The clinical significance of low level viremia during treatment with combination antiretroviral therapy

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Goals of treatment with cART

- Maximal suppression of viral replication
  - Aim for plasma viral loads below detection by current assays
  - LLOD range from 20 to 50 copies/mL plasma depending on the assay
- Reverse immunological decline
- Promote long term health
  - Avoid both AIDS-related and non-AIDS related morbidity and mortality
- Prevent HIV transmission
Definitions of terms
(Ryscavage et al, Antimicrobial Agents and Chemotherapy 2014)

- **Low level viremia**
  - HIV-1 RNA between 50 and 500 c/mL

- **Viral blip**
  - An episode of low-level viremia that is preceded and followed by suppression below the LOQ

- **Persistent low level viremia**
  - At least 2 consecutive episodes of low level viremia

- **Very low level viremia**
  - HIV-1 RNA levels detectable by assays with LOQ below 50 c/mL

- **Residual viremia**
  - Cryptic viremia during “suppressive therapy” in the 1-10 c/mL range that is not responsive to treatment intensification

- **Virologic failure**
  - Rebound viremia >1000c/mL after having achieved a pVL <1000c/mL
Frequency of LLV and VLLV

• Most first episodes of LLV are viral blips\textsuperscript{1}
  • 70-82%
• A minority progress to higher degrees of viremia\textsuperscript{1}
• Approximately 4-8% of patients reaching suppression subsequently develop pVL>500c/mL
WHO Guidelines on monitoring plasma viremia and definitions of terms

• After treatment initiation pVL levels should be determined at 6 months and then yearly thereafter.

• The optimal threshold for defining virologic failure and for switching ART regimens has not been established.

• WHO recommends a threshold of 1000c/mL based on the risk of HIV transmission and disease progression.

• Below 1000c/mL viral blips or intermittent viremia (50-1000 c/mL) can occur during effective therapy but has not been associated with an increased risk of treatment failure.
DHHS Guidelines on monitoring plasma viremia and definitions of terms

• Plasma VL should be measured no later than 8 weeks after treatment initiation and every 4-8 weeks thereafter until below detection.

• Once below detection pVL should be measured every 3-6 months

• Virologic suppression is defined as a confirmed pVL below the level of detection of any validated assay

• Conflicting data on the significance of isolated viral blips and LLV between the LLD and 200c/mL

• Virologic failure is defined as the failure to maintain a pVL below 200c/mL
Impact of low-level viremia on clinical and virological outcome in treated HIV-1 infected patients
The Antiretroviral Therapy Cohort Collaboration (ART-CC)
AIDS 2015 29:373-383

• Collected data from 18 cohorts in Europe and North America from naïve patients started on cART beginning in 1996

• Participants were treated with 2NRTI and either an NNRTI or boosted PI and achieved suppression (pVL<50) within 3-9 months

• 3 categories
  • No LLV
  • LLV 50-199- at least 2 consecutive pVLs between 50 and 199 for at least a month
  • LLV 200-499- al least 2 consecutive pVLs between 50 and 499 for at least one month with at least one between 200 and 499.

• Outcomes
  • Primary: AIDS defining clinical events or death
  • Secondary: Virologic failure defined as 2 consecutive pVL above 500
Results

• Total of 17,902 patients
  • No LLV; N=16,796 (93.8%); LLV 50-199; N=624 (3.5%); LLV 200-499; N=482 (2.7%)

• Factors associated with LLV
  • CDC Stage C at treatment initiation
  • Lower CD4 cell counts
  • Higher pVLs at the start of therapy
Low level viremia 200-499 was associated with increased risk of virologic failure
Factors associated with risk of virologic failure

• Univariate
  • LLV 200-499
  • Low CD4 cell count
  • CDC Class C
  • Age>50
  • Female sex
  • Transmission group non-MSM
  • Earlier cART era

• Adjusted
  • LLV 200-499 (Adjusted HR 3.97)
  • CDC Class C (AHR 1.2)
  • IDU or heterosexual as opposed to MSM (AHR 1.75, 1.48)
  • Period of ART initiation (lowest 2007-2011; highest 1997-2002)
LLV did not impact on rates of AIDS or death
Conclusions

• Low level viremia after suppression with initial regimens containing NNRTI or a boosted PI is associated with virologic failure when between 50 and 500 copies/mL
  • LLV between 50 and 199 in this cohort is not

• Low level viremia is not associated with increased rates of AIDS defining conditions or death

• These data support current guidelines which define VF as a confirmed pVL> 200c/mL

• Caveats
  • No resistance testing results
  • VF defined as >500c/mL plasma
  • Other studies have found that LLV 50-200 is associated with VF but treatment regimens may have been less than ideal (3NRTI and unboosted PI) and also included subjects with a history of virologic failure

The Antiretroviral Therapy Cohort Collaboration (ART-CC) AIDS 2015 29:373-383
Management of a patient with low level viremia between LLOD and 200

DHHS Guidelines

• Confirm that this is LLV and not a viral blip

• Adherence assessment
  • Drug tolerability

• Drug-drug interaction
  • Attention to all medications including OTC products
  • Drug-food interaction

• Monitor with pVL measurements every 3 months
Management of a patient with low level viremia between 200 and 1000c/mL

DHHS Guidelines

• Confirm

• Assess
  • Adherence
  • Drug-drug and drug-food interactions

• Persistence is consistent with virologic failure
  • Resistance testing to guide a change in therapy

• No resistance detected
  • Likely an adherence issue - reassess tolerability

• Resistance detected
  • Change therapy with at least 2-3 fully active agents
Low level viremia and the emergence of drug resistance

• ARV resistance is well documented at levels of viremia between 50 and 1000c/mL\textsuperscript{1,2}

• Success of sequencing depended on pVL and ranged from 67-93% in 6,617 samples

• Caveats
  • Used both commercial kits as well as “home brews”
  • At very low copy numbers results may not be representative of viral quasispecies due to PCR artifact

1. Gonzalez-Serna et al CID 2014
2. Santoro et al CID 2014
The presence of resistance associated mutations identifies patients with LLV at high risk for VF.
LLV and markers of inflammation

• Patients with pVL between 50 and 1000c/mL in >50% of determinations had higher levels of activated CD8+ T cells

• Mean CD8+ T cell activation was 1.9% higher in patients with LLV compared to suppressed below detection

• Increased levels of CD38+ and HLA-DR+ CD8+ T cells in patients with at least one detectable VL over 24 months of treatment (mean level 81c/mL)

• Positive correlation between pVL and IL-6 levels in patients with LLV

• Other cohorts do not show associations between LLV and markers of inflammation

1. Karlsson et al 2004 AIDS
2. Zheng et al 2013 Antivir Ther
3. Ostrowski et al 2005 J Inf Dis
4. Bastard et al 2012 Antivir Ther
Managing first failures
DHHS Guidelines

• First regimen is NNRTI-based
  • Resistance to both NRTI and NNRTI is likely
  • Boosted PI based therapy is recommended for second line

• First regimen is boosted PI-based
  • Resistance to boosted PI is unlikely
  • VF most likely due to non-adherence
  • Attention to tolerability

• First regimen is InSTI-based
  • Resistance to NRTI and InSTI likely with RAL and EVG
  • Resistance to DTG has yet to be well defined
  • Switch to boosted PI-based regimen
Managing first failures
WHO guidelines

<table>
<thead>
<tr>
<th>Population</th>
<th>Failing first-line regimen</th>
<th>Preferred second-line regimen</th>
<th>Alternative second-line regimens</th>
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<tbody>
<tr>
<td>Adults and adolescents</td>
<td>2 NRTIs + EFV (or NVP)</td>
<td>2 NRTIs&lt;sup&gt;b&lt;/sup&gt; + ATV/r or LPV/r</td>
<td>2 NRTIs&lt;sup&gt;b&lt;/sup&gt; + DRV/r&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>2 NRTIs + DTG</td>
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<tr>
<td>Pregnant or breastfeeding women</td>
<td>2 NRTIs + EFV (or NVP)</td>
<td>2 NRTIs&lt;sup&gt;b&lt;/sup&gt; + ATV/r or LPV/r</td>
<td>2 NRTIs&lt;sup&gt;b&lt;/sup&gt; + DRV/r</td>
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b. NRTIs in second regimen: if TDF or ABC used in first AZT used in second and vice versa
Second line therapy in patients failing NNRTI-based first line therapy

Second line study Group Lancet 2013

- Open-label 96-week non inferiority study

- Randomization
  - 2-3 NRTIs plus LPV/rit versus RAL plus LPV/rit

- Inclusion criteria
  - Failed first line therapy with NNRTI and 2NRTI
  - PI/InSTI naïve
  - VF defined as 2 consecutive VLs above 500c/mL

- Procedures
  - LPV/rit taken once or twice daily based on investigator preference
  - NRTIs selected by investigators based on resistance testing or a simple algorithm
Second line therapy in patients failing NNRTI-based first line therapy
Second line study Group Lancet 2013

<table>
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<tr>
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<th>CONTROL GROUP (N=271)</th>
<th>RALTEGRAVIR (N=270)</th>
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<tbody>
<tr>
<td>Duration of infection (years)</td>
<td>5.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Plasma viral load (Log_{10} copies/mL)</td>
<td>4.3 (3.7-4.9)</td>
<td>4.2 (3.6-4.8)</td>
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<tr>
<td>CD4+ T cell count (cells/μL)</td>
<td>189 (80-289)</td>
<td>190 (104-307)</td>
</tr>
<tr>
<td>Subjects with 1-3 TAMs</td>
<td>46%</td>
<td>44%</td>
</tr>
<tr>
<td>M184V alone</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>M184V with other NRTI mutations</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td>1 or more or more NNRTI mutations</td>
<td>96%</td>
<td>97%</td>
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Second line therapy in patients failing NNRTI-based first line therapy

Second line study Group Lancet 2013

Figure 2: Proportion of participants with plasma HIV viral load less than 200 copies per mL
In the modified intention-to-treat population.

Figure 3: Virological response at week 48, stratified by baseline viral load and analytical population
The non-inferiority margin is -2. *Based on samples tested locally. † Equivalent to the FDA snapshot analysis.
Second line therapy in patients failing NNRTI-based first line therapy
Second line study Group Lancet 2013

• LPV/rit in combination with either 2-3 NRTIs or RAL provided effective second line therapy in patients failing NNRTI-based first line therapy
  • Approximately 80% below 200c/mL
  • Approximately 70% below 50c/mL

• No major safety issues emerged

• Unanswered question
  • Would an earlier switch in therapy improve patient outcomes?
Conclusions

• Goals of treating HIV-1 infection with cART remain durable suppression of viral replication
• Advances in technology have provided assays that are more sensitive in measuring plasma viremia
  • Identify a subset of patients with low level viremia
• Low level viremia may be associated with subsequent virologic failure
• Virologic failure is more likely in patients with LLV and detectable resistance mutations
• Revisiting current definitions of VF and monitoring of such may be indicated to improve responses to second line treatment regimens