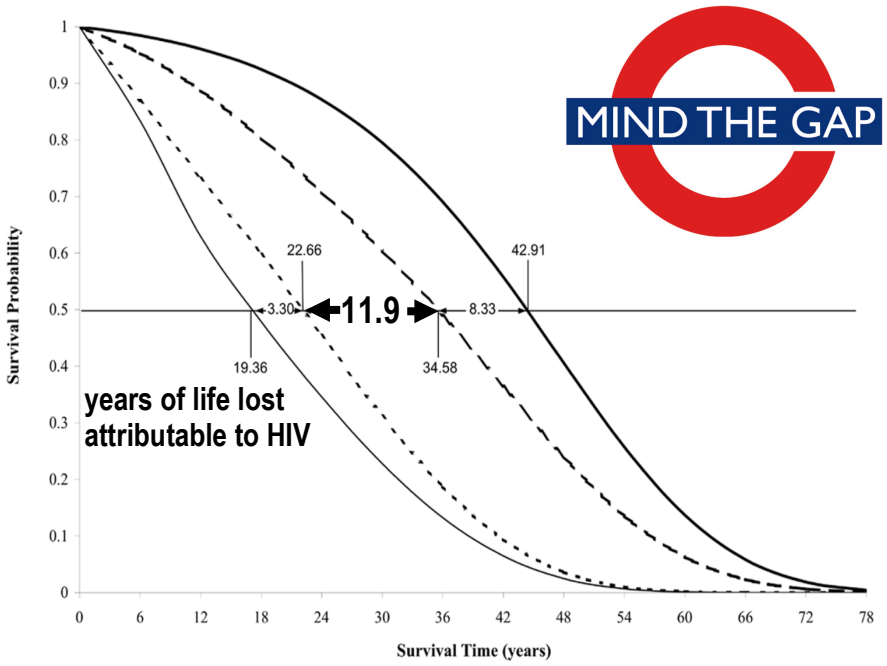
# Excess Mortality in Treated HIV-Infection




## Internal Medicine Grand Rounds

## 20 November 2015

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Henning Drechsler, M.D. has disclosed that he has no financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Drechsler will not be discussing off-label uses in his presentation.

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## Purpose & Overview

This presentation discusses the maximum mortality benefit for people with HIV infection that can be achieved with modern combination antiretroviral therapy and the accuracy by which life expectancy estimates can be made. Finally it addresses implications of a recent worldwide change in treatment recommendations.

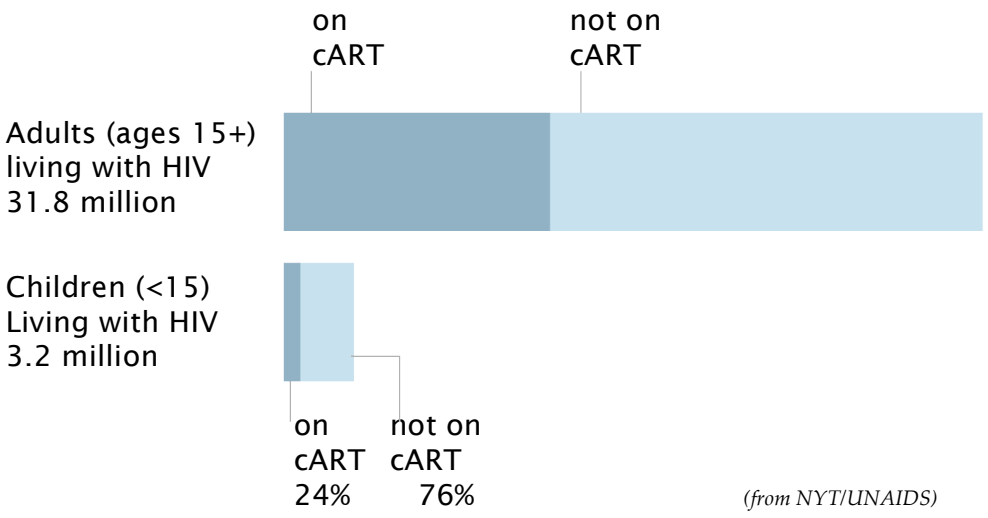
## Objectives

- To describe current antiretroviral treatment recommendation for HIV infection.
- To describe changes in HIV-related mortality that have occurred over the last 20 years.
- To describe predictors for mortality for people on stable antiretroviral therapy.

## Emerged Consensus on HIV Treatment

Combination Antiretroviral therapy (cART) has transformed the HIV epidemic by reducing the incidence of AIDS and related death and disease.(1) A major clinical trial to determine whether starting cART immediately upon HIV diagnosis rather than later, based on the level of CD4+ T-cells will clinically benefit patients was terminated early in May of 2015 after the data and safety monitoring board determined that the study question had been answered.(2) Previously, data from randomized clinical trials only supported cART initiation in patients with CD4 <350 cells/mm$^3$ and, as a consequence antiretroviral treatment guidelines had differed globally with regard to the timing of treatment initiation in asymptomatic HIV-infection for many years. The multinational Strategic Timing of Antiretroviral Treatment (START) trial had enrolled nearly 4,700 asymptomatic treatment-naïve patients with CD4 counts >500/mm$^3$ in roughly equal parts from the Americas, Africa, and Europe. The median age was 36, the median CD4 count at enrollment 650 cells/mm$^3$, and 27% were women. Patients were randomized to either receive cART immediately, or wait until reaching a CD4 <350/mm$^3$ or a clinical indication (deferred treatment arm), which was the case in 48% of patients. After a median follow-up time of 2.8 years the patients who had started cART immediately were found to have a hazard ratio of 0.43 of reaching the primary end point which was combined risk of death, serious AIDS, or serious non-AIDS event (42 vs. 96 events). Almost twice as many patients died in the deferred treatment arm (21 vs. 12) but this difference was not statistically significant. After 5 years of follow-up the mean CD4 count had reached ~940/mm$^3$ in the immediate treatment arm and ~680/mm$^3$ in the deferred treatment arm (~420/mm$^3$ if cART was initiated).

While also considering the enormous potential to curb the HIV epidemic (3) both the WHO and the European have now aligned their guidelines with the universal antiretroviral treatment recommendation that was part of the US guidelines since 2012. This move greatly increases the number of cART eligible people around the world:




*(from NYT/UNAIDS)*

# National and Global Mortality Trends

In the US of the mid 1990s, just before the availability of triple cART ("HAART"), HIV/AIDS had emerged as the leading cause of death among adults between the ages of 25-44.(4) Mortality rates for people living with HIV (PLWH) <55 years of age has since changed dramatically. The introduction of cART resulted in an average life expectancy (LE) increase after HIV diagnosis from 10.5 to 22.5 years from 1996 to 2005.(5)

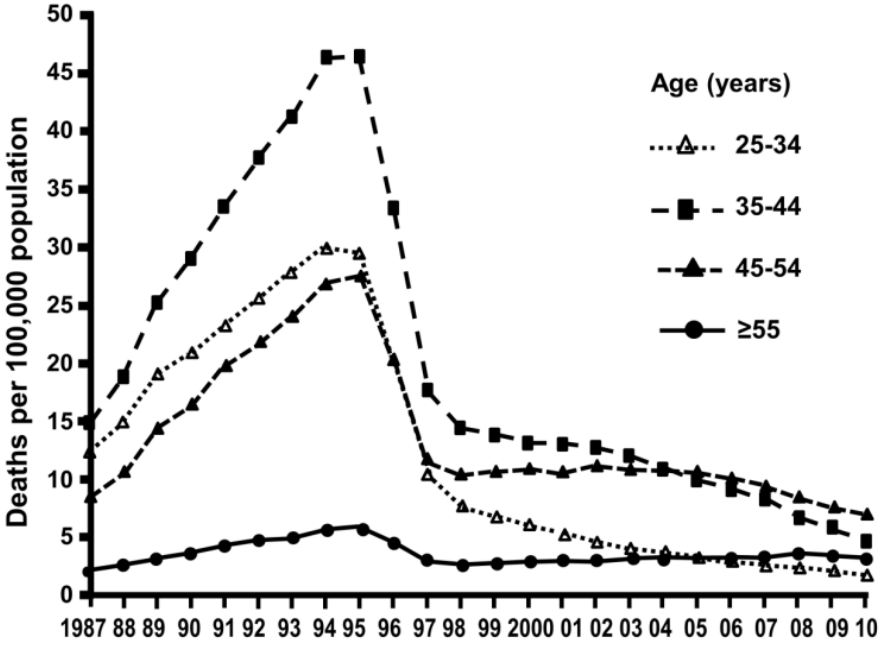



*Fig.1 from (4)*

Similar increases in LE of PLWH have been observed across the globe after the widespread introduction of cART. (6) Remarkably, in some regions of southern Africa with the highest HIV prevalence the *life expectancy of the general population* has increased by >10 years in the past decade.(7, 8)

While life-expectancy and mortality for all PLWH have steadily improved in high-and low-income countries with consistent use of cART in the past decade,(6) there are important demographic disparities that have been observed in high-income countries.

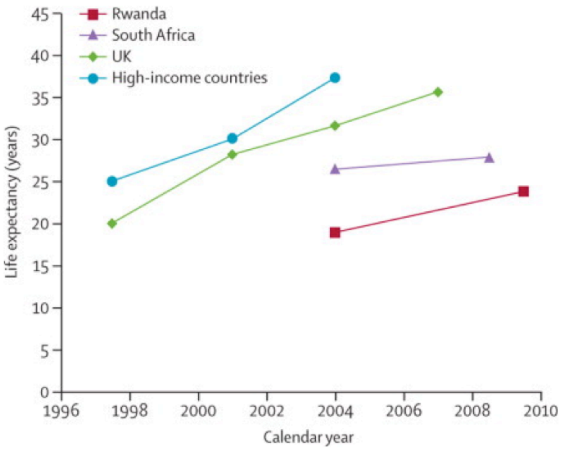



*Fig.2 Trends in LE for individuals initiating antiretroviral therapy at age 35 years.* (6)

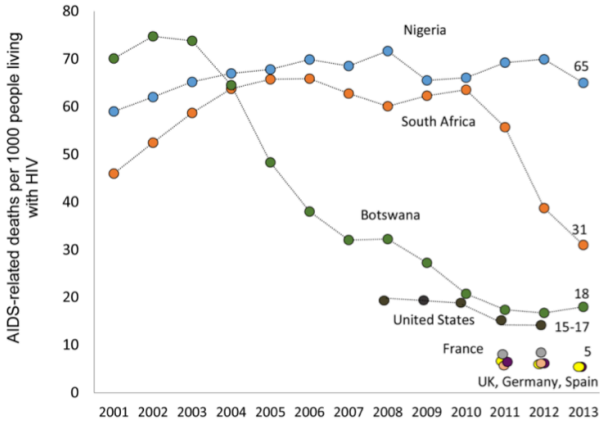



*Fig.3 Trends in AIDS related mortality in high-and low income countries(9)*

## Normal Life Expectancy?

During the first decade of the 'HAART era' LE improved less for African American males than for Caucasian males, and improved overall very little for intravenous drug users.(5) The mortality rate for PLWH >55 years ('older people') in our country has remained stable since 1998.(4). On the level of the general population level any improvement of LE in older PLWH since 1998 (Fig.1) would have been offset by their ~2% annual increase among the overall PLWH population reaching 24% of all PLWH in 2012(10). Yet, it has not been established that, on a population level, older people benefit to the same degree from cART as younger ones do.

There is a notion that PLWH on stable cART will have a 'normal' LE, i.e. comparable to a segment of the general population matched for HIV-typical risk factors like the smoking, drug, and alcohol use, and hepatitis co-infection.(11). For the past 5 years several large European cohort studies have reported such 'normal' life-expectancies for PLWH on stable cART after controlling for population based risk factors, particularly if cART was started early and/or patients had reached CD4 counts >500/mm$^3$.(12-14)

Yet the effect of earlier treatment on CD4 counts at a population level may be small as CD4 counts at treatment initiation in New York City have only marginally increased over the past 7 years despite a longstanding attempt at universal HIV treatment there.(15)

## Geographic Disparities

There are significant differences between calculated life-expectancy estimates for PLWH in Europe and North America. While the data from the US is about 3 to 5 years less recent, cART induced LE at the age of 35 was only 23 years.(5, 16) This estimate was based on national HIV surveillance data(5) and a computer model assuming universal treatment for all PLWH with <500 CD4+ cells/mm$^3$ and survival data of a large seroconverter cohort. The described US model leaves a LE 'gap' of 12 years compared with a risk factor matched sample of the general population (see figure on title page).

In a recent comparative multi-cohort analysis on patients from 3 continents (n=67,000) between 2001-2009, PLWH from the South African cohorts who had commenced cART with a baseline CD4 count from 50-200 cells/mm3 had a slightly lower cumulative 4-year mortality than the ones from the North American cohorts whereas European mortality rates were always lowest.(17) There is currently no single satisfying explanation for the significant mortality differences between North American and European cohorts.

Of note, if LE estimates in HIV are often derived from cohort study data of a younger population with more recent acquisition of disease. In one of the largest European LE studies in

PLWH only 4% of follow-up years were contributed by people >60 years age.(12) Because of the much higher baseline mortality rate for older age groups, even a slight increase of standardized mortality rates (mortality ratio between people with or without disease will) over time when PLWH age would lead to inflated LE estimates.

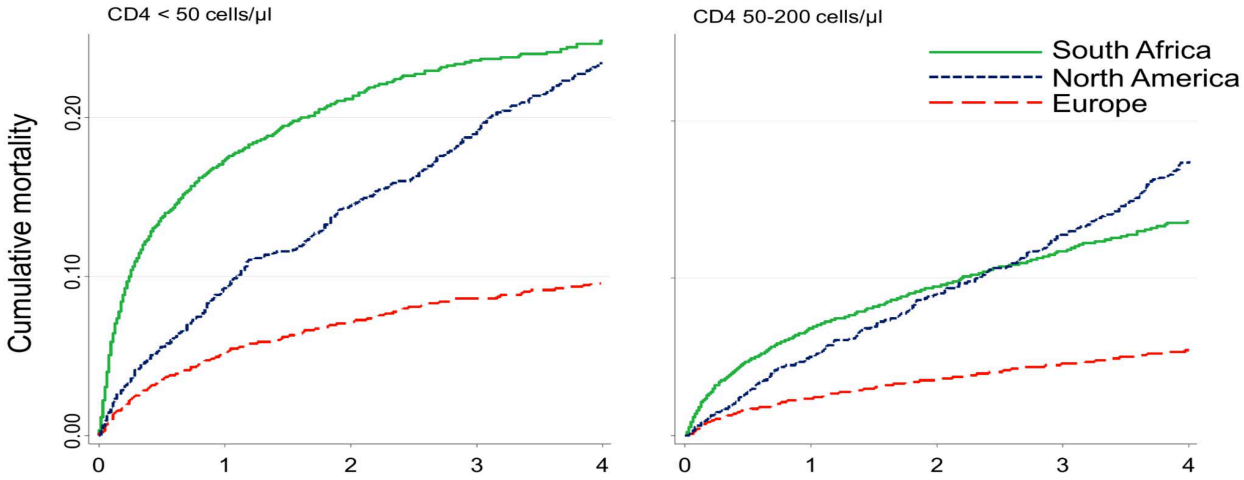



*Fig.4 Cumulative incidence of mortality up to 4 years after start of ART by region, corrected in South Africa for mortality under-ascertainment.(17)*

We recently analyzed age specific mortality rates from the VA Clinical Case Registry of HIV-infected veterans (CCR), with a median age 56 arguably one of the older HIV-cohorts. We selected group of US veterans corresponding to a 'best case scenario' who had achieved virologic suppression for >1 year on HAART and had also reached a CD4 count >500/mm$^3$.

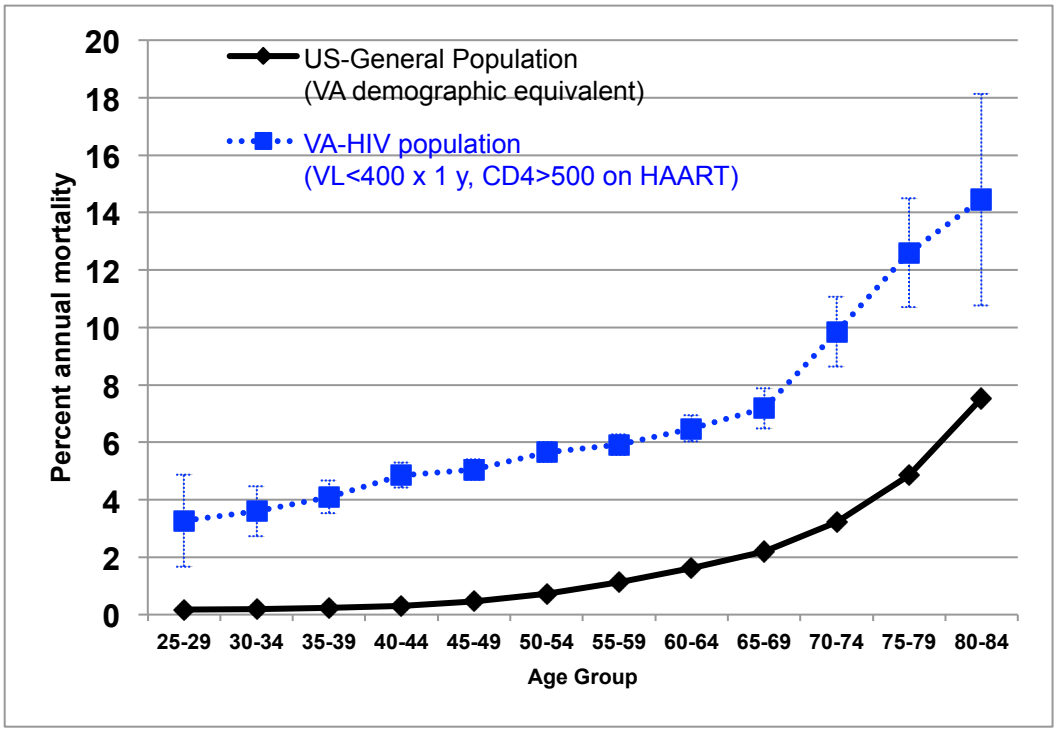



*Fig. 5 Comparison of age-specific mortality rates of US veterans on successful HAART with the general population. 43,000 follow up years, unpublished.*

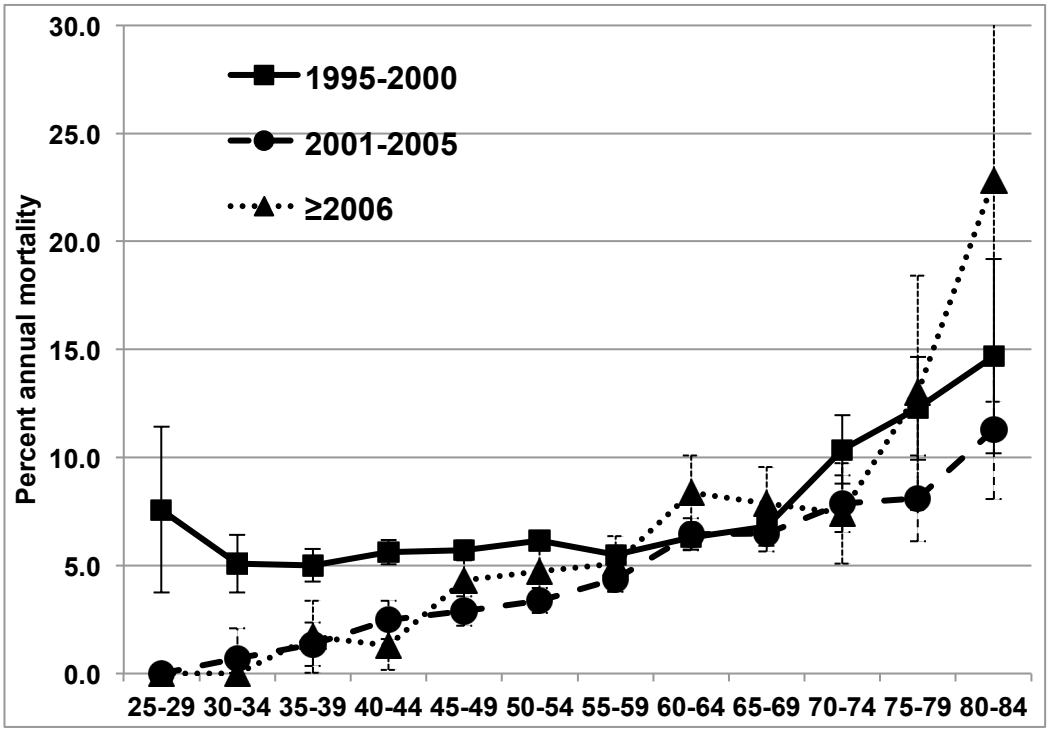



*Fig. 6 Comparison of age-specific mortality rates of US veterans starting successful HAART during different time periods. 43,000 follow up years, unpublished.*

There was an earlier and steeper increase in age specific mortality rates compared with a demographically matched sample of the US population(18) and no clear trends for an improvement in age-specific mortality rates for veterans >55 years commencing HAART after the year 2000.

# Shift in Causes of Death

## AIDS

In the aforementioned START trial, AIDS defining events still comprised 43% of all endpoints in the immediate treatment arm - versus 63% in the deferred treatment arm. The majority of AIDS event in the immediate treatment arm were pulmonary TB and lymphoma.(2) In a large European Analysis on AIDS and non-AIDS events from 2001 to 2009, the risk of AIDS events depended greatly on current CD4 count and was greatly reduced in patients with CD4 counts >700 cells/mm$^3$.(19)

## "Non-AIDS"

In the past decade, non-AIDS causes of death have been reported to outnumber AIDS as cause of death from nearly 2:1(19, 20) to 5:1 (hospitalized patients (21)) in resource-rich countries. In the U.S., in a nationwide survey, PLWH had higher age-specific mortality rates if the death was due to liver- or kidney disease or cardiomyopathy.(22) Cardiovascular disease, non-AIDS defining cancers, and (progression of) liver and kidney disease have been grouped together by many researchers as "HIV-associated non-AIDS events", as they have been shown to not only

more often lead to death but also occur more frequently in PLWH. (23, 24) In addition, serious non-AIDS defining infections (sepsis, non-recurrent pneumonia) have been reported to be the most common cause of death in hospitalized patients(21) and are three times more likely to occur in PLWH who are not taking cART.(25) The risk of developing non-AIDS defining cancers in PLWH on stable cART has been reported as ≥2 fold increased for the most common cancers without known viral involvement.(26, 27) Lower CD4 counts on cART have been described to be an independent risk factor for both serious non-AIDS infections (<200/$mm^3$)(25) and non-AIDS defining cancers(<500/$mm^3$)(28), highlighting the importance of both persistent immune activation and subclinical immune deficiency as pathogenetic factors driving non-AIDS morbidity and mortality in PLWH on stable cART.

# Predictors of Mortality

## Socio-Demographic Predictors

While age is the obviously most important demographic factor determining all-cause mortality, it remains to be seen whether old age amplifies the residual risk of 'stable', i.e. virologically suppressed HIV infection with normalized CD4 count. In our country, non-white race and conjoined socioeconomic status are important reasons for increased mortality rates due to insufficient retention in care.(29) In my humble opinion, this may be the single most important reason for the embarrassingly high mortality rates in our country.

## Lifestyle, Mental Health, and Behavioral Predictors

The single most important factor driving HIV and hepatitis acquisition and mortality is injection drug use.(30) Smoking has been postulated to shorten LE more than HIV infection in the Danish population.(31) Recreational (non-injection) drug use and alcohol use, often associated with mental disease affect life expectancy both directly and indirectly(11) by interfering with good adherence to cART (see below).

## Comorbidity

Liver, cardiac, and renal disease may be clustered among the same at-risk socioeconomic groups and groups with behaviors that furnish increased rates of HIV acquisition. It can be argued that in some circumstances, HIV co-infection may be associated with sub-standard treatment being offered for these conditions.

## Timing and Effectiveness of cART

Effectiveness of cART is usually assessed by CD4 counts and HIV-RNA levels. CD4 recovery depends on HIV viral suppression, which in turn depends on cART adherence. While protease inhibitor based cART regimens without the additional use of ritonavir to 'boost' levels had very

unfavorable pharmacodynamics and pharmacokinetic properties and required compulsive attention to medication adherence from PLWH during the first decade of the HAART era (32), regimens now have a much bigger 'forgiveness-factor'.(33, 34)

## Viral Load

Viral Suppression <400 copies in the first 18 months of cART initiation are strongly and independently associated with overall survival(35) while intermittent low level viral load 'blips' <1000 copies/mL or baseline viral load are not.(36) Most cohort studies also demonstrate significantly increased mortality during the first year of virologic suppression.(17)

## CD4 count

Immune Reconstitution as judged by the level of CD4+ T-lymphocytes reached on treatment is one of the most important predictors of all-cause mortality.(37) When controlling for current CD4 count (on treatment), baseline CD4 count usually is no longer an independent predictor of mortality in most long-term observational studies. The level of CD4 cells reached on cART depends highly on the CD4 count before starting and thus on the early treatment. While "full" immune reconstitution has usually been defined as reaching above normal (i.e. >500/mm$^3$) CD4 counts on cART, (12), high CD4 levels within the normal range ('high normal', e.g. >700/mm$^3$) have been shown to be clinically relevant for all cause mortality in US veterans (36) and occurrence of AIDS events in Europe.(19) Yet these high CD4 counts, albeit leading to mortality rates comparable with the general population were only seen in a fifth of our veterans were often not maintained for a long time.(36)

LE estimates usually assume stable CD4 counts after immune reconstitution has been reached in while patients continue to take cART.

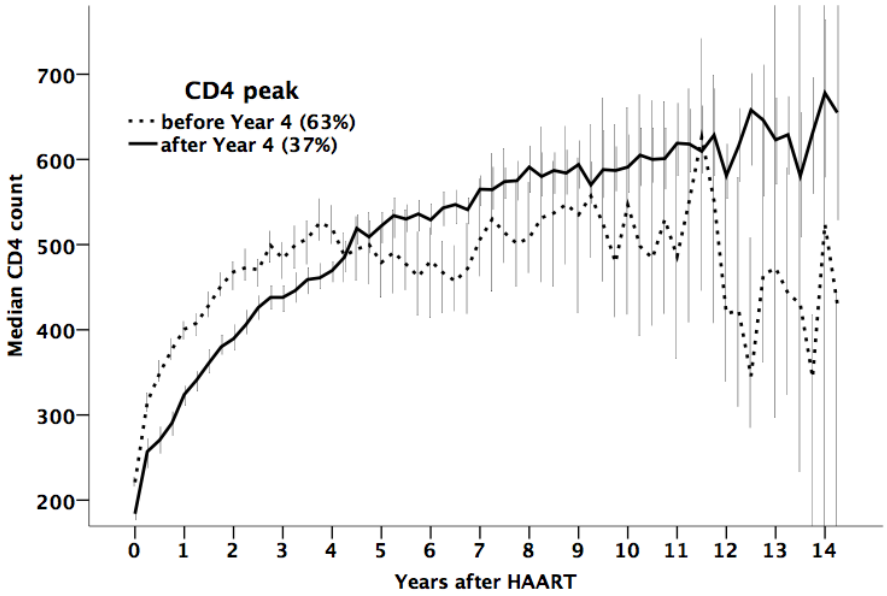



*Fig. 7 Median CD4 counts in US veterans with HIV VL <400 cop/mL, HAART possession rate ≥80% by timing of CD4 peak (±95% confidence intervals, unpublished)*

Unpublished data from the VA however show that almost 1/3 of all veterans who maintained virologic control and HAART possession rates ≥80% had net losses of CD4 cells after year 4 of HAART (Figure 7, dotted line). As a caveat, the data include very few patients on integrase inhibitors that are widely considered standard of care.

### Adherence to cART

If adherence to cART can be quantified as medication possession rate as is the case in US veterans, better adherence is an independent and powerful predictor of lower mortality even after controlling for virologic control and CD4 recovery.(36)

## Immunologic and Miscellaneous Predictors

### Immune Activation Markers

Immune Activation of T-cells has been recognized as a key element of HIV disease and AIDS since the very beginning of the epidemic in the US(38) and also since the early 1990s as a key element independently driving predicting clinic disease progression and death.(39) In the era of suppressive cART when the focus has shifted on HIV-associated non-AIDS defining events (HANA), soluble markers of immune activation like IL-6 and soluble CD14 have been shown to independently predict HANA and HANA associated mortality.(40, 41) While these markers are not used in clinical practice they are inversely correlated with the CD4/CD8 ratio. (42)

### CD4/CD8 ratio

If very low, the CD4/CD8 ratio may add to the prediction on HANA.(42, 43) Of note, while elevated CD8 counts have not been linked to increased mortality, median CD8 cell counts of most PLWH remain stably elevated at ~1 standard deviation above normal even after a decade of suppressive HAART.(44)

### Hemoglobin

Anemia, even if mild, has long been recognized as a powerful independent predictor of all-cause mortality in PLWH in European(45) and recently also in Africans.(46) In the same study both ferritin and transferrin but not serum iron levels were also independently associated with increased mortality, arguably rather because of their role as acute phase proteins.(46)

Interestingly, in HIV-infected US veterans, low normal hemoglobin values (13.5-15.3g/dL) 6 months before the event independently contributed to increased mortality compared with high normal (>15.3g/dL) values. (unpublished).

### Serum Lipids

Low serum cholesterol has to date only been linked to low virologic suppression rates and lack of CD4 reconstitution in a small single center study.(47) Unpublished data from the VA CCR show that serum total cholesterol (and to a lesser extent triglyceride) levels after cART initiation 6 months before the event are powerful independent (inverse) predictors of all cause mortality.

## Conclusions

Published life expectancy estimates that are based on standardized mortality rates of younger segments of the population and on the assumption of long-term stable CD4 counts may be inaccurate for our aging HIV-positive population. Even a minor decrease in life expectancy is relevant as it affects 1 to 1.3 million Americans.

The pathologic mechanisms that cause or worsen HIV-associated non-AIDS events and lead to excess mortality in virologically suppressed PLWH are not well understood. Likely both subclinical immune deficiency and immune activation contribute to disease processes. Permanently elevated peripheral CD8 counts in most and decreasing CD4 counts in many PLWH on long-term cART remind us that the adaptive immune system usually does not return to 'normal'.

While universal treatment and immediate antiretroviral treatment regardless of CD4 count has the potential to decrease overall morbidity and mortality by reducing the number of transmissions and improving long-term CD4 counts via cART earlier initiation, the size of this effect may be small.

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