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Comparative Efficacy versus Effectiveness of Initial Antiretroviral Therapy in Clinical Trials versus Routine Care

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Background. The applicability of clinical trial findings (efficacy) to the routine care setting (effectiveness) may be limited because of study eligibility criteria and volunteer bias. Although well-chronicled in many conditions, the efficacy versus effectiveness of antiretroviral therapy (ART) remains understudied.

Methods. A retrospective study of the University of Alabama at Birmingham 1917 Clinic Cohort evaluated ART-naive patients who started ART from 1 January 2000 through 31 December 2006. Patients received ART through clinical trials or routine care. Multivariable logistic and linear regression models were fit to evaluate factors associated with virological failure (virological failure was defined as a viral load >50 copies/mL) and change from baseline $CD4^+$ cell count 6 and 12 months after ART initiation. Sensitivity analyses evaluated the impact of missing data on outcomes.

Results. Among 570 patients starting ART during the study period, 121 (21%) enrolled in clinical trials, and 449 (79%) received ART via routine care. ART receipt through routine care was not associated with viral failure at either 6 months (odds ratio [OR], 1.00; 95% confidence interval [CI], 0.54–1.86) or 12 months (OR, 1.56; 95% CI, 0.80–3.05) in primary analyses. No statistically significant differences in $CD4^+$ cell count responses at 6 and 12 months were observed.

Conclusions. Although marked differences in efficacy versus effectiveness have been observed in the therapeutic outcomes of other conditions, our analyses found no evidence of such divergence among our patients who initiated antiretroviral therapy for human immunodeficiency virus infection.

Randomized clinical trials (RCTs) are the cornerstone of level I evidence-based medicine treatment recommendations and provide the highest level of evidence [1]. However, some RCT-tested interventions have not performed as well when implemented in routine care settings [2–5]. Factors such as selection bias introduced by trial eligibility criteria and volunteer bias among participants choosing to participate in research studies have been linked to this discrepancy [2, 4–10]. Selected patient samples may show improved treatment outcomes in trials (efficacy) when compared with the more heterogeneous population treated through routine care (effectiveness), raising concerns about the applicability of RCT findings to routine care settings.

Efforts to characterize differential efficacy versus effectiveness of treatments have been undertaken in many medical conditions [2, 4–6, 9, 10], yet this relationship regarding antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection and AIDS has been notably understudied, particularly in the contemporary ART era [11]. Although numerous studies have separately evaluated either the efficacy or the effectiveness of initial ART regimens when used in RCTs and routine care, respectively, relatively few have studied the comparative effectiveness of treatment modality (RCT vs routine care) on outcomes among patients starting ART in the same clinical setting. Therefore, we conducted a retrospective study to evaluate the impact of

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receiving initial ART through a clinical trial versus through routine care on short-term viral load and CD4$^+$ cell outcomes among ART-naive individuals initiating therapy. Because treatment-naive ART studies are commonly available, are ingrained in the culture of HIV care at many treatment centers, and provide a means to access medications and laboratories at little to no cost to patients, we hypothesized that volunteer bias would be less apparent in an HIV-infected cohort, relative to cohorts of patients with other diseases. Accordingly, we posited that the sociodemographic composition of those treated through clinical trials would be reflective of the larger clinic population and mirror the characteristics of those patients who received ART through routine care. We further hypothesized that similar virological and CD4$^+$ cell outcomes would be observed between patients treated in clinical trials and those treated through routine care because of the similarities in the patient populations.

METHODS

Sample and procedure. Since 1988, the University of Alabama at Birmingham (UAB) 1917 HIV/AIDS Clinic (1917 Clinic) has provided HIV care for >6000 HIV-infected individuals. The UAB 1917 HIV/AIDS Clinic Cohort Database Project (UAB 1917 Clinic Cohort), which was recently recognized for excellence in information integrity [12], is a 100% quality controlled, institutional review board–approved prospective clinical cohort study that includes detailed sociodemographic, psychosocial, and clinical information from HIV-infected patients receiving primary HIV and subspecialty care at the clinic [13]. The 1917 Clinic uses a locally programmed electronic medical record (EMR) that imports laboratory values from the central UAB laboratory, requires electronic prescriptions for all medications, and contains detailed encounter notes. Both the UAB 1917 Clinic Cohort and local EMR have been described in detail elsewhere [14–16].

A dedicated clinical trials program and staff have been part of the 1917 Clinic since its inception. At our center, RCTs for antiretroviral-naive patients are frequently available and open for enrollment. Prior to study enrollment, providers ascertain patients' willingness to learn more about clinical trial participation and refer interested patients to clinical trial study nurses who screen patients and begin the informed consent process. Once enrolled in a research study, patients receive additional follow-up from study personnel (nurses, mid-level health care providers, and physicians) as determined by specific study protocols, in addition to regular outpatient care at the clinic. Patients who initiate ART through routine care meet with a clinic pharmacist to discuss their regimen. Otherwise, no specific treatment protocol is in place, and all clinic and laboratory follow-up is at the discretion of the primary health care provider (a nurse practitioner or infectious diseases fellow) and attending physician.

Here, we present a retrospective study of the UAB 1917 Clinic Cohort that evaluates antiretroviral-naive patients who initiated ART from 1 January 2000 through 31 December 2006. Patients were categorized into 2 groups: those who initiated ART through a clinical trial, and those who started treatment through routine care. A comparison of viral load and CD4$^+$ cell outcomes between these groups, efficacy in RCTs versus effectiveness in routine care, was the primary focus of this study. Patients whose initial ART regimen lasted longer than 14 days were included.

Independent variables previously reported [17, 18] to impact virological outcomes were chosen a priori and included sociodemographic characteristics (age, sex, race, HIV risk factor, and health insurance status), psychosocial information (history of affective mental disorder, defined as depression, anxiety, or bipolar disease; alcohol abuse; and substance abuse), and baseline laboratory values (CD4$^+$ cell count and plasma HIV load, with viral load expressed in HIV RNA copies/mL). Outcome measures included plasma HIV virological failure (defined as a viral load >50 copies/mL) and change from baseline CD4$^+$ cell count following ART initiation at 6-month and 12-month time points (measure closest to time point in a $\pm$90-day window was used).

Statistical analyses. Study variables were evaluated using descriptive statistics to determine the distributions of variables among patients who were treated through routine care versus among those who received ART through a clinical trial. Bivariate analyses were used to identify independent variables associated with clinical trial enrollment. Student's t tests and χ^2 tests were applied for continuous and categorical variables, respectively. Univariate and multivariable logistic regression models were fit to determine factors associated with virological failure at 6 and 12 months after ART initiation. Univariate and multivariable linear regression models evaluated factors associated with change from baseline CD4$^+$ cell count value after 6 months and 12 months of therapy. Primary analyses included only patients with available laboratory measures at the 6-month and 12-month time points, and those with missing data were excluded analytically (ie, missing equals missing).

To investigate the potential impact of missing data on study outcomes, sensitivity analyses were conducted for viral load and CD4$^+$ cell count end points at both 6 and 12 months. For those with missing viral load values, single imputation methods were employed to assign outcomes [19]. Missing viral load outcomes were based upon predicted probabilities of virological failure derived from a multivariable model that included patients with available measures. A cut-point for assignment of virological failure was selected erring on the side of misclassification of patients with missing viral load data as having experienced treatment failure (>50 copies/mL). For missing

Table 1. Treatment-Naive Trials and Number of Patients Enrolled at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic from 1 January 2000 through 31 December 2006

Study name	Study arm(s)	No. of patients
ACTG 5202	1. ABC-3TC + EFV 2. ABC-3TC + ATV + RTV 3. FTC-TDF + EFV 4. FTC-TDF + ATV + RTV	54
ACTG 5142	1. LPVr + EFV 2. LPVr + 3TC + (ZDV or TDF or d4T XR) 3. EFV + 3TC + (ZDV or TDF or d4T XR)	20
ACTG 5095	1. ABC-3TC-ZDV + EFV 2. ABC-3TC-ZDV 3. 3TC-ZDV + EFV	11
Pfizer A4001026 "MERIT"	1. UK-427,857 (MVC) daily + ZDV-3TC 2. UK-427,857 (MVC) bid + ZDV-3TC 3. EFV + ZDV-3TC	11
AIEDRP AI-08–002 "ERADICATE"	1. d4T bid + 3TC bid + IDV q12h + NFV bid	8
Roche NR15720	1. 2 NRTIs per physician + SQV + RTV 2. 2 NRTIs per physician + EFV	6
Merck 021–00 "STARTMRK"	1. TDF-FTC + EFV 2. TDF-FTC + Mk-0518 (RAL)	4
BI-IATEC 2NN	1. 3TC + d4T + NVP (200 mg bid) 2. 3TC + d4T + NVP (400 mg daily) 3. 3TC + d4T + EFV (600 mg daily) 4. 3TC + d4T + NVP (400 mg daily) + EFV (800 daily)	2
ACTG 5146	1. All drugs at standard doses 2. PI dose adjusted per study + standard of care	1
AIEDRP AIN501	1. ABC-3TC-ZDV + LPVr 2. ABC-3TC-ZDV + LPVr + cyclosporine for the first 28 days of treatment	1
Glaxo-Welcome ESS40002	1. 3TC + d4T + NFV 2. 3TC + d4T + NFV + ZDV-3TC 3. 3TC + d4T + ABC + ZDV-3TC	1
Merck 094 "CRX463"	1. IDV bid + RTV bid + 3TC bid + d4T bid	1
Triangle FTC-301	1. FTC + (ddI or ddI-EC) + EFV 2. d4T + (ddI or ddI-EC) + EFV	1

NOTE. 2NN, 2 nonnucleoside reverse transcriptase inhibitors; 3TC, lamivudine; ABC, abacavir; ACTG, AIDS Clinical Trials Group; AIEDRP, Acute Infection and Early Disease Research Program; ATV, atazanavir; BI, Boehringer Ingelheim; bid, twice daily; d4T, stavudine; d4T XR, stavudine extended-release; ddI, didanosine; ddI-EC, time-release didanosine; EFV, efavirenz; FTC, emtricitabine; IATEC, International Antiviral Therapy Evaluation Center; IDV, indinavir; LPV/r, ritonavir-boosted lopinavir; MVC, maraviroc; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protease inhibitor; q12h, every 12 h; RAL, raltegravir; RTV, ritonavir; SQV, saquinavir; TDF, tenofovir; ZDV, zidovudine.

$CD4^+$ cell count results, the last value recorded was carried forward for sensitivity analyses. All statistical analyses were performed using SAS, version 9.1.3 (SAS Institute), and statistical significance was defined as $P < .05$.

RESULTS

Among 570 ART-naive patients who initiated therapy from 1 January 2000 through 31 December 2006, 21% ($n = 121$) were treated through a clinical trial, and 79% ($n = 449$) were treated through routine care. Patients participated in 13 clinical trials during the study period, including 4 Adult AIDS Clinical Trial Group (ACTG) studies, which enrolled 86 (71%) of the 121 patients treated through RCTs (Table 1). Overall, most patients were between the ages of 31 and 49 years (66% of patients), male (77%), black (54%), had no health insurance (37%), and were men who have sex with men (MSM; 51%). Baseline $CD4^+$ cell count values were <200 cells/mm^3 in 56% of patients, whereas a baseline viral load <100,000 copies/mL was found in 63% of individuals. Patient histories included diagnoses of affective mental health disorders in 47%, substance abuse in 23%, alcohol abuse in 16%, and opportunistic infections in 31%. The most commonly used third drug was a nonnucleoside reverse-transcriptase inhibitor (NNRTI; 66%) (Table 2).

In bivariate analysis, clinical trial enrollment was more common among patients with higher baseline $CD4^+$ cell count values (61% of patients in clinical trials vs 40% of patients receiving routine care had $CD4^+$ cell counts >200 cells/mm^3). Black patients were significantly less likely than others to par-

Table 2. Baseline Characteristics and Bivariate Analysis of Factors Associated with Clinical Trial Participation among 570 Antiretroviral Therapy–Naive Patients Who Initiated Therapy at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic from 1 January 2000 through 31 December 2006

Characteristic	All patients (n = 570)	Routine care group (n = 449)	Clinical trial group (n = 121)	P[a]
Age				.21
⩽30 Years	131 (23)	103 (23)	28 (23)	
31–49 Years	376 (66)	291 (65)	85 (70)	
⩾50 Years	63 (11)	55 (12)	8 (7)	
Sex				.38
Male	440 (77)	343 (76)	97 (80)	
Female	106 (23)	106 (24)	24 (20)	
Race				<.001
White	263 (46)	185 (41)	78 (64)	
Black	307 (54)	264 (59)	43 (36)	
HIV infection risk factor				.04
Heterosexual sex	231 (41)	194 (44)	37 (31)	
MSM	289 (51)	216 (49)	73 (61)	
IDU	42 (8)	33 (7)	9 (8)	
Baseline CD4$^+$ cell count				<.001
<50 cells/mm^3	172 (31)	148 (34)	24 (20)	
50–199 cells/mm^3	141 (25)	117 (27)	24 (20)	
200–350 cells/mm^3	154 (27)	111 (25)	43 (35)	
>350 cells/mm^3	93 (17)	63 (14)	30 (25)	
Baseline viral load				.24
<100,000 plasma HIV RNA copies/mL	353 (63)	272 (62)	81 (68)	
⩾100,000 plasma HIV RNA copies/mL	203 (37)	165 (38)	38 (32)	
Health insurance				.11
Private	280 (49)	216 (48)	64 (53)	
Public	81 (14)	71 (16)	10 (8)	
Uninsured	209 (37)	162 (36)	47 (39)	
Affective mental health disorder				.08
No	304 (53)	248 (55)	56 (46)	
Yes	266 (47)	201 (45)	65 (54)	
Substance abuse				.56
No	441 (77)	345 (77)	96 (79)	
Yes	129 (23)	104 (23)	25 (21)	
Alcohol abuse				.38
No	480 (84)	375 (84)	105 (87)	
Yes	90 (16)	74 (16)	16 (13)	
Virological failure[b]				
At 6 months	156 (33)	123 (34)	33 (29)	.31
At 12 months	137 (32)	108 (33)	29 (27)	.20
Change in CD4$^+$ cell count, mean cells/mm^3 (±SD)				
At 6 months	120 ± 121	115 ± 123	137 ± 115	.39
At 12 months	175 ± 153	171 ± 158	187 ± 139	.11
Opportunistic infection				<.001
Yes	177 (31)	157 (35)	20 (17)	
No	393 (69)	292 (65)	101 (83)	
Third drug				<.001
NRTI	50 (9)	50 (11)	0 (0)	
PI	46 (8)	36 (8)	10 (8)	
PIr	76 (13)	33 (7)	43 (36)	
NNRTI	379 (66)	330 (74)	49 (41)	
Unknown/other	19 (3)	0 (0)	19 (16)	

NOTE. Data are no. (%) of patients, unless otherwise indicated. HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PIr, ritonavir-boosted protease inhibitor; Unknown/other, currently blinded, raltegravir, or maraviroc.

[a] By χ^2 and Student's t tests.

[b] Virological failure was defined as a viral load >50 plasma HIV RNA copies/mL.

Table 3. Factors Associated with 6-Month and 12-Month Virological Failure following Antiretroviral Therapy (ART) Initiation among ART-Naive Patients Who Initiated Therapy at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic from 1 January 2000 through 31 December 2006 with an Available 6-Month Viral Load Measure

	Virological failure at 6 months (n = 479)		Virological failure at 12 months (n = 431)	
Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Clinical trial				
No vs Yes	1.27 (0.80–2.01)	1.00 (0.54–1.86)	1.37 (0.84–2.22)	1.56 (0.80–3.05)
Age group, years				
⩽30 vs ⩾50	1.93 (0.96–3.87)	1.98 (0.91–4.32)	1.14 (0.57–2.31)	0.78 (0.35–1.73)
31–49 vs ⩾50	0.92 (0.49–1.74)	0.92 (0.46–1.86)	0.74 (0.40–1.39)	0.61 (0.30–1.22)
Sex				
Female vs Male	0.83 (0.52–1.34)	0.81 (0.41–1.60)	1.56 (0.98–2.50)	1.09 (0.54–2.18)
Race				
Black vs white	1.58 (1.07–2.32)	1.73 (1.07–2.82)	1.86 (1.23–2.81)	2.11 (1.27–3.53)
HIV infection risk factor				
Heterosexual sex vs IDU	0.53 (0.25–1.12)	0.29 (0.11–0.81)	0.97 (0.42–2.25)	0.91 (0.31–2.70)
MSM vs IDU	0.68 (0.33–1.39)	0.46 (0.17–1.21)	0.74 (0.33–1.69)	0.95 (0.33–2.74)
Baseline $CD4^+$ cell count, cells/mm^3				
<50 vs >350	1.80 (1.01–3.22)	1.53 (0.78–3.01)	0.99 (0.55–1.81)	0.73 (0.36–1.46)
50–199 vs >350	1.42 (0.77–2.62)	1.42 (0.71–2.83)	0.98 (0.52–1.83)	0.85 (0.42–1.71)
200–350 vs >350	0.75 (0.40–1.43)	0.88 (0.44–1.76)	0.56 (0.29–1.08)	0.61 (0.30–1.23)
Baseline viral load, plasma HIV copies/mL				
⩾100,000 vs <100,000	2.55 (1.71–3.79)	2.51 (1.58–4.01)	1.74 (1.15–2.64)	1.65 (1.01–2.71)
Third drug				
NRTI vs NNRTI	1.21 (0.61–2.42)	2.14 (0.97–4.71)	0.84 (0.38–1.85)	0.91 (0.38–2.17)
PI vs NNRTI	2.01 (1.00–4.04)	1.97 (0.89–4.34)	4.39 (2.06–9.33)	5.24 (2.30–11.92)
PIr vs NNRTI	1.22 (0.71–2.10)	1.29 (0.65–2.54)	1.39 (0.77–2.50)	1.80 (0.87–3.72)
Unknown/other vs NNRTI	0.48 (0.14–1.71)	0.49 (0.11–2.13)	0.90 (0.31–2.57)	1.50 (0.43–5.22)
Health insurance:				
Uninsured vs private	1.39 (0.91–2.13)	1.21 (0.75–1.94)	1.36 (0.87–2.13)	1.19 (0.72–1.95)
Public vs private	2.37 (1.36–4.13)	2.06 (1.07–3.95)	1.94 (1.07–3.52)	1.29 (0.66–2.55)
Affective mental health disorder				
Yes vs no	1.02 (0.70–1.49)	1.13 (0.72–1.75)	1.11 (0.74–1.66)	1.09 (0.69–1.73)
Substance abuse				
Yes vs no	1.07 (0.67–1.70)	0.82 (0.42–1.61)	1.26 (0.78–2.05)	1.56 (0.81–2.99)
Alcohol abuse				
Yes vs no	0.63 (0.36–1.11)	0.58 (0.30–1.12)	0.55 (0.30–1.01)	0.62 (0.31–1.24)

NOTE. Virological failure was defined as a viral load >50 plasma HIV RNA copies/mL. Univariate and multivariable logistic regression was performed using a "missing equals missing" approach. CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PIr, ritonavir-boosted protease inhibitor; Unknown/other, currently blinded, raltegravir, or maraviroc.

ticipate in clinical trials ($P < .001$). HIV risk factor impacted study enrollment, as well; among clinical trial patients, 61% were MSM and 31% were heterosexual, whereas among routine care patients, 49% were MSM and 44% were heterosexual ($P = .04$). However, patient age, sex, baseline viral load value, insurance status, presence of an affective mental health disorder, substance abuse and alcohol abuse were not associated with clinical trial enrollment (Table 2).

Among patients with available viral load measures at 6 months, 66% of those treated through routine care and 71% of those treated through clinical trials achieved virological suppression (viral load <50 copies/mL); at 12 months, 67% and 73% achieved virological suppression, respectively. In primary multivariable analysis (missing equals missing; Table 3), a statistically significant association between method of ART receipt (routine care vs clinical trial) and virological failure was not observed at either time point (routine care vs clinical trial [referent] 6-month OR, 1.00 [95% CI, 0.54–1.86]; 12-month OR, 1.56 [95% CI, 0.80–3.05]). Six-month and 12-month virological failure were associated with black race (6-month OR, 1.73 [95% CI, 1.07–2.82]; 12-month OR, 2.11 [95% CI, 1.27–3.53]) and baseline viral load >100,000 copies/mL (6-month OR, 2.51 [95% CI, 1.58–4.01]; 12-month OR, 1.65 [95% CI, 1.01–2.71]). Compared with patients who had private health insurance, those who had public health insurance had higher odds of virological failure at 6 months (OR, 2.06; 95% CI, 1.07–3.95),

Table 4. Sensitivity Analysis of Factors Associated with 6-Month and 12-Month Virological Failure following Antiretroviral Therapy (ART) Initiation among ART-Naive Patients Who Initiated Therapy at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic from 1 January 2000 through 31 December 2006 (Imputation Approach)

Variable	Adjusted OR (95% CI)	
	Virological failure at 6 months (n = 570)	Virological failure at 12 months (n = 570)
Clinical trial		
No vs yes	1.22 (0.68–2.19)	1.77 (0.98–3.23)
Age, years		
⩽30 vs ⩾50	2.00 (0.98–4.06)	0.87 (0.42–1.80)
31–49 vs ⩾50	0.79 (0.42–1.48)	0.74 (0.39–1.41)
Sex		
Female vs male	0.87 (0.48–1.56)	0.87 (0.49–1.53)
Race		
Black vs white	2.23 (1.44–3.46)	4.94 (3.13–7.80)
HIV infection risk factor		
Heterosexual sex vs IDU	0.29 (0.12–0.70)	0.86 (0.35–2.10)
MSM vs IDU	0.47 (0.20–1.09)	0.84 (0.35–2.03)
Baseline $CD4^+$ cell count, cells/mm^3:		
<50 vs >350	1.48 (0.79–2.77)	0.70 (0.38–1.31)
50–199 vs >350	1.41 (0.75–2.66)	0.89 (0.48–1.67)
200–350 vs >350	1.14 (0.62–2.12)	0.73 (0.40–1.34)
Baseline viral load, plasma HIV RNA copies/mL		
⩾100,000 vs <100,000	2.58 (1.68–3.97)	1.33 (0.86–2.06)
Third drug		
NRTI vs NNRTI	1.76 (0.88–3.52)	0.57 (0.27–1.18)
PI vs NNRTI	1.65 (0.81–3.37)	7.66 (3.49–16.81)
PIr vs NNRTI	1.01 (0.53–1.92)	1.42 (0.74–2.70)
Unknown/other vs NNRTI	0.75 (0.21–2.62)	1.36 (0.39–4.73)
Health insurance		
Uninsured vs private	1.19 (0.78–1.82)	1.11 (0.72–1.71)
Public vs private	1.89 (1.05–3.39)	1.59 (0.88–2.86)
Affective mental health disorder		
Yes vs no	0.89 (0.59–1.33)	0.84 (0.56–1.26)
Substance abuse		
Yes vs no	1.09 (0.62–1.90)	1.74 (0.99–3.06)
Alcohol abuse		
Yes vs no	0.56 (0.31–1.00)	0.71 (0.40–1.26)

NOTE. Virological failure was defined as a viral load >50 plasma HIV RNA copies/mL. Univariate and multivariable logistic regression was performed using imputation for missing outcomes. CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PIr, ritonavir-boosted protease inhibitor; Unknown/other, currently blinded, raltegravir, or maraviroc.

but not at 12 months (OR, 1.29; 95% CI, 0.66–2.55). When compared with NNRTIs, only unboosted protease inhibitors were associated with higher odds of 12-month virological failure (OR, 5.24; 95% CI, 2.30–11.92). No other study variables were significantly associated with 6-month or 12-month virological failure in primary analyses.

Sensitivity analyses that used imputation to assign virological outcomes to patients with missing values were performed (Table 4). In multivariable sensitivity analysis, method of ART receipt (routine care vs clinical trial) was not associated with virological failure at 6 months (OR, 1.22; 95% CI, 0.68–2.19). Although the association was not statistically significant, patients who received ART through routine care had a trend toward increased odds of virological failure at 12 months (OR,

1.77; 95% CI, 0.98–3.23). Additional sensitivity analyses using a missing equals failure approach yielded largely consistent findings, although, relative to the primary sensitivity analyses, slightly higher (and statistically significant) odds of virological failure (OR, 2.10; 95% CI, 1.21–3.66) were observed in the routine care group at 12 months, because that group included a higher proportion of patients with missing values (data not shown).

The increased odds of virological failure associated with black race, as well as with the use of an unboosted protease inhibitor (vs NNRTI) as a third drug, and the lack of statistically significant associations with age, sex, history of mental health disorder, substance abuse, or alcohol abuse observed in primary analyses were consistent in sensitivity analyses (Table 4).

Finally, univariate and multivariable linear regression analyses of factors associated with 6-month and 12-month change from baseline $CD4^+$ cell count value were modeled (missing equals missing; Table 5). Baseline viral load >100,000 copies/mL was associated with a significantly greater increase in $CD4^+$ cell count ($P < .001$ at 6 months; $P = .03$ at 12 months). Twelve months after initiation of ART, no other factors were associated with a difference in $CD4^+$ cell count response. Notably, similar $CD4^+$ cell count responses were observed in patients treated through a clinical trial and those treated through routine care. Sensitivity analyses (with the last value carried forward; Table 6) of $CD4^+$ cell count outcomes yielded findings similar to those of the primary analyses.

DISCUSSION

Among HIV-infected patients who received care at an academic HIV clinic in the Southeastern United States, our primary analysis revealed similar virological suppression (defined as a viral load <50 copies/mL) and $CD4^+$ cell count responses in ART-naive patients who initiated treatment through a clinical trial and those who initiated treatment through routine care. Though the efficacy versus effectiveness relationship has been examined thoroughly in cardiac care [2, 4, 5], substance abuse programs [20], and psychotherapy [9, 10, 21], it has been notably understudied in HIV/AIDS therapy [11]. A comparison of viral load suppression, $CD4^+$ cell responses, and mortality among patients who received the same protease inhibitor regimens through the Danish Protease Inhibitor Study clinical trial and routine care showed that trial participants had better responses to ART than did patients who received routine care [3]. In contrast, we found that 6-month and 12-month virological failure and $CD4^+$ cell count response were not statistically significantly different between patients who received ART through a clinical trial and those who received treatment through routine care in our study (Tables 3 and 5).

This study also sought to characterize factors associated with clinical trial enrollment in an HIV-infected cohort. Consistent with prior findings in other specialties [7, 8, 22, 23] and with earlier studies involving HIV infection [24], we found that black individuals were less likely to participate in clinical trials than were white individuals ($P < .001$; Table 2). Previously identified factors that may contribute to these findings include mistrust of physicians and researchers [22, 24–29], patient fears (eg, being treated as "guinea pigs," being subjected to purposeful infection, or historical precedents such as the Tuskegee syphilis study) [24–26, 28–31], and inequality in requests for research participation among racial/ethnic minorities [23, 26, 31–34]. In addition to underrepresentation in clinical trial participation, racial disparities in viral load outcomes were also observed. Black race was associated with increased odds of virological failure in our population at both 6 and 12 months in primary and sensitivity analyses (Tables 3 and 4). Bivariate comparisons of sociodemographic and clinical characteristics among patients with missing versus available viral load and $CD4^+$ cell count values in both the routine care and clinical trial groups showed a statistically significant increase in the frequency of missing data among black patients who received ART through routine care at both 6 and 12 months (data not shown). It has been proposed that limited access to health care and increased frequency of missed clinic appointments may contribute to the poor clinical outcomes observed among black patients with HIV infection [11, 15, 35, 36]; these factors may also impact the availability of laboratory measures.

We found that individuals with public health insurance were more likely than those with private insurance to experience 6-month virological failure. These findings identify another vulnerable and underserved group at risk for worse health outcomes. Consistent receipt of and adherence to ART among this group with lower socioeconomic status may be complicated by gaps in coverage imposed by public insurance programs [37] and the need to balance the costs of therapy for an initially asymptomatic illness with other economic priorities and competing needs. Health care system reforms that facilitate the acquisition and consistent receipt of therapy in vulnerable populations with limited access to health care are an important prerogative.

Regimen and clinical characteristics associated with virological failure were also identified. Patients with drug regimens that included unboosted protease inhibitors had a higher rate of virological failure, which result is not surprising given the multitude of data that illustrate the poor outcomes associated with use of unboosted protease inhibitors, compared with other ART strategies (Tables 3 and 4) [38–40]. Elevated baseline viral load has also been linked to increased risk of subsequent virological failure [11, 41, 42], which is a finding echoed by our study. With regards to analyses concerning the change from initial $CD4^+$ cell count value, only baseline viral load >100,000 copies/mL was associated with a statistically significant $CD4^+$ cell count change at 12 months (Tables 5 and 6).

Table 5. Factors Associated with 6-Month and 12-Month Change from Baseline CD4⁺ Cell Count following Antiretroviral Therapy (ART) Initiation among ART-Naive Patients Who Initiated Therapy at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic from 1 January 2000 through 31 December 2006

Variable	6-Month change in CD4⁺ cell count, mean cells/mm³ (±SD)	Adjusted *P*[a]	12-Month change in CD4⁺ cell count, mean cells/mm³ (±SD)	Adjusted *P*[a]
Clinical trial		.63		.85
No	114.6 ± 122.8		171.0 ± 158.2	
Yes	136.5 ± 114.6		187.3 ± 139.0	
Age, years		.62		.98
≤30	115.9 ± 108.2		175.8 ± 164.0	
31–49	119.5 ± 129.3		177.3 ± 151.5	
≥50	131.1 ± 94.1		161.9 ± 144.7	
Sex		.57		.15
Female	114.0 ± 122.1		207.6 ± 183.6	
Male	121.6 ± 121.0		165.9 ± 142.5	
Race		.02		.64
Black	100.8 ± 108.5		171.6 ± 158.3	
White	139.3 ± 130.1		178.8 ± 148.8	
HIV infection risk factor		.09		.46
Heterosexual sex	111.7 ± 119.3		191.1 ± 160.1	
IDU	104.8 ± 103.3		164.4 ± 155.1	
MSM	127.4 ± 123.6		165.6 ± 148.4	
Baseline CD4⁺ cell count, cells/mm³		.01		.69
<50	98.2 ± 70.9		174.6 ± 115.0	
50–199	126.1 ± 104.9		170.6 ± 132.2	
200–350	137.9 ± 126.6		179.1 ± 172.3	
>350	122.4 ± 184.2		177.5 ± 208.6	
Baseline viral load, plasma HIV RNA copies/mL		<.001		.03
≥100,000	140.7 ± 133.3		193.3 ± 160.4	
<100,000	107.7 ± 112.4		164.7 ± 149.6	
Third drug		.87		.10
NNRTI	119.0 ± 112.1		166.9 ± 144.7	
NRTI	96.2 ± 150.4		127.6 ± 170.7	
PI	125.9 ± 141.2		225.1 ± 204.0	
PIr	128.1 ± 130.1		208.1 ± 146.6	
Unknown/other	146.9 ± 124.7		188.1 ± 126.2	
Health insurance		.08		.16
Uninsured	110.2 ± 120.1		170.4 ± 146.2	
Public	98.4 ± 100.3		159.3 ± 141.4	
Private	132.6 ± 126.0		182.6 ± 161.3	
Affective mental health disorder		.29		.42
No	120.7 ± 123.1		164.8 ± 153.7	
Yes	119.1 ± 119.4		185.3 ± 152.9	
Substance abuse		.02		.37
No	115.4 ± 117.4		172.5 ± 149.3	
Yes	136.6 ± 133.4		185.2 ± 168.0	
Alcohol abuse		.69		.43
No	118.9 ± 119.4		174.7 ± 154.7	
Yes	125.1 ± 130.7		178.1 ± 147.9	

NOTE. HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PIr, ritonavir-boosted protease inhibitor; SD, standard deviation; Unknown/other, currently blinded, raltegravir, or maraviroc.

[a] Multivariable linear regression; for patients with missing data, a "missing equals missing" approach was used.

Table 6. Sensitivity Analysis of Factors Associated with 6-Month and 12-Month Change from Baseline CD4⁺ Cell Count following Antiretroviral Therapy (ART) Initiation among ART-Naive Patients Who Initiated Therapy at the University of Alabama at Birmingham 1917 HIV/AIDS Clinic from 1 January 2000 through 31 December 2006 (Last Value Carried Forward)

Characteristic	6-Month change in CD4⁺ cell count, mean cells/mm³ (±SD)	Adjusted P[a]	12-Month change in CD4⁺ cell count, mean cells/mm³ (±SD)	Adjusted P[a]
Clinical trial		.24		.33
No	96.4 ± 120.2		141.7 ± 155.8	
Yes	129.8 ± 115.6		182.7 ± 138.6	
Age, years		.78		.98
≤30	99.9 ± 108.1		149.9 ± 159.6	
31–49	104.0 ± 127.1		153.4 ± 152.9	
≥50	109.6 ± 98.9		137.7 ± 141.0	
Sex		.52		.09
Female	96.1 ± 119.5		173.8 ± 182.9	
Male	105.9 ± 120.1		144.0 ± 142.5	
Race		.001		.12
Black	81.8 ± 105.4		134.9 ± 155.1	
White	129.0 ± 130.4		168.9 ± 148.9	
HIV infection risk factor		.28		.50
Heterosexual sex	94.1 ± 116.8		156.1 ± 161.9	
IDU	89.8 ± 102.4		133.6 ± 147.1	
MSM	113.0 ± 123.2		150.2 ± 147.1	
Baseline CD4⁺ cell count, cells/mm³		.06		.88
<50	87.1 ± 73.7		150.0 ± 119.9	
50–199	106.3 ± 106.7		148.1 ± 152.4	
200–350	114.4 ± 126.4		148.1 ± 167.2	
>350	111.9 ± 179.3		160.7 ± 203.8	
Baseline viral load, plasma HIV RNA copies/mL		<.001		.01
≥100,000	124.5 ± 133.2		175.4 ± 159.5	
<100,000	92.9 ± 110.8		137.9 ± 148.6	
Third drug		.87		.21
NNRTI	101.8 ± 111.8		145.6 ± 142.9	
NRTI	80.5 ± 141.9		95.4 ± 166.8	
PI	101.2 ± 136.0		184.7 ± 200.4	
PIr	122.8 ± 129.9		181.4 ± 155.3	
Unknown/other	131.5 ± 126.3		188.1 ± 126.2	
Health insurance		.07		.08
Uninsured	93.3 ± 117.4		141.3 ± 147.0	
Public	83.3 ± 98.9		130.7 ± 136.5	
Private	117.1 ± 125.8		163.2 ± 160.8	
Affective mental health disorder		.86		.06
No	98.1 ± 120.6		133.2 ± 151.1	
Yes	109.9 ± 119.0		171.0 ± 153.0	
Substance abuse		.21		.44
No	101.7 ± 116.4		149.6 ± 149.9	
Yes	110.4 ± 131.5		154.9 ± 164.1	
Alcohol abuse		.63		.49
No	102.8 ± 118.2		150.2 ± 154.2	
Yes	108.2 ± 128.9		153.9 ± 147.4	

NOTE. IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PIr, ritonavir-boosted protease inhibitor; Unknown/other, currently blinded, raltegravir, or maraviroc.

[a] Multivariable linear regression; for patients with missing values, the last recorded value was carried forward.

In sensitivity analyses of virological outcomes using imputation methods, significant differences in 6-month virological failure were not observed between patients who were treated in clinical trials and those who received routine care, in accordance with primary analyses (Table 4). However, at 12 months, ART receipt through routine care was associated with a trend toward increased odds of virological failure (OR, 1.77; 95% CI, 0.98–3.23). We suspect that this trend may reflect the greater frequency of missing viral load values among the routine care group (in the routine care group, 126 [28%] of patients had missing values; in the clinical trial group, 13 [11%] of patients had missing values), which may relate to several factors. Volunteer and selection bias for clinical trial participation may result in a sample of patients who are more likely to attend clinic appointments and have laboratory measures obtained than are patients in the routine care population. Study selection criteria are known to contribute to differences in clinical trial enrollment rates among different groups [2, 5, 6, 8, 9, 24] and may have played a role in the current study. Participation in a clinical trial also entails close follow-up with study personnel. Such close monitoring and aggressive rescheduling after missed study visits is beyond the capacity of our clinic for all patients in routine clinical care. In summary, regarding efficacy versus effectiveness in HIV therapy, 6-month virological outcomes were consistent in primary and sensitivity analyses, although a trend toward differences in viral load outcomes appeared at 12 months in sensitivity analyses. By using 2 strategies to evaluate the impact of missing data on virological outcomes, a more complete understanding of the efficacy-effectiveness gap is obtained, which underscores the importance of a comprehensive approach.

Our findings should be interpreted with respect to the limitations of our study. As a retrospective study from a single HIV cohort, our findings may not be generalizable to other national or international settings, although our analysis may provide insights applicable to such settings. As with all observational studies, we were able to identify associations but cannot attribute causality. Although we controlled for measured confounders using multivariable models, there is the potential for unmeasured confounding, which is inherent to observational studies and which may impact outcomes interpretation. Other studies have implicated patient education level in contributing to clinical trial participation [7, 8, 22, 24–28, 30, 31], but we were unable to systematically ascertain this variable in our sample. Because of our modest sample size, we were able to assess treatment modality (clinical trial vs routine care) but had insufficient numbers to assess efficacy versus effectiveness at the regimen level. Such analyses are on-going through larger, multisite cohort collaborations.

A notable strength of this study is the use of multiple strategies to analyze the impact of missing data on outcomes, which enabled a more comprehensive understanding of the efficacy versus effectiveness relationship within the constraints of the measurements available. Many prior studies of HIV outcomes have neither explicitly stated the handling of missing data nor evaluated the impact of missing data on outcomes interpretation.

In conclusion, clinical research studies have played a vital role in the improvement of HIV treatment and outcomes. However, it is critical to evaluate both the efficacy and the effectiveness of therapy to ensure that the results obtained from clinical trials are generalizable to other populations treated through routine care. In primary analyses evaluating patients with available measures, we found similar 6-month and 12-month virological failure and $CD4^+$ cell count responses among antiretroviral-naive patients treated through routine care, compared with responses among those patients who participated in clinical trials. These findings provide insight into the efficacy-effectiveness relationship of ART for HIV infection and suggest that, in the contemporary treatment era, similar first-year responses are observed in treatment-naive patients who start ART in clinical trials and in those who start ART in routine care.

1917 CLINIC COHORT TEAM

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