Title: Strategies for optimizing HIV monitoring among adults, children and pregnant women living with HIV receiving antiretroviral therapy: a systematic review

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1. PICO question

<table>
<thead>
<tr>
<th>Population</th>
<th>People living with HIV taking antiretroviral therapy (including adults, children and pregnant women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Routine monitoring with CD4 count versus viral load</td>
</tr>
<tr>
<td>Reference standard or comparators</td>
<td>Routine management with clinical decision-making (present in both arms of the study)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality (primary), morbidity, especially AIDS-associated illness (secondary), adverse outcomes</td>
</tr>
<tr>
<td>Study design</td>
<td>Evaluation studies, conference abstracts and ongoing studies included</td>
</tr>
<tr>
<td>Other</td>
<td>No language, date or geographical restrictions; no restrictions on duration of ART</td>
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<tbody>
<tr>
<td>Interventions</td>
<td>Routine viral load monitoring</td>
</tr>
<tr>
<td>Reference standard or comparators</td>
<td>Viral load thresholds for switching ART – 5000, 2000 and 1000 and less copies/ml (thresholds for children: (1) 5000 copies/ml; (2) 10 000 copies/ml; and (3) 30 000 copies/ml)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Mortality, morbidity, virological suppression, resistance, switching rates, adverse outcomes</td>
</tr>
<tr>
<td>Study design</td>
<td>Evaluation studies, conference abstracts and ongoing studies included</td>
</tr>
<tr>
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</table>
2. Search strategy

**ART term**
1 exp Antiretroviral Therapy, Highly Active/
2 exp Anti-Retroviral Agents/
3 Antiviral Agents/
4 (anti adj3 hiv) OR antiretroviral OR (anti adj3 retroviral) OR HAART OR (anti adj3 acquired immunodeficiency) OR (anti adj3 acquired immunodeficiency) OR (anti adj3 acquired immunodeficiency)
   OR (anti adj3 acquired immune-deficiency) OR (anti adj3 (acquired immun* adj3 deficiency))
5 1 or 2 or 3 or 4

**Monitoring term**
6 CD4 lymphocyte count/
7 viral load/
8 RNA, Viral/
9 Monitoring, Physiologic/
10 Monitoring, immunologic/
11 Treatment failure/
12 (viral adj2 load) OR (drug adj2 monitoring) OR (treatment adj2 outcome) OR (CD4 adj3 T-cell) OR (CD4 adj3 cell adj3 count)
13 5 and (6 or 7 or 8 or 9 or 10 or 11 or 12)

**HIV term**
14 HIV Infections/
15 HIV/
16 hiv OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus
   OR human immunodeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR (human immun* adj3 deficiency virus) OR acquired immunodeficiency
   syndrome OR acquired immunedeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immunodeficiency syndrome
   OR acquired immunedeficiency syndrome OR (acquired immun* adj3 deficiency syndrome)
17 13 and (14 or 15 or 16)
3. Flow diagram of screening process

4138 citations identified
1448 from PubMed
991 from EMBASE
151 from Cochrane Central
435 from Scopus
318 from Gateway NLM
300 from Web of Science
196 from Clinical-trials.gov
299 from Clinicaltrials.com

68 records screened for abstract-level review

24 articles assessed for full-text eligibility

44 records excluded
Interventions did not compare monitoring strategies, outcomes were non-empirical, studies compared monitoring algorithms, studies measured drug-resistance patterns

2360 records excluded

276 duplicates removed

6 articles included in qualitative synthesis

18 articles excluded with reasons
-- Studies compared clinical versus laboratory monitoring (VL and CD4)
-- Studies assessed CD4 monitoring and VL confirmation of treatment failure
-- Studies did not compare CD4 and VL
-- Outcome measured was time to switch

6 articles included in quantitative synthesis
4. Evidence summaries

Background
Monitoring people living with HIV is critical for determining when to switch from first-line to second-line ART and what factors underpin clinical, immunological or virological failure. Advances in point-of-care technology expand the potential use of viral load technology for monitoring in several settings, but evidence is needed to clarify their appropriate use. The purpose of this study is to systematically review original research on CD4 and viral load monitoring of people living with HIV and compare various viral load thresholds for switching to second-line ARV regimens. This was prepared in November 2012 at the request of WHO to inform the development of HIV guidelines.

Objective
To investigate CD4 monitoring and viral load monitoring of adults, children, and pregnant women living with HIV in low-income, middle-income and high-income settings and examine optimal viral load thresholds for switching to second-line ARV regimens. A secondary objective was to examine cost-effectiveness analyses to inform modelling.

Search strategy
We formulated a comprehensive search strategy in an attempt to identify all relevant studies regardless of language or publication status. In November 2012 we searched the following electronic journal and trial databases: MEDLINE, EMBASE, CENTRAL, Scopus, NLM Gateway (for HIV/AIDS conference abstracts before 2005), Conference on Retroviruses and Opportunistic Infections, International AIDS Conference and International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention from 2005 to 2009, Web of Science Conference Proceedings since 1990, Clinicaltrials.gov and Current Controlled Trials. We contacted researchers and relevant organizations and checked reference lists for all included studies.

Selection criteria
We selected studies that examined routine clinical monitoring, immunological monitoring (CD4 measurement) or virological monitoring (viral load measurement) or examined viral load thresholds to inform switching to second-line regimens. Study types included randomized controlled trials and observational studies.

Data collection and analysis
One author performed initial screening. Two authors performed detailed screening. Two authors independently assessed study eligibility, extracted data and graded methodological quality. A third reviewer resolved differences.

Main findings
A total of nine studies were identified, including seven randomized controlled trials (RCTs) and two observational studies. All seven RCTs (Mermin et al. 2011, Jourdain et al. 2011, Koethe et al. 2011, Babiker et al. 2011, Mugyenyi et al. 2010, Laurent et al. 2011, Saag et al. 2012) were complete, with two available in manuscript form except two studies that were only available as abstracts (Jourdain et al. 2011, Saag et al. 2012). Of the evidence available, the following five designs were identified: clinical versus clinical + immunological; clinical versus clinical + virological; clinical + immunological versus clinical + virological; clinical + immunological versus clinical + virological; and comparisons of one viral load threshold to another viral threshold.

1) Clinical versus clinical + immunological. Two RCTs (Mermin et al. 2011, Mugyenyi et al. 2010) found increased AIDS-defining illness and mortality in routine clinical monitoring compared to immunological monitoring (moderate- to high-quality evidence).

This work was commissioned by the World Health Organization and carried out by The London School of Hygiene & Tropical Medicine
2) **Clinical versus clinical + immunological + virological.** One RCT (Laurent et al. 2011) found no difference between mortality and disease progression between these two groups but found a greater increase in mean CD4 cell count at 24 months in the clinical + immunological + virological study arm (moderate-quality evidence).

3) **Clinical + immunological versus clinical + immunological + virological.** Two RCTs (Mermin et al. 2011, Saag et al. 2012) and one observational study (Keiser et al. 2011) among adults found no difference in clinical and immunological monitoring compared to clinical and immunological and virological monitoring in terms of mortality (moderate-quality evidence) and new AIDS-defining illness (moderate-quality evidence).

4) **Clinical + immunological versus clinical + virological.** An RCT (Jourdain et al. 2011) among adults found no difference in clinical failure (low-quality evidence), switch to second-line regimens (low-quality evidence) and resistance mutations (low-quality evidence).

5) **Viral load threshold comparisons.** One RCT (Babiker et al. 2011) among children found no difference in virological suppression or resistance mutations between children switched at a viral threshold of 1000 copies/ml compared to 30 000 copies/ml (medium). Based on one observational study among children (Siberry et al. 2012), viral load thresholds of 2600 and 30 000 copies/ml predicted WHO Stage 3 or 4 events (low-quality evidence).

**Authors’ conclusions**

- Moderate-quality evidence supports the use of CD4 monitoring compared to routine clinical monitoring among people living with HIV receiving ART.
- Evidence is limited on the additional benefit of viral load monitoring and viral load thresholds among people living with HIV receiving ART.
- No studies on pregnant women were identified, no studies on viral load thresholds among adults and no studies among children comparing viral load and CD4 count monitoring.
- Point-of-care CD4 monitoring feasibility and accuracy are excellent, but point-of-care viral load measurement lags behind CD4 monitoring in feasibility and accuracy.
- Moderate-quality evidence from two randomized controlled trials (Mermin et al. 2011, Mugyenyi et al. 2010) among adults suggests that clinical and immunological monitoring offers mortality and morbidity benefits compared to clinical monitoring alone.
- Moderate-quality evidence from two randomized controlled trials among adults (Mermin et al. 2011, Saag et al. 2012) suggests that there is no difference between clinical + immunological + virological monitoring and clinical + immunological monitoring. Complete data from the one other randomized controlled trial (Jourdain et al. 2011) will help inform the development of appropriate HIV monitoring guidelines.
- Two small studies (Babiker et al. 2011, Siberry et al. 2012) provided low- to medium-quality evidence on which viral load threshold should be used to guide switching to second-line regimens. One randomized controlled trial (Babiker et al. 2011) found no difference in virological suppression or resistance mutations among children switched at a viral threshold of 1000 copies/ml compared to 30 000 copies/ml.
- Further research is needed to create a stronger evidence base for developing HIV monitoring guidelines.
5. Quality assessment

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Key: "+" denotes present in study, "-" denotes absent in study, and "?" denotes unable to assess

6. Bibliography of included studies


