Is there a trial effect in HIV clinical trials?
Identifying who participates in clinical trials
And assessing the effect of trial participation on the response to highly active antiretroviral therapy

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ABSTRACT

PREMA MENEZES

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(Under the direction of William C. Miller, MD, MPH, PhD)

There is a widespread belief, that participation in a clinical trial provides an additional benefit called a trial effect. In HIV infection this claim appears to have been unexamined and therefore is unsubstantiated. Evidence of a trial effect may be confounded by systematic differences between trial and non trial participants. Women, minorities and heterosexuals represent an increasing proportion of HIV infected persons but are reportedly underrepresented in clinical trials. We examined if gender/sexual orientation or race/ethnicity differed by trial participation and if there was a trial effect in HIV clinical trials.

Using the UNC CFAR HIV/AIDS Clinical Cohort we conducted a cross sectional study of 738 antiretroviral treatment naïve HIV positive adults. Of these, 30% initiated highly active antiretroviral therapy (HAART) in 13 different clinical trials. Subjects were characterized as trial participants if HAART was initiated in a clinical trial. Heterosexual men and women participated in trials at the same rate as men who have sex with men (PR 0.79, 95% CI 0.57, 1.11 and PR 0.97, 95% CI

0.94, 1.66 respectively). Blacks were slightly less likely than non blacks to participate in clinical trials (PR 0.80, 95% CI 0.60, 1.06).

This lack of substantial race/ethnicity and gender differences between groups supported our further investigation of a trial effect. For this analysis virologic success was assessed within strata of early (1996-1999) and current (2000-06) HAART periods and was defined as a plasma HIV RNA ≤400 copies/ml at six months post HAART initiation. Trial participants initiating HAART in the early period were more likely to achieve virologic success than non trial participants (RR 1.33; 95% CI 1.15, 1.54), but this difference was not observed in the current period (RR 0.98; 95% CI 0.87, 1.11).

We found no difference in participation rates between women contrasted with men and a small insignificant difference for blacks contrasted with non blacks. In the current HAART period, both trial and non trial participants were equally likely to achieve virologic success suggesting that there is no evidence for a trial effect. These results suggest that data from HIV clinical trials can be generalized to clinical practice.

For Brice and Peter Menezes

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AA	African American
ACTG	AIDS Clinical Trial Group
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARV	antiretroviral
CDC	Centers for Disease Control
CFAR	Center for AIDS research
CI	confidence interval
DHHS	Department of Health and Human Services
EMM	effect measure modification
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HAART	highly active antiretroviral therapy
ID	infectious disease
IDU	injecting drug use
PR	prevalence ratio
MAR	missing at random
MSM	men who have sex with men
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMAR	not missing at random

NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
RCT	randomized clinical trial
RR	risk ratio
UNC	University of North Carolina at Chapel Hill
US	United States
UCHCC	UNC CFAR HIV/AIDS clinical cohort
WIHS	Women's Interagency HIV Study

CHAPTER ONE - OVERVIEW

Human immunodeficiency virus (HIV) infection is a pandemic representing a global health challenge. The introduction of highly active antiretroviral therapy (HAART) has made HIV a chronic (long-term), but usually manageable condition. Clinical trials have unequivocally demonstrated the efficacy of HAART for the treatment of HIV and data from these trials have been used to guide all aspects of HIV care and treatment[1-15]. However, clinical trials include selected patient volunteers and are conducted in a medical and social environment created by the trial which likely differs from routine clinical care in several aspects including patient characteristics and health care provision bringing about a trial effect[16-20]. A trial effect may result in improved outcomes for trial participants compared to non trial participants decreasing the generalizability of clinical trials data and questioning the soundness of the data as the basis for HIV care and treatment guidelines.

Our primary goal was to determine whether a trial effect exists in HIV clinical trials by comparing outcomes among trial and non-trial participants. Systematic differences between these groups might lead to improved outcomes for one group relative to another and this might be erroneously identified as a trial effect[17, 18]. HIV clinical trials have frequently been criticized for under enrolment

of minorities, women and heterosexuals[21-25]. Gender and race are associated with socio economic status which can influence health related behavior and the course of disease. Therefore, in order to truly attribute a trial effect to trial participation alone, we must first ensure that the racial/ethnic gender and sexual orientation distribution of trial and non-trial participants is comparable

What are the implications of a trial effect in HIV clinical trials? Evidence suggesting that trial participants have better outcomes than those who do not participate in HIV clinical trials could have important implications for clinical care. At the very least clinical care would need to be modified to incorporate some of the components of a trial effect, such as protocol effect which refers to the way treatments are delivered and a care effect which covers the incidental aspects of care[17, 18]. Currently, clinical care tends to be highly individualized whereas clinical trials are strictly protocol driven. It is possible that a protocol driven approach to HIV clinical care would result in achieving similar improved outcomes in routine care. An incidental aspect of care in clinical trials is frequent, closely-spaced-in-time study visits irregardless of need. This may be contrasted with a quarterly visit schedule observed in routine clinical care. Incorporation of the frequency of study visits into clinical care could result in better provider-patient relationships leading to improved medication adherence and the improved outcomes associated with clinical trials. A trial effect may influence interpretation of clinical trials data and suggests that these data may be more applicable to medical and social environments similar to those in which the trial was conducted.

Despite the importance of a trial effect, it has received very little research attention in HIV infection. We were unable to identify any study that had examined a trial effect in HIV clinical trials. For this dissertation, we examined a trial effect in HIV clinical trials and whether this effect could be attributed to differences in gender/sexual orientation or race/ethnicity between trial and non trial participants.

1.1 Aim One

Aim One: To determine if HIV clinical trial participants differ from non-trial participants with respect to demographics (gender/sexual orientation and race/ethnicity).

Hypothesis: Clinical trial participants are more likely to be non black, male and men who have sex with men.

Rationale: In both National Institutes of Health AIDS Clinical Trial Group (ACTG) and pharmaceutical sponsored clinical trials the enrollment of men vs. women and persons of Caucasian ethnicity vs. other racial/ethnic groups is greater. ACTG 5095 and Gilead 934 enrolled 19% and 13.5% women respectively and both these trials were large multi-center studies conducted throughout the United States[4, 7]. Unpublished data from the University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC) suggests that ethnicity may be a predictor in enrollment of patients in clinical trials.

1.2 Aim Two

Aim Two: To determine if there is evidence for a trial effect in HIV clinical trials.

Hypothesis: Antiretroviral treatment naive HIV positive subjects who initiate HAART within a clinical trial will have greater virologic success six months after treatment initiation than non-trial participants after controlling for differences in baseline characteristics.

Rationale: Although no studies of HIV infection have examined a trial effect there is some evidence from other medical specialties that such an effect might exist[20, 26-31]. Our empiric clinical observations suggest that more trial participants will achieve response to HAART due to positive benefits associated with a 'trial effect' such as a care effect and a protocol effect.

1.3 References:

1. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis.* Oct 1 2004;39(7):1038-1046.

2. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* Aug 5 2006;368(9534):476-482.

3. Fischl MA, Ribaudo HJ, Collier AC, et al. A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced human immunodeficiency virus disease. *J Infect Dis.* Sep 1 2003;188(5):625-634.

4. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* Jan 19 2006;354(3):251-260.

5. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *Jama.* Jul 14 2004;292(2):191-201.

6. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med.* Sep 11 1997;337(11):734-739.

7. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* Apr 29 2004;350(18):1850-1861.

8. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med.* Sep 11 1997;337(11):725-733.

9. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results. *Aids.* Jan 5 2001;15(1):F1-9.

10. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* Dec 11 2003;349(24):2293-2303.

11. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* Apr 17 2004;363(9417):1253-1263.

12. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department

of Health and Human Services. January 29, 2008; 1-128. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 25, 2008.

13. Anderson J BA, Boffito M, Brook G, Churchill D, Collins S, Fisher M, Freedman A, Gazzard B, Geretti AM, Johnson M, Khoo S, Leen C, Nair D, Peters B, Phillips A, Pillay D, Pozniak A, Walsh J, Wilkins E, Williams I. BHIVA guidelines for the treatment of HIV-infected adults with antiretroviral therapy 2005. 2005.

14. Gazzard B. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). *HIV Medicine.* 2006;7:487-503.

15. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *Jama.* Aug 16 2006;296(7):827-843.

16. ECRI Evidence Report: Patients' reasons for participating in clinical trials and effect of trial participation on patient outcomes. Available at https://www.ecri.org/Documents/Clinical_Trials_Patient_Guide_Evidence_Report.pdf 2002. Accessed June 27,2008.

17. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol.* Mar 2001;54(3):217-224.

18. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet.* Jan 24 2004;363(9405):263-270.

19. Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. *Bmj.* May 21 2005;330(7501):1175.

20. Lantos JD. The "inclusion benefit" in clinical trials. *J Pediatr.* Feb 1999;134(2):130-131.

21. El-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *Jama.* Feb 19 1992;267(7):954-957.

22. Madge S, Mocroft A, Wilson D, et al. Participation in clinical studies among patients infected with HIV-1 in a single treatment centre over 12 years. *HIV Med.* Oct 2000;1(4):212-218.

23. Moore DA, Goodall RL, Ives NJ, Hooker M, Gazzard BG, Easterbrook PJ. How generalizable are the results of large randomized controlled trials of antiretroviral therapy? *HIV Med.* Jul 2000;1(3):149-154.

24. Stone VE, Mauch MY, Steger K, Janas SF, Craven DE. Race, gender, drug use, and participation in AIDS clinical trials. Lessons from a municipal hospital cohort. *J Gen Intern Med.* Mar 1997;12(3):150-157.

25. Diaz T, Chu SY, Sorvillo F, et al. Differences in participation in experimental drug trials among persons with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol.* Dec 15 1995;10(5):562-568.

26. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria. *J Am Coll Cardiol.* Jan 1984;3(1):114-128.

27. Bertelsen K. Protocol allocation and exclusion in two Danish randomised trials in ovarian cancer. *Br J Cancer.* Dec 1991;64(6):1172-1176.

28. Chen CI, Skingley P, Meyer RM. A comparison of elderly patients with aggressive histology lymphoma who were entered or not entered on to a randomized phase II trial. *Leuk Lymphoma.* Jul 2000;38(3-4):327-334.

29. Davis S, Wright PW, Schulman SF, et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. *Cancer.* Oct 1 1985;56(7):1710-1718.

30. Davis S, Wright PW, Schulman SF, Scholes D, Thorning D, Hammar S. Long-term survival in small-cell carcinoma of the lung: a population experience. *J Clin Oncol.* Jan 1985;3(1):80-91.

31. Lennox EL, Stiller CA, Jones PH, Wilson LM. Nephroblastoma: treatment during 1970-3 and the effect on survival of inclusion in the first MRC trial. *Br Med J.* Sep 8 1979;2(6190):567-569.

CHAPTER TWO - BACKGROUND

2.1. HIV clinical trials and HAART

Worldwide there are 38.6 (33-46) million people living with HIV and in 2005 alone there were 4.1 (3.4-6.2) million new HIV infections[1]. The advent of HAART has dramatically changed the HIV landscape decreasing mortality and morbidity.

2.1.1 Evidence for the efficacy of HAART

The evidence in support of HAART efficacy comes largely from clinical trials. The first clinical trial to establish the superiority of triple drug regimens for the treatment of HIV was the seminal Merck 035 study[2]. Preliminary data from this study, presented in early 1996 showed that 90% of chronically infected patients treated with two nucleoside inhibitors (zidovudine and lamivudine) and a protease inhibitor (indinavir) achieved undetectable plasma HIV RNA levels through 24 weeks of follow up and these results were sustained to week 52. The AIDS Clinical Trials Group (ACTG) 320 study also provided convincing support of this treatment combination[3]. This large study of 1156 subjects, followed for a median duration of 38 weeks, was halted early by the Data Safety Monitoring Board, citing the clear clinical superiority of the three drug combination in decreasing the progression to AIDS, death from AIDS and increasing viral suppression. These trials heralded the advent of combination therapy, specifically the use of three antiretroviral drugs as standard

of care for the treatment of HIV. Combination therapy with three or more antiretroviral drugs then became referred to as highly active antiretroviral therapy (HAART). Since then, numerous studies conducted by the NIAID-supported ACTG and by the pharmaceutical industry have validated these observations[4-13]. Today the treatment of HIV infected persons with non HAART regimens would be unethical.

The years following the Merck 035[2] and ACTG 320[3] studies have seen the conduct of numerous clinical trials providing a broad spectrum of data on HIV treatment and resulting in the continuous evolution of HIV treatment guidelines. Since 1996, the International AIDS Society-USA (IAS-USA) has published revised antiretroviral therapy guidelines seven times, most recently in August 2006[14]. In 2006 the United States (US) Department of Health and Human Services (DHHS)[15] and the British HIV Association[16] published updated guidelines of which drug combinations may be considered first line HAART regimens for treatment naïve persons. A change in the new guidelines with regard to HAART provision was the inclusion of a specific boosted protease inhibitor (fosamprenavir/ritonavir) combination. This recommendation was based on data from the KLEAN[5] trial demonstrating non-inferiority of fosamprenavir/ritonavir to the comparator drug, clearly showing the rapid influence of clinical trials data in the formulation of treatment guidelines within and outside the US.

Data from HIV clinical trials has been used to guide other aspects of HIV care such as when to start HAART, when to change a regimen, and recommendations for

the use of resistance tests. Several clinical trials have used baseline resistance testing prior to study entry to guide HAART selection. Two such studies, the TORO1[17] and TORO2 [18] trials enrolled approximately 1000 treatment experienced persons at over 100 centers worldwide. Baseline resistance testing prior to study entry was used to guide selection of a HAART regimen to be combined with or without study drug. These and other trials have provided indirect support of the clinical benefit of resistance testing prior to the selection of new HAART for treatment experienced persons. Data from these trials persuaded the British HIV association[19] to recommend resistance tests for new HAART selection in treatment experienced persons . Likewise, the DHHS[15] recommends resistance testing for treatment experienced persons, citing evidence from several trials including the VIRADAPT[20] trial where genotypic testing was found to have significant benefit on virologic response when choosing a new HAART regimen.

Clinical trials data is not just used to establish care and treatment guidelines, but is used by clinicians in clinical practice to provide evidence based care. Pharmaceutical companies use this data to support the superiority of a particular drug or combination of drugs and to directly influence patients and providers behavior. However, study participants may differ substantially from the general HIV infected population suggesting that clinical trials data has limitations and should be interpreted with caution.

2.2. The limitations of HIV clinical trials data.

Although randomized clinical trials (RCT) provide the best evidence in support of treatment efficacy, there are several limitations when using clinical trials data to make population level/policy decisions and individual/clinical care decisions. The applicability of clinical trials data may be limited because trial populations differ substantially from the general HIV infected population and/or because of an effect of trial participation that is independent of individual patient/participant characteristics.

2.2.1 Clinical trial populations differ from non trial populations.

The distribution of HIV by race, gender and transmission category has changed. Several epidemiologic shifts have occurred in the US in HIV infection over the last several years: 1) The HIV epidemic now disproportionately affects people of color. Of the estimated 184,991 adult and adolescent HIV infections diagnosed during 2001-2005, more (51%) occurred among blacks than among all other racial/ethnic populations combined[21]. The 2005 US census[22] showed that African American (AA) and Hispanic women comprised only 24% of all women in the US, yet in that same year 64% of all women living with HIV/AIDS were AA compared with 19% white and 15% Hispanic[23]. 2) Heterosexual intercourse has emerged as one of the major routes of HIV acquisition. Of all HIV/AIDS cases diagnosed in 2005 high risk heterosexual contact accounted for 32%[23]. When stratified by gender, 80% of the newly diagnosed women reported high risk heterosexual intercourse as the route for acquiring HIV infection. 3) Early in the epidemic relatively few women were

diagnosed with HIV infection. Today, women account for more than one quarter of all new HIV diagnoses, and HIV infection is the leading cause of death for AA women between the ages 25-34, and the third leading cause of death for ages 35-44 surpassed only by heart disease and cancer[23].

Race/ethnicity, gender, and HIV transmission category can influence the pharmacokinetics and response to HAART[24, 25]. Efavirenz clearance is strongly associated with race, and lower rates of clearance have been reported in African Americans and Hispanics as compared to whites resulting in higher plasma concentrations[26]. Increasing plasma concentrations of efavirenz are associated with a trend towards increasing rates of drug discontinuation, possibly due to greater side effects associated with higher drug concentrations. A possible genetic basis for the difference in clearance rates exists. Efavirenz is metabolized by the enzyme CYP2B6 and an allelic variant of this enzyme associated with higher plasma drug concentrations is more common in African Americans than in Caucasians[27].

Gender based variations in HIV infection have also been described. Despite HAART, gender based variations in HIV infection persist and women continue to be more likely than men to experience HIV disease progression after adjustment for race, age and route of HIV transmission[28]. Metabolism of antiretrovirals can differ by gender and for Efavirenz, female subjects have a 25% higher area under the curve than male subjects[29]. Women are also more likely to experience side effects from protease inhibitors and have an increased incidence of rash and risk for

hepatotoxicity with Nevirapine[30-32]. A differential response to HAART has been observed among specific risk groups. An analysis of 5735 patients from the French Hospital Database on HIV showed that homosexual patients have a better immunological response than heterosexual patients and injecting drug use (IDU) patients and the virological response is poorer among IDU patients than among homosexual and heterosexual patients[33].

Although HAART is effective, there may be a differential efficacy among women, ethnic minorities and IDU patients and these groups are under-represented in clinical trials[34-37].The ACTG 5095 clinical trial convincingly established the inferiority of a triple nucleoside regimen for initial HAART and is cited by the guidelines as providing evidence against use of this treatment combination[9]. Yet, in this large trial of over 1000 subjects only 19% were women and approximately 36% were non-Hispanic black. The demographics of patients in earlier landmark trials such as ACTG 320[3] and ACTG 384[11] were 83% male, 28% black and approximately 80% male and 34% black respectively. Pharmaceutical sponsored studies have been equally unsuccessful in enrolling women and minorities. The recent Gilead 934 study only enrolled 13.5% women and 22.5% blacks[7], and ABT378/r the preliminary study to confirm the efficacy of lopinavir/ritonavir had 90% male and 24% black participants[10]. None of these studies reported risk factors for HIV transmission. However, several early trials have shown an under-representation of persons who acquired HIV infection heterosexually or through injecting drug use and an over representation of men who have sex with men[38-40]. A further study involving HIV

infected patients receiving care at three separate ambulatory clinics in Boston City Hospital found that women, persons of color and those who had acquired HIV through injection drug use were significantly less likely to have ever participated in a clinical trial[37]. In a probability sample of 2684 person's non-Hispanic blacks and Hispanics and persons under care with private HMO's were less likely to participate in clinical trials[35].

Thus the generalizability and external validity of results from HIV clinical trials is questionable due to the lower participation rates of groups of patients who might have differential responses to HAART.

2.2.2 Reporting bias in HIV clinical trials

Reporting bias may limit the generalizability of clinical trials data. Eligibility criteria in published reports of clinical trials are usually abbreviated due to space issues and therefore differ greatly from the detailed eligibility criteria available in the actual protocol. Gandhi et al[41] applied a broad range of eligibility criteria, employed for entry into 32 HIV randomized controlled trials conducted by the ACTG (n= 20) and the Community Programs for Clinical Research on AIDS (n=12), to the Women's Interagency HIV Study (WIHS), the largest cohort study of HIV infected women in the US. The criteria used included patient demographics, concurrent or past illnesses including opportunistic infections and malignancies, life expectancy, substance abuse, general laboratory parameters, concurrent medications and

pregnancy/lactation status. Based on eligibility criteria obtained directly from the ACTG trial protocols, a median of 50.6% of the WIHS cohort would have been excluded from ACTG trial participation. However, when using eligibility criteria listed in published reports of these protocols a much smaller proportion (median 21.2%) of WIHS women would have been excluded. These findings raise several issues of which we highlight two 1) there is a significant discrepancy between published eligibility criteria and actual protocol eligibility criteria making direct application of the clinical trials data to clinical practice difficult. 2) a large proportion of a representative cohort of HIV infected women would have been excluded from trial participation based on eligibility criteria. The implications of these findings are there is exclusivity in selection of HIV clinical trial participants which suggests the applicability of clinical trials data to the general patient population may be limited.

2.2.3 The conduct of clinical trials

A large number of antiretroviral drug trials, particularly those involving new drugs, are undertaken by pharmaceutical companies to obtain licensing approval or further indications for drug use. In these trials patients are usually required to take the drug or drug combination under study with little or no flexibility. By contrast, in clinical care drug provision is highly individualized and patients participate in decisions involving drug choices. Therefore, these trial designs likely do not reflect how drugs are used in clinical care. Another key limitation is the high frequency of follow-up visits in clinical trials which is rarely if ever mimicked in clinical care.

2.3 Trial effect: Current knowledge

Despite 25 years of HIV clinical trials, the largest limitation to the use of data from clinical trials is the unaddressed question: “Is there a ‘trial effect’ in HIV clinical trials?” A trial effect is considered a benefit that trial participants experience merely by the act of trial participation. An experimental treatment effect, protocol effect, care effect, Hawthorne effect, and placebo effect are all potential components of an overall trial effect and we provide a brief explanation of each effect. An experimental treatment effect is thought to occur when experimental treatment offered in a study is better than current standard of care. A protocol effect is a possible benefit arising from the treatment regimens and procedures that are clearly outlined in the clinical trials manual. A care effect arises from differences in care between trial and non trial participants. Hawthorne effect is due to changes in patient or clinician behavior as a result of the trial. Placebo effect is thought to arise from the fact that patients experience intangible psychologically mediated benefits from trial participation. It has been hypothesized that these components of a trial effect might lead to improved outcomes among trial participants. The differences observed between clinical trials and clinical care including provision of close follow up, strict adherence to protocol and differences in outcomes measurement might be covered under the broad umbrella of a ‘trial effect’.

The current state of knowledge regarding a trial effect has been summarized in the last ten years by four published systematic reviews (Braunhotz2001[42],

Emergency Care Research Institute [ECRI] 2002[43], Peppercorn 2004[44], Vist 2005 [Cochrane Collaboration][45]). Most of the reviews predominantly focused on cancer care, though some included other medical specialties such as heart disease, post operative care, and gynecology. None of these reviews included any HIV related clinical trial.

None of the four reviews provided convincing evidence in support of a trial effect. While admitting that the evidence available is limited in breadth coming mainly from cancer clinical trials, Braunholtz concluded that on average clinical trials have a positive rather than a negative effect on outcomes[42]. Peppercorn et al suggested that there was little high quality evidence in support of trial effect in cancer trials[44] and the Cochrane review found no strong evidence of either a harmful or beneficial trial effect if trial participants received similar treatments to non trial participants[45]. The Emergency Care Research Institute (ECRI) concluded that though patients in trials survive longer they had limited confidence in these results due to the small evidence base.

Table 1.1: Summary of the conclusions of the systematic reviews that examined a trial effect

Review	Year	Number of trials included	Disease	Number of patients in trials	Number of patients not in trials	Conclusions
Braunholtz	2001	14	Cancer Heart Pulmonary Post-op care	NR**	NR**	Weak evidence that well conducted trials benefit the participants and do not seem on average to result in harm.
ECRI[$]	2002	10	Cancer Heart	1793	2654	Limited confidence in these results. Some evidence that patients in Phase II/III trials survive longer than similar patients not in trials.
Peppercorn	2004	24	Cancer	NR**	NR**	Insufficient data to conclude that enrolment in clinical trials improves outcomes in patients with cancer
Cochrane Review	2005	5 (RCT)* 50 (cohort studies)	Cancer/Heart Pulmonary Gynecology Drug abuse Surgery	412* 30,862	20,246	Results suggest that participation in RCTs is likely to result in similar outcomes if similar treatments are received outside a trial.

*RCT-randomized controlled trial. Total number of patients was 412. Number in and out of trials was not reported; **NR-Not reported; [$] Emergency Care Research Institute

2.3.1 Summary of limitations to prior research and current research

Limitations to prior research

While all four reviews were conducted with the highest integrity they are subject to several limitations. First, these reviews are limited by publication bias as they only included published studies. The implication is if more unpublished studies had negative or neutral results and published studies had positive results it may over estimate the effect of the intervention. Second, they included both adult and pediatric

trials and therefore may have been unable to identify a trial effect due to the heterogeneity between these two populations. Third, they compared all patients treated within trials to all patients treated outside trials regardless of differences in patient populations and in clinical interventions. This approach means we are unsure if the reported results truly reflect a trial effect or are due to these differences. Fourth, the main focus of three reviews was cancer trials. However, a trial effect might be disease dependent and oncology might not be the best medical specialty in which to study trial effect as the interventions used are frequently experimental and not available to the general patient population. Finally, systematic reviews are limited both by the quality and the strength of the data available in the original published study. Specifically there are limitations associated with sample sizes and outcome measures in the included studies. If additional requisite data is needed, it must first be ascertained if this is available and then requested from the authors. This is a labor and time intensive process and likely results in only obtaining incomplete or poorer quality data.

Current research

This dissertation addressed the limitations of these systematic reviews. We were not limited by publication bias as the primary data necessary to conduct this study was available through the University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC). We had a clearly defined sample size, and our outcome measurement (plasma HIV RNA) is likely one of the best surrogate markers of response to therapy for most diseases. The antiretroviral

treatments provided to the clinical trial participants were in most instances available to and similar in the non trial participants and were non experimental. Since we conducted our own independent analysis of the primary data, our results are not subject to the limitations of how variables were handled or adjusted for.

In summary, there is mixed evidence available in support of trial participation benefit or trial effect. What evidence there is comes mainly from cancer trials and is limited in breadth, quality and quantity. HIV infection differs appreciably from cancer in the chronicity of the illness, treatment options, the modes of transmission, and the basic biology and pathogenesis of disease. HIV treatments (HAART vs. radiation/chemotherapy) are, in general, less toxic, likely more effective and following trial termination more readily and rapidly available for clinical practice due to accelerated regulatory approval and expanded access programs. These factors may enhance or diminish any possible clinical trials effect. There are also important psychosocial and stigmatization issues that make HIV uniquely different from cancer. These meaningful differences between HIV infection and cancer, and the implications of these differences in the application of clinical trials data to the care and treatment of the HIV infected community, strongly supported our separate study of a trial effect in HIV clinical trials.

2.4 Implications of this research

Positive evidence for a trial effect

We believe this study is the first, or one of the first, to examine the question of trial effect in HIV clinical trials. Evidence in support of a trial effect on antiretroviral

treatment outcome may result in modifications to clinical care to incorporate aspects of 'trial effect'. An incidental aspect of care in clinical trials is frequent, closely-spaced-in-time, study visits irregardless of need. This may be contrasted with a quarterly visit schedule generally followed in routine clinical care. Incorporation of the frequency of study visits into clinical care could result in better provider-patient relationships leading to improved medication adherence and the improved outcomes associated with clinical trials. Currently clinical care is highly individualized whereas clinical trials are strictly protocol driven. Treatment regimens in a trial are carefully outlined in the trial protocol and consideration is also given to if, when and how deviations from protocol should be permitted. Protocol effect is another aspect of trial effect that might be included in clinical care.

Any diminished response to HAART among non-trial participants increases the risk for the development of resistant virus. This is clearly an issue of great public health importance as increase in the prevalence of resistant virus raises the likelihood of transmission of resistant virus to uninfected persons, as well as the transmission of a resistant strain of virus to an infected person. If there is a true benefit to trial participation due a trial effect, it is possible that modification to clinical care may provide the needed parity in response to HAART between trial and non-trial participants decreasing the likelihood for the development of resistance virus.

No evidence for a trial effect

Perhaps more important than support of a trial effect is the absence of one. The findings of no trial effect would suggest clinical equipoise between trial and non trial participants and has far reaching implications. First, it would address the perception that participation in clinical trials confers benefits in addition to those derived from treatment. This has long been a widespread but unsubstantiated belief. Second, it would help address a major concern regarding the external validity of clinical trials data. Clinicians would be reassured that extrapolating treatments from clinical trials to clinical practice does not result in variations to treatment effects. Third, it reinforces the utility and applicability of treatment guidelines which are formulated using data from clinical trials. Fourth, it would encourage patients to enroll in clinical trials by suggesting there is no reduction in treatment effects in a trial compared to clinical practice.

Knowledge of the absence of a trial effect would also enable investigators to enroll patients in clinical trials without over promising the benefits of trial participation. The American Federation of Clinical Oncologic Societies[46] maintains that "treatment in a clinical trial is often a cancer patient's best option". However, in HIV care which effects over 40 million people and with that number projected to increase exponentially, HIV clinicians and researchers have thus far been inadequately equipped to make any statement regarding trial participation. This study will enable providers to encourage enrollment in clinical trials while being realistic about the potential benefits and harms associated with participation.

There are 40 million HIV infected persons and greater than 95% of these persons will begin HAART outside of clinical trials. These persons and their providers will no doubt be reassured about the efficacy of treatment in the absence of a trial effect.

2.5 Trial effect in HIV treatment trials

We believe that HIV provides an excellent substrate for the measurement of a trial effect. It is a severe but chronic illness for which excellent and well characterized treatments are available. There are numerous well conducted clinical trials of antiretroviral therapy. As already mentioned, there is a well validated easily available test for the measurement of HIV RNA making definitions of outcome clear and precise. Moreover, our ability to examine trial effect was further enhanced by the availability of primary patient data on a well characterized set of patients from the same population.

In sum, we employed a systematic approach to study the evidence in support of a trial effect in HIV clinical trials. First, we established who participates in clinical trials**.** It has been widely hypothesized that if a trial effect exists it may largely be explained by the differences between trial and non-trial populations. Identifying the extent and magnitude of these differences is essential prior to examining whether there is a true outcome effect associated with clinical trials participation. In particular

we assessed if specific demographics (race/ethnicity and gender/sexual orientation) are barriers to trial participation. This is important, as clinicians need to be aware of which patients may not enter clinical trials, to facilitate targeted enrolment of these groups resulting in more heterogeneous study populations thereby increasing the generalizability of clinical trials data.

Second, we determined if a trial effect was present in HIV treatment trials by assessing if trial participation alone was responsible for improved outcomes. The primary purpose of HAART is to achieve maximal and durable viral suppression. In treatment naïve persons the success of HAART is demonstrated by a decrease in HIV RNA of 1log by week 4 post HAART and an HIV RNA of <50copies/ml by 16-24 weeks. However, as our study period encompassed a time when HIV RNA was measured using four different assays with different ranges we defined viral suppression as an HIV RNA of $\leq$400copies/ml at six months. We defined our outcome of virologic success as having a plasma HIV RNA level ≤400 copies/ml at six months after HAART initiation. We controlled for baseline demographic, clinical and laboratory parameter differences and compared this outcome among antiretroviral treatment naïve persons who were initiated on HAART as part of or outside a clinical trial.

2.6 References:

1. UNAIDS-Report on the global AIDS epidemic 2006 [http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp].

2. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med.* Sep 11 1997;337(11):734-739.

3. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med.* Sep 11 1997;337(11):725-733.

4. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis.* Oct 1 2004;39(7):1038-1046.

5. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* Aug 5 2006;368(9534):476-482.

6. Fischl MA, Ribaudo HJ, Collier AC, et al. A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced human immunodeficiency virus disease. *J Infect Dis.* Sep 1 2003;188(5):625-634.

7. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* Jan 19 2006;354(3):251-260.

8. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *Jama.* Jul 14 2004;292(2):191-201.

9. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* Apr 29 2004;350(18):1850-1861.

10. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results. *Aids.* Jan 5 2001;15(1):F1-9.

11. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* Dec 11 2003;349(24):2293-2303.

12. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in

the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* Dec 16 1999;341(25):1865-1873.

13. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet.* Apr 17 2004;363(9417):1253-1263.

14. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *Jama.* Aug 16 2006;296(7):827-843.

15. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1-128. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed June 25, 2008.

16. Gazzard B. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). *HIV Medicine.* 2006;7:487-503.

17. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med.* May 29 2003;348(22):2175-2185.

18. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med.* May 29 2003;348(22):2186-2195.

19. Anderson J BA, Boffito M, Brook G, Churchill D, Collins S, Fisher M, Freedman A, Gazzard B, Geretti AM, Johnson M, Khoo S, Leen C, Nair D, Peters B, Phillips A, Pillay D, Pozniak A, Walsh J, Wilkins E, Williams I. BHIVA guidelines for the treatment of HIV-infected adults with antiretroviral therapy 2005. 2005.

20. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet.* Jun 26 1999;353(9171):2195-2199.

21. CDC. Racial/Ethnic Disparities in Diagnoses of HIV/AIDS --- 33 States, 2001--2005. MMWR 56(09): 189-193. March 9, 2007.

22. National Center for Health Statistics. Bridged-race vintage 2005 postcensal population estimates for July 1, 2000–July2005, by year, county, single-year age, bridged-race, Hispanic origin, and sex. Available at http://www.cdc.gov/nchs/about/major/dvs/popbridge/ Accessed March 1, 2007.

23. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2005. Vol. 17. Atlanta: U.S.Department of Health and Human Services, Centers for Disease Control and Prevention; 2006:[1-54].
Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/.

24. Andrade A, Flexner C. Genes, ethnicity, and efavirenz response: clinical pharmacology update from the 11th CROI. *Hopkins HIV Rep.* May 2004;16(3):1-7.

25. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol.* 2004;44:499-523.

26. Ribaudo H CD, Gulick R, Shikuma C, Klingman K, Snyder S, Acosta E. Relationships between Efavirenz Pharmacokinetics, Side Effects, Drug Discontinuation, Virologic Response, and Race: Results from ACTG A5095/A5097s. 11th Conf Retrovir Opportunistic Infect Febr 8-11 2004 San Franc CA Conf Retrovir Opportunistic Infect 11th 2004 San Franc Calif. Abstract no. 132.

27. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *Aids.* Dec 3 2004;18(18):2391-2400.

28. Poundstone KE, Chaisson RE, Moore RD. Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy. *Aids.* Jun 15 2001;15(9):1115-1123.

29. Hitti J RS, Cohn S, Kamemoto L, Kashuba A, Caten E, Aweeka F. Sex and Weight as Covariates in the Pharmacokinetics of Efavirenz, Indinavir, and Nelfinavir.11th Conf Retrovir Opportunistic Infect Febr 8 11 2004 San Franc CA Conf Retrovir Opportunistic Infect 11th 2004 San Franc Calif. 2004 Feb 8-11; 11: abstract no. 604.

30. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis.* Mar 15 2005;191(6):825-829.

31. Mazhude C, Jones S, Murad S, Taylor C, Easterbrook P. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *Aids.* Jul 26 2002;16(11):1566-1568.

32. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* Jan 2001;32(1):124-129.

33. Fardet L, Mary-Krause M, Heard I, Partisani M, Costagliola D. Influence of gender and HIV transmission group on initial highly active antiretroviral therapy prescription and treatment response. *HIV Med.* Nov 2006;7(8):520-529.

34. el-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *Jama.* Feb 19 1992;267(7):954-957.

35. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med.* May 2 2002;346(18):1373-1382.

36. Hankins C, Lapointe N, Walmsley S. Participation in clinical trials among women living with HIV in Canada. Canadian Women's HIV Study Group. *Cmaj.* Dec 1 1998;159(11):1359-1365.

37. Stone VE, Mauch MY, Steger K, Janas SF, Craven DE. Race, gender, drug use, and participation in AIDS clinical trials. Lessons from a municipal hospital cohort. *J Gen Intern Med.* Mar 1997;12(3):150-157.

38. Madge S, Mocroft A, Wilson D, et al. Participation in clinical studies among patients infected with HIV-1 in a single treatment centre over 12 years. *HIV Med.* Oct 2000;1(4):212-218.

39. Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Concorde Coordinating Committee. *Lancet.* 1994;343:871-881.

40. Delta Coordinating Committee. Delta: a randomized double blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV infected individuals. *Lancet.* 1996;348:283-291.

41. Gandhi M, Ameli N, Bacchetti P, et al. Eligibility criteria for HIV clinical trials and generalizability of results: the gap between published reports and study protocols. *Aids.* Nov 4 2005;19(16):1885-1896.

42. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol.* Mar 2001;54(3):217-224.

43. ECRI Evidence Report: Patients' reasons for participating in clinical trials and effect of trial participation on patient outcomes. 2002. Available at https://www.ecri.org/Documents/Clinical_Trials_Patient_Guide_Evidence_Report.pdf Accessed June 27,2008.

44. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet.* Jan 24 2004;363(9405):263-270.

45. Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. *Bmj.* May 21 2005;330(7501):1175.

46. American Federation of Clinical Oncologic Societies, Access to quality cancer care: consensus statement. *J Clin Oncology.* 1998;16:1628-1630.

CHAPTER THREE - RESEARCH DESIGN AND METHODS

3.1. Overview

Despite widespread belief that clinical trial participation leads to improved outcomes, there is little empirical data in support of such a trial effect. What data exists comes largely from cancer trials and has been inconclusive. To address this unknown we conducted these analyses using the University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC).

3.2. Data Source

The University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC) was created with two primary objectives:

1) to document clinical strategies, therapeutic outcomes, and socio-demographic-behavioral risk information for use in planning effective research objectives, and facilitating new scientific discoveries in translational, clinical and behavioral HIV/AIDS research
2) to inform clinicians of current patient status in critical components of HIV care such as, medication and illness history, screening tests, vaccinations and immune status.

The UCHCC is a longitudinal cohort database that has enrolled over 2000 HIV positive trial and non trial participants. This represents over 10% of the HIV infected population in North Carolina. The UCHCC captures information from a variety of sources, including, daily electronic transfers from existing UNC electronic databases, medical record abstractions, in-person interviews, and additional data such as nucleotide sequences. The data is transferred nightly through a secured link from the UNC Hospital's DB2 system to the UCHCC SAS/WAREHOUSE ® (version 2.2) software. This includes demographic, laboratory, pathology and all clinical visit information. Critical HIV therapeutic and clinical trials data not available reliably in an electronic format, is obtained through medical chart abstraction procedures that are tailored to the organization of medical records at UNC.

At enrollment (which is the date that patients provide informed consent and HIPPA authorization to participate in the UCHCC) and prospectively at 6-month intervals, comprehensive and standardized medical chart abstractions are performed by trained research staff, and include demographic and clinical data including all prescribed medications, viral resistance reports, diagnosed illnesses, and hospitalizations. A high quality of abstracted data is ensured by extensive preliminary training and periodic retraining of data abstractors and quarterly quality control checks on data collected. Implausible or out of range values are flagged for supervisors to check and correct/confirm. Prior to data acquisition, a

data use agreement and pledge of confidentiality must be signed by all investigators.

The UCHCC has been approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill (UNC-CH)

3.3. Specific Aim one

Using the UNC CFAR HIV/AIDS Clinical Cohort we examined if trial participants differed from non trial participants by either race/ethnicity or gender/sexual orientation.

Study design

We used the UCHCC and conducted an analysis of baseline cross-sectional data from a cohort of antiretroviral treatment naïve HIV positive adults (≥18years). The UCHCC is a comprehensive database that incorporates a wide array of information from various hospital medical record systems into an accessible, standardized computerized format. Numerous checks and validation steps ensure the integrity of the data. Of particular relevance to this study was the availability of detailed antiretroviral medication history including dates of use, and trial participation history. In addition, laboratory results are imported electronically from the hospital record-keeping system eliminating human data entry error and allowing for accurate tracking of patients' virologic response.

Study population

The study population is antiretroviral treatment naïve HIV positive adults ≥ 18 years of age who received care in the UNC Infectious Diseases (ID) clinic between the years 1996 – 2006, and initiated HAART defined as any combination of three or more antiretroviral agents, or a regimen that contains a protease inhibitor (PI) plus a non nucleoside reverse transcriptase inhibitor (NNRTI) with or without additional agents. To date, over 2000 HIV positive adults receiving primary HIV care at the UNC ID clinic have consented to participate in the UCHCC. This represents most of the UNC ID clinic and over 10% of known HIV infected persons in North Carolina, with less than 5% refusing to participate. The characteristics of those declining to participate in the UCHCC do not differ from participants.

The UCHCC includes one-third women (33%), and two-thirds racial/ethnic minorities (61% African American, 31% White, 4% Hispanic, 2% American Indian/Alaskan Native, and 2% Other). Most patients acquired HIV infection through heterosexual contact, with 16% acquiring HIV through injection drug use, and 26% being men who have sex with men. Almost one-half of the UHCC participants reside in rural or small urban areas (49%) and over half of the patients travel more than 60 miles one way to receive HIV care. Twenty-nine percent have no insurance coverage at initiation of HIV care, with 42% having public insurance coverage (Medicare and Medicaid) , and 29% private insurance coverage. The median length of follow-up for the entire cohort representing the time from entry to HIV care is 5.3 years (IQR; 2.9, 8.3), with an accumulated

8701 person-years of follow-up. The characteristics of this patient population resemble those of the HIV infected population in the state of North Carolina. This is supported in Table 2 which presents the demographics of UCHCC participants and that of the HIV/AIDS cases for 2006 in the state of North Carolina[1]. Moreover, six southeastern states (North Carolina, South Carolina, Mississippi, Alabama, Georgia, Louisiana) report demographically similar epidemics supporting the generalizability of these results to the southeast US[2-4].

Table 3.1 : Demographics of UCHCC participants and North Carolina State HIV/AIDS patients

UCHCC participants 2000-06		North Carolina State HIV/AIDS cases- 2002-06	
	Percent		Percent
Gender		Gender	
Male	67	Male	70.8
Female	33	Female	29.2
Race		Race	
White	31	White	26
Black	61	Black	66
Other	8	Other	8
Health insurance			
Private	29		
Medicaid/Medicare/Public	42		
None	29		
Residence			
Rural/Small town	49		
Urban	51		

Main Study Variables

Exposure:

The two main exposure variable were gender/sexual orientation and race/ethnicity.

Gender/sexual orientation: Men who have sex with men (MSM) and bisexual men were placed in one category. However, because there were no homosexual females and MSM is a subset of all men, we specified a joint gender and sexual preference variable with three categories (females/heterosexual males/MSM) to clarify interpretation of coefficients in multivariable regression.

Race/ethnicity: Race/ethnicity was categorized as black or non black.

Outcome:

Subjects were characterized as trial participants if HAART was initiated as part of a clinical trial. Clinical trials included AIDS Clinical Trials Group (ACTG) supported or industry sponsored trials and may or may not have been randomized, placebo controlled or blinded.

Covariates:

1. Age: Age was initially coded as a continuous variable, calculated from birth date to date of HAART initiation, and subsequently dichotomized into two categories.
2. AIDS Diagnosis: We used the Centers for Disease Control and Prevention (CDC) 1993 AIDS Surveillance Case Definition[5] as our guide to assign an AIDS diagnosis to a subject. Based on this we categorized subjects as Yes (1) for an AIDS diagnosis and No (0) for the absence of an AIDS diagnosis. This variable excluded persons with a CD4 cell count ≤200 cells/uL.

3. Insurance status: Health insurance status was classified as three categories: private, public (including Medicare, Medicaid, and other state and federal programs), or none. Injection Drug Use (IDU) as a route of HIV acquisition: This variable was categorized as positive if there was self reported IDU as a risk for HIV acquisition and negative if not.
4. Distance traveled from home to the ID clinic (miles): This was initially coded as a continuous variable but did not satisfy the criteria for linearity and was subsequently dichotomized as ≤50 miles vs. >50 miles
5. Time from HIV diagnosis to HAART initiation (months): This was initially coded as a continuous variable but did not satisfy the criteria for linearity and was subsequently dichotomized to ≤3 vs. >3 months.
6. Mental Illness was dichotomized as present or absent.
7. Substance abuse was self reported and was also dichotomized as present or absent.

9. Laboratory tests.

- Baseline alanine aminotransferase (ALT), absolute neutrophil count (ANC), hemoglobin and creatinine were initially coded as continuous variables and subsequently dichotomized as normal or abnormal. Gender appropriate normal ranges were accounted for when forming categories.
- Baseline viral load: Plasma HIV RNA was transformed to the log base 10 scale to arrive at an approximately normal distribution and retained as a continuous variable.

- Baseline CD4 cell count: Baseline CD4 count was initially coded as a continuous variable and subsequently categorized into two clinically meaningful categories (≤200 vs. >200)

All of the above covariables were evaluated at baseline, which was defined as the date of HAART initiation, except for AIDS diagnosis, mental illness and substance abuse, which were evaluated at any time before and up to 14 days after the date of HAART initiation.

For laboratory results not available on the same day HAART was initiated an extended baseline period was considered, with baseline values being defined as those closest to the day of HAART initiation within a window spanning 180 days before and up to 14 days after the date of HAART was started.

Analytic Techniques

Univariate analysis:

Basic descriptive statistics (proportions, mean, median, range, standard deviation) were generated for all variables considered in the analysis. Visual summaries of histograms and box plots were used to assess if continuous variables were normally distributed. Variables that deviated substantially from normality were transformed (e.g. HIV RNA levels were transformed to the log base 10 scale) to arrive at an approximately normal distribution.

Outliers were identified for each variable and, when possible, corrected if inconsistent with raw data. Each variable was checked for missing values. A complete case analysis was used in all analyses.

Alternate approaches to coding that appeared to be more meaningful were explored for each variable. For example, some continuous variables were categorized at meaningful cut points. Similarly, some categorical variables were dichotomized if necessary, while other nominal variables were transformed into indicator variables to avoid enforcing ordinality.

The comparison of baseline characteristics between trial and non trial participants was performed using chi square test for categorical variables, t test for normally distributed continuous variables and Wilcoxon rank sum test for non normally distributed continuous variables.

Bivariable Analysis:

An unadjusted prevalence ratio (PR) and a 95% CI to assess the association between race/ethnicity and gender/sexual orientation and trial participation were calculated as follows:

$$PR = \frac{A_1/N_1}{A_0/N_0}$$

where A_1, A_0, N_1, and N_0 are defined as shown below.

Table 3.2: Schematic for bivariate data analysis-Prevalence ratio

Characteristics	Trial=Yes	Trial=No	Total
Index level	A_1	B_1	N_1
Referent	A_0	B_0	N_0
Total	$A.$	$B.$	$N.$

Assessment of Linearity:

Linearity of the log prevalence was assessed by 1) using a quadratic spline model with knots at 10^{th}, 50^{th} and 90^{th} percentile and 2) a likelihood ratio test comparing a model that included only the variable to the model with the restricted splines. Variables were considered to be non linear if the quadratic spline curve appeared non linear and the likelihood ratio comparing the two models had a p value <0.05. For variables where there was disagreement between these two tests, a decision was made based on the quadratic spline curve and substantive knowledge. This preliminary analysis and substantive knowledge informed decisions about creation of category boundaries or whether to retain continuous variables in linear models.

Assessment of Potential for Collinearity:

The PR for the association between each covariate and trial participation was examined. A PR of ≤0.3 or ≥3 was considered a strong association. However no association reached these predetermined cut of levels.

Multivariable analysis:

In cross sectional studies with common outcomes use of an odds ratio is known to overestimate the prevalence ratio[6]. Therefore, in our data set where the proportion of those experiencing the outcome was 30% our effect estimate of choice was a prevalence ratio. However, when the study requires adjustment for multiple variables (continuous and categorical), the log binomial model which is

used to calculate the prevalence ratio frequently fails to converge. Under these circumstances using a binomial model with a poisson distribution and robust error variance produces estimates that are close approximations of the prevalence ratios[7-9]. The robust variance estimator is used to correct for overestimation of the error term resulting from use of Poisson regression with binomial data[10].Use of the binomial model with a poisson distribution and robust variance estimator does result in confidence interval estimates that are less precise than a log binomial model but still close to the true confidence interval [8].

Effect measure modification:

In data analysis, effect measure modification (EMM) of the PR is detected when the PR is greater for one of the strata, indicating a stronger relationship. To identify variables for which the association between gender/sexual orientation or race/ethnicity and trial participation varied between different levels of potential effect measure modifiers, we calculated stratum-specific risk ratios across each category for every variable of interest. To determine if there was effect measure modification by a specific variable, we compared stratum-specific risk ratios to each other. Variables were considered to be effect measure modifiers if the chi square test for homogeneity had a p value ≤ 0.1. In this analysis no variable was identified as an effect measure modifier.

Assessment of Confounding:

Confounding was assessed based on a change in estimate method, a directed acyclic graph and substantive knowledge. In initial multivariable models, we used a manual change in estimate backwards elimination procedure to identify the particular set of confounding variables to include in the final model[11]. We calculated the change in estimate resulting from removing the potential confounder from the model during the model building process using the following formula: 100*(adjusted – crude)/crude. A change in estimate of 10% or more was considered indicative of confounding. We used a directed acyclic graph to assess the direct and indirect causal pathways linking gender/sexual orientation and race/ethnicity with trial participation. Figure one shows the directed acyclic graph.

Model Building:

Our choice of covariables to be included in the final model was based on 1) the directed acyclic graph 2) a change in estimate method and 3) a priori knowledge. We conducted a complete case analysis using a binomial model with a poisson distribution and robust variance estimator.

Missingness:

As reported above a complete case analysis was first conducted excluding all observations with missing data. We then assessed missingness by the three mechanisms identified by Little and Rubin[12] i.e. missing completely at random (MCAR), missing at random (MAR), and not missing at random (NMAR). We

determined for this analysis missingness of covariables may be categorized as MAR as the probability of the missing value is likely independent of the value itself but dependent on the values of other variables in the data set.

Missing data is a common problem and may lead to biased results. Studies have suggested that multiple imputation techniques can give more accurate results than complete case analysis or single imputation techniques and optimal results can be achieved with 3-10 imputations[12-16]. Therefore we assessed the potential effect of missing data on our effect estimates by using a multiple imputation method with five imputed data sets. Similar to the complete case analysis a poisson regression model with robust error variance was run on the imputed data sets.

Intercooled Stata (version 9.0), Stata Corporation, (College Station, TX) was used for all analyses. The multiple imputation was conducted using Stata's ICE program[17]. The ICE (imputation with chained equations) program imputes missing values using an iterative regression switching procedure[18]. The imputed values are obtained by sampling from the distribution of the incomplete variable, given the observed values and the explanatory variables included in the imputation model. Values for any incomplete continuous variables are obtained using linear regression and for categorical variables using logistic regression.

Summary: Specific aim 1:

This aim utilized a poisson regression model with robust error variance estimator to examine the association between the two main exposures of gender/sexual orientation and race/ethnicity and the outcome of trial participation.

3.4. Specific Aim two

Using the UCHCC we determined if a trial effect exists in HIV treatment trials by comparing the outcome of virologic success among trial and non trial participants.

Study design

We used the UCHCC and conducted a retrospective cohort study of antiretroviral treatment naïve HIV positive adults (≥18years).

Study population

Please refer to study population, specific aim one.

Main Study Variables

Exposure:

The main exposure variable was trial participation and subjects were characterized as trial participants if HAART was initiated as part of a clinical trial. Clinical trials included AIDS Clinical Trials Group (ACTG) supported or industry sponsored trials and may or may not have been randomized, placebo controlled or blinded.

Outcome:

We defined our outcome of virologic success as having a plasma HIV RNA level ≤ 400 copies/mL at six months after HAART initiation. For those subjects for whom plasma HIV RNA result was not available at the six month time point an extended period spanning five to nine months from the date of HAART initiation was considered.

Covariables:

1. Gender/sexual orientation (heterosexual/homosexual/bisexual): This variable was categorized as follows 1) men who have sex with men (MSM) and bisexual men 2) heterosexual men and 3) women.
2. Race/ethnicity: This variable was initially categorized as white, black and other and subsequently dichotomized as black or non black.
3. Type of HAART: To accommodate the changes in HAART regimens over the study period we categorized type of HAART into five different

categories as follows 1) A boosted protease inhibitor (PI) or two PIs combined with either two or three nucleoside reverse transcriptase inhibitors (NRTIs) 2) A nucleoside reverse transcriptase inhibitors (NNRTI) combined with either two or three NRTIs 3) An unboosted PI combined with either two or three NRTIs 4) An NNRTI and a PI with or without NRTIs and 5) Three NRTIs.

4. Year HAART was initiated: The year HAART was initiated was dichotomized to more accurately represent the differences in antiretroviral treatment regimens as the early HAART period (1996-99) and the current HAART period (2000-06).

For all other covariables please refer to, specific aim one.

Analytic Techniques

Univariate analysis:

Basic descriptive analysis was conducted as in specific aim one. Differences in demographic and behavioral, clinical, access to care, treatment and laboratory characteristics were explored using the chi square test, t test and Wilcoxon rank sum test with 2-sided P values reported in all cases.

Bivariate analysis:

An unadjusted risk ratio (RR) and a 95% CI to assess the relationship between trial participation and the risk of virologic success at six months post HAART initiation was calculated as follows:

$$\hat{RR} = \frac{A_1/N_1}{A_0/N_0}$$

where A_1, A_0, N_1, and N_0 are defined as shown below.

Table 3.3: Schematic for bivariate data analysis- Risk Ratio

Clinical trials	VL ≤400	VL >400	Total
Yes	A_1	B_1	N_1
No	A_0	B_0	N_0
Total	$A.$	$B.$	$N.$

Multivariable analysis:

We estimated the influence of other variables on the unadjusted effect estimate using a generalized linear model with log link and binomial error distribution. However, due to non convergence of the binomial model a Poisson model without an offset term and with a robust variance estimator was used to obtain a valid estimate of the risk ratio.

Effect measure modification:

In data analysis, effect measure modification (EMM) of the RR is detected when the RR is greater for one of the strata, indicating a stronger relationship. To identify variables for which the association between trial participation and virologic success varied between different levels of potential effect measure modifiers, we calculated stratum-specific risk ratios across each category for every variable of interest. To determine if there was effect measure modification by a specific variable, we compared stratum-specific risk ratios to each other. Variables were considered to be effect measure modifiers if the chi square test for homogeneity had a p value ≤ 0.1. We accounted for any effect measure modifiers by including interaction terms with the main factor of interest in our models.

Assessment of Confounding:

Variables that were not identified as effect measure modifiers were assessed as potential confounding variables. For those variables that were effect measure modifiers, we examined potential confounding within each strata of the effect measure modifier(s). During the model building process we used a change in estimate method to identify potential confounders. A change in estimate of 10% or more was considered indicative of substantial confounding.

Model Building:

To estimate an unbiased RR of the association between trial participation and virologic success, we used a backwards elimination process. The full model consisted of the main factor of interest, interaction terms for variables identified as potential effect measure modifiers, and all other variables identified as potential confounders. In the first step of the backwards elimination process, we removed from the full model any interaction terms and compared the resulting models using a likelihood ratio test. The interaction term was retained in the model if the likelihood ratio test had a p value of ≤0.10. In the next step, we assessed each covariate for its potential to confound the main association. The covariate with the largest Wald p value was removed from the model and the estimate from the full model was compared to the reduced model. If the change in the estimate was less than 10% that covariate was not considered to be a confounder and was dropped from the model. This elimination process was repeated for each covariate until the cumulative change in the RR of the exposure was ≥10%.

Sensitivity Analysis:

HIV RNA result at the six month time point was unavailable for 33% of subjects. The missing data were assessed to be not missing at random as the probability of the HIV RNA result being missing is likely dependent on the true value. For example subjects having missing values may be more likely to be non-

adherent to HAART and to follow-up care and therefore not have virologic success.

Sensitivity analyses were done to explore the plausible impact of this missing data. We conducted an extreme case analysis to obtain the upper and lower bounds of the RR. For this we assumed that among the subjects with missing outcome, every trial participant achieved virologic success while non-trial participants were virologic failures; and vice versa that among the subjects with missing outcome, all trial participants were virologic failures while non-trial participants had virologic success. A second analysis assigned virologic success to all missing values for trial and non-trial participants and virologic failure to all missing values for trial and non-trial participants[19, 20]. In this second analysis we varied the proportion of subjects achieving virologic success. This additional information on the intermediate possibilities of the RR examined if the majority of effect estimates supported the results of the primary analysis.

Summary: Specific aim two

This aim utilized a poisson regression model with robust error variance and examined a trial effect in HIV clinical trials by comparing virologic success among ARV naïve trial and non trial participants.

3.5. References:

1. North Carolina HIV/STD Quarterly Surveillance Report: Vol. 2006, No. 2. Accessed September 2007
Available at http://www.epi.state.nc.us/epi/hiv/pdf/vol06no2.pdf.

2. Phillips AN, Grabar S, Tassie JM, Costagliola D, Lundgren JD, Egger M. Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. EuroSIDA, the French Hospital Database on HIV and the Swiss HIV Cohort Study Groups. *Aids.* Oct 22 1999;13(15):2075-2082.

3. Reif S, Whetten K, Ostermann J, Raper JL. Characteristics of HIV-infected adults in the Deep South and their utilization of mental health services: A rural vs. urban comparison. *AIDS Care.* 2006;18 Suppl 1:S10-17.

4. Whetten-Goldstein K, Nguyen TQ, Heald AE. Characteristics of individuals infected with the human immunodeficiency virus and provider interaction in the predominantly rural Southeast. *South Med J.* Feb 2001;94(2):212-222.

5. Medicaid in North Carolina Annual Report.;North Carolina Department of Health and Human Services. Division of Medical Assistance. Accessed at http://www.ncdhhs.gov/dma/annreport.htm 20May2008.

6. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *Bmj.* Mar 28 1998;316(7136):989-991.

7. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol.* Oct 20 2003;3:21.

8. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol.* May 15 2003;157(10):940-943.

9. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* Apr 1 2004;159(7):702-706.

10. Zocchetti C, Consonni D, Bertazzi PA. Estimation of prevalence rate ratios from cross-sectional data. *Int J Epidemiol.* Oct 1995;24(5):1064-1067.

11. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol.* Dec 1 1993;138(11):923-936.

12. Little RJA, Rubin, D.B. Statistical Analysis with Missing Data. *J. Wiley & Sons, New York. 1987.*

13. Choi YJ, Nam CM, Kwak MJ. Multiple imputation technique applied to appropriateness ratings in cataract surgery. *Yonsei Med J.* Oct 31 2004;45(5):829-837.

14. Horton NJ, Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. *Am Stat.* Feb 2007;61(1):79-90.

15. Patrician PA. Multiple imputation for missing data. *Res Nurs Health.* Feb 2002;25(1):76-84.

16. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res.* Jun 2007;16(3):199-218.

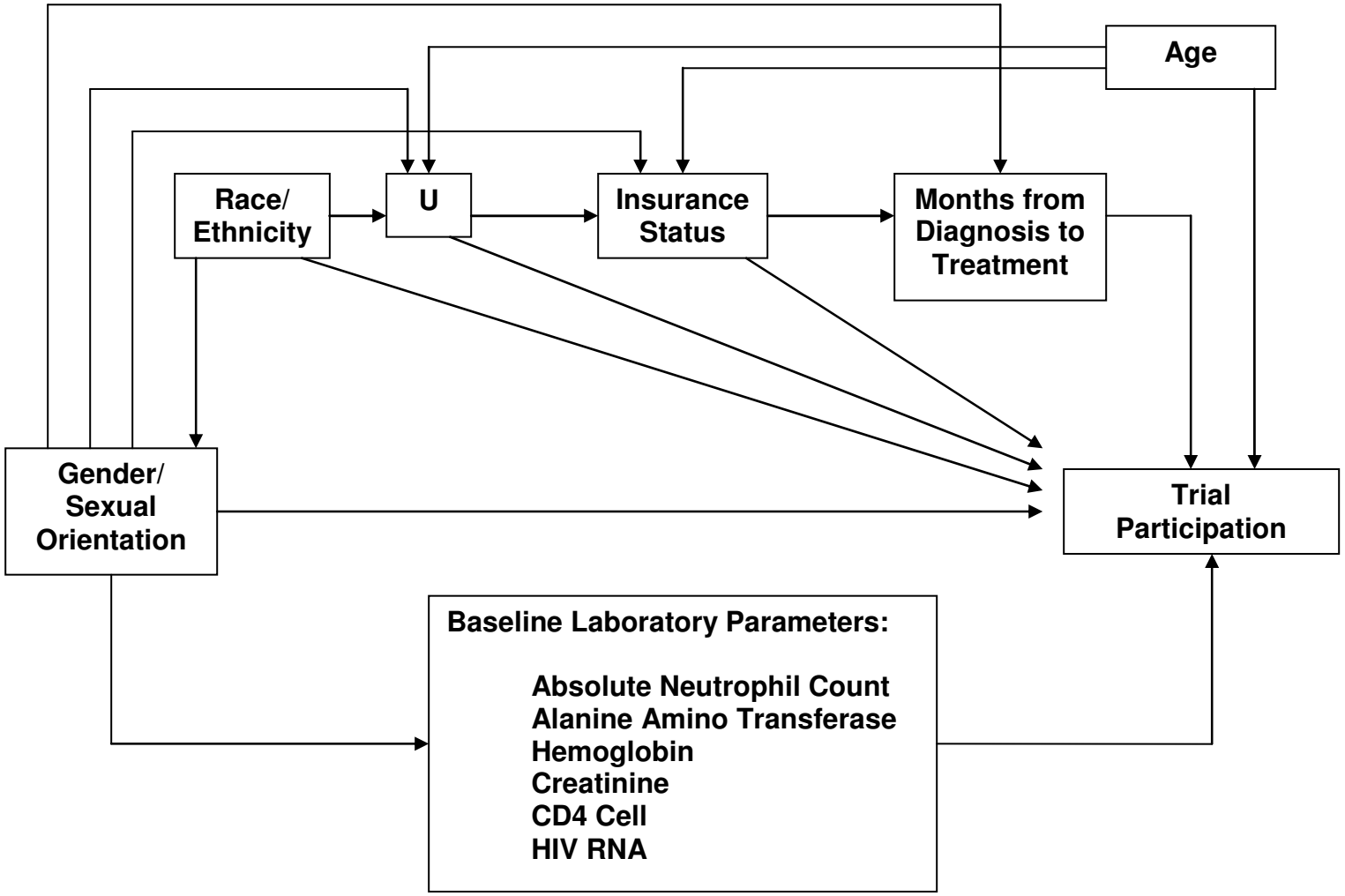
17. Royston P. Multiple Imputation using ICE. UCLA: Academic Technology Services, Statistical Consulting Group. *Available at: http://www.ats.ucla.edu/stat/stata/ado/analysis/.*

18. Yu LM, Burton A, Rivero-Arias O. Evaluation of software for multiple imputation of semi-continuous data. *Stat Methods Med Res.* Jun 2007;16(3):243-258.

19. The European Agency for the Evaluation of Medicinal Products. Evaluation of Medicines for Human Use. Committee for Proprietary Medicinal Products. Points to Consider on Missing Data. London, 15 November 2001.

20. Hollis S. A graphical sensitivity analysis for clinical trials with non-ignorable missing binary outcome. *Stat Med.* Dec 30 2002;21(24):3823-3834.

Figure one: Specific Aim one
Assessment of Confounding - Directed Acrylic Graph



U= Unmeasured variables eg. socioeconomic status

CHAPTER FOUR - INFLUENCE OF RACE, GENDER AND SEXUAL ORIENTATION ON PARTICIPATION IN HIV/AIDS CLINICAL TRIALS IN THE HAART ERA

4.1 Abstract:

Background: Women, racial/ethnic minorities and persons who acquire HIV infection through heterosexual intercourse represent an increasing proportion of HIV infected persons, yet they are reportedly underrepresented in clinical trials.

Objective: To determine if participation in HIV treatment trials differs by gender/sexual orientation or race/ethnicity.

Methods: We conducted a cross sectional study of antiretroviral treatment naïve HIV positive adults who initiated highly active antiretroviral therapy (HAART) between 1996-2006 and were within the University of North Carolina Center for AIDS Research, HIV/AIDS clinical cohort. Subjects were characterized as trial participants if HAART was initiated as part of a clinical trial. Prevalence ratios

(PR) were estimated using binomial models with a poisson distribution and robust variance estimator.

Results: Of 738 patients initiating HAART, 30% participated in 13 different clinical trials. In multivariable analysis heterosexual men and women were as likely to participate in these trials as men who have sex with men (MSM) (PR 0.79, 95% CI 0.57, 1.11 and PR 0.97, 95% CI 0.68, 1.39 respectively). Blacks were slightly less likely than non blacks to participate in clinical trials (adjusted PR 0.80, 95% CI 0.60, 1.06).

Conclusions: In this cohort, high rates of participation in HIV treatment trials were observed. Women were well represented in these trials and the representation by blacks was close to that of non blacks. In this population, we report some success in enrolling these underrepresented groups into clinical trials.

4.2 Introduction:

Well designed randomized clinical trials remain the principal source of reliable evidence about treatment efficacy. Persons living with HIV infection are a diverse and heterogeneous population and the ability to generalize the results of HIV treatment trials is directly related to how well participants in these trials represent the larger HIV-infected population. Treatment guidelines are based on data from clinical trials, but some have expressed concern that participants in these trials do not reflect the overall HIV infected community[1, 2].

In the decade since the introduction of highly active antiretroviral therapy (HAART), the demographics of the HIV/AIDS epidemic in the United States (US) have changed. In 2006 blacks represented 13% of the US population but accounted for 49% of reported AIDS cases and currently women account for more than one quarter of all new HIV diagnoses[3]. High risk heterosexual contact has emerged as a major route of transmission, representing 80% of all new HIV diagnoses in women[3]. Despite these notable increases in the rates of infection among blacks, women and heterosexuals, these groups are reportedly underrepresented in HIV treatment trials.

Most studies that evaluated participation in HIV/AIDS clinical trials were conducted early in the HIV epidemic prior to these demographic changes and prior to the widespread use of HAART. These studies may therefore not

accurately reflect the participation of women, blacks and heterosexuals in clinical trials [4-9]. Furthermore, these studies had conflicting and inconclusive results with some studies reporting women were not under represented in clinical trials, others disagreeing and still others unable to address this issue[5-7, 9]. Although, there appears to be greater consensus that non white persons are less likely to participate in clinical trials, this was not found to be the case in all studies[4-9]. The results of a more recent study, which reported that women were more likely than men and blacks were less likely than whites to participate in HIV treatment trials, are limited as participation in trials was self reported and the influence of other factors (clinical and laboratory parameters) associated with HAART initiation and trial participation was not addressed[10]. Given the changes in the face of the epidemic and the contradictory nature of earlier results, an updated assessment of trial participation is needed to inform clinicians, researchers and policy makers about the generalizability of treatment trial data and whether enrollment into such trials achieves the goals for the inclusion of women and minorities in clinical trials established by National Institutes of Health (NIH) and Food and Drug Administration (FDA) guidelines[11-13].

The University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC) comprises over 2000 HIV-positive trial and non-trial patients and is one of the largest ongoing clinical cohorts in the southeast US. Since its inception, the UCHCC has captured the changing demographics of the HIV epidemic; more than one-third of cohort participants are

women and almost two-thirds are African American. The UCHCC provided us with an opportunity to examine the influence of demographics on participation in HIV treatment trials.

4.3 Methods:

Study design:

We performed a cross sectional study of access to care and baseline demographic, behavioral and clinical characteristics for trial and non-trial participants using the UNC CFAR HIV/AIDS Clinical Cohort. This cohort comprising HIV positive persons (≥18years) who receive health care at the UNC Hospital Infectious Disease (ID) clinic has been described previously[14, 15]. Over 95% of the UNC ID clinic population has consented to participate in the UCHCC and non participants do not differ significantly from participants. This study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill.

Study population:

For this analysis the study population comprised antiretroviral treatment naïve HIV positive subjects who received care in the UNC ID clinic between the years 1996 – 2006, and initiated HAART, defined as any combination of three or more antiretroviral agents or at least one protease inhibitor and one non nucleoside reverse transcriptase inhibitor. Subjects were characterized as trial

participants if HAART was initiated as part of a treatment trial. Treatment trials included NIH AIDS Clinical Trial Group (ACTG) supported or industry sponsored trials and may or may not have been randomized, placebo controlled or blinded.

Variable Specification:

Gender (male/female) and sexual orientation (heterosexual, homosexual or bisexual) were primary exposure variables. Men who have sex with men (MSM) and bisexual men were placed in one category. However, because there were no homosexual females and MSM is a subset of all men we specified a joint gender and sexual orientation variable with three categories (females, heterosexual males and MSM) to clarify interpretation of coefficients in the multivariable regression. Race/ethnicity was categorized as black or non black.

Additional variables included Centers for Disease Control and Prevention (CDC) categorization of AIDS[16] (excludes subjects with a CD4 <200 cells/uL if they had no other AIDS defining illness), mental illness, insurance status (Medicaid/Medicare, none and private/other), distance traveled from home to the ID clinic, substance use, injection drug use (IDU) as a risk for HIV acquisition and time from HIV diagnosis to HAART initiation. IDU and substance use were self reported, while date of HIV diagnosis was based on either self report or testing. These variables were evaluated at baseline, which was defined as the date of HAART initiation, except for AIDS diagnosis, mental illness and substance

abuse, which were evaluated at any time before and up to 14 days after the date of HAART initiation.

Selected laboratory values that may influence initiation of HAART were analyzed including CD4 cell count, plasma HIV RNA level, hemoglobin, creatinine, alanine aminotransferase [ALT], and absolute neutrophil count [ANC]. However, as laboratory results may not be available on the same day HAART was initiated an extended baseline period was considered, with baseline values being defined as those closest to the day of HAART initiation within a window spanning 180 days before and up to 14 days after the date HAART was started. For ALT, ANC, creatinine and hemoglobin, gender appropriate normal ranges were accounted for and these variables were categorized as normal or abnormal.

Statistical Analyses:

Basic descriptive statistics (proportions, mean, median, range, standard deviation) were generated for all variables considered in the analysis. Visual summaries (histograms and box plots) were used to assess if continuous variables were normally distributed. Variables that deviated substantially from normality were transformed (e.g. HIV RNA levels were transformed to the log base 10 scale) to arrive at an approximately normal distribution. Linearity was assessed using a quadratic spline model and a likelihood ratio test comparing a model that included only the variable to the model with the restricted splines. This preliminary analysis and substantive knowledge informed decisions about

creation of category boundaries or whether to retain continuous variables in linear models.

Predictors of trial participation were contrasted by trial participation status using the Pearson χ^2 test for categorical variables, the Wilcoxon sum rank test for non-normally distributed continuous variables, or the Student's t test for normally distributed continuous variables.

Gender/sexual orientation and race/ethnicity were the two factors of interest in this analysis of clinical trial participation. All variables listed above under variable specification were considered as possible confounding factors and included in the full model.

Multivariable models were fit using a binomial model with a poisson distribution and robust variance estimator[17-20]. Separate models were fit for each of the primary factors of interest. Interaction was assessed between each primary exposure and each covariate relying on a likelihood ratio test P value < 0.1. To assess the impact of covariates on the estimates for our primary factors of interest, we constructed a multivariable model with all of the predictor variables.

Missingness:

A complete case analysis was first conducted excluding all observations with missing data. We then assessed missingness by the three mechanisms

identified by Little and Rubin[21] i.e. missing completely at random, missing at random (MAR), and not missing at random. We determined in this data set missingness may be categorized as MAR, as the probability of the missing value is likely independent of the value itself but dependent on the values of other variables in the data set. We assessed the potential effect of missing data on our effect estimates, by using a multiple imputation method with five imputed data sets[21-23]. Similar to the complete case analysis, a Poisson regression model with robust error variance was run on the imputed data sets.

Intercooled Stata (version 9.0), Stata Corporation, (College Station, TX) was used for all analyses. The multiple imputation was conducted using Stata's ICE program[24].

4.4 Results:

Sample Characteristics

Between1996-2006, 738 treatment naïve persons initiated HAART. Of these, 224 (30.4%) initiated HAART in 13 different clinical trials, including nine sponsored by the ACTG and four by pharmaceutical companies (Table 4.1). The mean age of study subjects was 38.5 years (sd 9.0), 31% were women, 62% were Black, 28% were White, 6.8% were Hispanic and almost 2% were Native American (Table 4.2). More women self-identified as black than did men (72%

vs. 57%). Greater than a third (37.4%) of subjects had no insurance; one quarter (25.6%) had public insurance (Medicaid and/or Medicare). At baseline, 26% of subjects had an AIDS diagnosis, the median CD4 cell count was 157 cells/uL (IQR 40-345) and the mean viral load was 4.7 $\log_{10}$ (sd 1.0). One-half of subjects initiated HAART within 5 months of receiving a diagnosis of HIV. The median distance traveled one way to receive care at the UNC ID clinic was 47 miles (IQR 27-71). The major risk factor for HIV acquisition was heterosexual intercourse (54.1%) with only 13% of subjects reporting IDU as a risk factor.

Gender/Sexual Orientation and Trial Participation

Trial participants differed significantly from non trial participants by gender/sexual orientation (p=0.02). Thirty-seven percent of all MSM, 30% of all heterosexual men and 24% of all women enrolled in a trial. The unadjusted prevalence ratios (PR) for trial participation of heterosexual men were 0.81 (95%CI 0.63, 1.04) and for women were 0.67 (95%CI 0.50, 0.88).

After adjustment for age, race, insurance status, distance traveled to receive care at UNC ID clinic, baseline CD4 cell counts, baseline plasma HIV RNA levels, months from HIV diagnosis to HAART initiation, and laboratory parameters (ALT, ANC, creatinine, hemoglobin), heterosexual men and women were almost as likely to enter HIV treatment trials as MSM (PR 0.79, 95% CI 0.57, 1.11 for heterosexual men and PR 0.97, 95%CI 0.68, 1.39 for women).

The multivariable model described above showed a substantial change in the prevalence ratio for women compared to MSM. To evaluate which variables were responsible for this change, we eliminated variables one at a time from the multivariable model. The two variables that most accounted for the change were insurance status and months from HIV diagnosis to HAART initiation.

The distribution of MSM, heterosexual men and women by receipt of HAART within 3 months of HIV diagnosis was similar (42%, 39%, 36% respectively) ($p>0.05$). However, fewer of these women entered treatment trials than men (16% vs. 84%). In multivariable analysis more subjects entered trials three months after diagnosis than in the first three months of diagnosis (PR 1.19, 95%CI 0.88, 1.59). When stratified by gender women were almost twice as likely to enter trials three months after diagnosis than in the first three months of diagnosis (PR 1.89, 95%CI 0.98,3.65) but this difference was not observed for men (PR1.02, 95%CI 0.74,1.42).

More women (56%) had public insurance than MSM (14%) and heterosexual men (30%). Persons with public insurance were less likely to enter treatment trials than those with private or no insurance (PR 0.42, 95% CI 0.29, 0.61).

Race/ethnicity and Trial Participation

Trial participants differed significantly from non trial participants by race/ethnicity (p=0.001).Although blacks comprised the greater proportion (62%) of study subjects only 26% of them enrolled in clinical trials. In bivariable analysis blacks were significantly less likely to participate in treatment trials (blacks vs. non blacks PR 0.69 95%CI 0.56, 0.86).

After adjustment for age, race, insurance status, distance traveled to receive care at UNC ID clinic, CD4 cell count, plasma HIV RNA levels, months from HIV diagnosis to HAART initiation, and laboratory parameters (ALT, ANC, creatinine, hemoglobin), blacks remained slightly less likely to participate in treatment trials than non blacks (PR 0.80, 95% CI 0.60, 1.06).

Blacks had a greater delay in HAART provision than non blacks. Two thirds of blacks (68%), as compared to less than a third of non blacks (32%), received HAART greater than three months after HIV diagnosis (p<0.001). More blacks had public insurance (34% vs. 14%) and fewer had private insurance than non blacks (30% vs. 44%) (p≤0.001). Among trial participants with private insurance 46% were black and 54% were non black , and among those who had public insurance 83% were black and only 17% were non black (p=0.002).

Table 4.3 provides the adjusted and unadjusted prevalence ratios.

Imputed data

The imputed data sets produced adjusted prevalence ratio estimates that were generally similar to the results obtained in the complete case analysis (Table 4.3). The point estimate for heterosexual men was closer to the null after imputation (PR 0.90; 95% CI 0.70, 1.16), while the point estimate for women was slightly further from the null, although the confidence interval included the null (PR 0.91; 95% CI 0.68, 1.22). The point estimate for blacks was virtually unchanged (PR 0.78, 95% CI 0.62, 097). Overall, the confidence interval estimates of the imputed prevalence ratios were narrower than those obtained in the complete case analysis.

4.5 Discussion

Gender and race differences between trial and non trial populations may limit the generalizability of trial findings. In HIV infection, these differences may have greater importance as increasing numbers of women and minorities are HIV infected. While limited, there is some data, supporting a differential response to specific antiretroviral's in women and minorities[25-28]. In this analysis, blacks were less likely to participate in HIV treatment trials and there was no influence of gender/sexual orientation on trial participation. Although in the clinic population, women were less likely than MSM to enter into trials as observed in the bivariable relationship, this association approached parity after accounting for

confounding variables. For blacks compared to non-blacks, the strength of the bivariable estimate was decreased after adjustment, but they remained slightly less likely to participate in HIV treatment trials.

Our finding, of no difference in participation rates between women and MSM, is supported by other studies in HIV infection where women were as likely and in some instances more likely to enroll in trials than men[5, 7, 10]. A five year review of women's participation in clinical trials by the US FDA found that overall women participate in clinical trials at almost the same rate as men[29]. Perhaps guidelines and policies adopted both in the US and other countries to correct years of gender imbalance in trial participation are finally coming to fruition[13, 30]. Likewise, compared with MSM participation rates for heterosexual men though slightly lower were also not significantly different. This contrasts with earlier observations that heterosexual men were underrepresented in clinical trials[8]. Our results suggest that, in our setting, both gender and sexual orientation do not significantly influence participation in HIV treatment trials. When such differences are observed, the influence on these results of other factors, such as geographic location, type of trial, and study site, needs to be evaluated.

In unadjusted analyses, women were less likely than MSM to participate in HIV treatment trials, but with adjustment the difference was markedly diminished. The two variables that were most responsible for this change in estimate were insurance status and months from HIV diagnosis to treatment. More women had

health insurance (public or private) than men and almost one half of all women had public insurance (Medicaid and/or Medicare). While not a program restricted to women, over two thirds of adults (≥18 years) on Medicaid are women[31, 32]. To qualify for Medicaid, women must meet defined category and income requirements. Categories include being pregnant, being the mother of a child under 18, or having a disability; additionally all categories have income limitations[31, 33]. Over one half of the women in our study were under 40 years of age and consequently likely to be pregnant, rearing a child or both. Although having HIV/AIDS is a Medicaid defined disability, one study reported that in North Carolina women comprised 47% of all HIV infected Medicaid beneficiaries[34]. Having health insurance provides women with access to treatment, care and other health benefits and may limit their need to participate in clinical trials.

The number of months from HIV diagnosis to treatment was the second variable associated with changing the adjusted effect estimate between women and trial participation. For all subjects, but especially for women trial participation was more likely to occur when HAART was delayed for greater than three months after diagnosis. Conceivably, a three month period may be needed to conduct the rigorous screening, consent and enrollment procedures required for trial participation. In our study, twice as many women trial participants received HAART three months after HIV diagnosis than in the first three months. In general, untreated HIV infected women have an approximately 0.2 log lower viral load than men[35]. This difference in baseline viral load was also observed in our

study cohort. Reportedly women may also delay entry into care by more than three months after receiving an HIV diagnosis[36]. Because women voluntarily or involuntarily delayed receipt of HAART, it may have provided opportunity for investigators to encourage enrollment, provide counseling on trial specific aspects, such as the need for contraception, and arrange for assistance with familial obligations, such as child care. Therefore, we suspect that the combination of two effects - 1) a delay in receipt of HAART appeared to increase participation and 2) women were more likely to delay receipt of HAART - were at least partly responsible for our results.

Although, in the crude analysis blacks were less likely than non blacks to participate in trials, the strength of this association diminished when accounting for other variables and the adjusted absolute difference (8%) was even smaller (data not shown). These results, though similar to other HIV related studies suggesting blacks were less likely than either Caucasians or other ethnicities to enter clinical trials, are also dissimilar in that though a difference was observed, it was not substantial and could partially be explained by adjustment for other variables[4-6, 9]. Possibly additional adjustment for unmeasured variables, such as socioeconomic status, might have further diminished this observed difference.

Research in other areas has shown that participation rates for blacks can be comparable or higher than other races and we feel that our results reflect a trend supporting decrease in disparities for black enrolment into trials [37, 38].

However, as we included only HIV treatment trials and in our study more subjects without insurance were black this might have influenced our results. The UNC ID clinic has a high proportion of black patients, but there are likely other reasons why the difference we observed was small including lack of clinician bias in referral and enrolment of patients into trials and strong patient provider trust. A major barrier to blacks participating in HIV treatment trials is not being asked to participate and in fact a systematic review of health research studies showed that when invited to participate blacks were as likely and sometimes more likely to participate in research[1, 38]. Provider endorsement of trials, provision of clinical trial information by providers and trust in providers is associated with trial participation[5, 39-41].

Since our data represent a single clinic population, these results may not be generalizable to other settings or parts of the country. However, as the UCHCC comprises about 10% of all HIV infected individuals in NC, it is probably representative of the HIV population in NC. Moreover, six southeastern states (North Carolina, South Carolina, Mississippi, Alabama, Georgia, Louisiana) report demographically similar epidemics supporting the generalizability of these results to the southeast US[42-44]. The comparability of enrolment between blacks and non blacks and between genders and those of different sexual orientations may partly be attributed to the demographic make up of the ID clinic and to the existing ACTG. Previous studies have shown that, compared to other ACTG sites, the UNC ACTG has high trial enrolment rates for racial/ethnic minorities,

and for women trial participation is associated with living in an area with a NIH or CDC supported research network[10, 45] . In addition, NC has historically had strict eligibility criteria for the state funded AIDS Drug Assistance Program (ADAP). Limited access to ADAP may leave participation in HIV treatment trials as the only option for access to antiretroviral therapy.

In summary, we found that in the clinical setting studied, blacks can and will participate in HIV treatment trials at similar rates to non blacks and women are as likely as men to participate in these trials. An exploration of barriers to clinical trial participation must look beyond demographics to other factors including awareness and information about clinical trials and trial characteristics.

4.6 References:

1. Garber M, Hanusa BH, Switzer GE, Mellors J, Arnold RM. HIV-infected African Americans are willing to participate in HIV treatment trials. *J Gen Intern Med.* Jan 2007;22(1):17-42.

2. el-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *Jama.* Feb 19 1992;267(7):954-957.

3. HIV/AIDS Statistics and Surveillance. Department of Health and Human Services. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/hiv/topics/surveillance/index.htm. Accessed June 25, 2008.

4. Diaz T, Chu SY, Sorvillo F, et al. Differences in participation in experimental drug trials among persons with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol.* Dec 15 1995;10(5):562-568.

5. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med.* May 2 2002;346(18):1373-1382.

6. Hankins C, Lapointe N, Walmsley S. Participation in clinical trials among women living with HIV in Canada. Canadian Women's HIV Study Group. *Cmaj.* Dec 1 1998;159(11):1359-1365.

7. Madge S, Mocroft A, Wilson D, et al. Participation in clinical studies among patients infected with HIV-1 in a single treatment centre over 12 years. *HIV Med.* Oct 2000;1(4):212-218.

8. Moore DA, Goodall RL, Ives NJ, Hooker M, Gazzard BG, Easterbrook PJ. How generalizable are the results of large randomized controlled trials of antiretroviral therapy? *HIV Med.* Jul 2000;1(3):149-154.

9. Stone VE, Mauch MY, Steger K, Janas SF, Craven DE. Race, gender, drug use, and participation in AIDS clinical trials. Lessons from a municipal hospital cohort. *J Gen Intern Med.* Mar 1997;12(3):150-157.

10. Sullivan PS, McNaghten AD, Begley E, Hutchinson A, Cargill VA. Enrollment of racial/ethnic minorities and women with HIV in clinical research studies of HIV medicines. *J Natl Med Assoc.* Mar 2007;99(3):242-250.

11. US Food and Drug Administration, Department of Health and Human Services. Guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs. *Federal Register1993July22;58:39406-16.*

12. NIH Revitalization Act, Subtitle B, Part1, Sec 131-133, June 10, 1993.

13. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. Federal Register, Part VIII (59 FR 14508-14513), March 28, 1994.

14. Napravnik S, Edwards D, Stewart P, Stalzer B, Matteson E, Eron JJ, Jr. HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. *J Acquir Immune Defic Syndr.* Sep 1 2005;40(1):34-40.

15. Napravnik S, Eron JJ, Jr., McKaig RG, Heine AD, Menezes P, Quinlivan E. Factors associated with fewer visits for HIV primary care at a tertiary care center in the Southeastern U.S. *AIDS Care.* 2006;18 Suppl 1:S45-50.

16. Center for Disease Control and prevention 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR 1992:41(RR-17): 1-11).*

17. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol.* Oct 20 2003;3:21.

18. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *Bmj.* Mar 28 1998;316(7136):989-991.

19. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol.* May 15 2003;157(10):940-943.

20. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* Apr 1 2004;159(7):702-706.

21. Little RJA, Rubin, D.B. Statistical Analysis with Missing Data. *J. Wiley & Sons, New York. 1987.*

22. Horton NJ, Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. *Am Stat.* Feb 2007;61(1):79-90.

23. Patrician PA. Multiple imputation for missing data. *Res Nurs Health.* Feb 2002;25(1):76-84.

24. Royston P. Multiple Imputation using ICE. UCLA: Academic Technology Services, Statistical Consulting Group. *Available at:* *http://www.ats.ucla.edu/stat/stata/ado/analysis/.*

25. Andrade A, Flexner C. Genes, ethnicity, and efavirenz response: clinical pharmacology update from the 11th CROI. *Hopkins HIV Rep.* May 2004;16(3):1-7.

26. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol.* 2004;44:499-523.

27. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *Aids.* Dec 3 2004;18(18):2391-2400.

28. Hitti J RS CS, Kamemoto L, Kashuba A, Caten E, Aweeka F. Sex and Weight as Covariates in the Pharmacokinetics of Efavirenz, Indinavir, and Nelfinavir. *11th Conf Retrovir Opportunistic Infect Febr 8 11 2004 San Franc CA Conf Retrovir Opportunistic Infect 11th 2004 San Franc Calif. 2004 Feb 8-11; 11: abstract no. 604.*

29. Evelyn B, Toigo T, Banks D, et al. Participation of racial/ethnic groups in clinical trials and race-related labeling: a review of new molecular entities approved 1995-1999. *J Natl Med Assoc.* Dec 2001;93(12 Suppl):18S-24S.

30. Medical Research Council of Canada. Final Report:Advisory committee on Women in Clinical Trials. *Ottawa:The Council; Nov 1996.*

31. Kaiser Commission on Medicaid and the Uninsured analysis of 2004 MSIS data, 2007. *Accessed at http://www.kff.org/womenshealth/upload/7213_03.pdf on 20May2008.*

32. Medicaid in North Carolina Annual Report.;North Carolina Department of Health and Human Services. Division of Medical Assistance. Accessed at http://www.ncdhhs.gov/dma/annreport.htm 20May2008.

33. Medicaid Eligibility Summary.;North Carolina Department of Health and Human Services. Division of Medical Assistance. Accessed at http://www.dhhs.state.nc.us/DMA/covgroups.htm 20May2008.

34. Kates J MJ, Patel P. Medicaid and HIV/AIDS: A Gender Analysis of the Experiences of HIV-Infected Medicaid Beneficiaries in Four States. *Abstract at the Academy of Health Services Research Health Policy Meeting.* 2002.

35. Gandhi M, Bacchetti P, Miotti P, Quinn TC, Veronese F, Greenblatt RM. Does patient sex affect human immunodeficiency virus levels? *Clin Infect Dis.* Aug 1 2002;35(3):313-322.

36. Ickovics JR, Forsyth B, Ethier KA, Harris P, Rodin J. Delayed entry into health care for women with HIV disease. *AIDS Patient Care STDS.* Feb 1996;10(1):21-24.

37. Corbie-Smith G, Viscoli CM, Kernan WN, Brass LM, Sarrel P, Horwitz RI. Influence of race, clinical, and other socio-demographic features on trial participation. *J Clin Epidemiol.* Apr 2003;56(4):304-309.

38. Wendler D, Kington R, Madans J, et al. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med.* Feb 2006;3(2):e19.

39. Baquet CR, Commiskey P, Daniel Mullins C, Mishra SI. Recruitment and participation in clinical trials: socio-demographic, rural/urban, and health care access predictors. *Cancer Detect Prev.* 2006;30(1):24-33.

40. Comis R. L. DDCDD, Kimmel L.G., Miller J.D. Barriers to Clinical Trial Participation "We have met the enemy and he is us". *Abstract No. 6567, Poster No. C11. Poster presented at American Society of Clinical Oncology Annual Meeting, June 2, 2007, Chicago, IL.*

41. Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R. Strategic physician communication and oncology clinical trials. *J Clin Oncol.* Oct 1999;17(10):3324-3332.

42. Pence BW, Reif S, Whetten K, et al. Minorities, the poor, and survivors of abuse: HIV-infected patients in the US deep South. *South Med J.* Nov 2007;100(11):1114-1122.

43. Reif S, Whetten K, Ostermann J, Raper JL. Characteristics of HIV-infected adults in the Deep South and their utilization of mental health services: A rural vs. urban comparison. *AIDS Care.* 2006;18 Suppl 1:S10-17.

44. Whetten-Goldstein K, Nguyen TQ, Heald AE. Characteristics of individuals infected with the human immunodeficiency virus and provider interaction in the predominantly rural Southeast. *South Med J.* Feb 2001;94(2):212-222.

45. Sengupta S, Strauss RP, DeVellis R, Quinn SC, DeVellis B, Ware WB. Factors affecting African-American participation in AIDS research. *J Acquir Immune Defic Syndr.* Jul 1 2000;24(3):275-284.

Table 4.1: Description of Clinical Trials in which subjects in this study were enrolled, 1996-2006

Study	N	Percent	Study Treatments
ACTG 384	34	15.18	ZDV/3TC + EFV ZDV/3TC + NFV ddI/ d4T + EFV ddI/ d4T + NFV ZDV/3TC + EFV + NFV ddI/ d4T + EFV + NFV
ACTG 388	10	4.46	ZDV/3TC + IDV ZDV/3TC + IDV + EFV ZDV/3TC + IDV + NFV
A5015	6	2.68	d4T + FTC + LPV/ RTV
A5073	6	2.68	FTC+TFV + LPV/RTV FTC + d4T + LPV/ RTV
A5095	51	22.77	ZDV/3TC/ABC ZDV/3TC + EFV ZDV/3TC/ABC + EFV
A5142	25	11.16	ZDV (or d4t XR) + 3TC + EFV ZDV (or d4t XR) + 3TC + LPV/RTV EFV + LPV/RTV
A5164	19	8.48	The study provided ARVs including LPV/r,d4T and TDF/FTC but clinicians were free to use any standard ART.
A5175	8	3.57	ZDV/3TC + EFV ddI/FTC + ATV FTC/TFV + EFV
A5202	36	16.07	FTC/TFV + EFV ABC/3TC + EFV FTC/TFV + EFV FTC/TFV + ATV/ RTV
Abbott M97	9	4.02	d4T + 3TC+ LPV/RTV
Gilead 903	12	5.36	d4T + 3TC + EFV TDF + 3TC + EFV
Gilead 934	1	0.45	FTC/TFV + EFV ZDV/3TC + EFV
KLEAN	7	3.13	ABC/3TC + FPV/RTV ABC/3TC + LPV/RTV
Total	224	100	

Table 4.2: Baseline sample characteristics comparing trial participants to non-trial participants, 1996-2006

	Total		Non Trial		Trial		p value*
	N(738)	%	N (514)	%	N (224)	%	
Demographic and Behavioral Characteristics							
Age (years)							
<40	429	58.1	300	58.4	129	57.6	0.84
>40	309	41.9	214	41.6	95	42.4	
Gender/sexual preference							
MSM[1]/Bisexual men	252	34.2	160	31.1	92	41.1	0.02
Heterosexual men	260	35.2	183	35.6	77	34.4	
Heterosexual women	226	30.6	171	33.3	55	24.6	
Race							
Black	455	61.7	337	65.6	118	52.7	0.001
Non Black	283	38.3	177	34.4	106	47.3	
IDU[2] as HIV risk							
No	642	87	435	84.6	207	92.4	0.004
Yes	96	13	79	15.4	17	7.6	
Substance Abuse							
No	627	85	436	84.8	191	85.3	0.87
Yes	111	15	78	15.2	33	14.7	
Access to Care Characteristics							
Insurance Status							
Public[3]	191	25.9	162	31.5	29	13.0	0.000
None	276	37.4	176	34.2	100	44.6	
Private/Other	258	35.0	170	33.1	88	39.3	
Distance to ID[4] clinic (miles)							
<50	182	24.7	123	23.9	59	36.3	0.1
>50	527	71.4	390	75.8	137	61.2	
Clinical Characteristics							
AIDS[5] Diagnoses							
No	546	74	387	75.4	159	71	0.22
Yes	192	26	127	24.6	65	29	
CD4 cells/uL							
≤200	321	43.5	200	38.9	121	54	0.02
>200	246	33,5	176	34.2	70	31.3	
Mean HIV RNA (log_{10}) (sd)	4.7	(1.0)	4.7	(0.95)	4.7	1.03	0.88
Mental Illness							
No	654	88.6	454	88.3	200	89.3	0.14
Yes	84	11.4	60	11.7	24	10.7	

Diagnosis to treatment (months)							
≤3	250	33.9	195	37.9	55	24.6	0.2
>3	393	53.3	289	56.2	104	46.4	
Other Laboratory Parameters							
ANC[6] (10^9/L)							
Normal	348	47.2	223	43.4	125	55.8	0.2
Abnormal	221	30	130	25.3	91	40.6	
Hemoglobin (g/dL)							
Normal	258	34.9	152	29.6	106	47.3	0.14
Abnormal	311	42.1	202	39.3	109	48.7	
Creatinine (mg/dL)							
Normal	685	93.1	469	91.3	216	96.4	0.008
Abnormal	51	6.9	44	8.6	7	3.1	
[7]ALT U/L							
Normal	451	61.1	276	53.7	175	78.1	0.88
Abnormal	100	13.6	61	11.9	39	17.4	

* p values comparing trial to non trial participants
[1]MSM=Men who have sex with Men; [2]IDU=Injection Drug Use; [3]Public insurance= Medicaid/Medicare; [4] ID= University of North Carolina Infectious Disease;
[5]AIDS=Acquired Immune Deficiency Syndrome; [6]ANC=Absolute Neutrophil Count
[7]ALT=Alanine aminotransferase

Table 4.3: Unadjusted, adjusted and imputed prevalence ratios and 95% confidence intervals for trial participation by gender/sexual orientation and race/ethnicity

	Prevalence Ratios (95%Confidence Interval)					
	Unadjusted		Adjusted		Adjusted Imputed	
Gender/Sexual Orientation*						
MSM/Bisexual men	1.0		1.0		1.0	
Heterosexual men	0.81	(0.63, 1.04)	0.79	(0.57, 1.11)	0.89	(0.69, 1.15)
Heterosexual women	0.67	(0.50, 0.88)	0.97	(0.68, 1.39)	0.87	(0.65, 1.18)
Race/Ethnicity**						
Non Black	1.0		1.0		1.0	
Black	0.69	(0.56,0.86)	0.80	(0.60,1.06)	0.78	(0.62,0.97)

MSM= Men who have sex with men
Non Black= White, Hispanic, Native American and other.

* adjusted for age, race, insurance status, distance traveled to receive care at UNC ID clinic, baseline CD4 cell counts, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, ALT, ANC, creatinine, hemoglobin

** adjusted for age, gender/sexual orientation, insurance status, distance traveled to receive care at UNC ID clinic, baseline CD4 cell counts, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, ALT, ANC, creatinine, hemoglobin

CHAPTER FIVE - DOES HAART EFFICACY TRANSLATE TO EFFECTIVENESS? EVIDENCE FOR A TRIAL EFFECT.

5.1 Abstract:

Background: There is a widespread belief, that participants in clinical trials experience improved outcomes due to a trial effect. Yet, in HV infection this claim appears to have been unexamined and therefore is unsubstantiated.

Objective: To determine whether a trial effect exists in HIV treatment trials by comparing virologic success among antiretroviral (ARV) naïve trial and non-trial participants who initiated highly active antiretroviral therapy (HAART).

Methods: This analysis included ARV naïve subjects who initiated HAART between 1996-2006. Subjects were characterized as trial participants if HAART was initiated in a clinical trial and virologic success was defined as a plasma HIV RNA ≤400 copies/ml at six months post HAART initiation. Virologic success was assessed within strata of early (1996-1999) and current (2000-06) HAART periods. Risk ratios (RR) were estimated using binomial models with a poisson distribution and robust variance estimator.

Results: The virologic success of trial participants contrasted with non trial participants differed by the period in which HAART was initiated (p=0.001). Trial participants initiating HAART in the early period were significantly more likely to achieve virologic success than non trial participants. (adjusted RR 1.33; 95% CI 1.15, 1.54), but this difference was not observed in the current period (adjusted RR 0.98; 95% CI 0.87, 1.11).

Conclusions: We found no strong evidence supporting a trial effect in HIV treatment trials in the current HAART period suggesting the results of these trials are relevant to comparable HIV infected patients.

5.2 Introduction:

Patients who participate in clinical trials are thought to have better outcomes than those who do not, due to a trial effect. Yet, there is limited evidence that such a trial effect exists, and to date there appears to be no study in HIV infection examining such an effect.

A trial effect may arise due to a treatment effect (newer, better or experimental treatments available to trial participants but unavailable outside the trial), protocol effect (differences in the way treatment regimens are delivered), care effect (differences in care), Hawthorne effect (behavior change secondary to being under observation) and placebo effect ("psychologically mediated" benefits that arise due to being in a trial)[1-4].

Several studies in oncology, cardiology, psychiatry, and surgery have examined the hypothesis that trial participation improves outcomes and five reviews have summarized the results of these studies with varied conclusions[1, 3, 5-7]. While the largest review found no strong evidence of either a harmful or beneficial trial effect, previous reviews have concluded that patients in trials survive longer and that there was weak evidence that well conducted trials tend to benefit the participants[1, 6, 7]. More recently, Peppercorn et. al. reported there was little evidence in support of trial participation leading to improved outcomes[3]. These reviews included both pediatric and adult studies, but the influence on the results of the diversity in these

populations was not addressed. In most reviews the predominant studies were cancer related, where unlike current HIV infection, survival is an important outcome. Some reviews compared patients within trials to those not in trials regardless of differences between interventions or subjects, therefore it is unclear whether these results truly reflect a trial effect[1, 3, 5, 6]. Additionally, these reviews are subject to all the constraints of systematic reviews such as publication bias. Notably, none of the five reviews included any HIV clinical trial.

Our primary goal is to determine whether a trial effect exists in HIV treatment trials by comparing virologic success among antiretroviral (ARV) naïve trial and non-trial participants who are initiated on highly active antiretroviral therapy (HAART). A trial effect in HIV clinical trials could have important implications. The benefit of HAART is unquestionable, but if a trial effect results in a difference in the magnitude of benefit for trial participants there are implications for clinical care. At the very least, clinical care may need to be modified to incorporate aspects of trial effect such as protocol effect or care effect to achieve similar results. A trial effect might argue for the reduced applicability of clinical trials data to non-trial participants and clinicians would need to exert caution when extrapolating this data to the general HIV infected population. Finally, the basis for the care and treatment guidelines of HIV infected persons is clinical trials data and a trial effect might raise the question of different sets of guidelines for trial and non-trial participants.

Differences in characteristics between trial and non-trial participants may lead to differences in outcomes between these groups and this might erroneously be identified as a trial effect. The University of North Carolina (UNC) Center for AIDS Research (CFAR) HIV/AIDS clinical cohort (UCHCC) comprises over 2000 HIV-positive trial and non-trial patients. This cohort provided us with the opportunity to address differences between these groups and to investigate the evidence for a trial effect in HIV clinical trials.

5.3 Methods:

Study design:

We conducted a retrospective cohort study using the UCHCC. This cohort comprising adult (≥18years) HIV positive persons who receive health care at the UNC Hospital Infectious Diseases (ID) clinic has been described previously[8, 9]. Over 95% of the UNC ID clinic population has consented to participate in the UCHCC and non participants do not differ significantly from participants. This study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill.

Study population:

Antiretroviral naïve HIV positive adults who initiated HAART between 1996-2006 were included in this analysis. HAART was defined as any combination of three or more antiretroviral agents, or at least one protease inhibitor (PI) and one non nucleoside reverse transcriptase inhibitor (NNRTI). Subjects were characterized as trial participants if HAART was initiated as part of a clinical trial. Clinical trials included NIH AIDS Clinical Trial Group (ACTG) supported or industry sponsored trials.

Variable Specification:

We defined our outcome of virologic success as having a plasma HIV RNA level ≤ 400 copies/mL at six months from the date of HAART initiation, using a window of five to nine months and selecting the plasma HIV RNA value nearest six months if more than one value occurred in this window. We considered trial participation as the factor of interest.

Sexual orientation (heterosexual/homosexual/bisexual) and gender were considered jointly and resulted in a variable with three categories -1) men who have sex with men (MSM) and bisexual men 2) heterosexual men and 3) women. Race was categorized as black or non black. Additional variables included insurance status (Medicaid/Medicare, none and private/other), distance traveled from home to

the ID clinic in miles and the duration in month's from the date of HIV diagnosis to HAART initiation.

Selected clinical laboratory values that may influence trial participation and initiation of HAART including CD4 cell count, plasma HIV RNA level, hemoglobin, creatinine, alanine aminotransferase [ALT], and absolute neutrophil count [ANC] were analyzed at baseline which was defined as the day HAART was initiated. For laboratory results not available at baseline an extended window spanning 180 days before and up to 14 days after the date HAART was initiated was considered. ALT, ANC, creatinine and hemoglobin were categorized as normal or abnormal and gender appropriate normal ranges were accounted for.

Treatment characteristics included type of HAART and the date HAART was initiated. HAART was categorized as 1) a ritonavir-boosted PI or two PIs combined with either two or three nucleoside reverse transcriptase inhibitors (NRTIs) 2) a NNRTI combined with either two or three NRTIs 3) an unboosted PI combined with either two or three NRTIs 4) a NNRTI and a PI with or without NRTIs and 5) three NRTIs. The year HAART was initiated was dichotomized to more accurately represent the differences in initial treatment regimens as the early HAART period (1996-99) and the current HAART period (2000-06).

Statistical Analysis:

Differences in demographic, clinical, treatment and laboratory characteristics were explored using the chi square test, t test and Wilcoxon rank sum test with 2-sided P values reported in all cases.

We estimated an unadjusted risk ratio (RR) and a 95% Confidence Interval (CI), to assess the relationship between trial participation and the risk of virologic success at six months after HAART initiation. The influence of other variables on the unadjusted effect estimate was assessed using a Poisson model with a robust variance estimator[10-12]. Regression analysis with interaction terms between the relevant covariates was used to assess for effect measure modification. Variables were considered to be effect measure modifiers if the coefficient estimate for the interaction term differed significantly from zero ($p \leq 0.1$). This analysis indicated a significant interaction between trial participation and the period in which HAART was initiated.

A backward elimination procedure was used to arrive at the final model. Confounding was evaluated by both substantive (a priori) and change in estimate criteria. A covariate was retained as a confounding variable if it changed the effect estimate by at least 10 percent. The variable type of HAART did not change the effect estimate by ≥10% but was included in one of the two final models based on substantive knowledge.

For our primary analysis we conducted a complete case analysis using a Poisson model with a robust variance estimator.

Sensitivity Analysis:

HIV RNA result at the six month time point was unavailable for 33% of subjects. The missing data were assessed to be not missing at random as the probability of the HIV RNA result being missing is likely dependent on the true value of this result[13]. For example, subjects having missing values may be more likely to be non-adherent to HAART and therefore not have virologic success.

Sensitivity analyses were done to explore the impact of the missing data. We conducted an extreme case analysis to obtain the upper and lower bounds of the RR[14-16]. For this we assumed that among the subjects with missing outcome, every trial participant achieved virologic success while non-trial participants were virologic failures and vice versa. A second analysis assigned virologic success to all missing values for trial and non-trial participants and virologic failure to all missing values for trial and non-trial participants[14-16]. In this second analysis we varied the proportion of subjects achieving virologic success. This additional information on the intermediate possibilities of the RR examined if the majority of effect estimates supported the results of the primary analysis[15, 16].

Intercooled Stata (version 9.0), Stata Corporation, (College Station, TX) was used for all analyses.

5.4 Results:

Sample Characteristics:

Of the 738 ARV naïve persons initiating HAART, 67% had an HIV RNA result available at the six month time point. The mean age of study subjects was 38.5 years (standard deviation 9.9), 37.3% were women, 60.1% were Black, 27.4% were White, and 8.3% were Hispanic (Table 5.1). When comparing subjects who achieved virologic success to those who did not there were no differences by age, gender/sexual orientation (p=0.9), race (p=0.1), insurance status (p=0.7) CD4 cell count (p=0.6) and baseline HIV RNA (RR 0.96 per $\log_{10}$ increase, 95% CI 0.92, 1.00; p=0.06)

Description of trials

Subjects participated in 13 different clinical trials, nine sponsored by the ACTG and four by pharmaceutical companies (Table 5.2) [17-30]. Both the specific aims and the study designs for these trials varied widely. Ten trials had a randomized design and of these, six were open label, two were double blind, and two were partially blinded[18, 19, 21-29]. The remainder three trials were non randomized

and open label[17, 21, 30]. Most trials (n=11) were Phase III or IV. Two ACTG and one industry sponsored trial enrolled subjects in the early, and seven ACTG and three industry sponsored trials enrolled subjects in the current HAART periods respectively.

HAART regimens

Predictably HAART regimens differed substantially between the early and current HAART periods ($p<0.001$). Unboosted PI regimens were initiated in over one-half (53%) of subjects in the early period, but in only 15% of subjects in the current period. By contrast, in the current HAART period more persons were initiated on an NNRTI based regimen (45%) followed by a boosted PI based regimen (27%). The majority of subjects initiating an NNRTI regimen received efavirenz (85%) while the majority of those initiating a boosted PI regimen received lopinavir/ritonavir (70.8%). Of the 134 subjects who received unboosted PI regimens, 64% were initiated on nelfinavir. The most commonly used nucleoside/nucleotide backbone was lamivudine/zidovudine (49.7%), followed by lamivudine/stavudine (14.7%), tenofovir/emtriciatbine or lamivudine (13.8%), and lamivudine/abacavir (7%).

Virologic success:

The proportion of subjects achieving virologic success in this cohort was high (78%, 95%CI 74-82%). Both trial and non-trial participants had high rates of virologic success (86%, 95%CI 79-91% for trial; 74% 95%CI 69-79% for non-trial participants). Overall, in unadjusted analysis, trial participants were 16% more likely to achieve virolgoic success when compared to non-trial participants (RR 1.16, 95%CI 1.06, 1.27).

Sample characteristics contrasted by period (early vs. current) of HAART initiation:

To examine the influence of baseline differences between subjects on our results, we compared subjects across the period (early vs. current) of HAART initiation. Participation in clinical trials was higher in the current than in the early HAART period (39.4% vs. 23%, $p<0.001$). Baseline plasma HIV RNA levels (median 4.7$\log_{10}$ vs. 4.8 $\log_{10}$, $p=0.9$) did not differ between these periods, but more subjects had a CD4 cell count >200 cells/uL in the current period (52% vs. 38%, $p=0.006$). The insurance status of study subjects differed considerably between these periods with more subjects having no insurance (40% vs. 24%) and fewer having public insurance (23% vs. 32%) in the current than in the early period ($p=0.003$). No interval differences in gender/sexual orientation ($p=0.9$), mean age ($p=0.6$) and distance traveled to the ID clinic ($p=0.2$) were observed.

Primary (Complete Case) Analysis:

The virologic success contrasting trial and non-trial participants differed by the period in which HAART was initiated (p=0.001) (Table 5.3). In bivariable analysis trial participants initiating HAART in the early period were significantly more likely to achieve virologic success than non-trial participants (RR 1.42, 95%CI 1.24, 1.62) but a similar difference was not observed in the current period (RR 1.07, 95%CI 0.95, 1.19) . After adjustment trial participants in the early period remained more likely to achieve virologic success than non-trial participants (RR 1.33; 95% CI 1.15, 1.54). By contrast, in the current period, there was no difference in virologic success between trial and non-trial participants (RR 0.98; 95% CI 0.87, 1.11).

Missing Data:

The outcome of virologic success measured by an HIV RNA result within the specified 5-9 month window was unavailable for 242 (33%) subjects. Of these, over one-half (56.6%) were in the current HAART period. Subjects with missing HIV RNA result were similar to those not missing this result in terms of age (mean age 37 vs. 39 years), race (65% vs. 60% black) and gender (29% vs. 31% female). Likewise, we found no differences in clinical characteristics (baseline HIV RNA and CD4 cell count) and laboratory parameters (ALT, ANC, creatinine, hemoglobin) (all p values >0.05). However, more subjects missing HIV RNA result had no insurance (45% vs. 34.6%) and fewer had private insurance (27.6 vs.39.5) (p=0.004). Among subjects

with missing outcome more were non-trial participants (77% vs. 23%, p <0.001). When stratified by HAART period, we found no difference in the proportion of trial versus non-trial participants missing the outcome for the early period (p=0.1), but a difference was observed for the current period with more non-trial participants missing the outcome (p=0.03).

Sensitivity analysis:

Sensitivity analyses were conducted to assess the impact of the missing data on our effect estimate (Tables 5.4 and 5.5). For those subjects missing HIV RNA result, we assumed virologic success for trial participants and virologic failure for non-trial participants and obtained an upper bound for the RR of 1.89 for the early HAART and 1.40 for the current HAART periods. Conversely, when assuming that all trial participants had virologic failure and non-trial participants had virologic success a lower bound of the RR for the early and current HAART period of 1.17 and 0.83 respectively was obtained. In a second analysis, where all subjects missing data were considered to be virologic failures a RR of 1.75 for the early and 1.19 for the current HAART periods was obtained. In the early period, all the sensitivity analyses that were performed supported greater virologic success for trial participants with the lowest rate of virologic success being 17%. In the current period our sensitivity analyses showed that at a 70% or lower rate of virologic failure there was no difference between trial and non trial participants.

5.5 Discussion:

To our knowledge, this is the first study to examine a trial effect in HIV clinical trials by comparing virologic success among ARV naïve trial and non-trial participants initiating HAART. The results of our primary analysis showed that in the early HAART period (1996-99), there was a beneficial effect to trial participation. Both in bivariable and multivariable analysis, trial participants were significantly more likely to achieve virologic success than non-trial participants. However, in the current HAART period (2000-06) we found no difference in virologic success comparing trial to non-trial participants.

The demographics and HIV disease status of subjects in the early and current HAART periods was comparable. Therefore, we believe, that our results reflect the noteworthy improvements in ARV therapy between these periods. Other cohorts examining the efficacy of triple combination therapy have reported chronological improvements in viral suppression[31, 32]. Like other studies, we observed changes in the initial HAART regimen with a significant increase in the use of a boosted PI or NNRTI and a decline in the use of an unboosted PI [31]. The superiority of NNRTI and boosted PI versus unboosted PI regimens in ARV naïve persons has been clearly demonstrated[19, 33, 34] . Other improvements to ARV therapy include increased tolerability and decreased pill burden and frequency. Moreover, calendar time may also be associated with other unmeasured factors such as provider experience, medication adherence and increased patient awareness about the benefits of and

improvements to HAART. The period in which HAART was initiated likely acted as a surrogate for these temporal factors.

A beneficial effect to trial participation was observed in the early HAART period, suggesting a trial effect. Results from cancer trials have suggested a trial effect in trials conducted before 1986, a time of rapid change for cancer care and treatments[3]. This might also be the case in our study where during the early period trial participants might have experienced a treatment effect. In this period there were differences in the type of HAART with more trial participants initiated on an NNRTI /PI combination and more non-trial participants initiated on an unboosted PI regimen (data not shown*)*. However, even after controlling for potential differences in the type of HAART, the beneficial effect of trial participation persisted. Although, suggestive of a trial effect, these results may also be attributed to unmeasured characteristics such as medication adherence where trial participants in this period may have had higher virologic success due to better medication adherence.

We found no strong evidence supporting a trial effect in the current HAART period. Earlier studies have reported higher rates of virologic suppression for clinical trials, and this has been of concern as viral suppression is associated with better outcomes and decreased development of drug resistant virus [35]. The efficacy of ARV therapy is likely a function of patient, drug and virus related factors. Patients want treatments that are convenient and tolerable, clinicians want treatments that can suppress viral replication. The results of our study suggest that in the current period

HAART achieves these goals of convenience, tolerability and viral suppression. The assumption thus far has been, that the improved outcomes experienced by trial participants relative to non-trial participants are due to 1) patient selection biases (healthier patients in clinical trials) 2) the trial effect and 3) to intrinsic differences between trial and non-trial participants which are beyond socioeconomic, health or other measurable differences[1-3, 5, 7, 36]. However, our results suggest that, regardless of measured or unmeasured differences between trial and non-trial participants, HAART is equally effective both in a clinical practice and in a clinical trial setting. Our definition of virologic success (plasma HIV RNA value ≤400 copies/ml at six months) may have limited our ability to detect a trial effect in the current period. Possibly a longer outcome period, might have favored trial participants and supported a trial effect. In the current period, all but one of the trials included in our study was a Phase III or later trial therefore we feel that these results are most applicable to Phase III or later trials.

Lack of a trial effect has important public health implications. First, it demonstrates that irrespective of the setting, HAART achieves viral suppression which is known to result in immune reconstitution, decrease in opportunistic infections and improved quality of life making HIV infection a chronic long-term illness. However HIV infection differs from other chronic illnesses in co-morbidities, treatments, and psychosocial issues. Consequently we need to advocate for and implement a HIV specific chronic care model. Second, in our study the efficacy of HAART was no different from the effectiveness. This suggests that the results of

clinical trials are generalizable to the larger HIV infected population. Third, clinicians and public health officials can have confidence that treatment guidelines that are formulated based on clinical trials data, are relevant to routine clinical care and that data from these trials can be extrapolated to clinical care.

The large proportion (33%) of this cohort who were missing the outcome of virologic success at the six month time point is concerning. Reassuringly, subjects with missing data were similar to those for whom complete data was available. Sensitivity analyses were conducted, to determine the influence of the missing data on effect estimates obtained in our primary analysis. In an intention to treat analysis where all missing data was assigned virologic failure trial participants in the early and current periods were more likely to achieve success. We varied the proportion of virologic failures and found that, irrespective of the proportion of failures, in the early period trial participants remained more likely to achieve virologic success. By contrast, in the current period at a 100% rate of virologic failure there was a modest (20%) benefit to trial participation. This benefit to trial participation was not observed at a 70% rate or lower rate of virologic failure. These analyses substantiate the results of the primary analysis and suggest that the exclusion of subjects with missing data did not bias our results.

We examined potential sources of bias that could either mask or create a trial effect[37, 38]. We defined virologic success based on a single measurement, to minimize bias due to possible differences in measurement frequency between trial

and non-trial participants. In our study, care setting bias and clinician selection bias appear less likely since all subjects were followed at the UNC Infectious Disease Clinic and received their health care from a single group of physicians who were both principal investigators and health care providers[1, 3]. We addressed potential confounding arising from differences in baseline characteristics between the groups by fitting a fully adjusted model with all the variables and found similar results for the fully adjusted and the more parsimonious final model. A limitation to these comparisons, is we are unable to control for unmeasured confounders such as the above mentioned medication adherence or socio-economic status. However, the efficacy of HAART in the current period suggests less emphasis may be placed on unmeasured confounders.

Although, we found no trial effect, there are advantages to participation in clinical trials. These include access to 1) free treatments 2) follow up by a dedicated team of study personnel 3) close monitoring for potential side effects or adverse events 4) free health assessments and 5) monetary compensation. In keeping with other studies, we did not observe worse outcomes for trial participants in either period[39-43]. Therefore, we feel a reasonable corollary, is that trial participation does not increase the risk of a bad outcome. Though, there may be a difference in the magnitude of the observed benefit conferred by trial participation, most studies appear not to refute that a positive benefit exists [1, 36, 44]. A frequently unrecognized, but important benefit provided by trial participation, is patients are able to use the study team as a support group and a coping strategy. Lastly, there is an inherent

altruism involved in trial participation which affords patients' a sense of pride and self worth which is immeasurable[45-48].

In sum, we found no strong evidence supporting a trial effect in HIV clinical trials in the current HAART period. Therefore, the message is clear; regardless of setting or patient characteristics HAART is effective. Rather than detracting from the utility of clinical trials, our results support the position that well conducted randomized HIV clinical trials remain one of the best ways to demonstrate the efficacy of an intervention or treatment, and that the results of such trials are generalizable.

5.6 References:

1. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol.* Mar 2001;54(3):217-224.

2. Lantos JD. The "inclusion benefit" in clinical trials. *J Pediatr.* Feb 1999;134(2):130-131.

3. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet.* Jan 24 2004;363(9405):263-270.

4. Silverman WA. Disclosing the "inclusion benefit". *J Perinatol.* Jun 2002;22(4):261-262.

5. ECRI Evidence Report: Patients' reasons for participating in clinical trials and effect of trial participation on patient outcomes. Available at https://www.ecri.org/Documents/Clinical_Trials_Patient_Guide_Evidence_Report.pdf Accessed June 27,2008. 2002.

6. Stiller CA. Centralised treatment, entry to trials and survival. *Br J Cancer.* Aug 1994;70(2):352-362.

7. Vist GE, Hagen KB, Devereaux PJ, Bryant D, Kristoffersen DT, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. *Bmj.* May 21 2005;330(7501):1175.

8. Napravnik S, Edwards D, Stewart P, Stalzer B, Matteson E, Eron JJ, Jr. HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. *J Acquir Immune Defic Syndr.* Sep 1 2005;40(1):34-40.

9. Napravnik S, Eron JJ, Jr., McKaig RG, Heine AD, Menezes P, Quinlivan E. Factors associated with fewer visits for HIV primary care at a tertiary care center in the Southeastern U.S. *AIDS Care.* 2006;18 Suppl 1:S45-50.

10. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol.* Oct 20 2003;3:21.

11. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol.* May 15 2003;157(10):940-943.

12. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* Apr 1 2004;159(7):702-706.

13. Little RJA, Rubin, D.B. Statistical Analysis with Missing Data. *J. Wiley & Sons, New York. 1987.*

14. The European Agency for the Evaluation of Medicinal Products. Evaluation of Medicines for Human Use. Committee for Proprietary Medicinal Products. Points to Consider on Missing Data. London, 15 November 2001.

15. Delucchi KL. Methods for the analysis of binary outcome results in the presence of missing data. *J Consult Clin Psychol.* Jun 1994;62(3):569-575.

16. Hollis S. A graphical sensitivity analysis for clinical trials with non-ignorable missing binary outcome. *Stat Med.* Dec 30 2002;21(24):3823-3834.

17. Kalayjian RC, Landay A, Pollard RB, et al. Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. *J Infect Dis.* Jun 15 2003;187(12):1924-1933.

18. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med.* May 15 2008;358(20):2095-2106.

19. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* Dec 11 2003;349(24):2293-2303.

20. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med.* Dec 11 2003;349(24):2304-2315.

21. Zolopa A AJ, Komarow L, Sanchez A, Suckow C, Sanne I, et al. Immediate vs Deferred ART in the Setting of Acute AIDS-related Opportunistic Infection: Final Results of a Randomized Strategy Trial, ACTG A5164.[Abstract 142]. 15th Conference on Retroviruses and Opportunistic Infections. Boston 2008.

22. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* Aug 5 2006;368(9534):476-482.

23. Fischl MA, Ribaudo HJ, Collier AC, et al. A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced human immunodeficiency virus disease. *J Infect Dis.* Sep 1 2003;188(5):625-634.

24. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med.* Jan 19 2006;354(3):251-260.

25. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *Jama.* Jul 14 2004;292(2):191-201.

26. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* Apr 29 2004;350(18):1850-1861.

27. Once-Daily PI/NNRTI Therapy Combinations for Treatment Naive, HIV Infected Patients in Resource-Limited Conditions Available at http://clinicaltrials.gov/ct2/show/NCT00084136?term=ACTG+5175&rank=2.

28. Efavirenz or Atazanavir/Ritonavir Given With Emtricitabine/Tenofovir Disoproxil Fumarate or Abacavir/Lamivudine in HIV Infected Treatment-Naive Adults Available at http://clinicaltrials.gov/ct2/show/NCT00118898?term=actg+5202&rank=2.

29. Mildvan D TC, Gross R, Andrade A, Lalama C, Eshleman S. et al. Randomized Comparison in Treatment-naïve Patients of Once-daily vs Twice-daily Lopinavir/ritonavir-based ART and Comparison of Once-daily Self-administered vs Directly Observed Therapy. [Abstract 138] 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, 2007.

30. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results. *Aids.* Jan 5 2001;15(1):F1-9.

31. Lampe FC, Gatell JM, Staszewski S, et al. Changes over time in risk of initial virological failure of combination antiretroviral therapy: a multicohort analysis, 1996 to 2002. *Arch Intern Med.* Mar 13 2006;166(5):521-528.

32. Moore RD, Keruly JC, Gebo KA, Lucas GM. An improvement in virologic response to highly active antiretroviral therapy in clinical practice from 1996 through 2002. *J Acquir Immune Defic Syndr.* Jun 1 2005;39(2):195-198.

33. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* Dec 16 1999;341(25):1865-1873.

34. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med.* Jun 27 2002;346(26):2039-2046.

35. Madge S, Mocroft A, Wilson D, et al. Participation in clinical studies among patients infected with HIV-1 in a single treatment centre over 12 years. *HIV Med.* Oct 2000;1(4):212-218.

36. Flather M, Delahunty N, Collinson J. Generalizing results of randomized trials to clinical practice: reliability and cautions. *Clin Trials.* 2006;3(6):508-512.

37. Phillips AN, Grabar S, Tassie JM, Costagliola D, Lundgren JD, Egger M. Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. EuroSIDA, the French Hospital Database on HIV and the Swiss HIV Cohort Study Groups. *Aids.* Oct 22 1999;13(15):2075-2082.

38. Sabin CA, Phillips AN. Treatment comparisons in HIV infection: the benefits and limitations of observational cohort studies. *J Antimicrob Chemother.* Apr 2001;47(4):371-375.

39. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria. *J Am Coll Cardiol.* Jan 1984;3(1):114-128.

40. King SB, 3rd, Barnhart HX, Kosinski AS, et al. Angioplasty or surgery for multivessel coronary artery disease: comparison of eligible registry and randomized patients in the EAST trial and influence of treatment selection on outcomes. Emory Angioplasty versus Surgery Trial Investigators. *Am J Cardiol.* Jun 1 1997;79(11):1453-1459.

41. McKay JR, Alterman AI, McLellan AT, Boardman CR, Mulvaney FD, O'Brien CP. Random versus nonrandom assignment in the evaluation of treatment for cocaine abusers. *J Consult Clin Psychol.* Aug 1998;66(4):697-701.

42. Strandberg TE, Salomaa VV, Vanhanen HT, Naukkarinen VA, Sarna SJ, Miettinen TA. Mortality in participants and non-participants of a multifactorial prevention study of cardiovascular diseases: a 28 year follow up of the Helsinki Businessmen Study. *Br Heart J.* Oct 1995;74(4):449-454.

43. Williford WO, Krol WF, Buzby GP. Comparison of eligible randomized patients with two groups of ineligible patients: can the results of the VA Total Parenteral Nutrition clinical trial be generalized? *J Clin Epidemiol.* Sep 1993;46(9):1025-1034.

44. Elting LS, Cooksley C, Bekele BN, et al. Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. *Cancer.* Jun 1 2006;106(11):2452-2458.

45. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. Attitudes and beliefs of African Americans toward participation in medical research. *J Gen Intern Med.* Sep 1999;14(9):537-546.

46. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med.* May 2 2002;346(18):1373-1382.

47. Cheung AM, Lee Y, Kapral M, et al. Barriers and motivations for women to participate in cardiovascular trials. *J Obstet Gynaecol Can.* Apr 2008;30(4):332-337.

48. Fayter D, McDaid C, Eastwood A. A systematic review highlights threats to validity in studies of barriers to cancer trial participation. *J Clin Epidemiol.* Oct 2007;60(10):990-1001.

Table 5.1: Baseline sample characteristics comparing trial participants to non-trial participants, restricted to complete cases, 1996-2006

	Total		No Trial		Trial		p value*
	N (496)	%	N=327	%	N=169	%	
Virologic Success							
HIV RNA ≤400 c/mL	327	65.9	242	74	145	85.8	0.003
HIV RNA >400 c/mL	169	34.1	85	26	24	14.2	
Demographic and Behavioral Characteristics							
Age (years)							
<40	273	55	183	56	93	53.3	0.6
>40	223	45	144	44	79	46.7	
Gender/sexual preference							
MSM/Bisexual men	175	35.3	101	30.9	74	43.8	0.02
Heterosexual men	136	27.4	114	34.9	51	30.2	
Heterosexual women	185	37.3	112	34.2	44	26.0	
Race							
Black	298	60.1	211	64.5	87	51.5	0.005
Non Black	198	31.9	116	35.5	82	48.5	
Substance Abuse							
No	327	65.9	212	64.8	118	69.8	0.3
Yes	169	34.1	115	35.2	51	30.2	
Access to Care Characteristics							
Insurance Status							
Public	126	25.9	103	31.8	23	14.1	0.001
None	168	34.6	96	29.7	72	44.2	
Private/Other	192	39.5	124	38.4	68	41.7	
Distance to ID clinic (miles)							
<50	130	26.3	77	23.6	53	31.4	0.06
>50	365	73.7	249	76.4	116	68.6	
Clinical Characteristics							
AIDS Diagnoses							
No	343	69.2	233	71.3	110	65.9	0.2
Yes	153	30.8	94	28.7	59	34.1	
CD4 cells/uL							
<200	257	57.6	151	54.1	106	63.4	0.1
200-350	81	18.2	53	19.0	28	16.8	
>350	108	24.2	75	26.9	33	19.8	
Mean HIV RNA (log_{10}) (sd)	4.9	(1.0)	4.7	(1.0)	4.8	(1.0)	0.6
Mental Illness							
No	398	80.2	262	80.1	136	80.5	0.9
Yes	98	19.8	65	19.9	33	19.5	
Diagnosis to treatment (months)							
<1	56	12.5	45	14.4	11	8.1	0.08
1-3	112	24.9	71	22.7	41	29.9	
3-24	177	39.4	119	38.1	58	42.3	
>24	104	23.2	77	24.7	27	19.7	

Treatment Characteristics							
HAART Initiation Year							
1996-99	161	32.5	124	37.9	37	21.9	0.001
2000-06	335	67.5	203	62.1	132	78.1	
HAART category							
n2pib/n3pib/n2pi2	99	20.0	39	11.9	60	35.5	0.001
n2nnrti/n3nnrti	192	38.7	132	40.4	60	35.5	
n2pi/n3pi	134	27.0	116	35.4	18	10.7	
n2nnrtipi/nnrtipi	40	8.1	20	6.1	20	11.8	
3nrti	31	6.3	20	6.1	11	6.5	
Other Laboratory Parameters							
ANC (10^9/L)							
Normal	268	62.2	173	65.3	95	57.2	0.09
Abnormal	163	37.8	92	34.7	71	42.8	
Hemoglobin (g/dL)							
Normal	195	41.1	116	43.6	79	47.6	0.4
Abnormal	237	54.9	150	56.4	87	52.4	
Creatinine (mg/dL)							
Normal	462	93.2	298	91.1	164	97	0.01
Abnormal	34	6.8	29	8.9	5	3	
ALT U/L							
Normal	338	81.1	204	81.3	134	80.7	0.9
Abnormal	79	18.9	47	18.7	32	19.3	

* p values comparing trial to non trial participants
MSM=Men who have sex with Men; Public insurance= Medicaid/Medicare;
ID= University of North Carolina Infectious Disease;
AIDS=Acquired Immune Deficiency Syndrome; ANC=Absolute Neutrophil Count
ALT=Alanine aminotransferase

HAART Category
n2pib=2 NRTIs + boosted PI
n3pib= 3 NRTIs + boosted PI
n2pi2= 2 NRTIs + 2 PIs
n2nnrti= 2NRTIs + 1NNRTI
n3nnrti= 3NRTIs + 1NNRTI
n2pi= 2 NRTIs + 1 PI
n3pi= 3 NRTIs + 1 PI
n2nnrtipi=2 NRTIs + 1PI + 1NNRTI
nnrtipi= 1PI + 1NNRTI
3nrti= 3 NRTIs

Table 5.2 Description of Clinical Trials in which subjects in this study were enrolled, 1996-2006

Study	N	Percent	Study Treatments
ACTG 384	34	15.18	ZDV/3TC + EFV ZDV/3TC + NFV ddI/ d4T + EFV ddI/ d4T + NFV ZDV/3TC + EFV + NFV ddI/ d4T + EFV + NFV
ACTG 388	10	4.46	ZDV/3TC + IDV ZDV/3TC + IDV + EFV ZDV/3TC + IDV + NFV
A5015	6	2.68	d4T + FTC + LPV/ RTV
A5073	6	2.68	FTC+TFV + LPV/RTV FTC + d4T + LPV/ RTV
A5095	51	22.77	ZDV/3TC/ABC ZDV/3TC + EFV ZDV/3TC/ABC + EFV
A5142	25	11.16	ZDV (or d4t XR) + 3TC + EFV ZDV (or d4t XR) + 3TC + LPV/RTV EFV + LPV/RTV
A5164	19	8.48	The study provided ARVs including LPV/r,d4T and TDF/FTC but clinicians were free to use any standard ART.
A5175	8	3.57	ZDV/3TC + EFV ddI/FTC + ATV FTC/TFV + EFV
A5202	36	16.07	FTC/TFV + EFV ABC/3TC + EFV FTC/TFV + EFV FTC/TFV + ATV/ RTV
Abbott M97	9	4.02	d4T + 3TC+ LPV/RTV
Gilead 903	12	5.36	d4T + 3TC + EFV TDF + 3TC + EFV
Gilead 934	1	0.45	FTC/TFV + EFV ZDV/3TC + EFV
KLEAN	7	3.13	ABC/3TC + FPV/RTV ABC/3TC + LPV/RTV
Total	224	100	

Table 5.3: Unadjusted and adjusted risk ratios and 95% confidence intervals for virologic success by trial participation within strata of HAART period

	Risk Ratios (95% Confidence Interval)					
	Unadjusted		Adjusted*		Adjusted**	
HAART period						
Early (1996-99)						
No Trial	1		1		1	
Trial	1.42	(1.24, 1.62)	1.40	(1.22, 1.62)	1.33	(1.15, 1.54)
Current (2000-06)						
No Trial	1		1		1	
Trial	1.07	(0.95, 1.19)	1.01	(0.90, 1.14)	0.98	(0.87, 1.11)

* adjusted for age, distance traveled to receive care at UNC ID clinic, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, creatinine

** adjusted for age, distance traveled to receive care at UNC ID clinic, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, creatinine, type of HAART

Table 5.4 Sensitivity Analysis: risk ratios for trial participation following different adjustment scenarios for missing data in the early HAART period

	Risk Ratios (95% Confidence Interval			
	Unadjusted		**Adjusted***	
Assigning virologic success to missing values for trial participants and virologic failure to missing values for non trial participants				
No Trial	1		1	
Trial	2.46	(1.74, 3.47)	1.89	(1.59, 2.29)
Assigning virologic failure to missing values for trial participants and virologic success to missing values for non trial participants				
No Trial	1		1	
Trial	0.83	(0.58, 1.19)	1.17	(1.02, 1.35)
Assigning virologic failure to all missing values in both groups				
No Trial	1		1	
Trial	1.70	(1.15, 2.51)	1.75	(1.44, 2.13)
Assigning virologic failure to 80% of all missing values in both groups				
No Trial				
Trial	1.42	(1.16, 1.75)	1.47	(1.24, 1.74)
Assigning virologic failure to 70% of all missing values in both groups				
No Trial	1		1	
Trial	1.37	(1.13, 1.67)	1.46	(1.23, 1.73)
Assigning virologic failure to 60% of all missing values in both groups				
No Trial	1		1	
Trial	1.35	(1.14, 1.60)	1.40	(1.19, 1.65)
Assigning virologic failure to 40% of all missing values in both groups				
No Trial	1		1	
Trial	1.36	(1.19, 1.55)	1.45	(1.25, 1.68)
Assigning virologic failure to 20% of all missing values in both groups				
No Trial	1		1	
Trial	1.36	(1.19, 1.55)	1.45	(1.25, 1.68)
Assigning virologic failure to 0% and virologic success to 100% of all missing values in both groups				
No Trial	1		1	
Trial	1.20	(0.88, 1.64)	1.27	(1.14, 1.42)

* adjusted for age, distance traveled to receive care at UNC ID clinic, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, creatinine

Table 5.5 Sensitivity Analysis: risk ratios for trial participation following different adjustment scenarios for missing data in the current HAART period

	Risk Ratios (95% Confidence Interval)			
	Unadjusted		Adjusted*	
Assigning virologic success to missing values for trial participants and virologic failure to missing values for non trial participants				
No Trial	1		1	
Trial	1.66	(1.33, 2.07)	1.40	(1.23, 1.60)
Assigning virologic failure to missing values for trial participants and virologic success to missing values for non trial participants				
No Trial	1		1	
Trial	0.75	(0.60, 0.94)	0.83	(0.73, 0.94)
Assigning virologic failure to all missing values in both groups				
No Trial	1		1	
Trial	1.22	(0.96, 1.56)	1.19	(1.02, 1.40)
Assigning virologic failure to 80% of all missing values in both groups				
No Trial	1		1	
Trial	1.22	(1.06, 1.41)	1.17	(1.01, 1.36)
Assigning virologic failure to 70% of all missing values in both groups				
No Trial	1		1	
Trial	1.18	(1.03, 1.34)	1.10	(0.95, 1.27)
Assigning virologic failure to 60% of all missing values in both groups				
No Trial	1		1	
Trial	1.16	(1.02, 1.31)	1.10	(0.96, 1.26)
Assigning virologic failure to 40% of all missing values in both groups				
No Trial	1		1	
Trial	1.08	(0.96, 1.21)	1.03	(0.90, 1.17)
Assigning virologic failure to 20% of all missing values in both groups				
No Trial	1		1	
Trial	1.08	(0.97, 1.21)	1.02	(0.90, 1.17)
Assigning virologic failure to 0% and virologic success to 100% of all missing values in both groups				
No Trial	1		1	
Trial	1.02	(0.83, 1.25)	0.98	(0.89, 1.08)

* adjusted for age, distance traveled to receive care at UNC ID clinic, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, creatinine

CHAPTER SIX - CONCLUSIONS

HIV clinical trials should involve diverse populations of patients to ensure external validity. However, available studies have suggested that racial/ethnic minorities, women and persons who acquire HIV infection through heterosexual intercourse are under represented in clinical trials[1-5]. These differences between trial and non trial participants are thought to undermine the generalizability of data from clinical trials. Additionally, as treatment guidelines are based on data from clinical trials, the utility and applicability of treatment guidelines to clinical practice has also been questioned.

Beyond the fundamental issue of demographic differences, there is a broader and more important issue, namely 'Is there a trial effect in HIV clinical trials?'. A trial effect is perceived to be a benefit obtained by trial participants that results in improved outcomes. A trial effect may arise due to a treatment effect (newer, better or experimental treatments available to trial participants but unavailable outside the trial) or to a participation effect. This latter effect has been further subdivided into a protocol effect (differences in the way treatment regimens are delivered), care effect (differences in care), Hawthorne effect (behavior change secondary to being under observation) and placebo effect ("psychologically mediated" benefits that arise due to being in a trial)[6-8]. Several studies in oncology, surgery, psychiatry and other medical disciplines have studied differences in outcomes between trial and non trial

participants. However, to date, no study has examined a trial effect in HIV clinical trials.

In this dissertation we examined if trial and non trial participants differed by gender/sexual orientation and race/ethnicity. We further examined if there was a trial effect in HIV clinical trials by comparing virologic success among trial and non trial participants.

Influence of race, gender and sexual orientation on participation in HIV treatment trials.

Our assessment of participation in HIV treatment trials showed that blacks when compared to non blacks were slightly less likely to participate in treatment trials. We feel that our results reflect a trend supporting decrease in disparities for black enrolment into trials. A recent study assessed the willingness of blacks to participate in HIV treatment trials and found that of study subjects only 57% had been invited to participate in research and 86% of those invited did participate in research[9]. Not being informed about research or not being invited to participate in research has been previously cited as major reasons for blacks not to participate in clinical research[2, 10-12]. In certain settings, health care providers may themselves be poorly informed about the clinical trials and this could result in potential subjects not being informed about the research, or principal investigators may not be practicing clinicians and thus are not in direct contact with subjects resulting in potential subjects not being invited to participate. Our success in enrolment of blacks might in

part be attributed to the fact that the trial investigators were also the clinicians providing care to the subjects and therefore both information provision and invitation to participate were optimized. In fact a recent study showed that when invited blacks were equally likely and sometimes more likely than non blacks to participate in clinical trials[13].

Lack of trust in researchers is another reason for non participation by blacks in clinical trials. It is not difficult to understand why blacks may have fears or misunderstandings about the intentions of researchers. Historically the non participation of blacks has been attributed to the history of racism in medical research exemplified by the Tuskegee Syphilis study. However, trust developed between a primary care provider and a patient, has been suggested to be a means to overcome this fear of participation in research[14]. In fact, this may well have been the case in our study. Since most if not all of the study subjects were established patients of the investigators, there might have been interpersonal trust which decreased the fear of trial participation.

In keeping with other HIV trials we demonstrated that women were as likely as men to enroll in clinical trials. In the early 90's the need for proportionate representation of women and minorities in clinical trials was mandated by law in the National Institutes of Health revitalization act[15, 16]. It is heartening, that at least for women in HIV clinical trials significant progress has been made towards compliance with this mandate. It is worth mentioning that in our study regardless of gender

subjects with public insurance (Medicaid/Medicare) were less likely, while those without insurance were more likely to participate in trials, . This suggests that insurance status influences trial participation and that persons without insurance might perceive enrolment in a trial as a means to obtain treatment and health care. Clearly trial participation can provide primary care, treatment and other health benefits to patients who have limited resources. We must caution investigators to be vigilant, as insurance status not race or gender might be a bigger determinant of trial participation and clinical trials might become studies of the uninsured or under insured.

In sum, we found no significant differences in trial participation rates for blacks compared with non blacks and for women compared with men. Clinical trialists must understand that successful enrolment of under represented groups can be enhanced by communication and trust. Investigators must communicate their intentions to subjects and to the community clearly, constantly and continuously through the study period. Moreover, it is vital for this communication to continue once the study has ended. This will ensure appropriate dissemination of study results. Additionally, subjects will be reassured that their health and well being remains of interest to investigators even after study completion. Trust (interpersonal or institutional) is an iterative process fostered by honest and frequent communication.

Trial effect in HIV treatment trials.

A trial effect has been posited to result in improved outcomes for trial relative to non trial participants. In the early HAART period (1996-99) trial participants were more likely than non trial participants to achieve virologic success. However, we are unable to say with confidence that this difference in virologic success is purely attributable to a trial effect. Although we were able to assess the influence of diverse demographic, clinical, and laboratory characteristics on our results we were unable to assess the influence of unmeasured confounders such as medication adherence and socio-economic status. Therefore we conclude that in this period there was a benefit to trial participation which may be attributable to several causes including a trial effect.

In the current HAART period (2000-06) we found no strong evidence supporting a trial effect. The importance of this finding cannot be over stated. During this period advancements in the treatment of HIV led to highly potent and more tolerable antiretroviral (ARV) treatment combinations which are equally effective regardless of trial participation. Therefore, at an individual level, non trial participants should feel secure in the knowledge that their likelihood of virologic success subsequent to antiretroviral treatment is no different from trial participants. Since a clinical trial is by definition experimental and can result in either a beneficial or harmful outcome, trial participants can be reassured that they are unlikely to experience a harmful outcome of virologic non response.

Lack of a trial effect has overarching public health implications. An evidence based approach to patient care requires that the results of well designed clinical trials be incorporated into clinical practice. However, the widely held belief that a trial effect improves outcomes for trial participants has led clinicians and public health advocates to express reservations about extrapolating these results to clinical practice. Our finding of no trial effect should reassure both these groups as it suggests that results of HIV treatment trials can be applied to other HIV infected persons. It also supports the validity of the treatment guidelines which are formulated based on data from clinical trials. Clinicians can have more confidence that these guidelines are relevant to routine clinical care and that data from these trials can be extrapolated to their patient populations.

Rather than being perceived as a discouragement, the absence of a trial effect should encourage patients to enroll in clinical trials. Many trials do offer participants advantages. In certain situations, for example the treatment of patients with resistant HIV, or for highly ARV experienced patients trials might provide newer and more effective treatments that are unavailable as standard of care. Patients in trials interact one-on-one and frequently with a dedicated team of study personnel which fosters trust in the providers and belief in the trial intervention leading to better adherence. Other benefits associated with trial participation include careful monitoring, free health care and laboratory assessments and sometimes compensation. Patients also experience both pride and self worth from the

knowledge that they are contributing to science and to improving the lives of other HIV infected persons.

Randomized clinical trials are critical to the advancement of HIV treatment and care. The absence of a trial effect should be perceived as strong support that well designed and conducted clinical trials provide valid and generalizable information and should neither hinder enrolment into nor conduct of clinical trials. Patients who are considering participation in a trial should be clearly informed about the potential benefits and risks of the intervention being compared in the trial and about other options that may be available. Investigators and clinicians should be cautious about over promising the potential outcomes from trial participation. However, these caveats notwithstanding, we feel that both patients and clinicians can recognize the crucial role of clinical trials in the advancement of knowledge.

Perhaps, the single most important message that the absence of a trial effect highlights, is that HAART efficacy does translate into effectiveness. Regardless of the setting, HAART achieves durable and sustained suppression of HIV replication.

6.1References:

1. Diaz T, Chu SY, Sorvillo F, et al. Differences in participation in experimental drug trials among persons with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol.* Dec 15 1995;10(5):562-568.

2. Gifford AL, Cunningham WE, Heslin KC, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med.* May 2 2002;346(18):1373-1382.

3. Hankins C, Lapointe N, Walmsley S. Participation in clinical trials among women living with HIV in Canada. Canadian Women's HIV Study Group. *Cmaj.* Dec 1 1998;159(11):1359-1365.

4. Madge S, Mocroft A, Wilson D, et al. Participation in clinical studies among patients infected with HIV-1 in a single treatment centre over 12 years. *HIV Med.* Oct 2000;1(4):212-218.

5. Moore DA, Goodall RL, Ives NJ, Hooker M, Gazzard BG, Easterbrook PJ. How generalizable are the results of large randomized controlled trials of antiretroviral therapy? *HIV Med.* Jul 2000;1(3):149-154.

6. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol.* Mar 2001;54(3):217-224.

7. Lantos JD. The "inclusion benefit" in clinical trials. *J Pediatr.* Feb 1999;134(2):130-131.

8. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet.* Jan 24 2004;363(9405):263-270.

9. Garber M, Hanusa BH, Switzer GE, Mellors J, Arnold RM. HIV-infected African Americans are willing to participate in HIV treatment trials. *J Gen Intern Med.* Jan 2007;22(1):17-42.

10. Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R. Strategic physician communication and oncology clinical trials. *J Clin Oncol.* Oct 1999;17(10):3324-3332.

11. Baquet CR, Commiskey P, Daniel Mullins C, Mishra SI. Recruitment and participation in clinical trials: socio-demographic, rural/urban, and health care access predictors. *Cancer Detect Prev.* 2006;30(1):24-33.

12. Comis R. L. DDCDD, Kimmel L.G., Miller J.D. Barriers to Clinical Trial Participation "We have met the enemy and he is us". *Abstract No. 6567, Poster No. C11. Poster presented at American Society of Clinical Oncology Annual Meeting, June 2, 2007, Chicago, IL.*

13. Wendler D, Kington R, Madans J, et al. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med.* Feb 2006;3(2):e19.

14. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. Attitudes and beliefs of African Americans toward participation in medical research. *J Gen Intern Med.* Sep 1999;14(9):537-546.

15. NIH Revitalization Act, Subtitle B, Part1, Sec 131-133, June 10, 1993.

16. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. Federal Register, Part VIII (59 FR 14508-14513), March 28, 1994.

APPENDIX ONE – CHAPTER FOUR

Table A1.1: Unadjusted, adjusted and imputed prevalence ratios and 95% confidence intervals comparing trial participants to non-trial participants by baseline demographic, access to care and clinical characteristics

	Prevalence Ratios (95% Confidence Interval)		
	Unadjusted	Adjusted *	Adjusted imputed*
Demographic and Behavioral Characteristics			
Age (years)			
<30	1	1	1
30-39	0.88 (0.62, 1.25)	0.86 (0.60, 1.23)	0.88 (0.65, 1.17)
40-49	0.98 (0.68, 1.41)	1.12 (0.78, 1.63)	1.03 (0.76, 1.40)
>50	0.85 (0.53, 1.38)	0.85 (0.51, 1.41)	0.93 (0.62, 1.39)
Gender/sexual preference			
MSM/Bisexual men	1	1	1
Heterosexual men	0.72 (0.51, 1.01)	0.87 (0.62, 1.22)	0.95 (0.73, 1.25)
Heterosexual women	0.76 (0.57, 1.03)	1.01 (0.70, 1.43)	0.91 (0.67, 1.23)
Race			
Black	1	1	1
White	1.38 (1.03, 1.85)	1.21 (0.88, 1.67)	1.26 (0.97, 1.63)
Other	1.61 (1.09, 2.37)	1.27(0.87, 1.86)	1.29 (0.95, 1.75)
IDU as HIV risk			
No	1	1	1
Yes	0.55 (0.33, 0.90)	0.61 (0.35, 1. 03)	0.61 (0.39, 0.97)
Access to Care Characteristics			
Insurance Status			
Public	1	1	1
None	2.39 (1.58, 3.61)	1.99 (1.23, 3.24)	1.99 (1.35, 2.92)
Private/Other	2.25 (1.48, 3.42)	1.97 (1.18, 3.30)	1.78 (1.19, 2.67)
Distance to ID clinic (miles)			
<25	1	1	1
25-50	0.92 (0.57, 1.37)	0.90 (0.63, 1.27)	0.92 (0.66, 1.28)
>50	0.74 (0.44, 0.98)	0.84 (0.61, 1.15)	0.83 (0.61, 1.12)
Clinical Characteristics			
Diagnoses to treatment(months)			
<1	1	1	1
1-3	2.19 (1.18, 4.08)	1.85 (1.00, 3.41)	2.04 (1.21, 3.43)
3-24	2.37 (1.31, 4.29)	2.14 (1.18, 3.87)	2.38 (1.45, 3.90)
>24	1.61 (0.85, 3.05)	1.75 (0.92, 3.32)	1.77 (1.02, 3.06)
CD4 cells/uL			
<200	1	1	1
200-350	0.84 (0.58, 1.23)	0.92 (0.61, 1.38)	0.85 (0.61, 1.18)
>350	0.69 (0.47, 1.00)	0.82 (0.53, 1.26)	0.72 (0.47, 1.10)
HIV RNA (log_{10})	0.99 (0.86, 1.15)	0.87 (0.76, 0.99)	0.92 (0.82, 1.04)

* adjusted for all variables in this table and for mental illness, substance abuse, baseline absolute neutrophil count, hemoglobin, creatinine and ALT

TABLE A1.2: Unadjusted and adjusted prevalence ratios and 95% confidence intervals comparing trial participants to non-trial participants for selected baseline characteristics stratified by gender

	Prevalence Ratios (95% Confidence Interval)			
	Women		Men	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Access to Care Characteristics*				
Insurance Status				
None	1	1	1	1
Public	0.39 (0.21, 0.70)	0.44 (0.23, 0.86)	0.48 (0.30, 0.79)	0.44 (0.21, 0.92)
Private/Other	0.97 (0.58, 1.62)	0.97 (0.54, 1.74)	0.93 (0.72, 1.21)	0.92 (0.27, 1.96)
Clinical Characteristics**				
Diagnosis to treatment (months)				
<3	1	1	1	1
>3	2.15 (1.10, 4.02)	1.89 (0.98, 3.65)	1.02 (0.74,1.40)	1.02 (0.74, 1.42)

*adjusted for age, race, distance traveled to receive care at UNC ID clinic, baseline CD4 cell counts, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, ALT, ANC, creatinine, hemoglobin

** adjusted for age, race, insurance status, distance traveled to receive care at UNC ID clinic, baseline CD4 cell counts, baseline HIV RNA levels, months from HIV diagnosis to HAART initiation, ALT, ANC, creatinine, hemoglobin

APPENDIX TWO – CHAPTER FIVE

Table A.2.1: Baseline sample characteristics comparing early and current HAART periods, restricted to complete cases

	Total		Early period 1996-99		Current period 2000-06		p value*
	N(496)	%	N(161)	%	N(335)	%	
Primary Exposure							
No Trial	327	65.9	124	77	203	60.6	0.001
Trial	169	34.1	37	23	132	39.4	
Demographic and Behavioral Characteristics							
Age (years)							
<40	273	55	91	56.5	67	54.3	0.6
>40	223	45	79	43.5	42	45.7	
Gender/sexual preference							
MSM[1]/Bisexual men	175	35.3	54	33.5	121	36.1	0.9
Heterosexual men	136	27.4	55	34.2	110	32.8	
Heterosexual women	185	37.3	52	32.3	104	31.1	
Race							
Black	298	60.1	107	66.5	191	57	0.04
Non Black	198	31.9	54	33.5	144	43	
IDU[2] as HIV risk							
No	435	87.7	136	84.5	299	89.3	0.1
Yes	61	12.3	25	15.5	36	10.7	
Substance Abuse							
No	350	70.6	118	72.4	232	69.3	0.4
Yes	146	29.4	43	27.6	103	30.7	
Access to Care Characteristics							
Insurance Status							
Public[3]	126	25.9	51	31.7	75	23.1	0.003
None	168	34.6	39	24.2	129	39.7	
Private/Other	192	39.5	71	44.1	121	37.2	
Distance to ID[4] clinic (miles)							
<50	130	26.3	37	23	93	27.8	0.2
>50	365	73.7	124	77	241	72.2	
Clinical Characteristics							
AIDS[5] Diagnoses							
No	343	69.2	119	73.9	224	66.9	0.1
Yes	153	30.8	42	26.1	111	33.1	
CD4 cells/uL							
<200	257	57.6	62	47.7	195	61.7	0.006
200-350	81	18.2	24	18.5	57	18.0	
>350	108	24.2	44	33.9	64	20.3	
Mean HIV RNA (log_{10}) (sd)	4.9	(1.0)	4.7	(1.0)	4.8	(0.97)	0.9
Mental Illness							
No	398	80.2	135	83.9	263	78.5	0.2
Yes	98	19.8	26	16.1	72	21.5	

Diagnosis to treatment (months)							
<1	56	12.5	20	13.3	38	12.1	0.5
1-3	112	24.9	31	20.5	81	27.2	
3-24	177	39.4	64	42.4	113	37.9	
>24	104	23.2	36	23.8	68	22.8	
Treatment Characteristics							
HAART category[8]							
n2pib/n3pib/n2pi2	99	20.0	8	5.0	91	27.2	0.001
n2nnrti/n3nnrti	192	38.7	42	26.1	150	44.8	
n2pi/n3pi	134	27.0	85	52.8	49	14.6	
n2nnrtipi/nnrtipi	40	8.1	23	14.3	17	5.1	
3nrti	31	6.3	3	1.9	28	8.4	
Other Laboratory Parameters							
ANC[6] (10^9/L)							
Normal	268	62.2	73	59.4	195	63.3	0.4
Abnormal	163	37.8	50	40.6	113	36.7	
Hemoglobin (g/dL)							
Normal	195	41.1	57	46	138	44.8	0.8
Abnormal	237	54.9	67	54	170	55.2	
Creatinine (mg/dL)							
Normal	462	93.2	153	95	309	92.2	0.2
Abnormal	5134	6.8	8	5	26	7.8	
[7]ALT U/L							
Normal	338	81.1	93	80.2	245	81.4	0.8
Abnormal	10079	18.9	23	19.8	56	18.6	

* p values comparing early to current periods
[1]MSM=Men who have sex with Men; [2]IDU=Injection Drug Use; [3]Public insurance= Medicaid/Medicare;
[4] ID= University of North Carolina Infectious Disease;
[5]AIDS=Acquired Immune Deficiency Syndrome; [6]ANC=Absolute Neutrophil Count
[7]ALT=Alanine amino transferase

HAART Category[8]
n2pib=2 NRTIs + boosted PI
n3pib= 3 NRTIs + boosted PI
n2pi2 = 2 NRTIs + 2 PIs
n2nnrti= 2NRTIs + 1NNRTI
n3nnrti = 3NRTIs + 1NNRTI
n2pi= 2 NRTIs + 1 PI
n3pi= 3 NRTIs + 1 PI
n2nnrtipi-=2 NRTIs + 1PI + 1NNRTI
nnrtipi= 1PI + 1NNRTI
3nrti= 3 NRTIs

Table A 2.2: Baseline sample characteristics comparing subjects with virologic success to subjects without virologic success, restricted to complete cases

	Total		Viral Load <400 c/mL		Viral Load >400 c/mL		p value*
	N (496)	%	N (387)	%	N (109)	%	
Primary Exposure							
No Trial	327	65.9	242	62.5	85	78.0	0.003
Trial	169	34.1	145	37.5	24	22.0	
Demographic and Behavioral Characteristics							
Age (years)							
<40	273	55	206	53.2	67	61.5	0.1
>40	223	45	181	46.8	42	38.5	
Gender/sexual preference							
MSM[1]/Bisexual men	175	35.3	138	35.6	37	33.9	0.9
Heterosexual men	136	27.4	105	27.1	31	28.5	
Heterosexual women	185	37.3	144	37.2	41	37.6	
Race							
Black	298	60.1	225	58.1	73	67	0.1
Non Black	198	31.9	162	41.9	36	33	
IDU[2] as HIV risk							
No	435	87.7	340	87.9	95	87.2	0.8
Yes	61	12.3	47	12.1	14	12.8	
Substance Abuse							
No	350	70.6	280	72.4	70	64.2	0.1
Yes	146	29.4	107	27.6	39	35.8	
Access to Care Characteristics							
Insurance Status							
Public[3]	126	25.9	96	25.4	30	27.8	0.7
None	168	34.6	129	34.1	39	36.1	
Private/Other	192	39.5	153	40.5	39	36.1	
Distance to ID[4] clinic (miles)							
<50	130	26.3	99	25.7	31	28.4	0.6
>50	365	73.7	287	74.3	78	71.6	
Clinical Characteristics							
AIDS[5] Diagnoses							
No	343	69.2	266	68.7	77	70.6	0.7
Yes	153	30.8	121	31.3	32	29.4	
CD4 cells/uL							
<200	257	57.6	201	56.9	56	60.2	0.6
200-350	81	18.2	63	17.9	18	19.4	
>350	108	24.2	89	25.2	19	20.4	
Median HIV RNA (log_{10}) (sd)	4.9	(1.0)	4.7	(1.0)	4.9	(0.9)	0.05
Mental Illness							
No	398	80.2	312	80.6	86	78.9	0.7
Yes	98	19.8	75	19.4	23	21.1	

Diagnosis to treatment (months)							
<1	56	12.5	42	12.0	14	14.3	0.001
1-3	112	24.9	94	26.8	18	18.4	
3-24	177	39.4	148	42.2	29	29.6	
>24	104	23.2	67	19.1	37	37.8	
Treatment Characteristics							
HAART Initiation Year							
1996-99	161	32.5	121	31.3	40	36.7	0.3
2000-06	335	67.5	266	68.7	69	63.3	
HAART category[8]							
n2pib/n3pib/n2pi2	99	20.0	84	21.7	15	13.8	0.001
n2nnrti/n3nnrti	192	38.7	155	40.1	37	33.9	
n2pi/n3pi	134	27.0	89	23.0	45	41.3	
n2nnrtipi/nnrtipi	40	8.1	36	9.3	4	3.7	
3nrti	31	6.3	23	5.9	8	7.3	
Other Laboratory Parameters							
ANC[6] (10^9/L)							
Normal	268	62.2	217	62.9	51	59.3	0.5
Abnormal	163	37.8	128	37.1	35	40.7	
Hemoglobin (g/dL)							
Normal	195	41.1	162	46.8	33	38.4	0.2
Abnormal	237	54.9	184	53.2	53	61.6	
Creatinine (mg/dL)							
Normal	462	93.2	359	92.8	103	94.5	0.5
Abnormal	5134	6.8	28	7.2	6	5.5	
[7]ALT U/L							
Normal	338	81.1	274	81.6	64	79.0	0.6
Abnormal	10079	18.9	62	18.4	17	21.0	

* p values comparing persons with viral load $\leq$400 to >400
[1]MSM=Men who have sex with Men; [2]IDU=Injection Drug Use; [3]Public insurance= Medicaid/Medicare;
[4] ID= University of North Carolina Infectious Disease;
[5]AIDS=Acquired Immune Deficiency Syndrome; [6]ANC=Absolute Neutrophil Count
[7]ALT=Alanine amino transferase

HAART Category[8]
n2pib=2 NRTIs + boosted PI
n3pib= 3 NRTIs + boosted PI
n2pi2 = 2 NRTIs + 2 PIs
n2nnrti= 2NRTIs + 1NNRTI
n3nnrti = 3NRTIs + 1NNRTI
n2pi= 2 NRTIs + 1 PI
n3pi= 3 NRTIs + 1 PI
n2nnrtipi-=2 NRTIs + 1PI + 1NNRTI
nnrtipi= 1PI + 1NNRTI
3nrti= 3 NRTIs

Table A 2.3: Comparison of antiretroviral treatment regimens provided within clinical trials to antiretroviral treatment regimens provided within clinical care, 1996-2006

	Trial		Non Trial	
HAART regimen*	Freq.	Percent	Freq.	Percent
n2pib/n3pib/n2pi2	53	10.31	75	33.48
n2nnrti/n3nnrti	205	39.88	83	37.05
n2pi/n3pi	196	38.13	22	9.82
n2nnrtipi/nnrtipi	26	5.06	29	12.95
3nrti	34	6.61	15	6.7
Total	514	100	224	100

HAART regimen*
n2pib- 2 NRTIs + boosted PI
n3pib- 3 NRTIs + boosted PI
n2pi2 - 2 NRTIs + 2 PIs
n2nnrti- 2NRTIs + 1NNRTI
n3nnrti - 3NRTIs + 1NNRTI
n2pi- 2 NRTIs + 1 PI
n3pi- 3 NRTIs + 1 PI
n2nnrtipi- 2 NRTIs + 1PI + 1NNRTI
nnrtipi- 1PI + 1NNRTI
3nrti- 3 NRTIs

Table A 2.4: Comparison of antiretroviral treatment regimens provided in the early HAART period to antiretroviral treatment regimens provided in the current HAART period

HAART regimen*	Early Period 1996-99 n=266 %	Current Period 2000-06 n=438 %	Total n=738 %
n2pib/n3pib/n2pi2	12	116	128
	4.51	24.58	17.34
n2nnrti/n3nnrti	69	219	288
	25.94	46.4	39.02
n2pi/n3pi	148	70	218
	55.64	14.83	29.54
n2nnrtipi/nnrtipi	32	23	55
	12.03	4.87	7.45
3nrti	5	44	49
	1.88	9.32	6.64

* HAART regimen
n2pib- 2 NRTIs + boosted PI
n3pib- 3 NRTIs + boosted PI
n2pi2 - 2 NRTIs + 2 PIs
n2nnrti- 2NRTIs + 1NNRTI
n3nnrti - 3NRTIs + 1NNRTI
n2pi- 2 NRTIs + 1 PI
n3pi- 3 NRTIs + 1 PI
n2nnrtipi- 2 NRTIs + 1PI + 1NNRTI
nnrtipi- 1PI + 1NNRTI
3nrti- 3 NRTIs

Table A 2.5: Study number, study design and official title of clinical trials included in this study

Study	Study Design	Official Title
ACTG 384	Treatment, Double-Blind, Pharmacokinetics Study	Study of Protease Inhibitor and/or Non-Nucleoside Reverse Transcriptase Inhibitor With Dual Nucleosides in Initial Therapy of HIV Infection
ACTG 388	Treatment, Open Label, Safety Study	A Phase III Randomized, Controlled Trial of Efavirenz (EFV) or Nelfinavir (NFV) in Combination With Fixed-Dose Combination Lamivudine/Zidovudine (3TC/ZDV) and Indinavir (IDV) in HIV-Infected Subjects With Less Than or Equal to 200 CD4 Cells/mm3 or Greater Than or Equal to 80,000 HIV RNA Copies/Ml in Plasma
ACTG 5015	Treatment, Efficacy Study	A Phase II Exploratory Study Examining Immunologic and Virologic Indices in Two Age-Differentiated Cohorts of HIV-Infected Subjects to Explore the Basis of Accelerated HIV-Disease Progression Associated With Aging
ACTG 5073	Treatment, Randomized, Open Label, Uncontrolled, Parallel Assignment, Safety/Efficacy Study	A Randomized, Phase II, Open Label Study to Compare Twice Daily and Once Daily Potent Antiretroviral Therapy and to Compare Self-Administered Therapy and Therapy Administered Under Direct Observation
ACTG 5095	Treatment, Active Control, Safety/Efficacy Study	Phase III, Randomized, Double-Blind Comparison of Three Protease Inhibitor-Sparing Regimens for the Initial Treatment of HIV Infection
ACTG 5142	Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	A Phase III, Randomized, Open-Label Comparison of Lopinavir/Ritonavir Plus Efavirenz Versus Lopinavir/Ritonavir Plus 2 NRTIs Versus Efavirenz Plus 2 NRTIs as Initial Therapy for HIV-1 Infection
ACTG 5164	Diagnostic, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study	A Phase IV Study of Antiretroviral Therapy for HIV Infected Adults Presenting With Acute Opportunistic Infections: Immediate Versus Deferred Initiation of Antiretroviral Therapy
ACTG 5175	Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study	A Phase IV, Prospective, Randomized, Open-Label Evaluation of the Efficacy of Once-Daily Protease Inhibitor and Once-Daily Non-Nucleoside Reverse Transcriptase Inhibitor-Containing Therapy Combinations for Initial Treatment of HIV-1 Infected Individuals From Resource-Limited Settings (PEARLS) Trial
ACTG 5202	Other, Randomized, Active Control, Parallel Assignment, Safety/Efficacy Study	A Phase IIIB, Randomized Trial of Open-Label Efavirenz or Atazanavir With Ritonavir in Combination With Double-Blind Comparison of Emtricitabine/Tenofovir or Abacavir/Lamivudine in Antiretroviral-Naive Subjects
Abbott M97	Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Parallel Assignment, Safety/Efficacy Study	Phase I/II Study of ABT-378/Ritonavir in Combination With Reverse Transcriptase Inhibitors in Antiretroviral Naive HIV-Infected Patients
Gilead 903	Treatment, Parallel Assignment	A Phase 3, Randomized, Double-Blind, Multicenter Study of the Treatment of Antiretroviral-Naive, HIV-1-Infected Patients Comparing Tenofovir Disoproxil Fumarate Administered in Combination With Lamivudine and Efavirenz Versus Stavudine, Lamivudine, and Efavirenz
Gilead 934	Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Phase 3/Randomized/Open-Label Study of the Treatment of Antiretroviral-Naive HIV-1-Infected Subjects Comparing Tenofovir Disoproxil Fumarate and Emtricitabine in Combination With Efavirenz vs. Combivir (Lamivudine/Zidovudine) and Efavirenz
KLEAN	Treatment, Randomized, Open Label, Dose Comparison, Parallel Assignment, Safety/Efficacy Study	A Phase IIIB, Randomized, Open-Label, Multicenter Study of the Safety and Efficacy of GW433908 (700mg BID) Plus Ritonavir (100mg BID) Versus Lopinavir/Ritonavir (400mg/100mg BID) When Administered in Combination With the Abacavir/Lamivudine (600mg/300mg) Fixed-Dose Combination Tablet QD in Antiretroviral-Naive HIV-1 Infected Adults Over 48 Weeks