EDITORIAL REVIEW

Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons

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Guidelines for the initiation of combination antiretroviral therapy (cART) in those living with HIV are provided by several national and international treatment guidelines committees. Following recent changes to some of these guidelines, there is now considerable variation between the guidelines in terms of the recommendations for initiation of cART among asymptomatic individuals with high (>350 cells/μl) CD4 cell counts. In this review we compare the schemes used for rating evidence by the various committees and assess the strengths and weaknesses of the available evidence for initiating cART at higher CD4 cell counts.

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Introduction

Due to the rapid development of new pharmaceutical agents, together with exponentially increasing healthcare costs, physicians are increasingly dependent on guidelines for the appropriate management of their patients. However, individual guidelines vary considerably in their methodology and in the weight they give to expert opinion in the absence of data from randomized controlled trials (RCTs). Whilst RCTs usually provide the most rigorous answer to a question, they are not always feasible to conduct for low-incidence or long-term conditions (and, even when they are feasible, they may not have been performed for recently identified issues).

Furthermore, although most guidelines apply a grading system for the level of evidence on which recommendations are made, this often gets lost as a footnote when the guidelines are used in practice.

The optimal CD4 cell count at which an antiretroviral therapy should be initiated in asymptomatic HIV-positive individuals has been an essential question since the first antiretroviral drug was licensed in 1987 [1–4]. When weighing up the risks and benefits for starting treatment, side effects, pill burden, dosing frequency, efficacy and the availability of specific drugs in different countries/settings must all be taken into consideration. Historically, prior to the introduction of combination antiretroviral therapy

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(cART) in 1996, mono-therapy and dual-therapy with nucleoside reverse transcriptase inhibitors (NRTIs) had limited efficacy and some of the drugs themselves were associated with severe toxicities that precluded their long-term use. Toxicities continued to be of concern even after the introduction of drugs from the protease inhibitor and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes, whose potency far exceeded that of NRTI mono-therapy and dual-therapy. These regimens were also complex and difficult to adhere to, leading to development of antiretroviral resistance, which limited subsequent treatment options. Thus, recommendations for the CD4 cell count at which cART should be initiated fluctuated between 200 and 500 cells/µl over time and from country to country.

Antiretroviral drugs in current use generally have improved toxicity profiles and are less demanding on adherence. Simplified regimens based on fixed-dose or single-tablet regimens, available in some settings, may also have promoted improved adherence. The perceived advantages of earlier treatment, the comparable safety of the different drugs, and the availability of new data showing that viral suppression with cART reduces HIV transmission [5], has led several guidelines committees to recommend that the CD4 threshold for initiation of cART should be raised even further (or, indeed, that cART should be universally recommended shortly after diagnosis, regardless of CD4 cell count).

Guidelines for the management and treatment of those living with HIV are provided by several groups, including the WHO [6,7], the US Department of Health and Human Services (DHHS) [8], the International Antiviral Society-USA (IAS-USA) [9], the European AIDS Clinical Society (EACS) [10], and the British HIV Association (BHIVA) [11], as well as several other national groups. Following further revisions to some of these guidelines in 2012 [6,8,9], there is now considerable variation between the different guidelines for this patient population. The objectives of this review are therefore to compare the schemes used for rating evidence by these committees and to assess whether the available evidence is sufficiently strong to support recent changes to recommend earlier initiation of cART.

Treatment guidelines for HIV

A summary of the main treatment guidelines for the initiation of cART in asymptomatic individuals is provided in Table 1. Two of the treatment guidelines committees, the DHHS and IAS-USA committees [8,9], now recommend that cART be initiated in all HIV-positive individuals regardless of the CD4 cell count. For those with a CD4 cell count of 350−500 cells/µl, the DHHS group states that the evidence for this

recommendation is strong and based on data from 'well designed nonrandomized trials or observational cohort studies with long-term clinical outcomes', whereas the IAS-USA group states that there was 'strong support for the recommendation based on evidence from one or more randomized controlled clinical trials published in the peer-reviewed literature'. In contrast, WHO guidelines (developed largely for use within resource-restrained settings and published in 2010) do not recommend the initiation of cART for asymptomatic individuals with a CD4 cell count above 350 cells/µl, unless the individual is in a serodiscordant partnership and wishes to take treatment to prevent transmission to his/her partner [6,7]. It should be noted that even among individuals with a CD4 cell count below 350 cells/µl, the WHO Treatment Guidelines [6] rates the quality of evidence as only 'moderate', whereas the more recent WHO Couples HIV Testing and Counselling Guidelines [7] rate the quality of evidence as 'high', a rating similar to that given by BHIVA [11]. The different calendar periods covered by each set of guidelines, and hence the available literature on which to base any decision, as well as differences in panel membership, may partly explain these discrepancies. The 2011 EACS guidelines [10] recommend that cART be 'considered' (as opposed to 'recommended') in asymptomatic individuals with a CD4 cell count of 350−500 cells/µl (and deferred in those with a count >500 cells/µl) unless, again, the individual is in a serodiscordant partnership and wishes to take it to prevent onward transmission.

Rating schemes used by treatment guidelines committees

Traditionally, treatment guidelines were largely based on expert opinion and reviews of the available evidence. This approach continues to be taken by many guidelines committees, including the DHHS, IAS-USA and EACS groups [8−10]. Members of each group conduct literature reviews to identify relevant new information, synthesize the information obtained and make recommendations which are then voted upon. In general, no details are provided about the approach taken for performing literature reviews or for synthesizing the evidence itself.

One of the criticisms of this approach to guideline development is that the methods (e.g. choice of terms for literature review and the method of evidence synthesis) are not entirely transparent. Information on how the committees balance evidence from different types of studies (e.g. randomized trials versus observational studies) or weigh the different possible outcomes of treatment (e.g. virological suppression rates versus rates of treatment-limiting toxicity) may be lacking. As such, it is

Table 1. Summary of guidelines for the recommendation of when to initiate cART among asymptomatic HIV-positive individuals.

Guidelines committee (reference number); publication date	Use of GRADE	CD4 cell count	Recommendation for treatment	Level of recommendation and strength of evidence (as rated by the guidelines committee)
WHO Couples HIV Testing and Counselling (6); April 2012	Yes	<350 cells/μl	Start treatment	Strong recommendation, high-quality evidence
		>350 cells/μl	Offer treatment if patient is in serodiscordant couple to reduce HIV transmission to uninfected partner	Strong recommendation, high-quality evidence
WHO Treatment Guidelines (7); November 2009	Yes	<350 cells/μl	Start treatment	Strong recommendation, moderate quality evidence
		>350 cells/μl	Do not start treatment, unless patient meets other clinical criteria	Insufficient data to make recommendation
DHHS (8); updated March 2012	No	<350 cells/μl	Start treatment	Strong recommendation, data from randomized controlled trials
		350–500 cells/μl	Start treatment	Strong recommendation, data from well designed nonrandomized trials or observational cohort studies with long-term clinical outcomes
		>500 cells/μl	Start treatment	Moderate recommendation, expert opinion
IAS-USA (9); published July 2012	No	<350 cells/μl	Start treatment	Strong recommendation, evidence from one or more randomized controlled clinical trials published in the peer-reviewed literature
		350–500 cells/μl	Start treatment	Strong recommendation, evidence from one or more randomized controlled clinical trials published in the peer-reviewed literature
		>500 cells/μl	Start treatment	Moderate recommendation, based on the panel's analysis of the accumulated available evidence
EACS (10); October 2011	No	<350 cells/μl 350-500 cells/μl	Start treatment Consider treatment unless patient is in serodiscordant couple and wishes to take treatment to prevent transmission of HIV to partner	Not provided
		>500 cells/μl	Defer treatment unless patient is in serodiscordant couple and wishes to take treatment to prevent transmission of HIV to partner	
BHIVA (11); published August 2012	Yes	<350 cells/μl	Start treatment	Strong recommendation, high-quality evidence from consistent results from well performed randomized controlled trials (RCTs) or over-whelming evidence of some other sort (such as well executed observational studies with consistent strong effects and exclusion of all potential sources of bias)
		>350 cells/μl	Do not start treatment (unless other clinical condition is present or if patient wishes to start ART to reduce the risk of transmission to partners)	Insufficient data to make recommendation

BHIVA, British HIV Association; DHHS, US Department of Health and Human Services; EACS, European AIDS Clinical Society; IAS-USA, International Antiviral Society-USA.

possible for different guidelines committees to make different recommendations on the basis of the same evidence or similar recommendations based on different evidence [12].

In order to adopt a more rigorous approach to the methodology of guideline development, some treatment guidelines committees, including the WHO [6,7] and the BHIVA [11] groups, have switched to using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [13]. This provides a transparent and structured process for developing and presenting summaries of evidence for systematic reviews and treatment guidelines. The GRADE system starts by defining the question of interest using the PICO (patient/intervention/comparator/outcome) approach; a systematic review of the literature relating directly to the question is then performed, and the results of this review then determine the recommendation as well as the strength of evidence for that recommendation. Note that by stating the research question in advance, this approach requires the guidelines groups to define the most important outcome(s) and intervention prior to performing the systematic review, an approach which is somewhat different to traditional models where the evidence (or lack of) largely determines the choice of outcome, intervention and resulting recommendation. Thus, if HIV viral load suppression to levels 50 copies/ml or less is considered to be the most clinically relevant outcome, studies that report only rates of suppression to 400 copies/ml or less or 1000 copies/ml or less would not be viewed as providing direct evidence for the question of interest. Similarly, if the intervention of interest is to initiate cART at a CD4 cell count above 350 cells/μl rather than deferring to a CD4 cell count 350 cells/μl or less, then a study that includes a comparator arm of deferral to a CD4 cell count 250 cells/μl or less would also be seen as providing only indirect evidence for the question, regardless of the quality of that study. GRADE then provides a transparent system for grading the recommendations in terms of the strength of the available evidence; this is based on factors including study design and quality, as well as the consistency of any findings and their directness to the question of interest [13]. The level of evidence is categorized on a four-point scale: high, moderate, low and very low.

Under the GRADE system, evidence from randomized controlled trials is initially rated as being of high quality – the evidence may then be down-rated under several scenarios (likelihood of bias, inconsistent results across studies, indirectness of evidence to the question, imprecision of the synthesized estimate or if publication bias is likely), with the number of down-rating points determined by the potential level of each (e.g. a study with a very serious risk of bias would be down-rated by 2 points on the scale) [14]. In contrast, evidence from observational studies is initially rated as being of low quality due to the high risk of bias with such studies [15]. In some specific circumstances, GRADE permits the up-rating (by 1 or 2 points) of evidence from an observational study – this might occur where the magnitude of the effect size is large (and so it is unlikely that the effect can fully be explained by confounding bias), where there is a clear dose–response gradient, and where all plausible confounders have either been adjusted for, or where they would be expected to act in a direction that would weaken the effect rather than strengthen it [14,15]. On this basis, GRADE is able to distinguish between large, rigorously designed prospective cohorts (which were initiated with the primary aim of addressing this question, and where all attempts have been made to minimise any possibility of bias) and smaller retrospective studies (e.g. case-control studies or post-hoc analyses of existing cohort studies) and/or cross-sectional studies.

The evidence for a benefit of combination antiretroviral therapy at CD4 cell counts of 350–500 cells/μl

Whilst no RCT has, to date, formally addressed the question of whether or not to initiate cART at a CD4 cell count above 350 cells/μl, four large cohort collaborations have published data relevant to the question: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study [16], the When to Start Consortium [17], the Concerted Action on Sero-Conversion to Aids and Death in Europe (CASCADE) Collaboration [18] and the HIV-CAUSAL Collaboration [19]. Table 2 summarizes the key results from these studies for the endpoint of all-cause mortality and the combined endpoint of AIDS/all-cause mortality. All four studies use recently developed statistical methods designed to reduce any impact of selection bias to the extent possible given the data available, with methods generally based on inverse probability weighting, although the implementation of these methods differs across studies. Two key findings can be seen from this table: firstly, the estimates, particularly for the mortality endpoint, vary widely across studies, and more importantly, none of the estimates reported in this table would classify as 'large' according to the GRADE criteria which suggest a minimum effect size of a two to five-fold increase in risk [15].

The potential for confounding is a major limitation with cohort studies that has been well documented. Findings from these studies are based on patients followed over the period 1996–2010; over this period, few patients would have been expected to start cART at CD4 cell counts above 350 cells/μl, and those that did start would be expected to differ from those that deferred in many ways (e.g. their attitudes and beliefs to medication in general

Table 2. Summary of findings from observational studies of deferred vs. immediate initiation of cART.

Study	Comparison	Relative hazard (deferred vs. immediate) (95% confidence interval)	
		AIDS/all-cause mortality	All-cause mortality
NA-ACCORD [16]	<500 vs. >500 cells/μl	n/a	1.94 (1.37, 2.79)
	<350 vs. 351–500 cells/μl	n/a	1.69 (1.26, 2.26)
When to start [17]	351–450 vs. 451–550 cells/μl	0.99 (0.76, 1.29)	0.93 (0.60, 1.44)
	251–350 vs. 351–450 cells/μl	1.28 (1.04, 1.57)	1.13 (0.80, 1.60)
CASCADE Collaboration [18]	<500 vs. 500–799 cells/μl	0.91 (0.56, 1.49)	0.98 (0.47, 2.04)
	<350 vs. 350–499 cells/μl	1.33 (0.88, 2.04)	1.96 (1.25, 3.03)
HIV-CAUSAL [19]	<350 vs. 351–500 cells/μl	1.38 (1.23, 1.56)	1.01 (0.84, 1.22)

cART, combination antiretroviral therapy.

[20], lifestyle factors, including drug and alcohol abuse). Although it could be speculated that those that start cART at higher CD4 cell counts may be those who are sicker (who were, perhaps, prompted to seek care because of their symptoms), a group with a higher underlying mortality risk, it could equally be argued that patients who start cART at higher CD4 cell counts may be those who wish to play a more active role in their own health, who may also exhibit other positive health-seeking or lifestyle behaviours, or who have financial support for the choice of earlier treatment. Thus, the direction of bias induced by confounding in these studies is unpredictable. The size of such bias could also be expected to be substantial [21]. Ultimately, however, whatever the motivation for initiating cART in those with higher CD4 cell counts, this motivation in itself would be expected to affect adherence to cART when it is started. This would question the generalizability of the findings from these studies to a wider population that has no such motivation for starting cART.

All cohorts contributing to these collaborations are well executed studies; however, none of them was designed to answer the question of when to initiate cART. Thus, the information required to eliminate possible confounding, as well as other sources of bias (e.g. loss-to-follow-up), is unlikely to be complete. More importantly, these cohorts were set up at a time when the primary interest of study investigators was the progression of HIV disease; information on any potential 'harms' of treatment, other than those that lead to death, are unlikely to have been captured. Although antiretroviral drugs have become increasingly safe over time, they are not without harms, with many potential toxicities reported. For example, an increasing body of literature has suggested associations with particular antiretroviral drugs and the development of cardiovascular disease [22], between the use of tenofovir, renal impairment and reduced bone mineral density [23], and between the use of efavirenz and central nervous system disorders leading, in some, to depression and suicide attempts [5,24]. This is of particular relevance to the question of initiation of cART at CD4 cell counts above 350 cells/μl, where any small incremental benefit of earlier cART in terms of HIV outcomes (the risk of HIV progression is very low at this level) may be more than outweighed by even a small increase in some of these events in otherwise healthy individuals. The Strategies for Management of AntiRetroviral Therapy (SMART) study [25] provided the first compelling evidence that some of the events previously considered to be unrelated to HIV infection (e.g. cardiovascular, renal, hepatic disease and non-AIDS cancers) may actually be associated with HIV. Thus, even if these events are captured, it is unlikely that standardized case definitions will have been used consistently. Indeed, whilst many cohorts now attempt to capture detailed information on important non-AIDS clinical outcomes, a survey of 90 HIV cohort studies from Europe and the US conducted in 2007 reported that a third did not capture information on serious non-AIDS clinical events, coding systems varied from cohort to cohort, and only 28% performed any review of these endpoints (B. Ledergerber, personal communication). Thus, high-quality information on the potential harms of treatment, other than death itself, is unlikely to be available. Furthermore, information on potential risk factors for non-AIDS events (i.e. potential confounders) is rarely captured.

Other evidence for a possible benefit of earlier combination antiretroviral therapy

In addition to the evidence for a potential benefit of cART in those with higher CD4 cell counts as reviewed above, several of the guidelines groups have also based their decision on two additional factors: the findings from some studies that individuals with uncontrolled viraemia have a higher risk of clinical events (AIDS and non-AIDS-related) than individuals with controlled viraemia [26,27], and that an individual's nadir CD4 cell count (his/her lowest reported CD4 cell count) appears to be predictive of subsequent clinical outcomes (again AIDS and non-AIDS-related) [28–34]. However, as will be shown below, this evidence would likely be down-rated under the GRADE system for indirectness, inconsistency and the strong potential for bias.

For example, whilst Mugavero et al. [26] reported a strong association between the cumulative exposure to viraemia, measured on cART, and an individual's risk of mortality, a higher level of cumulative exposure to viraemia in this setting was essentially driven by patients who experienced viral rebound or blips on cART, or who interrupted cART for other reasons – lifestyle and behavioural confounders may therefore introduce bias into these analyses. Furthermore, the population of patients included in the study (on cART with a median CD4 cell count of 222 cells/μl at study entry) differs to that of particular interest for guidelines committees (i.e. untreated individuals with a CD4 cell count >350 cells/μl). Finally, results from at least one other observational study do not support the finding of a strong association between the latest viral load and the onset of serious non-AIDS events (non-AIDS malignancies, cardiovascular disease and hepatic/liver events) [27]. Thus, under the GRADE approach, this evidence would also be down-rated for indirectness, inconsistency and the potential for bias.

Many studies have reported associations between the nadir CD4 cell count and either AIDS or non-AIDS clinical events [28–34]. For many of these studies, however, a strong association between the nadir CD4 cell count and outcome in univariate analysis is weakened substantially (or becomes non-existent) after adjustment for the current CD4 cell count, suggesting that an individual's risk of an event is determined more by their current CD4 cell count than their past CD4 history [28–31,33]. When an association is found with the nadir CD4 cell count, this association is generally only found in those with the lowest nadirs (i.e. <200 cells/μl), a population again divergent from the one being discussed. Thus, as before, this evidence would be down-rated for indirectness, inconsistency and the potential for bias. Although it is true that individuals with low pre-cART CD4 cell counts are less likely to attain a high CD4 cell count on cART [35], this is also generally only of clinical relevance to those with the lowest pre-cART nadirs (<200 cells/μl), again a population divergent from the one being discussed. Furthermore, even if there remains a small residual risk of these events in those with higher nadir counts, this risk is likely to be small and may well be outweighed by any detrimental effects of cART.

Combination antiretroviral therapy as a means to prevent onward HIV transmission

Results from the HIV Prevention Trials Network (HPTN) 052 trial [5], a randomized controlled trial in which HIV-positive persons in serodiscordant partnerships were randomized to receive either early (CD4 between 350 and 550 cells/μl) or deferred (CD4 <250 cells/μl) cART, provide strong evidence of a benefit of earlier treatment for the prevention of new HIV infections among HIV-negative partners. In addition to the primary prevention endpoint, the trial also included a co-primary clinical endpoint that considered progression to any serious HIV-related event or death. The authors initially reported 40 progression events among those initiating cART early compared to 65 events in the group deferring cART, a 41% reduction in the hazard of progression. An analysis with further follow-up no longer found a difference for the co-primary clinical outcome, but reported more AIDS events in the deferred group [36]. Of note, the difference in AIDS events was largely driven by a higher rate of extra-pulmonary tuberculosis (reported from a single clinical site), with no difference in rates of pulmonary tuberculosis; rates of other AIDS events (e.g. bacterial infections) were non-significantly higher in the immediate treatment group.

But do these data contribute to the current discussion of whether to initiate cART at CD4 cell counts higher than 350 cells/μl? Despite the fact that patients were allocated to the treatment groups at random (and hence the results of the study are unlikely to be affected by confounding), patients in the deferral arm of the trial did not receive cART until their CD4 cell counts had fallen to below 250 cells/μl (the median CD4 cell count at the time of initiation of cART in the deferred group was 234 cells/μl) – thus the intervention here differs from that of interest (deferral to <350 cells/μl) and so this evidence is indirect to the question of interest. Importantly, it is well documented that there is an excess risk of AIDS, death and various non-AIDS events among individuals who defer cART to such low levels (e.g. the treatment interruption group in SMART who initiated cART at a similar level [25]) and all existing guidelines are consistent in recommending cART at this level. Furthermore, as the HPTN 052 trial was not placebo-controlled, it is difficult to rule out the possibility that bias may have been introduced by an individual's knowledge of his/her randomized strategy.

Summary

Current treatment guidelines for HIV infection are derived using a variety of different approaches. Those that use the GRADE system do not generally recommend the initiation of cART for asymptomatic individuals with a CD4 cell count above 350 cells/μl, unless the individual wishes to take cART to prevent onward transmission. The evidence to support the earlier initiation of cART derives from observational studies (with potential for significant bias). The findings from these studies are often inconsistent, the evidence may be indirect to the question of interest, and the observational studies may fail to capture all important outcomes. This should question a decision to rate revised recommendations as based on

strong evidence. Use of more stringent criteria, such as those proposed by the GRADE approach, would likely reach the conclusion that the evidence is insufficient to make firm recommendations.

Whilst there is robust data to demonstrate that among those with symptomatic infection, or those with a CD4 cell count below 350 cells/μl, the net effect of cART is beneficial to both the individual and the population, this is not the case for asymptomatic patients with higher CD4 cell counts, as demonstrated by the differences in recommendations made by the various committees. The question of the optimal time to initiate ART requires data from prospective RCTs – results from the ongoing Strategic Timing of AntiRetroviral Treatment (START) trial, initiated in 2009 in response to the paucity of robust data on the relative benefits and disadvantages of cART at any CD4 cell count above 500 cells/μl compared to waiting until the CD4 cell count falls below 350 cells/μl, are expected in 2016 [37]. The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) 12136 TEMPRANO trial (ClinicalTrials.gov ID: NCT00495651), conducted in Cote d'Ivoire and due to complete in September 2014, will also provide randomized evidence for this question. However, whilst both trials will produce definitive evidence for initiating (or not) cART in asymptomatic individuals with CD4 cell counts above 350 cells/μl, the accumulating evidence from different studies (and in the absence of data on any 'harms' of earlier cART), means that many clinicians feel uncomfortable about allowing their patients to remain off treatment with uncontrolled HIV viraemia (particularly when putting the expected additional few years of treatment into the context of a life–long cART regimen). Furthermore, the potential impact of earlier cART as a prevention tool increases the view of some that cART should be initiated early, regardless of what the trials will ultimately show, placing public health arguments for earlier initiation of cART on an equal footing as arguments relating to individual benefits. Of note, a past history of reversals of established medical practices [38] serves as a helpful reminder that treatment guidelines based on less robust data may not always lead to benefits for patients; robust evidence from RCTs relating to both the benefits and harms of treatment is essential when weighing up the public and individual arguments for earlier treatment.

In summary, we believe that the limitations of the existing data make it premature to recommend earlier initiation of cART for an individual's own health based on the available data on the risk of disease progression or death over the short or medium term. Currently, the evidence for supporting earlier treatment remains firmly grounded by the limitations of expert opinion. Most importantly, it must be recognized that our comments within this article refer to guidelines for initiation of cART that will be applied at a population level – the decision to start cART within any particular individual must always be based on that individual's readiness and willingness to start.

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