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WHEN TO START: A CLINICAL PERSPECTIVE ON DEVELOPING DATA ADDRESSING EARLY VS. LATE TREATMENT INITIATION

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As an HIV-positive patient who spends most of her time in search of clinically relevant and evidence-based information about HIV in order to provide effective education at both the clinical and community levels (see www.freehivinfo.com), I was impressed once again with the energy that eminent scientists still apply to creating a research agenda around the question of "when to start" HIV treatment. This continuing debate raises the following questions for me:

- Why is the HIV treatment question, "when to start," still such a hot topic?
- How do top HIV researchers evaluate and utilize data from existing and developing science to validate —or challenge— the current HIV guideline recommendations on the "when to start" issue?

Early vs. late initiation of treatment meeting

This article is written from a patient's perspective on the discussions and presentations that took place at the *Early vs. Late Initiation of Treatment Meeting*, September 25th and 26th (2003) in Atlanta, GA. I am focusing on the information that struck me as having the most potential for future clinical relevance. The following analysis might stimulate thought about the questions posed above as well as other challenges healthcare providers and patients face in reacting to the evolving science and the constantly changing HIV research landscape. For example, over the past years, the answer to the "when to start" question has gone through dramatic

reconditioning — from "hit hard, hit early, and treat everyone" to "don't treat unless you have to and certainly not before CD4 T cell counts are below 350 cells/ μ L." There is still complete consensus on the need to treat all patients with <200 cells/ μ L CD4 counts¹, but that is the only firm ground in sight in the "when to start" question. During the meeting, discussions on this topic occurred mostly in what I term "the grey areas," that is, patients with intermediate immunodeficiency (asymptomatic and CD4 counts ranging between 200-350 cells/ μ L) and the newly infected, another group in which treatment was still wide open for discussion at this meeting.

Discussions

This meeting of researchers included attendees from developed countries only (US, UK and Europe), although the challenges faced by undeveloped nations were often mentioned. It was a rarified atmosphere, sometimes far removed from real life and the multifactorial clinical considerations of individualized HIV treatment. For example, it is clear from this meeting and other recent conference presentations that discussions are broadening to explore how the rate of disease progression is influenced by individual genetic factors such as HLA genotype (HLA-A,-B,-C) given that specific changes (polymorphisms) are associated with altered natural immune response and viral control and some interesting immunologic factors.² Although this information is quite fascinating, the viability of genotyping each patient is not feasible within our current healthcare system. In addition, the potential clinical benefit that might be derived from such genotyping — even if it were possible — remains unclear. Research continues with the hope that in the future it may be possible, in some

patients, to guide treatment decision-making through genotyping. Such testing could influence early vs. late treatment initiation, treatment of primary infections, and structured treatment interruptions, in which case, genotyping would facilitate a truly "individualized" therapy.

Within the confines of this type of research, can we expect that researchers will discover the "best evidence" to set a course for simultaneously prolonging life while delivering a decent quality of life for patients who have unique concerns, expectations, and values? Of course not, because any "evidence" researchers deliver is only part of the story. From this patient's perspective, the best evidence is usually found when clinically relevant research, which has been conducted using sound methodology, is applied in the context of individual patients' lives. And to their credit, a few of the researcher attendees strongly and openly expressed this view as well.

Large cohort studies, immune recovery, and CD4 nadir

It was noted by more than one participant that we (researchers, clinicians, community educators) are making decisions for the future based on outdated information and data generated using possibly outmoded antiretroviral therapy (ART). This was cited as the primary challenge of cohort studies. For example it was noted that the much revered Mellors Model, which explored patient prognosis without high active antiretroviral therapy (HAART) and with a 3-year probability of developing AIDS in 1604 men enrolled in the Multicenter AIDS Cohort Study (MACS)³, was somewhat clinically irrelevant in an age in which healthcare providers make treatment decisions based on prognostic tests and patient interactions that are re-evaluated every 3 months.

An observation made by one attendee centered on the variability of CD4 testing results (± 100 cells), which throws some of the research discussed into murky light. While using one laboratory exclusively to process study samples reduces the likelihood of variability, the results may not be absolutely reliable. The International AIDS Society-USA (IAS-USA) and

Department of Health and Human Services (DHHS) guidelines both recommend making treatment decisions based on patients' CD4 values, thus making variability a major point of concern. If you choose to initiate treatment at ≤ 350 cells/ μ L, can you trust the lab values? Is it really 350 cells/ μ L?

As someone who started CART with a nadir of CD4 cells <50 / μ L and who has suffered severe lipoatrophy and moderate neuropathy, I was particularly interested in the discussion of comparative data generated by the HIV Outpatient Study (HOPS) cohort.⁴ In this study, 546 patients participated in two separate assessments (Surveys 1 and 2) that were roughly two years apart. The incidence of lipoatrophy was significantly higher in those who started CART with CD4 counts <100 cells/ μ L; 337 (61.7%) had no lipoatrophy at Survey 1 and 44 (13.1%) of these developed moderate to severe lipoatrophy by Survey 2. However, duration of CART use was not associated with lipoatrophy. The presentation of HOPS data that related to increased incidence of peripheral neuropathy (ACTG 384) and chronic renal failure in patients who initiated

