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 Intermittences

HIV-1 RNA (copies per ml plasma)

CD4 T-Lymphocytes (cells per ml blood)

On ART
Off ART
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 \( \sim 0.2 \log_{10} \) 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 \((\text{Lopez, ICAAC 99 LB24})\)

- 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 \((\text{Pitcher, Nat Med 99})\)
  - Is there sufficient antigen present in patients with viral load BLQ and restored immune system?
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 $\Delta VL$

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

Standard Error of Linear Regression = $0.480 \log_{10}$ copies
Before Subsequent ART Interruptions (14/18)

- Interruption resulting in largest ΔVL is shown.

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

Slide 1 of 2
Before Subsequent ART Interruptions (14/18)

<table>
<thead>
<tr>
<th>Pt. #</th>
<th>Interruption #</th>
<th>ART</th>
<th>Duration of ART</th>
<th>Duration BLD</th>
<th>Reason for Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>2</td>
<td>D4T/3TC/NVP</td>
<td>43</td>
<td>&gt;1 (&lt;400)</td>
<td>Fatigue</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>DDI/3TC/NVP</td>
<td>231</td>
<td>126 (&lt;50)</td>
<td>Left USA</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>D4T/3TC/NFV</td>
<td>273</td>
<td>89 (&lt;400)</td>
<td>Oral Cancer</td>
</tr>
<tr>
<td>54</td>
<td>4</td>
<td>D4T/3TC/RTV/SQV</td>
<td>76</td>
<td>14 (&lt;400)</td>
<td>?</td>
</tr>
<tr>
<td>25</td>
<td>2</td>
<td>DDI/3TC/NVP</td>
<td>225</td>
<td>69 (&lt;400) +</td>
<td>Fatigue &amp; Headaches</td>
</tr>
<tr>
<td>225</td>
<td></td>
<td></td>
<td></td>
<td>73 (&lt;50)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>AZT/3TC/NVP</td>
<td>348</td>
<td>99 (&lt;400) +</td>
<td>Noncompliance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>217 (&lt;50)</td>
<td></td>
</tr>
</tbody>
</table>
Return to Baseline After Subsequent Interruptions: Responders (10/18)

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Inter #</th>
<th>Duration</th>
<th>ΔCD4</th>
<th>ΔVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>3</td>
<td>39</td>
<td>+273</td>
<td>-1.39</td>
</tr>
<tr>
<td>70</td>
<td>2</td>
<td>153</td>
<td>+245</td>
<td>-1.21</td>
</tr>
<tr>
<td>79</td>
<td>3</td>
<td>25</td>
<td>+219</td>
<td>-1.10</td>
</tr>
<tr>
<td>27</td>
<td>3</td>
<td>86</td>
<td>+333</td>
<td>-1.09</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>109</td>
<td>+199</td>
<td>-1.06</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>70</td>
<td>+92</td>
<td>-1.06</td>
</tr>
<tr>
<td>107</td>
<td>6</td>
<td>21</td>
<td>+194</td>
<td>-1.03</td>
</tr>
<tr>
<td>23</td>
<td>2</td>
<td>57</td>
<td>+314</td>
<td>-0.93</td>
</tr>
<tr>
<td>67</td>
<td>2</td>
<td>21</td>
<td>+80</td>
<td>-0.86</td>
</tr>
<tr>
<td>112</td>
<td>2</td>
<td>112</td>
<td>+151</td>
<td>-0.72</td>
</tr>
</tbody>
</table>
## Return to Baseline After Subsequent Interruptions: Non-Responders (8/18)

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Inter #</th>
<th>Duration</th>
<th>ΔCD4</th>
<th>ΔVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>3</td>
<td>49</td>
<td>0</td>
<td>-0.61</td>
</tr>
<tr>
<td>113</td>
<td>2</td>
<td>73</td>
<td>0</td>
<td>-0.54</td>
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<tr>
<td>77</td>
<td>2</td>
<td>69</td>
<td>+136</td>
<td>-0.46</td>
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<tr>
<td>15</td>
<td>3</td>
<td>92</td>
<td>+72</td>
<td>-0.34</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>86</td>
<td>+46</td>
<td>-0.33</td>
</tr>
<tr>
<td>54</td>
<td>4</td>
<td>106</td>
<td>+10</td>
<td>-0.22</td>
</tr>
<tr>
<td>25</td>
<td>2</td>
<td>77</td>
<td>+5</td>
<td>0.00</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>71</td>
<td>+27</td>
<td>+0.58</td>
</tr>
</tbody>
</table>
Effect of $\Delta CD4$ on $\Delta VL$ for Subsequent Interruptions

- Slope = $-3.26 \times 10^{-3}$
- Standard Error of Linear Regression = $0.659 \log_{10}$ copies
Effect of $\Delta$CD4 on $\Delta$VL 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
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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