Suboptimal Immune Recovery on Antiretroviral Therapy

Causes, Consequences, and the Search for Solutions

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TAG
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Outline

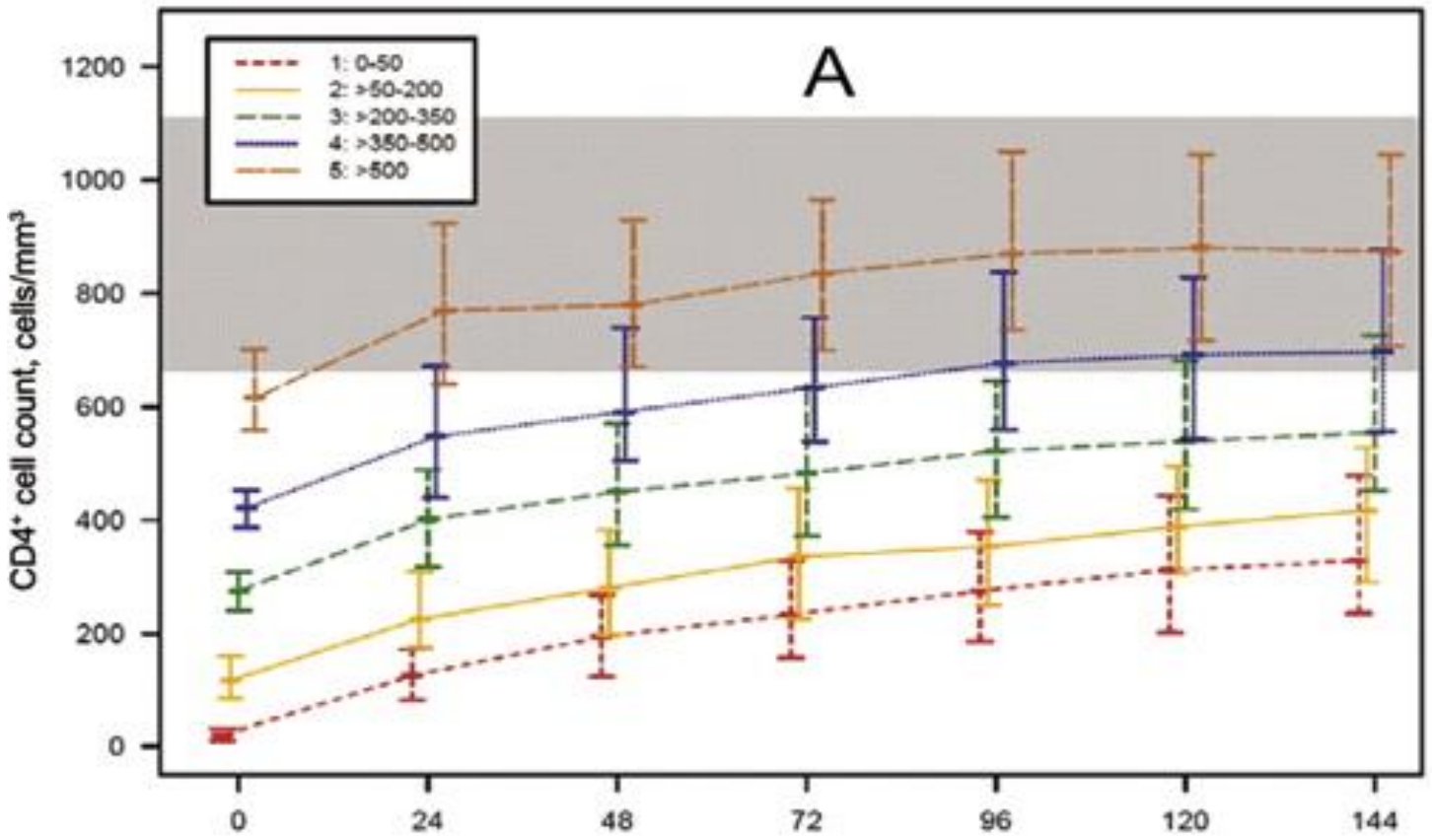
- Immune system recovery on antiretroviral therapy (ART)
  - Factors associated with persistently low CD4 T cell counts despite HIV viral load suppression
- Studies reporting increased risk of morbidity & mortality associated with lower CD4 counts on ART
- Candidate therapies for improving immune reconstitution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

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

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

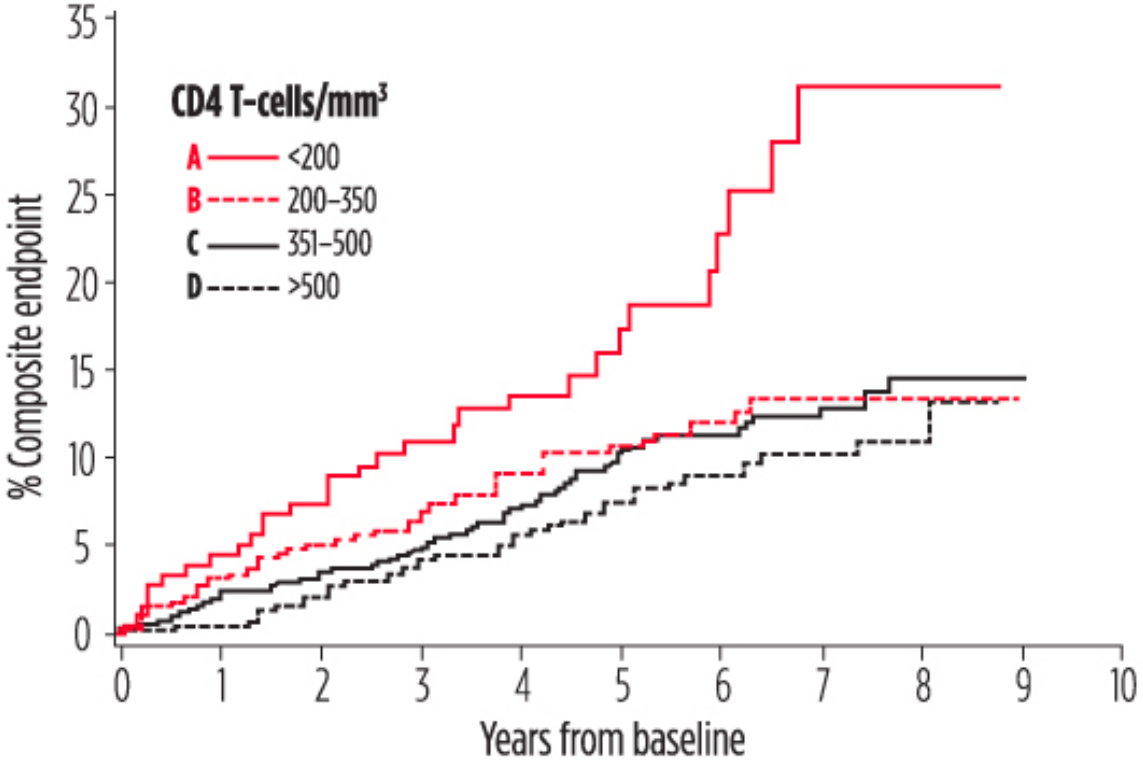
Absence of CD4+ T Cell Count Recovery Despite Receipt of Virologically Suppressive Highly Active Antiretroviral Therapy: Clinical Risk, Immunological Gaps, and Therapeutic Options, Gazzola et al Clinical Infectious Diseases, Volume 48, Issue 3, 1 February 2009, Pages 328–337

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

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.

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 in development by Korean Company NeoImmuneTech, but no studies planned in HIV (as yet)

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
- Despite advocacy efforts, biotech manufacturer Sangamo BioSciences has not shown interest in pursuing development of SB-728-T for this population

Candidate therapies

- A variety of other approaches under study by academic investigators
- Probiotics
  - Some reports of anti-inflammatory and other benefits but relatively few published studies in people with suboptimal immune recovery (ongoing trial of VSL#3 in Canada)
- Mesenchymal stem cells
  - Under study in China and Spain, initial report of CD4 count and anti-inflammatory benefits in small pilot trial
- Pyridostigmine (acetylcholinesterase inhibitor used to treat myasthenia gravis)
  - Randomized trial ongoing in Mexico, some evidence of CD4 benefit reported in uncontrolled pilot study

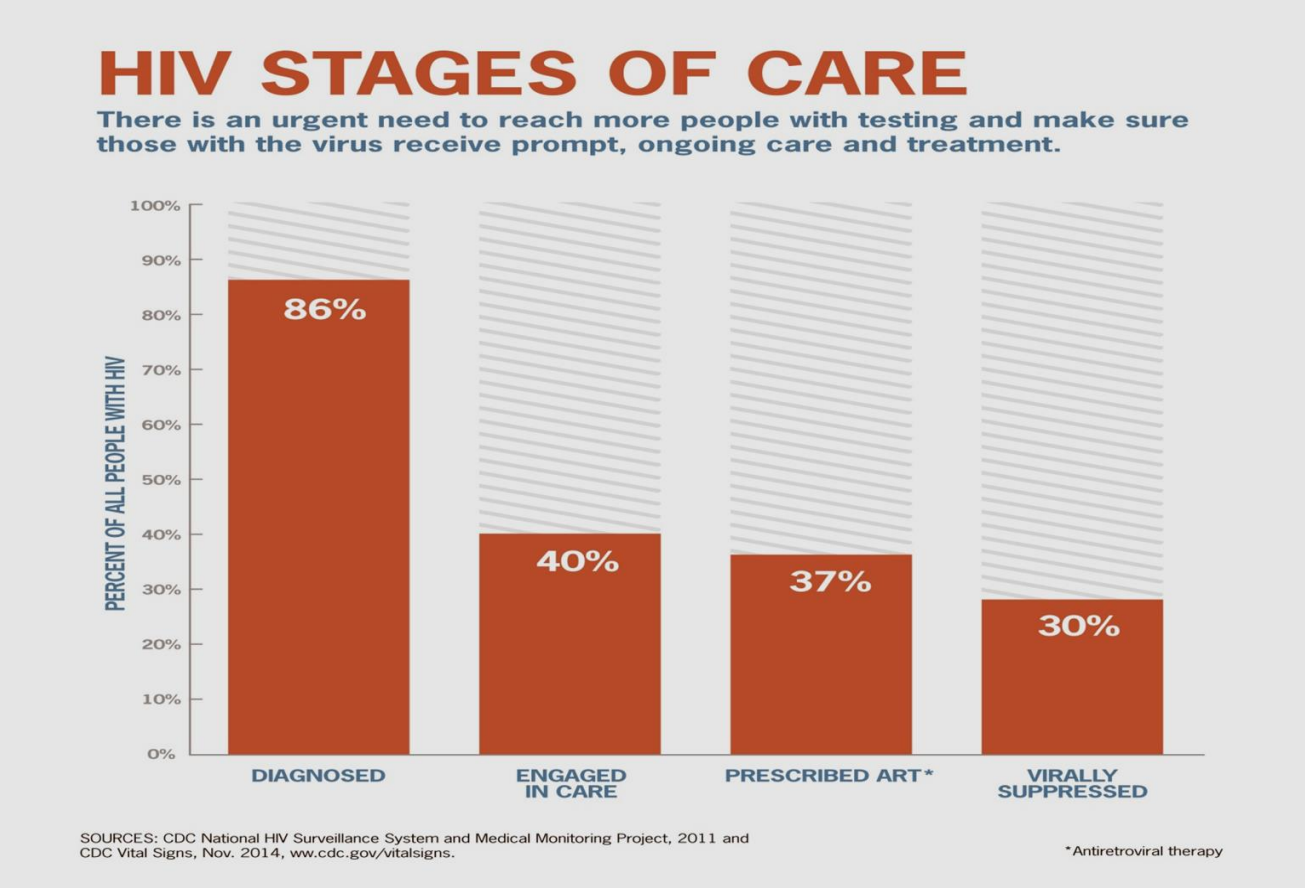
Candidate therapies

- Antifibrotic drug losartan
  - Published study reported CD4 T cell benefit from antifibrotic drug added to ART in the SIV/macaque model
  - Two ongoing trials of losartan in HIV+ people on ART with CD4 T cells <600 (clinicaltrials.gov listings: NCT01852942 and NCT02049307)
- Arabinoxylan rice bran supplementation (BRM4)
  - Nutritional supplement being studied in HIV+ people on ART with CD4 T cells 100-350 at the University of Southern California

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

US population estimates



- Total HIV+ Population in the US: 1.3 Million
- 30% Virally Suppressed = 390,000 people
- ~20% of 390,000 may have suboptimal immune recovery = 78,000
- Rough estimate: may have increased with recent increases in proportion of people with HIV suppression

Predicted yearly additions to population

- The most recent CDC surveillance report states:
  - Among persons with an HIV diagnosis during 2015, 21.6% of infections (8,617) were classified as stage 3 (AIDS) at the time of diagnosis
  - This proportion has decreased slightly in recent years: in 2013, it was 23.6% of infections
- A conservative estimate would be that ~20% of these late-diagnosed individuals might become INRs (~1,500-2,000 individuals per year)
- This trend should hopefully continue to decline in the future depending on outreach/education efforts for treatment and prevention
- At the current rate, it is extremely unlikely that there will ever be over 200,000 HIV+ individuals with suboptimal immune reconstitution in the US (the orphan drug designation patient population maximum)

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1 - 25 of 30 >>

Designations: 30

#	Generic Name	Orphan Designation	Designation Date	Designation Status
1	9-nitro-20-(S)-camptothecin	Treatment of pediatric HIV infection/AIDS	05/15/2001	Designated
2	Alfentanil	Treatment of painful HIV-associated neuropathy	08/09/2005	Designated
3	Atovaquone	Primary prophylaxis of HIV-infected persons at high risk for developing Toxoplasma gondii encephalitis.	03/16/1993	Designated/Withdrawn
4	Atovaquone	Prevention of Pneumocystis carinii pneumonia (PCP) in high-risk, HIV-infected patients defined by a history of one or more episodes of PCP and/or a peripheral CD4+ (T4 helper/inducer) lymphocyte count less than or equal to 200/mm3.	08/14/1991	Designated/Approved
5	capsaicin	Treatment of painful HIV-associated neuropathy	05/02/2003	Designated
6	Carbovir	Treatment of persons with AIDS and in patients with symptomatic HIV infection and a CD4 count less than 200/mm3.	12/13/1989	Designated/Withdrawn
7	Daunorubicin citrate liposome injection	Treatment of patients with advanced HIV-associated Kaposi's sarcoma.	05/14/1993	Designated/Approved
8	Deslorelin		11/05/1987	Designated
9	Dihydrotestosterone	Treatment of weight loss in AIDS patients with HIV-associated wasting.	02/05/1996	Designated
10	Epoetin alfa	Treatment of anemia associated with HIV infection or HIV treatment.	07/01/1991	Designated/Approved
11	Epoetin alpha	Treatment of HIV associated anemia related to HIV infection or HIV treatment.	03/07/1989	Designated
12	Human immunodeficiency virus immune globulin	Treatment of HIV-infected pediatric patients.	01/04/1995	Designated/Withdrawn
13	Human immunodeficiency virus immune globulin	Treatment of HIV-infected pregnant women and infants of HIV-infected mothers.	03/25/1992	Designated/Withdrawn
14	ibalizumab	Treatment of HIV-1 infection in treatment experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy	10/20/2014	Designated
15	Marijuana	Treatment of HIV-associated wasting syndrome.	05/25/1999	Designated
16	mepivacaine	Treatment of painful HIV-associated neuropathy	10/18/2006	Designated
17	Natural human lymphoblastoid interferon-alpha	Treatment of papillomavirus warts in the oral cavity of HIV positive patients.	08/10/2000	Designated
18	nevirapine	Prevention of HIV infection in pediatric patients under the age of 16 years	11/25/2009	Designated
19	Oxandrolone	Adjunctive therapy for AIDS patients suffering from HIV-wasting syndrome.	09/06/1991	Designated
20	Recombinant human CD4 immunoglobulin G	Treatment of AIDS resulting from infection with HIV-1.	08/30/1990	Designated
21	Recombinant human nerve growth factor	Treatment of HIV-associated sensory neuropathy.	04/16/1999	Designated
22	Recombinant soluble human CD4 (rCD4)	Treatment of AIDS in patients infected with HIV virus.	03/23/1989	Designated
23	REMUNE HIV 1	Treatment of pediatric HIV/AIDS (age through 16 years)	02/14/2014	Designated
24	Rifabutin	Prevention of disseminated Mycobacterium avium complex disease in patients with advanced HIV infection.	12/18/1989	Designated/Approved
25	Somatropin	Treatment of patients with HIV-associated adipose redistribution syndrome	03/16/2004	Designated

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<< 26 - 30 of 30

Designations: 30

#	Generic Name	Orphan Designation	Designation Date	Designation Status
26	tenofovir	Treatment of pediatric HIV infection.	03/17/2009	Designated/Approved
27	Testosterone	For use as physiologic testosterone replacement in androgen deficient HIV+ patients with an associated weight loss.	09/22/1997	Designated
28	Testosterone	Treatment of weight loss in AIDS patients with HIV-associated wasting.	02/05/1996	Designated/Withdrawn
29	Thalidomide	Treatment of HIV-associated wasting syndrome.	03/11/1996	Designated
30	Tramadol hydrochloride	Treatment of painful HIV-associated neuropathy	01/28/2005	Designated

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. However there is also a lack of information on non-serious clinical symptoms in people with suboptimal immune recovery that needs to be addressed
- 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?