Intermittent Antiretroviral Therapy (ART) Can Induce Reduction of Viral Rebounding During ART-Interruption

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Intermittent Antiretrovral Therapy (ART) Can Induce Reduction of Viral Rebound During ART-Interruption.

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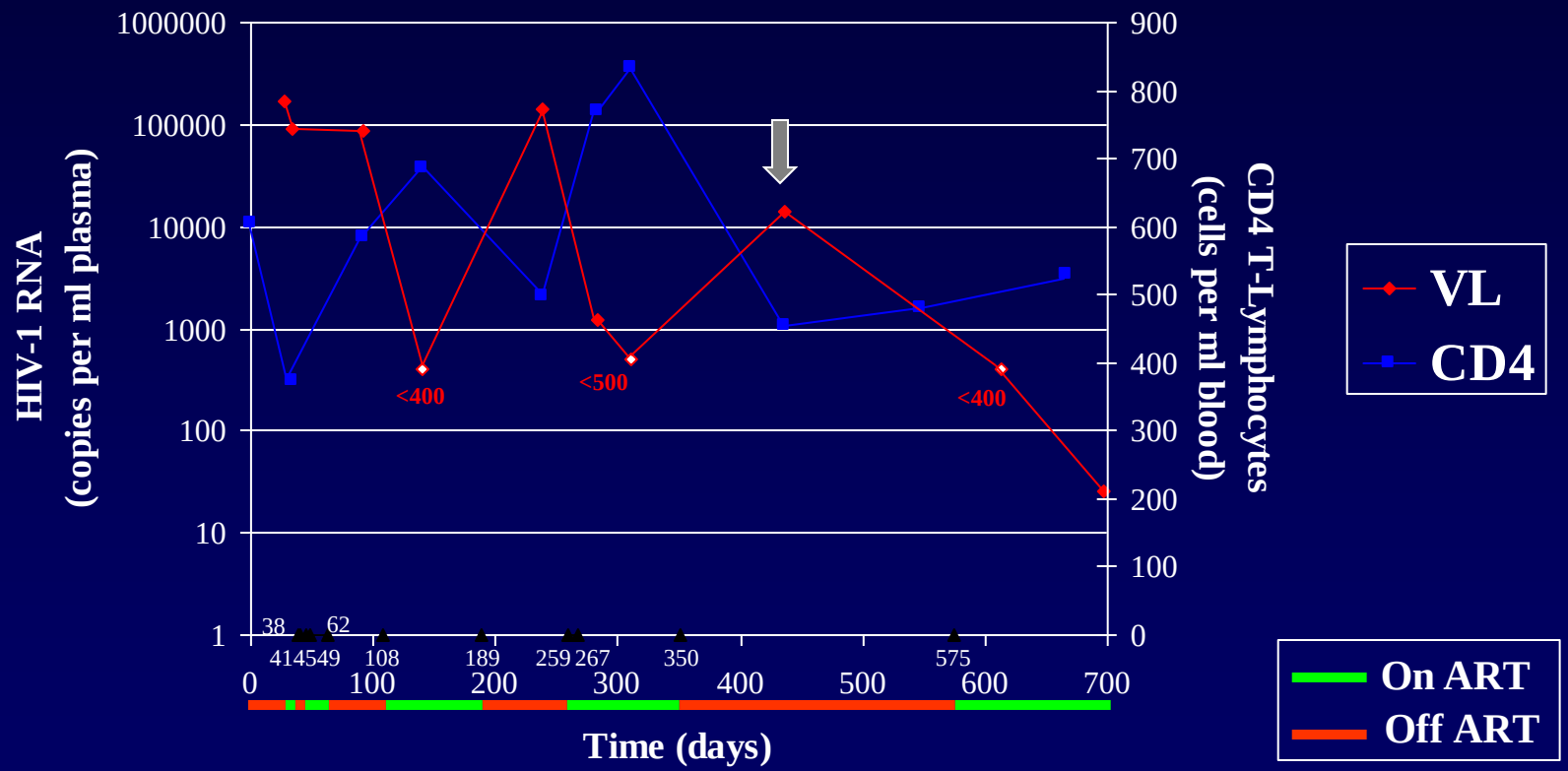
Response to ART Interruption
Patient 27 (JP) - 3 Interruptions



Background - Why?

- Why is this of interest when current therapy has dramatically altered the course of HIV?
  - Long term complications of ART
  - Can ART be taken indefinitely
- Strategies to deal with ART complications
  - simplification
  - switch
  - ART interruption (STI, i-ART)
    - “Structured” implies understanding?

Background - Initial Reports

- Interruption: Viral load returns to baseline after long term suppression.
  - Rapid return to baseline *(Jubault, AIDS 98 & Staszewski, AIDS 98)*
  - Intermittent ART lead to increased time to rebound (n=3) *(Lori, 6th CROI)*
  - COMET: Rapid return to baseline but no deleterious effect after re-initiation (n=10) *(Neumann, AIDS 99)*
  - Increase of ~0.2 $\log_{10}$ in total viral burden/day (n=6) *(Harrigan, AIDS 99)*

Background - Recent Studies

- Prospective study (n=8) all returned to baseline (doubling time = 2.01 days) and all re-suppressed. No viral drug resistance. *(Garcia, AIDS 99)*
- Some patients remain suppressed or, after initial rebound, decline toward level of quantification.
  - "Berlin patient" *(Lisziewicz NEJM 99)*
  - Long term suppression in PHI (n=4) doubling time ~ 1.6 days. 3/4 peaked at 4.32 $\log_{10}$ and declined to 3.53 $\log_{10}$ *(Markowitz, ICAAC 99, LB16)*
  - NoHRT study 12/18 received IL-2. 1/18 has VL 50 - 500. *(Davey, ICAAC 99, I-689)*

Background - Immunology

- Protective cellular immunity returns after ART
  - Discontinuation of PCP Prevention *(Lopez, ICAAC 99 LB24)*
- HIV antibody response
- CD8 cytotoxic response (CTL)
- HIV-specific CD4 response strong in long term non-progressors
  - may be present in many patients but significantly decreases after PHI. Wanes with ART *(Pitcher, Nat Med 99)*
  - Is there sufficient antigen present in patients with viral load BLQ and restored immune system?

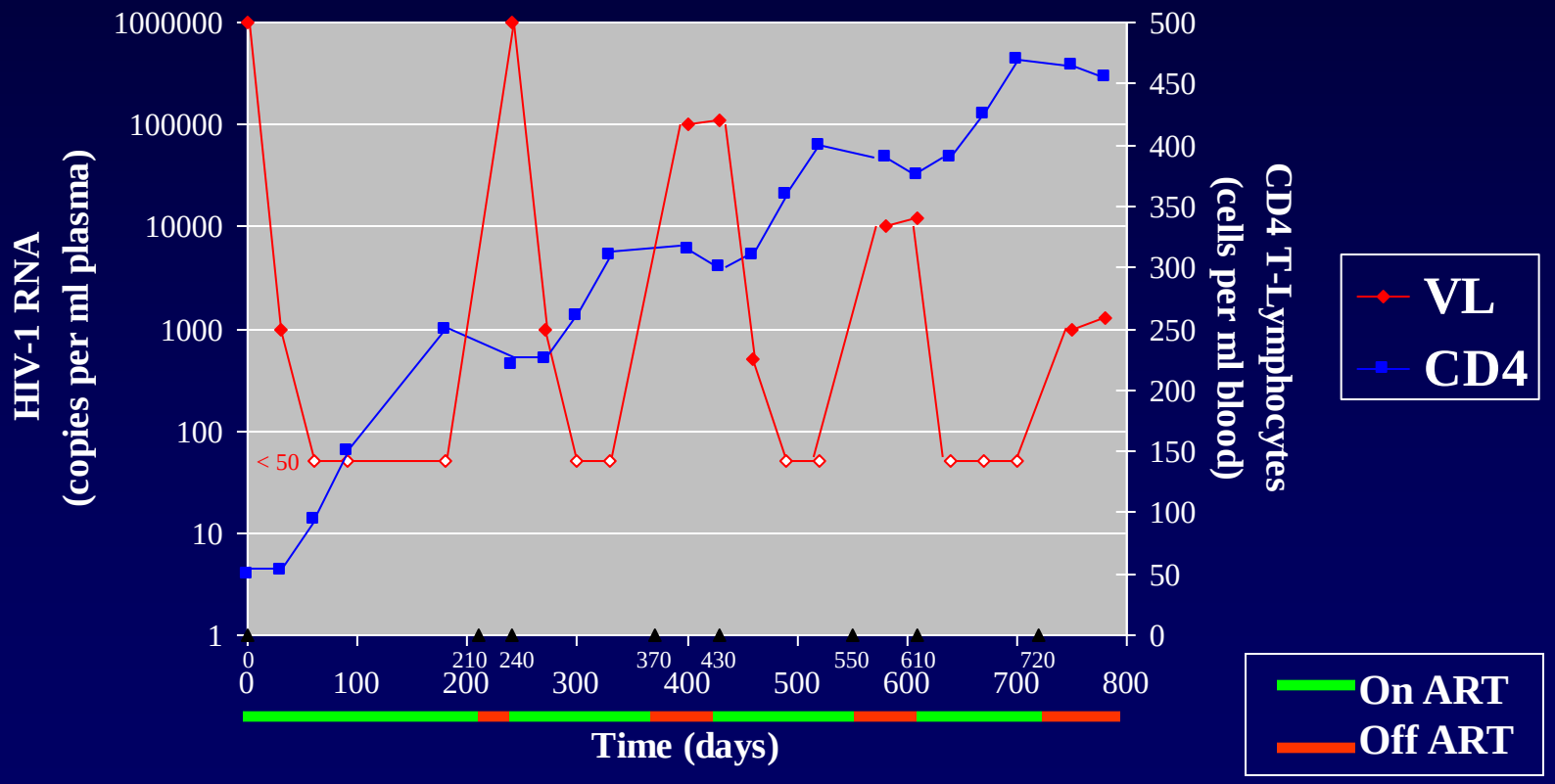
Working Hypothesis

Patients with long-term viral suppression and a significant increase in CD4 T-cells, should have an increase in naïve CD4 T-cells.

Naïve CD4 cells should be able to “respond” to HIV antigen during initial interruption.

Subsequent ART interruption may result in a reduction of rebound viral load (reduced set point) due to immunologic control of HIV.

Idealized Patient Response to ART Interruption



Methods

- A retrospective analysis of 268 patient charts (N ~ 500) to identify patients who interrupted ART.
- 123 (45.9%) interrupted ART at least once. 36 had baseline and follow-up data.
  - 23 had data for an initial interruption.
  - 18 had data for a subsequent interruption.
  - 5 had data for initial and subsequent interruptions (overlap)

Methods

- Charts examined for:
  - Composition and duration of ART regimen.
  - Duration viral load was BLQ (< 50 mid-1997.)
  - Change in CD4 levels on ART.
  - Reason(s) for interruption.
  - Duration of interruption.
  - Change in viral load.

ART Interruption - Why?

- Common event in clinical practice
- Why do patients interrupt ART?
  - Rule One, All or None!
- Reasons for interruption:
  - Side Effects
  - Ran Out of Meds
  - Active Drug Use
  - No Insurance
  - Viral Resistance
  - Non-adherence
  - Prison
  - Depression/Anxiety
  - Difficulty Eating
  - Leaving U.S.A.
  - RTV Oral Solution
  - Patient Choice

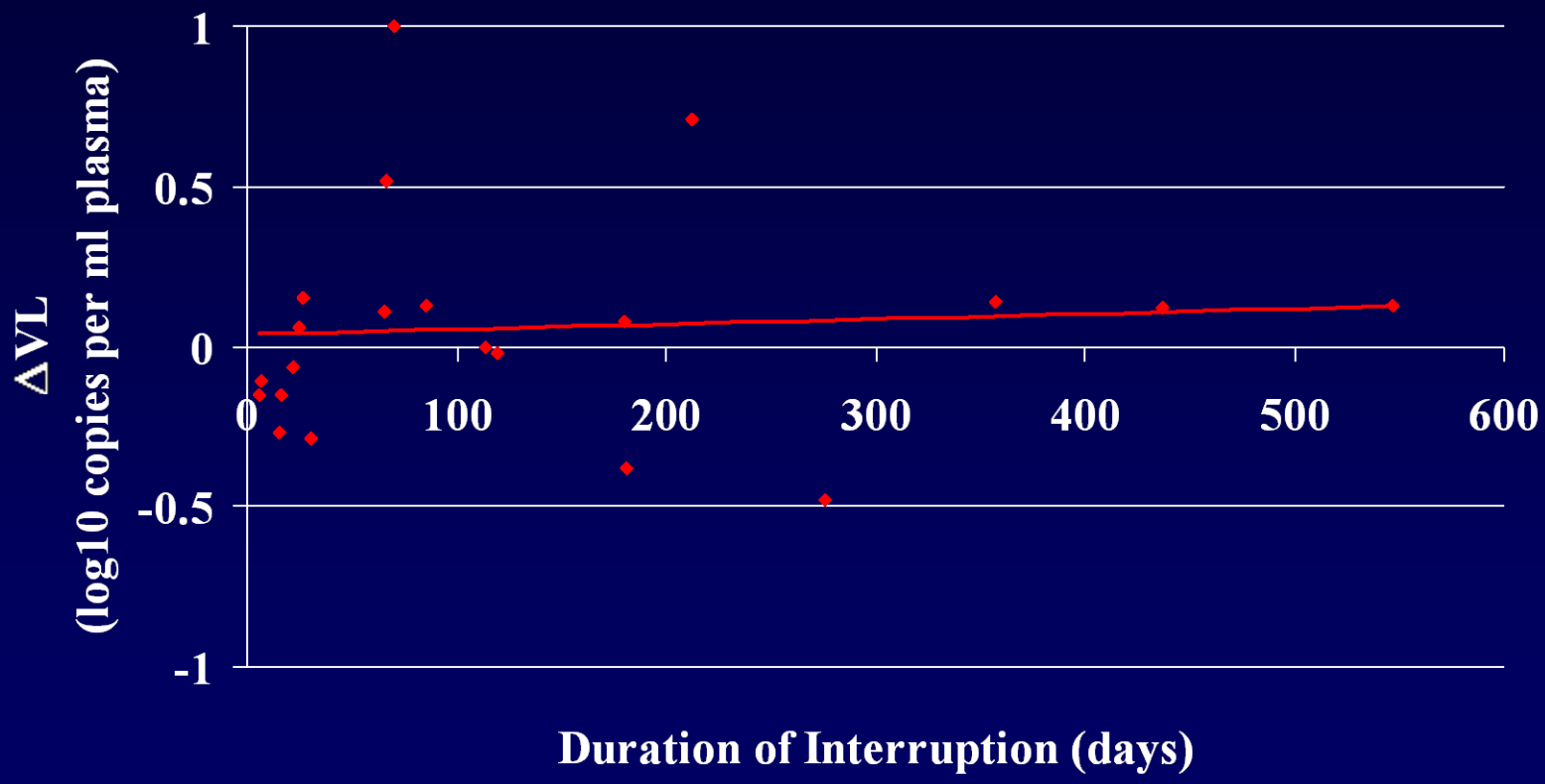
Return to Baseline After First Interruption

- ΔVL*
  - n = 23‡
  - Mean = +0.059 $\log_{10}$
  - Median = +0.028 $\log_{10}$
  - Standard Deviation = 0.35 $\log_{10}$

* VL at longest duration of interruption used for each patient

‡ Patients #81 and #104 were not included in calculations due to unquantified results (> upper limit of test).

Effect of Duration of First Interruption on ΔVL



Slope = 1.64 x 10^{-4}

Standard Error of Linear Regression = 0.480 log10 copies

Before Subsequent ART Interruptions (14/18)

- Interruption resulting in largest ΔVL is shown.

Pt. #	Interruption #	ART	Duration of ART	Duration BLD	Reason for Interruption
70	2	AZT/3TC/NFV	264	132 (<25) + 92 (<400)	Depression
79	3	D4T/3TC/NVP	84	0	Viral Failure
27	4	AZT/3TC/NFV/SQV	91	40 (<500)	N/V
12	2	D4T/3TC/NVP	486	266 (<400) + 192(<50)	Drug Use
30*	4	NFV/SQV	5	0	Pt. Choice
23	2	D4T/3TC/RTV/SQV	278	255 (<200)	Not Tolerating RTV Solution
67*	2	AZT/3TC/RTV/SQV	8	0	Ran Out
69	3	D4T/3TC/RTV/SQV	23	0	Abdominal Enlargement

Before Subsequent ART Interruptions (14/18)

Pt. #	Interruption #	ART	Duration of ART	Duration BLD	Reason for Interruption
77	2	D4T/3TC/NVP	43	>1 (<400)	Fatigue
15	3	DDI/3TC/NVP	231	126 (<50)	Left USA
14	3	D4T/3TC/NFV	273	89 (<400)	Oral Cancer
54	4	D4T/3TC/RTV/SQV	76	14 (<400)	?
25	2	DDI/3TC/NVP	225	69 (<400) + 73 (<50)	Fatigue & Headaches
24	2	AZT/3TC/NVP	348	99 (<400) + 217 (<50)	Noncompliance

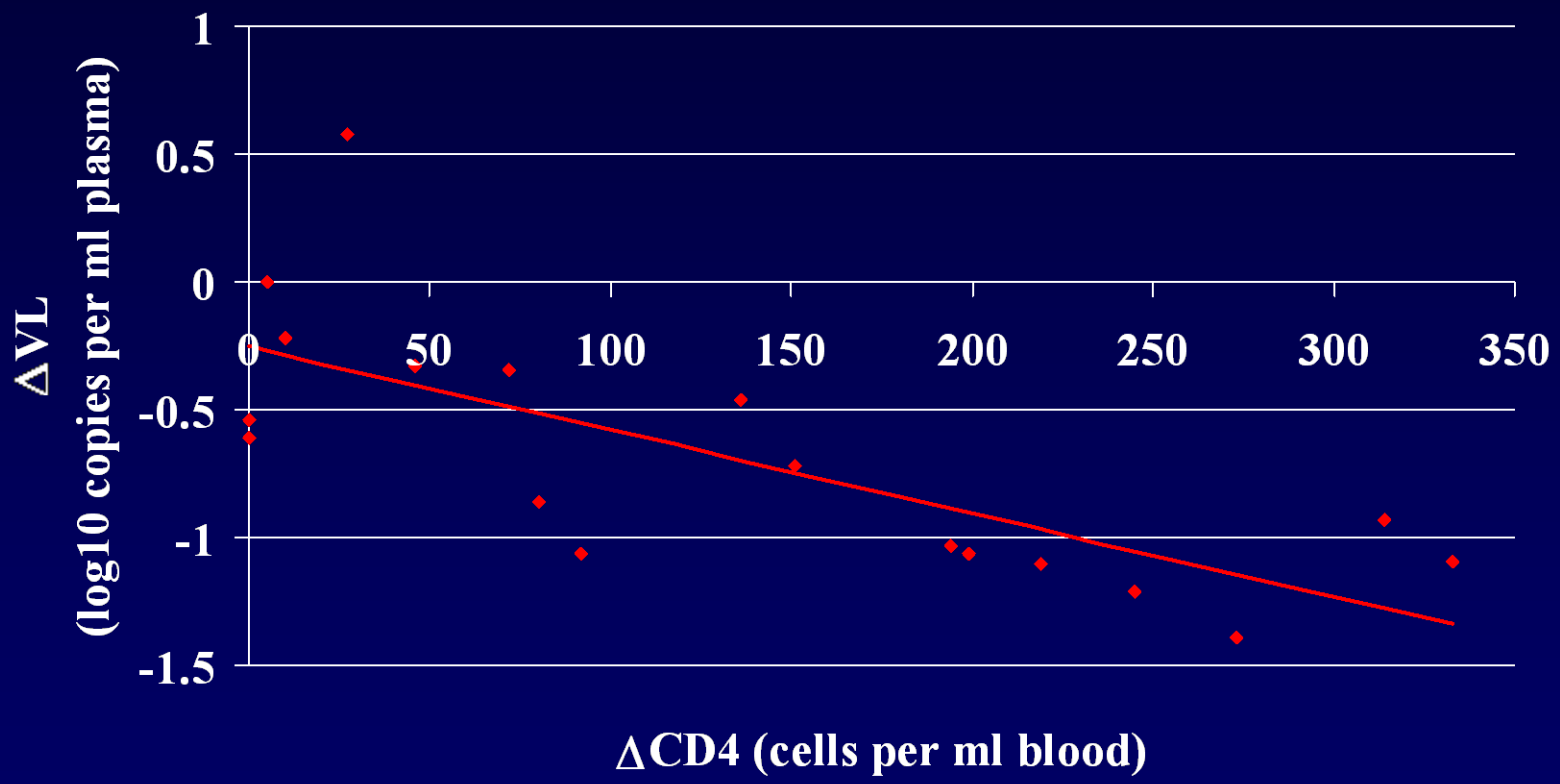
Return to Baseline After Subsequent Interruptions: Responders (10/18)

Pt #	Inter #	Duration	ΔCD4	ΔVL
108	3	39	+273	-1.39
70	2	153	+245	-1.21
79	3	25	+219	-1.10
27	3	86	+333	-1.09
12	2	109	+199	-1.06
30	4	70	+92	-1.06
107	6	21	+194	-1.03
23	2	57	+314	-0.93
67	2	21	+80	-0.86
112	2	112	+151	-0.72

Return to Baseline After Subsequent Interruptions: Non-Responders (8/18)

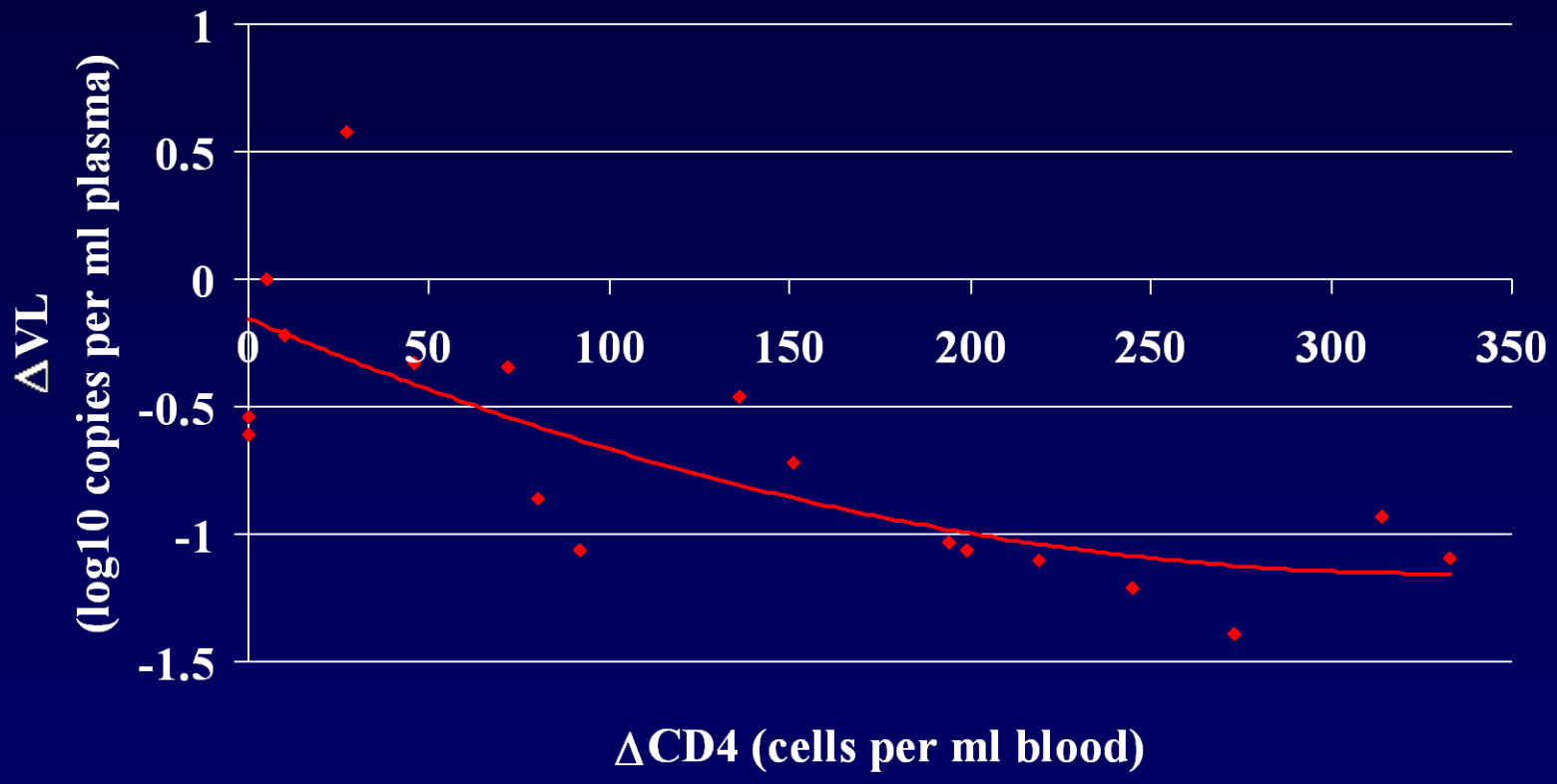
Pt #	Inter #	Duration	ΔCD4	ΔVL
69	3	49	0	-0.61
113	2	73	0	-0.54
77	2	69	+136	-0.46
15	3	92	+72	-0.34
14	3	86	+46	-0.33
54	4	106	+10	-0.22
25	2	77	+5	0.00
24	2	71	+27	+0.58

Effect of ΔCD4 on ΔVL for Subsequent Interruptions



- Slope = -3.26×10^{-3}
- Standard Error of Linear Regression = 0.659 log10 copies

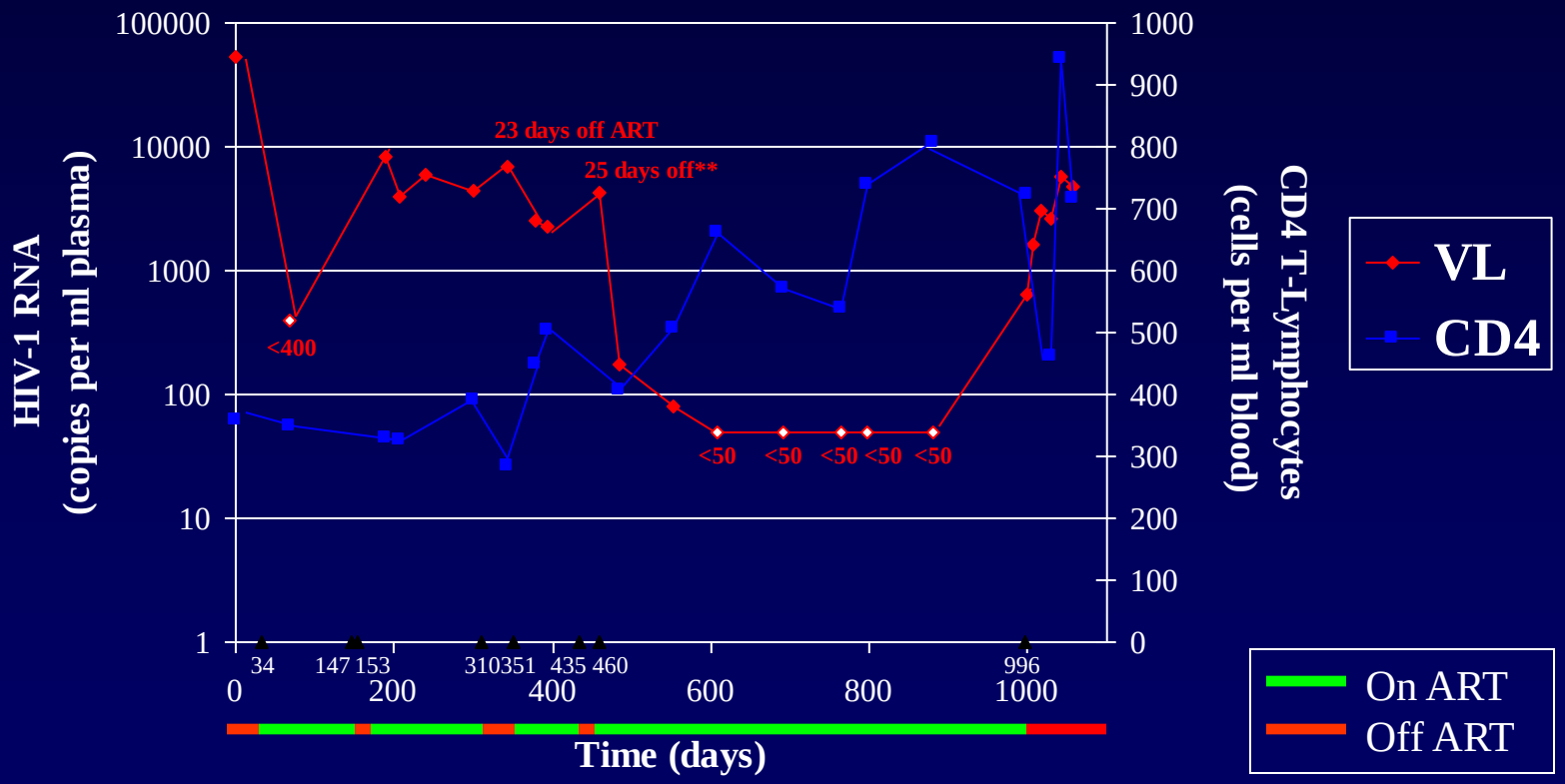
Effect of ΔCD4 on ΔVL for Subsequent Interruptions



Summary: Subsequent Interruptions (n=18)

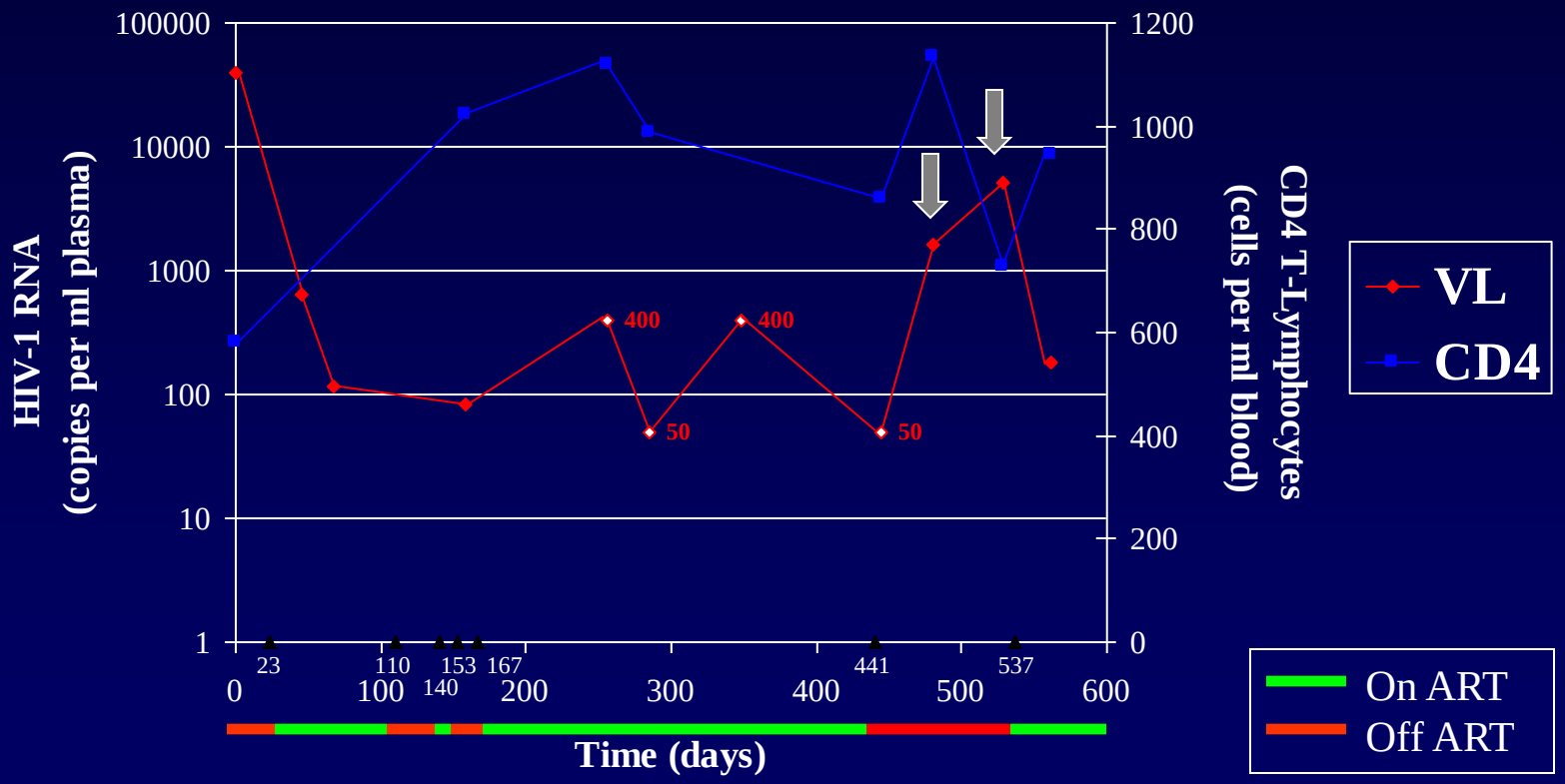
- Virologic Response (At longest duration of interruption.)
  - 10/18 (56%) “reset” set point > 0.70 log10 below baseline viral load for 21 - 153 days. 4/10 reset > 1.0 log10 for > 70 days. (6/10 on PI
- CD4 Response (prior to interruption)
  - **Responders (10/18):** average CD4 cell increase = 210 (95% CI: 149, 271)
  - **Non-Responders (8/18):** average CD4 increase = 37 (95% CI: -2, 76)
  - absolute CD4 does not appear to correlate
- 6/10 responders on PI, 3/8 non-responders on PI

Response to ART Interruption
Patient 79 (DJ) - 4 Interruptions



Note: DJ <5000 @ 3 months during 4th interruption

Response to ART Interruption
Patient 108 (LG) - 3 Interruptions



Note: LG <5000 @ 3 months during 4th interruption

Reduction of Viral Set Point - Why?

- With the return of HIV-naïve T-cells, the first interruption may result in HIV "vaccination."
- If ART restarted before these cells are lost, HIV-specific responses should be retained.
- A second ART interruption may stimulate HIV-specific proliferative responses with reduction in viral rebound (reduced set point).
- By preventing depletion of HIV-specific CD4 T-cells during interruption, successive interruptions may result in further set point reduction.

Alternative Explanations

- Type I error - this is a small retrospective analysis with limited data points.
- Original virus replaced with a less fit virus.
- Original set point not accurately determined.
- Laboratory variation and error
- Further analysis of the entire cohort is planned

Conclusions - Questions

- Randomized, controlled trials are required to answer the following questions:
  - How is balance maintained between activated HIV-specific CD4 cells (target) and virus?
  - What is the optimal duration of ART interruption?
  - OR, What is the optimal VL rebound? **(BOTH?)**
  - Is the response different between PI and NNRTI?
  - What are the predictive immunologic parameters?
  - Will this be an “insurance policy” for occasional non-adherence?

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