Stable patients and patients with advanced disease: consensus definitions to support sustained scale up of antiretroviral therapy

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Abstract

Objective As guidelines are evolving towards recommending starting antiretroviral therapy (ART) in all HIV-positive individuals irrespective of clinical and immunological status, HIV programmes will be challenged to manage an increasingly diverse set of patient needs. To support global guideline recommendations for differentiated service delivery, WHO developed consensus definitions for two distinct patient populations: patients presenting with advanced disease and patients who are stable on ART.

Methods An expert panel consisting of 73 respondents from 28 countries across all six WHO regions supported the development of these definitions. The panel included clinicians, researchers, programme managers, technical advisors and patient group representatives.

Results Patients presenting with advanced disease at presentation to care were defined as CD4 count <200 CD4 cells/mm$^3$ or WHO Stage III & IV defining illness. Patients stable on ART were defined as those who were receiving ART for at least 1 year with no adverse drug reactions requiring regular monitoring, no current illnesses or pregnancy, a good understanding of lifelong adherence, and evidence of treatment success. Treatment success was defined as two consecutive undetectable viral load measures or, in the absence of viral load monitoring, rising CD4 counts or CD4 counts above 200 cells/mm$^3$ and an objective adherence measure.

Conclusions Patients who are stable on ART should be offered a less intensive care package that can lead to improved outcomes while saving resources, including less frequent clinic visits, out-of-clinic drug refills and reduced laboratory monitoring. This will allow for clinic resources to be directed towards reducing morbidity and mortality among patients presenting with advanced disease.

Keywords advanced disease, antiretroviral therapy, differentiated care, stable patients

Introduction

As of the end of 2010, 7.5 million people had started antiretroviral therapy (ART). By mid-2015 this number had doubled to 15 million people [1]. Despite this progress, the majority of people start ART late in their disease progression, with around one in four people in low- and middle-income settings starting ART at CD4 <100 cells/mm$^3$ [2, 3].

As guidelines evolve towards recommending starting ART in all HIV-positive individuals irrespective of clinical and immunological status [4], HIV programmes will be challenged to manage an increasingly diverse set of patient needs. For the growing cohort of individuals who have been on treatment for several years, the need to travel frequently (often every month) to health centres to pick up ART medication when they are clinically well is a leading cause of poor adherence and defaulting from care [5]. At the same time, programmes need to retain capacity to respond to the needs of patients who present with advanced disease and are at heightened risk of severe morbidity and mortality [6].

In response to these diverse needs, WHO and other agencies are promoting approaches to differentiated care, whereby intensity of clinical care is based on individual need, for the benefit of patients, healthcare workers and health systems [7]. To further this approach clear definitions are needed to help identify individuals who may require intensive clinical and laboratory follow-up, and those who are clinically stable on ART and would benefit from less intensive follow-up. While clinical guidelines from high-income settings include definitions of patients presenting late to care [8], the focus of this work was to support implementation of global guideline
recommendations for differentiated service delivery within a public health approach, by developing consensus definitions for two populations with diverse clinical needs: patients presenting with advanced disease and patients who are stable on ART.

Methods

We undertook a Delphi study to seek consensus among experts on definitions for patients presenting with advanced disease and patients who are stable on ART [9]. The Delphi method has been widely used to establish consensus on a range of definitions within the context of health and medical practice [10–12]; advantages include anonymity (avoiding undue influence and bias based on career position), iteration with feedback, and the potential to solicit expert input without geographical constraints [13, 14]. The conduct of this survey followed recommended criteria for reporting Delphi studies [15]. Consensus was sought through a series of iteratively developed questions that were sent to experts who had been invited to participate in the WHO HIV guideline development process; this group were selected because, according to established procedures for WHO guideline development [16], guideline development groups must include representation from all six WHO geographical regions, include representatives from all key stakeholders – health providers, researchers, policy makers, programme managers and people living with HIV – and be balanced with regards to sex. All survey rounds were administered through an online survey.

The Delphi survey questions sought participants’ views on different potential elements of definitions for stable patients and patients presenting with advanced disease, as well as potential key elements of a package of support. The survey questions were guided by the results of a literature review for which Medline (via Pubmed) and EMBASE were searched from inception to 01 March 2015 without language, age, or geographical restriction using terms for HIV, antiretroviral therapy, patient stability and late presentation to care (see Appendix S1).

The qualitative data from the first survey round and the free text from comments in all rounds were thematically analysed to identify key issues and triangulated with the multiple choice questions and other responses. The second round included the addition of quantitative analysis of agreement. Agreement was assessed by individual agreement on each survey question, and the survey was concluded when a majority (defined as >60% agreement) was reached. In round 3, questions from round 2 were repeated together with the summary results of round 2 to provide an opportunity to gather additional comments. Study procedures and qualitative results are summarised in Appendix S1. Participation in this survey was optional, and all results were de-identified, therefore ethics approval was not required.

Results

The survey went through three rounds. The expert panel consisted of 73 respondents representing 28 countries across all six WHO regions (http://www.who.int/about/regions/en/). Respondents included clinicians (19), researchers (29), programme managers (7), technical advisors (12), and patient group representatives (6); participants primary population focus was adults (57 participants), children (13) and adolescents (3). Participants are listed in the Appendix S1.

Patients presenting with advanced disease

The literature review identified 12 articles that provided differing definitions of patients presenting with advanced disease across three broad terms: delayed access to care [17], late presentation [18], and presentation with advanced disease [19]; the latter two terms were used by several reports to differentiate between degree of immune deficiency at presentation [18, 20, 21]. With few exceptions [19], all published definitions were used to describe patient populations in high-income settings (Table 1). Immune status among patients defined as presenting with advanced disease varied widely, from <50 cells/mm³ [22] to <350 mm³ [18] (Table 1).

In the present survey, a majority of respondents favoured the term ‘presenting with advanced disease’, which was considered to be non-judgemental and reflecting the need for clinical action. A single definition was also preferred over multiple definitions because of concern that subdivisions could lead to confusion and add complication. In anticipation of policy shifts towards starting ART irrespective of CD4 cell count, respondents did not recommend that definitions be related to thresholds for initiation of antiretroviral therapy, in contrast to previously proposed definitions [18]. Rather, it was considered important that any definition should imply clinical action. A threshold of 200 cells/mm³ was put forward, consistent with the increased risk of severe opportunistic infections and death below it.

A minimum package of care for patients presenting with advanced disease was suggested, as follows: rapid initiation of ART (once risk of severe IRIS is ruled out); systematic cryptococcus antigen screening (for patients with CD4 <100 cells/mm³ as per WHO guidelines [4]);
<table>
<thead>
<tr>
<th>Publication</th>
<th>Country</th>
<th>Terminology</th>
<th>Definitions used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinori et al. [18]</td>
<td>Europe</td>
<td>Late presentation for treatment &amp; presentation with advanced HIV disease</td>
<td>Late presentation &lt;350 CD4 cells/mm³ or an AIDS-defining event regardless of CD4 cell count</td>
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<tr>
<td></td>
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<td></td>
<td>Advanced disease &lt;200 CD4 cells/mm³ or an AIDS-defining event regardless of CD4 cell count</td>
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<td></td>
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<td></td>
<td>Time period: Presentation to care</td>
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<tr>
<td>d’Arminio Monforte et al. [20]</td>
<td>Italy</td>
<td>Late diagnosis &amp; AIDS presenters</td>
<td>Late presentation ≤350 CD4 cells/mm³ Present with AIDS At baseline</td>
</tr>
<tr>
<td>Dickson et al. [38]</td>
<td>New Zealand</td>
<td>Late presentation &amp; advanced HIV disease</td>
<td>Late presentation &lt;350 CD4 cells/mm³ or an AIDS-defining event regardless of CD4 cell count</td>
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<tr>
<td></td>
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<td></td>
<td>CD4 count &lt;200 cells/mm³ and also includes all who have an AIDS-defining event regardless of CD4 cell count</td>
</tr>
<tr>
<td>de Olalla et al. [39]</td>
<td>Spain</td>
<td>Late presenters</td>
<td>Late presentation &lt;350 CD4 cells/mm³ or with an AIDS-defining event, regardless of the CD4 cell count</td>
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<td></td>
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<td>Time period: Within 3 months of HIV diagnosis</td>
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<tr>
<td>Geng et al. [19]</td>
<td>East Africa</td>
<td>Presentation with advanced disease</td>
<td>Late presentation N/A &lt;50 CD4 cells/mm³ or WHO Stage 4</td>
</tr>
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<td></td>
<td></td>
<td>Time period: Presentation to care</td>
</tr>
<tr>
<td>Jevtovic et al. [40]</td>
<td>Serbia</td>
<td>Late presenters</td>
<td>Late presentation ≤50 CD4 cells/mm³</td>
</tr>
<tr>
<td>Lanoy et al. [17]</td>
<td>France</td>
<td>Delayed access to care (DAC)</td>
<td>Late presentation &lt;200 CD4 cells/mm³ or an AIDS-defining event regardless of CD4 cell count</td>
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<td></td>
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<td>Time period: At initiation of HAART Presentation to care</td>
</tr>
<tr>
<td>Mocroft et al. [41]</td>
<td>Europe</td>
<td>Late presentation</td>
<td>Late presentation &lt;350 CD4 cells/mm³ or an AIDS diagnosis</td>
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<td></td>
<td></td>
<td></td>
<td>Time period: At HIV diagnosis or within 6 months of diagnosis</td>
</tr>
<tr>
<td>Montlahuc et al. [21]</td>
<td>France</td>
<td>Late presentation &amp; advanced HIV disease</td>
<td>Late presentation &lt;350 CD4 cells/mm³ or an AIDS-defining event regardless of CD4 cell count</td>
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<td></td>
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<td>Time period: First entry to database</td>
</tr>
<tr>
<td>Sabin et al. [22]</td>
<td>United Kingdom</td>
<td>Late presenters</td>
<td>Late presentation &lt;350 CD4 cells/mm³</td>
</tr>
<tr>
<td>Wolbers et al. [42]</td>
<td>Switzerland</td>
<td>Delayed diagnosis</td>
<td>Late presentation &lt;50 CD4 cells/mm³ or &lt;200 CD4 cells/mm³</td>
</tr>
<tr>
<td>Zoufaly et al. [43]</td>
<td>Germany</td>
<td>Late diagnosis &amp; late presentation</td>
<td>Late presentation &lt;350 CD4 cells/mm³ or clinical AIDS (a CDC category C event)</td>
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<td></td>
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<td>Time period: First reported HIV test or first contact at treatment centre</td>
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TB screening and isoniazid preventive therapy (if indicated); toxoplasmosis diagnosis and treatment, and co-trimoxazole prophylaxis; and intensive clinical follow-up. It was further emphasised that additional screening, prophylaxis and treatment for severe opportunistic infections would be required according to local HIV epidemiology and resources. For example, a high prevalence of cytomegalovirus retinitis is reported among patients presenting with advanced disease in South East Asia suggesting the value of including routine eye examination for these patients [23].

Finally, some concern was expressed about the use of clinical symptoms alone to identify children who present late for care as children do not show symptoms or clinical signs as rapidly as adults.

### Patients who are stable on ART

No consensus definition has previously been put published for stable patients, although the term has been variously used by clinical trialists to describe virologically suppressed patients who are eligible to switch to alternative regimens [24], clinical guidelines to recommend reduced frequency of laboratory monitoring [25, 26] and programme implementers to refer patients to a less intensive model of ART delivery [27–31] (Table 2). Among

#### Table 2 Published definitions of stable patients

<table>
<thead>
<tr>
<th>Publication</th>
<th>Country/database/ cohort</th>
<th>Terminology</th>
<th>Definitions used</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemelmans et al. [27]</td>
<td>Southern Africa</td>
<td>Clinically stable</td>
<td>Undetectable viral load</td>
<td>Time on treatment (at least 12 months)</td>
</tr>
<tr>
<td>Grimsrud et al. [28]</td>
<td>South Africa</td>
<td>Stable patients</td>
<td>Self-reported adherence, &gt;12 months on ART and viral suppression</td>
<td>No time component to definition</td>
</tr>
<tr>
<td>Hyle et al. [44]</td>
<td>USA</td>
<td>Clinically stable patients</td>
<td>Suppressed viral load</td>
<td>No time component to definition</td>
</tr>
<tr>
<td>Leon et al. [45]</td>
<td>Spain</td>
<td>Stable patients</td>
<td>CD4 &gt;250 cells/mm³ &amp; no OIs</td>
<td>At least three months prior to inclusion in study</td>
</tr>
<tr>
<td>MacLeod et al. [29]</td>
<td>South Africa</td>
<td>Stable visits</td>
<td>Most recent CD4 &gt;75% of previous (if absolute CD4+ value &lt;200 cells/mm³ in the presence of a HIV viral load ≥400 copies/ml) within 12 months &amp; viral load &lt;400 copies/ml &amp; weight change &lt;5% as previous medical visit &amp; not pregnant &amp; no comorbidity &amp; no regimen change within 3 months &amp; normal hemoglobin, ALT, &amp; creatinine clearance</td>
<td>At any clinic visit on ART ≥6 months</td>
</tr>
<tr>
<td>Maselle et al. [33]</td>
<td>Uganda</td>
<td>Stable patients</td>
<td>On ART &amp; Adherence &gt;95% &amp; Karnofsky score &gt;90%</td>
<td>No time component to definition</td>
</tr>
<tr>
<td>O’Connor et al. [30]</td>
<td>South Africa</td>
<td>Stable patients</td>
<td>Clinical progression &amp; improved CD4 count &amp; undetectable viral load &amp; absence of opportunistic infections &amp; good adherence to treatment</td>
<td>&gt;6 months</td>
</tr>
<tr>
<td>Reekie et al. [32]</td>
<td>Europe, Israel, Argentina (EuroSIDA)</td>
<td>Stable and fully suppressed cART regimen</td>
<td>CD4 &gt;200/mm³ &amp; all viral loads &lt;500 copies/ml</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Young et al. [31]</td>
<td>USA</td>
<td>Clinically and immunologically stable ART-treated patients</td>
<td>VL &lt;50 copies/ml for at least 2 years</td>
<td>&gt;2 years on ART</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; OI, opportunistic infection; VL, viral load
the 9 articles reviewed, definitions of stable patients varied in terms of time on ART (6 months \[29\] to 2 years \[31\]) and immune status (200 cells/mm\(^3\) \[32\] to 300 cells/mm\(^3\) \[31\]), and the use of additional criteria such as level of adherence to ART \[33\] (Table 2).

In the present survey, there was unanimous agreement that clinical parameters for treatment success such as undetectable viral load and improved immunologic status should define stability. The need for objective measures of adherence, such as pharmacy refill claims, was emphasised as well as the importance of understanding of lifelong adherence and resistance. Viral load was preferred over immunological criteria as a more reliable measure of both adherence and response to treatment. Finally, consistent with the definition of patients with advanced disease, a single definition was preferred over subdivisions.

To support differentiated care, the latest WHO ART guidelines recommend several service delivery adaptations for stable patients, including less frequent (3–6 monthly) clinic visits and drug dispensing, and stopping CD4 monitoring in settings where viral load monitoring is available \[4\]. These guidelines also summarise different approaches taken by pilot programmes to reduce clinic contact for stable patients and provide adherence and other support outside of the clinic setting, through for example community adherence clubs \[27\].

Consensus definitions for patients presenting with advanced disease and patients who are stable on ART are provided in Panel 1.

**Panel 1 Consensus definitions**

**HIV-positive patients presenting with advanced disease**

The following criteria define individuals presenting with advanced disease at presentation to care:
- CD4 count <200 CD4 cells/mm\(^3\) OR
- WHO Stage III & IV defining illness

**Stable patients on antiretroviral therapy**

The following criteria define stable patients on antiretroviral therapy*:
- Receiving ART for at least 1 year AND
- No adverse drug reactions requiring regular monitoring AND
- No current illnesses or pregnancy AND
- Good understanding of lifelong adherence AND
- Evidence of treatment success: two consecutive undetectable viral load measures (or, in the absence of viral load monitoring, rising CD4 counts or CD4 counts above 200 cells/mm\(^3\) and objective adherence measure)

*Note: Stable, rapidly growing young children may need to be monitored more frequently due to greater risk of disease progression and for treatment dosing/weight changes.

**Discussion**

The first decade of scaling up access to ART in low- and middle-income settings was achieved through a public health framework that emphasised standardised and simplified protocols \[34\]. In order to achieve sustained reductions in incidence and mortality, HIV programmes are encouraged to refine this framework so that clinical service intensity is responsive to needs. Individuals who are stable on ART should be offered a less intensive care package that has been shown to lead to improved outcomes while saving resources through less frequent clinic visits, out-of-clinic drug refills and less frequent laboratory monitoring \[28, 35–37\]. Exceptions to this include young children who may need more frequent monitoring due to increased risk of disease progression and for treatment dosing/weight changes.

Differentiated care is now recommended by WHO as a way to focus programme resources for maximum efficiency. The latest guidelines for delivery of antiretroviral therapy include evidence-based recommendations to reduce the frequency of clinic visits, ART dispensing and intensity of treatment monitoring for patients where are stable on ART \[4\]. The definitions provided by this survey are intended to support the implementation of these recommendations. A number of countries are in the process of implementing differentiated care models, both as pilots and at scale and several ongoing research projects aim to further refine the models of care, for example by integrating care for other chronic diseases. As new experience and evidence accumulates, WHO will revisit the current recommendations for service delivery, including the definitions for stable patients and patients with advanced diseases, to ensure that global guidelines are optimally supportive of country needs.

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References


**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Study Procedure for Delphi Consensus Method.

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