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Latent, Acute, or Neuro-Syphilis does not increase HIV-1 Replication in Central Nervous System

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BACKGROUND:

- HIV-1 RNA "blip" is a timely limited virus load increase, that disappears without intervention, and had previously been associated with otherwise often asymptomatic, acute Syphilis infection.
- The mechanism of this phenomenon is yet not fully understood. One hypothesis explains HIV to cross the bloodbrain barrier by so-called "Trojan Horse"-mechanism, being carried in migrating monocytes and lymphocytes, because these immune cells are attracted by another neurotropic, sexually transmitted infection, such as syphilis.
- Syphilis activity beyond the bloodbrain barrier may support the immune-activation of monocytes, macrophages and microglia, all being able to replicate HIV-1 as well.
- While antiretroviral therapy (ART) is otherwise suppressive, HIV-1 replication could escape in compartmentalized central nervous system (CNS) reservoir, in particular during inflammation due to syphilis at any clinical stage.
- **OBJECTIVE** was to explore if syphilis-co-infection is connected to increased CNS-replication of HIV-1.

METHODS:

Clinical setting:

- Frankfurt HIV Cohort collects patient data since 1987 and is approved by ethics committee; patients give written informed consent.
- Serological syphilis testing is performed as routine diagnostic procedures for all patients admitted to Frankfurt HIV Cohort and in the course
- Simultaneous determination of HIV-1 RNA in both plasma and cerebrospinal fluid (CSF) is a routine differential diagnostic procedure in Frankfurt HIV Cohort-patients, if CSF-collection is needed for any clinical reason and indication.
- All HIV-1 RNA determinations in both blood plasma and CSF, are routinely sent to the local Medical Virology Department since 2005.

Study-Design:

- Cross-section study in a large ongoing HIV Treatment Cohort. The study was performed as controlled sub-analysis on all patients with available results for quantitative HIV-1 RNA from simultaneously collected CSF and blood plasma, drawn between 2005 and 2013, and syphilis serology result, respectively.
- The local reference laboratory's database query identified all patients who had undergone paired HIV-1 RNA assessments, allowing a maximal time variation of 7 days between CSF- and plasma/serum results.
- Identified patients' clinical case charts were assessed retrospectively. Patient data on prior ART-history, current and prior comorbidities and concomitant diseases and medications, including the reasons and clinical indication for the CSF investigation, and prior HIV resistance profile were systematically extracted for all included individuals.

Study procedures and statistical analysis:

- Virus-load (VL)-ratio for CSF/blood-quotient was built for each patient's dataset.
- Patient characteristics were evaluated according to syphilis serology details: If TPPA-screening result was positive, further tests (VDRL, IgM, CSF/blood-antibody ratio) followed.
- Patients were allocated to groups (see patient selection diagram), according to diagnostic evaluation criteria in concordance with CDC.
- Univariate group statistics and Pearson's regression analysis for time-dependent results for PI-patients were generated.

RESULTS:

Diagram: Patient selection

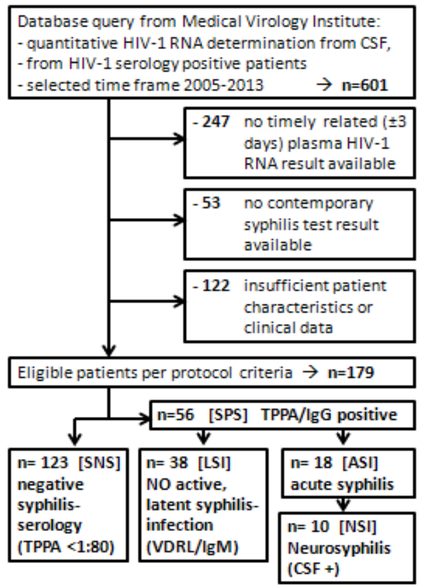
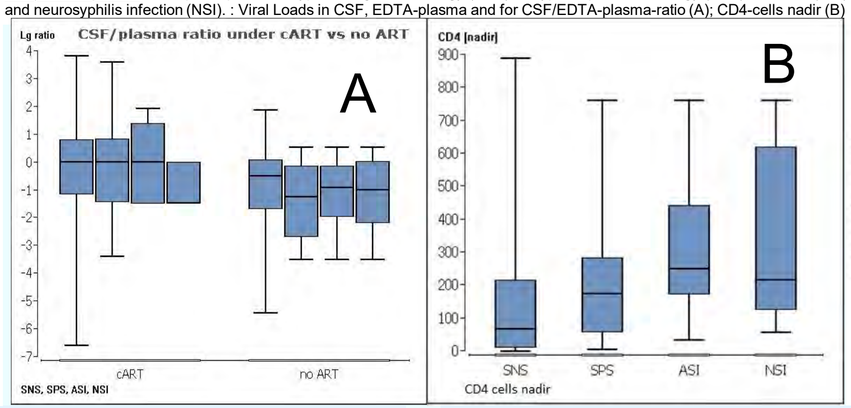


Table: Subject Characteristics at time of Lumbal puncture (LP) Results for HIV-1 infected patients with latent, acute and neuro-syphilis co-infection

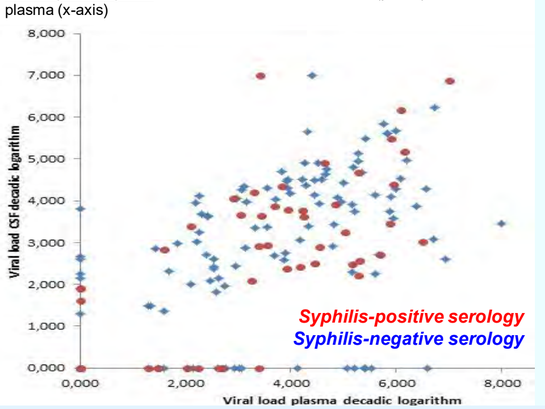
Legend: differences: red - highly significant; orange - significant; yellow - level of significance hardly not met; LP - lumbal puncture, ART - antiretroviral therapy, µL – microliter, mL - milliliter

	All patients (n=179)	Syphilis negative serology [SNS] (n=123)	Syphilis positive serology [SPS] (n=56)	p-value SNS vs. SPS	Acute Syphilis infection [ASI] (n=18)	Latent Syphilis infection [LSI] (n=38)	p-value SNS vs. ASI	p-value ASI vs. LSI	Neuro-Syphilis infection [NSI] (n=10)	p-vaue SNS vs. NSI
Gender: Males (%)	138 (77)	87 (71)	51 (91)	0.005	17 (94)	34 (89)	0.042	0.542	10 (100)	0.066
Mean age at LP (years/y)	44.8	43.1	48.5	0.003	45.3	50.0	0.437	0.165	47.6	0.206
CDC-category at LP (A/B/C)	44/27/104	25/17/79	19/10/25	0.052	8/3/5	11/7/20	0.014	0.282	4/2/3	0.115
Mean age at 1st HIV+ test (y)	36.7	34.4	42.3	<0.001	36.7	44.6	0.545	0.026	39.4	0.276
Patients on ART (%)	60.5	61.0	59.3	0.830	35.3	70.3	0.044	0.033	33.3	0.103
Primary HIV-transmission risk: - Men having Sex with Men (%)	31.3	26.0	42.9	0.024	38.9	44.7	0.254	0.901	40	0.837
- Intravenous Drug User (%)	12.9	16.3	5.4	0.043	5.6	5.26	0.233	1.000	10	0.602
Median CD4 cell count (/µL) at LP	175	162	209	0.570	239	153	0.347	0.333	218	0.450
Median CD4 cell count (/µL) at nadir	79	64	171	0.001	247	104	<0.001	0.006	214	0.004
Median viral load (copies/mL) in CSF	760	1018	340	0.137	585	230	0.502	0.572	650	0.456
Median viral load (copies/mL) in blood	2720	4970	2450	0.335	7620	1440	0.886	0.439	7620	0.785
Median viral load-ratio CSF/blood	0.740	0.930	0.375	0.157	0.345	0.695	0.246	0.788	0.195	0.176

Boxplot Diagrams: Group comparisons/ syphilis-negative serology (SNS) vs syphilis-positive serology (SPS), vs acute (ASI) and neurosyphilis infection (NSI). : Viral Loads in CSF, EDTA-plasma and for CSF/EDTA-plasma-ratio (A); CD4-cells nadir (B)



Scatterplot Diagram: Quantitative HIV-1 RNA in CSF (y-axis) and in EDTA-plasma (x-axis)



Conclusions 1:

- HIV-1 replication in CSF, blood, and CSF/blood VL-ratio was not higher and not significantly different between patient groups with syphilis seropositive status, confirmed acute, or neuro-infection, respectively, and syphilis seronegative controls.
- The ratio of HIV-1 replication in CSF and Plasma was hardly influenced by overall administrated ART.

Conclusions 2:

- This unselected cross-section study from a large real-life treatment cohort could not support the hypothesis of a CNS reservoir for HIV-1 throughout different stages of syphilis infection.
- Patient characteristics including higher CD4-cases nadir may reflect the clinical fact that symptomatic syphilis may lead to earlier HIV-diagnosis, followed by specific treatment, if compared to syphilis-negative late presenters