Immune Reconstitution on Long-Term Highly Active Antiretroviral Therapy

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Definitions

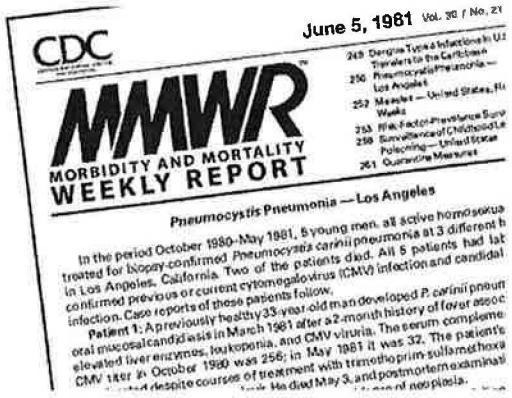
Immune Reconstitution refers to improvement of immunity manifested by clinical outcomes and laboratory values. The Immune Reconstitution Inflammatory Syndrome (IRIS) at the onset of antiretroviral therapy will not be discussed.

The term 'long-term' refers to clinical and laboratory outcomes after more than four years of antiretroviral therapy with a particular focus on patients beyond 5 years of treatment.

The term 'highly active' antiretroviral therapy (HAART) is used synonymously with 'combination antiretroviral therapy' (cART) and refers in most cases to triple-therapy meeting commonly accepted definitions.

Perspective

History


CDC

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MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexua treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different h in Los Angeles, California. Two of the patients died. All 5 patients had lat confirmed previous or current cytomegalovirus (CMV) infection and candidal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed P. carinii pneum oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc elevated liver enzymes, leukopenia, and CMV viruria. The serum complem CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's despite courses of treatment with trimethoprim-sulfamethoxa He died May 3, and postmortem examinati of neoplasia.

Fig. 1 At the same time as Dr. Michael Gottlieb and colleagues from UCLA reported 5 cases of PCP, the CDC pharmacy, had already noticed an unusual demand for pentamidine.

June 5th 2011 marks the 30th anniversary of the first AIDS case reports in the medical literature.[1] The first clinical study of combination antiretroviral therapy dates back more than 20 years,[2] and the first randomized clinical trials with 'highly active' triple-therapy were published 15 years ago.[3] The first anti-HIV compounds (AZT, ddC) had originally been developed as cytostatic drugs at the National Cancer institute in the 1960s and their development into antiretroviral drugs was pioneered by cancer biologists and pharmacologists who were used to developing drugs providing only marginal survival benefits, often of greater benefit when used in combination.[4] Severe side effects were easily accepted as antiretroviral therapy with AZT was already shown early on to provide clinical benefit and increase T-helper cells.[5] The use of antiretrovirals (ARVs) as long-term or even life-long therapy was not anticipated in the first years of antiretroviral development.

Importance

At the end of 2009 more than 6 million people worldwide were taking antiretroviral therapy. Of these, 5 million live in low- and middle-income countries. In 2009, 1.2 Million people started HAART for the first time.[6,7] The number of people on HAART in high-income countries is between 1-1.3 Million; approximately 650,000 people are on HAART in the US (estimated by antiretroviral (ARV) sales figures and estimated annual costs of $10,000 – 12,000).[8,9] The United States contribute a large share of the funding for antiretroviral therapy in low- and middle-income countries by PEPFAR (Presidential Emergency Plan for AIDS Relief), established in 2003, and the Global Fund established by Bill Gates.

Treatment coverage for HIV patients in need is approaching 40% in sub-Saharan Africa, > 50% in South America and the Caribbean, while it remains <20% in Eastern Europe and central Asia.[7] Annual AIDS related mortality has started to decline by almost 25% in sub-Saharan Africa (300,000 deaths avoided), following the trend of most other regions in the world after introduction of HAART.[7]

HIV incidence has decreased by ~25% in most countries in Southern Africa and is decreasing world-wide.[7] This is likely a direct and indirect result of increased availability of HAART, reducing not only patient infectivity but also leading to increasing acceptance of HIV testing, and subsequent behavioral changes in people aware of their HIV serostatus.[7]

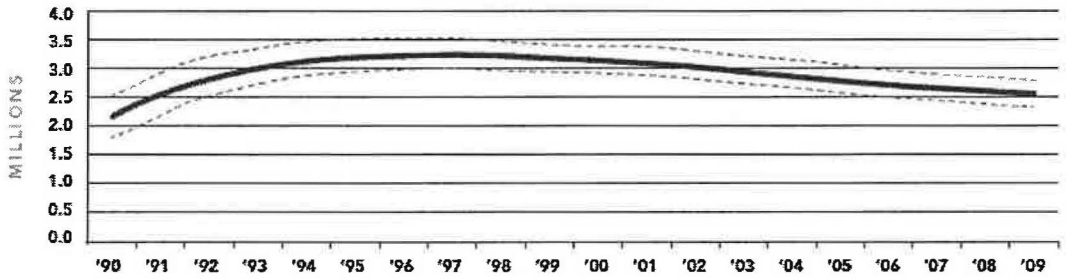


Fig.2 Number of people newly infected with HIV UNAIDS Report on the Global AIDS Epidemic

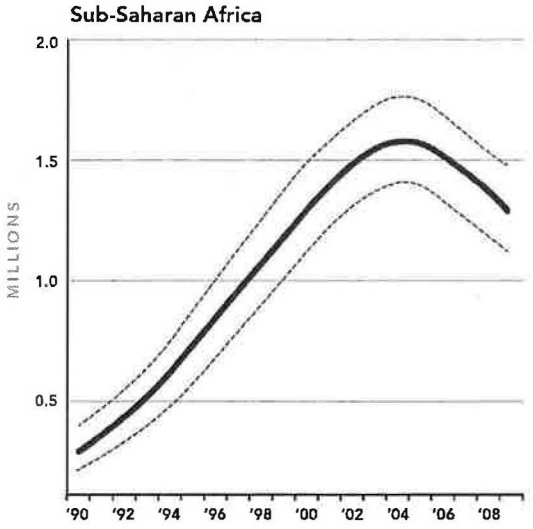


Fig.3 Annual AIDS related deaths in Millions in sub-Saharan Africa 1990-2009
UNAIDS Report on the Global AIDS Epidemic

HIV and its preferred T-cell subsets and receptors

The initial 1981 case report in the New England Journal of Medicine[10] described four previously healthy men with Pneumocystis jiroveci pneumonia (PCP) and "...extensive mucosal candidiasis and multiple viral infections..." The authors postulated an underlying T-cell defect and correctly identified massive depletion of CD4+ T-cells as the hallmark of the new syndrome. Interestingly, they also noticed intense T-cell activation – which would not be appreciated as a major pathogenetic factor until 10-15 years later.[11] The role of the CD4 receptor for virus cell entry was first recognized in 1984.[12] It has been estimated that 90% of all HIV infected cells are T-cells, almost all of them CD4+. CD4 expressing activated macrophages comprise only 7%.[13] Only few CD4-negative human cells can become infected, mainly brain astrocytes, which express CCR5 abundantly. The rate-limiting step though occurs right before cell entry: binding to the so-called 'co-receptor' CCR-5.[14] CCR5 is the exclusive co-receptor for mucosally transmitted virus and plays a dominant role for the pathophysiology of HIV infection, likely due to its ubiquitous expression on many cell types (T-cell subsets, macrophages, dendritic cells, and microglia). The V3 loop of the HIV gp120 surface protein binds CCR5 only after first undergoing a conformational change, which is induced by the prior binding with CD4. Only in the late stages of HIV infection and most often associated with profound immunodeficiency, HIV strains emerge that can enter T-cells through CXCR4 receptors which predominate on naïve T-cells.[15,16]
Hypotheses to explain the persistence of HIV on HAART have included:

- The latent infection of extremely long-lived CD4+ central memory cells,[17]
- Self-renewal mechanisms within the central memory compartment,[18,19]
- Occasional infection of CD34+ hematopoietic stem cells,[20]
- The fact that HIV-reactive CD4+ T-cells are 4 times as likely to become HIV infected themselves,[21] making an effective CD4-dependent immunologic control unlikely.

What causes immunodeficiency? How do CD4+ T-cells go out of stock?

Within 2-3 weeks after primary HIV infection (PHI) the majority of resting CD4+-effector memory cells in extra-lymphatic tissues become either infected or undergo apoptosis, leading to a significant decrease in CD4 counts in peripheral blood and plasma viral loads of up to 10^8 copies/mL.[22] This is particularly pronounced in the GALT, possibly leading to disruption of intestinal mucosal integrity and persistent bacterial translocation as measured by elevated bacterial lipopoly–saccharide levels (LPS) and thus potentially contributing to chronic immune activation.[23] It has been argued that the majority of human T-cells reside in the GALT, which would make this massive loss of T-effector memory cells during PHI even more significant. However, newer estimates for the proportion of human T-cells residing in the GALT are closer to 10%.[24] After 2-3 weeks the emerging HIV-specific CTL responses as well as decreased target cell availability curtail viral replication and CD4 counts in peripheral blood subsequently rebound because of ongoing massive T-cell regeneration in the central memory compartment. Tissue CD4+ effector memory cell populations stabilize at low absolute levels, seemingly at the expense of the central memory and naïve compartment which decreases in size relative to the effector memory compartment.[22,25] HIV replication now mainly occurs in dispersed patches of highly activated cells but at an overall level that is ~100x decreased compared with acute infection.[22] Decreased immunity to de-novo and recall antigens is likely a result of the decreased diversity and cell count in the central memory compartment which is likely the key 'player' during chronic HIV infection (even though there is also a significant decrease in naïve CD4+ T-cells of B-cells during chronic infection).[25,26]

Several facts about chronic HIV infection remain incompletely understood: During the chronic phase only 1/10,000 CD4+ T-cells in lymphoid tissues are HIV-infected. Massive immune activation and increased rates of apoptosis affect CD4+ and CD8+ T-cells equally, yet the gradual decline affects predominantly CD4+ T-cells.[27] It has been argued that CD4 cells eventually decline because of 'exhaustion' or premature senescence, however telomere length does not appear to be affected.[28] Simian immunodeficiency virus (SIV) infection is very prevalent and has likely co-evolved for a long period of time in most African primates. The study of these natural hosts of SIV has been very informative. The name SIV is a misnomer, as the virus does not cause immunodeficiency in most natural hosts - despite chronic viral replication at levels of human HIV diseases and robust immune responses during acute infection. Extensive studies in chronically SIV infected African primates have revealed 3 significant differences to human HIV disease: 1) African primates display massive down-regulation of CD4/CCR5 co-expression on T-cells, 2) Natural hosts have normal levels of IL-17 producing T-cells (TH-17 cells) in the lamina propria of the gut. IL-17 is induces local G-CSF production, thus attracting neutrophils and is thus likely an important factor for maintained mucosal integrity and prevention of microbial translocation. This in turn is an explanation for 3) the absence of systemic immune activation in these animals.[23,29]

Measures of Immunodeficiency

CD4/CD8 counts

Measurements of absolute CD4+ T-cell values in peripheral blood were the only prognostic tool available in the early days of the epidemic and rapidly became a standard measurement in the clinical care of HIV infected patients. CD4 counts correlate well with the risk of opportunistic infections (OIs) in HIV disease[30,31] and have stayed an important marker for HIV disease staging. The CD4 count is still the main criterion for decision making about prophylaxis of OIs[32] and HIV treatment.[33] The current recommendation for CD4 testing is every 3-6 months in untreated HIV-disease.[33] CD8+ T cells comprise the other major fraction of T-cells in peripheral blood. Absolute CD8 numbers are often elevated early on due to immune activation and proliferation and tend to decline only in the late stages of HIV disease. Thus the CD4/CD8 ratio (≈CD4% value) is diminished early on but has not been shown to provide additional prognostic information.[34]

Detection of plasma virus

Quantitative nucleic acid amplification techniques became the standard of care in 1996 at the onset of the HAART era and proved to be an extremely useful monitoring tool.[35,36] Plasma viral load peaks during PHI and then reaches an individual set point, typically ~100x lower than in PHI. Plasma viral load is a strong independent predictor of clinical disease progression but interestingly correlates poorly with CD4 decline.[31,37]

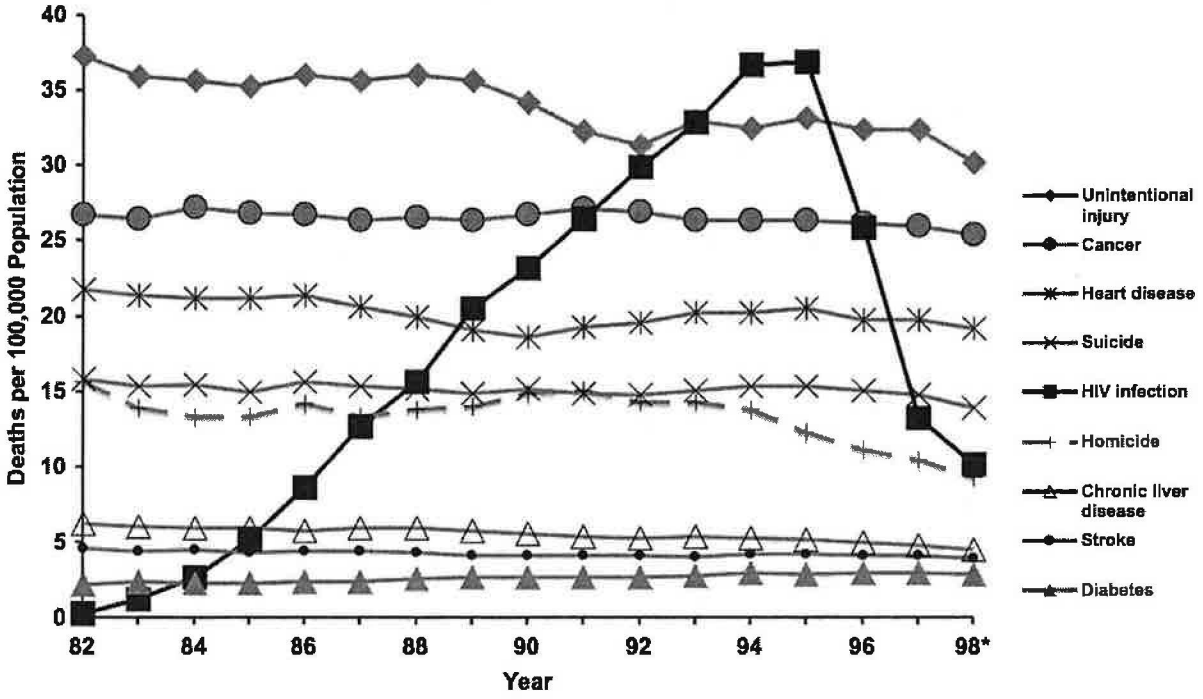
Skin Test Anergy

Impaired delayed type hypersensitivity skin testing to common recall antigens (in use were mainly mumps and candida) has been shown to be an independent predictor for AIDS progression and mortality in the early 1990s.[38,39] Anergy in conjunction with routine PPD testing was abandoned by the CDC in 1997.

Immune Activation

Immune activation markers on CD4+ and CD8+ T-cells have a stronger predictive value for disease progression and death than CD4 count and plasma viral load.[11,40] The most commonly used marker is CD38 either alone or in combination with HLA-DR. However, due to lack of standardization this method has not been used in clinical routine. Serum markers of immune activation like $ß_2$-microglobulin, neopterin, and soluble IL-2 receptor are less discriminatory.[41]

HAART



The acronym HAART was first used 1996 for triple drug combinations including 2 nucleoside analogue reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI) – later the definition was expanded to other forms of combination antiretroviral therapy (cART) including 3 or more drugs. By combining drugs with different genetic pathways to resistance, the durability of the immunological benefit greatly increased. Previously, with most antiretrovirals in mono-therapy there had only been temporary improvement of immune status and CD4-counts, typically lasting from 3-12 months. In the mid 90s, dual NRTI therapy was producing much longer lasting effects but was still marred by high rates of immunologic failure because of viral resistance. By adding protease inhibitors (first one was FDA approved 12/95) to dual NRTI regimens, plasma viremia became rapidly undetectable and patients with preexisting severe opportunistic infections started to recover in ways that was exceeding most physicians expectations.

The steep drop in HIV-mortality between 1995-1997 is often credited to HAART (which was not widely prescribed until late 1996). The initial decrease is more likely a consequence of widespread use of dual NRTI therapy in 1994 and 1995.

Pathophysiology of Immune Reconstitution

T-Cell Renewal After Depletion

T-cell reconstitution following lymphopenia from chemotherapy or stem cell transplantion is often slow and incomplete as de novo T-cell production is impaired in this setting. T-cells can be generated from two pathways: 1) thymus derived through active thymopoiesis and 2) peripheral

expansion of clones through homeostatic proliferation.[42] The thymus has a remarkable capacity for renewal but its ability to recover is also significantly influenced by age. Over the age 45, the frequency of significant renewal of thymopoiesis is severely reduced. Phenotypically naïve CD4 T cells exported into the periphery approach normal levels in adults only after 2 years. In many older adults recovery of naïve cells takes 3 – 5 years; in some, naïve cells remain below normal levels even after decades, as without robust thymopoiesis, CD4+ T-cell reconstitution is permanently impaired. The alternatively is IL-7 dependent homeostatic peripheral expansion of T-cells, which can lead to a rapid expansion of the T-cell pool, which is associated with a phenotypic shift from naïve to activated memory cells. It is distinct from 'homeostatic cycling', whereby naïve and memory cells cycle in an immuno-competent host, without change in cell phenotype or overall T-cell expansion.[42]

Effects of HAART

New sensitive assays to measure drug potency in vitro together with the knowledge of achievable intracellular drug levels have led to the hypothesis that currently recommended HAART regimens will *completely* inhibit retroviral replication, i.e. prevent infection of any new target cells.[43] This concept is backed up by the failure of multiple HAART-'intensification' studies[44-48] and the lack of viral evolution on HAART in treatment interruption studies.[49]
The rapid expansion of peripheral T-cells observed 1-2 weeks after initiation of HAART is due to redistribution of memory cells from peripheral lymphoid tissues (lymphocytes in peripheral blood comprise only 2% of total body lymphocytes).[50] After 7-14 days of HAART all activated virus-producing T-cells have died off – these cells are responsible for 99% of overall HIV replication in untreated HIV infection. Subsequently the rate of T-cell expansion in the peripheral blood slows down markedly, resulting in a biphasic curve, which mirrors the decline of plasma viremia.[50] Reconstitution of the T-cell repertoire with naïve cells is age-dependent and is lagging behind the overall restoration of CD4+ T-cells and can remain incomplete. Pre-HAART levels of naïve T-cells have been shown to have a strong predictive value for overall CD4 recovery,[51] whereas high pre-HAART percentages for CD127- CD45RA- cells (T-effector memory cells) have a negative predictive value.[52,53]

Immune Activation

Markers of immune activation on T-cells as well as the CD4/CD8 ratio rapidly decrease after the initiation of HAART, but absolute CD8 numbers and absolute and relative values of activated CD8 cells do not normalize even after 6 years of suppressive HAART. The degree of CD8+ T-cell activation does not correlate well with absolute peripheral CD4 counts.[54-56] Markers of decreased monocyte function associated increased fibronectin fragments resulting from a chronic inflammatory state may also persist for years on effective HAART and has been shown to go along with increased mortality.[57] Similarly, markers of microbial translocation (LPS, soluble CD14, and bacterial DNA) can remain elevated for years on HAART. By some reports this is not correlated with markers of T-cell activation.[58,59]

Mortality on HAART

A mortality benefit was observed as early as 6 weeks after starting HAART in multiple cohort studies. This seems to be more pronounced in resource-limited settings but a similar trend can be observed for hospitalization rates in resource-rich settings.[60-62] The marked decrease of morbidity and mortality observed in the first 6-12 weeks after starting HAART is 'above and beyond' from what would be expected given the initial increase in CD4 cells and is may be more

reflective of the rapid decrease in immune activation (see below). All-cause mortality continues to decline dramatically during the first year of HAART – but the overall number of deaths in the first year is still manifold higher than during subsequent years, when survival curves become much flatter.[61,63,64] Life expectancy estimates of on HAART vary greatly between Europe and the US, and by the underlying clinical scenario. A recent Dutch publication estimated the 'years of life lost' because of HIV infection as only 1-2 years (when initiating HAART during asymptomatic HIV infection, assuming no drug use).[65] The estimate of a recent US publication analyzing 'real life patients' with late treatment initiation and high rate of treatment discontinuations was 12 years of life lost (up to 16 years for black women).[66]

Opportunistic Diseases on HAART

Pathogen Specific Immunity

In vitro T-cell reactivity to common recall antigens like candida or tetanus toxoid were restored after more than one year on HAART, whereas HIV-specific T-cell responses were not observed within the first 2.5 years of HAART in an early study.[67] Pathogen specific T-cell reactivity has also been shown to correlate with clinical outcomes for Kaposi sarcoma (KSV), pneumocystis jiroveci pneumonia (PCP), and CMV disease.[68-70] Interestingly, relatively little literature exists. Response to some vaccines remains impaired even after 4-5 years of HAART, especially for patients with low CD4 nadir values.[71] Immunity against antigens to which the immune system is no longer exposed (e.g. smallpox) may not be restored at all.[72]

Clinical Events

Prophylactic use of sulfonamides in combination with folate synthetase inhibitors and later pentamidine to prevent pneumocystis carinii pneumonia were first advocated in 1983 and became standard of care in 1990 despite initial concerns about toxicity.[73,74] It had become apparent that the risk of developing distinct OIs could be accurately estimated by the patient's current CD4-count.[30] The dramatic rise of many patients' CD4 counts after starting HAART in 1997 led some clinician to discontinue OI prophylaxis. The safety of this approach was first demonstrated in 1999 for primary PCP prophylaxis, if patient's CD4 values had crossed the PCP "specific" threshold of 200 CD4+ T-cells/μL.[75] This approach was later replicated for primary and secondary prophylaxis for most other HIV associated OIs.[76]

Weeks after starting HAART, there is a dramatic decline in OI incidence, most pronounced in resource limited settings, yet in the first year after starting HAART the absolute number of OI-events remains high compared with the experience in resource rich settings. IRIS may contribute to some of the morbidity (but little to mortality) and both nadir CD4 count and actual CD4 count remain strong predictors for opportunistic disease and death (actual CD4 count only for low counts < 100cells/μL).[64] Over longer periods on HAART, even low CD4 counts lose much of their predictive value for the occurrence of AIDS defining events.[63,77]

Non-AIDS disease on HAART

One year after the start of the widespread use of HAART, reports about patients with characteristic body habitus changes (buffalo hump, "Crix-belly", named after Crixivan®, the first "block-buster" protease inhibitor on the market), as well as dyslipidemia, insulin resistance, and premature atherosclerotic and coronary disease in the medical literature became very prevalent.[78-80] Initially, these manifold abnormalities were thought to represent different degrees of a complex clinical syndrome, triggered by the cumulative use of protease inhibitors.[81]

Throughout the next decade it became clear that members of all 3 classes of antiretroviral drugs could be linked to unique manifestation of what was once thought to be the "lipodystrophy metabolic syndrome" and that HIV infection itself is an important contributor, possibly mediated by persistent low level immune activation.[82]
In the second decade of HAART, non-AIDS defining events have gained much prominence, as mortality from these events on long-term HAART now clearly outweighs mortality from AIDS events.[83,84] Diseases for which an increased incidence and mortality in HIV patients on long-term HAART has been shown include: End-stage renal disease, atherosclerotic disease, liver cirrhosis from various causes, and non-AIDS defining malignancies.[84] Updated (actual) CD4 counts on HAART have been shown to be a predictor for many of these events,[85] which points to the central role of incomplete or protracted immune restoration.

Numeric Recovery of Peripheral CD4+ T-Cells

Normal CD4 values

The normal range of CD4+ T-cell values varies by age, ethnicity, and gender and has a large standard deviation. Children have much higher values, and mean values for females are typically 10-15% higher than in males. Certain African and Asian ethnicities have lower mean values. A CD4 count between 500-1200 is commonly accepted as normal. Of note, there is marked diurnal variation in HIV uninfected individuals, likely reflective of the fact that peripheral CD4 counts significantly drop by up to 400 cells/μL when healthy volunteers rested for 60 minutes prior to CD4 sampling.[86-88]

Rationale for Monitoring

It is undisputed that most patients on uninterrupted HAART will breach the "AIDS-threshold" of 200 cells/μL.[76] Due to the low number of opportunistic events beyond the first year of stably treated HIV infection, the CDC has recently changed its recommendation for CD4 testing and now recommends to check CD4 counts only every 6-12 months in stably treated HIV-disease.[33]

Discordant CD4 response to HAART

There have been various definitions for patients with 'insufficient or discordant' CD4 responses to virologically suppressive HAART. One commonly accepted definition is an increase of <50 CD4 cells/μL in the first 9 months of HAART. This occurs in ~10% of patients and is mainly predicted by very low nadir CD4 count, multiple prior treatment interruptions and a history of invasive atypical mycobacterial infection.[89,90] Patients who maintain very low CD4 values for years are often concerned about their immune status, even in the absence of any health complaints. If the relative CD4 count (CD4%) is much closer to normal than the absolute value, patients are usually lymphopenic and should be investigated for alcoholism and liver disease. There have been multiple attempts to affect immune restoration in these patients, either with cytokine administration or 'intensification' of fully suppressive HAART, typically with novel antiretroviral agents, but a durable impact of CD4 counts has never been demonstrated.[44-48]

Time Course and Clinical Predictors of CD4 Recovery

There is an abundance of medical literature investigating the time course of CD4 recovery and its clinical predictors. In the late nineties, some investigators reported a flattening of the CD4 curves after 1-2 years of treatment – likely a reflection of the end of the redistribution phase.[50] In the mid 2000s many investigators reported that CD4 cells reached a plateau effect after 4-6 years of HAART after which further increases were unlikely to occur.[91,92] The recent literature

highlights the fact that about half of patients on long-term HAART show continued CD4 increases for up to 10 years. However, as many as 10-20% of patients have not reached normal CD4 values and the trajectory of their individual CD4 slopes indicates that they may never achieve normal values.[93,94]
The following predictors have convincingly been linked with greater short and long-term CD4+ T-cell increases on HAART by multiple cohort studies:[89,92-98]

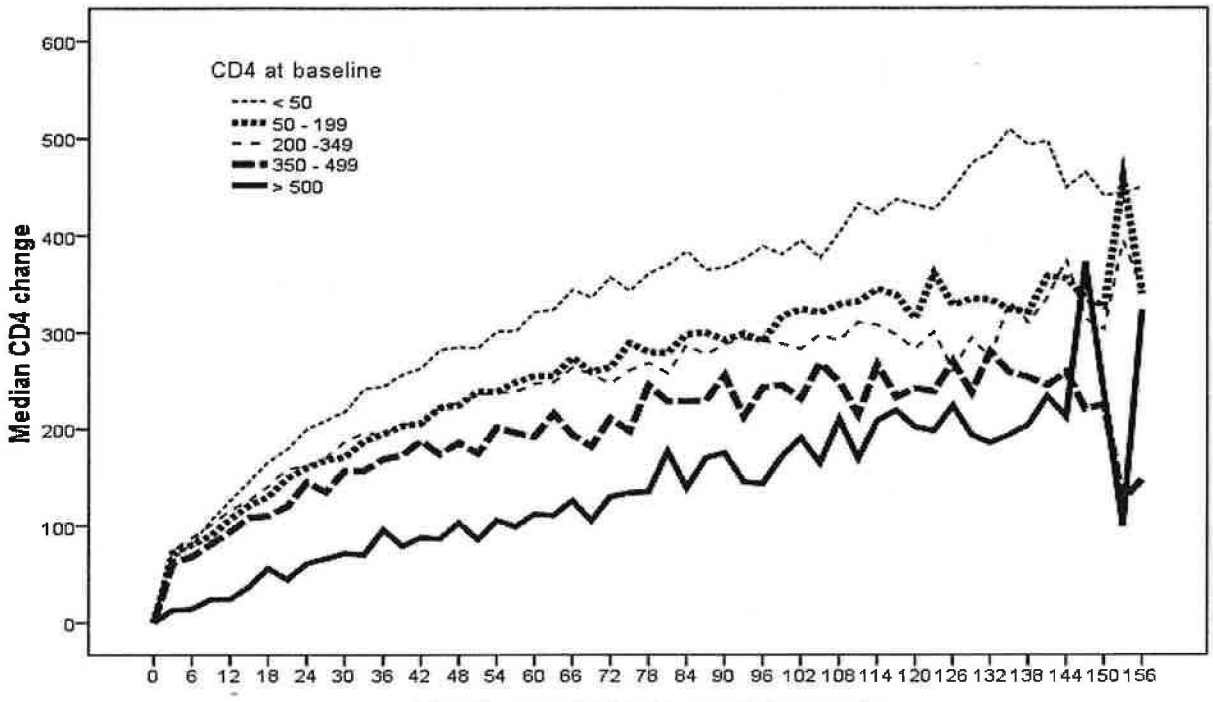
- Younger age (thymic reserve)
- Higher baseline HIV-RNA (greater number of virus producing salvageable CD4-cells)
- Lower baseline CD4 counts (a baseline CD4 count < 200/μL is a strong *negative* predictor for reaching a CD4 count > 500/μL)
- Short duration of prior HAART interruptions (uninterrupted HAART is best)

Additional *positive* predictive factors for CD4 increases on HAART have been identified by some cohort studies only and have not been replicated by others and have not been shown yet to influence long-term CD4 recovery:

- Hepatitis B surface antigen negativity[99]
- Hepatitis C antibody negativity[98]
- No prior clinical AIDS event[98]
- Steeper decline of CD4 cells before HAART[100,101]
- No injection drug use[92]
- Receipt of stavudine versus zidovudine or abacavir as part of HAART[97]
- No zidovudine in HAART (only for absolute, not relative CD4 values)[102]
- Low level viremia during HAART (viral load 'blips')[103-105]

Unpublished Data from the Department of Veterans Affairs

The HIV data from the US Veterans Administration contains the non-narrative elements of the medical record of 65,775 HIV-infected veterans between 1980-2009 (demographics, lab values, ICD9 codes, pharmacy refill data, admission data). Sixty percent ever took antiretrovirals, and 21,441 were ever prescribed HAART for more than 14 days.
We tried to assess the patients CD4 responses while on HAART utilizing the pharmacy benefits database refill data, which enabled us to assess patient adherence. We selected 14,263 veterans who had less than 30 days of any antiretroviral exposure prior to starting HAART and at least 2 CD4 values (baseline and ≥ 6 months). About 42% were African American, 41% European American. Median age was 48 years; median CD4 before starting HAART was 232/μL, median HIV-RNA before HAART was 31,600 cop/mL. 34% had evidence for HCV infection, 12% for chronic Hepatitis B, 43% ever had an ICD9 code indicative of drug use and 6% indicative of liver cirrhosis. Patients were censored if they had no refills for any antiretroviral medication for > 90 days. The median CD4 counts of all CD4 baseline strata (<50, 50-199, 200-349, 350-499, ≥500) showed continuous increases for at least 10 years; if their baseline CD4 count was <200/μL the median CD4 count showed continued increase for at least 12 years.



Month	0	12	24	36	48	60	72	84	96	108	120	132	144	156
<50	2288	1439	967	753	564	476	387	301	243	183	127	101	60	29
50-199	3735	2296	1703	1321	1075	849	668	557	423	343	257	181	121	36
200-349	3826	2271	1727	1252	1003	793	612	481	390	298	205	144	79	21
350-499	2223	1336	981	778	618	498	415	325	245	199	139	99	57	16
500+	2191	1309	1013	811	612	485	395	287	226	174	122	74	42	5

We conducted a mixed model analysis to identify predictors for the initial increase of CD4 values in the first 4 years and the subsequent changes > 4 years of continuous HAART. We found the following predictors for greater (+) and lesser (-) changes in CD4 counts over time:

Predictor	Effect on CD4 Change Year 0-4	P	Effect on CD4 Change Year 4-13	P
Baseline CD4 count	-	<0.0001	-	<0.0001
Baseline HIV-RNA	+	<0.0001	+	<0.0001
Age	-	<0.0001	+	0.02
Ever clinical AIDS	-	<0.0001	-	<0.0001
African American race	+	<0.0001	+	0.04
HCV co-infection	-	<0.0001	0	n.s.
HBV co-infection	0	n.s.	0	n.s.
Duration of HIV infection	0	n.s.	0	n.s.
HAART Adherence > 94%	+	<0.0001	0	n.s.
Completely suppressed HIV RNA	+	<0.0001	-	0.001
Receipt of 'modern' HAART (thymidine free NRTI backbone + boosted PI or NNRTI anchor)	+	<0.0001	-	<0.0001

Conclusions

Long-term immune reconstitution on HAART is still incompletely understood and changes in peripheral CD4 counts continue in many patients even after a decade on antiretroviral therapy. Factors that impact the long-term CD4 recovery are likely different from well established factors determining short-term CD4 recovery. The importance of uninterrupted HAART is paramount, as treatment interruptions have now convincingly been shown to have a variety of negative consequences.

Endnotes

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