Title: How accurately do the WHO 2010 immunological or clinical criteria predict virological failure in adults and children receiving ART?

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1. PICT question

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>People living with HIV</td>
</tr>
<tr>
<td>I</td>
<td>2010 WHO clinical and immunological criteria*</td>
</tr>
<tr>
<td>C</td>
<td>Other clinical and immunological criteria</td>
</tr>
<tr>
<td>T</td>
<td>Treatment failure</td>
</tr>
</tbody>
</table>

2. Search strategy

PubMed search strategy: Predicting treatment failure

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
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</thead>
<tbody>
<tr>
<td>#5</td>
<td>Search #1 AND #2 AND #3 AND #4</td>
</tr>
<tr>
<td>Search</td>
<td>Query</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>#3</td>
<td>Search (&quot;CD4-Positive T-Lymphocytes&quot;[Mesh] OR CD4[tw]) OR (&quot;Viral Load&quot;[Mesh] OR &quot;viral load&quot;[tw])</td>
</tr>
</tbody>
</table>
3. Flow diagram of screening process

TOTAL RESULTS  
n=3543

DUPLICATES EXCLUDED  
n=816

REFERENCES SCREENED BY ONE AUTHOR  
n=2727

CLEARLY IRRELEVANT REFERENCES EXCLUDED  
n=2299

REFERENCES SCREENED BY TWO AUTHORS  
n=428

REFERENCES EXCLUDED  
n=2299

FULL TEXT REVIEW BY TWO AUTHORS  
n=34

REFERENCES EXCLUDED  
n=16

STUDIES INCLUDED IN REVIEW  
n=18

Adult studies: n=14  
Pediatric studies: n=4

This work was commissioned by the World Health Organization and carried out by The University of California, San Francisco (UCSF), Cochrane Review Group on HIV/AIDS
4. Evidence summaries

4.1. Treatment failure among adults

In 2006, WHO published clinical and immunological criteria for diagnosing treatment failure (WHO 2006). These criteria were:

- a new or recurrent WHO stage 4 condition, which is not immune reconstitution inflammatory syndrome (IRIS) (clinical criterion);
- fall of CD4 count to baseline or below OR 50% fall in CD4 count from on-treatment peak value OR persistent CD4 levels below 100 cells/mm$^3$ in the absence of concomitant infection that can cause a transient CD4 cell count decline (immunological criterion).

In 2010, this definition was expanded to include viral load testing, which is triggered when clinical or immunological criteria are met, with a threshold value of 5000 copies/ml. Thus, the 2010 definition is:

- a new or recurrent WHO stage 4 condition, which is not IRIS;
  OR
- fall of CD4 count to baseline or below OR 50% fall in CD4 count from on-treatment peak value OR persistent CD4 levels below 100 cells/mm$^3$ in the absence of concomitant infection that can cause a transient CD4 cell count decline;
  AND
- plasma viral load >5000 copies/ml.

We identified 25 studies conducted in adults that addressed various aspects of how to define treatment failure. Of these, 14 actually assessed the WHO definition of treatment failure comparing immunological and/or clinical criteria to different plasma viral load levels and provide sufficient data to calculate individual cell sizes. Three studies reported how these criteria predicted a plasma viral load >5000 copies/ml (Labhardt, 2012; Moore, 2009; Reynolds, 2009); one of these provided sufficient data to calculate positive predictive value only (Labhardt, 2012). The overall performance characteristics of the immunological criterion were a sensitivity of 68.8%, a specificity of 92.1%, a positive predictive value of 27.0% and a negative predictive value of 98.6% (of these, only positive predictive value was calculated using data from all three studies). Only one study (Labhardt 2012) reported the performance of clinical criteria and either immunological or clinical criteria. In this study, the clinical criterion had a positive predictive value of 100% (based on a single patient), and either immunological or clinical criteria had a positive predictive value of 51.1%.

Thirteen studies evaluated the clinical and immunological criteria using lower plasma viral load values, ranging from 400 to 1000 copies/ml (Abouyannis, 2011; Chaiwarth, 2007; Hosseinipour, 2011; Kantor, 2009; Labhardt, 2012; Mee, 2006; Mee 2008; Meya, 2009; Moore, 2008; Rawizza, 2011; Rewari, 2010; Reynolds, 2009; van Oosterhout, 2009), and two evaluated a less stringent plasma viral load level of 10 000 copies/ml (Mee, 2008; Rewari 2010). Of those defining virological failure based on plasma viral loads <5000 copies/ml, 12 reported the performance of immunological criteria, seven the performance of clinical criteria and seven the performance of either immunological or clinical criteria (Table 1).

Two studies used a higher plasma viral load (>10 000 copies/ml) to define virological failure (Keiser, 2009; Reynolds, 2009). Comparing WHO immunological criteria, they found a sensitivity of 16.8%, a specificity of 95.5%, a positive predictive value of 15.0% and a negative predictive value of 96.0%.
4.2. Treatment failure among children

Table 1. Ability of WHO immunological and criteria to predict viral failure (plasma viral load 50–1000 copies/ml)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Studies</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological</td>
<td>Abouyannis 2011; Chaiwarth 2007; Kantor 2009; Labhardt 2012; Mee 2006; Mee 2008; Meya 2009; Moore 2008; Rawizza 2011; Rewari 2010; Reynolds 2009; van Oosterhout 2009</td>
<td>55.6%</td>
<td>74.5%</td>
<td>29.8%</td>
<td>89.6%</td>
</tr>
<tr>
<td>Clinical</td>
<td>Chaiwarth 2007; Hosseinipour 2011; Labhardt 2012; Mee 2006; Mee 2008; Rewari 2010; van Oosterhout 2009</td>
<td>54.8%</td>
<td>86.3%</td>
<td>45.2%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Immunological or clinical</td>
<td>Abouyannis 2011; Chaiwarth 2007; Labhardt 2012; Mee 2008; Meya 2009; Rewari 2010; van Oosterhout 2009</td>
<td>75.1%</td>
<td>76.9%</td>
<td>49.4%</td>
<td>91.1%</td>
</tr>
</tbody>
</table>

For 2- to 4-year-old children, WHO defines immunological failure as a CD4 count of <200 cells/mm$^3$ or a CD4 percentage of <10% and <100 cells/mm$^3$ for children ≥5 years old and virological failure as >5000 copies/ml. There are not comparable clear-cut clinical criteria as there are for adults. The guidance reads: “New or recurrent WHO clinical stage 4 conditions may warrant a switch in treatment regimen, although if the CD4 value remains above the age-related thresholds, it may be acceptable to delay switching.” Thus, we evaluated the performance of immunological criteria for predicting virological failure.

We identified nine studies. Four studies compared the 2010 WHO immunological failure criteria with viral load in children. Three studies used >5000 copies/ml to define virological failure (Barlow-Mosha 2012; Davies, 2012; Westley 2012) and evaluated a total of 4100 patients. In combination, these studies found that WHO immunological criteria had a sensitivity of 4.5%, a specificity of 99.2%, a positive predictive value of 54.9% and a negative predictive value of 85.4%. One study evaluated the 2010 criteria using a definition of virological failure of >400 copies/ml (Davies, 2011), evaluating 2256 patients. The investigators found that the immunological criteria had a sensitivity of 6.3%, a specificity of 97.7%, a positive predictive value of 20% and a negative predictive value of 91.8% using the more stringent virological failure criteria.

Table 2 summarizes the results for adults and children.
Table 2. Ability of WHO immunological criteria to predict virological failure, adults and children on antiretroviral therapy, by viral load

<table>
<thead>
<tr>
<th>Population</th>
<th>Viral load</th>
<th>No. of studies</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults &gt;5 000 copies/ml</td>
<td>3</td>
<td>2288</td>
<td>68.9%</td>
<td>92.1%</td>
<td>27.0%</td>
<td>98.6%</td>
<td></td>
</tr>
<tr>
<td>Adults 50–4 999 copies/ml</td>
<td>12</td>
<td>15581</td>
<td>55.6%</td>
<td>74.5%</td>
<td>29.8%</td>
<td>89.6%</td>
<td></td>
</tr>
<tr>
<td>Adults &gt;10 000 copies/ml</td>
<td>2</td>
<td>3142</td>
<td>16.8%</td>
<td>95.5%</td>
<td>15.0%</td>
<td>96.0%</td>
<td></td>
</tr>
<tr>
<td>Children &gt;5 000 copies/ml</td>
<td>3</td>
<td>4100</td>
<td>4.5%</td>
<td>99.3%</td>
<td>54.9%</td>
<td>85.5%</td>
<td></td>
</tr>
<tr>
<td>Children &gt;400 copies/ml</td>
<td>1</td>
<td>2256</td>
<td>6.3%</td>
<td>97.7%</td>
<td>20.0%</td>
<td>91.8%</td>
<td></td>
</tr>
</tbody>
</table>

4.3. References


5. Bibliography of included studies

5.1. Population: adults


5.2. Population: children


6. Excluded studies

6.1. Population: adults


This work was commissioned by the World Health Organization and carried out by The University of California, San Francisco (UCSF), Cochrane Review Group on HIV/AIDS

6.2. Population: children


