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Recruitment in HIV/AIDS treatment naïve clinical trials in the HAART era - influence of gender, sexual orientation and race

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Abstract

Background—In the United States, women, racial/ethnic minorities and persons who acquire HIV infection through heterosexual intercourse represent an increasing proportion of HIV infected persons, yet are frequently underrepresented in clinical trials. We assessed the demographic predictors of trial participation in antiretroviral naïve patients.

Methods—Patients were characterized as trial participants if highly-active antiretroviral therapy (HAART) was initiated within a clinical trial. Prevalence ratios (PR) were obtained using binomial regression.

Results—Between 1996–2006, 30% of 738 treatment naïve patients initiated HAART in a clinical trial. Trial participation rates for MSM, heterosexual men, and women were respectively 36.5%, 29.6% and 24.3%. After adjustment for other factors, heterosexual men appeared less likely to participate in trials compared to MSM (PR: 0.79, 95%CI 0.57, 1.11) while women were as likely to participate as MSM (PR 0.97, 95%CI 0.68, 1.39). The participation rate in blacks (25.9%) was lower compared to non-blacks (37.5%) (adjusted PR 0.80, 95%CI 0.60, 1.06).

Conclusions—In our clinical setting gender did not appear to impact participation in HIV treatment trials but blacks were slightly less likely to participate in these trials. Considering the substantial proportion of HIV patients who are black, future trials need to consider strategies to incorporate underrepresented populations.

Keywords

HIV infection; clinical trials; highly active antiretroviral therapy; gender; sexual orientation; race

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.

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Treatment guidelines are based on treatment trials data but participants in these trials may 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) has changed. In 2006 blacks made up 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 diagnosis 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[4, 5].

Most studies evaluating participation in HIV/AIDS clinical trials are limited as they were conducted very early in the HIV epidemic, prior to the widespread use of HAART and are therefore unable to address these demographic changes[6–11]. Furthermore, these studies had conflicting results with some studies reporting women were not underrepresented in clinical trials, others disagreeing, and still others unable to address this issue[7–9, 11]. 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[6–11]. A recent study observed that women were more likely than men to participate in HIV treatment trials only when stratifying by risk for HIV transmission thus excluding MSM a high proportion of the study population[12]. Answering specific questions in HIV infected women and underrepresented minorities may require trials that actually enrich for participation of these groups. Nonetheless, 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 in National Institutes of Health (NIH) and Food and Drug Administration guidelines[13–15].

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 with over one third of the cohort being women and close to two thirds African American. The UCHCC provided us with an opportunity to examine the influence of demographics on participation in HIV treatment trials.

Methods

Study design

We conducted a cross sectional study of baseline demographic and behavioral, access to care, and clinical characteristics for trial and non-trial participants using the UNC CFAR HIV/AIDS Clinical Cohort. This cohort comprising HIV positive persons (≥ 18 years) who receive health care at the UNC Hospital Infectious Disease (ID) clinic has been described previously[16, 17]. Over 95% of the UNC ID clinic population has consented to participate in the UCHCC. Patients who decline participation in the UCHCC do not differ significantly from those who participate. 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/bisexual) were primary and mutually exclusive 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/MSM) to clarify interpretation of coefficients in the multivariable regression. Race/ethnicity was categorized as black or non black and this category included White, Hispanic, Native American and other races. Race/ethnicity and sexual orientation were self reported and based on subject's characterization of personal self-identity.

Additional variables included Centers for Disease Control and Prevention (CDC) categorization of AIDS[18] (excludes subjects with a CD4 <200 cells/uL if they had no other AIDS defining illness) insurance status (Medicaid/Medicare, none and private/other), distance traveled from home to the ID clinic, injection drug use (IDU) as a risk for HIV acquisition and time from HIV diagnosis to HAART initiation. IDU was 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, which was 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' values were categorized as normal or abnormal.

Statistical Analyses

Descriptive statistics (proportions, mean, median, range, standard deviation) were generated for all variables considered in the analysis. Visual summaries 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 considered as the two predictors of interest for this analysis. Additional sub-group analysis was not conducted due to small sample sizes. All other variables listed under variable specification were considered as possible confounding factors and included in the full model.

To estimate adjusted prevalence ratios, we fit binomial models each with a poisson distribution and robust variance estimator[19–22]. Note that the poisson distribution was used to allow for convergence of the multivariate binomial models[22]. Interaction between each primary predictor and each covariate was assessed with a likelihood ratio test (LRT) of a product interaction term. A LRT p-value < 0.1 was considered evidence of interaction..

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[23] 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[23–25]. Similar to the complete case analysis, a binomial regression model with a poisson distribution and a 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[26].

Results

Population Characteristics

Between1996–2006, 738 treatment naïve persons initiated HAART. One-third (n=224) of patients initiated and received HAART by participating in 13 different HIV treatment trials. Nine trials were sponsored by the ACTG and four by pharmaceutical companies (Table 1). The mean age of patients 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 2). 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 participation rates for MSM, heterosexual men, and women were respectively 36.5%, 29.6% and 24.3% and these rates differed significantly (p=0.02). In bivariable analysis compared to MSM, heterosexual men (PR 0.81 95%CI 0.63, 1.04) and women (PR 0.67 95%CI 0.50, 0.88) were less likely to enroll in HIV treatment trials. After adjustment heterosexual men were slightly less likely (PR 0.79, 95% CI 0.57, 1.11) and women were no less likely (PR 0.97, 95%CI 0.68, 1.39) to enter these trials than MSM (Table 3).

To evaluate which variables were responsible for the substantial change in the adjusted prevalence ratio comparing women to MSM, we eliminated variables one at a time from the multivariable model and found that insurance status and months from HIV diagnosis to

HAART initiation accounted for most of the change. Without adjusting for months from HIV diagnosis to HAART initiation women were 14% less likely to participate in trials (PR 0.86 95% CI 0.62, 1.18). Similarly without adjusting for insurance status women were 15% less likely to participate in these trials (PR 0.85 95% CI 0.60, 1.19).

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 patients only 26% of them enrolled in treatment trials. In bivariable analysis blacks compared to non-blacks were significantly less likely to participate in treatment trials (PR 0.69, 95%CI 0.56, 0.86). After adjustment, blacks remained slightly less likely to participate in treatment trials than non blacks (PR 0.80, 95% CI 0.60, 1.06) (Table 3).

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 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.

Discussion

We observed a high rate of participation in HIV treatment trials in this cohort. In multivariable analysis compared to MSM, heterosexual men were less likely while women were as likely to participate in HIV treatment trials. Blacks were slightly less likely to participate in these trials when compared to non-blacks.

Almost one-third of treatment naïve persons received HAART through participating in a treatment trial. Previous studies using the HIV cost and services utilization data and the HIV/AIDS surveillance project data reported lower participation rates of 14% and 17% respectively[7, 12]. Participation in HIV research is reportedly influenced by concern about receiving placebo, lack of information about research, and travel or transport obstacles[27].. In terms of lack of information we have a dedicated research screener in the ID clinic whose role is to provide information about clinical trials to patients and a social worker who assists with transportation issues. All the clinical trials included in this analysis involved active antiretrovirals; placebos were only used for the purpose of blinding in combination with active treatments. Our success in recruiting patients into clinical trials may partly be related to the ability of our research site to address these factors and other sites wishing to increase trial participation might consider and address similar factors.

In our cohort women were less likely than MSM to participate in clinical trials. However, after adjusting for other factors we found no difference in participation rates between women and MSM a finding supported by other studies [7, 9, 12]. We found that women's participation in clinical trials was particularly influenced by insurance status and months from HIV diagnosis to HAART initiation. Although having no or sub-optimal health insurance may influence trial participation there are multiple other reasons for trial participation as evidenced by the fact that a significant proportion of subjects with health insurance participated in these trials. 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[28, 29]. Furthermore, one study reported that in North Carolina women comprised 47% of all HIV infected Medicaid beneficiaries[30]. Having health insurance likely provides women with access to treatment, care and other health benefits and may limit their need to participate in clinical trials. Insurance status could also be a marker for unmeasured variables, such as socio-economic stability or education level, which could potentially influence decisions about trial participation.

Several reasons might explain why months from HIV diagnosis to treatment appeared to influence women's participation in trials. In general, untreated HIV infected women have an approximately 0.2 log lower viral load than men[31]. This difference was also observed in our cohort. As our study encompasses 1996–2006 during which the US Department of Health and Human Services guidelines indicated that both CD4 cell count and HIV RNA should be used to guide therapy decisions especially for asymptomatic persons this may have been partly responsible for delay in women initiating HAART. Reportedly, women may also delay entry into care by more than three months after receiving an HIV diagnosis[32]. 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.

We sought to distinguish the effect of gender from that of sexual orientation on trial participation. Previous studies included gender and sexual orientation (or risk group) in the same model and thus could not achieve this distinction [6, 7, 9]. Compared with MSM participation rates for heterosexual men though slightly lower were not significantly different. Prior reports of lower representations by heterosexuals may have simply been a reflection that this group included mostly women. Our results suggest that, in our setting, both gender and sexual orientation do not significantly influence participation in HIV treatment trials.

Although, blacks appeared less likely than non blacks to participate in trials, the strength of this association diminished when accounting for other variables and the absolute difference (8%) was even smaller (data not shown). These results are similar to other HIV related studies suggesting blacks were less likely than either Caucasians or other ethnicities to enter clinical trials[6–8, 11]. It is however noteworthy that the difference observed was not substantial and could partially be explained by adjustment for other variables. Possibly additional adjustment for unmeasured variables, might have further diminished this observed difference. Historically blacks have been less likely to participate in clinical trials due to distrust in medical research, lack of confidence in providers and to the belief that the informed consent process provides patients with little protection[33, 34].

We feel that our results reflect a trend supporting decrease in disparities for black enrolment into trials. 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, 35]. Provider endorsement of trials, provision of clinical trial information by providers and trust in providers is associated with trial participation[7, 36–38].

We did not examine trends in participation over time and changes in demographics by calendar year. Our results were likely less influenced by demographic changes in trial participation over time but instead may reflect the availability or lack thereof of a treatment

naïve trial and the type of therapy being offered in the trial. Unfortunately, we do not have precise data on the availability of a clinical trial when a treatment naïve person eligible for ART presented for care. We would like to note that other studies that have looked at participation in clinical trials have likely been unable to address this issue and have therefore broadly categorized participation as self reported participation in any medication trial or study[7,12]. We submit that our study has additional merit as we were able to refine our study by 1) only identifying persons who enrolled in treatment naive studies and 2) independently confirming participation without reliance on self report. As with study availability, clinician influence both positive and negative is likely to impact any study of this type. Literacy and education level are potential barriers to trial participation. To address this we ensure that all consent forms are written at a 6th–8th grade level of understanding. Moreover, if literacy is noted as a problem, there is a provision in all our studies to have the entire informed consent read to the subject.

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[39–41]. The comparable rates 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[12, 34]. 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. Finally, we recognize that several unmeasured variables including work pressures, child bearing wishes and vertical transmission issues could have influenced our study results.

In summary, in the clinical setting studied we achieved high rates of participation in HIV treatment trials. Gender did not appear to impact participation in HIV treatment trials but blacks were slightly less likely to participate in these trials. We hypothesize, that in part our results might be explained by guidelines and policies adopted both in the US and other countries to correct imbalance in trial participation[15, 42]. Considering the substantial proportion of HIV-patients who are black, future trials need to consider strategies to further incorporate underrepresented populations. Further investigation into the role of insurance in trial participation is needed. A continued exploration of barriers to clinical trial participation must consider other factors including trust issues, awareness and information about clinical trials and trial characteristics.

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Table 1

Description of Clinical Trials included in the study

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	

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Table 2

Sample Characteristics stratified by trial participation

	Total		Non Trial		Trial	
	N (738)	%	N (514)	%	N (224)	%
Demographic and Behavioral Characteristics						
Age (years)						
<40	429	58.1	300	58.4	129	57.6
Gender/sexual preference						
MSM[1]/Bisexual men	252	34.2	160	31.1	92	41.1*
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**
Access to Care Characteristics						
Insurance Status						
Public[2]	191	25.9	162	31.5	29	13.0**
None	276	37.4	176	34.2	100	44.6
Private/Other	258	35.0	170	33.1	88	39.3
Distance to ID[3] clinic (miles)						
<50	182	24.7	123	23.9	59	36.3
>50	527	71.4	390	75.8	137	61.2
Clinical Characteristics						
CD4 cells/uL						
≤200	321	43.5	200	38.9	121	54*
>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)
Diagnosis to treatment (months)						
≤3	250	33.9	195	37.9	55	24.6
>3	393	53.3	289	56.2	104	46.4

	Total		Non Trial		Trial	
	N (738)	%	N (514)	%	N (224)	%
Other Laboratory Parameters						
ANC[4] (10^9/L)						
Normal	348	47.2	223	43.4	125	55.8
Abnormal	221	30	130	25.3	91	40.6
Hemoglobin (g/dL)						
Normal	258	34.9	152	29.6	106	47.3
Abnormal	311	42.1	202	39.3	109	48.7
Creatinine (mg/dL)						
Normal	685	93.1	469	91.3	216	96.4*
Abnormal	51	6.9	44	8.6	7	3.1
[5] ALT U/L						
Normal	451	61.1	276	53.7	175	78.1
Abnormal	100	13.6	61	11.9	39	17.4

* p <0.05 comparing trial to non trial participants;

** p≤0.001 comparing trial to non trial participants

[1] MSM=Men who have sex with Men;

[2] Public insurance= Medicaid/Medicare;

[3] ID= University of North Carolina Infectious Disease;

[4] ANC=Absolute Neutrophil Count

[5] ALT=Alanine aminotransferase

Table 3

Unadjusted and Adjusted Prevalence Ratios (PR) for Gender/Sexual Preference and Race/ethnicity

	Unadjusted PR	95% CI*	Adjusted PR	95% CI*	Imputed PR	95% CI*
Gender/Sexual Preference*						
MSM[1]/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**						
Non Black[2]	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

*CI = Confidence Intervals

[1]MSM= Men who have sex with men

[2]Non Black= White, Native American, Hispanic 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