Title: How have guidelines on when to start ART affected survival of people living with HIV infection?

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Abstract

Purpose of review:

Until recently, conflicting data led to discrepancies in guideline recommendation on 'when to start' antiretroviral therapy in asymptomatic HIV infection. This review focuses on evidence underpinning guidelines over the past decade and recent RCT data in this area which definitively informed the debate.

Recent findings:

In 2015, the landmark START trial demonstrated clear clinical benefit in terms of a reduction in serious AIDS and non AIDS related events and death from any cause in HIV-positive individuals randomised to start ART with a CD4 count >500 cells/μL compared to deferring starting until CD4 count declined to 350 cells/μL. Further RCT data was also available from the Temprano trial in Côte D'Ivoire which also demonstrated a reduced risk of death associated with earlier ART initiation.

Summary:

Following the results of the START trial, guidelines that had previously set CD4 thresholds for treatment initiation were universally changed. This is likely to reduce mortality in people living with HIV who are diagnosed early and have immediate access to ART. However unless HIV testing rates and ART coverage are increased globally, raising the threshold for initiation of ART in clinical guidelines may be of limited benefit in reducing mortality in HIV.

Introduction

Until 2015, conflicting data mainly from observation studies led to discrepancies in guideline panel recommendations on 'when to start' antiretroviral therapy (ART) in asymptomatic HIV infection. This review focuses on the evidence underpinning guidelines over the past decade, recent RCT data which definitively informed the debate on when to start ART as well as other factors such as testing rates that may impact on affected survival of people living with HIV infection despite guideline recommendations on treatment thresholds.

History of guideline development and when to start

Untreated HIV-infection causes progressive CD4 depletion and an increasing risk of AIDS-defining illnesses and death. Although many antiretroviral drugs are associated with adverse events, there is now irrefutable evidence that at lower CD4 counts the benefits of antiretroviral therapy (ART) far outweigh any risks of treatment. Until recently, however, there was no clear consensus regarding precisely when (i.e. at what CD4 count) an HIV-positive person should start ART. This lack of consensus was reflected in considerable variation between 'when to start' guidelines. For example, the European AIDS Clinical Society (EACS) guidelines from as recently as 2012 recommended commencement of ART in individuals who had a CD4 count below 350 cells/μL, consideration of ART in asymptomatic individuals who had a CD4 count between 350-500 cells/μL and deferral of ART among individuals with CD4 counts >500 cells/μL [1]. Similar recommendations (at similar CD4 thresholds) were made in the UK 2012 British HIV Association (BHIVA) guidelines [2]. However from July 2012, World Health Organization (WHO) guidelines, developed primarily for resource-poor settings, recommended starting ART at a threshold of 500 CD4 cells/μL [3] and subsequently the 2014 EACS guidelines recommended considering starting ART in individuals with a CD4 count >500 cells/μL [4].

In the US however, the Department of Health and Human Services (DHHS) [5], and the International AIDS Society-USA (IAS-USA) [6] guidelines were both changed in 2012 to recommend that ART be initiated in all people with HIV, regardless of CD4 count. This change in US guidelines to start ART at higher CD4 counts was based on evidence from observational studies in particular the North American AIDS Cohort Collaboration on Research and Design (NA-ACCCORD) research cohort [7] and trials without a clinical

endpoint such as the set point study [8]; these changes in recommendations were, at the time, controversial [9] as observational studies could not fully adjust for the potentially strong effects of all potential confounders. In light of the changes to the US guidelines, the UK BHIVA guidelines group reviewed the available evidence in 2013 and issued updated guidelines with the unchanged recommendation to start ART at a CD4 count of 350 cells/µL stating that this was based on the lack of data available from any randomised clinical trial with a suitable comparator arm that demonstrated that the individual benefits of ART outweighed any risks. [10]

However even within those guidelines, such as those from EACS and BHIVA, which carried general recommendations not to start ART in all people with HIV at higher CD4 counts, commencement of ART was recommended for certain groups of people with HIV including: those with hepatitis B and hepatitis C virus confections, those with any AIDs defining condition, pregnant women, patients needing immunosuppressive treatments for cancer, and also those with some HIV-related conditions including neurocognitive disorders, thrombocytopenia and HIV-associated nephropathy [2,4]

Treatment as Prevention

The potential individual clinical benefit of earlier treatment was not the only factor influencing the debate regarding when people diagnosed with HIV should start ART. There was increasing recognition that early ART also had the potential to reduce onward transmission of HIV. A number of observational studies had reported that people on ART with a suppressed viral load have markedly reduced infectiousness [11-13]. The first randomised evidence however came from the HIV Prevention Trials Network (HPTN) 052 Trial, which prospectively evaluated the effect of ART on prevention of HIV transmission to HIV negative heterosexual partners [14]. This study reported a 96% reduction in transmissions of HIV in serodifferent couples with a CD4 count of 350-550 cells/µL at entry who were assigned to the early ART arm compared to those in whom ART was deferred to a CD4 count <250 cells/µL; this protective effect persisted [15]. The results of this landmark trial dramatically increased interest in the use of ART for prevention and European, WHO and US treatment guidelines were revised to recommend that clinicians provide an explanation to all HIV-positive individuals of the beneficial effect of ART on infectiousness, with the offer of ART to anyone who wants to take it to reduce transmission risk, regardless of CD4 count [4, 16,17]. Data on transmission risk through anal sex in the context of

suppressive ART was provided through the PARTNER observational study. This study followed serodifferent heterosexual and men having sex with men (MSM) couples in which the HIV-positive partner was using suppressive ART and who reported condomless sex. Over a median follow-up of 1238 total couple-years-follow-up, the investigators found no documented cases of within-couple HIV transmission [18, JAMA in press].

Evidence informing the 'when to start' question

Initial evidence informing the 'when to start' question and the potential mortality benefits of ART initiation at higher CD4 counts came from observational cohort data from North American and European cohort collaborations. However these collaborations reported conflicting results. The NA-ACCCORD research group evaluated data from 22 research cohorts in the US and Canada to simulate a randomized strategy trial of early versus deferred therapy comparing all-cause mortality among those who started ART with a CD4 count >500 cells/μL and those who started within 1.5 years of their CD4 count falling to <500 cells/μL [7]. Deferral of therapy until the CD4 count fell <500 cells/μL was associated with a statistically significant 60% increase in the hazard of death, although there were inevitable concerns about confounding as with all cohort data. However these data strongly influenced the US guidelines in 2012 to recommend starting ART at any CD4 count.

The findings of the European led groups were perhaps not surprisingly different given the different study designs and different populations studied. The Antiretroviral Therapy Cohort Collaboration (ART-CC) analysis of 18 cohorts which accounted for lead time and unseen AIDS and death events prior to treatment initiation, reported that at progressively lower CD4 thresholds for starting ART, the risk of AIDS or death increased and that delaying ART to <350 (but not <375) cells/μL was associated with an increased risk of AIDS or death [19]. The HIV-CAUSAL collaboration used prospective observational data and dynamic marginal structural models to compare ART initiation strategies for CD4 thresholds between 200 and 500 cells/μL, and reported that whilst initiation of ART at a CD4 threshold of 500 cells/μL increased AIDS-free survival, mortality did not vary substantially if ART was initiated between 300 and 500 cells/μL [20]

A more recent analysis examined the impact of CD4 count at ART initiation on longer-term mortality after starting ART using ART-CC cohort data [21]. The analysis found a clear increase in cumulative 15 year mortality with ART initiation at decreasing CD4 counts, from 7.1% with initiation at >500 cells/μL increasing to 10.6% with initiation at <50 cells/μL. The

inverse association of CD4 count at ART initiation with mortality was strongest during the first year after ART initiation, but subsequently reduced over the next 4 years so that from 5 years after initiation of ART even those who had initiated with very low baseline CD4 values had similar mortality risk to those who initiated ART at intermediate or high CD4 counts.

The evidence for potential individual clinical benefit of earlier treatment came from three trials which randomized people with a CD4 cell count >350 cells/μL to start ART or to defer treatment. The first of the trials which reported evidence to inform the 'when to start' debate was the HPTN 052 study which randomized individuals to start ART when their CD4 count was between 350-500 cells/μL (early therapy) or when their CD4 counts had fallen below 250 cells/μL or when symptoms developed (delayed therapy). A relative reduction of 41% was reported in the number of HIV-related clinical events in the early ART group and this was largely due to reduced incidence of extra-pulmonary tuberculosis in this group. However those in the delayed comparator arm started treatment at a significantly lower CD4 cell counts than recommended in any guidelines since 2008. [14,22]

The second trial, the ANRS 12136 Temprano trial [23], recruited 1600 participants in Côte D'Ivoire and presented results in early 2015. This study randomized HIV-positive people with a CD4 cell count <800 cells/μL to immediate ART or to receipt of ART in accordance with WHO criteria for initiation of therapy. However the WHO criteria changed several times over the course of the trial from <200 cells/μL (Mar to Dec 2009) to <350 cells/μL (Dec 2009 to Jul 2012) and then to <500 cells/μL (Jul 2012 to Dec 2014). Again, while the trial results demonstrated a reduced risk of death associated with earlier ART initiation this was against a comparator of <200 cells/μL for much of the follow-up time which was a much lower level than would be considered clinically acceptable in published guidelines.

The pivotal evidence informing when to initiate ART in people with asymptomatic HIV infection came from the Strategic Timing of Antiretroviral Treatment (START) trial [24]. In START, HIV-positive individuals with a CD4 count >500 cells/μL were randomized to immediate ART initiation or deferral until their CD4 count declined to 350 cells/μL. In May 2015 the trial Data Safety and Monitoring Board (DSMB) recommended on the basis of an interim analysis that all participants be offered ART as immediate initiation of therapy was associated with clear clinical benefit in terms of a reduction in the incidence of serious AIDS-related, serious non-AIDS-related events and death from any cause compared to deferring ART until the CD4 count declined to <350 cells/μL. A total of 86 events occurred among

those randomised to the deferred ART arm, whereas 41 events occurred among those starting ART immediately, representing a 57% reduction among those treated early; notably, this overall reduction included a reduction in tuberculosis, lymphoma and Kaposi's Sarcoma. In both groups, most events occurred when CD4 counts were higher than 500 cells/μL.

Following the results of the START trial, guidelines that had previously set CD4 thresholds for treatment initiation were universally changed, with the WHO guidelines in September 2015 recommending that ART should be initiated in all adults living with HIV at any CD4 cell count [25] (though with priority given to treating people with severe or advanced HIV clinical disease or a CD4 count ≤350 cells/μL) and the BHIVA and EACS guidelines following suit shortly afterwards [26,27].

Impact of other factors on survival of people living with HIV

With the evidence now clear for the mortality benefits of ART initiation at higher CD4 counts, the reality is that ART roll-out to all those in need of HIV treatment remains far from complete, particularly in countries with a high HIV burden. Only 41% of all people with HIV were on ART by March 2015 [25] and the median CD4 count at ART initiation, although increasing, remains lower than a threshold of 350 cells/μL in both low and high-income settings. [28,29]

The reasons for this are multiple and complex, but HIV testing rates remain too low. It is widely acknowledged that the biggest obstacle to meeting the UNAIDS 90-90-90 global targets by 2020 (90% knowing their HIV status, 90% with diagnosed HIV infection on ART and 90% on ART achieving virological suppression) remains the high proportion of people living with HIV who remain undiagnosed. Globally, 47% of people living with HIV remain undiagnosed and often present only when their CD4 cell counts have fallen to a level where immune systems are badly damaged and clinical complications have arisen [30]. In a study of late presenters in Europe, those who presented with a CD4 cell count of <350 cells/μL or an AIDS diagnosis within 6 months of HIV diagnosis had over a 10-fold increased risk of dying within a year of diagnosis, compared to those diagnosed earlier [31]

Testing rates remain less than recommended even among groups at risk in resource-rich settings with 25% of MSM in the UK never having tested for HIV [32]. In addition very few

MSM meet the recommended frequency of testing, with only 55% testing every year and only 27% of those considered at high risk (defined as having a new condomless sex partner in the last 3 months or a diagnosis of an STI) testing every 3 months [33]. Testing frequency in people of Black African ethnicity in the UK who are at increased risk of presenting late with HIV is also low with an estimated 39% to 57% having never been tested. [34]

In addition, the success of ART is highly dependent on readiness to start and motivation to adhere to treatment. Trial participants are a selected group who necessarily must agree in principle to randomisation to early treatment, and may well have a preference for early ART, and/or a high motivation to adhere to ART. The prospect of what may be perceived as a slight health gain set against the potential negative impact on quality-of-life of long-term ART may reduce the incentive of some people to start ART at high CD4 counts and individual preferences and concerns need to be taken into account [35].

Summary

The clinical benefits of starting ART at higher CD4 thresholds on mortality have been clearly demonstrated in a clinical trial setting, and there may in fact be even greater long-term survival benefits of earlier ART which only become apparent after many years of treatment. However, unless HIV testing rates and ART coverage are increased globally with diagnosis and initiation of ART early in the clinical course of HIV infection before the immune system is damaged, raising the threshold for initiation of ART in clinical guidelines may be of limited benefit in reducing mortality in HIV.

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Conflicts of interest

The authors have no conflicts of interest.

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

References

1. http://europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1-2edition.pdf (accessed 14th May 2016).
2. Williams I, Churchill D, Anderson J, et al (2012). British HIV Association Guidelines for the Treatment of HIV-1-positive adults with antiretroviral therapy 2012. HIV Med 13 (Suppl 2):1–85.
3. Hirnschall G, Harries AD, Easterbrook PJ, et al (2013). The next generation of the World Health Organization's global antiretroviral guidance. J Int AIDS 30;16:18757
4. http://www.eacsociety.org/files/guidelines-7.1-english.pdf (accessed 14th May 2016).
5. US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Updated Febuary 2013. https://aidsinfo.nih.gov/contentfiles/adultandadolescentgl003371.pdf (downloaded 14th May 2016).
6. Thompson MA, Aberg JA, Hoy JF, et al (2012). Antiretroviral treatment of adult HIV infection. 2012 Recommendations of the International Antiviral Society – USA Panel. JAMA 308:387–402.
7. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009; 360(18):1815–1826.
8. Hogan CM, Degruttola V, Sun X, et al. The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. *J Infect Dis*. 2012;205(1):87-96.
9. Sabin C, Cooper D, Collins S, et al (2013). Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons. AIDS. 27(12):1839-46
10. British HIV Association (BHIVA) guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012 (updated November 2013). http://www.bhiva.org/HIV-1-treatment-guidelines-2012.aspx

11. Quinn TC, Wawer MD, Sewankambo N, et al (2000). Viral load and heterosexual transmission of HIV type 1. N Engl J Med 342:921–929.
12. Donnell D, Baeten JM, Kiarie J, et al (2010). Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet 375:2092–2098.
13. Attia S, Egger M, Müller M, et al (2009). Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS 23:1397–1404.
14. Cohen MS, Chen YQ, McCauley M, et al (2011). Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 365:493–505.
15. Safren SA1, Mayer KH, Ou SS, McCauley M, Grinsztejn B, Hosseinipour MC, Kumarasamy N, Gamble T, Hoffman I, Celentano D, Chen YQ, Cohen MS; HPTN 052 Study Team. Adherence to Early Antiretroviral Therapy: Results From HPTN 052, a Phase III, Multinational Randomized Trial of ART to Prevent HIV-1 Sexual Transmission in Serodiscordant Couples. J Acquir Immune Defic Syndr. 2015 Jun 1;69(2):234-40. NEED ANOTHER REF ?CROI
16. World Health Organization. Guidance on Couples HIV Testing and Counseling, including antiretroviral therapy for treatment and prevention in serodiscordant couples. Recommendations for a public health approach. 2012. http://www.who.int/hiv/pub/guidelines/9789241501972/en/ (downloaded 14th November 2013).
17. Department of Health. BHIVA and EAGA position statement on the use of antiretroviral therapy to reduce HIV transmission. https://www.gov.uk/government/publications/bhiva-and-eaga-position-statement-on-the-use-of-antiretroviral-therapy-to-reduce-hiv-transmission (downloaded 14th November 2013).
18. *Rodger AJ, Cambiano V, Bruun T et al for the PARTNER Study Group. Association between sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. In press, JAMA
19. Sterne JA, May M, et al. When To Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: A collaborative analysis of 18 HIV cohort studies. Lancet. 2009; 373(9672):1352–1363.

20. Cain LE, Logan R, et al. HIV-CAUSAL Collaboration. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: An observational study. Ann Intern Med. 2011; 154(8):509–515.
21. **May MT, Vehreschild JJ, Trickey A, et al for the Antiretroviral Therapy Cohort Collaboration (ART-CC). Mortality According to CD4 Count at Start of Combination Antiretroviral Therapy Among HIV-infected Patients Followed for up to 15 Years After Start of Treatment: Collaborative Cohort Study. Clin Infect Dis. 2016 Mar 2
22. *Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis 2014; 14: 281-90.
23. **TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D et al. Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22. doi: 10.1056/NEJMoa1507198. Epub 2015 Jul 20.
24. **INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, et al Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795-807
25. *World Health Organization (WHO). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV, September 2015. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en (web page)
26. European AIDS Clinical Society (EACS) Guidelines for clinical management and treatment of HIV positive persons (2015). http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf
27. British HIV Association (BHIVA) guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy (2015) http://www.bhiva.org/HIV-1-treatment-guidelines.aspx
28. Avila D, Althoff KN, Mugglin C, et al; IeDEA, ART Cohort Collaborations;. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle , and high-income countries. J Acquir Immune Defic Syndr 2014;65:e8-16.
29. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013. Clin Infect Dis 2015;60:1120-7.

30. UNAIDS. 90-90-90: An Ambitious Treatment Target To Help End the AIDS Epidemic. UNAIDS, 2014. Available at: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf
31. Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med 2013;10:e1001510
32. Skingsley A, Yin Z, Kirwan P et al. HIV in the UK – Situation Report 2015: data to end 2014. November 2015. Public Health England, London. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477702/HIV_in_the_UK_2015_report.pdf
33. McDaid LM, Aghaizu A, Frankis J et al. Frequency of HIV testing among gay and bisexual men in the UK: implications for HIV prevention. HIV Med. 2016 Mar 15. doi: 10.1111/hiv.12373.
34. Sadler KE, McGarrigle CA, Elam G, Ssanyu-Sseruma W, Davidson O, Nichols T, Mercey D, Parry JV, Fenton KA. Sexual behaviour and HIV infection in black-Africans in England: results from the Mayisha II survey of sexual attitudes and lifestyles. Sex Transm Infect. 2007;83(7):523-9.
35. Rodger AJ, Phillips A, Speakman A, et al for the ASTRA (Antiretrovirals, Sexual Transmission Risk and Attitudes) Study Group. Attitudes of people in the UK with HIV who Are Antiretroviral (ART) Naïve to starting ART at high CD4 counts for potential health benefit or to prevent HIV transmission. PLoS One. 2014 May 28;9(5):e97340