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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/mm³ 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 2 consecutive undetectable viral load measures or, in the absence of viral load monitoring, rising CD4 counts or CD4 counts above 200 cells/mm³ 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

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Introduction

As of the end of 2010, 7.5 million people had started antiretroviral therapy (ART). By mid-2011 this number had doubled to 15 million people.(UNAIDS 2015) 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/mm³ (leDea, Collaborations et al. 2014, Siedner, Ng et al. 2015).

As guidelines evolve towards recommending starting antiretroviral therapy (ART) in all HIV-positive individuals irrespective of clinical and immunological status (WHO 2016), 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. (Shubber, Mills et al. 2016) 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.(Braitstein, Brinkhof et al. 2006)

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.(Duncombe, Rosenblum et al. 2015) 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,(EACS 2015) 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.(Dalkey and Helmer 1963) The Delphi method has been widely used to establish consensus on a range of definitions within the context of health and medical practice;(Via, Hussain et al. 2014, Jorm 2015, Weir, Holmich et al. 2015) 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.(Goodman 1987, Hasson, Keeney et al. 2000) The conduct of this survey followed recommended criteria for reporting Delphi studies.(Diamond, Grant et al. 2014) Consensus was sought through a series of iteratively de-

veloped 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,(WHO 2014) 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 Supplementary Appendix).

The qualitative data from the first survey round and the free text from comments in all rounds were thematically analyzed 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 summarized in *Supplementary Appendix*. 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 *Supplementary Appendix*.

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 (Lanoy, Mary-Krause et al. 2007), late presentation (Antinori, Coenen et al. 2011), and presentation with advanced disease (Geng, Hunt et al. 2011); the latter two terms were used by several reports to differentiate between

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degree of immune deficiency at presentation (Antinori, Coenen et al. 2011, d'Arminio Monforte, Cozzi-Lepri et al. 2011, Montlahuc, Guiguet et al. 2013). With few exceptions (Geng, Hunt et al. 2011), 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 (Sabin, Smith et al. 2004) to <350 mm³ (Antinori, Coenen et al. 2011). (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 (Antinori, Coenen et al. 2011). 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 patient presenting with advanced disease was also defined as follows: rapid initiation of ART (once increase risk of severe IRIS is ruled out); systematic cryptococcus antigen screening (for patients with CD4 <100 cells/mm³ as per WHO guidelines(WHO 2016); TB screening and isoniazid preventive therapy (if indicated); toxoplasmosis infection and cotrimoxazole prophylaxis; and intensive clinical follow-up. It was further emphasized 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.(Ford, Shubber et al. 2013)

Finally, some concern was expressed about the use of clinical symptoms alone to identify children who present late for care as children 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 (Murphy, Berzins et al. 2010), clinical guidelines to recommend reduced frequency of laboratory monitoring (Anon 2015, Anon 2015) and programme implementers to refer patients to a less intensive model of ART delivery (O'Connor, Osih R Fau - Jaffer et al. , MacLeod, Maskew et al. 2013, Bemelmans, Baert et al. 2014, Grimsrud, Sharp et al. 2015,

Young, Hart et al. 2015) (Table 2). Among the 9 articles reviewed, definitions of stable patients varied in terms of time on ART (6 months (MacLeod, Maskew et al. 2013) to 2 years (Young, Hart, et al. 2015) and immune status (200 cells/mm³ (Reekie, Mocroft et al. 2008) to 300 cells/mm³ (Young, Hart et al. 2015)), and the use of additional criteria such as level of adherence to ART (Maselle, Muhanguzi et al. 2014). (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 emphasized as well as the importance of understanding of life-long 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.

In order 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.(WHO 2016) These guidelines also summarize 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.(Bemelmans, Baert et al. 2014)

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

Discussion

The first decade of scaling up access to ART in low- and middle-income settings was achieved through a public health framework that emphasized standardized and simplified protocols (Gilks, Crowley et al. 2006). In order to achieve sustained reductions in incidence and mortality, HIV programmes are encouraged 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 (Luque-Fernandez, Van Cutsem et al. 2013, Koole, Tsui et al. 2014, Ford, Stinson et al. 2015, Grimsrud, Sharp et al. 2015). 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 included evidence-based recommendations to reduce the frequency of clinic visits, ART dispensing, and intensity of treatment monitoring for patients where are stable on ART.(WHO 2016) 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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Table 1: Published Definitions for Late Presentation &/or Advanced Disease

Publication	Country	Terminology	Definitions Used		
			Late Presentation	Advanced Disease	Time Period
Antinori, Coenen et al. 2011	Europe	Late Presentation for Treatment & Presentation with Advanced HIV disease	<350 CD4 cells/mm ³ OR an AIDS-defining event regardless of CD4 cell count	<200 CD4 cells/mm ³ OR an AIDS-defining event regardless of CD4 cell count	Presentation to care
d'Arminio Monforte, Cozzi-Lepri et al. 2011	Italy	Late Diagnosis & AIDS Presenters	≤ 350 CD4 cells/mm ³	Present with AIDS	At Baseline
Dickson, McAllister et al. 2012	New Zealand	Late Presentation & Advanced HIV Disease	<350 CD4 cells/mm ³ OR an AIDS-defining event, regardless of the CD4 count	CD4 count <200 cells/mm ³ and also includes all who have an AIDS defining event regardless of CD4 count	Within 3 months of HIV diagnosis
de Olalla, Manzardo et al. 2011	Spain	Late Presenters	< 350 CD4 cells/mm ³ OR with an AIDS-defining event, regardless of the CD4 cell count.	N/A	Within 3 months of HIV diagnosis
Geng, Hunt et al. 2011	East Africa	Presentation with Advanced Disease	N/A	< 50 CD4 cells/mm ³ OR WHO Stage 4	Presentation to care
Jevtovic, Salemovic et al. 2010	Serbia	Late presenters	≤ 50 CD4 cells/mm ³	N/A	At initiation of HAART
Lanoy, Mary-Krause et al. 2007	France	Delayed Access to Care (DAC)	<200 CD4 cells/mm ³ OR an AIDS-defining event regardless of CD4 cell count	N/A	Presentation to Care
Mocroft, Lundgren et al. 2013	Europe	Late Presentation	<350 CD4 cells/mm ³ OR an AIDS diagnosis	NA	At HIV Diagnosis OR within 6 Months of Diagnosis
Montlahuc, Guiguet et al. 2013	France	Late Presentation & Advanced HIV Disease	<350 CD4 cells/mm ³ OR an AIDS-defining event regardless of CD4 cell count	<200 CD4 cells/mm ³ OR an AIDS-defining event regardless of CD4 cell count	First entry to database
Sabin, Smith et al. 2004	United Kingdom	Late Presenters	< 50 CD4 cells/mm ³	N/A	Presentation to care

Wolbers, Bucher et al. 2008	Switzerland	Delayed Diagnosis	< 50 CD4 cells/mm ³ OR <200 CD4 cells/mm ³	N/A	First cohort visit OR Second cohort visit
Zoufaly, an der Heiden et al. 2012	Germany	Late Diagnosis & Late Presentation	< 350 CD4 cells/mm ³ OR clinical AIDS (a CDC category C event)	N/A	First reported HIV test OR First contact at Treatment Centre

Table 2: Published Definitions of Stable Patients

Publication	Country/Database/Cohort	Terminology	Definitions Used	
			Stable Patients	Time Period
Bemelmans, Baert et al. 2014	Southern Africa	Clinically stable	Undetectable viral load	Time on treatment (at least 12 months)
Grimsrud et al 2015 ¹⁴	South Africa	Stable Patients	Self-reported adherence, >12 months on ART and viral suppression	No time component to definition
Hyle, Sax et al. 2013	USA	Clinically stable patients	Suppressed viral load	None
Leon, Caceres et al. 2011	Spain	Stable Patients	>CD4 250 cells/mm ³ & No OIs	At least the three months prior to inclusion to the study
MacLeod, Maskew et al. 2013	South Africa	Stable Visits	Most recent CD4+ value >75% of previous (if absolute CD4+ value <200 cells/mm ³ in the presence of a HIV viral load ≥400 copies/ml) within 12 months & viral load <400 copies/ml & weight change <5% since previous medical visit & not pregnant & no comorbidity & no regimen change within 3 months & normal hemoglobin, ALT, & creatinine clearance	At any clinic visit on ART ≥ 6 months
Maselle, Muhanguzi et al. 2014	Uganda	Stable patients	On ART & Adherence > 95% & Karnofsky score > 90%	No time component to definition
O'Connor, Osih et al. 2011	South Africa	Stable patients	Clinical progression & improved CD4 count & undetectable viral load & absence of opportunistic in-	>6 months

			fections & good adherence to treat- ment.	
Reekie, Mocroft et al. 2008	Europe, Israel, Argentina (EuroSIDA)	Stable and fully suppressed cART regimen	CD4 cell count >200/mm ³ & all viral loads <500 cop- ies/ml	>1 year
Young, Hart et al. 2015	USA	Clinically and immunologically stable ART- treated patients	VL < 50 copies/mL for at least 2 years	> 2 years on ART

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/mm³ 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: 2 consecutive undetectable viral load measures (or, in the absence of viral load monitoring, rising CD4 counts or CD4 counts above 200 cells/mm³ 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.*