Effects of Switching to a Darunavir Based Regimen on Low Level Viremia, Immune Activation and Neurocognitive Performance

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Introduction

- A minority of people living with HIV demonstrate persistent low level viremia (LLV) despite good adherence to cART.
- It remains unknown whether LLV is the consequence of viral production by activated HIV-infected cells or ongoing viral replication as well.
- As a result of this uncertainty, and to reduce the risk of treatment failure, a switch to a high-genetic barrier therapy is often considered.
- It is hypothesized that suppressing LLV may also have additional benefits on immune activation and co-morbidities.

Methods

- A multicenter prospective observational study (LOWERIT) evaluating 30 patients with persistent LLV despite effective therapy and adherence counseling who switched to a darunavir (DRV) based therapy for 48 weeks.
- Definition of LLV: multiple viral loads (VL) between 50-1000cp/mL.
- VL was performed by standard diagnostics assays (Roche & Abbott). Virological response was categorized in responders (VL<50 cp/mL) and non-responders (VL>50 cp/mL) at WK24. RNA was isolated according to a LLV protocol using higher plasma inputs varying from 1 to 6 mL depending on the VL, followed by ultracentrifugation, a RT-PCR of *pol* and Sanger sequencing of reverse transcriptase and protease.
- Stanford 8.5 was used to compare RNA sequences. Evolution was examined by dN/dS ratio.
- Immune activation was evaluated at baseline and WK24 by cell-bound ($CD38^+$-HLA-DR) and soluble markers (IL-6, IL-1b, IP-10, MCP-1 MIP-1a, MIP-1b, sICAM-1, sCD14, sCD163, CXCL9).
- DRV drug levels were measured at WK4 and WK24.
- Neurocognitive performance was evaluated with the Trail Making Test, Digitspan, Verbal Learning Task, Grooved pegboard, Paced Auditory Serial Addition Test (PASAT), Color Word Interference Test and Random Number Generation test

Table 1. Baseline characteristics (N=30)

Age (median, range)	49 (IQR 41-57)
Sex (Male %)	86,7%
Viral load (mean, range)	161 (95% CI 66-254)
CD4 count (median, range)	661 (95% CI 521- 802)
cART backbone	TDF/TAF +FTC: 22 ABC + 3TC: 6 TDF + AZT: 1 3TC+TDF: 1
Switched drug	EFV:8; DTG:8; NVP:4; EVG:3; RIL:2; ATV:2; LPV:2; RAL:1
Education level (median)	5 (range 1-7)
Substance use	Nicotine: 13 (43,3%) Alcohol >2 per day: 2 (6,7%) Cannabis: 7 (23,3%)
Co-morbidities	DM: 0% CVD: 10% COPD:10%
Self-reported adherence	99,5% (95% CI 98,9-100)

Results

HIV-RNA and virological response

- Overall no significant decrease in VL was seen between different time points (figure 1).
- 16 patients (53%) were responders and 13 (43%) were non-responders and 1 was unassigned (table 2).
- Patient L-13 stopped therapy on own initiative (table2).

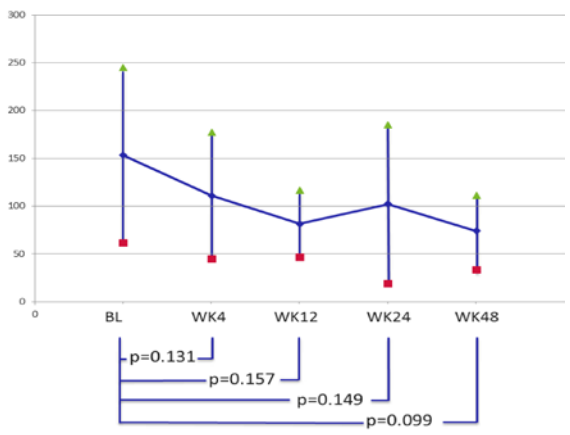

Figure 1. Mean viral load dynamics with 95% confidence interval at each time point. BL=161 cp/mL; WK4=112 cp/mL; WK12=81 cp/mL; WK24=102 cp/mL; WK48=74 cp/mL

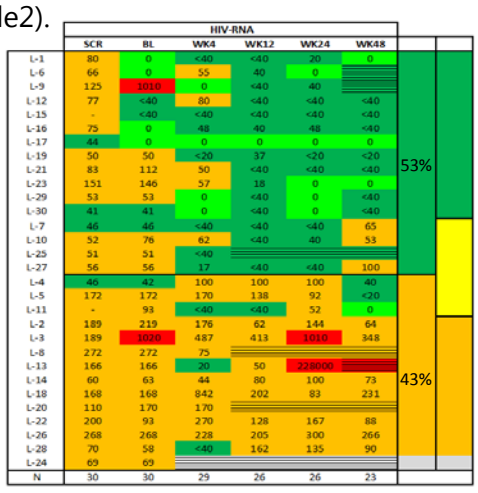

Table 2.. Viral load dynamics. Bright green: target not detected; dark green: VL<50; orange: VL=50-1000cp/mL; red: VL>1000 cp/mL). Primary endpoint for virological response at WK24.

HIV-RNA genotyping and evolution

- Genotyping at multiple time points was successful in 11 patients with LLV.
- Based upon the characterization of protease and RT there were no signs of HIV evolution or selection of drug resistance.
- In two patients the viral population consisted fully or partly of defective viruses.
- In patient 2 multiple stopcodons (W88*, W212*, W266*) were found in *reverse transcriptase* at baseline implying production as the source of low level viremia (Table 3).
- In patient 22 the protease active-site mutation D25N was found in a majority (±70%) of the viral population (table 4). The presence of this mutation still allows dimer formation of protease, but the enzyme is unable to cleave viral proteins.

Table 3. Reverse transcriptase mutations

L-2	M16I	M41I	G45K	G51R	S68G	W88*	G99R	K122E	S162C	Q174H	G190R	T200A	I202V	W212*	G231R	K238R	V245E	W266*	G273R	K277R	R307K	H315Y

Table 4. Protease mutations

L-22	L10I	D25DN	E35EK	N37S	R41K	L63C	V77IV	I93L	L97IL

Immunology

- Higher levels of MIP-1b, IL-1b and activated (CD38+ HLA-DR+) CD4 T-cell memory cells were seen at week 24.
- Higher levels of sICAM were seen in non-responders as compared to responders at WK24.
- No correlation was observed between viral load and any of the immune markers.

Neurocognitive performance

- 30% (n=9) of all subjects showed some signs of neuropsychological impairment in one of the cognitive domains memory, psychomotor function or executive functioning.
- No association between cognitive performance and viral load or immune activation could be identified.

Pharmacology

- Mean self-reported adherence was >98% at all time points.
- DRV levels were undetectable in L-13.
- DRV levels were low in L-5 (WK4); L-27 (WK24); L-29 (WK24).

Conclusion

- Half of the patients responded to a therapy switch.
- DRV is a suitable high-genetic barrier drug in patients with LLV due to viral replication.
- In non-responders the most likely source of LLV is viral production, which was demonstrated in two patients who had defective HIV.

LOWERIT Study Team

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