Community statement on the START trial and the change in the US DHHS treatment guidelines

By *moderator*
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The following statement has been sent to the chairs of the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.

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Introduction

The following statement is produced in response to a change in the US treatment guidelines in December 2009 that stated that antiretroviral (ARV) treatment should be universally started at any CD4 count below 500 cells/mm3.

The START study is currently enrolling patients to look at whether there is evidence to support such a recommendation. Currently no randomised trial has provided data on the advantages and risks of earlier treatment. This statement affirms both the importance of the START trial and the safety for people who enrol.

We believe that the priority for HIV-positive people is to have accurate, reliable data on both the risks and benefits of earlier treatment in order to base any decision for when to start treatment.

Statement

When to start antiretroviral treatment is one of the most important outstanding questions for people with HIV and their clinicians. A large clinical trial, Strategic Timing of Antiretroviral Treatment (START), has begun and will hopefully help answer this and other important questions. [1]

The START trial includes antiretroviral-naive HIV-positive people with CD4 counts greater than 500 cells/mm3. It is taking place at about 90 sites in nearly 30 countries. Participants are randomised to either receive antiretroviral treatment immediately or to defer treatment until their first CD4 count less than 350 cells/mm3 or they have clinical signs of AIDS. Eventually, START will recruit 4,000 people.

The deferred arm is the current standard of care throughout the world, with guidelines recommending treatment at a CD4 count of 350 cells/mm3. Clinical trials have demonstrated that once the CD4 count drops to below 350 cells/mm3, antiretroviral treatment should begin. [2, 3] However, the recent US guideline change requires a community response for US patients who still want to take part in this study.

On 1 December 2009, the United States (US) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults

and Adolescents were changed to recommend treatment for patients with CD4 counts between 350 and 500 cells/mm3. Of the more than two-thirds of Panel members who supported this recommendation, 55% recommended it strongly and 45% moderately. As explained in the guidelines, this recommendation is based solely on observational data primarily from two large cohorts known as ART CC and NA-ACCORD. As with all observational data the findings from these cohorts could be subject to confounding factors. [4]

Indeed, the ART CC investigators have stated, ?We are concerned that some may interpret the new [US] recommendations as implying that the deferral group of this trial is no longer ethical. Such an interpretation would endanger the future of the trial in the [US].? [5]

They further state, ?We ? do not believe that there is convincing evidence to conclude that deferral of initiation of ART to a CD4 count of [350 cells/mm3] causes net harm, particularly in terms of mortality, compared with starting at any higher level. We strongly support continued enrolment into START. Large randomised studies represent the only means of eventually obtaining the definitive result we need to properly inform future patient care.

We agree with the ART CC investigators. The available evidence is insufficient to determine if the adherence challenges and long-term side-effects of early antiretroviral treatment are outweighed by reduced risk of illness conferred by these medicines. Only a randomised controlled trial, such as START, can determine this.

The NA-ACCORD data is also challenged by the researchers who orginally developed the new statistical methodology. They were not convinced that the application thereof was without problems. [6]

We too are concerned that the new US recommendation:

(1) raises theoretical concerns about continued enrolment of patients in the US, a substantial source of patients, and

(2) is based on poor evidence and therefore might not be in the best interests of patients.

We also have further concerns that:

(3) previous recommendations to use earlier treatment failed to recognise the negative impact of resistance and side effects, and

(4) a minority of individuals have normal CD4 counts between 350-500 and would therefore be using treatment prior to any significant immune damage.

We support research findings that the absolute risk of HIV-related complications remains very low at a CD4 count 350?500 and that individuals enrolled in START will be carefully monitored and access treatment if their health circumstances change.

We also support the unique importance of sub-studies in START.

These studies have the potential to answer important questions relating to the impact of HIV, treatment and ageing on neurology and mental health, bone health, heart disease, lung disease and behaviour risk.

We support the START investigators, community advocates and HIV-positive people interested in this dynamic research which will help close the essential gap in our current knowledge on the safety and risks of earlier treatment.

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