Long-Term Probability of Detecting Drug-Resistant HIV in Treatment-Naive Patients Initiating Combination Antiretroviral Therapy

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(See the editorial commentary by Harrigan, on pages 1286–1287.)

Background. Robust long-term estimates of the risk of development of drug resistance are needed for human immunodeficiency virus (HIV)–infected patients starting combination antiretroviral therapy (cART) regimens currently used in routine clinical practice.

Methods. We followed a large cohort of patients seen in 1 of 11 HIV clinics in the United Kingdom after starting cART with nucleoside reverse-transcriptase inhibitors and either a nonnucleoside reverse-transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r). Survival analysis was employed to estimate the incidence of virological failure and of detected drug resistance.

Results. Seven thousand eight hundred ninety-one patients were included; 6448 (82%) started cART with an NNRTI and 1423 (17%) with a PI/r. The cumulative risk of virological failure by 8 years was 28%. The cumulative probabilities of detecting any mutation, ⩾1 major nucleoside reverse-transcriptase inhibitor International AIDS Society–United States of America (IAS-USA) mutation, ⩾1 major NNRTI IAS-USA mutation (in those starting an NNRTI), and ⩾1 major PI IAS-USA mutation (in those starting a PI) were 17%, 14%, 15%, and 7%, respectively, by 8 years. The probability of detecting PI mutations in people who started PI/r-based regimens was lower than that of detecting NNRTI mutations in those starting NNRTI-based regimens (adjusted relative hazard, 0.36; 95% confidence interval, 0.26–0.50; $P < .001$). The risk of detecting nucleoside resistance did not vary according to whether an NNRTI or a PI/r was used in the regimen (adjusted relative hazard, 1.00; 95% confidence interval, 0.80–1.26; $P = .98$).

Conclusions. In patients who started modern cART in clinical practice in the United Kingdom, virological failure by 8 years was relatively common and was paralleled by an appreciable risk of resistance detection, although the detection rate of class-specific resistance was lower for those who started a PI/r-based regimen.

Millions of people globally depend on combination antiretroviral therapy (cART) to maintain their health. One threat to continued effectiveness of cART in such people is the risk of development of resistance during receipt of therapy [1–5]. The long-term rate with which we can expect to see resistance mutations emerging after the start of treatment and the extent to which this differs according to choice of first-line regimen are crucial factors for understanding the potential success of cART over the coming decades, but both remain uncertain. Earlier estimates from cohort studies have tended to include patients who started with noncurrent regimens, such as those including a non–ritonavir-boosted protease inhibitor (PI), and thus, it is unclear how relevant they are [1–4, 6]. Furthermore, longer-term estimates of virological failure and drug resistance are needed. Several randomized trials have compared occurrence of resistance mutations at virological failure between patients starting nonnucleoside reverse-transcriptase inhibitor (NNRTI) and ritonavir-boosted PI (PI/r) regimens, but the limitation of such studies is the relatively short follow-up [5–26]. Also, patients in

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Table 1. Main Characteristics of the Study Population at the Initiation of Combination Antiretroviral Therapy (cART), According to the Class of Third Drug Started

Characteristic	Class of third drug started		Overall (n = 7891)
	NNRTI (n = 6468)	PI/r (n = 1423)	
Female sex	1774 (27)	352 (25)	2126 (27)
Mode of HIV transmission			
Homosexual contacts	3339 (52)	772 (54)	4111 (52)
IDU	184 (3)	54 (4)	238 (3)
Heterosexual contacts	2651 (41)	530 (37)	3181 (40)
Other/unknown	294 (5)	67 (5)	361 (5)
Age, median years (range)	36 (18–84)	37 (18–74)	36 (18–84)
Viral load at cART initiation			
501–100,000 copies/mL	2476 (38)	425 (30)	2901 (37)
>100,000 copies/mL	2228 (34)	542 (38)	2770 (35)
Missing	1764 (27)	456 (32)	2220 (28)
Median log copies/mL (IQR)	4.96 (4.49–5.38)	5.10 (4.55–5.53)	4.98 (4.51–5.41)
CD4 count at cART initiation			
<200 cells/μL	2525 (39)	568 (40)	3093 (39)
201–350 cells/μL	1824 (28)	275 (20)	2099 (27)
>350 cells/μL	701 (11)	205 (14)	906 (11)
Missing	1418 (22)	375 (26)	1793 (23)
Median cells/μL (IQR)	201 (120–286)	187 (80–310)	200 (112–290)
Diagnosis of AIDS pre-cART	1294 (20)	362 (25)	1656 (21)
Calendar year of cART initiation			
1998	451 (7)	66 (5)	517 (7)
1999	706 (11)	91 (6)	797 (10)
2000	757 (12)	46 (3)	803 (10)
2001	821 (13)	114 (9)	935 (12)
2002	809 (13)	188 (14)	997 (13)
2003	1044 (16)	186 (13)	1230 (16)
2004	910 (14)	280 (19)	1190 (15)
2005	775 (12)	355 (25)	1130 (14)
2006	195 (3)	97 (7)	292 (4)
Median year (range)	2002 (1998–2006)	2004 (1998–2006)	2002 (1998–2006)
NRTI pair started			
Abacavir-lamivudine	358 (6)	97 (7)	455 (6)
Stavudine-lamivudine	574 (9)	162 (11)	735 (9)
Didanosine-lamivudine	253 (4)	43 (3)	292 (4)
Didanosine-abacavir	17 (0.3)	11 (1)	28 (0.4)
Didanosine-stavudine	484 (7)	41 (3)	522 (7)
Tenofovir-lamivudine	452 (7)	182 (12)	632 (8)
Tenofovir-abacavir	4 (0.1)	23 (2)	26 (0.3)
Tenofovir-stavudine	32 (0.5)	7 (0.5)	39 (0.5)
Tenofovir-didanosine	91 (1)	55 (4)	146 (2)
Tenofovir-emtricitabine	496 (8)	224 (15)	717 (9)
Tenofovir-zidovudine	9 (0.1)	13 (1)	22 (0.3)
Zidovudine-lamivudine	3424 (53)	558 (38)	3959 (50)
Zidovudine-abacavir	14 (0.2)	11 (1)	25 (0.3)
Zidovudine-didanosine	198 (3)	24 (2)	221 (3)
Other pairs	62 (1)	12 (0.7)	72 (2)
Third drug started			
Nevirapine	2590 (40)	0 (0)	2590 (33)
Efavirenz	3878 (60)	0 (0)	3878 (49)
Saquinavir/r	0 (0)	196 (14)	196 (2)

Table 1. ***(Continued.)***

Characteristic	Class of third drug started: NNRTI (n = 6468)	Class of third drug started: PI/r (n = 1423)	Overall (n = 7891)
Indinavir/r	0 (0)	123 (9)	123 (2)
Amprenavir/r	0 (0)	18 (1)	18 (1)
Lopinavir/r	0 (0)	873 (61)	873 (11)
Atazanavir/r	0 (0)	208 (15)	208 (3)
Tipranavir/r	0 (0)	5 (0.4)	5 (0.1)
Transmitted resistance	(n = 1997)	(n = 629)	(n = 2626)
65R	5 (0.3)	0 (0)	5 (0.2)
74V	5 (0.3)	3 (0.6)	8 (0.3)
TAM	78 (4)	48 (8)	126 (5)
184IV	49 (2)	31 (5)	80 (3)
⩾1 IAS-USA NRTI mutations	113 (6)	64 (10)	177 (7)
⩾1 IAS-USA NNRTI mutations	84 (4)	63 (10)	147 (6)
⩾1 IAS-USA PI major mutations	54 (3)	23 (4)	77 (3)
⩾1 IAS-USA mutations	184 (9)	104 (17)	288 (11)

NOTE. Data are no (%) of patients, unless otherwise indicated. HIV, human immunodeficiency virus; IAS-USA, International AIDS Society–United States of America; IDU, injection drug use; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted; TAM, thymidine analogue mutations.

trials may be generally more adherent to cART, which may give an optimistic picture of outcomes to be expected [27].

METHODS

Patients. To date, the United Kingdom Collaborative HIV Cohort Study (UK CHIC) contains data on all patients seen at ⩾1 of 11 large HIV clinics in London, Brighton, Bristol, and Edinburgh since January 1996. The study has been described in detail elsewhere [28]. In brief, data collected include information used as part of routine clinical care, such as demographic information, all start and stop dates of antiretroviral treatments, CD4 cell counts, viral loads, AIDS-related diseases, and dates of death. Data on resistance were obtained from a linked database, the UK HIV Drug Resistance Database, which contains information on genotypic resistance tests performed on behalf of most HIV clinics in the UK. All test results recorded after the date of starting first cART, regardless of whether the patient was currently receiving ART, were used in this analysis.

Statistical analysis. Patients eligible for inclusion in the analysis were all those in UK CHIC who started 1 of the following regimens as their first cART regimen: 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus either a PI/r or an NNRTI (efavirenz or nevirapine) after 31 December 1997. The drug dosage is not recorded in the database; thus, it was assumed that if ritonavir was used with another PI then it was always used as a pharmacological booster rather than at full dosage. Another inclusion criterion for this analysis was to have a pre-ART viral load >400 copies/mL, although we did additionally include patients for whom a viral load measurement was not available. All patients who satisfied the above criteria had at least 1 additional viral load measurement obtained >6 months after therapy initiation.

The time of virological failure was defined as the date of the first of 2 consecutive viral load measurements >400 copies/mL at least 6 months after starting therapy while patients were still receiving at least 1 antiretroviral (ie, viral failure while patients were not receiving ART was not considered to be treatment failure). A single viral load measurement >400 copies/mL was used to define failure in a sensitivity analysis. For the definition of resistance mutations, we adopted the mutations listed in the International AIDS Society–United States of America (IAS-USA) list updated in December 2008 [29]. Conditional on having experienced virological failure according to our definition, factors associated with the probability of having a resistance test performed in a time window ranging between 6 months before and 12 months after the estimated date of failure were identified using logistic regression.

Kaplan-Meier curves were used to estimate the proportion of patients who experienced virological failure by a given time. In addition, the Kaplan-Meier approach was also used to estimate the proportion of patients for whom ⩾1 resistance mutations had been detected by a given time. For example, time to detection of thymidine analogue mutations (TAMs) was defined as the time to detection of ⩾1 TAMs described in the IAS-USA list [29]. Of note, mutations might have been detected before cART was initiated but were not counted until they were detected again on a test during follow-up.

Patient follow-up was right-censored at the last viral load

Table 2. Predictors of Having a Resistance Test Performed around the Time of Virological Failure, from Fitting of a Logistic Regression Model (1359 Patients Experienced Virological Failure)

	Crude analysis		Adjusted analysis	
Factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex				
Male	1.00		1.00	
Female	0.83 (0.66–1.06)	.13	0.92 (0.67–1.27)	.61
Mode of HIV transmission				
Homosexual contact	1.00		1.00	
IDU	0.78 (0.45–1.32)	.35	0.89 (0.50–1.58)	.69
Heterosexual contact	0.88 (0.71–1.11)	.28	0.94 (0.69–1.27)	.67
Other/unknown	1.01 (0.62–1.66)	.96	1.01 (0.60–1.72)	.95
Age, per 10 years older	1.10 (0.96–1.27)	.18	1.02 (0.90–1.20)	.63
Viral load at cART initiation				
1–100,000 copies/mL	1.00		1.00	
>100,000 copies/mL	1.24 (0.96–1.60)	.10	1.09 (0.83–1.44)	.54
Missing	0.93 (0.71–1.21)	.59	0.93 (0.64–1.35)	.77
Viral load at treatment failure (1st of 2 values)				
401–30,000 copies/mL	1.00		1.00	
30,000–100,000 copies/mL	0.88 (0.66–1.17)	.37	0.84 (0.63–1.14)	.26
>100,000 copies/mL	0.95 (0.73–1.23)	.69	0.93 (0.70–1.23)	.60
CD4 count at cART initiation				
>350 cells/μL	1.00		1.00	
201–350 cells/μL	2.27 (1.56–3.29)	<.001	2.15 (1.45–3.19)	<.001
<200 cells/μL	2.75 (1.95–3.89)	<.001	2.86 (1.97–4.16)	<.001
Missing	2.03 (1.40–2.94)	<.001	2.36 (1.50–3.73)	<.001
Diagnosis of AIDS pre-cART				
No	1.00		1.00	
Yes	1.22 (0.95–1.57)	.12	1.13 (0.86–1.49)	.36
Calendar year of cART initiation, per more-recent year	1.06 (1.01–1.11)	.02	1.03 (0.98–1.12)	.22
NRTI pair received				
Abacavir-lamivudine	0.68 (0.37–1.27)	.23	0.55 (0.29–1.05)	.07
Stavudine-lamivudine	0.81 (0.57–1.13)	.21	0.87 (0.60–1.27)	.48
Didanosine-lamivudine	0.91 (0.50–1.65)	.75	0.76 (0.40–1.41)	.38
Didanosine-abacavir	0.96 (0.32–2.90)	.95	0.90 (0.29–2.82)	.87
Didanosine-stavudine	1.33 (0.98–1.82)	.07	1.38 (0.96–1.99)	.09
Tenofovir-lamivudine	2.19 (1.23–3.88)	.008	1.71 (0.93–3.14)	.09
Tenofovir-abacavir	3.37 (0.35–32.56)	.29	2.52 (0.25–25.29)	.46
Tenofovir-stavudine	3.37 (0.35–32.56)	.29	2.53 (0.25–25.40)	.44
Tenofovir-didanosine	1.40 (0.65–3.05)	.39	1.29 (0.58–2.90)	.50
Tenofovir-emtricitabine	3.24 (1.50–7.03)	.003	2.10 (0.91–4.83)	.08
Tenofovir-zidovudine	0.37 (0.04–3.62)	.40	0.13 (0.01–3.44)	.34
Zidovudine-lamivudine (comparator)	1.00		1.00	
Zidovudine-abacavir	2.25 (0.20–24.89)	.51	2.27 (0.20–25.34)	.53
Zidovudine-didanosine	0.55 (0.34–0.90)	.02	0.58 (0.35–0.98)	.04
Other pairs	0.84 (0.35–2.03)	.15	0.99 (0.39–0.69)	.96
Regimen				
NNRTI based	1.00		1.00	
PI/r based	0.97 (0.74–1.28)	.82	0.80 (0.58–1.09)	.17
Transmitted resistance (≥1 IAS-USA mutations)				
No	1.00		1.00	
Yes	1.24 (0.73–2.13)	.43	1.26 (0.72–2.23)	.42
Not tested	0.49 (0.38–0.64)	<.001	0.51 (0.38–0.68)	<.001

NOTE. cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IAS-USA, International AIDS Society–United States of America; IDU, injection drug use; NRTI, nucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI/r, ritonavir-boosted protease inhibitor.

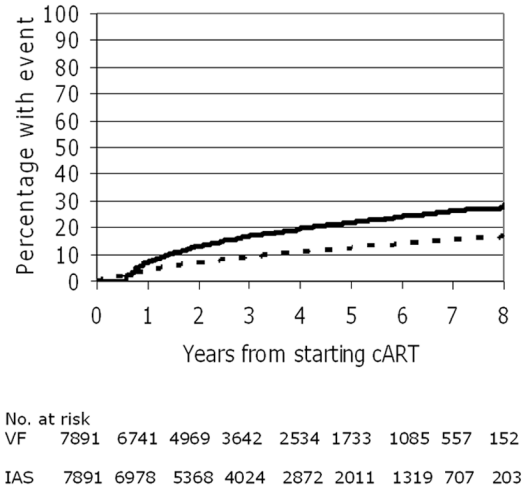

Figure 1. Cumulative proportion of patients with virological failure (>400 copies/mL; *black line*) and with ⩾1 detected International AIDS Society (IAS)–USA resistance mutations (*dashed line*) yearly after starting combination antiretroviral therapy (cART) (ie, resistance might have been detected before ART initiated but not counted until detection during follow-up). VF, virological failure.

measurement, regardless of the end point. Cox proportional hazards regression models were used to assess factors associated with the hazard of detecting resistance mutations. Sex, mode of HIV transmission, age, viral load/CD4 count at initiation of cART, a diagnosis of AIDS prior to starting cART (yes/no), exact NRTI pair started, pre-cART genotypic testing, and whether transmitted resistance was detected in those who were tested (yes/no) were included as potential confounders. Models were stratified by calendar year of starting ART. The logistic regression model included the same set of potential confounders used in the Cox regression models with the addition of calendar year of cART (fitted as continuous) and viral load at time of the test. For the main comparison, sensitivity analyses were performed after restricting analysis to patients who were tested before initiation of cART and in whom no IAS-USA mutations could be detected and to those who started currently recommended NRTI pairs (ie, lamivudine-abacavir, lamivudine-tenofovir, emtricitabine-tenofovir, and zidovudine-lamivudine) [6].

RESULTS

Patients. We studied a total of 7891 patients; their characteristics, stratified by class of the third drug started, are shown in Table 1. The majority of patients started a regimen containing 2 NRTIs and an NNRTI (82%). There was a small, although not negligible, 4% prevalence of NNRTI- and PI-resistance mutations detected in patients before starting these drug classes.

Determinants of having a resistance test performed at virological failure. Overall, 1359 patients (17%) showed evidence of virological failure while receiving ART (only 3% of patients were receiving <3 drugs at failure). Of all patients who experienced failure, 653 (48%) were tested for drug resistance in the time window ranging between 6 months before and 12

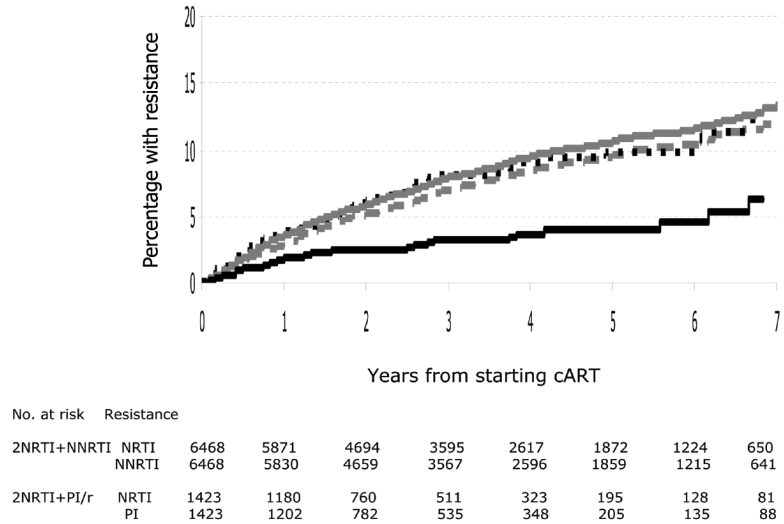

Figure 2. Cumulative proportion of patients with ⩾1 detected International AIDS Society–USA nucleoside reverse-transcriptase inhibitor (NRTI) resistance mutations, ⩾1 nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance mutations (in those who started NNRTI), and ⩾1 protease inhibitor (PI) resistance mutations (in those who started ritonavir-boosted PI [PI/r]), yearly after initiation of combination antiretroviral therapy (cART). *Dashed gray line,* NRTI resistance in patients who started 2 NRTIs plus an NNRTI; *dotted black line,* NRTI resistance in patients who started 2 NRTIs plus a PI/r; *solid gray line,* NNRTI resistance in patients who started 2 NRTIs plus an NNRTI; *solid black line,* PI resistance in patients who started 2 NRTIs plus a PI/r.

Table 3. Kaplan-Meier Estimates of the Percentage of Patients with Detected Resistance by Type of Resistance and Class of Third Drug Started

Detected resistance, drug class	Kaplan-Meier estimate, % of patients (95% CI)		
	By 4 years	By 6 years	By 8 years
TAM			
NNRTI	3.5 (3.0–4.1)	4.2 (3.6–4.9)	5.0 (4.0–6.1)
PI/r	4.3 (2.9–5.6)	5.5 (3.5–7.4)	6.4 (3.8–8.9)
184IV			
NNRTI	6.1 (5.4–6.7)	8.0 (7.1–8.8)	10.7 (9.0–12.3)
PI/r	7.0 (5.2–8.7)	8.9 (6.3–11.4)	8.9 (6.3–11.4)
⩾1 NRTI IAS-USA mutation			
NNRTI	8.6 (7.8–9.4)	10.7 (9.7–11.6)	13.9 (12.1–15.8)
PI/r	9.3 (7.4–11.3)	12.1 (9.1–15.0)	13.7 (10.0–17.3)
⩾1 major class- specific[a] IAS-USA mutation			
NNRTI	9.8 (8.9–10.6)	11.9 (10.9–12.9)	15.2 (13.3–17.0)
PI/r	3.8 (2.5–5.1)	5.2 (3.1–7.2)	6.8 (3.8–9.8)
⩾1 IAS-USA mutation			
NNRTI	11.2 (10.3–12.1)	14.0 (12.9–15.1)	18.3 (16.3–20.2)
PI/r	11.2 (9.1–13.4)	14.7 (11.5–17.9)	17.0 (13.0–21.1)

NOTE. CI, confidence interval; IAS-USA, International AIDS Society–United States of America; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TAM, thymidine analogue mutations.

[a] Major IAS-USA NNRTI resistance mutation for patients starting an NNRTI-based regimen and major IAS-USA PI resistance mutation for those starting a PI/r-based regimen

months after the estimated date of virological failure. The date of genotypic testing was a median of 1 month after the date of failure (range, −6 to 12 months; interquartile range, 0–3 months). Patients with a low CD4 count were more likely to be tested for drug resistance at the time of virological failure than those with less advanced HIV disease at baseline (Table 2). In addition, patients who did not undergo resistance testing before initiation of cART were less likely to be tested at virological failure than patients who were tested when they were ART naive and for whom no IAS-USA mutations were detected in major populations (Table 2).

Incidence of virological failure and drug resistance. By 8 years after starting cART, 28% of patients (95% confidence interval [CI], 27%–31%) had experienced virological failure with viral loads >400 copies/mL (Kaplan-Meier estimates; Figure 1). The Kaplan-Meier estimate of the probability that any resistance was detected by that point was somewhat lower at 17% (95% CI, 15%–19%). The absolute number of patients with detected IAS-USA resistance during the entire follow-up was 798 (10% of patients analyzed). Interestingly, in further Kaplan-Meier analyses, though there was no evidence that the proportion of patients with any nucleoside resistance was different in patients who started 2 NRTIs and an NNRTI, compared with those who started 2 NRTIs and a PI/r ($P = .19$, by log-rank test; $P = .10$, by Wilcoxon test; Figure 2), there was a significant difference in the incidence of class-specific drug resistance. Patients who started a regimen including a PI/r as the third drug were at significantly lower risk of having a PI mutation detected over time than those who started an NNRTI were of having NNRTI resistance detected ($P < .001$, by log-rank and Wilcoxon test; Figure 2). Of note, in the group of patients who started 2 NRTIs and an NNRTI, the rate of detection of NNRTI resistance seemed to be similar to that of nucleoside resistance (Figure 2, *solid and dashed gray lines*). The median number of genotypic tests available was similar in the 2 groups (2 tests; $P = .37$).

Table 3 shows the same Kaplan-Meier estimates reported in Figure 2 but extended to specific subgroups of nucleoside mutations (eg, TAMs, 184IV, etc) presented only at specific time points (4, 6, and 8 years). In addition, the overall incidence of detection of ⩾1 IAS-USA mutation at these same time points is shown separately for the NNRTI and PI/r groups (instead of overall as in Figure 1). Overall, as expected, the incidence of the 184IV mutation (11% by 8 years) was ~2-fold higher than that of ⩾1 TAMs (5%). When we compared the incidence of TAMs and 184IV between the NNRTI and PI/r group, we again found no difference between the groups (adjusted relative hazard [RH], 1.26; 95% CI, 0.88–1.78; $P = .20$ vs RH, 1.04; 95% CI, 0.80–1.35; $P = .77$) (Table 4). The estimates presented in Table 3 also show that the longer the time since starting therapy, the lower the rate of detection of resistance ($P < .001$). The Kaplan-Meier estimates of the percentage of patients switching from their initial third-drug class to the alternative group by 2, 4, 6, and 8 years were 9%, 16%, 23%, and 31%,

Table 4. Relative Hazards (RH) of Resistance Detection by Type of Resistance and Class of Third Drug Started

	Crude analysis		Adjusted analysis[a]	
Detected resistance, drug class	RH (95% CI)	*P*	RH (95% CI)	*P*
TAM				
NNRTI	1.00		1.00	
PI/r	1.55 (1.12–2.14)	.008	1.26 (0.88–1.78)	.20
184IV				
NNRTI	1.00		1.00	
PI/r	1.14 (0.88–1.47)	.32	1.04 (0.80–1.35)	.77
⩾1 NRTI IAS-USA mutation				
NNRTI	1.00		1.00	
PI/r	1.17 (0.94–1.45)	.16	1.00 (0.80–1.26)	.98
⩾1 major class-specific IAS-USA mutation				
NNRTI	1.00		1.00	
PI/r	0.42 (0.31–0.58)	<.001	0.36 (0.26–0.50)	<.001
⩾1 IAS-USA mutation				
NNRTI	1.00		1.00	
PI/r	1.09 (0.90–1.32)	.40	0.92 (0.75–1.13)	.45

NOTE. RHs are calculated by fitting a proportional hazards Cox regression model, stratified by calendar year of starting combination antiretroviral therapy. CI, confidence interval; IAS-USA, International AIDS Society–United States of America; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TAM, thymidine analogue mutations.

[a] Adjusted for sex, mode of human immunodeficiency virus transmission, age, viral load/CD4 count at cART, a diagnosis of AIDS prior to starting cART (yes/no), exact NRTI pair started, pre-cART genotypic testing, and whether transmitted resistance was detected in those who were tested (yes/no).

respectively, in the NNRTI group and 17%, 27%, 31%, and 38%, respectively, in the PI/r group.

Determinants of the risk of detecting different types of resistance mutations over follow-up. Table 4 shows all adjusted RHs of detection of drug resistance according to type of mutation and class of third drug included in the initial regimen. There was a 64% (adjusted RH, 0.36; 95% CI, 0.26–0.50; $P < .001$) lower risk of detecting PI resistance in patients starting PI/r-containing regimens, compared with the risk of detecting NNRTI resistance in those who started NNRTI-based regimens (Table 4). The result for this comparison was similar in 5763 patients who started currently recommended nucleoside pairs (RH, 0.32; 95% CI, 0.21–0.50; $P < .001$) and after restricting the comparison to patients who started before the year 2003 (RH, 0.38; 95% CI, 0.53–0.90; $P < .001$). When using an on-treatment analysis, censoring patients' follow-up 6 months after the date of the switch from the original drug class, results were again similar (RH, 0.33; 95% CI, 0.23–0.47; $P < .001$).

Other factors (not shown in Tables 3 and 4) independently associated with a lower risk of detecting ⩾1 IAS-USA mutations were older age (RH, 0.72 per 10 years older; 95% CI, 0.66–0.79; $P < .001$) and female sex (RH, 0.74; 95% CI, 0.60–0.91; $P = .004$). In contrast, patients with a pre-cART CD4 count of 201–350 cells/μL (RH, 1.25; 95% CI, 0.95–1.65; $P = .11$) or 0–200 cells/μL (RH, 1.71; 95% CI, 1.33–2.21; $P < .001$) were at higher risk of resistance detection than those with a CD4 count >350 cells/μL. Similarly, patients with a pre-cART viral load of >100,000 copies/mL were at increased risk of resistance detection, compared with those with a viral load of 501–10,000 copies/mL (RH, 1.22; 95% CI, 1.02–1.45; $P = .03$). When comparing the initial nucleoside usage, patients who started didanosine-stavudine (RH, 2.26; 95% CI, 1.80–2.84; $P < .001$), tenofovir-lamivudine (RH, 1.52; 95% CI, 1.13–2.06; $P = .006$) or tenofovir-didanosine (RH, 2.70; 95% CI, 1.77–4.11; $P < .001$) showed an increased risk of resistance detection, compared with those who started zidovudine-lamivudine. Among the third drugs in cART regimens, with use of efavirenz as the comparator, starting nevirapine (RH, 1.98; 95% CI, 1.66–2.36; $P < .001$) or amprenavir (RH, 3.75; 95% CI, 1.17–11.99; $P = .03$) was associated with a higher rate of resistance detection. Finally, not surprisingly, patients in whom resistance was detected before starting cART showed a 5-fold increased risk of both virological failure (RH, 2.03; 95% CI, 1.56–2.63; $P < .001$) and long-term detection of resistance (RH, 5.03; 95% CI, 3.87–6.52; $P < .001$), compared with those who were tested and in whom no IAS-USA mutations could be detected before initiation of cART. In contrast, there was no difference for those with no test available with regard to virological failure (RH, 1.06; 95% CI, 0.92–1.21; $P = .45$) or probability of detecting resistance (RH, 0.97; 95% CI, 0.80–1.16; $P = .70$). Of note, there was no evidence that the rate of detection of ⩾1 IAS-USA mutations was higher in injection drug users, compared

with homosexual men (RH, 1.21; 95% CI, 0.81–1.80; $P = .34$).

Sensitivity analyses in patients with a genotypic test performed before cART initiation. Of the subset of 2626 (33%) patients for whom a genotypic test performed before starting cART was available, 2338 (89%) had no major IAS-USA mutations detected at this test. In this subset of patients, the 8-year Kaplan-Meier estimate of the probability of virological failure was 22% (95% CI, 18%–26%), and the estimate of the probability of detection of ⩾1 IAS-USA mutations was 14% (95% CI, 10%–18%) overall, 15% (95% CI, 11%–19%) in those who started an NNRTI, and 6% (95% CI, 2%–10%) in those who started a PI/r. This difference was maintained after adjusting for potential confounding factors (PI/r vs NNRTI RH, 0.49; 95% CI, 0.28–0.84; $P = .009$). When we compared the rate of detection of class-specific mutations between the NNRTI and PI/r group in the 2338-patient subset, the magnitude of the difference in rates was even larger and remained highly statistically significant (PI/r vs NNRTI RH, 0.11; 95% CI, 0.03–0.34; $P < .001$). The association of the risk of detection of ⩾1 IAS-USA resistance mutation with other factors identified in the main analysis (younger age, high viral load, and low CD4 count at cART initiation; didanosine-stavudine, tenofovir-lamivudine, and tenofovir-didanosine vs zidovudine-lamivudine; and nevirapine vs efavirenz) was confirmed in this subgroup analysis.

DISCUSSION

This study provides estimates of the long-term risk of virological failure and of acquiring resistance mutations in the first 8 years of treatment in patients who started cART with currently recommended treatments in routine clinical practice. Detection of resistance mutations was relatively common, with 5%, 11%, and 17% of patients estimated to have TAM, 184IV, and ⩾1 IAS-USA–listed mutations, respectively, detected by 8 years from the start of cART (the latter percentage decreased to 14% when we studied only patients with no detected resistance before starting cART). In patients who started an NNRTI-based regimen, we estimated a rate of detection of NNRTI resistance mutations of 15%, which is double the rate of PI resistance mutations detected in those who started PI/r-based regimens.

Our results are likely to be an underestimation of the true percentage of people with resistance for 2 reasons. First, because resistance testing was performed in <50% of those who experienced virological failure and, second, because routinely used genotypic assays are not sufficiently sensitive to detect the presence of mutations in minority variants. The true estimate of the likelihood of resistance emerging is likely to lie between our estimate (17% by 8 years) and the risk of experiencing confirmed virological failure (28% by 8 years). When considered against the background of a likely lifelong need for ART, these levels of risk of resistance emergence are of some concern. Nevertheless, a nonnegligible proportion of patients in our study populations started combinations that may be less potent than those started by the average patient initiating therapy today; therefore, it is possible that our estimates are somewhat pessimistic.

After controlling for confounders, the risk of detecting PI-specific mutations in people receiving regimens containing a PI/r was one-third that of detecting NNRTI-specific mutations in those receiving NNRTI regimens. This did not appear to be explained by a greater rate of transmitted resistance in the PI/r group, because the difference was even more marked in a sensitivity analysis including only patients who were tested before starting cART and in whom no IAS-USA mutations could be detected. This finding is consistent with other evidence suggesting that resistance mutations have a low probability of emerging in patients who use PI/r-based regimens [1, 2], although the overall rate of detection of resistance appears to be higher in our analysis, compared with the estimates from clinical trials [5]. Of note, we used an intention-to-treat approach to the analysis, and although the percentage of patients switching from one to the other group was relatively small, our results cannot be interpreted as the difference between patients who continued receiving their initial treatment for the whole length of follow-up. Nevertheless, results were similar when we used an on-treatment approach to the analysis.

In addition, analyses of clinical trials data have shown a difference in the rate of detection of both resistance to NRTIs and class-specific mutations [5, 17], whereas in our analysis we could only find a significant difference for the latter. When restricting the analysis to patients with no detection of resistance before initiating cART, we also found a higher rate of any IAS-USA mutation detected in the NNRTI group, compared with the PI/r group. However, despite the apparent similarities between the NNRTI and PI/r group at cART initiation, we cannot rule out that our comparison may be biased by confounding by indication [30, 31]. Because NNRTIs are often prescribed to patients with unstable lifestyles (eg, injection drug users), this analysis cannot prove that the difference in rate of resistance is truly an effect of the drug class (inherent fragility of the NNRTI class) or a behavioral effect that cannot be adequately controlled for (eg, nonadherence).

We also found that patients who started their first cART with a regimen including didanosine and/or tenofovir had an increased risk of acquiring ⩾1 resistance mutations, compared with those who received zidovudine-lamivudine as their initial nucleoside pair. This is inconsistent with the results of a smaller Italian study [32]. Observational studies conducted so far have produced medium- to long-term estimates of the probability of detecting resistance from the start of ART, although these studies included patients starting regimens that are no longer

used as first-line treatments [1–4]. The estimates of resistance development coming from the analysis of data of the HOMER cohort seem to be consistent with ours, including 8% for nonlamivudine nucleoside resistance, 6% for PI resistance, and 10% for NNRTI resistance by 3 years after initiation of cART, but their estimate for lamivudine resistance and any IAS-USA mutation appear to be higher than ours [3, 4]. In agreement with the results of Wood et al [3], we found that the rate of detection of resistance was not different in patients who acquired HIV via intravenous injection of drugs, compared with those infected through other modes of transmission. A high viral load at the time of cART initiation was independently associated with a higher risk of detecting resistance, possibly suggesting that patients who receive a diagnosis and treatment late are also those who are likely to be less adherent to ART. The results of an analysis of the Swiss HIV Cohort Study [2] are consistent with ours in showing that patients who started an NNRTI-based regimen demonstrate a markedly higher risk of losing multiple drug classes in cases of treatment failure. Our analysis cannot prove that factors indicated (eg, CD4 count at cART initiation) were solely associated with the risk of resistance, because they were also associated with the chance of being tested. The main limitations of our analysis, besides the lack of randomization, are the limited frequency of genotypic testing available at treatment failure and the lack of information regarding patients' adherence to cART.

In conclusion, in patients starting currently recommended first-line regimens in routine clinical practice, the rates of virological failure and of resistance detection are appreciable, although the rates are lower for those who started cART with a PI/r-based regimen.

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