Cohort Profile: The HIV Atlanta Veterans Affairs Cohort Study (HAVACS)

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Summary

HAVACS (HIV Atlanta VA Cohort Study) was initiated in 1982 in order to enhance clinical care and research for all HIV-positive veterans receiving care at the Atlanta VA Medical Center (AVAMC). Every HIV-positive patient ever seen at the AVAMC has been included in HAVACS; to date over 4,268 patients have been entered into this cohort. Prospective collection of data began in 1982 and includes a complete summary of the patient's HIV history including any care they received before HAVACS. The data are collected at each clinic visit and hospitalization in a prospective manner. Cohort enrollment dates started in 1982 and are ongoing.

Data are collected on patient demographics (gender, race, age, HIV risk group), HIV biomarkers (including CD4 cell count and viral load levels at date of diagnosis, nadir levels, date of threshold levels and current levels), antiretroviral regimens including time not on a regimen, start and stop dates, genotype data, data on HIV-related and AIDS-defining conditions, other comorbid conditions, hepatitis B and hepatitis C virus testing, immunization status, dates of mortality or loss to follow-up and causes of death.

Key Messages

- Marked decrease in mortality since 1996 with the minority of deaths occurring in the hospital or being caused by AIDS-defining opportunistic infections since 1996. Deaths due to end-stage renal disease and myocardial infarction were also uncommon with a stable incidence over the past 30 years.
- In a population with a high rate of Hepatitis C (HCV) (32%), HCV is significantly associated with decreased survival time from date of AIDS diagnosis. This trend is supported by evidence of a significant decrease in CD4 counts over the course of HIV-positive/HCV-positive compared to HIV-positive/HCV-negative patients.
- When comparing patients followed in HAVACS to those followed by the Department of Defense, despite substantial differences in baseline characteristics and large differences in crude mortality rates, after controlling for important clinical and demographic variables, both 12-year survival and AIDS-free survival rates were similar between the two study cohorts who have open access to care and medication.
- Both protease inhibitors and non-nucleoside reverse transcriptase inhibitors were found to be associated with elevated apolipoproteins, specifically apoc-III. In women, an additional association was found with elevated total cholesterol level that was not seen with the men while an elevation was seen in triglyceride levels for the men but not the women; these data add to the growing evidence of gender-related differences in the natural history, pharmacokinetics and toxicity of antiretroviral therapy.
- Analysis of the continuum of care demonstrated a higher level of diagnosis, linkage to care, receipt of antiretrovirals and viral suppression than any U.S. cohort.

Why was the cohort created?

HAVACS (HIV Atlanta VA Cohort Study) was initiated in 1982 to enhance clinical care and research for all HIV-positive veterans seeking care at the Atlanta VA Medical Center. The HAVACS database provides health care providers with a summary of patient information while also being used for surveillance and research analyses. Moreover, it has been used to assess the feasibility of new studies and aids in the identification of patients eligible for approved research protocols. Essentially, it serves as an ongoing prospective, observational study for interdisciplinary HIV research in clinical, basic, epidemiological, biostatistical, and social sciences. Today, HAVACS is a powerful database utilized for the investigation of HIV-positive patients with respect to HIV and aging, non AIDS-related malignancies, hepatitis B and C co-infections, novel immunological markers for inflammation, and highly-active antiretroviral therapy (HAART) start time and drug sequencing. HAVACS has no independent funding; maintenance of data and reports are supported by a combination of research coordinators and clinicians.

Who is in the cohort?

This database includes all HIV-positive patients ever seen at the AVAMC. To date, 4268 patients have been entered into this cohort and database. Prospective data collection began in 1982 and includes the full HIV history of patients including any care they received for their HIV disease before receiving care at the AVAMC.

The patient population is 97.5% (*n*=4162) male, 71.6% (*n*=3054) African-American/Black, 25.8% (*n*=1101) Caucasian/White and 1.6% Hispanic. Mean age is 52 years. Men who have sex with men (MSM) represent the largest population [50.8% (*n*=2169)], followed by individuals with a history of injection drug use (IDU) which accounts for an additional 16.1% (*n*=687), and 4.4% (*n*=187) of individuals with high-risk heterosexual contact. Twenty-two percent of the patients were naïve to antiretrovirals at entry; 30.7% were naïve before starting HAART. Co-infection with hepatitis C is common with 21.9% of the cohort being dual infected, although the recent prevalence of HCV co-infection has decreased to 15.1% in current patients. Over 80% of our patients currently on therapy have undetectable viral loads. Since 1982, only 2.8% (*n*=120) of patients have been lost to follow-up (not seen in the last 24 months); 40.4% (*n*=1723) have died, 32.7% (*n*=1395) were seen in the 2014 calendar year, and 20.4% (*n*=869) have moved to other locations but remain in care.

This cohort study was approved by the Emory IRB with a HIPAA waiver allowing entry and collection of data without requiring informed consent. Each study is separately approved by the Emory IRB.

Characteristics of the entire HAVACS population as well as the current HAVACS population are shown in Table 1.

How often have they been followed up?

The Veterans Affairs (VA) population is unique in that these patients are likely to receive all treatment and care within the VA system. Since 1997, the data obtained through routine clinic visits have been supplemented with data from the VA Computerized Patient Record System (CPRS), an electronic system that houses all data for every patient seen in any hospital or clinic within the VA healthcare system allowing for the acquisition of data such as laboratory and non-ID clinic visits which would not have been available otherwise.

Information is collected on patients seen in the AVAMC ID Clinic on standardized forms that include demographic characteristics, clinical symptoms, HIV-related diagnoses, prophylaxes, antiretroviral regimens, vaccinations, inpatient visits and diagnoses and laboratory measurements. Data are collected retrospectively for the entire clinical history of each patient if they were diagnosed elsewhere and prospectively once care is initiated at the AVAMC. Each inpatient and outpatient encounter is documented and the database is updated weekly for every patient contact with the AVAMC including inpatient and clinic visits as the patients are seen for routine clinical care or for research visits. Pharmaceutical data are also collected from the computerized pharmacy database. All data are kept in a secured and centralized database. If the patient has left care from the VA system, outcome data are collected from active sources such as family members and passive sources such as National Death Index and the National Veterans Benefits Database. The database is routinely checked for quality of data during analyses and routine use of the patient summary sheets.

For those patients who received healthcare from other providers before enrolling in the VA system, we attempt to determine the source of their HIV diagnosis. Over twenty-seven percent were diagnosed at the AVAMC. This proportion has increased over the years, particularly since 2009 when routine testing became the model in the VA system. Twenty-three percent come from other VA locations, 21.6% are diagnosed outside of the VA system in private medical practices, 12.4% were diagnosed in the military, 4.1% were diagnosed in a health department or the county hospital, and 1.5% diagnosed in the prison system.

The age distribution for HAVACS has changed dramatically over time. Almost 50% of our patients were between 30-39 years of age in 1986 compared to 10% in this age range in 2014 (Figure 1). In 1986, 88% of our patients were under 49 years of age. Today, 60% of our patients are over the age of 50 years. This significant shift to an older population in HAVACS is influenced by the dramatically improved survival now seen as well as a significant increase in those diagnosed over the age of 50.

Trends in HIV and AIDS diagnoses have dramatically changed over the years in HAVACS (Figure 2). HIV diagnoses peaked in year 1989 with 250 new diagnoses. Since 1990-1992, the number of new diagnoses of HIV and AIDS cases declined before reaching the current steady state of 40 to 70 new cases each per year. The current trend of fewer patients diagnosed with AIDS is encouraging and likely represents the 2009 policy change to test everyone seen in the VA system. HIV mortality has also

changed substantially over the decades. In 1994, a quarter of patients in HAVACS died (rate of 25 deaths per 100 patients seen) (Figure 3). Just three years later, the rate dropped to 3 deaths/100 patients seen and has not been over a rate of 5/100 patients since. Much of this is correlated with the use of antiretroviral therapy in HAVACS. In 1994, only 35% of the patients were receiving antiretrovirals (Figure 4). By 1997, this increased to 70% and is now at 88% of current patients. In 1996, 60% of HAVACS patients had viral load levels above 10,000 copies/mL and only 10% of the patients had a CD4 level above 500 cells/mm^3 and 20% were below 50 cells/mm^3 (Figures 5 and 6). In 2014, 55% of patients had a CD4 cell count >500 cells/mm^3 and 60% were virologically suppressed.

What has been measured?

Phase	Measurements
Baseline 1982 and ongoing	Demographic data
	PCP prophylaxis data
1990	Antiretroviral data including all dates of regimens
	Genotype data
	HCV, HBV data
	VACS study data
Ongoing	Causes of mortality

Types of Data collected:

Clinical, laboratory and pharmaceutical data are collected for every patient. Laboratory data include CD4 cell count, HIV viral load, hepatitis serologies, G6PD, HLA B-5701, and vitamin D. In addition, immunization history including hepatitis, pneumococcal and TDaP vaccine status is obtained. Using the National VA HIV Clinical Case Registry (CCR), all patients in HAVACS are linked to ICD-9 morbidity data. The CCR is also used to generate important denominator data such as total number of patients seen on as inpatient or outpatient, and number on antiretrovirals. CD4 cell count and HIV viral load data, summaries of any laboratory test, medications and risk factor distribution can also be generated. These data allow the calculation of incidence for all parameters. On an annual basis, patients not seen in over 24 months are evaluated for mortality by review of remote VA data, the VA national death index and the Social Security Death Index.

Selected patients with vitamin D deficiency had DEXA studies done to assess bone density. Patients enrolled in the FRAM studies had targeted studies including CT scans, DEXA studies and anthropomorphic measurements. Patients enrolled in Veterans Aging Cohort Study (VACS) studies had phlebotomy for plasma and cells; in addition to other phlebotomy for selected sub-studies.

What has it found? Key findings and publications

Hepatitis C Coinfection Increases Mortality in HIV Infected Patients in the Pre and Post-HAART Era

Although studies have consistently documented the negative impact of HIV coinfection on HCV disease, the effect of HCV coinfection on HIV disease is still unclear and even controversial. A study in 1999 in HAVACS found no association between HCV-positive/HIV-positive coinfection and progression to death in the pre-HAART era[1]. We speculated that many factors, including the hepatotoxicity of HAART regimens and increased survival times for patients on HAART, might yield different findings and reexamined this association in the post-HAART era in 2004[2]. We found that: 1) In accordance with the previous HAVACS study, the prevalence of HCV coinfection was still high (31.6%).[3] 2) Coinfected patients were less likely to have received HAART than HCV- patients. 3) Coinfection with HCV results in significantly decreased survival from HIV and AIDS diagnoses. 4) Coinfection does not affect short or long-term CD4 cell count recovery with HAART.

Association between antiretroviral therapy in men and women increased lipid levels

In 2005 and 2006, we performed cross-sectional studies in both men and women to consider the association between antiretroviral therapy and increased lipid levels[3,4]. We found both protease inhibitors and non-nucleoside reverse transcriptase inhibitors were

associated with elevated apolipoproteins, specifically apoc-III. In women, elevated total cholesterol level was also associated with therapy but this was not seen in men[4]. However, an elevation was seen in triglyceride levels for men but not women[3]. These findings suggest impaired metabolism of triglyceride-rich lipoproteins and, in an older population with additional risk factors of smoking and diabetes, portend future atherosclerotic events in these patients. These data added to the growing evidence of gender-related differences in the natural history, pharmacokinetics and toxicity of antiretroviral therapy.

Methicillin-resistant *Staphylococcus aureus* colonization in HIV-positive outpatients

Data on the interaction between methicillin-resistant Staphylococcus aureus (MRSA) colonization and clinical infection are limited. During 2007-2008, we enrolled 600 patients from HAVACS in a prospective cohort study [5-7]. MRSA colonization was detected in 15% of HIV-infected participants at baseline and 6 and 12 months; 41% in nares only, 21% in groin only, and 38% at both sites. Over a median of 2.1 years of follow-up, rate of infection was 2.5/100 person-years. Skin and soft tissue infections were the most common and 13% of these required hospitalization. Forty-eight percent of patients who developed a MRSA clinical infection had MRSA colonization at baseline compared with 6% of those where no infection developed ($p<0.0001$). In multivariate analysis, MRSA clinical infection was significantly associated with colonization of the groin (adjusted risk ratio (RRa) 4.8) and a history of MRSA infection (RRa 3.1). A suppressed HIV viral load and use of antiretroviral therapy were associated with a lower

risk for development of MRSA clinical infection. MRSA prevention strategies that can effectively prevent or eliminate groin colonization are likely necessary to reduce clinical infections in this population.

A Comparison of HAART Outcomes between the US Military HIV Natural History Study and HAVACS

In 2013 we performed the first analysis comparing data from the US Military HIV Natural History Study (NHS) and HAVACS[8]. We assessed the clinical outcomes for individuals with HIV from two very similar government-sponsored healthcare systems that reduced or eliminated many barriers associated with accessing treatment and care. The combined total mortality rate was less than 10% for those diagnosed with HIV and initiating HAART since 1996. The NHS patients were younger, started HAART at a higher CD4 cell count, and experienced less mortality than HAVACS patients. Despite these substantial differences in baseline characteristics and large differences in crude mortality rates, 12-year survival and AIDS-free survival rates were similar between the two cohorts who have open access to care and medication after controlling for important clinical and demographic variables. These similarities existed despite dramatic differences in socioeconomic and behavioral characteristics. Our analysis highlighted the need for comparisons of clinical outcomes in fee-for-care systems, as well as impact of early HIV screening. Our data suggest that early screening, with subsequent higher CD4 cell count at diagnosis, will result in improved outcomes.

Comparison of Colorectal Cancer Screening and Diagnoses in HIV-positive and HIV-negative Veterans

In 2014 we examined the use of appropriate colorectal cancer (CRC) screening in HIV-positive and HIV-negative veterans[9]. The results from this analysis suggest that patients are not properly being screened for CRC as roughly half of cases and their matched controls were not screened during the four year study period. At the time of the study, guidelines called for annual CRC screening for all 50 years and older. We found that cases had a significantly higher number of outpatient visits than their controls, resulting in more chances to be screened. The "first line" screening method of FOBT was utilized similarly in both populations (42.5% for cases vs. 41.4% for controls) though at a higher rate than in the non-VA population (38% national average screening rate) [10]. Even with the limited number of diagnoses, differences were seen by race and age; 80% of HIV-positive cases diagnosed with CRC during the study were black and two were less than 50 years of age suggesting the need for larger studies to evaluate the need for earlier screening among HIV-positive and black individuals.

Continuum of Care in HAVACS

Also in 2014, the continuum of care in HAVACS was modeled in order to determine similarities and differences with national models[11]. Using a cross-sectional analysis of 1,474 individuals who were currently receiving care in the ID clinic, we estimated that 95.3% of individuals were diagnosed with HIV, 89.8% of individuals were linked to care, 73.0% of individuals were retained in care, 65.9% of individuals were eligible for antiretroviral treatment (ART), 62.8% were prescribed ART, and 52.4% had a

suppressed viral load (VL). Using an independent stage categorization, it was estimated that 83.9% of individuals were prescribed ART and 61.5% had a suppressed VL. These analyses showed that the HAVACS estimates were significantly better than national estimates at every stage. This may have reflected the benefits of a universal healthcare system. Since this publication, many similar analyses have opted to use independent stages for the continuum as this more accurately represents healthcare utilization.

Contributions to VACS

The Atlanta VA has been part of the NIH-funded Veterans Aging Cohort Study (VACS) since 2002. This longitudinal cohort study, comparing an HIV-positive population with an age, gender, race and site-matched HIV-negative population has addressed important comorbidities, influence of alcohol and drug abuse and prediction models for morbidity and mortality using the VACS Index. Overall, approximately 600 HIV-positive and 600 HIV-negative veterans have enrolled in this study as part of the VACS-8 series of investigations. A description of VACS, questionnaire tools and a list of over 200 publications produced from this study are available at www.va.cohort.org.

Contributions to ART-CC

In 2008, HAVACS joined 18 other cohorts in the established Antiretroviral Therapy Cohort (ART-CC). This cohort was created to study the prognosis and mortality of HIV-positive patients treated before the end of 2009[12]. Highlights of some of the work published by ART-CC with HAVACS are summarized here.

In 2011, we compared the relative effectiveness of initial ART regimens estimated in AIDS Clinical Trial Group (ACTG) randomized controlled trials with that among patients receiving ART at ART-CC study sites[13]. We found the virologic and clinical efficacy observed in clinical trials were mirrored in the routine care setting at ART-CC clinical sites suggesting ART regimen performance in clinical trials likely translates to routine care settings.

In 2012 we estimated the incidence of and risk factors for modifications to first ART regimen, treatment interruption and death in 21,801 patients from 18 cohorts in Europe and North America using competing-risks methods.[14] Rates of modification and interruption were high, particularly in the first year of ART. During median 28 months follow-up, 40.3% patients modified their first ART. Rates of substitution and switches to nonstandard regimens were lower in 2006-2009 likely due to greater use of well tolerated once-daily drugs.

In 2013, we published data on adult HIV-positive patients who started ART from 1998 without a previous AIDS diagnosis from 17 cohorts in North America and Europe[15]. We examined between-cohort heterogeneity in crude and adjusted rates of AIDS and mortality using random-effects meta-analysis and meta-regression. Between-cohort variance in mortality rates was reduced from 0.84 to 0.24 (0.73 to 0.28 for AIDS rates) after adjustment for patient characteristics. Heterogeneity between settings in outcomes of HIV treatment has implications for collaborative analyses, policy and clinical care.

In 2013, we published data on differences in all-cause mortality, as well as AIDS and non-AIDS death rates, among patients started on ART according to their geographical origin and ethnicity/race in Europe, Canada, and the United States between 1998 and 2009[16]. Migrants from sub-Saharan Africa (SSA) (AHR, 0.79; 95% confidence interval [CI], .68-.92) and Asia/West (AHR, 0.62; 95% CI, .41-.92) had lower mortality than Europeans; these differences appeared mainly attributable to lower non-AIDS mortality. Compared with white Canadians, mortality in Canadian First Nations people was 48% higher; both for AIDS and non-AIDS mortality rates and among US patients, when compared with whites, African Americans had higher AIDS and non-AIDS mortality. The lower mortality observed in migrants suggests "healthy migrant" effects, whereas the higher mortality in First Nations people and African Americans in North America suggests social inequality gaps.

What are the main strengths and weaknesses?

One of the main strengths of the study is that it represents a complete population cohort of all patients ever seen at the AVAMC with HIV with a long period of follow-up (mean 82 months). The AVAMC has the largest HIV-positive population in the VA system in the United States and offers very high rates of follow-up for routine record linkages. The VA population is unique in that these patients are likely to receive all treatment and care in the VA system. Only 2.8% have been lost to follow-up since 1982. Therefore, unlike many large clinical and research databases, loss to follow-up or missing clinical information is not a source of bias.

One limitation of this cohort may be generalizability as the HAVACS cohort consists of veterans who are primarily black and male. This is not a product of lack of inclusion but rather a product of the low number of veterans in the US who are female and HIV-positive. In addition, at the current time we do not have any stored biomedical specimens other than those used for specific studies.

Can I get hold of the data? Where can I find out more?

A subset of patients from HAVACS have been enrolled in VACS (n=500), SMART, OPTIMA, and FRAM 1 and 2. Additionally, HAVACS is a member of the Antiretroviral Therapy Cohort Collaboration (ART-CC). The studies using data from this cohort are funded through multiple grants and contracts including the CDC, the National Institute on Aging and The National Institute for Mental Health.

HAVACS Cohort Contact:

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therapy in Canada, Europe and the United States. *Clin Infect Dis*. 2013 Jun;56(12):1800-9.

Table 1. Demographic and selected characteristics of the HIV Atlanta VA Cohort Study, 1982-2014

Covariate	All patients (n=4268)	Active patients (n=1533)
Demographics		
Age at first visit	43.1 (21-82)	43.8 (21-82)
Age at HIV diagnosis	36.0 (17-76)	36.0 (18-76)
Male sex	97.5% (4162)	96.9% (1486)
Race		
African-American/Black	71.6% (3054)	79.5% (1219)
Caucasian/White	25.8% (1101)	18.0% (276)
Hispanic	1.6% (67)	1.4% (22)
Other or unknown	1.1% (46)	1.0% (16)
Primary Risk Factor		
MSM	50.8% (2169)	55.4% (849)
IVDU	16.1% (687)	8.5% (130)
High Risk Heterosexual	4.4% (187)	6.1% (93)
Unknown	23.2% (990)	26.0% (399)
Other	5.5% (235)	4.0% (62)
Referral		
Internal (AVAMC)	27.2% (1159)	23.2% (356)
Other VAMC	23.0% (980)	16.8% (258)
Private practice	21.6% (917)	27.3% (418)
Military	12.4% (526)	15.9% (243)
Other	15.8% (674)	16.8% (258)
Current status		
Died	40.4% (1723)	-
Active	35.9% (1533)	100.0% (1533)
Moved	20.4% (869)	-
Lost to follow-up	2.8% (120)	-
Other	0.54% (23)	-
Medical history		
HIV to Death (years)	7.5 (0-29.9)	-
AIDS diagnosis	66.5% (2839)	56.2% (926)
Diagnosed by OI	50.3% (1428)	31.9% (295)
Diagnosed by CD4	49.7% (1411)	68.1% (631)
Hepatitis C- co-infection	21.9% (732)	15.1% (231)
Chronic Hepatitis B co-infection	6.4% (274)	5.7% (87)

MSM - men who have sex with men; IVDU - intraveneous drug user; OI - opportunistic infection

Figure 1: Age Distribution by Year in HAVACS

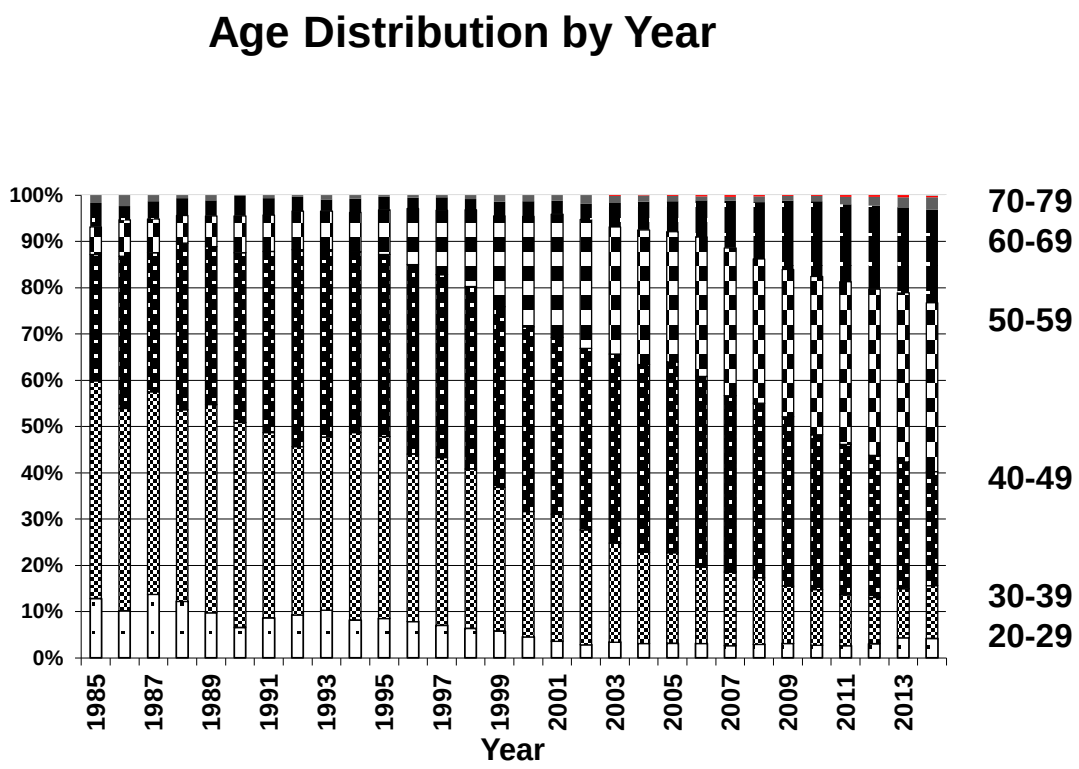

Figure 2: Trends in HIV and AIDS Diagnoses by Year in HAVACS

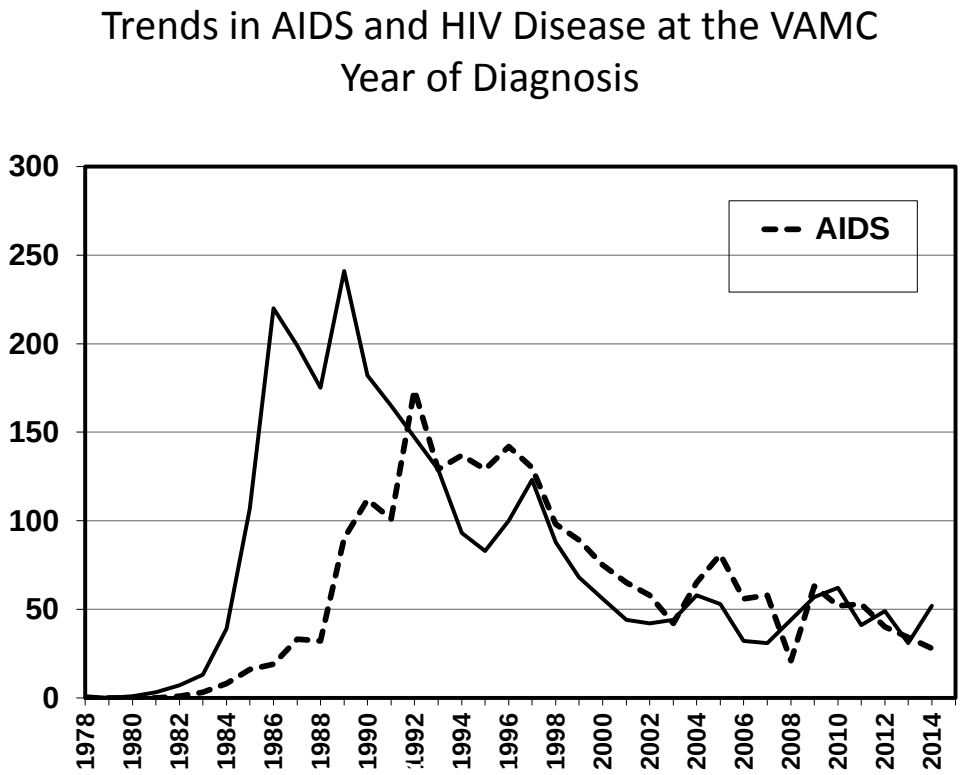

Figure 3: HIV Mortality Rates by Year in HAVACS

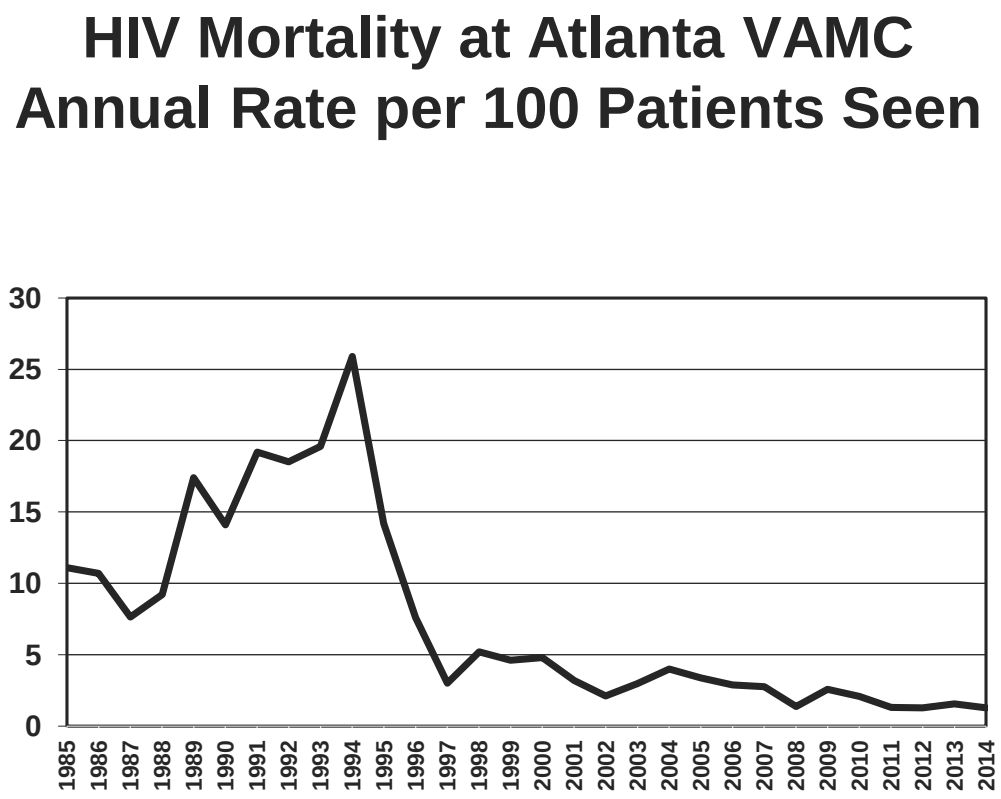

Figure 4: Antiretroviral Therapy by Year in HAVACS

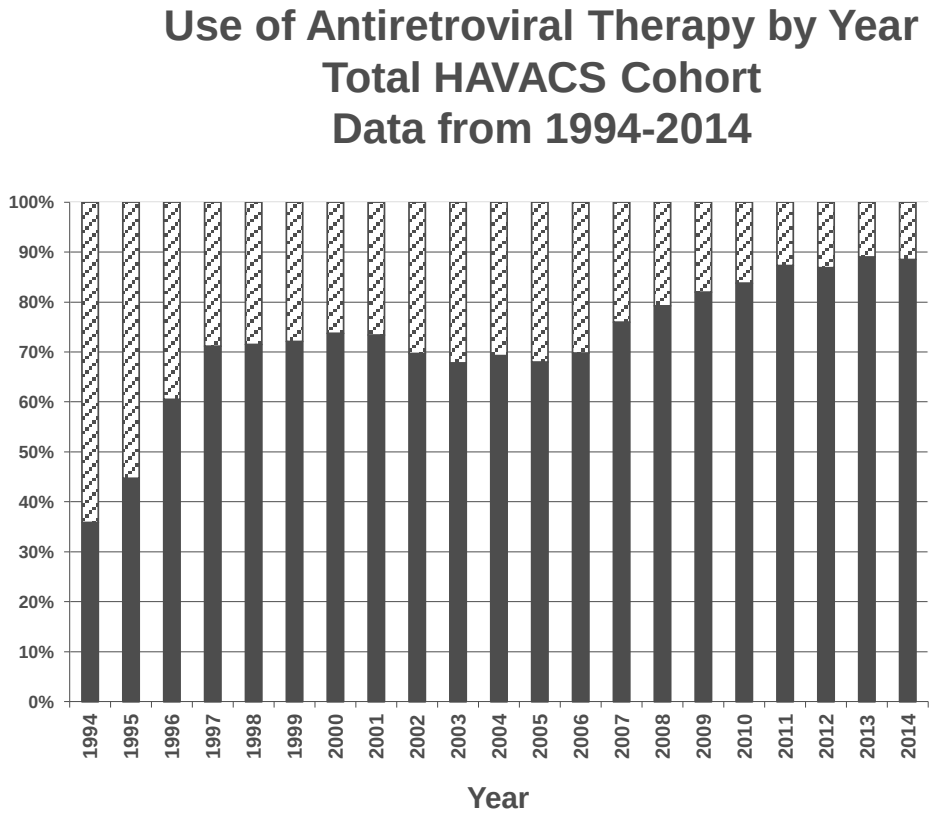

Figure 5: HIV RNA Results by Year in HAVACS

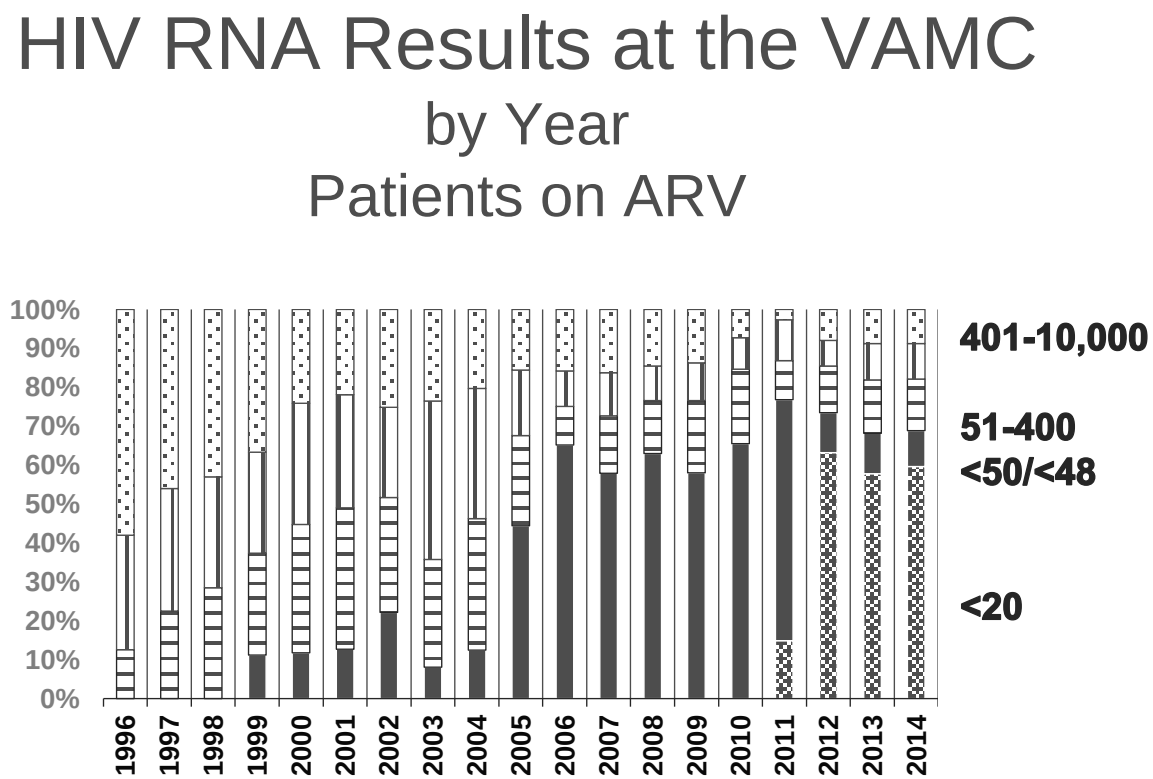

Figure 6: CD4 Distribution by Year in HAVACS