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Improved Virological Outcome in White Patients Infected With HIV-1 Non-B Subtypes Compared to Subtype B

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Background. Antiretroviral compounds have been predominantly studied in human immunodeficiency virus type 1 (HIV-1) subtype B, but only ~10% of infections worldwide are caused by this subtype. The analysis of the impact of different HIV subtypes on treatment outcome is important.

Methods. The effect of HIV-1 subtype B and non-B on the time to virological failure while taking combination antiretroviral therapy (cART) was analyzed. Other studies that have addressed this question were limited by the strong correlation between subtype and ethnicity. Our analysis was restricted to white patients from the Swiss HIV Cohort Study who started cART between 1996 and 2009. Cox regression models were performed; adjusted for age, sex, transmission category, first cART, baseline CD4 cell counts, and HIV RNA levels; and stratified for previous mono/dual nucleoside reverse-transcriptase inhibitor treatment.

Results. Included in our study were 4729 patients infected with subtype B and 539 with non-B subtypes. The most prevalent non-B subtypes were CRF02_AG (23.8%), A (23.4%), C (12.8%), and CRF01_AE (12.6%). The incidence of virological failure was higher in patients with subtype B (4.3 failures/100 person-years; 95% confidence interval [CI], 4.0–4.5]) compared with non-B (1.8 failures/100 person-years; 95% CI, 1.4–2.4). Cox regression models confirmed that patients infected with non-B subtypes had a lower risk of virological failure than those infected with subtype B (univariable hazard ratio [HR], 0.39 [95% CI, .30–.52; $P < .001$]; multivariable HR, 0.68 [95% CI, .51–.91; $P = .009$]). In particular, subtypes A and CRF02_AG revealed improved outcomes (multivariable HR, 0.54 [95% CI, .29–.98] and 0.39 [95% CI, .19–.79], respectively).

Conclusions. Improved virological outcomes among patients infected with non-B subtypes invalidate concerns that these individuals are at a disadvantage because drugs have been designed primarily for subtype B infections.

The human immunodeficiency virus (HIV) epidemic is characterized by a high genotypic diversity with multiple distinct viral subtypes and circulating recombinant forms (CRFs) [1]. In Western countries, where most antiretroviral compounds were designed and initially tested, subtype B is predominant [2]. However, only ~10% of global HIV infections are caused by subtype B. The most prevalent subtype is C, which occurs mainly in South Africa and East Africa [1].

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With the introduction of combination antiretroviral therapy (cART), HIV/AIDS–related morbidity and mortality have been markedly reduced [3, 4], but concerns exist that antiviral susceptibility derived from studies with subtype B may not be applicable to non-B infections [5]. It was suggested that pretreatment genetic variation in HIV reverse transcriptase and protease among different subtypes may affect treatment response [6]. Studies in areas where non-B infections are predominant, mostly resource-limited settings, show promising results; however, these data cannot be directly compared with data derived from resource-rich settings. To reduce biases, it is essential that intersubtype comparisons in single settings be performed [7]. A few studies have been performed in Western countries to analyze the effect of viral subtype on treatment response [8–15]. However, all of these studies had limitations and suffered from a short follow-up time, a small sample size, or the strong correlation of ethnicity and subtype.

Our goal was to analyze the effects of HIV subtype on the viral response after cART initiation in the Swiss HIV Cohort Study (SHCS). The SHCS provides the unique opportunity to study different subtypes in a single ethnic group, namely whites. This is advantageous because HIV subtype and ethnicity are strongly correlated and ethnicity is potentially associated with treatment response and a different natural history of HIV [16–20]. Furthermore, the study allows the exclusion of potential bias due to different host genetic backgrounds [21].

METHODS

Study Population

The SHCS is a nationwide, multicenter, clinic-based cohort with continuous enrollment and semiannual study visits [22]. The SHCS has been approved by the ethical committees of all participating institutions, and written informed consent has been obtained from all participants. Data from the SHCS up to 12 January 2011 were included. The present study was restricted to white patients with known HIV subtype. Subtyping was based on sequences from the SHCS drug resistance database that are stored in SmartGene's Integrated Database Network System (version 3.6.0) [23]. Subtyping was performed using the REGA 2 System. If the results were inconclusive, we repeated subtyping using the Star analyzer (http://www.vgb.ucl.ac.uk/starn.shtml) [24]. Sequences were excluded if the subtype remained unequivocally undetermined.

Study Design

cART was defined as any antiretroviral therapy consisting of ≥2 drug classes. Detection limits of HIV RNA assays changed over the course of time (<400 copies/mL before 1999, <50 copies/mL after 1999). Therefore, we performed 2 analyses with different definitions for viral suppression and virological failure. Analysis A included patients who started cART between 1 January 1996 and 31 December 2009. The following definition of viral suppression was used: ≥1 viral load below the detection limit (<400 copies/mL) between days 90 and 365 after cART initiation. Virological failure was defined as (1) 2 consecutive viral loads >1000 copies/mL after previous suppression to <400 copies/mL with uninterrupted treatment, (2) 1 viral load >1000 copies/mL after previous suppression to <400 copies/mL followed by a treatment change or interruption, or (3) 1 viral load >1000 copies/mL after 180 days of treatment without previous suppression. If patients changed the cART regimen when viral load was suppressed, owing to toxicity, for example, the definition of virological failure for (1) and (2) was adapted, and previous suppression to <400 copies/mL was not required during the new treatment. Analysis B included a subset of patients from analysis A. Analysis B was limited to treatment-naive patients who started cART between 1 January 1999 and 31 December 2009. In 1999, all SHCS laboratories had changed their HIV RNA assays and achieved detection limits of 50 copies/mL. Viral load measurements with higher detection limits in this transition period occurred rarely and were excluded from analysis. The definitions of viral suppression and virological failure were adapted in analysis B. Viral suppression was achieved when HIV RNA levels were <50 copies/mL. For the definition of virological failure, the viral load limits in definitions (1), (2), and (3) were changed as follows: The lower limit was <50 copies/mL (instead of <400 copies/mL), and the upper limit was >500 copies/mL (instead of >1000 copies/mL).

Statistical Analysis

Baseline characteristics at cART initiation were analyzed using the Fisher exact test (categorical variables) and the Wilcoxon rank sum test (continuous variables). Baseline HIV RNA levels and CD4 cell counts were considered when measured within 180 days before cART initiation. The time to viral suppression was analyzed using univariable and multivariable logistic regressions. Multivariable models were adjusted for sex, age, transmission category, baseline HIV RNA level, baseline CD4 cell count, initial cART (unboosted protease inhibitor [PI], ritonavir-boosted PI [PI/r], nonnucleoside reverse-transcriptase inhibitor [NNRTI], or other), calendar period (analysis A, 1996–1998, 1999–2003, 2004–2009; analysis B, 1999–2002, 2003–2006, 2007–2009), and previous treatment with mono/dual nucleoside reverse-transcriptase inhibitor (NRTI) therapy (only analysis A). Continuous variables were categorized if likelihood-ratio tests indicated significant departures from linearity.

Virological failure rates were analyzed using Kaplan–Meier curves and log-rank tests. Additionally, univariable and multivariable Cox regression models were performed and adjusted for the same potential confounders described above. The

proportional hazard assumption was checked with Schoenfeld residuals and by using graphical methods. Although pretreatment with mono/dual NRTI therapy in analysis A did not satisfy the proportional hazard assumption, we stratified the Cox models for this variable. Colinearity was checked, and a variance inflation factor <3 was tolerated for regression models. All analyses assumed intention to continue treatment and did not consider treatment changes after the start of cART. Patient follow-up was censored when the treatment was changed to a non-cART regimen. Periods of treatment interruptions were subtracted from the exposure time, and viral loads measured during treatment interruptions were not considered for analysis.

Self-reported adherence has been measured since May 2003 in the SHCS and has been validated for treatment outcome [25]. We compared the lowest self-reported adherence between cART initiation and censoring or virological failure. Statistical analyses were performed with Stata 11 SE software (StataCorp). All *P* values were 2 sided, and the level of significance was set at .05.

RESULTS

Study Population and Baseline Characteristics

Analysis A (cART start, 1996–2009) included 4729 of 5268 patients (89.8%) with subtype B infections and 539 (10.2%) with non-B subtypes (Table 1). The most common non-B subtypes were CRF02_AG (23.8%), A (23.4%), C (12.8%), CRF01_AE (12.6%), and other (27.5%). Most patients infected with "other" subtypes had a subtype F (29.1%; n = 43), subtype G (28.4%; n = 42), or subtype D (16.9%; n = 25) infection. CD4 cell counts at baseline tended to be lower in patients with subtype B infection (median, 223 cells/μL; interquartile range [IQR], 106–357) than in those with non-B infection (median, 243 cells/μL; IQR, 134–366; $P = .088$). The median $\log_{10}$ HIV RNA level at baseline was similar in the 2 groups (subtype B, 4.7 copies/mL [IQR, 3.9–5.2]; non-B, 4.7 copies/mL [IQR, 3.9–5.3]). In analysis B (cART start, 1999–2009), 2166 of 2549 patients (85.0%) had subtype B infections and 383 had non-B infections (15.0%). Most baseline characteristics were similar to those in analysis A (Table 1).

First Combination Antiretroviral Therapy

In analysis A, 34.3% and 13.7% of patients infected with subtype B or non-B, respectively, were pretreated with mono/dual NRTIs (Table 2). The median year of cART initiation was earlier for patients infected with subtype B (1999; IQR, 1997–2004) than for those infections with non-B subtypes (2003; IQR, 1999–2007), and patients with subtype B infections received unboosted PIs more frequently, (52.0% compared with 30.2% for those with non-B infections). In analysis B, there was no difference in cART between groups (Table 2). The median years of cART start were similar: 2004 (subtype B; IQR, 2001–2007) and 2005 (non-B subtypes; IQR, 2002–2007), respectively.

In both analyses, the most frequent NRTI combination was lamivudine and zidovudine. Efavirenz was the most common NNRTI, and lopinavir the most frequently used PI/r. Patients treated with unboosted PIs received nelfinavir or indinavir most frequently. Patients for whom treatment was not classified into the categories of PI, PI/r, and NNRTI (analysis A, n = 95; analysis B, n = 35) often had combinations of PIs and NNRTIs (analysis A, n = 90/95; analysis B, n = 33/35).

Time to Viral Suppression

In analysis A, 4433 of 4729 (93.7%) and 516 of 539 patients (95.7%) infected with subtype B and non-B had ≥1 viral load measured between day 90 and day 365 after cART initiation ($P = .070$). Viral suppression was achieved in 3870 of 4433 (87.3%) and 481 of 516 (93.2%), respectively ($P < .001$). The probability of achieving viral suppression was higher in patients infected with non-B subtypes in the univariable logistic regression model (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.4–2.8), but not in the multivariable model (OR, 1.2; 95% CI, .8–1.8). Results were similar in analysis B: 2076 of 2166 patients (95.8%) infected with subtype B and 375 of 285 (97.9%; $P = .060$) infected with non-B subtypes had a viral load measured, of whom 1856 of 2076 (89.4%) and 338 of 375 patients (90.1%) achieved viral suppression ($P = .715$). Compared with subtype B–infected patients, those infected with non-B subtypes had a similar probability to achieve viral suppression (univariable OR, 1.1 [95% CI, .8–1.6]; multivariable OR, 1.0 [.7–1.5]). When missing values were considered as treatment failures, similar results were achieved in analyses A and B. No specific non-B subtype had significantly different viral suppression rates compared with subtype B (data not shown).

Time to Virological Failure

In analysis A, 5268 patients contributed 29 446 person-years of follow-up. The incidence of virological failure was higher in patients infected with subtype B (4.3 failures/100 person-years; 95% CI, 4.0–4.5) than in those infected with non-B subtypes (1.8 failures/100 person-years; 1.4–2.4). Incidences of failure were lower in analysis B, but patients infected with subtype B also had a higher incidence of failure (2.6 failures/100 person-years; 95% CI, 2.3–3.0) than those infected with non-B subtypes (1.4 failures/100 person-years; .9–2.1); 2549 patients contributed 10 803 person-years of follow-up in analysis B.

Kaplan–Meier curves illustrate the time to virological failure differentiated by type of treatment (Figure 1). As shown in Cox regression models, the probability of experiencing a virological failure was lower among patients infected with non-B subtypes compared with subtype B (Table 3). In analysis A, the univariable hazard ratio (HR) was 0.39 (95% CI, .30–.52; $P < .001$) and the multivariable HR was 0.68 (95% CI, .51–.91; $P = .009$). Analysis B had similar results. The univariable HR was 0.54

Table 1. Patients' Characteristics at Combination Antiretroviral Therapy Initiation

Characteristic	Analysis A (cART initiation, 1996–2009) by subtype, no. (%) of patients									Analysis B (cART initiation, 1999–2009) by subtype, no. (%) of patients								
	B	Non-B	P^a	01_AE	02_AG	A	C	Other	P^b	B	Non-B	P^a	01_AE	02_AG	A	C	Other	P^b
Sex									<.001			<.001						<.001
Male	3768 (79.7)	363 (67.3)	<.001	43 (63.2)	121 (94.5)	60 (47.6)	47 (67.1)	93 (62.4)		1801 (83.2)	268 (70.0)		33 (61.1)	95 (97.9)	40 (48.8)	30 (68.2)	70 (66.0)	
Female	961 (20.3)	176 (32.6)		25 (36.8)	7 (5.5)	66 (52.4)	21 (32.9)	56 (37.6)		365 (16.9)	115 (30.0)		21 (38.9)	2 (2.1)	42 (51.2)	14 (31.8)	36 (34.0)	
Age, median (IQR), years	47 (43–53)	50 (41–61)	<.001	47.5 (42–59.5)	51.5 (43–58)	56 (45–67)	51 (45–61)	45.5 (39.5–59.5)	<.001	45 (39–51)	50 (40–61)	<.001	46 (41–60)	52 (42–57)	55 (40–65)	51.5 (40–61)	46 (39–60)	<.001
Transmission category			<.001						<.001			<.001						<.001
HET	1082 (22.9)	388 (72.0)		58 (85.3)	84 (65.6)	101 (80.2)	50 (71.4)	96 (64.4)		533 (24.6)	265 (69.2)		44 (81.5)	63 (65.0)	62 (75.6)	30 (68.2)	66 (62.3)	
MSM	2253 (47.6)	91 (16.9)		7 (10.3)	36 (28.1)	10 (7.9)	10 (14.3)	28 (18.8)		1147 (53.0)	76 (19.8)		7 (13.0)	32 (33.0)	6 (7.3)	7 (15.9)	24 (22.6)	
IDU	1250 (26.4)	37 (6.9)		1 (1.5)	4 (3.1)	8 (6.3)	5 (7.1)	20 (13.4)		409 (18.9)	28 (7.3)		1 (1.9)	2 (2.1)	8 (9.8)	3 (6.8)	14 (13.2)	
Other	144 (3.0)	23 (4.3)		2 (2.9)	4 (3.1)	7 (5.6)	5 (7.1)	5 (3.4)		77 (3.5)	14 (3.7)		2 (3.7)	0 (0.0)	6 (7.3)	4 (9.1)	2 (1.9)	
CDC stage			<.001						<.001			.044						.050
A	2536 (53.6)	366 (67.9)		47 (69.1)	93 (72.7)	79 (62.7)	50 (71.4)	98 (65.8)		1390 (64.2)	269 (70.2)		39 (72.2)	73 (75.3)	53 (64.6)	33 (75.0)	71 (67.0)	
B	1255 (26.5)	101 (18.7)		16 (23.5)	13 (10.2)	25 (19.8)	14 (20.0)	34 (22.8)		422 (19.5)	68 (17.8)		12 (22.2)	8 (8.3)	16 (19.5)	8 (18.2)	24 (22.6)	
C	938 (19.8)	72 (13.4)		5 (7.3)	22 (17.2)	22 (17.5)	6 (8.6)	17 (11.4)		354 (16.3)	46 (12.0)		3 (5.6)	16 (16.5)	13 (15.9)	3 (6.8)	11 (10.4)	
CD4 count, cells/μL			.081						.182			.284						.813
<200	1861 (44.4)	193 (40.2)		22 (37.9)	55 (48.3)	41 (36.9)	22 (34.9)	53 (39.3)		819 (42.5)	134 (39.3)		17 (37.0)	37 (43.5)	27 (37.0)	16 (41.0)	37 (37.8)	
≥200	2330 (55.6)	287 (59.8)		36 (62.1)	59 (51.8)	70 (63.1)	41 (65.1)	82 (60.7)		1108 (57.5)	207 (60.7)		29 (63.0)	48 (56.5)	46 (63.0)	23 (59.0)	61 (62.2)	
NA	538 (11.4)	59 (10.9)	.830	10 (14.7)	14 (10.9)	15 (11.9)	7 (10.0)	14 (9.4)	.910	239 (11.0)	42 (11.0)	1.000	8 (14.8)	12 (12.4)	9 (11.0)	5 (11.4)	8 (7.5)	.809
HIV-1 RNA level, copies/mL			.884						.193			.528						.546
<10 000	1258 (28.5)	141 (27.4)		14 (22.2)	23 (18.6)	43 (35.5)	19 (28.4)	43 (30.5)		450 (21.5)	89 (24.1)		11 (21.6)	15 (16.1)	25 (30.9)	10 (23.8)	28 (27.2)	
10 000–99 999	1583 (35.9)	187 (36.4)		25 (39.7)	47 (37.9)	44 (36.4)	27 (40.3)	45 (31.9)		764 (36.5)	132 (35.7)		20 (39.2)	36 (38.7)	27 (33.3)	17 (40.5)	32 (31.1)	
≥100 000	1571 (35.6)	186 (36.2)		24 (38.1)	54 (43.5)	34 (28.1)	21 (31.3)	53 (37.6)		882 (42.1)	149 (40.3)		20 (39.2)	42 (45.2)	29 (35.8)	15 (35.7)	43 (41.8)	
NA	317 (6.7)	25 (4.6)	.065	5 (7.3)	4 (3.1)	5 (4.0)	3 (4.3)	8 (5.4)	.415	70 (3.2)	13 (3.4)	.876	3 (5.6)	4 (4.1)	1 (1.2)	2 (4.5)	3 (2.8)	.774

Abbreviations: cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HET, heterosexual; HIV-1, human immunodeficiency virus type 1; IDU, injection drug user; IQR, interquartile range; MSM, men who have sex with men; NA, not available.

[a] Fisher exact test comparing subtype B and non-B infections.

[b] Fisher exact test comparing all particular subtypes.

Table 2. First Combination Antiretroviral Therapy

	Analysis A (cART initiation, 1996–2009) by subtype, no. (%) of patients			Analysis B (cART initiation, 1999–2009) by subtype, no. (%) of patients		
	Subtype B	Non-B subtypes	P^a	Subtype B	Non-B subtypes	P^a
Year of cART initiation, analysis A/analysis B			<.001			.001
1996–1998/1999–2002	2198 (46.5)	113 (21.0)		617 (28.5)	75 (19.6)	
1999–2003/2003–2006	1164 (24.6)	165 (30.6)		660 (30.5)	138 (36.0)	
2004–2009/2007–2009	1367 (28.9)	261 (48.4)		889 (41.0)	170 (44.4)	
Pretreated with mono/dual NRTIs	1624 (34.3)	74 (13.7)	<.001	0 (0.0)	0 (0.0)	–
Treatment included			<.001			.062
NNRTI	1035 (21.9)	177 (32.8)		863 (39.8)	157 (41.0)	
PI/r	1143 (24.2)	197 (36.5)		896 (41.4)	171 (44.6)	
PI	2458 (52.0)	163 (30.2)		373 (17.2)	54 (14.1)	
Other	93 (2.0)	2 (0.4)		34 (1.6)	1 (0.3)	
NRTI backbone			<.001			.087
ETC TDF	644 (13.6)	114 (21.1)		598 (27.6)	108 (28.2)	
3TC AZT	1994 (42.2)	247 (45.8)		956 (44.1)	188 (49.1)	
3TC D4T	857 (18.1)	44 (8.2)		114 (5.3)	11 (2.9)	
D4T DDI	387 (8.2)	30 (5.6)		81 (3.7)	6 (1.6)	
3TC ABC	172 (3.6)	31 (5.8)		152 (7.0)	29 (7.6)	
3TC TDF	177 (3.7)	25 (4.6)		146 (6.7)	24 (6.3)	
Other NRTIs	498 (10.5)	48 (8.9)		119 (5.5)	17 (4.4)	
NNRTI			.895			1.000
EFV	880 (85.5)	149 (84.2)		758 (87.8)	138 (87.9)	
NVP	148 (14.3)	27 (15.3)		103 (11.9)	19 (12.1)	
Other NNRTIs	7 (0.7)	1 (0.6)		2 (0.2)	0 (0.0)	
PI/r			<.001			.083
LPV	625 (54.7)	136 (69.0)		589 (65.7)	127 (74.3)	
ATV/r	224 (19.6)	37 (18.8)		195 (21.8)	33 (19.3)	
IDV/r	92 (8.1)	7 (3.6)		70 (7.8)	6 (3.5)	
Other PI/r	202 (17.7)	17 (8.6)		42 (4.7)	5 (2.9)	
Unboosted PI			<.001			.629
NFV	910 (37.0)	93 (57.1)		307 (82.3)	47 (87.0)	
IDV	949 (38.6)	42 (25.8)		31 (8.3)	5 (9.3)	
RTV	402 (16.4)	12 (7.4)		2 (0.5)	0 (0.0)	
Other PI	197 (8.0)	16 (9.8)		33 (1.1)	2 (3.7)	

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; cART, combination antiretroviral therapy; D4T, stavudine; DDI, didanosine; EFV, efavirenz; ETC, emtricitabine; IDV, indinavir; IDV/r, ritonavir-boosted IDV; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PI/r, ritonavir-boosted PI; RTV, ritonavir; TDF, tenofovir.

[a] Fisher exact test.

(95% CI, .35–.82; $P = .004$) and the multivariable HR, 0.63 (.40–.96; $P = .041$). We also differentiated between the particular subtypes (Figure 2). The multivariable Cox regression of analysis A showed that subtypes A ($P = .042$) and CRF01_AG ($P = .009$) had significantly lower virological failure rates than subtype B. No differences were found in analysis B; however, sample sizes were small.

Although adherence to treatment is a potential bias, self-reported adherence was similar between groups. In analysis A, 71.5% (subtype B) and 87.4% (non-B) of patients had ≥1 documented self-reported adherence between cART initiation and the date of censoring or virological failure. Patients infected with subtype B and non-B had similar adherence: 45.7% and 49.9% never missed a dose, 27.7% and 28.2% missed a maximum of 1 dose per month, and 26.6% and 21.9% missed >1 dose per month ($P = .073$). In analysis B, 87.6% (subtype B) and 93.5% (non-B) of patients had ≥1 documented self-reported adherence. Results were similar to those in analysis A. Other factors potentially associated with low adherence are high rates of treatment changes and an increased number of

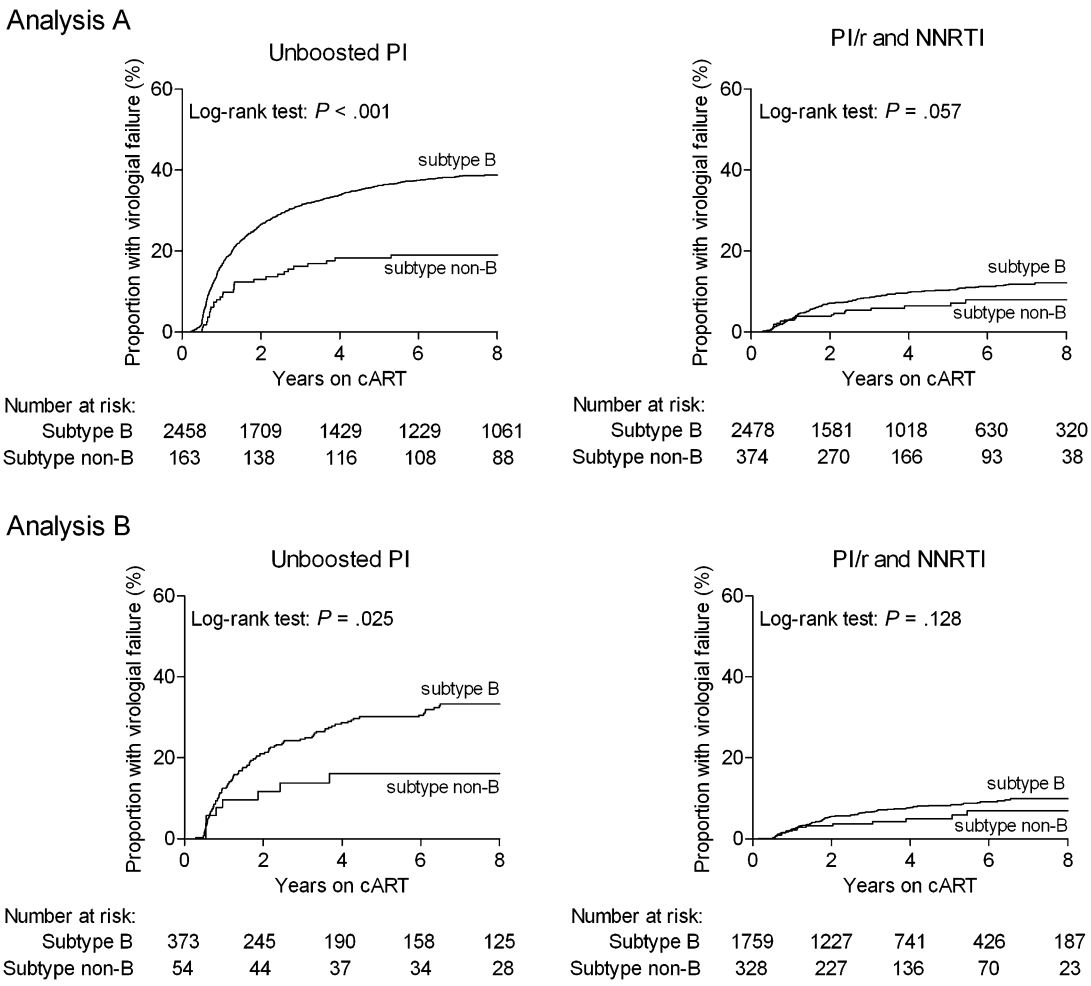

Figure 1. Kaplan–Meier curves differentiated by the first combination antiretroviral treatment (cART): unboosted protease inhibitor (PI), ritonavir-boosted PI (PI/r), or nonnucleoside reverse-transcriptase inhibitor (NNRTI) show the time to virological failure. Analyses A and B included patients who started cART in 1996–2009 or 1999–2009, respectively.

treatment interruptions. Both factors were similar between groups (data not shown).

To assess the robustness of the finding that non-B subtypes have lower virological failure rates compared with subtype B, we performed several sensitivity analyses. Kaplan–Meier curves indicated that the effect of subtype was greatest in patients treated with unboosted PIs. Excluding these patients from analysis reduced the power of the model, but point estimates of the Cox regression model were not altered substantially (analysis A, univariable and multivariable HRs, 0.63 [95% CI, .36–1.09] and 0.78 [.43–1.40] respectively; analysis B, univariable and multivariable HRs, 0.64 [95% CI, .37–1.08] and 0.71 [.40–1.27]). In analysis A, results were similar if we excluded patients who were treated with mono/dual NRTIs before cART initiation (univariable HR, 0.46 [95% CI, .32–.65]; multivariable HR, 0.58 [.40–.84]). If analyses A and B are limited to patients with known CD4 cell and RNA values at baseline, univariable HRs were 0.40 (95% CIs, .29–.53) and 0.56 (.36–.87), respectively. Multivariable HRs were 0.71 (95% CI, .52–.97) and 0.66 (.41–1.06), respectively. Results remained robust if we censored the follow-up when a treatment interruption occurred (analysis A, univariable and multivariable HRs, 0.38 [95% CI, .28–.52] and 0.62 [.45–.86], respectively; analysis B, univariable and multivariable HRs, 0.62 [.39–.99] and 0.69 [.42–1.13]). The frequencies of HIV RNA measurements were comparable between patients infected with subtype B and those infected with non-B subtypes, the median durations between measurements were 96 (IQR, 79–119) and 92 (77–115) days in analysis A and 93 (79–117) and 91 (77–112) days in analysis B, respectively. Because irregular or long durations without HIV RNA measurements might bias the results, we censored patients' follow-up if the interval between 2 HIV RNA measurements was longer than 180 days. Results remained robust (analysis A, univariable and multivariable HRs, 0.38 [95% CI, .28–.50] and 0.68 [.50–.93]; analysis B, univariable and multivariable HRs, 0.56 [.37–.85] and 0.63 [0.40–0.98]).

Table 3. Cox Regression Models Analyzing the Time to Virological Failure

	Analysis A (cART initiation, 1996–2009)							Analysis B (cART initiation, 1999–2009)						
	Failures, no.	At risk, no.	Failures, %	Univariable HR (95% CI)	*P*	Multivariable[a] HR (95% CI)	*P*	Failures, no.	At risk, no.	Failures, %	Univariable HR (95% CI)	*P*	Multivariable[a] HR (95% CI)	*P*
Subtype														
B	1140	4729	24.11	Reference		Reference		240	2166	11.08	Reference		Reference	
Non-B	52	539	9.65	0.39 (.30–.52)	<.001	0.68 (.51–.91)	.009	23	383	6.01	0.54 (.35–.82)	.004	0.63 (.40–.98)	.041
Age, per 10 years				1.09 (1.03–1.15)	.003	0.92 (.86–.99)	.021				0.97 (.86–1.09)	.614	0.86 (.75–.99)	.030
Sex														
Male	946	4131	22.90	Reference		Reference		215	2069	10.39	Reference		Reference	
Female	246	1137	21.64	0.90 (.78–1.03)	.132	0.75 (.64–.87)	<.001	48	480	10.00	0.96 (.70–1.32)	.808	0.76 (.54–1.07)	.110
Transmission category					<.001		.355					<.001		.099
MSM	496	2344	21.16	Reference		Reference		101	1223	8.26	Reference		Reference	
HET	280	1470	19.05	0.86 (.75–1.00)		1.09 (.92–1.29)		81	798	10.15	1.17 (.88–1.57)		1.23 (.89–1.72)	
IDU	387	1287	30.07	1.43 (1.25–1.63)		1.11 (.96–1.28)		72	437	16.48	2.05 (1.52–2.78)		1.52 (1.09–2.10)	
Other	29	167	17.37	0.79 (.54–1.15)		0.87 (.60–1.27)		9	91	9.89	1.15 (.58–2.28)		1.40 (.70–2.80)	
CD4 cell count, cells/μL					<.001		<.001					.002		.055
<200	596	2054	29.02	Reference		Reference		129	953	13.54	Reference		Reference	
≥200	415	2617	15.86	0.53 (.47–.60)		0.62 (.54–.71)		100	1315	7.60	0.65 (.50–.84)		0.74 (.56–.97)	
NA	181	597	30.32	1.06 (.90–1.25)		1.11 (.79–1.55)		34	281	12.10	1.04 (.71–1.52)		1.11 (.66–1.84)	
HIV RNA level, copies/mL					<.001		<.001					.063		.838
<10 000	252	1399	18.01	Reference		Reference		45	539	8.35	Reference		Reference	
10 000–99 999	409	1770	23.11	1.36 (1.16–1.59)		1.65 (1.40–1.93)		85	896	9.49	1.09 (.76–1.57)		1.02 (.71–1.47)	
≥100 000	387	1757	22.03	1.24 (1.06–1.45)		1.59 (1.34–1.89)		117	1031	11.35	1.20 (.85–1.69)		1.13 (.79–1.62)	
NA	144	342	42.11	2.39 (1.95–2.93)		1.32 (.90–1.93)		16	83	19.28	2.27 (1.28–4.02)		1.21 (.59–2.48)	
Treatment					<.001		<.001					<.001		<.001
PI	951	2621	36.28	Reference		Reference		116	427	27.17	Reference		Reference	
PI/r	126	1340	9.40	0.27 (.23–.33)		0.66 (.54–.82)		70	1067	6.56	0.27 (.20–.37)		0.51 (.36–.73)	
NNRTI	97	1212	8.00	0.22 (.18–.27)		0.61 (.47–.79)		69	1020	6.76	0.25 (.19–.34)		0.46 (.33–.65)	
Other	18	95	18.95	0.53 (.33–.84)		0.71 (.44–1.15)		8	35	22.86	0.8 (.40–1.68)		0.94 (.45–1.95)	
Year of cART initiation, analysis A/analysis B					<.001		<.001					<.001		<.001
1996–1998/1999–2002	899	2311	38.90	Reference		Reference		164	692	23.70	Reference		Reference	
1999–2003/2003–2006	239	1329	17.98	0.43 (.37–.49)		0.73 (.60–.87)		65	798	8.15	0.33 (.25–.44)		0.48 (.34–.68)	
2004–2009/2007–2009	54	1628	3.32	0.10 (.07–.13)		0.21 (.15–.30)		34	1059	3.21	0.19 (.13–.28)		0.30 (.19–.47)	

Abbreviations: cART, combination antiretroviral treatment; CI, confidence interval; HET, heterosexual; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug user; MSM, men who have sex with men; NA, not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted PI.

[a] Multivariable analyses are adjusted for age, sex, transmission category, first cART, and baseline CD4 cell count and HIV RNA level. Analysis A is additionally stratified for previous mono/dual nucleoside reverse-transcriptase inhibitor treatment.

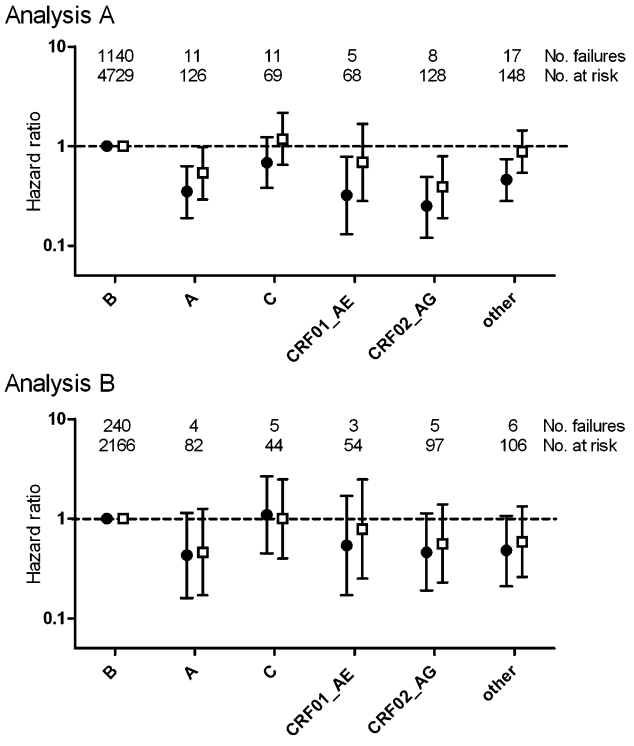

Figure 2. Univariable (solid circles) and multivariable (open squares) Cox regression analyses comparing time to virological failure between patients infected with different HIV subtypes and circulating recombinant forms. Multivariable analyses are adjusted for age, sex, transmission category, first combination antiretroviral therapy, and baseline CD4 cell counts and HIV RNA levels. Analysis A is additionally stratified for previous mono/dual nucleoside reverse-transcriptase inhibitor treatment. Hazard ratios <1 indicate a better virological response than in patients infected with subtype B; 95% confidence intervals are indicated.

The mode of transmission may also be a critical issue. However, limiting the analysis to heterosexual patients did not alter conclusions (analysis A, univariable and multivariable HRs, 0.41 [95% CI, .29–.59] and 0.61 [95% CI, .43–.88], respectively; analysis B, univariable and multivariable HRs, 0.41 [.23–073 and 0.46 [.26–.83]). Moreover, adjusting the models for AIDS (Centers for Disease Control and Prevention stage C) or stratifying analyses for year of treatment initiation confirmed findings (data not shown). It was shown elsewhere that transmitted antiretroviral resistance levels differ by subtype [26]. To assess whether our results could be due to differential baseline resistance, we performed a sensitivity analysis in a subset of patients in whom genotypic resistance was determined before cART initiation (analysis A, n = 3137 [59.6%]; analysis B, n = 2121 [83.2%]). The number of patients with transmitted mutations affecting the initial cART was slightly higher in the subtype B group (analysis A, 5.4%; analysis B, 4.3%) compared with non-B (each 2.4%). Hazard ratios of the multivariable Cox model for the effect of viral subtype (analysis A, 0.66 [95% CI, .40–1.10]; analysis B, 0.80 [.48–1.33]) were not substantially altered when information on transmitted resistance in multivariable models was added (analysis A, 0.68 [.41–1.14]; analysis B, 0.83 [.50–1.39]).

DISCUSSION

We showed that white patients infected with HIV non-B subtypes had an improved virological success rate during cART, compared with patients infected with B subtype. In particular, subtype A and CRF01_AG infections were associated with lower virological failure rates. The time to viral suppression did not differ between subtypes. In the last decade, a debate has arisen as to whether antiretroviral compounds are less active against non-B infections, because most antiretroviral drugs were designed to be used against subtype B infections [7]. Our findings indicate that these concerns are unwarranted.

We analyzed the impact of different HIV subtypes on treatment response in a single ethnic group, that is, whites. Restricting the analysis to a single ethnic group is advantageous and avoids potential serious biases caused by the association of ethnicity and subtype. Ethnic differences in host genetic factors influence the natural history of HIV infection and the tolerability and potentially the efficacy of cART [27]. Furthermore, cultural differences between diverse ethnicities could influence virological outcome. The homogeneity of our cohort with regard to genetic and cultural backgrounds allowed us to assess the impact of viral subtypes on virological response independent of ethnic variability [8, 16–19]. Although most patients infected with non-B subtypes are nonwhite, the question of susceptibility to cART among white patients infected with non-B subtypes becomes more important, because the prevalence of non-B infections is increasing in Western countries [26, 28].

Several in vitro studies were conducted to test the drug susceptibility of non-B subtypes. Overall, most non-B subtypes possessed susceptibilities similar to those of subtype B (reviewed in [6]). However, 1 study showed that CRF02_AG samples were more susceptible to nelfinavir and ritonavir [29]. In our study, the proportion of patients receiving these PIs was quite high, which could partially explain our findings.

Our results differ from those of previously published observational studies [8–15, 18, 30]. However, most of these studies were limited either by a small sample size, a short follow-up time, missing adherence data, or the correlation of ethnicity and transmission category with the HIV subtype. To date, Geretti et al have published the largest study analyzing the effect of HIV subtype on cART response. They found no significant intersubtype differences in treatment response [14]. However, owing to the strong correlation of HIV subtype with ethnicity and transmission group, they could not adjust their model for these 2 potential confounders [16, 17, 21]. In contrast, our study is unbiased by ethnicity, and a sensitivity analysis clearly demonstrated that results remained robust even when our analysis was

limited to patients with heterosexual transmission. Furthermore, we used more restrictive criteria for virological failures. Geretti et al did not ignore virological failures during treatment interruptions in their main analysis, only in a sensitivity analysis with highly reduced statistical power. However, both studies exhibit a rather small number of virological failures among patients infected with specific non-B subtypes. Contrary to that of Geretti et al, our study comprised a higher proportion of patients infected with subtype A, CRF01_AE, or CRF02_AG and fewer patients infected with subtype C or D.

Although this is a large study addressing the question of cART response among different HIV subtypes in a single ethnic group, the sample sizes of some specific non-B subtypes were small, and therefore the CIs for HRs remained wide. Larger cohort collaborations will be necessary to strengthen our findings. In our study, some baseline and treatment characteristics that are predictive for response to cART (eg, treatment with unboosted PI) differed between patients infected with subtype B and those infected with non-B subtypes, especially in analysis A. However, results remained robust when we adjusted the models for these factors. A sensitivity analysis confirmed that our findings are not substantially biased by different resistance levels of transmitted viruses. However, we cannot fully exclude unsolved biases.

In conclusion, previous concerns that antiretroviral treatment response might be hampered by development and testing of antiretroviral compounds in resource-rich countries with high subtype B prevalence are no longer tenable, and concerns that non-B infections are less susceptible to cART are unwarranted. In fact, patients infected with particular non-B subtypes had lower virological failure rates than patients with subtype B infections in Switzerland.

Notes

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