TREATMENT ACTION GROUP **ISSUE BRIEF**

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TAG
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SUBOPTIMAL IMMUNE RECOVERY ON ANTIRETROVIRAL THERAPY

INTRODUCTION

For many HIV-positive people—particularly those who initiate treatment soon after infection—combination antiretroviral therapy (ART) is associated with robust improvements in CD4+ T cell counts, enhanced immune function, and a life expectancy comparable to that of similar HIV-negative individuals.

But a subset of people on ART experience limited or no recovery of CD4+ T cell counts despite achieving and maintaining undetectable HIV viral loads, and these individuals have an elevated risk of illness and death compared with counterparts who obtain greater CD4+ T cell gains.

Various terms have been used to describe this phenomenon, with the most common being 'immunologic non-responder' (INR). TAG has adopted the descriptor 'suboptimal immune recovery,' out of concern that non-responder may be interpreted as assigning blame (an individual obviously cannot control their immunologic response to viral load suppression).

DEFINING SUBOPTIMAL IMMUNE RECOVERY

There is no consensus on exactly how to define suboptimal immune recovery, but suggested criteria include:

- A CD4+ T cell increase of less than 30% above baseline, or an absolute count of less than 200 cells after 6–12 months of ART.
- Lack of an increase in the CD4+ T cell count to more than 350–500 cells after 4–7 years of HIV suppression by ART.
- A rise of less than 50 CD4+ T cells after six months of ART in individuals who start with <350 CD4+ T cells.

The estimated frequency of suboptimal immune recovery among HIV-positive individuals initiating ART has varied between studies, but tends to be in the range of 15–30%. For example, one of the largest analyses involved a cohort of 5,550 HIV-positive people who started ART with less than 200 CD4+ T cells, and 835 (15%) of these individuals did not experience an increase to over 200 cells after three years of successful viral load suppression. Similar findings have been reported in cohorts from multiple geographic locations across the globe.

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POTENTIAL CAUSES

The most consistent risk factors for suboptimal immune recovery are older age and nadir (lowest ever) CD4+ T cell count. The association with age is likely explained by the well-known progressive decline in the regenerative capacity of the immune system that occurs with aging, including slowed T cell production by the bone marrow and shrinkage of the thymus—the organ in which T cells mature before entering the circulation.

Additional potential causes that have been identified include:

- Increased T cell activation and death, possibly caused by co-infections and/or leaking of normally friendly bacteria from the gut (microbial translocation).
- Scarring damage (fibrosis) in lymph tissue, affecting lymph node structures that normally provide sustenance to CD4+ T cells via the cytokine IL-7.
- Genetic factors (variation in genes related to immunity).
- Antibodies against the CD4 molecule, which may promote the premature death of CD4+ T cells.

HEALTH CONSEQUENCES

Multiple cohort studies in the Americas, Europe, and Africa have assessed health outcomes among people with suboptimal immune recovery, followed over several years. The results have been very consistent: the risk of both AIDS- and non-AIDS-related events is significantly increased (typically around two- to threefold) compared with individuals with superior CD4+ T cell count recovery.

These findings are consistent with analyses showing that individuals on ART who achieve CD4+ T cell counts over 500 have mortality rates comparable to those of uninfected individuals, whereas those with smaller CD4+ T cell gains continue to face a shortfall in life expectancy.

DEVELOPING CANDIDATE THERAPIES

A variety of possible adjunctive therapies for HIV-positive people with suboptimal immune recovery have been tested, or are subject to ongoing evaluation (see additional resource links below for more information). Most clinical trials are small in size and are only able to measure the effect of a therapeutic candidate on CD4+ T cell count or other markers (such as biomarkers of inflammation).

A major challenge facing researchers and companies aiming to develop therapies suitable for approval by the US Food and Drug Administration (FDA) is proving the benefits to health: that is, a reduction in the risk of serious AIDS or non-AIDS illnesses and death. The frequency of these events in people with suboptimal immune recovery is relatively low, meaning that large sample sizes would be needed to demonstrate a statistically significant reduction.

HIV treatment activists, including TAG, are exploring whether less serious clinical events and patient-reported outcomes might be considered as endpoints in trials, in an effort to make the pathway toward FDA approval less daunting. The FDA has also expressed willingness to consider therapies for HIV-positive people with suboptimal immune recovery as orphan drugs, which has the potential to help incentivize development.

POLICY IMPLICATIONS

- The increased risk of suboptimal immune recovery associated with late HIV diagnosis and low CD4+ T cell count nadir provides additional justification for efforts to increase early HIV diagnosis and treatment.
- Because older HIV-positive individuals are at greater risk for suboptimal immune recovery, early diagnosis and treatment is particularly important in this population.
- Because individuals experiencing suboptimal immune recovery face an increased risk of illness and death, there remains an important need to develop adjunctive therapies capable of enhancing immune recovery and reducing risks to health.
- The size of the population of individuals experiencing suboptimal immune recovery in the US means that therapeutic candidates likely meet FDA criteria for orphan drug status.
- The generation of guidance by the FDA could help manufacturers aiming to develop therapeutic candidates for HIV-positive people with suboptimal immune recovery.
- Continued advocacy is required to promote the development of potentially licensable therapies for HIV-positive people with suboptimal immune recovery, as well as additional research into the causative mechanisms.

ADDITIONAL TAG RESOURCES

Clinical Trials for People with Suboptimal Immune Reconstitution Despite HIV Suppression
http://www.treatmentactiongroup.org/basic-science/publications/clinical-trials-people-suboptimal-immune-reconstitution-despite-hiv-suppression

Webinar - Suboptimal Immune Recovery on Antiretroviral Therapy: Causes, Consequences, and the Search for Solutions
http://www.treatmentactiongroup.org/content/suboptimal-immune-recovery-antiretroviral-therapy-causes-consequences-search-solutions

Improving Health Outcomes in HIV Immunologic Non-Responders (INRs): Orphan Drug Designation Possibilities. A Community Initiated Proposal to the FDA.
http://www.treatmentactiongroup.org/basic-science/FDA-INR-notes

The Pipeline Report (see the Immune-Based and Gene Therapies chapter)
http://www.pipelinereport.org/