.991			
Other/unknown vs. Employed	0.95 (0.13, 7.21)	0.962			
TP diagnosis					
Yes vs. No	1.23 (0.73, 2.07)	0.441	1.62 (0.91, 2.86)	0.100	
Duration of suppression <=50 copies/mL					
per 6 months longer	0.11 (0.07, 0.17)	<.001	0.81 (0.74, 0.88)	<.001	

*Multivariable model included only variable shown in second column of the table (i.e. confounding factors for TP diagnosis and risk of VF>50 copies/mL);age mode of transmission and CD4 cout at enrolment in Icona are controlledby matching

Logistic regression estimates of factors associated with the riskof a single VL>200 copies/mL

Factor	Unadjusted		Adjusted*		
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Type III p-value
Female vs. Male	3.27 (1.31, 8.18)	0.011	2.16 (0.78, 5.98)	0.139	
Mode of HIV Transmission					
PWID vs. MSM	8.80 (3.49, 22.20)	<.001			
PWID vs. Heterosexual	1.62 (0.63, 4.17)	0.320			
Not Italian vs. Italian	2.31 (0.93, 5.75)	0.072	2.37 (0.86, 6.54)	0.096	
AIDS Yes vs. No	1.54 (0.58, 4.09)	0.384	0.98 (0.33, 2.92)	0.978	
Age per 10 years older	1.32 (0.94, 1.84)	0.104			
CD4 count, cells/mmc at TP/index date					
per 100 lower	0.90 (0.79, 1.04)	0.150	0.93 (0.81, 1.07)	0.335	
CD8 count, cells/mmc at TP/index date					
per 100 higher	1.15 (1.09, 1.20)	<.001			
Previous VF					<.001
1-3 vs. 0	8.68 (3.23, 23.32)	<.001	8.78 (3.13, 24.61)	<.001	
3+ vs. 0	19.74 (7.17, 54.38)	<.001	17.53 (6.08, 50.55)	<.001	
Anchor HIV drug used					
PI/r vs. NNRTI	1.17 (0.54, 2.52)	0.692			
INSTI vs. NNRTI	0.26 (0.06, 1.12)	0.071			
Employment, n(%)					
Unemployed vs. Employed	2.37 (0.84, 6.67)	0.103			
Self-employed vs. Employed	1.80 (0.75, 4.32)	0.191			
Occasional vs. Employed	2.19 (0.28, 17.22)	0.455			
Other/unknown vs. Employed	2.44 (0.31, 19.20)	0.398			
TP diagnosis					
Yes vs. No	0.95 (0.45, 2.00)	0.895	1.33 (0.58, 3.05)	0.499	
Duration of suppression <=50 copies/mL					
per 6 months longer	0.75 (0.65, 0.87)	<.001	0.78 (0.68, 0.90)	<.001	

*Multivariable model included only variable shown in second columnof the table (i.e. confounding factors for TP diagnosis and risk of VF>50 copies/mL);age mode of transmission and CD4 cout at enrolment in Icona are controlledby matching

Conclusions

- People with syphilis showed a trend toward an increased risk of viral blips (single value >50 cp/mL)

- less convincing evidence was found for the association between syphilis infection and transient viral elevation with the potential of HIV transmission (single value >200 cp/mL)

- In conclusion, the role of syphilis in HIV viral rebound is still to be determined.

Acknowledgements