

**9<sup>th</sup> CROI, Seattle WA, 2002. Abstract # 529M**

**Structured Treatment Interruptions (STI) in Patients Receiving HAART since Primary HIV-1 Infection (PHI): Spontaneous Control of Viremia in about One-third of Cases after the First Three Cycles Off Therapy**

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# **BACKGROUND**

- **Treatment of primary HIV-1 infection (PHI) before seroconversion with HAART can generate a strong HIV-specific T-helper cell response.**
- **Rosenberg ES et al (Nature, 2000) reported in a cohort of 8 patients treated from the onset of PHI and before seroconversion with HAART for at least one year, that one or two HAART interruptions increased HIV-1 specific T-cell responses (CD4+ and CTL) and that most of them could maintain plasma HIV viremia at a very low level (<500 copies/mL) without HAART for a median period of almost 7 months.**

# **OBJECTIVE**

**To determine whether four cycles of structured treatment interruptions (STI) can restore HIV-1 specific T-cell responses (CD4+ and CTL) and control HIV-1 replication without antiretroviral therapy in patients who started HAART within 90 days from onset of symptoms of PHI.**

# **PATIENTS & METHODS**

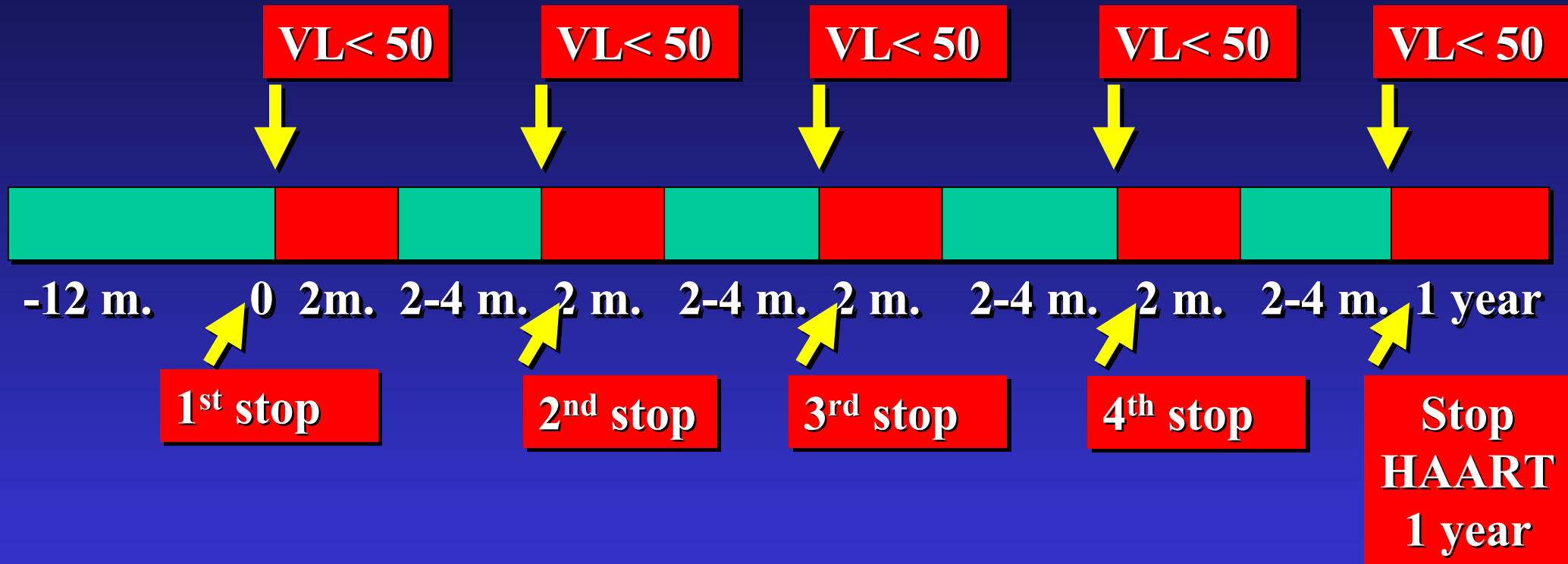
- **We planned to include in an STI program 14 consecutive patients with sustained viral suppression (<20 copies/mL), a CD4+ cell count >500 cells/mm<sup>3</sup> and a CD4+/CD8+ ratio >1 and treatment with d4T, 3TC and indinavir at standard doses for at least one year since onset of PHI.**
- **Plasma viral load (PVL), genotypic resistance, lymphocyte immunophenotyping, CD4+ lymphocyte proliferative responses (LPR) to HIV-1 proteins as well as HIV-1 specific CTL responses (ELISPOT) were assessed weekly after each discontinuation and monthly after reintroduction of the same antiretroviral treatment. A tonsillar biopsy was performed before STI.**

# Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)

## STUDY DESIGN

On HAART: d4T+3TC+ indinavir

Off HAART: 2 months



# **END POINTS**

## **AFTER THE 4 CYCLES OFF THERAPY**

- **Patients who have a CD4+ count  $>500$  cells/mm<sup>3</sup> & PVL  $<5,000$  copies/ml will remain off HAART. Therapy will be restarted in patients who will not meet these criteria.**

## **AFTER THE FIRST 3 CYCLES OFF THERAPY**

- **RESPONDERS: Patients with no PVL rebound after the 3<sup>rd</sup> stop or with PVL rebound  $<5,000$  copies/mL.**
- **PARTIAL RESPONDERS: Patients with a peak reduction of 3<sup>rd</sup> PVL rebound  $>0.5$  log<sub>10</sub>/mL in comparison with 1<sup>st</sup> PVL rebound.**
- **NON-RESPONDERS: Patients who did not meet the previous criteria.**

# **RESULTS**

- **In this poster we show the results of the first consecutive 12 patients who completed the first three cycles off therapy.**
- **10 patients were male and two were female. Mean (range) age was 35 years (22-54 years). HIV risk factors were: homosexuality in 8 cases, heterosexuality in 3 cases and i.v. drug abuse in one case.**
- **No genotypic resistance to antiretrovirals was found at PHI (before starting HAART). All patients had a WT CCR5 genotype.**

## Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)

# CHARACTERISTICS OF PHI EPISODES

| <b>Subject</b> | <b>Age (y)</b> | <b>Gender</b> | <b>HIV risk factor</b> | <b>Duration of symptoms (d)</b> |
|----------------|----------------|---------------|------------------------|---------------------------------|
| 2M-SMBL        | 35             | M             | HMX                    | 14                              |
| 17M-APR        | 28             | M             | HMX                    | 21                              |
| 20M-BCV        | 29             | M             | HTX                    | 7                               |
| 23M-JBS        | 30             | M             | HMX                    | 14                              |
| 11M-PSM        | 38             | M             | HMX                    | 7                               |
| 14M-JMG        | 54             | M             | HMX                    | 28                              |
| 15M-ARE        | 47             | M             | HMX                    | 14                              |
| 21M-LBG        | 47             | M             | HTX                    | SC                              |
| 8M-VAM         | 24             | F             | HTX                    | 28                              |
| 12M-VMC        | 27             | M             | HMX                    | 7                               |
| 19M-MACS       | 36             | M             | HMX                    | 28                              |
| 22M-NCC        | 22             | F             | IVDA                   | SC                              |

M=male; F=female; HMX: homosexuality; HTX: heterosexuality; IVDA: i.v. Drug abuser; SC: seroconversion.

**Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)**  
**IMMUNOLOGICAL & VIROLOGICAL DATA**  
**WHEN PATIENTS STARTED HAART**

| <b>Subject</b> | <b>Weeks from presentation to initiation HAART</b> | <b>CD4/CD8</b> | <b>CD4/CD8 ratio</b> | <b>PVL</b>     |
|----------------|--|----------------|----------------------|----------------|
| 2M-SMBL        | 12   | 255/377        | 0.65                 | 80,000         |
| 17M-APR        | 11   | 360/691        | 0.52                 | 127,000        |
| 20M-BCV        | 11   | 547/996        | 0.55                 | 7,219          |
| 23M-JBS        | 4  | 617/733        | 0.84                 | 142,000        |
| 11M-PSM        | 12   | 1434/1026      | 1.63                 | 21,352         |
| 14M-JMG        | 4  | 608/2163       | 0.28                 | 885,700        |
| 15M-ARE        | 10   | 526/639        | 0.82                 | 49,153         |
| 21M-LBG        | 12   | 422/1280       | 0.33                 | 3.215          |
| 8M-VAM         | 12   | 608/560        | 1.10                 | 164,000        |
| 12M-VMC        | 3  | 78/179         | 0.43                 | 162,000        |
| 19M-MACS       | 4  | 190/1490       | 0.13                 | 250,000        |
| 22M-NCC        | 12   | 492/600        | 0.82                 | 1,544,000      |
| <b>Mean</b>    | <b>9</b>   | <b>511/894</b> | <b>0.67</b>          | <b>286,306</b> |

# Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)

## IMMUNOLOGICAL & VIROLOGICAL DATA

### BEFORE STOPPING HAART (I)

| <b>Subject</b> | <b>Months on HAART<br/>before STI</b> | <b>CD4/CD8</b>   | <b>CD4/CD8<br/>ratio</b> | <b>PVL*</b>  |
|----------------|---------------------------------------|------------------|--------------------------|--------------|
| 2M-SMBL        | 29                                    | 556/313          | 1.78                     | <5           |
| 17M-APR        | 17                                    | 566/367          | 1.61                     | <5           |
| 20M-BCV        | 13                                    | 1,097/994        | 1.10                     | <5           |
| 23M-JBS        | 13                                    | 1,041/794        | 1.31                     | <5           |
| 11M-PSM        | 31                                    | 1,242/787        | 1.58                     | <5           |
| 14M-JMG        | 29                                    | 1,415/849        | 1.67                     | 12           |
| 15M-ARE        | 12                                    | 886/654          | 1.35                     | <5           |
| 21M-LBG        | 45                                    | 1,012/1,011      | 1.00                     | <5           |
| 8M-VAM         | 21                                    | 1637/898         | 1.82                     | <5           |
| 12M-VMC        | 24                                    | 726/725          | 1.00                     | <5           |
| 19M-MACS       | 19                                    | 1,647/878        | 1.86                     | <5           |
| 22M-NCC        | 40                                    | 810/612          | 1.32                     | <5           |
| <b>Mean</b>    | <b>24</b>                             | <b>1,053/740</b> | <b>1.45</b>              | <b>&lt;5</b> |

\* Plasma/Lymph tissue RNA HIV-1 viral load.

# Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)

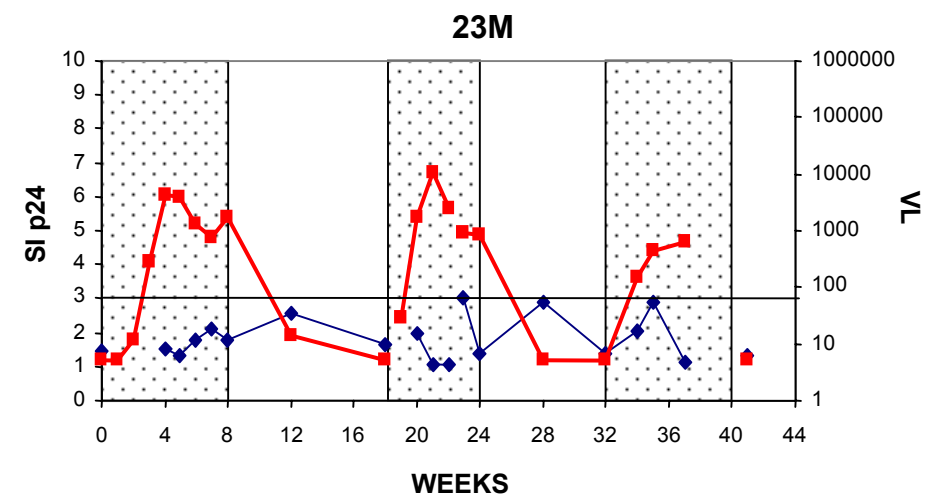
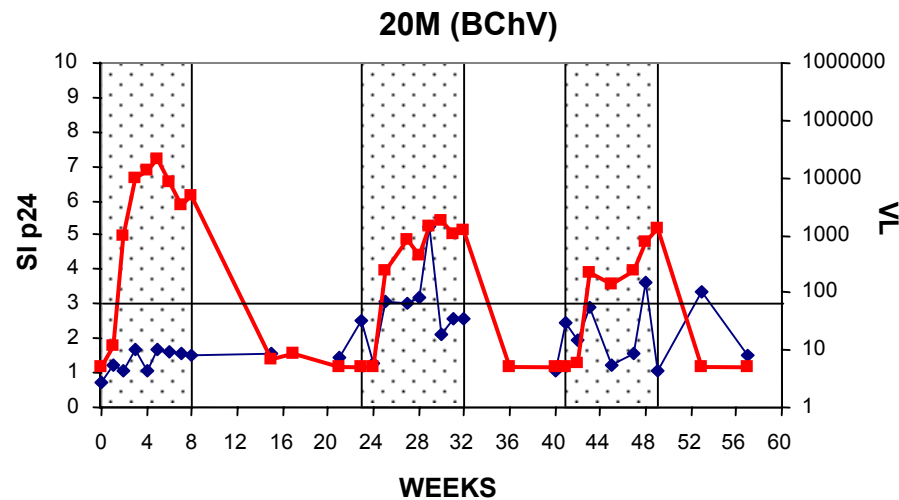
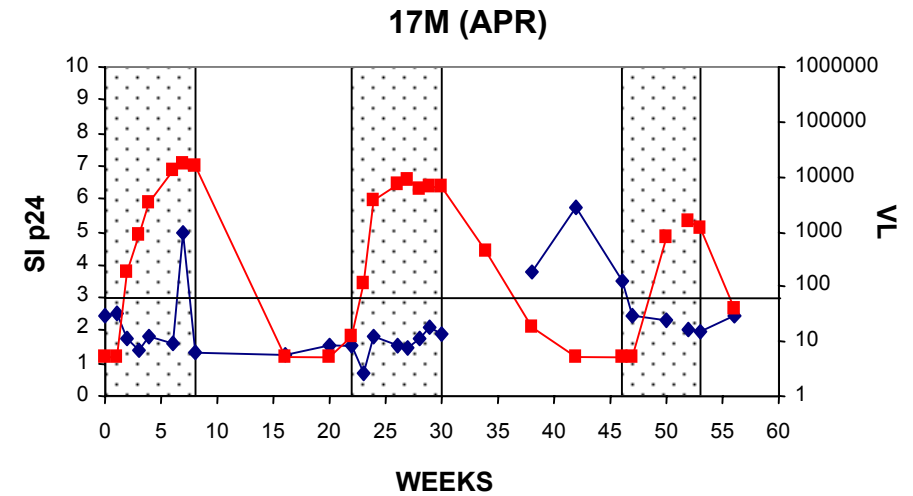
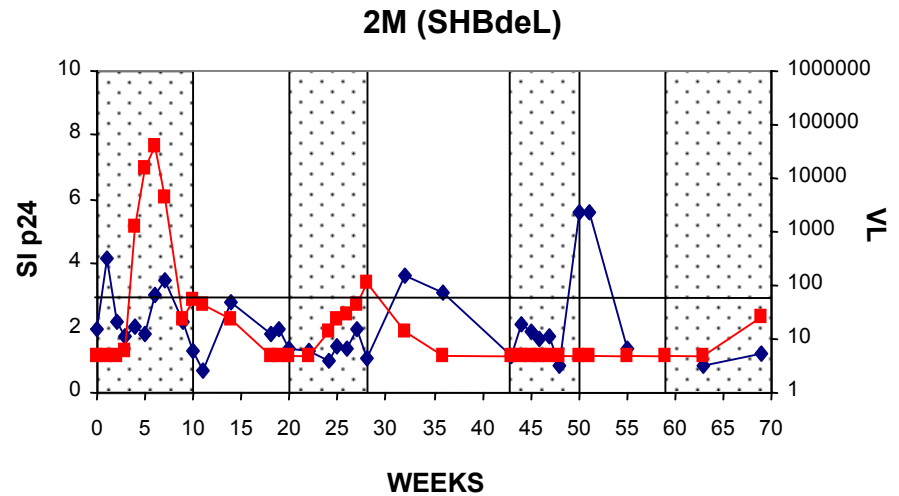
## IMMUNOLOGICAL & VIROLOGICAL DATA BEFORE STOPPING HAART (II)

| <b>Subject</b> | <b>TREC CD4+/CD8+<br/>x 10<sup>6</sup> T cells</b> | <b>CCR5<br/>genotype</b> | <b>Lymph<br/>Tissue VL</b> |
|----------------|--|--------------------------|----------------------------|
| 2M-SMBL        | 265/1260   | WT                       | <40                        |
| 17M-APR        | ND/ND  | WT                       | <40                        |
| 20M-BCV        | ND/ND  | WT                       | <40                        |
| 23M-JBS        | 306/ND   | WT                       | 104                        |
| 11M-PSM        | 978/624  | WT                       | <40                        |
| 14M-JMG        | 507/398  | WT                       | <40                        |
| 15M-ARE        | 2,880/1,030  | WT                       | <40                        |
| 21M-LBG        | 249/6  | WT                       | <40                        |
| 8M-VAM         | 1,120/1,190  | WT                       | <40                        |
| 12M-VMC        | 2,810/1,280  | WT                       | <40                        |
| 19M-MACS       | ND/ND  | WT                       | <40                        |
| 22M-NCC        | 1,640/1,470  | WT                       | <40                        |

**ND: Not done; WT: wild type.**

# HIV-1-SPECIFIC CD4 T CELL RESPONSE

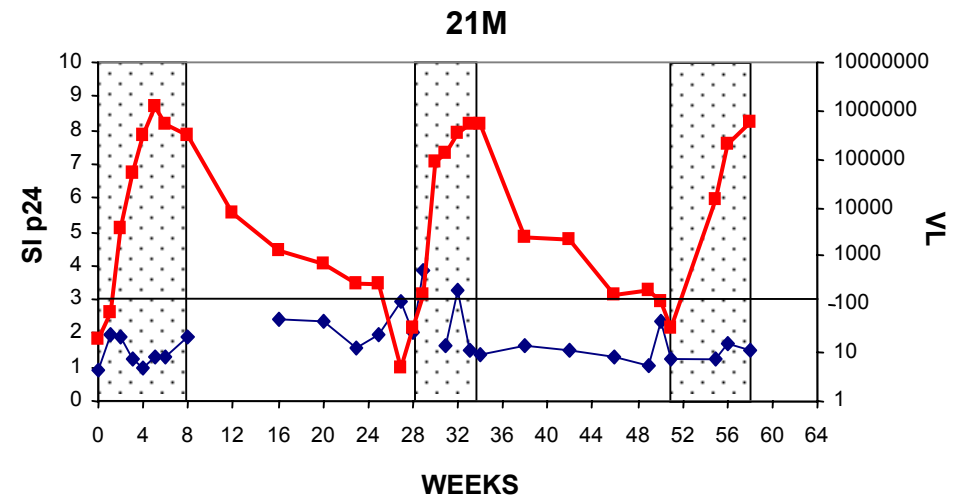
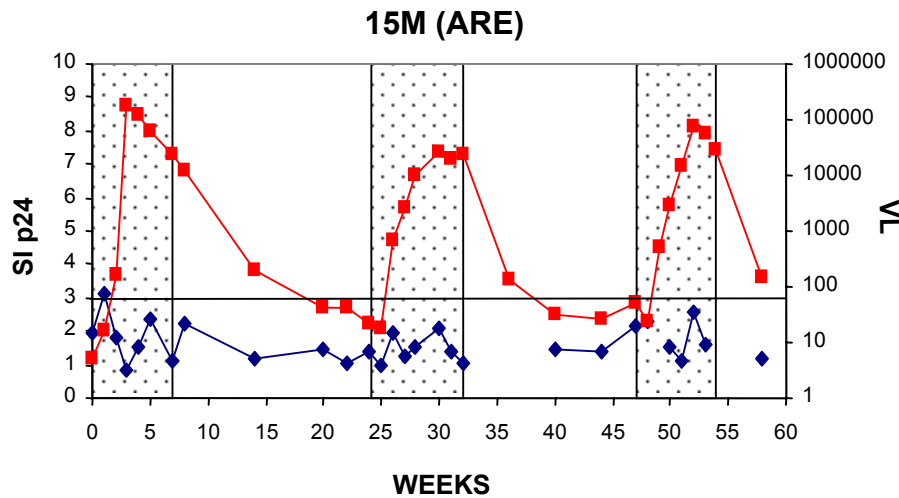
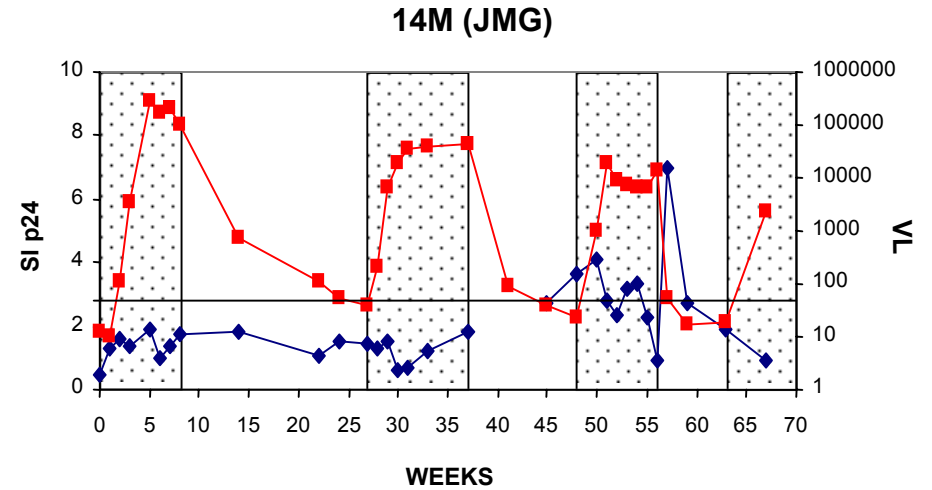
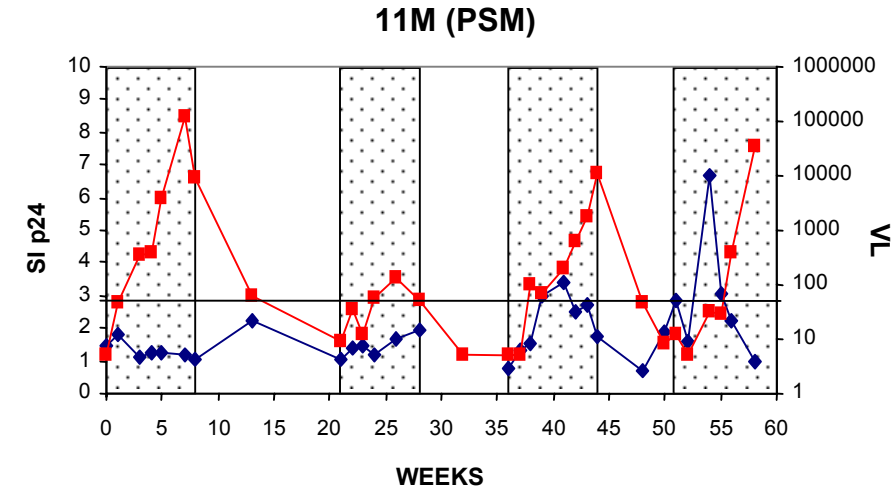
## R = RESPONDERS (4/12, 33%)



■ VL     
 ◆ SI p24     
  OFF TREATMENT     
  ON TREATMENT

# HIV-1-SPECIFIC CD4 T CELL RESPONSE

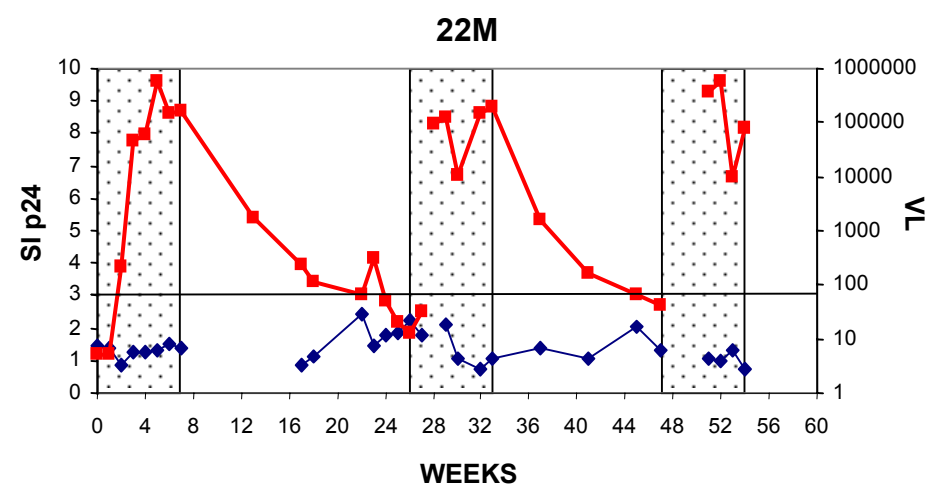
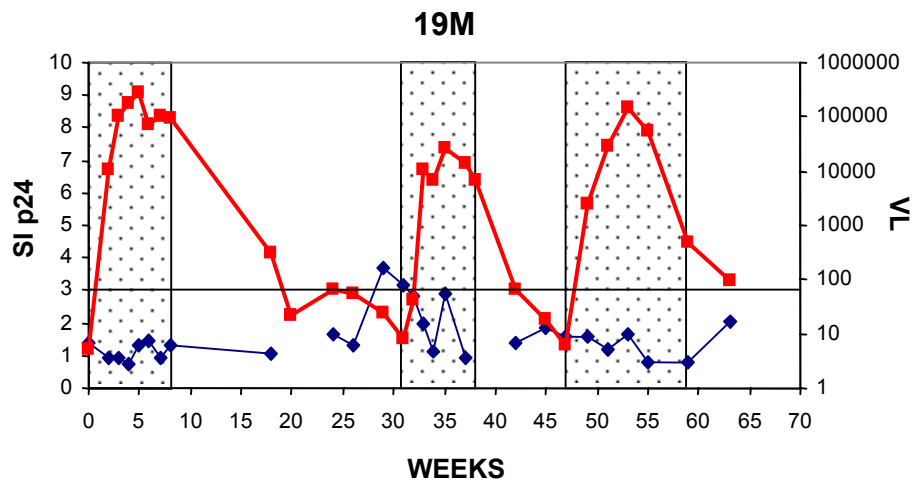
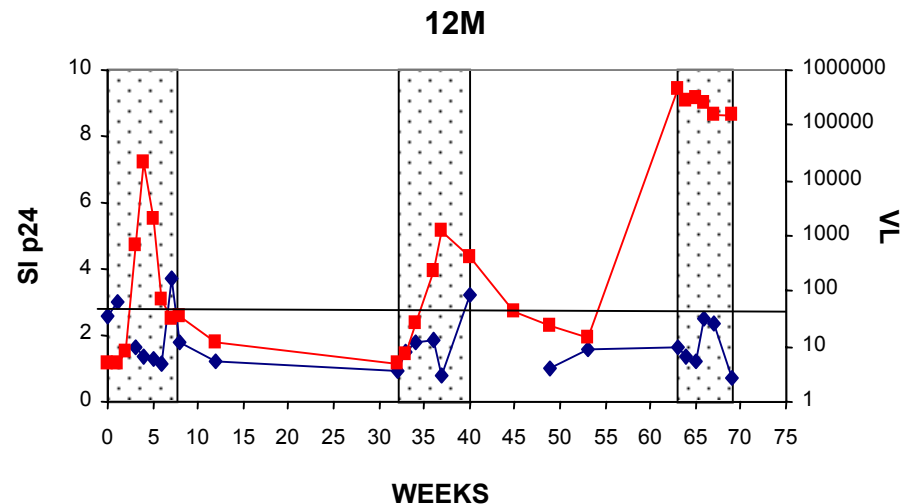
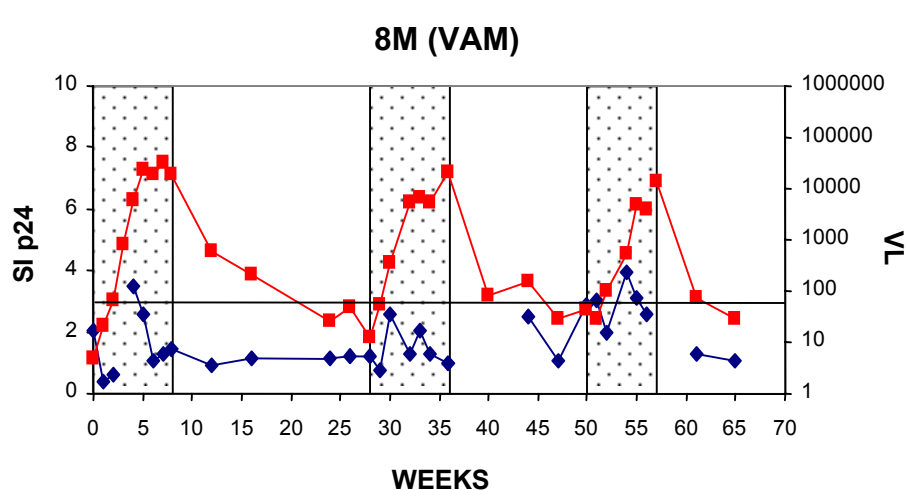
## PR = PARTIAL RESPONDERS (4/12, 33%)



—■— VL     
 —◆— SI p24     
  OFF TREATMENT     
  ON TREATMENT

# HIV-1-SPECIFIC CD4 T CELL RESPONSE

## NR = NON RESPONDERS (4/12, 33%)



—■— VL     
 —◆— SI p24     
  OFF TREATMENT     
  ON TREATMENT

**Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)**

# **VIROLOGIC AND IMMUNOLOGICAL CHANGES DURING EACH PERIOD OFF HAART**

|                        | <b>1<sup>st</sup> stop</b> | <b>2<sup>nd</sup> stop</b> | <b>3<sup>rd</sup> stop</b> |
|------------------------|----------------------------|----------------------------|----------------------------|
| <b>Plasma VL</b>       |                            |                            |                            |
| Peak                   | 4.89 (0.73)                | 3.89 (1.06)                | 4.04 (1.57)                |
| <b>CD4 cell counts</b> |                            |                            |                            |
| Absolute counts        | <b>-206 cells</b>          | <b>-93 cells</b>           | <b>-105 cells</b>          |
| Percentage             | <b>11%</b>                 | <b>4%</b>                  | <b>5%</b>                  |

# HIV-1-SPECIFIC CD4+ T CELL RESPONSE

|                           | Day 0       | 1 <sup>st</sup> Stop | 2 <sup>nd</sup> Stop | 3 <sup>rd</sup> Stop |
|---------------------------|-------------|----------------------|----------------------|----------------------|
| <b>Responders</b>         |             |                      |                      |                      |
| 2M                        | -           | +                    | +                    | +                    |
| 17M                       | -           | +                    | -                    | +                    |
| 20M                       | -           | -                    | +                    | +                    |
| 23M                       | -           | -                    | +                    | -                    |
| <b>Partial Responders</b> |             |                      |                      |                      |
| 11M                       | -           | -                    | -                    | +                    |
| 14M                       | -           | -                    | -                    | +                    |
| 15M                       | -           | +                    | -                    | -                    |
| 21M                       | -           | -                    | +                    | +                    |
| <b>Non Responders</b>     |             |                      |                      |                      |
| 8M                        | -           | +                    | -                    | +                    |
| 12M                       | -           | +                    | +                    | -                    |
| 19M                       | -           | -                    | +                    | -                    |
| 22M                       | -           | -                    | -                    | -                    |
| <b>Overall</b>            | <b>0/12</b> | <b>5/12</b>          | <b>6/12</b>          | <b>7/12</b>          |

(-): Negative proliferative response to HIV-1 p24 (SI<3) (+): Positive proliferative response to HIV-1 p24 (SI>3)

# HIV-1-SPECIFIC CD8+ T CELL RESPONSE

|                           | Day 0 | 1 <sup>st</sup> Stop | 2 <sup>nd</sup> Stop | 3 <sup>rd</sup> Stop |
|---------------------------|-------|----------------------|----------------------|----------------------|
| <b>Responders</b>         |       |                      |                      |                      |
| 2M                        | -     | -                    | -                    | +++                  |
| 17M                       | ++    | +++                  | +++                  | +++                  |
| 20M                       | +++   | +++                  | +++                  | +++                  |
| 23M                       | NT    | NT                   | NT                   | NT                   |
| <b>Partial Responders</b> |       |                      |                      |                      |
| 11M                       | -     | +++                  | +++                  | ++                   |
| 14M                       | +     | +++                  | +++                  | +++                  |
| 15M                       | +     | ++                   | ++                   | ++                   |
| 21M                       | ++    | +++                  | NT                   | NT                   |
| <b>Non Responders</b>     |       |                      |                      |                      |
| 8M                        | +     | ++                   | ++                   | +++                  |
| 12M                       | ++    | +++                  | +++                  | +++                  |
| 19M                       | -     | ++                   | +++                  | +++                  |
| 22M                       | -     | -                    | -                    | NT                   |

Results as Total SFC/10<sup>6</sup> PBMC:(-) <40; (+) 40-200; (++) 201-500; (+++) >500; NT: Non tested

# **RESULTS**

- **Known mutations associated with resistance to reverse transcriptase or protease inhibitors were not detected after each stop.**
- **A quick virological response was observed after reintroduction of the same antiretroviral treatment after each stop.**
- **There was no correlation between the level of TRECs and the type of virological response.**
- **Decreases in CD4+ T lymphocyte counts were observed after each stop. In none of the cases, did CD4 T lymphocyte counts drop below 500 cells/ $\mu$ L.**

# **CONCLUSIONS (I)**

- **Plasma viral load rebounded in all patients receiving HAART within 90 days after PHI during the first three cycles off therapy.**
- **Only four out of 12 patients (33%) had a rebound of viremia  $<5,000$  copies/mL after the third cycle of STI.**
- **A strong HIV-1 specific CD8+ (CTL) response was developed in seven out of nine patients tested after three cycles off therapy.**

## **CONCLUSIONS (II)**

- **HIV-1 specific CD4+ response was only transitorily restored at a low level after the first three cycles off therapy in seven out of 12 patients receiving HAART within 90 days since onset of PHI.**
- **No genotypic resistance to antiretrovirals was found after two cycles off therapy. None of the patients had a drop in CD4 T-cell count below 500 cells/ $\mu$ L.**

**Primary HIV-1 Infection (PHI) and Structured Treatment Interruptions (STI)**

# **ACKNOWLEDGEMENTS**

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