Why and when measure Viral Load?

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Access Campaign
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« Monitoring treatment efficacy in the context of resource limited settings »,
TULP01, WAC, Toronto 2006
Viral Load use between 2001-2005

- **MSF programs:**
  - VL was not routinely available nor recommended
  - The lack of laboratory monitoring should not delay treatment initiation in any case.

- **WHO 2003 guidelines**
  - VL is not being recommended to inform ‘When to Start’ decision making.
  - VL is not to be used as sole criterion for treatment failure at this time but availability encouraged.
  - If available, suspected clinical and/or CD4 failure should trigger ordering this test.

WHO guidelines 2003 – *a public health approach*
2006 WHO recommendations (1)

- **When to start:**
  - "HIV-RNA (viral load) measurement is not necessary prior to initiating ART"
  - Wide agreement regarding the impact of CD4 T cell count on survival after initiation of HAART
  - Initiation of a life long treatment (exposing the patient to side effect) based on VL when CD4 are well above a threshold of 350 is subject to controversy.
  - VL is of negligible pronostic value among adherent patients with more than 200 CD4* .

*Wood E and al, AIDS 2006, 20:1197-1198
2006 WHO recommendations (2)

- **Defining treatment failure:**
  - “The field needs to move toward (...)implementation of affordable VL testing. **CD4 and plasma HIV-1 RNA testing are not luxuries. They are (...) invaluable measures of program monitoring**”.

- **The threshold:**

<table>
<thead>
<tr>
<th>Clinical failure</th>
<th>Occurrence of new or recurrent WHO stage 4 condition</th>
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| CD4 cell failure                  | Fall of CD4 count to pre-therapy baseline (or below) or 
                                      | 50% fall from the on-treatment peak value (if known) or 
                                      | Persistent CD4 levels < 100 cells/mm³ |
| Virological failure               | Plasma HIV-1 RNA level >10,000 copies/ml⁹           |

a. The optimal viral load value at which ART should be switched has not been defined. However, values of more than 10,000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline.
What did happen?

WHY use VL?
1. Program mature
MSF presented data on 57’147 patients

- Few patients on second line:

- MSF data show that patients starting ARV at a very advanced stage have excellent outcome (May 2006).
  - Median CD4 104, 84% WHO stage 3 and 4) –
  - 9% death, 10% LTFU (<3m)
  - Probability of survival of 84% (74%) at 2 years (death only versus death + lost to follow-up)
  - Median follow-up is 9 months

- 1-3% of patients are on a second line regimen
- 3% of patients at 48 months

- The median duration of a first line regimen in the US is 1.6 years*.

* Chen RY Clin Inf Dis 2003; 37:714-722
Why do we rarely switch?

- The availability of a second line
  - Switching too early may leave patients without treatment options

- The criteria used to define failure
  - CD4 have a poor predictive value for failure*
    - OI might jeopardize CD4 rise
    - 51% patients identified with CD4 failure had VL < 50**

- No experience on when to switch if not using the fully suppressive strategy (DART and CDC studies still ongoing but main outcome is clinical)

- CROI 2006
- **Pepfar meeting 2006, SA, Cardellio and al
ART programmes mature and growing number of patients will inevitably fail. Detection of treatment failure will be the next burning issue.
2. Strategy to preserve the first line
Why and How to Wait?

- First line is cheap, easy to take, easy to store.

- Switching early enough in order to protect the patient from the occurrence of severe immunosuppression.

- Prevent the accumulation of resistance that would preclude future treatment options.
The fear for resistance: accumulation of mutation over time

- The main rational of using VL as a monitoring for early virological escape is resistance issue

*With the courtesy of S Yerly*
The *when to switch* strategy needs revisiting: DHHS guidelines

“There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia . . .”

*However*

“. . . a decision to change regimens might reduce future treatment options for that patient . . .”

Patients in LDC are in the same situation as experienced patients in wealthy countries.

*How did we arrive to a threshold of 10’000?*
The 10’000 Threshold: PLATO study

PLATO study, Lancet 2004
What did PLATO suggest?

- Goal: Maintaining CD4 above a threshold of 200 cells per µl.

« Treatment regimen that maintains the viral load below 10,000 copies (...) do not seem to be associated with appreciable CD4-cell count decline »

- Other cohort studies to confirm this trend*

* ICONA cohort,
3. Tools available
Simplification is NOT antagonist to the use of VL

- Cheaper, new technologies have become available for both CD4 and VL
- The goal: lab comes to the patients, instead of the patient going to the lab: the point of care test…

- **DBS allows a simple transportation**
- **Semi-quantitative test might be as useful as quantitative results** (survey in MSF sites, WAC Toronto, abstract number 14/08 MOPE0155 Dineva M; Goncalves G Guillerm M)
- **Point of care VL test are highly desirable**
The simplification paradox

How can we advocate for simplified, standardised guidelines, and continuously keep asking for tests, new research?

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DBS allows a simple transportation
Semi-quantitative test might be as useful as quantitative results (survey in MSF sites, WAC Toronto, abstract number 14/08 MOPE0155 Dineva M; Goncalves G Guillerm M)
The dipstick: a qualitative measurement of VL

Semi-quantitative viral load: tomorrow’s reality? Prototype HIV viral load dipstick

<table>
<thead>
<tr>
<th>Viral load (IU/ml)</th>
<th>$10^5$</th>
<th>$10^4$</th>
<th>$5 \times 10^3$</th>
<th>$10^3$</th>
<th>$5 \times 10^2$</th>
<th>Neg</th>
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<tbody>
<tr>
<td>Conventional detection</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Optimized detection</td>
<td></td>
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Courtesy: Helen Lee, Cambridge University
Perspective for the use of VL

All those points led WHO to introduce VL as a key player in the *when to switch* question –

However immense benefit could be obtained for long term management:
How can we maximize survival and quality of life for 10 years with two lines of ARV treatment?
1) Early Adherence monitoring: response to an early elevated VL

<table>
<thead>
<tr>
<th></th>
<th>3 month</th>
<th>6 month</th>
<th>&gt;= 12 months</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>114</td>
<td>54</td>
<td>64</td>
<td>232</td>
</tr>
<tr>
<td>&lt; 400</td>
<td>75%</td>
<td>61%</td>
<td>48%</td>
<td>64%</td>
</tr>
<tr>
<td>&gt;=400</td>
<td>10%</td>
<td>9%</td>
<td>25%</td>
<td>14%</td>
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Subsequent result after a first result >=400 copies/ml

Khayeslitsa, D Coetzee, E Goemare, K Hildebrand
Importance of strengthening early adherence

- The chances of returning to below 400 copies/ml after rebound are inversely proportional to duration of viremia.

- Adherence checks using viral load 4 months post-HAART initiation allows health care workers to institute adherence interventions early.

*This strategy was helpful to keep poorly adherent patients on their first-line regimen.*
2) Switching a regimen

- **The context:**
  - Clinic and CD4 limitations
  - Algorithm to predict virological failure with clinic and patients history have been developed* but not validated**

- **The goal:**
  - Intervention before the patient get severely immunosuppressed

- **The drugs:**
  - Strong independant second line including boosted PI

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*Colebunders and al, LID 2006
**Lawn and al, LID 2006
BREAKING THE VIROLOGICAL DOGMA

moving out of the intensive suppressive strategy
3) The sentinel monitoring

- Viral load testing also serves as a tool to assess HIV programme quality.
- The WHO has proposed that 70% of patients should achieve virological suppression (<400 copies/ml) at six months on ART in resource-limited settings as a quality benchmark.
- The availability of simple, affordable viral load tests would expand the number of sites undergoing quality assessments, as well as the scope of studies investigating predictors of treatment failure.
- Further research using simple viral load tests is needed to monitor programme effectiveness, assess adherence interventions, and identify factors associated with virological failure across a diversity of settings (such as urban versus rural care, and clinic versus home-based care).
VL is not a luxury

- There is a place for a wise use of a semi-quantitative VL in developing countries
- Help keeping the 1st line longer in detecting early escape
- Help preventing the prescription of useless 2nd line
- Help to prevent the occurrence of severe immunodeficiency
- Help monitor large scale programs
- Cost-effectiveness studies have not been performed yet
Viral load is not a luxury in LRS

- There is a place for a wise use of a semi-quantitative VL in developing countries
  - Help keeping the 1st line longer by detecting early escape
  - Help preventing the prescription of useless 2nd line
  - Help to prevent the occurrence of severe immunodeficiency
  - Critical to monitor large scale programs
  - Cost-effectiveness studies have not been performed yet
  - The point of care test would be the most suitable test for use -
end...
Reluctance to switch when future options are rare

Kaplan-Meier survival estimate or time to second viral load > 5000 cps/ml or start of SL regimen

Cumulatively 11.9% (95% CI 7.6 – 18.4) of patients were on second-line by 3 years on ART.

Khayelitsa, South Africa, with the courtesy of D Coetzee and E Goemaere
- No switch occur the first year of treatment
- High threshold for switch (10’000 copies)
- Routine VL and CD4
  - once a year (CD4 recommended q6 months)
OR
- Trigger is a clinical event
- Trigger is discordance (CD4 decrease in the absence of clinical symptoms)