Community views: balancing the public health benefits of earlier antiretroviral treatment with the implications for individual patients – perspectives from the community

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Purpose of review
When should people with HIV start treatment? This question is widely debated. The recent momentum to initiate treatment at a CD4 cell count above 350 cells/mm^3 is driven by the potential population benefits of antiretroviral treatment reducing infectiousness together with operational concerns. These are important. However, we focus on the clinical benefits and risks for the person taking treatment, and how this may vary depending on the background health setting.

Recent findings
We refer to the recent guideline changes and the limited evidence on which they are based. Many studies that have informed guideline changes reference plausible benefits, but have limited follow-up and are not designed to assess the potential risks. We note historical examples to show that expert opinion in the absence of data warrants caution.

Summary
Results from well powered studies designed to look at the question of when to start treatment are essential for quantifying the benefits and risks of earlier treatment. Meanwhile, the decision of when to start must be taken by the HIV-positive person in consultation with their health worker based on accurate information. That choice will vary depending on a person's individual health, their reason to want to treat and the resources of the health-care facility.

Keywords
community, HIV positive, risk:benefit ratio, when to start HIV treatment

INTRODUCTION

The last few years have seen an unprecedented focus on the CD4 threshold for starting antiretroviral treatment (ART). The move to a higher threshold has been largely driven by the improvements in treatment that make it safer to treat in earlier infection. The risk:benefit ratio for starting treatment at a higher CD4 cell count, therefore, varies in relation to treatment options available. However, whether the low absolute risks at higher CD4 cell counts are balanced by potential disadvantages of early treatment are only likely to be known following the results from randomized trials that are currently ongoing including the Strategic Timing of Anti-Retroviral Treatment (START) and TEMPRANO studies [1▪▪,2▪▪].

Earlier treatment is also driven by the hypothesis that HIV replication, even at higher CD4 cell counts, may contribute to an increased risk of serious complications that are not traditionally linked to HIV, mediated by increased immune activation and inflammation [3▪▪,4▪,5▪]. Even though the absolute risks for these events are low for many people in the short-term, the relative risks for cardiovascular, hepatic and renal complications and for some cancers are higher for those who are HIV positive, as a group, compared with the background

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KEY POINTS

- The move to earlier treatment in treatment guidelines is strongly influenced by the potential benefit to reduce HIV transmission.
- Data supporting clinical benefits at higher CD4 cell counts are limited.
- Benefits from earlier treatment may not always outweigh risks and are dependent on the treatment options and other healthcare factors.
- In some resource-limited settings, the risk:benefit ratio may support deferring treatment.
- There are likely to be low absolute risks from waiting until 350 cells/mm^3, and this may be safer in some settings. Conversely, the risks are also likely to be low from starting treatment earlier, especially when the motivation is to reduce risk of further transmission. Results from randomized studies are, therefore, urgently required to accurately inform the strategy of when to start treatment.

population. Non-AIDS events are now a significant and leading cause of morbidity and mortality [6,7▪▪].

However, although guidelines have moved towards earlier treatment, few studies have provided new evidence for clinical benefits when starting with a CD4 cell count above 350 cells/mm^3 [8▪▪]. The current evidence, especially for starting treatment with a CD4 cell count above 500 cells/mm^3, has the lowest evidence grade of expert opinion [9▪].

Recent recommendations for earlier treatment are, therefore, related to the impact that ART has on reducing the risk of transmission. We discuss this from individual and population perspectives and suggest that the two may not be closely connected.

The differences between a population-based and individualized treatment approach are also likely to vary between resource-limited and western settings. Trying to standardize HIV management in resource-rich and resource-poor settings is a good thing. However, we suggest that this could easily be undermined by the different standards of care and might result in poorer individual outcomes in resource-limited settings.

For earlier treatment to be an informed choice, a balance of advantages and the risks, both of which are currently unquantified in randomized studies, need to form part of the discussion with a patient prior to initiating ART. This approach has the best chance for retaining confidence in the patient's relationship with healthcare providers should evidence from randomized studies, when it becomes available, fail to highlight clinical benefits.

TREATMENT GUIDELINES

The history of the CD4 threshold for initiating HIV treatment in evidence-based guidelines is important for its many changes. For example, the US Department for Health and Human Services (DHHS) guidelines set the threshold at 500 cells/mm^3 when zidovudine (AZT) was first approved in 1987, and it remained at this level for 14 years. During this time, treatment was suboptimal with monotherapy, dual therapy and early triple combination therapy. Only after 5 years of accumulating data on the toxicity of the first triple combinations and the risk of drug resistance did experts finally agree that it was safer to delay treatment. In April 2001, the CD4 threshold was first reduced to 350 and then to 200 cells/mm^3 in 2003. The approval of new drugs and the development of a better understanding of how to use them (in terms of adherence and resistance – together with new concerns about being off-treatment) provided sufficient evidence for the guideline panel to then increased the threshold back to 350 cells/mm^3 in 2007 and to 500 cells/mm^3 in 2009. In 2013, the CD4 threshold was removed as a criterion for deciding when to start treatment [10▪▪].

In 2003, WHO guidelines that were produced for resource-limited settings set the CD4 threshold at 200. In 2010, this increased to 350 cells/mm^3, even when stavudine (d4T) was still widely being prescribed. Some of the potential harm this could have caused was avoided because, irrespective of guidelines, most people in resource-limited settings were still being diagnosed at CD4 cell counts well below 200 cells/mm^3 when the risk:benefit balance of treatment even supported d4T. In 2013, the WHO increased the threshold to 500 cells/mm^3, but also recommended treatment at any CD4 count above 500 cells/mm^3 for some groups of people: pregnant women, children under 5 years old and HIV-positive people with HIV-negative sexual partners [11▪▪].

However, these guideline changes were not universal. In 2012, several important guidelines retained the threshold at 350 cells/mm^3 after analyzing the same data [12▪,13]. This was because of the inconsistent evidence supporting clinical benefits from earlier treatment and concerns about harm [14–17].

ABSOLUTE VS RELATIVE DIFFERENCES IN RISK AND BENEFIT

It is confusing when guideline panels reach different conclusions after reviewing the same data. Important details including the quality of evidence supporting different recommendations are difficult to explain and are largely ignored in mainstream media reports [18,19].

The biggest impact on mortality comes from initiating treatment in people whose CD4 cell count is less than 200 cells/mm^3, and then from people with a CD4 cell count 200–350 cells/mm^3 [20,21,22▪]. Reducing late diagnoses is critical in normalizing life expectancy [23], but several studies already report broadly comparable life expectancy (for non-injecting drug user HIV positive compared with HIV negative) [24,25], especially when CD4 cell counts are above 500 cells/mm^3 [22▪].

In terms of the population impact of ART, the disagreement between different panels of experts on potential benefits of earlier treatment are fine-tuning a detail of HIV management that currently relates to a minority of people who are diagnosed prior to any significant immune damage. However, in the absence of data supporting safety, earlier treatment has the potential to cause harm and the risks from toxicity and drug resistance have not yet been quantified in different health settings.

At higher CD4 cell counts, there are relatively small absolute differences in benefits and risks at higher CD4 cell counts. To put this difference into context, the international START trial is expected to need to follow more than 4000 people for over 3 years to see a difference in clinical endpoints between starting above 500 cells/mm^3 compared with waiting until 350 cells/mm^3. Good data about the low risk of complications at CD4 cell counts above 350 cells/mm^3 ensure that current studies are appropriate to continue even when guidelines recommend earlier treatment. They should also lessen the sense of urgency that pressurizes all individuals to start early treatment [26▪▪].

Given that over 10 million people are currently on treatment globally, it is a very reasonable community demand to want evidence of both the benefits and risks from the earlier use of treatment, especially as these data can be obtained from studying a relatively modest group of several thousand people for a few years in a few carefully designed studies. Important substudies are being conducted (neurological and metabolic complications in START and tuberculosis in TEMPRANO) in which the relative impact of HIV and/or treatment and the overlap with comorbidities and ageing have yet to be understood [1▪▪,2▪▪]. This situation is especially true given the potential risks from earlier treatment are likely to be significantly higher in some settings because of the factors beyond the control of the individual person taking treatment, such as the continued use of stavudine or the instability of the drug supply, see Table 1 [27▪,28▪].

The examples in Table 1 are situations when, even in the context of 100% adherence, it might be preferable to defer treatment in individuals with a

Table 1. Circumstances when a CD4 threshold of 500 cells/mm^3 might not have a risk:benefit advantage for starting antiretroviral treatment

Circumstance	Comment
When d4T (stavudine) is still used in first-line treatment	Mitochondrial toxicity includes lactic acidosis and pancreatitis, which can be fatal; facial lipoatrophy which ages a person's appearance by 10–20 years, identifies a person as being HIV positive and is unlikely to be reversible; and peripheral neuropathy, which can be painful, debilitating, limit mobility and is also unlikely to be reversible
When AZT (zidovudine) is still used	Concerns about side-effects including increased risk of anaemia, which has a higher incidence in resource-limited settings and lipoatrophy (see d4T comment above)
When first-line therapy allows few options for switching due to side-effects – i.e. when no alternative to efavirenz	Severe CNS side-effects will make this an intolerable combination for less than 5% of patients; this is not only medically inappropriate – suicide, suicidal ideation and paranoia/anxiety requiring hospitalization have all been reported as severe symptoms making an alternative option essential
When drug supply cannot be guaranteed as stock-outs risk drug resistance	Stock-outs are still common in some settings; each time a person interrupts HIV treatment by more than a day the risk of developing resistance to one of the drugs in the combination is increased; this will compromise the efficacy of treatment when it is restarted and increase the risk of resistance developing to all the drugs in the combination
When second-line and third-line options are limited	A person could lose their only option for the treatment prior to any symptomatic clinical need because the motivation for perfect adherence is more difficult when the fear of HIV/AIDS is purely theoretical

CNS, central nervous system.

stable CD4 cell count above 350 cells/mm^3. Although d4T is now far less widely used, especially when initiating treatment, this phase out is steady but gradual, and more than 1 million people globally (10% of those on treatment) are estimated to still be using d4T [29▪]. If d4T is part of first-line regimen or the treatment site faces frequent stock-outs, the risk of serious adverse events and drug resistance [30–32], may even shift the risk:benefit back to a lower threshold than either 500 or 350 cells/mm^3.

TREATMENT AS PREVENTION AND QUALITY OF LIFE

The move to earlier treatment has also been informed by the impact of ART on reducing the risk of sexual transmission. An undetectable HIV viral load (<50 copies/ml) in peripheral blood is associated with a degree of protection that exceeds that of consistent condom use. This is supported by the results from randomized clinical trials and prospective cohort studies [33–36]. The potential for treatment to reduce infectiousness has been considered for many years, and it was included in the 1998 United States DHHS guidelines [37▪]. However, it is the degree and quality of the evidence that has correspondingly shifted the emphasis of treatment from the purely clinical benefits for the person taking treatment, to an indirect and assumed net public health population benefit. This is also new, and is controversial because antiretroviral treatment is still complex and because the evidence suggests that health benefits are marginal at higher CD4 cell counts.

However, many treatment guidelines already recommend treatment irrespective of CD4 cell count for HIV positive people with HIV negative sexual partners, if they want to use treatment to reduce the risk of transmission [9▪,10▪▪,11▪▪,12▪,13].

The evidence for the protective benefit of ART is an important reason for the individuals to be able to choose earlier treatment. The much-reported 96% reduction of transmission risk in the HPTN 052 study is likely to be an underestimate as the single transmission that occurred soon after starting treatment when viral load would still be declining. However, the data for treatment as prevention (TasP) comes almost exclusively from vaginal sex in heterosexual studies with no data for the residual risk of transmission for anal sex [whether between heterosexual or men who have sex with men (MSM) couples]. Because of the continued use of condoms in the four key studies, the data set for heterosexual transmission is also drawn from only 330-patient years of follow-up from people who were at risk of contracting HIV [38▪▪].

When merging clinical and prevention benefits, it is important to remember that many HIV-positive people present no risk for onward transmission. Condom use may be careful and consistent, and many HIV positive people have partners who are also positive [39▪]. Many people are not sexually active [40,41]. In all these cases, the prevention benefits have little relevance, and the decision to start treatment should focus singularly on the clinical risk:benefit ratio.

An HIV diagnosis is still a life-changing event, even when a person remains well and healthy. Our interaction with the world is changed and particularly the most intimate connection to sexual partners. Stigma and ignorance remain widespread, and this itself often limits social contact. Contrary to popular belief, HIV-positive people who are diagnosed take significantly fewer risks with sexual partners than people who are undiagnosed. Behavioural risks (by HIV-negative people) for acquiring HIV, specifically low condom use, are higher with partners who are untested or undiagnosed than with HIV-positive partners [42–44].

Despite these cautions, earlier access to treatment may indeed improve the quality of life for HIV positive people and their partners, through reducing anxiety about infectiousness. The positive impact this has on the quality of life is likely to continue to drive individual decisions to start earlier treatment.

In the context of a partnership wherein one partner is HIV positive and the other HIV negative, a residual risk of transmission felt by either or both partners can limit intimacy, even when condoms are routinely used. An example of the confidence in the dramatically reduced risk once a person has undetectable viral load is that HIV postexposure prophylaxis is no longer recommended if a condom breaks or slips off during vaginal intercourse [45].

The knowledge that an undetectable viral load makes us 'less infectious' is rarely discussed but for many people this is both tangible and unexpected. It is important that guidelines for different settings are consistent in recommending (TasP) at any CD4 cell count when someone wants to reduce transmission risks to their partner. Equally important is the social impact this can have on quality of life and the more difficult to measure potential to reduce discrimination by normalizing HIV testing and treatment.

INDIVIDUAL VS POPULATION IMPACT OF TREATMENT AS PREVENTION

The magnitude of the impact of TasP on an individual level is likely to be very different to the impact on HIV incidence on a population level – even though the two are frequently merged. Starting

treatment a couple of years earlier for people who are already diagnosed will not necessarily have much impact on the rate of new infections. This is because most epidemics are driven by people who are undiagnosed. Together, primary and chronic infection could account for 80–90% of new infections. Extremely high viral load during primary infection (often >1 000 000 copies/ml) will contribute more significantly in epidemics in which having multiple partners is common and chronic infection involves sustained risks over many years [46,47▪].

An increase in HIV testing, especially in people at the highest risk, together with early access to treatment and retention in care are also needed – and this may still take many years. Even increasing routine and regular HIV testing by people at highest risk may be insufficient to reduce HIV incidence by the use of earlier ART [48▪].

It is still unknown whether the 10–20% of infections that may be prevented from treating people a few years earlier in their infection will make a significant impact on population level.

PUBLIC HEATH BENEFITS IN RESOURCE-LIMITED SETTINGS

A public health approach to HIV involves simplifying to the most appropriate treatment in each setting. This enables benefits of economies of scale for treatment and tests. This needs to include alternative drugs when the preferred option is not clinically appropriate.

The larger the epidemic, the greater the challenge to provide treatment and services. For many resource-limited settings, this involves a population-based approach to treatment. The optimum threshold to initiate treatment in population-based settings is still unknown.

Resource-limited settings are heterogenous, even within countries. For example, the Ubuntu clinic in Cape Town South Africa is able to offer CD4 cell counts, viral loads and all the WHO's recommended regimens. The standard of care is comparable to good facilities in the USA and Europe. Yet, at clinics in the rural Eastern Cape of South Africa, drug stock-outs are common and monitoring is often poor. Across sub-Saharan Africa and Asia, the quality of treatment and the available regimens, diagnostics and monitoring tests vary greatly. Although some facilities are able to manage ART initiation at any threshold and place patients on optimal regimens, others continue to initiate patients on stavudine and do clinical monitoring.

When to start in many resource-poor settings is not only guided by what is the ideal CD4 threshold, but by operational and other concerns that differ across facilities, including choice of treatment and different health pressures.

Another example is that although tuberculosis is comparatively rare in Europe and America, it is a major cause of morbidity in resource-poor settings, even for patients on ART [49]. A meta-analysis of 11 studies from developing countries found that ART reduces the incidence of tuberculosis at all CD4 strata [50▪▪]. Also, patients in resource-limited settings might be more likely to be lost to the health system if they are not initiated on ART after presenting at facilities, even those patients with high CD4 cell counts; this concern has also been reported in the USA.

However, there are also likely to be significantly different risks from earlier initiation of ART in resource-limited settings related to fewer options for first-line and subsequent treatment, continued use in some settings of older drugs that are no longer recommended in treatment guidelines and drug supply issues in which stock-outs force treatment interruptions and associated risk of drug resistance.

From a public health perspective, a widespread rollout of ART to most people with HIV irrespective of CD4 cell count might reduce HIV incidence. But, the reduction might be small and the considerable resources needed for such a large scale-up might be better targeted elsewhere. These are difficult choices for policy makers in the face of incomplete information.

Four other studies will provide guidance on when to start in resource-limited settings.

(1) The Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO) trial is being run by the Agence Nationale de Recherche sur le Sida (ANRS) in Côte d'Ivoire. This four-arm study has already randomized 2000 treatment-naive patients with CD4 cell counts below 800 cells/mm^3 and includes early compared with deferred ART with a factorial design that includes isoniazid prophylaxis against tuberculosis. The trial is fully recruited and is expected to complete in December 2014 [2▪▪].
(2) The TasP study is an ANRS-sponsored randomized cluster controlled trial in South Africa looking at whether immediate ART initiation of all HIV positive people in a community will reduce HIV incidence. The study is in its pilot phase. It will randomize 34 communities either to current guidelines or immediate treatment. It is intended to enrol a population of 42 500 people of whom 8000 are expected to be HIV positive. The expected completion date is December 2015 [51].

(3) HPTN-071 (known as PopART) will be run in South Africa and Zambia. It is a randomized cluster controlled trial similar in design to the TasP trial, also with community HIV incidence as its primary endpoint. It has not yet started recruiting and is due to end in 2017 [52].
(4) In Kwazulu-Natal, South Africa, Médecins Sans Frontiéres (MSF) is examining the operational aspects of initiating people on treatment using a CD4 threshold of 500 cells/mm^3. This project also includes PMTCT B+, mobile testing units and door-to-door testing teams [53].

In addition to these, the START trial includes several African sites. The largest START site is in Cape Town, South Africa, an area with a high tuberculosis burden.

CONCLUSION

The caution in this article towards earlier treatment is related to important historical examples of when leading guidelines have later proved to be wrong. The widespread use of early treatment when combination therapy was first developed is an example in which harm was later found to have outweighed the benefits. It is not helpful when guidelines panels fail to have a more modest and cautious approach to making recommendations when good evidence is lacking.

Similarly, advocates and community perspectives can also in hindsight be wrong – the demand for data is to minimize this risk. However, we argue that the equipoise for the risks and benefits still strongly supports the safety and importance of the ongoing studies for those participants.

Until results from these studies are available, it is important to acknowledge the currently low evidence base for clinical benefits and that, as with guidelines from 1997 to 2001, this is largely based on expert opinion.

For many people, the merged clinical and prevention benefits will be sufficient to tip the balance towards earlier treatment. For some, the prevention benefits alone may be sufficient.

Other community perspectives see the higher CD4 threshold in terms of broadening access to effective treatment. The choice to use treatment should be made by the person taking medication, even when prescribed under population-based health guidelines.

In settings with high rates of loss to follow-up after diagnosis, the opportunity to engage and retain someone in care may be more important than whether the treatment is started slightly earlier.

In this case, the limited data supporting likely low risk of complications with long-term ART are reassuring for people who decide to start treatment earlier, including for participants in START and other studies, while recognizing that this information comes from studies that were not always designed to quantify risks [54▪,55▪].

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Conflicts of interest

S.C. has no financial conflicts of interest.
N.G. has no financial conflicts of interest.

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