

# Immunological and clinical consequences of sustained low-level viremia in patients receiving HAART

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# Objectives

- To determine the incidence of SLLV amongst patients on HAART who initially achieve an undetectable viral load ( $VL \leq 500$  cps/ml)
- To describe the virological, immunological and clinical outcomes in patients with SLLV
- To identify epidemiological correlates of high-level virological failure ( $VL > 20,000$  cps/ml) or return to undetectable VL ( $\leq 500$  cps/ml) amongst patients with SLLV

# Patients and Methods

- Eligible individuals had a VL  $\leq 500$  cps/ml on 2 occasions at least 3 months apart on HAART
- SLLV was defined as a VL of 501-20,000 cps/ml over  $\geq 6$  months (3+ measurements) in patients with initial undetectable VL
- SLLV ended when a patient's VL moved outside this range or when the patient stopped HAART; only first episodes of SLLV were considered for this analysis
- For this analysis, follow-up of those who did not experience high-level virological failure was censored at:
  - a) First VL  $\leq 500$  cps/ml (if VL became undetectable)
  - b) VL at stopping HAART (if patient came off HAART)
  - c) 12 months after last VL (if patient lost to follow-up)
  - d) Last VL (if patient had continuing SLLV)

# Table 1: CD4 and virological changes during SLLV

|  | Continuing<br>SLLV<br>N=48 | VL<br>>20,000<br>N=85 | VL<br>≤500<br>N=143  | Stopped<br>HAART<br>N=23 | P-<br>Value* |
|--|----------------------------|-----------------------|----------------------|--------------------------|--------------|
| <b>Duration of SLLV (mths)</b>                       | 14.7 (9.2,30.1)            | 13.5 (10.3,20.5)      | 10.3 (7.7,13.8)      | 12.5 (9.4,18.1)          | <0.001       |
| <b>Treatment change during SLLV</b>                  | 13 (27.1%)                 | 44 (51.8%)            | 103 (72.0%)          | 19 (82.6%)               | <0.001       |
| <b>Median (IQR) CD4 count (cells/mm<sup>3</sup>)</b> |                            |                       |                      |                          |              |
| <b>At start of SLLV</b>                              | 355 (219,490)              | 298 (220,533)         | 315 (210,440)        | 426 (190,510)            |              |
| <b>At end of SLLV</b>                                | 311 (218,450)              | 336 (221,490)         | 335 (232,453)        | 354 (270,478)            |              |
| <b>Change per 6 mths</b>                             | 6.6 (-16.2,19.7)           | -27.7 (-66.4,11.1)    | 19.6 (-4.4,43.6)     | -8.4 (-83.6,66.8)        | <0.001       |
| <b>Median (IQR) VL (cps/ml)</b>                      |                            |                       |                      |                          |              |
| <b>At start of SLLV</b>                              | 3.24 (2.98,3.53)           | 3.20 (2.95,3.55)      | 3.08 (2.85, 3.38)    | 3.30 (2.90, 3.70)        |              |
| <b>At end of SLLV</b>                                | 3.48 (3.18,3.74)           | 3.77 (3.29,-4.01)     | 3.29 (3.00, 3.63)    | 3.57 (2.81, 3.69)        |              |
| <b>Log change per 6 mths</b>                         | 0.07 (0.20,0.11)           | 0.37 (0.31,0.43)      | -0.15 (-0.19, -0.10) | 0.08 (-0.02, 0.19)       | <0.001       |

Viral load at end of SLLV refers to the last viral load prior to moving out of the range 501-20000 copies/ml.

\*P-Values comparing the 4 groups are obtained using Chi-squared and Mann Whitney Tests.

\*\*Treatment change made prior to stopping HAART

**Table 2: Results from a Cox regression analysis of factors associated with return to undetectable  $\leq 500$  cps/ml) as an outcome of SLLV**

| <b>Variables</b>                                      |              | <b>Hazard Ratio</b> | <b>95% CI</b> | <b>P-Value</b> |
|---|--------------|---------------------|---------------|----------------|
| <b>Male sex</b>                                       |              | 3.53                | 1.19-10.45    | 0.02           |
| <b>Age at start of SLLV (per 5 years)</b>             |              | 1.15                | 1.03-1.29     | 0.02           |
| <b>Ethnicity (compared to white)</b>                  | <b>Black</b> | 0.43                | 0.23-0.81     | 0.008          |
|   | <b>Other</b> | 0.74                | 0.47-1.16     | 0.19           |
| <b>Homosexual exposure</b>                            |              | 0.49                | 0.30-0.81     | 0.005          |
| <b>Onset of SLLV after 2000</b>                       |              | 2.02                | 1.36-3.00     | 0.0005         |
| <b>Treatment change</b>                               |              | 6.94                | 4.77-10.11    | 0.0001         |
| <b>Total no. of PIs (per 1 drug increase)</b>         |              | 1.22                | 1.01-1.45     | 0.03           |
| <b>Time from HAART initiation to SLLV (Per month)</b> |              | 0.97                | 0.95-0.99     | 0.005          |
| <b>Time from UD to SLLV (Per month)</b>               |              | 1.05                | 1.02-1.08     | 0.0003         |
| <b>VL at start of SLLV (Per log copies/ml)</b>        |              | 0.42                | 0.26-0.67     | 0.0004         |

# Summary

- SLLV is a rare phenomenon; using our strict definition, only 4.9% of patients who achieved viral suppression experienced an episode of SLLV
- CD4 changes over SLLV were minimal in most cases and were not significant
- The strongest predictors of regaining an undetectable VL after SLLV were treatment change during SLLV (OR=6.9), male sex (OR=3.5) and onset of SLLV after 2000 (OR= 2.0)
- There were no significant adverse clinical or immunological consequences of SLLV in the medium term. However, patients with ongoing SLLV had smaller CD4 cell gains than those who returned to VL<sub>≤</sub>500 copies/ml