Management of HIV-infected patients with low level viremia

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Introduction

• In clinical practice low level viremia and isolated blips are frequently observed

• Seems to be more present in recent years
  • Effect of overall better suppression
  • Effect of New Technology
Impact of low level viremia on time to next visit

viremia and viral blips generate uncertainty among clinicians and patients

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Nature of Low level viremia

- Assay Variation or Increased sensitivity
- Production of Virus
- Viral replication
- Discussion over relevance 50 cut-off for failure
• What do the guidelines say?
EACS guidelines

<table>
<thead>
<tr>
<th>Definition</th>
<th>Confirmed plasma HIV RNA &gt; 50 copies/mL 6 months after starting therapy (initiation or modification) in patients that remain on ART (1)</th>
</tr>
</thead>
</table>
| General measures | • Review expected potency of the regimen  
• Evaluate adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues  
• Perform resistance testing on failing therapy (usually routinely available for VL levels > 350-500 c/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations  
• Tropism testing  
• Consider TDM  
• Review antiretroviral history  
• Identify treatment options, active and potentially active drugs/combinations |
| Management of virological failure (VF) | If plasma HIV RNA > 50 and < 500-1000 copies/mL  
• Check for adherence  
• Check plasma HIV RNA 1 to 2 months later  
If genotype not possible, consider changing regimen based on past treatment and resistance history  
If plasma HIV RNA confirmed > 500/1000 copies/mL, change regimen as soon as possible. What to change will depend on the resistance testing results:  
• No resistance mutations found: re-check for adherence, perform TDM  
• Resistance mutations found: switch to a suppressive regimen based on drug history |
Optimal viral suppression <20–75 copies/mL

Isolated “blips” (<400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure [5].

Low-level positive viral load results (<200 copies/mL) appear to be more common with some viral load assays; no definitive evidence that patients are at increased risk for virologic failure [6-8].

<200 cut-off for virological failure may also be useful in clinical practice
On what data are these guidelines based?
DHSS guidelines

- Isolated “blips” (<400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure [5].

Havlir et al. JAMA 2001
Blips were not indicative for failure in patients on indinavir, lamivudine and zidovudine or stavudine
DHSS guidelines

- Low-level positive viral load results (<200 copies/mL) appear to be more common with some viral load assays; no definitive evidence that patients are at increased risk for virologic failure [6-8].

Two papers with Roche Taqman 1 and one short report in which the assay is not specified.
Does the Assay matter?

TaqMan 1 not generally available in Europe

The versions of the Roche TaqMan assay and Abbott RealTime assay with different cut-offs, calibration standards and test characteristics

Most clinical outcome data with Roche AMPLICOR assay (discontinued)
The International Viral Load Assay Collaboration

- N=4234 actual clinical samples
- 13 sites
- Comparison of four different assays
  - Abbott RealTime
  - Roche AMPLICOR,
  - Roche TaqMan 1
  - Roche TaqMan 2

Samples included tested with at least 2 assays
Amplicor vs Taqman 1

Percentage undetectable by AMPLICOR as function of TaqMan 1

- <40 (N=10)
- 40-49 (N=238)
- 50-74 (N=352)
- 75-99 (N=222)
- 100-124 (N=138)
- 125-149 (N=104)
- 150-174 (N=73)
- 175-199 (N=51)
- 200-249 (N=89)
- 250-499 (N=7)
- >500 (N=100)

100-125

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Amplicor vs Taqman 2

Percentage undetectable by Amplicor as function of Taqman 2

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Nature of low level viremia

- What is the nature?
  - Assay variation
  - Possibly increased sensitivity of the new assays
What is the clinical relevance?
Time to virologic rebound according to the T0 viral load


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Methods

Group A:
Patients with low-level viremia

Group B:
Patients with a single viral blip

Control group:
Patients with consistently suppressed VL

Analysis of viral loads in preceding year

• RNA detected (VL 1 - 50)
• Target Not Detected (TND: <1)

Hofstra EACS 2011

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Analysis of VL results in preceding year

- Group A (LLV)
- Group B (blip)
- Control group

TND in all VL determinations (VL<1 cp/mL)
RNA detected (1-50) / TND (<1)
RNA detected in all VL determinations (1 - 50 cp/mL)

Hofstra EACS 2011

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Clinical significance

• Are blips and low-level viremia associated with virological failure?

• In current literature no consensus:
  • *Increased risk of virological failure*
    • *Viral blips* ¹-⁴
    • *Low-level viremia* ², ⁵-⁷
  • *No association* ⁸-¹³
  • *Association with emergence of new drug resistant variants* ¹²,¹³

### Development of Resistance: evidence Viral replication

<table>
<thead>
<tr>
<th>ART regimen</th>
<th>Pretreatment CD4 count (cells/mm³)</th>
<th>Pretreatment VL (log₁₀ copies/mL)</th>
<th>Pretreatment RAM</th>
<th>RAM during low-level viremia</th>
<th>VL at time of RAM detection (copies/mL)</th>
<th>Week of treatment when RAM was detected</th>
<th>Follow-up VL after low-level viremia while on initial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2NRTI + EFV</td>
<td>327</td>
<td>3.2</td>
<td>V90I, V179D/V</td>
<td>M184V M230L/M</td>
<td>112</td>
<td>33</td>
<td>VF</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>636</td>
<td>4.7</td>
<td></td>
<td>M184V</td>
<td>&lt;50*</td>
<td>67</td>
<td>VF</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>37</td>
<td>4.8</td>
<td></td>
<td>K101E, K103N, M184V M230L</td>
<td>76</td>
<td>58</td>
<td>VL &lt;50 copies/mL</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>373</td>
<td>4.6</td>
<td>K103N, V106I, G190A T121Y</td>
<td>M184V (A62A/V)</td>
<td>101</td>
<td>32</td>
<td>Off treatment right after low-level viremia</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>6</td>
<td>4.9</td>
<td></td>
<td>V106I</td>
<td>120</td>
<td>32</td>
<td>VL &lt;50 copies/mL and then VF</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>192</td>
<td>5.3</td>
<td></td>
<td>K103N, M230L</td>
<td>105</td>
<td>72</td>
<td>VL &lt;50 copies/mL</td>
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<tr>
<td>2NRTI + EFV</td>
<td>71</td>
<td>6.4</td>
<td></td>
<td>M184V</td>
<td>8,322***</td>
<td>144</td>
<td>Off treatment right after low-level viremia</td>
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<tr>
<td>2NRTI + EFV</td>
<td>201</td>
<td>4.2</td>
<td></td>
<td>Y188C (D67D/N)</td>
<td>203</td>
<td>96</td>
<td>VF</td>
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<tr>
<td>2NRTI + EFV</td>
<td>14</td>
<td>5.9</td>
<td></td>
<td>K70K/R</td>
<td>105</td>
<td>33</td>
<td>Off treatment right after low-level viremia</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>304</td>
<td>4.2</td>
<td></td>
<td>K103N, M184V, G190A</td>
<td>494</td>
<td>26</td>
<td>One VL &gt;1000 copies/mL and one VL &lt;50 copies/mL</td>
</tr>
<tr>
<td>3NRTI + EFV</td>
<td>284</td>
<td>4.1</td>
<td></td>
<td>L74V, K103N, Y115F, M184V</td>
<td>368</td>
<td>111</td>
<td>Off treatment right after low-level viremia</td>
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<tr>
<td>3NRTI + EFV</td>
<td>16</td>
<td>5.0</td>
<td></td>
<td>K103N, M184V, P225H/P</td>
<td>238</td>
<td>32</td>
<td>One VL &lt;50 copies/mL, then low-level viremia range</td>
</tr>
<tr>
<td>2NRTI + EFV</td>
<td>267</td>
<td>4.6</td>
<td></td>
<td>K103N, M184V (V108I)</td>
<td>460</td>
<td>82</td>
<td>VF</td>
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<tr>
<td>2NRTI + LPV</td>
<td>74</td>
<td>4.8</td>
<td></td>
<td>V75I</td>
<td>253</td>
<td>64</td>
<td>VL &lt;50 copies/mL*****</td>
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<tr>
<td>2NRTI + LPV</td>
<td>88</td>
<td>5.8</td>
<td></td>
<td>M184V</td>
<td>362</td>
<td>80</td>
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<tr>
<td>3NRTI + EFV</td>
<td>52</td>
<td>6.0</td>
<td></td>
<td>K103N, M184V (P225H)</td>
<td>417</td>
<td>48</td>
<td>VF******</td>
</tr>
<tr>
<td>3NRTI + EFV</td>
<td>27</td>
<td>5.5</td>
<td></td>
<td>K103N (M184V)</td>
<td>531</td>
<td>73</td>
<td>VF</td>
</tr>
</tbody>
</table>

*References: Taiwo JID 2011

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Conclusion

In case of low level viremia:

- Check Adherence
- Perform Drug levels, food intake
- Perform Resistance Testing
- Check Therapy History
- Think about other compartments

- Consider the genetic barrier of the regimen
- In patients with low genetic barrier regimens try to switch therapy
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