Poster board no.

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21st th Conference on Retrovirus and Opportunistic Infections

March 2 – 6, 2014, Boston, MA / U.S.A.

HIV-1 Replication in Central Nervous System Increases over Time on Protease Inhibitor Only Therapy

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BACKGROUND:

- In neurologically asymptomatic HIV-1 positive individuals, without antiretroviral treatment (ART), the natural ratio of HIV-1 viral load in cerebrospinal fluid (CSF) and plasma was found in studies to be about 1:10.
- The CHARTER-study introduced a central nervous system (CNS) penetration efficacy-score system (CPE), to evaluate CNS-activity of available antiretroviral combinations.
  Outside CHARTER, clinical validation for CPE-score is scarce.
- Protease inhibitors (PI) vary broadly by drug, in terms of power to suppress HIV-1 replication in CSF; and neurological impairment is a major challenge for the otherwise successful PI-monotherapy concept. Dual PI therapy experience from Frankfurt HIV Cohort may give insights into the CNS activity of this drug class.
- **OBJECTIVE** was to evaluate risk factors for HIV-1 replication in CNS by cohort comparison of patients on only boosted PIs, versus nucleoside reverse transcriptase inhibitor (NRTI)-containing triple therapy.

METHODS:

Clinical setting:

- Frankfurt HIV Cohort collects patient data since 1987 and is approved by ethics committee; patients give written informed consent.
- Simultaneous determination of HIV-1 RNA in both plasma and CSF is routine differential diagnostics in Frankfurt HIV Cohort-patients, if CSF-collection is needed for any clinical reason and indication.
  - All tests are sent to the local Medical Virology Department.

Study-Design:

- Cross-section study of an ongoing HIV Treatment Cohort. The study was performed as controlled sub-analysis on patients with all simultaneously collected CSF/plasma HIV-1 RNA results. For comparability reasons of clinical data, the query was limited to a time frame for the years 2005-2013, after dual PI-therapy was well established local clinical care practice.
- The local reference laboratory's database query identified all patients who had undergone paired HIV-1 RNA assessments, allowing a maximal time variation of 3 days between CSF- and plasma test 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.

Patients were excluded from this analysis,
- if they were on ART-combinations other than (1) only PIs (cases), or (2) classical triple therapy (controls), consisting of 2N(t)RTI plus a recommended 3rd substance (boosted PI, NNRTI, or INI),
- or in case of missing and insufficient data.

Statistical analysis:

Virus-load (VL)-ratio for CSF/blood-quotient was built for each patient's dataset. Patient characteristics were evaluated according to used ART-combination. Univariate group statistics and Pearson's regression analysis for time-dependent results for PI-patients were generated.

RESULTS:

601 HIV-1 positive patients were identified, who had undergone CSF assessment for quantitative HIV-1 RNA.

After exclusion of ineligible individuals, i.e. due to
- missing timely related plasma test result (-247),
- antiretroviral combinations other than anticipated per protocol (-69)
- and insufficient patient characteristics or clinical data (-130),
- **there were remaining 155 patients for per protocol evaluation**.

Among those, 24 had been patients on only boosted dual PI), and 131 controls with 2NRTI plus PI/NNRTI/INI (=cART).

Table: Subject Characteristics at time of Lumbal puncture (LP)
(significant differences [$p<0.05$] in **bold**)

Demographics / n=	**All = 155**	**Dual PI = 24**	**cART = 131**
Median age [years] (range; SD)	47 (20-75;10.6)	48 (20-65;10.2)	47 (23-75;10.7)
Sex: male/female [n] (%males)	120 / 35 (77.4)	17 / 7 (70.8)	103 / 28 (78.6)
[Y] from 1st HIV+test to LP (r;SD)	**10.2 (0.04-27;11)**	**15.7 (4-27; 7)**	**9.2(0.04-26;7)**
Mean ART-regimens [n] (r;SD)	**4.75 (1-27; 4.6)**	**7.39 (1-27; 5.9)**	**4.24 (1-17; 4.2)**
Median CD4 count [cells/mm3] (r)	172 (1-741)	186 (9-741)	162 (1-678)
Median CD4-nadir [cells/mm³] (r)	59 (1-581)	50 (1-233)	59 (1-581)
HIV Disease stage: CDC-A [n]	26	2	24
CDC-B [n]	28	2	26
CDC-C [n]	97	20	77
Primary HIV-transmission risk			
men having sex with men: [n] (%)	50 (32.2)	9 (37.5)	7 (31.3)
intravenous drug user: [n] (%)	18 (11.5)	5 (20.8)	13 (9.8)
origin of a high risk country [n] (%)	10 (6.4)	1 (4.2)	9 (6.8)
other/unknown: [n] (%)	77 (49.4)	9 (37.5)	68 (51.6)
Used Antiretrovirals: Lopinavir	51	20	31
Saquinavir / Darunavir	35 / 19	21 / 0	14 / 19
Atazanavir / Fosamprenavir / IDV	29 / 14 / 2	4 / 2 / 1	25 / 12 / 1
3TC / FTC	*(only cART-group)*	n.a.	45 / 76
TDF / AZT / ABC		n.a.	94 / 32 / 21
EFV / NVP / RGV / MVC		n.a.	10 / 7 / 12 / 3
***HIV-1 RNA <50 cp/ml:* [n] *in* CSF** / in EDTA-blood	**71 (46%)** / 65 (42%)	**6 (25%)** / 11 (46%)	**65 (50%)** / 54 (41%)
***Median HIV-1 Loads:* in CSF** / in EDTA-blood [cp/ml] (range)	**90 (1-1.00E+7)** / 164 (1-1.00E+8)	**600 (1-58500)** / 115 (1-1.49E+5)	**50 (1-1.00E+7)** / 173 (1-1.00E+8)

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

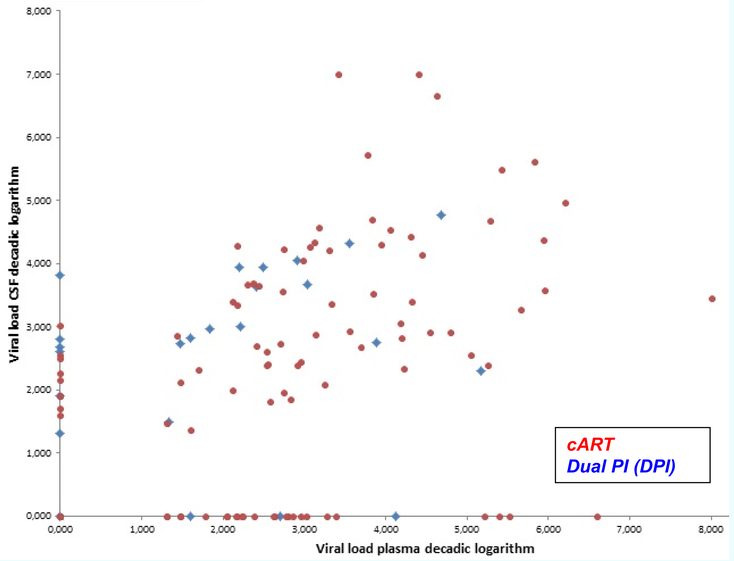
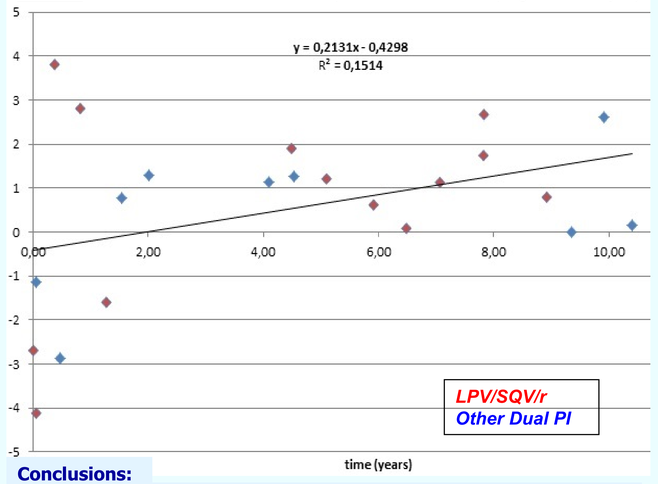
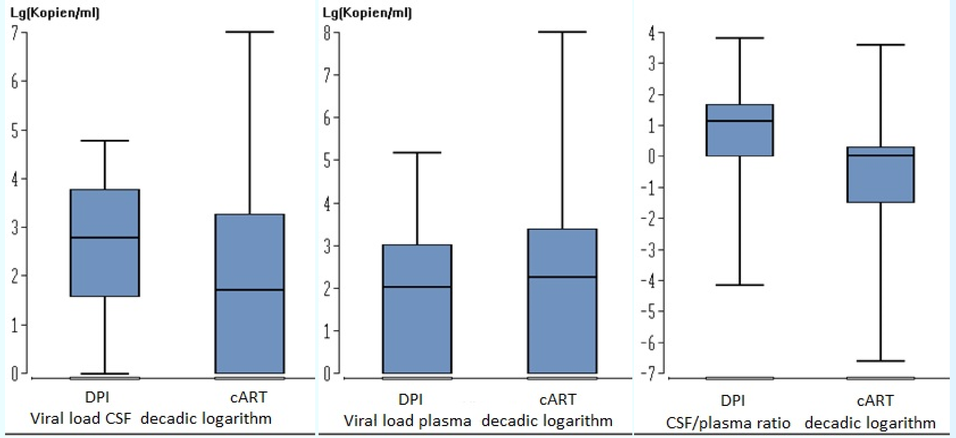


Diagram: Quantitative HIV-1 RNA-CSF/EDTA-plasma-Ratio over time (Regression analysis)



Boxplot Diagrams: Group comparisons/ Dual PI-group (DPI) vs cART: Viral Loads in CSF, EDTA-plasma and for CSF/EDTA-plasma-Ratio



Conclusions:

- In this unselected cohort, HIV-1 replication in CSF was higher for patients on only PI, than for those on NRTI-containing triple therapy. This finding suggests a worse CNS-penetration effectiveness for used PIs.
- The observed increase in CNS-viral replication over years suggests this to be a time-dependent effect.
- The main limitation of this study is its' non-interventional character, resulting in heterogenous patient group characteristics, e.g. concerning individuals with and without neurological symptoms. However any bias may be pronounced in particular for the initial time on therapy and should decrease over time.
- This large, real-life HIV-treatment cohort, confirms observations from CHARTER-study in regard to the need of a high CPE-score levels, as provided by N(t)RTIs, to treat more successfully HIV-1 in the CNS.
- The results suggest that only PI-containing ART showed increasingly worse antiretroviral activity beyond the blood-brain-barrier, compared to conventional triple ART. Moreover for the first time it was demonstrated that CSF-activity of HIV-1 increased over time on only PIs.