

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

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

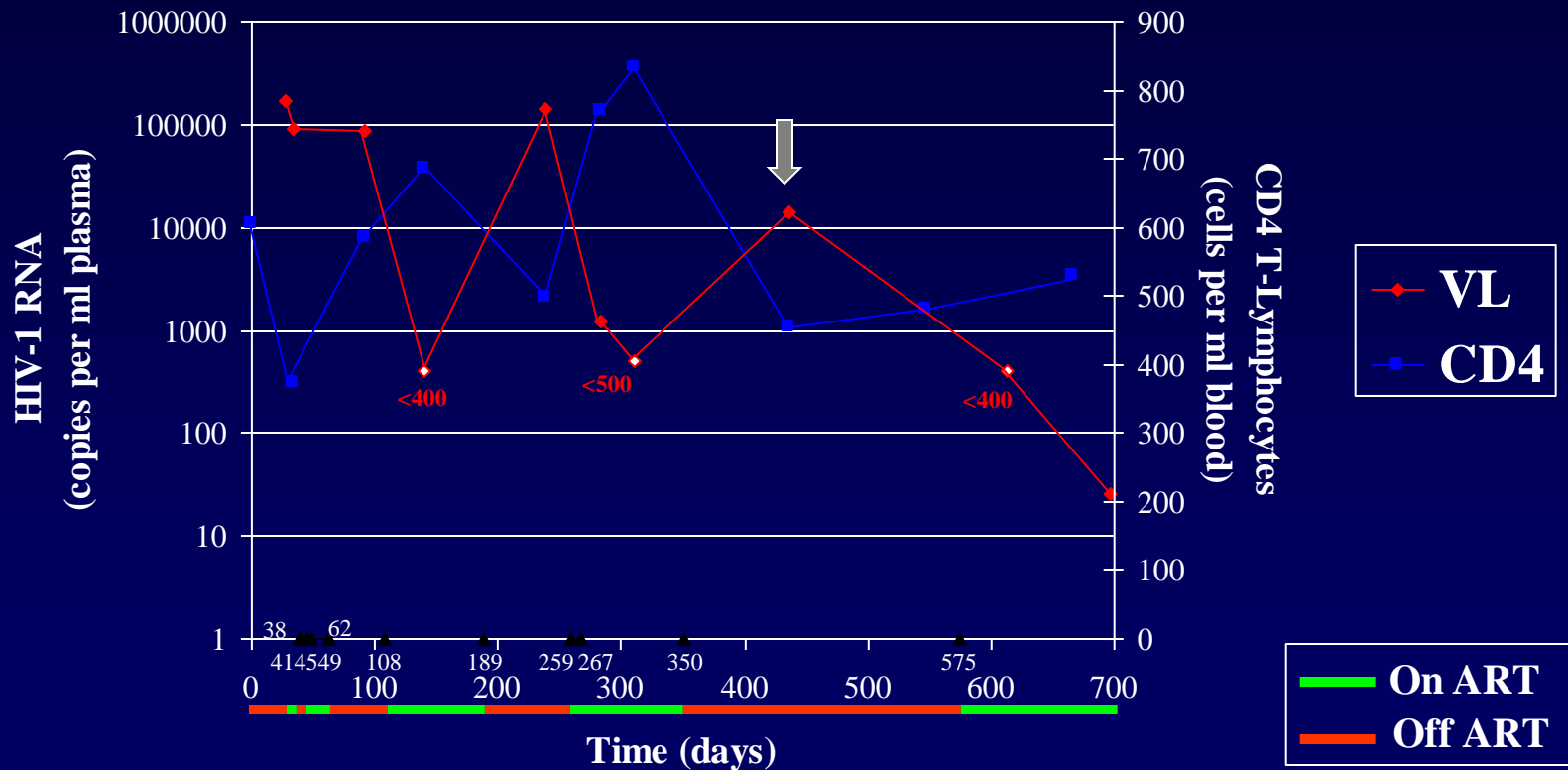
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# Response to ART Interruption

## Patient 27 (JP) - 3 Interruptions



# Background - Why?

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- 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

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- 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  $\sim 0.2 \log_{10}$  in total viral burden/day (n=6) (*Harrigan, AIDS 99*)

# Background - Recent Studies

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- 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” (*Liszewicz 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

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- 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

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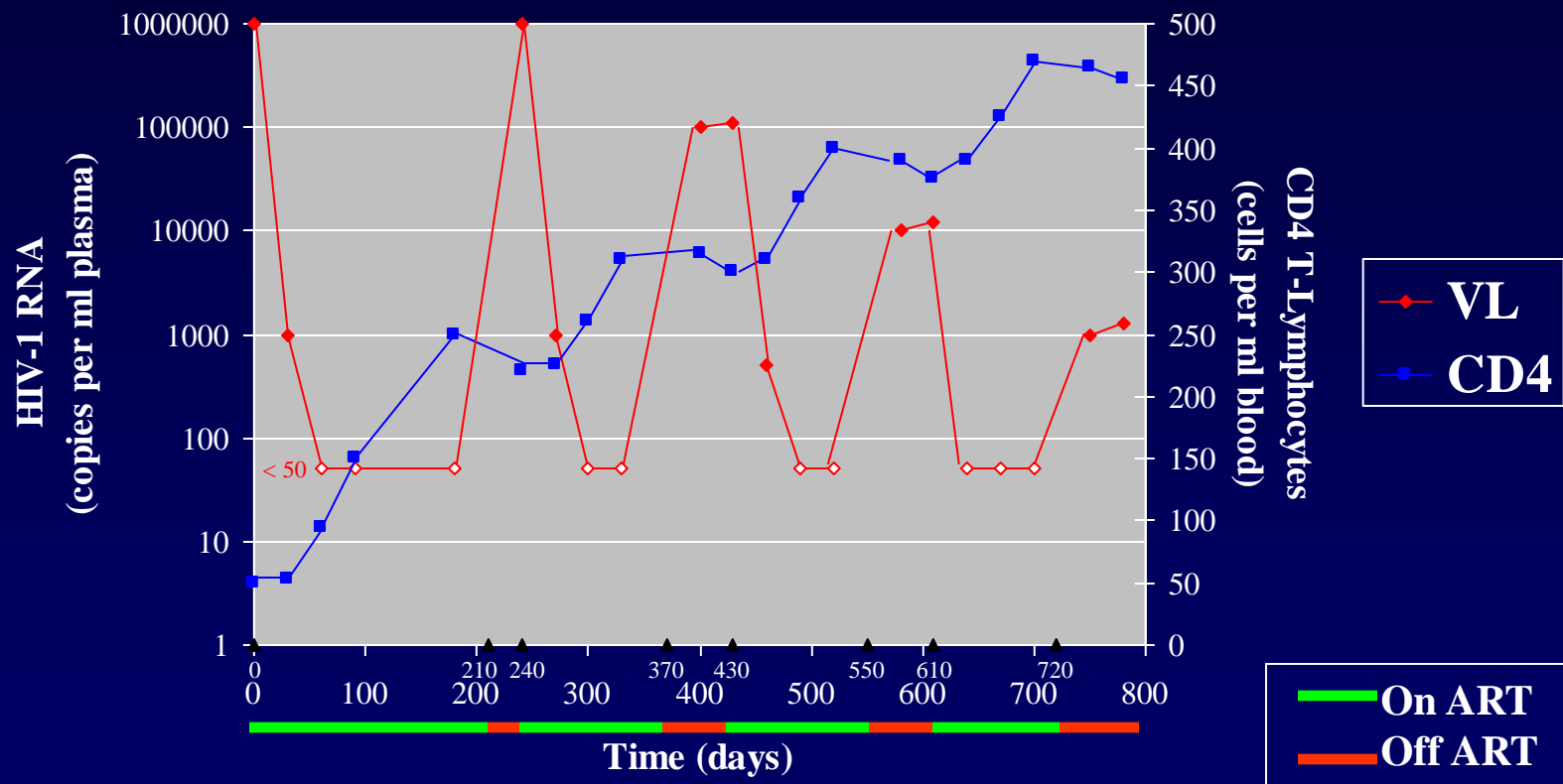
Patients with long-term viral suppression and a significant increase in CD4 T-cells, should have an increase in naïve CD4 T-cells.

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

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- A retrospective analysis of 268 patient charts ( $N \sim 500$ ) 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

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- 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?

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- 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

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- $\Delta VL^*$

- $n = 23^{\ddagger}$

- Mean =  $+0.059 \log_{10}$

- Median =  $+0.028 \log_{10}$

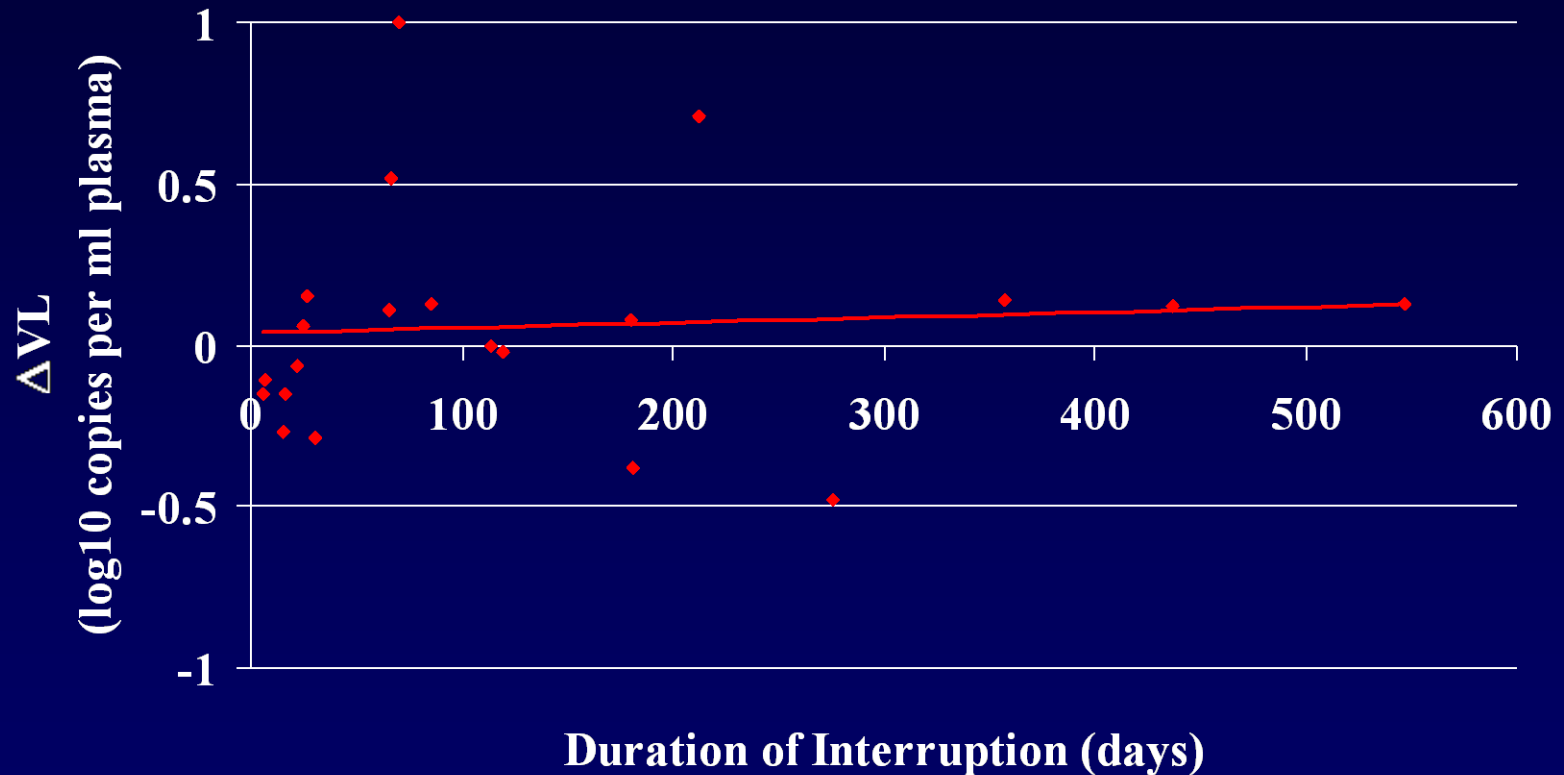
- Standard Deviation =  $0.35 \log_{10}$

- \* VL at longest duration of interruption used for each patient

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

# Effect of Duration of First Interruption on $\Delta VL$

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Slope =  $1.64 \times 10^{-4}$

Standard Error of Linear Regression = 0.480 log10 copies

# Before Subsequent ART Interruptions (14/18)

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- Interruption resulting in largest  $\Delta VL$  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)

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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)

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Pt #	Inter #	Duration	$\Delta$ CD4	$\Delta$ VL
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

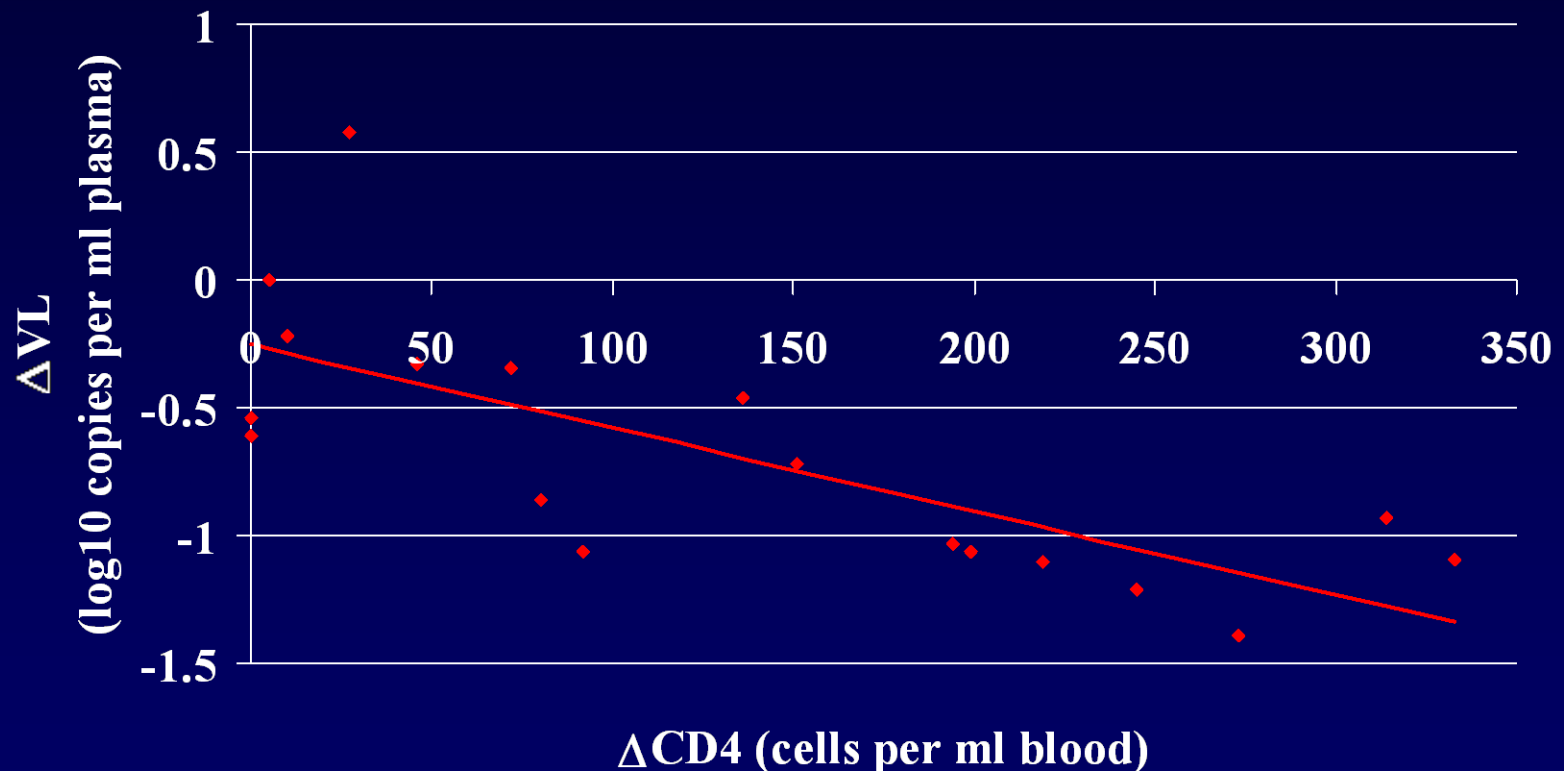
## Return to Baseline After Subsequent Interruptions: Non-Responders (8/18)

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Pt #	Inter #	Duration	$\Delta$ CD4	$\Delta$ VL
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 $\Delta\text{CD4}$ on $\Delta\text{VL}$ for Subsequent Interruptions

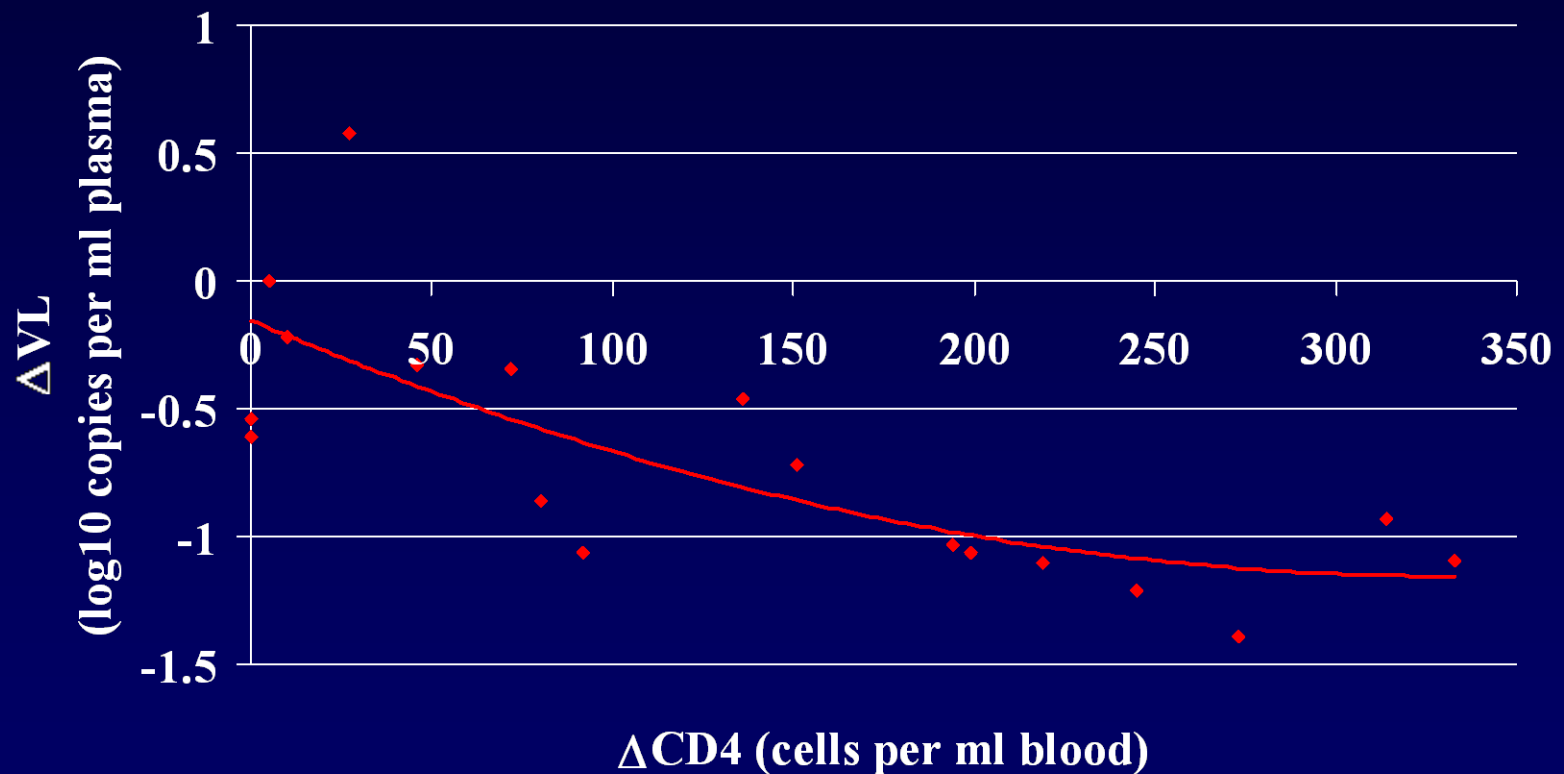
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- Slope =  $-3.26 \times 10^{-3}$
- Standard Error of Linear Regression = 0.659 log10 copies

# Effect of $\Delta\text{CD4}$ on $\Delta\text{VL}$ for Subsequent Interruptions

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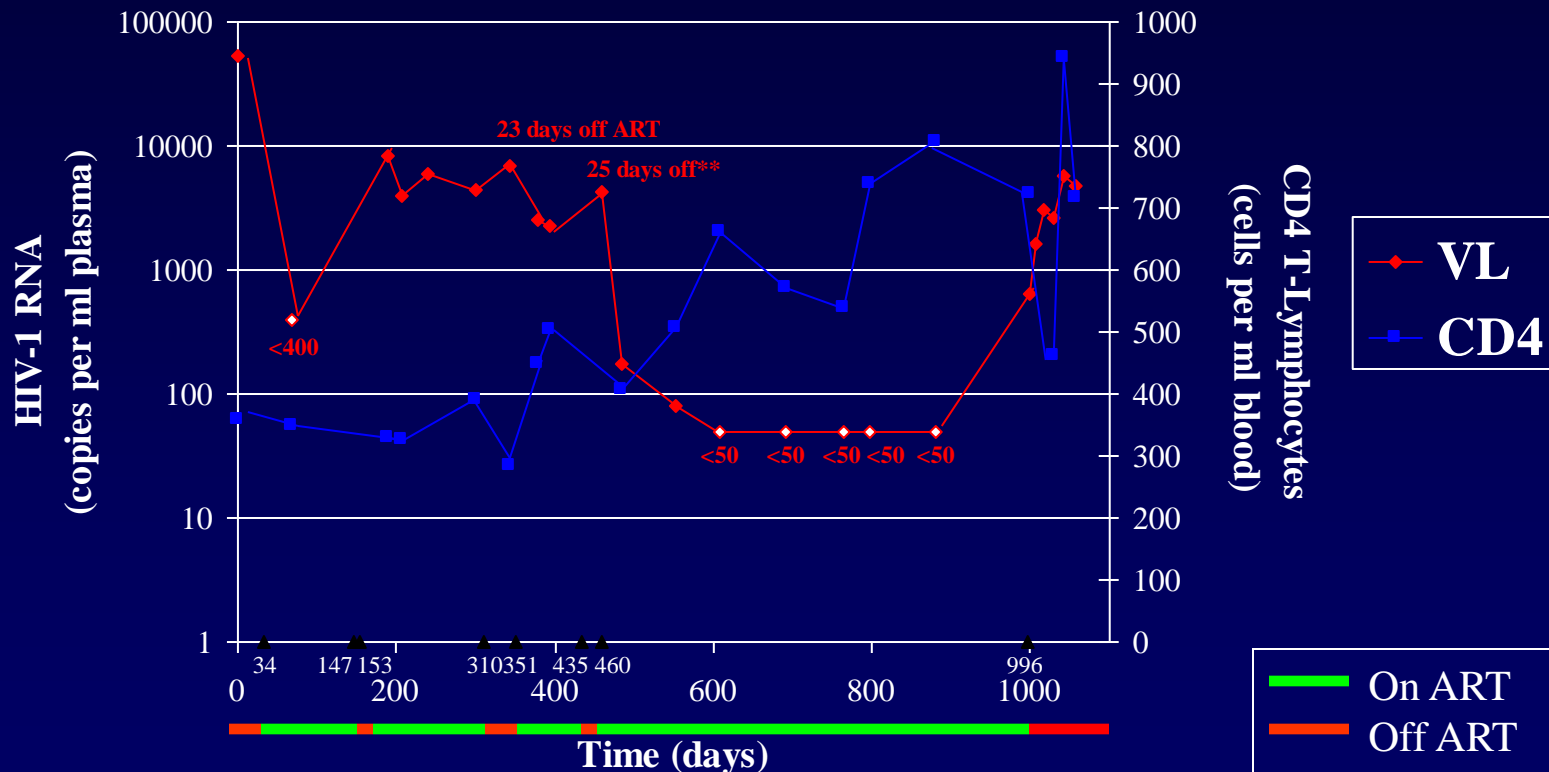
# Summary: Subsequent Interruptions (n=18)

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- Virologic Response (At longest duration of interruption.)
  - 10/18 (56%) “reset” set point  $> 0.70 \log_{10}$  below baseline viral load for 21 - 153 days. 4/10 reset  $> 1.0 \log_{10}$  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

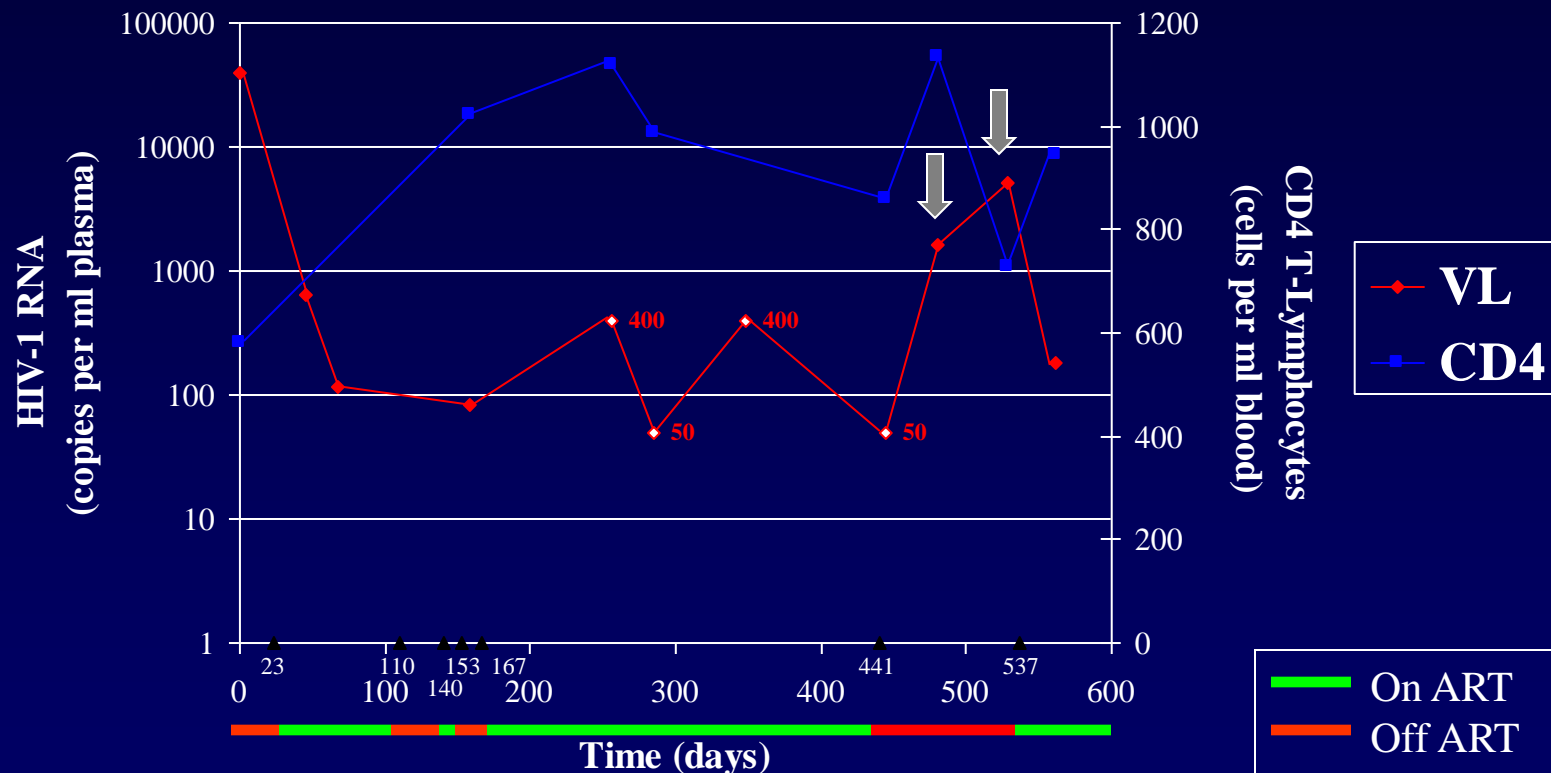
## Patient 79 (DJ) - 4 Interruptions



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?

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- 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

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- 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

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- 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?

# Acknowledgments

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