Suboptimal Immune Recovery on Antiretroviral Therapy

Causes, Consequences, and the Search for Solutions

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Outline

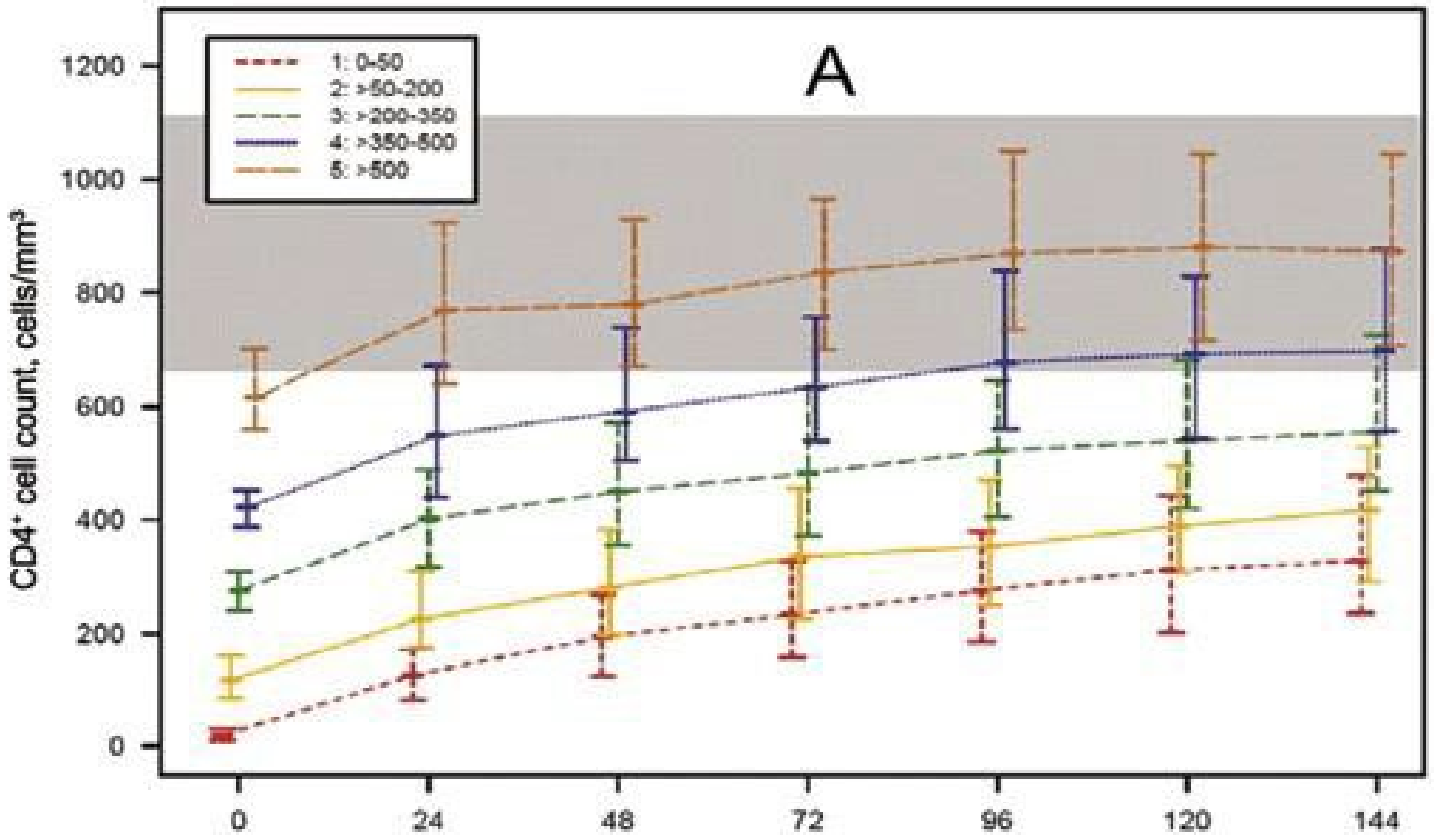
- Immune system recovery on antiretroviral therapy (ART)
  - Factors associated with persistently low CD4 T cell counts despite HIV viral load suppression
- Studies reporting increased risk of morbidity & mortality associated with lower CD4 counts on ART
- Candidate therapies for improving immune reconstitution
- Advocacy discussions with the FDA regarding encouraging the development of candidate therapies

Immune system recovery on ART

- Studies when triple combination ART first became available showed a consistent pattern of immune recovery associated with suppression of HIV viral load:
  - Rapid increases in numbers of memory CD4 T cells, reflecting both redistribution from lymph tissues and cell proliferation
  - Increased immune responses to pathogens that cause opportunistic infections (e.g. candida) and routine immunizations
  - Decreased over-activation of the immune system
  - Slow increase in naïve CD4 T cells from the thymus

E.g. see: Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease, Autran et al, Science. 1997 Jul 4;277(5322):112-6.

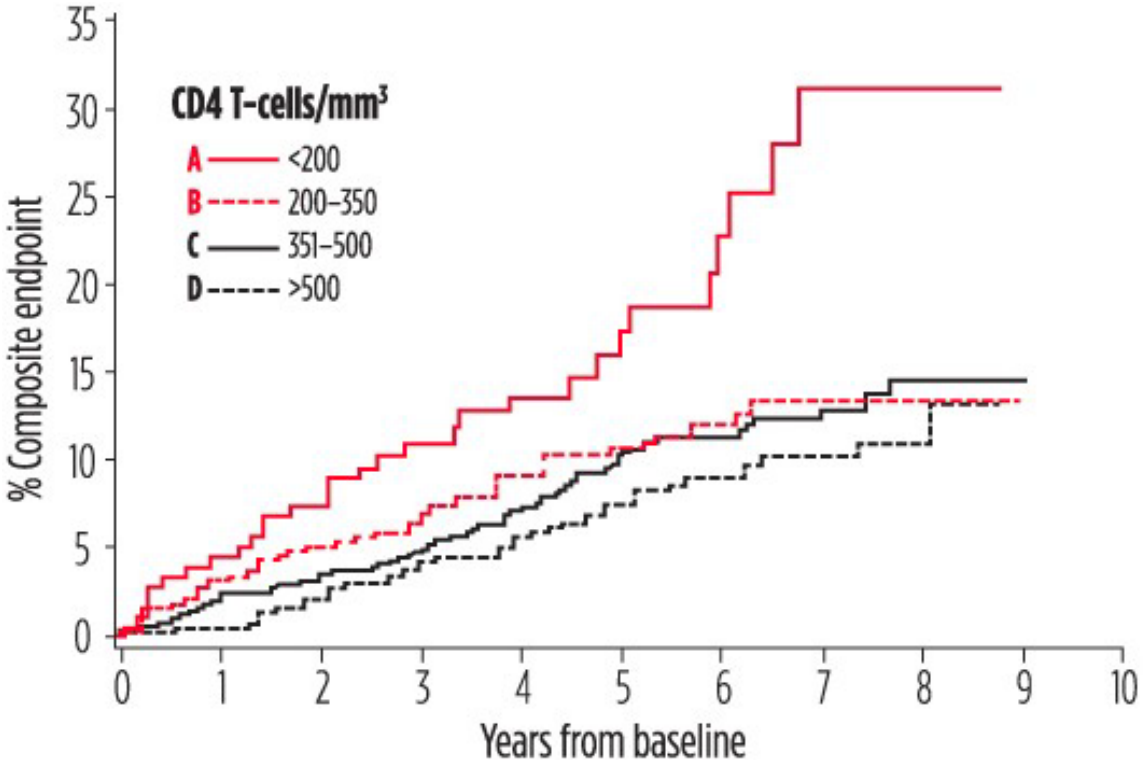
CD4 gains on ART relate to level at start



From: Incomplete Reconstitution of T Cell Subsets on Combination Antiretroviral Therapy in the AIDS Clinical Trials Group Protocol 384
Clin Infect Dis. 2009;48(3):350-361. doi:10.1086/595888
Clin Infect Dis | © 2009 by the Infectious Diseases Society of America

Increased risk of illness and death

- Most studies that have assessed risk of AIDS or non-AIDS events have also reported ~2 fold increased risk associated with suboptimal CD4 T cell recovery



Poor CD4 T-cell recovery despite suppression of viral load associated with an increased risk of death, AIDS, cancer, liver disease, and cardiovascular events (composite endpoint) in the Dutch ATHENA HIV cohort

Source: Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort

AIDS 26(4):465-474, February 20th, 2012.

Increased risk of illness and death

- HIV suppression by ART greatly decreases risk of illness and death
- But most studies have found risk is elevated 2- to 3-fold among individuals who experience suboptimal CD4 T cell recovery compared to those with greater increases
  - Reviewed in Kelly *et al* https://doi.org/10.1371/journal.pone.0156099
- In the ART-CC & COHERE study, there were 175 deaths among the 5550 individuals analyzed over three years:
  - 66 (7.9%) of those who did not attain a CD4 count >200 cells, compared to 109 (2.3%) of those who attained a CD4 count >200 cells

A subset of individuals experiences suboptimal CD4 T cell recovery

- No consensus as to how to define suboptimal CD4 T cell recovery (also referred to as immunological non-response or discordant response)
- A review of published literature found 14 differing definitions in 20 studies
- Suggested criteria have included:
  - A CD4 T cell increase of <30% or an absolute count <200 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
- Estimates are in the range of 15-30% of individuals on ART experiencing suboptimal immune recovery

Absence of CD4+ T Cell Count Recovery Despite Receipt of Virologically Suppressive Highly Active Antiretroviral Therapy: Clinical Risk, Immunological Gaps, and Therapeutic Options, Gazzola et al Clinical Infectious Diseases, Volume 48, Issue 3, 1 February 2009, Pages 328–337

A subset of individuals experiences suboptimal CD4 T cell recovery

- A combined analysis of two large international cohort studies (ART-CC & COHERE) looked at individuals who started ART at <200 CD4 T cells
  - Out of 5550 individuals, 835 (15%) did not experience a CD4 T cell count increase to >200 after three years of HIV suppression by ART
- The phenomenon has been reported in studies from multiple geographic locations
  - The Antiretroviral Therapy in Low Income Countries (ART-LINC) Collaboration reported 1,260 out of 7,160 (17.6%) individuals experiencing a lack of CD4 T cell recovery after ~6 months of ART

Estimated outcomes after seven years on ART based on starting CD4 T cell count

	Estimated % at year 7		
Pre-ART	**≤200**	**≤350**	**≤500**
>500	0	2	5
351–500	3	3	5
201–350	5	9	45
≤200	11	25	47

Estimated CD4+ T-cell count outcomes (cells/mm3) had all patients remained on antiretroviral therapy throughout the seven years of follow-up. All estimates were obtained using inverse probability of censoring weighting (IPCW).

Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection
Lok, Judith J; Bosch, Ronald J; Benson, Constance A; Collier, Ann C; Robbins, Gregory K; Shafer, Robert W; Hughes, Michael D; for the ALLRT team
AIDS 24(12):1867-1876, July 31st, 2010. doi: 10.1097/QAD.0b013e32833adbcf

Immuno-Virological Discordance (ID) and the Risk of Non-AIDS and AIDS Events in a Large Observational Cohort of HIV-Patients in Europe (EuroSIDA)

- 2,913 patients in EuroSIDA starting at least 1 new ARV with CD4<350 cells/µl and VL>500 copies/mL were followed up from the first day of VL< = 50 copies/ml **until a new fatal/non-fatal non-AIDS/AIDS event**.
- Patients were classified over time according to whether **current CD4 count > (non-ID) or < (ID) than baseline CD4 count.**
- The RR of developing pre-specified non-AIDS events for ID vs. non-ID was **1.96** (95% CI 1.37– 2.81, p<0.001). ID was not associated with the risk of AIDS events.
- **Long-term mortality in HIV-positive individuals virally suppressed for over three years with incomplete CD4 recovery.**
- The purpose of this study was to identify (1) risk factors for failure to achieve CD4 count >200 cells/µL after three years of sustained viral suppression and (2) the association of achieved CD4 count with subsequent mortality.
- Of 5,550 eligible individuals, **835 (15%) did not reach CD4 count >200 cells/µL after three years of suppression.**
- Increasing age, lower initial CD4 count, male heterosexual and injection drug use transmission, cART initiation after 1998 and longer time from initiation of cART to start of the virally suppressed period were risk factors for not achieving CD4 count >200 cells/µL.
- Individuals with CD4 ≤200 cells/µL after three years of viral suppression had **substantially increased mortality** (adjusted **hazard ratio 2.60**; 95% confidence interval 1.86-3.61) compared to those who achieved CD4 count >200 cells/µL.
- Increased mortality was seen across different patient groups and for all causes of death.

Clin Infect Dis. (2014) doi: 10.1093/cid/ciu038

Updated INR Patient Population Estimate

- According to the CDC, in 2019, an estimated 1.2 million people were living with HIV in the United States, of which 65.9% received some HIV care, 50.1% were retained in care, and **56.8% were virally suppressed or undetectable**[1]

- If 10% of virologically suppressed patients are INRs (CD4< 250), then the estimated INR patient population is: 1,200,000 x 0.56 x 0.10= **67,200 individuals.** (*References in Appendix*)

- In 2018, 21.5% of the 34,000/year HIV infections in the United States were classified as stage 3 (AIDS) at the time of diagnosis[1]. A conservative estimate would be that ~20% of these late-diagnosed individuals might become INRs (**~1,500-2,000 individuals per year**) (*References in Appendix*)

- At the current rate, it is improbable that there will ever be over 200,000 HIV+ individuals with suboptimal immune reconstitution in the US (the **orphan drug designation patient population maximum**) in the next 20 years.

*1- Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2019. HIV Surveillance Supplemental Report 2021;26(No.2). http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published **May 2021**.*

Factors associated with suboptimal CD4 T cell recovery

- The most consistently reported associations are with older age and CD4 T cell count at ART initiation
  - Production of new T cells by the bone marrow/thymus is known to decline with advancing age
- Studies have identified multiple possible contributing mechanisms
  - Low T cell production by bone marrow/thymus
  - Increased T cell activation and death, potentially caused by co-infections and/or leaking of normally friendly bacteria from the gut (microbial translocation)
  - Scarring damage (fibrosis) in lymph tissue
  - Genetic factors (variation in genes related to immunity)
  - Anti-CD4 antibodies

Absence of CD4+ T Cell Count Recovery Despite Receipt of Virologically Suppressive Highly Active Antiretroviral Therapy: Clinical Risk, Immunological Gaps, and Therapeutic Options, Gazzola et al Clinical Infectious Diseases, Volume 48, Issue 3, 1 February 2009, Pages 328–337

Candidate therapies

- Interleukin-2 (IL-2) is a type of immune system messenger protein known as a cytokine
- IL-2 triggers CD4 T cell proliferation and was studied in two large efficacy trials in people with HIV: ESPRIT and SILCAAT
- IL-2 was associated with increases in CD4 T cell counts but did not significantly reduce incidence of illness and death
- Additional studies found IL-2 also failed to improve response to routine vaccinations in people with HIV on ART
- May have preferentially increased levels of CD4 T cell subsets involved in immune regulation
  - **Not all CD4 T cells are created equal, health benefit of an immune-based intervention must be proven**

Candidate therapies

- Interleukin-7 (IL-7) is another cytokine that can increase CD4 T cell numbers via a different mechanism to IL-2
- Multiple studies in people with HIV on ART indicated potential to promote CD4 T cell increases
  - Some evidence of decreases in inflammation biomarkers
  - Possible risk of increase in HIV DNA levels
- Original manufacturer Cytheris had ambitious plans to conduct a large phase III clinical endpoint trial in HIV+ people with suboptimal immune recovery, but went out of business in 2015
- The rights to pursue IL-7 as a therapy for HIV-related immune impairment are reportedly now held by a collaboration involving the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), but fate currently unclear
- Long-acting IL-7 formulation (NT-17) being developed by Korean Company NeoImmuneTech, so far only being studied in PWHIV who have Kaposi's sarcoma

Candidate therapies

- SB-728-T gene therapy
  - Extraction of CD4 T cells via apheresis
  - Gene modification of the CD4 T cells to remove CCR5 receptor
  - Expansion and reinfusion of gene-modified cells
- One of the first trials included a cohort of individuals with suboptimal immune recovery
  - Demonstrated significant CD4 T cell increases and improvements in CD4:CD8 T cell ratio
- Approach now enhanced to focus on T-stem cell memory cells (Tscm) based on analyses of past recipients
- Licensing agreement announced between Case Western Reserve University and RORA Biologics to develop enhanced approach for HIV and other indications (February 23, 2023)

Candidate therapies

- Fostemsavir
  - HIV attachment inhibitor approved by FDA on July 2, 2020 for the treatment of people with multidrug resistant HIV and limited options
- Unexpected finding from studies: receipt of fostemsavir associated with CD4 T-cell count gains of greater magnitude than anticipated based on just direct suppression of HIV replication
- Effect was particularly prominent among participants with the lowest baseline CD4 T-cell counts:
  - After 96 weeks of follow-up, an average increase of 240 cells was demonstrated for those who started with less than 20 cells
  - Of the participants who began with less than 50 cells, 56% experienced immunologic recovery to greater than 200 cells
- The Orlando Immunology Center now collaborating with ViiV Healthcare on a study to investigate the phenomenon in greater detail

Advocacy discussions with FDA

- Meeting held on June 10, 2016
  - Notes available online: http://www.treatmentactiongroup.org/basic-science/FDA-INR-notes
- Possibility raised of using FDA's orphan drug designation in the US to encourage development of therapies for people with suboptimal immune recovery on ART
- Discussion of how to design trials to demonstrate efficacy

Advocacy discussions with FDA: candidate endpoints

- Potential ways to assess efficacy (clinical trial endpoints) of interventions for people with suboptimal immune recovery were discussed
- Biological markers:
  - CD4 T cell count
  - CD4:CD8 ratio
  - Immune response functionality assessed by routine vaccinations (e.g flu etc.)
  - Inflammatory & coagulation biomarkers
  - Immune activation biomarkers
  - T cell phenotypes
  - HIV DNA

Advocacy discussions with FDA: candidate endpoints

- Patient Reported Outcomes (PROs)
  - Increasingly used but so far only employed for one HIV-related treatment (Egrifta)
- Frailty Indexes
  - Several developed (e.g., the Veterans Aging Cohort Study Index), could be considered in determining if improvements can result from immune enhancement therapies, but data lacking on incidence in people with suboptimal immune recovery
- Comorbidities and clinical symptoms
  - E.g., diarrhea, fatigue, pain, upper respiratory infections, skin disorders, etc.
- FDA analysis of registrational HIV antiretroviral trials unable to identify candidate composite clinical endpoint but low representation of INRs (1.7%) due to study entry criteria
- FDA open to ideas, but made clear that marketing approval of an intervention would require some evidence of clinical benefit

Potential next steps

- Follow up webinar with researchers involved in studying suboptimal immune recovery
- Advocacy statement or article on global need for candidate interventions
- Continued dialogues with researchers, FDA and industry
- Other ideas?