MAJOR ARTICLE

Rates of Disease Progression according to Initial Highly Active Antiretroviral Therapy Regimen: A Collaborative Analysis of 12 Prospective Cohort Studies

The Antiretroviral Therapy Cohort Collaboration[a]

(See the editorial commentary by Hughes, on pages 542–4.)

Background. No large clinical end-point trials have been conducted comparing regimens among human immunodeficiency virus type 1–positive persons starting antiretroviral therapy. We examined clinical progression according to initial regimen in the Antiretroviral Therapy Cohort Collaboration, which is based on 12 European and North American cohort studies.

Methods. We analyzed progression to death from any cause and to AIDS or death (AIDS/death), comparing efavirenz (EFV), nevirapine (NVP), nelfinavir, idinavir, ritonavir (RTV), RTV-boosted protease inhibitors (PIs), saquinavir, and abacavir. We also compared nucleoside reverse-transcriptase inhibitor pairs: zidovudine/lamivudine (AZT/3TC), stavudine (D4T)/3TC, D4T/didanosine (DDI), and others.

Results. A total of 17,666 treatment-naive patients, 55,622 person-years at risk, 1617 new AIDS events, and 895 deaths were analyzed. Compared with EFV, the adjusted hazard ratio (HR) for AIDS/death was 1.28 (95% confidence interval [CI], 1.03–1.60) for NVP, 1.31 (95% CI, 1.01–1.71) for RTV, and 1.45 (95% CI, 1.15–1.81) for RTV-boosted PIs. For death, the adjusted HR for NVP was 1.65 (95% CI, 1.16–2.36). The adjusted HR for death for D4T/3TC was 1.35 (95% CI, 1.14–1.59), compared with AZT/3TC.

Conclusions. Outcomes may vary across initial regimens. Results are observational and may have been affected by bias due to unmeasured or residual confounding. There is a need for large, randomized, clinical end-point trials.

Several clinical trials have compared the effects that nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based and protease inhibitor (PI)–based highly active antiretroviral therapy (HAART) has on biological end points [1–3]. Most recently, the 2NN trial compared efavirenz (EFV)–based and nevirapine (NVP)–based NNRTI regimens and demonstrated that both were valid options for first-line therapy [2]. Other studies have compared the effectiveness of EFV-based and nelfinavir (NFV)–based HAART regimens [4, 5], and the Atlantic and Combine Studies compared NVP-based with idinavir (IDV)- and NFV-based HAART regimens, respectively [3, 6, 7]. However, no trials have compared the clinical efficacy of the most commonly prescribed regimens [8].

In the absence of large-scale trials directly comparing HAART regimens, observational studies might be the

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[a] Analysis and writing committee members are listed at the end of the text, and a complete list of study group members is given in the Appendix, which appears only in the electronic edition of the *Journal*.

only means of identifying potential differences in rates of clinical progression. Several studies have been undertaken [9–13], but none to date has been large enough to examine differences in rates of clinical progression or death. The objective of the present study was to examine whether rates of progression differed according to initial HAART regimen among patients initiating therapy with either a NNRTI- or PI-based regimen.

METHODS

ART Cohort Collaboration (ART-CC). The ART-CC is a multinational prospective study of ART-naive HIV-positive patients initiating HAART. The study has been described in detail elsewhere [14–17]. It includes 12 cohort studies from Canada, Europe, and the United States: the French Hospital Database on HIV; the Italian Cohort of Antiretroviral-Naive Patients; the Swiss HIV Cohort Study; the AIDS Therapy Evaluation Project Netherlands; the Multicenter Study Group on EuroSIDA; Collaborations in HIV Outcomes Research–US; the Frankfurt HIV Cohort Study; the Aquitaine Cohort Study; the HAART Observational Medical Evaluation and Research Cohort Study, British Columbia Centre for Excellence in HIV/AIDS; the Royal Free Hospital Cohort Study; the South Alberta Clinic Cohort Study; and the Köln/Bonn Cohort Study. All cohort studies have been approved by institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least once every 6 months. Patient selection and data extraction for the present study were performed at the cohorts' data centers. Anonymized data on a predefined set of demographic, laboratory, and clinical variables were pooled and analyzed centrally.

Statistical analyses. Analyses were restricted to patients who were HIV-1 positive, were ⩾16 years old, had an HIV-1 RNA level ⩾1000 copies/mL at treatment initiation, and first started HAART after 1 January 1996. The primary end points were death from any cause and the combined end point of a new AIDS-defining illness or death (AIDS/death). All centers used the 1993 US Centers for Disease Control and Prevention (CDC) criteria for the definitive or presumptive diagnosis of AIDS-defining opportunistic events [18]. A new AIDS diagnosis was defined as the first occurrence of each AIDS-defining condition; recurrences were not considered. Detectable HIV-1 RNA level (>500 copies/mL) and change in regimen at 6 months after initiation of HAART were secondary outcomes.

We measured time from the date of initiation of therapy to the date the end points occurred. For patients free of events, follow-up was censored either on the date of the most recent follow-up visit (for the combined end point) or on the date the patient was last known to be alive (for mortality). Cox regression was used to model the effect that initial treatment regimen and other prognostic factors have on disease progression [19]. All models were stratified by cohort (12 strata) and by calendar year of starting HAART (from 1996 onward, with 2002 and 2003 grouped together; 7 strata). We estimated hazard ratios (HRs) with 95% confidence intervals (CIs), comparing 8 third drugs: EFV, abacavir (ABC), a boosted PI (amprenavir, lopinavir, saquinavir [SQV], or IDV), IDV, NFV, NVP, ritonavir

Table 1. Baseline prognostic factors for study patients, by third drug and nucleoside reverse-transcriptase inhibitor (NRTI) pair.

Category	Patients, no. (%)	Age, median (IQR), years	CD4 cell count, median (IQR), cells/μL	HIV-1 RNA level, median (IQR), log copies/mL	CDC clinical stage C, %	IDU, %
Third drug						
EFV	2254 (13)	36 (31–43)	225 (111–341)	4.9 (4.5–5.4)	22	13
NVP	2378 (13)	36 (30–42)	293 (180–425)	4.7 (4.2–5.1)	12	17
NFV	3802 (22)	36 (31–42)	200 (76–353)	5.0 (4.5–5.4)	27	14
RTV	1148 (7)	36 (31–43)	200 (84–374)	5.1 (4.4–5.5)	22	19
SQV	1145 (6)	35 (31–41)	288 (130–417)	4.9 (4.4–5.4)	18	25
RTV-boosted PI	1285 (7)	37 (32–44)	130 (40–276)	5.2 (4.7–5.7)	34	9
IDV	4555 (26)	36 (31–42)	228 (81–380)	5.0 (4.5–5.5)	24	20
ABC	1099 (6)	36 (31–43)	260 (169–369)	4.7 (4.3–5.1)	15	15
NRTI pair						
AZT/3TC	10,964 (62)	36 (31–43)	236 (104–371)	4.9 (4.3–5.4)	21	15
D4T/3TC	3468 (20)	36 (31–42)	200 (70–357)	5.0 (4.4–5.5)	30	18
D4T/DDI	1716 (10)	35 (31–42)	230 (89–385)	4.9 (4.3–5.4)	23	15
Other	1518 (9)	36 (31–41)	256 (121–392)	4.9 (4.5–5.4)	19	26
Overall	17,666	36 (31–42)	230 (97–372)	4.9 (4.4–5.4)	22	17

NOTE. 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; CDC, Centers for Disease Control and Prevention; D4T, stavudine; DDI, didanosine; EFV, efavirenz; IDU, injection drug use; IDV, idinavir; IQR, interquartile range; NFV, nelfinavir; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir.

Table 2. Receipt of each drug, by cohort.

The table is available in its entirety in the online edition of *The Journal of Infectious Diseases*

(RTV), and SQV (soft or hard). These models also compared nucleoside reverse-transcriptase inhibitor (NRTI) pairs: zidovudine/lamivudine (AZT/3TC), stavudine (D4T)/3TC, D4T/didanosine (DDI), and others. Patients treated with 4 or more drugs (except when the fourth drug was low-dose RTV used as part of a boosted PI regimen) were excluded from the analyses. We used EFV as the comparator for the third drugs and AZT/3TC as the comparator for the NRTI pairs. Variables considered were age at initiation of HAART (16–29, 30–39, 40–49, and ⩾50 years), sex, transmission risk group (injection drug use [IDU] or non-IDU), CDC clinical stage (A/B or C), CD4 cell count (<25, 25–49, 50–99, 100–199, 200–349, and ⩾350 cells/μL), and plasma HIV-1 RNA level (1000–9999, 10,000–99,999, and ⩾100,000 copies/mL). Variables with Wald $P > .2$ were omitted from the final models. Analyses followed an "intent to continue initial regimen" principle, in that eligible patients were analyzed according to initial regimen, regardless of whether they later discontinued or modified their therapeutic regimen.

We compared the effect that initial regimen had on HIV-1 RNA levels and regimen change at 6 months. Logistic regression models were used to estimate the crude and adjusted odds ratios (ORs) for detectable HIV-1 RNA level (i.e., >500 copies/mL), first for patients with available measurements at 6 months and second for all patients, using the combined-failure end point: detectable HIV-1 RNA level, death, or missing data on HIV-1 RNA level. Logistic models were also used to estimate the crude and adjusted ORs at 6 months for not receiving the initial regimen, first restricted to patients who had clinical follow-up measurements at 6 months (i.e., failure was considered to be either a change of drug regimen or cessation of HAART) and second for all patients (i.e., failure included regimen change, cessation of HAART, death, or missing data). Finally, we assessed whether there was evidence of between-cohort heterogeneity in the effects that initial regimen had on progression to AIDS/death by estimating the effect of initial regimen separately in each cohort and then combining these estimates by use of random-effects meta-analysis. The proportion of the total variance due to heterogeneity between cohorts was estimated using the I^2 statistic [20].

RESULTS

A total of 17,666 patients (55,622 person-years at risk) were available for analyses. A total of 1617 new AIDS events, 895 deaths, and 2017 AIDS cases or deaths were observed over the study period. Table 1 shows prognostic factors by initial drug regimen. The most common third drugs in a combination were IDV (26%), NFV (22%), and EFV and NVP (13%, for both). The most widely used NRTI pair was AZT/3TC (62%), followed by D4T/3TC (20%) and D4T/DDI (10%). The percentage of patients with AIDS ranged from 12% to 34%, and the percentage of patients with a history of IDU ranged from 9% to 26%. At initiation of treatment, the median CD4 cell count was lower in patients receiving RTV-boosted PIs than in patients receiving other regimens (130 vs. 240 cells/μL). The number and percentage of patients receiving each drug by cohort and by calendar year is shown in tables 2 and 3.

Table 4 shows crude and adjusted HRs for AIDS/death and for death, for both third drugs and for NRTI pairs. When AIDS/death was considered, the adjusted HRs were 1.28 (95% CI, 1.03–1.60) for NVP, 1.31 (95% CI, 1.01–1.71) for RTV, and 1.45 (95% CI, 1.15–1.81) for boosted regimens. There was little difference in the effect of the NRTI pairs. When mortality was considered, patients receiving EFV appeared to do best, but there was little evidence that the HR for death differed according to other third drugs, except for NVP: the adjusted HR relative to EFV was 1.65 (95% CI, 1.16–2.36). Compared with patients receiving AZT/3TC, the adjusted HR for death for patients receiving D4T/3TC was 1.35 (95% CI, 1.14–1.59). Again, there was little evidence of differences in rates according to other NRTI pairs. We found little evidence of between-cohort heterogeneity in the effect that the drugs had on clinical outcomes, except for RTV-boosted PIs ($I^2 = 47\%$) and D4T/3TC ($I^2 = 56\%$). The heterogeneity of the effect that RTV-boosted PIs had among cohorts might have been due to different PIs being prescribed.

Table 5 shows crude and adjusted ORs for detectable HIV-1 RNA level at 6 months after initiation of HAART for each third drug and NRTI pair. Patients who started with EFV-containing regimens were more likely than patients who started with any other third drug to suppress HIV-1 RNA level by the 6-month time point: adjusted ORs for the comparison with EFV ranged from 1.67 (95% CI, 1.35–2.07) for boosted PIs to 5.33 (95% CI, 4.25–6.69) for SQV. These patterns were also seen when patients with missing data or who had died were considered to have experienced virological failure, although ORs were generally attenuated. Patients receiving other NRTI pairs were at greater risk of having a detectable HIV-1 RNA level at 6 months, compared with patients receiving AZT/3TC. Table 6 shows the crude and adjusted ORs for regimen change at 6 months after initiation of HAART for each third drug and NRTI pair. The drug most likely to result in regimen change

Table 3. Receipt of each drug, by year of starting highly active antiretroviral therapy.

The table is available in its entirety in the online edition of *The Journal of Infectious Diseases*

Table 4. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the end point of death from any cause and for the combined end point of AIDS or death (AIDS/death).

Category	Patients, no.	Events, no (%)	Follow-up, years	HR (95% CI)	
				Crude	Adjusted[a]
End point of AIDS/death					
Third drug					
EFV	2007	162 (8)	3617	1	1
NVP	2252	192 (9)	5341	1.04 (0.84–1.30)	1.28 (1.03–1.60)
NFV	3361	460 (14)	9339	1.50 (1.23–1.82)	1.18 (0.97–1.44)
RTV	1034	170 (16)	4082	1.60 (1.23–2.08)	1.31 (1.01–1.71)
SQV	1090	149 (14)	4181	1.32 (1.00–1.73)	1.21 (0.92–1.60)
RTV-boosted PI	1118	189 (17)	2478	2.07 (1.65–2.58)	1.45 (1.15–1.81)
IDV	4159	632 (15)	15,376	1.51 (1.21–1.87)	1.18 (0.94–1.47)
ABC	1006	63 (6)	1647	0.73 (0.54–0.99)	0.90 (0.66–1.22)
NRTI pair					
AZT/3TC	10,043	1139 (11)	27,867	1	1
D4T/3TC	3095	493 (16)	9380	1.37 (1.23–1.54)	1.11 (0.99–1.24)
D4T/DDI	1500	207 (14)	4440	1.23 (1.06–1.44)	1.14 (0.97–1.34)
Other	1389	178 (13)	4374	1.05 (0.89–1.24)	1.09 (0.92–1.29)
Overall	16,027	2017 (13)	46,060	…	…
End point of death					
Third drug					
EFV	2254	58 (3)	4344	1	1
NVP	2378	92 (4)	6127	1.41 (1.00–2.00)	1.65 (1.16–2.36)
NFV	3802	191 (5)	11,615	1.38 (1.00–1.89)	1.07 (0.77–1.47)
RTV	1148	91 (8)	5051	1.58 (1.06–2.35)	1.36 (0.91–2.02)
SQV	1145	67 (6)	4790	1.15 (0.75–1.75)	1.15 (0.75–1.75)
RTV-boosted PI	1285	52 (4)	3174	1.57 (1.07–2.32)	1.14 (0.77–1.69)
IDV	4555	318 (7)	18,658	1.47 (1.04–2.08)	1.20 (0.85–1.71)
ABC	1099	26 (2)	1862	1.07 (0.66–1.74)	1.27 (0.77–2.09)
NRTI pair					
AZT/3TC	10,964	462 (4)	32,927	1	1
D4T/3TC	3468	255 (7)	12,005	1.60 (1.36–1.88)	1.35 (1.14–1.59)
D4T/DDI	1716	96 (6)	5551	1.25 (0.99–1.57)	1.15 (0.91–1.45)
Other	1518	82 (5)	5139	1.10 (0.86–1.41)	1.13 (0.88–1.46)
Overall	17,666	895 (5)	55,623	…	…

NOTE. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; EFV, efavirenz; IDV, idinavir; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir.

[a] Adjusted for age, injection drug use, clinical stage, CD4 cell count, and HIV-1 RNA level and stratified by cohort and year of starting HAART.

was RTV (adjusted OR, 4.53 [95% CI, 3.69–5.57]). ORs were slightly attenuated when those patients with missing data or who had died were considered to have experienced treatment failure.

In sensitivity analyses, we examined whether the NRTI pair modifies the effect of NFV (compared with that of EFV) by including an interaction term in the model. There was no evidence of interaction between EFV or NFV and the NRTI pairs for AIDS/death ($P = .36$) or for death ($P = .78$). However, there was evidence of interaction for the outcome of detectable HIV-1 RNA level at 6 months ($P = .02$) and of regimen change at 6 months ($P = .04$). For suppression of HIV-1 RNA level, EFV was more effective with AZT/3TC than with D4T/DDI, but there was no evidence of a difference in efficacy between the NRTI pairs when combined with NFV. In light of the results for regimen change, it appears that the combination of EFV with D4T/DDI was less likely to be maintained than was AZT/3TC, whereas NFV was most frequently maintained with D4T/DDI as the NRTI pair.

We examined whether the adjusted HR for NVP (compared with EFV) for all-cause mortality remained elevated if we restricted follow-up to 6 months, when patients were most likely to be still receiving their initial regimen. Compared with EFV, the adjusted HR for all-cause mortality for NVP was 2.28 (95%

Table 5. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for detectable HIV-1 RNA level at 6 months after initiation of highly active antiretroviral therapy (HAART), for patients with a 6-month HIV-1 RNA measurement (end point considered as detectable HIV-1 RNA level at 6 months) and for all patients (end point considered as detectable HIV-1 RNA level at 6 months, missing, or dead).

Category	Patients, no.	Events, no (%)	OR (95% CI)	
			Crude	Adjusted[a]
Patients with an HIV-1 RNA measurement at 6 months				
Third drug				
EFV	1898	236 (12)	1	1
NVP	2095	455 (22)	1.95 (1.65–2.32)	2.19 (1.83–2.62)
NFV	3233	754 (23)	2.14 (1.83–2.51)	2.19 (1.85–2.59)
RTV	997	267 (27)	2.58 (2.12–3.13)	2.20 (1.75–2.78)
SQV	1033	508 (49)	6.81 (5.68–8.18)	5.33 (4.25–6.69)
RTV-boosted PI	1153	205 (18)	1.52 (1.24–1.87)	1.67 (1.35–2.07)
IDV	3907	984 (25)	2.37 (2.03–2.77)	2.05 (1.69–2.48)
ABC	956	190 (20)	1.75 (1.42–2.15)	1.89 (1.52–2.35)
NRTI pair				
AZT/3TC	9443	2090 (22)	1	1
D4T/3TC	2984	651 (22)	0.98 (0.89–1.08)	0.90 (0.81–1.00)
D4T/DDI	1494	380 (25)	1.20 (1.06–1.36)	1.14 (0.99–1.30)
Other	1351	478 (35)	1.93 (1.71–2.18)	1.31 (1.15–1.51)
Overall	15,272	3599 (24)	…	…
All patients				
Third drug				
EFV	2254	592 (26)	1	1
NVP	2378	738 (31)	1.26 (1.11–1.44)	1.62 (1.42–1.86)
NFV	3802	1323 (35)	1.50 (1.34–1.68)	1.53 (1.35–1.74)
RTV	1148	418 (36)	1.61 (1.38–1.87)	1.59 (1.32–1.91)
SQV	1145	620 (54)	3.32 (2.86–3.85)	3.29 (2.73–3.97)
RTV-boosted PI	1285	948 (74)	1.00 (0.85–1.17)	1.18 (1.01–1.39)
IDV	4555	1632 (36)	1.57 (1.40–1.75)	1.63 (1.41–1.88)
ABC	1099	333 (30)	1.22 (1.04–1.43)	1.46 (1.23–1.72)
NRTI pair				
AZT/3TC	10,964	3611 (33)	1	1
D4T/3TC	3468	1135 (33)	0.99 (0.91–1.07)	0.93 (0.85–1.01)
D4T/DDI	1716	602 (35)	1.10 (0.99–1.22)	1.06 (0.94–1.19)
Other	1518	645 (42)	1.50 (1.35–1.68)	1.19 (1.06–1.35)
Overall	17,666	5993 (34)	…	…

NOTE. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; EFV, efavirenz; IDV, idinavir; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir.

[a] Adjusted for age, injection drug use, clinical stage, CD4 cell count, HIV-1 RNA level, and year of starting HAART.

CI, 1.20–4.36) during the first 6 months, which decreased to 1.31 (95% CI, 0.81–2.18) after 6 months. We examined the hypothesis that, because of selective differences in toxicities, patients who initiated therapy at a high CD4 cell count would be at a greater risk of death if they were receiving NVP-based HAART than would those receiving other regimens. We believed that this difference would be especially pronounced in women and those who were positive for hepatitis C virus (HCV). Table 7 shows HRs for death, comparing NVP with all other third drugs in models including interaction terms for sex, high CD4 cell count ($\geq$350 cells/μL), and IDU, first for all patients and second restricted to patients with known HCV status. The data are consistent with the hypothesis that the risk of death is increased in women with high CD4 cell counts, especially those who are HCV positive. However, the power to detect interaction effects was low.

Table 6. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for regimen change at 6 months, for patients with 6 months of follow-up (end point considered as regimen change at 6 months) and for all patients (end point considered as regimen change at 6 months, missing, or dead).

Category	Patients, no.	Events, no. (%)	OR (95% CI)	
			Crude	Adjusted[a]
Patients with 6 months of follow-up				
Third drug				
EFV	2106	466 (22)	1	1
NVP	2146	539 (25)	1.18 (1.02–1.36)	1.40 (1.20–1.64)
NFV	3501	756 (22)	0.97 (0.85–1.10)	1.09 (0.94–1.27)
RTV	1055	483 (46)	2.97 (2.54–3.48)	4.53 (3.69–5.57)
SQV	1067	324 (30)	1.53 (1.30–1.81)	2.21 (1.78–2.74)
RTV-boosted PI	1182	473 (40)	2.35 (2.01–2.74)	2.82 (2.38–3.34)
IDV	4233	1203 (28)	1.40 (1.24–1.58)	2.03 (1.72–2.40)
ABC	996	199 (20)	0.88 (0.73–1.06)	0.88 (0.72–1.08)
NRTI pair				
AZT/3TC	10,101	2808 (28)	1	1
D4T/3TC	3159	685 (22)	0.72 (0.65–0.79)	0.64 (0.58–0.71)
D4T/DDI	1618	483 (34)	1.11 (0.99–1.24)	1.07 (0.95–1.22)
Other	1408	467 (34)	1.29 (1.14–1.45)	1.24 (1.09–1.42)
Overall	16,286	4443 (27)	…	…
All patients				
Third drug				
EFV	2254	614 (27)	1	1
NVP	2378	771 (32)	1.28 (1.13–1.45)	1.51 (1.31–1.73)
NFV	3802	1057 (28)	1.03 (0.92–1.16)	1.21 (1.06–1.38)
RTV	1148	576 (50)	2.69 (2.32–3.12)	4.37 (3.62–5.28)
SQV	1145	402 (34)	1.45 (1.24–1.68)	2.20 (1.80–2.68)
RTV-boosted PI	1285	576 (43)	2.17 (1.88–2.51)	2.71 (2.32–3.17)
IDV	4555	1525 (33)	1.34 (1.20–1.50)	2.09 (1.80–2.42)
ABC	1099	302 (27)	1.01 (0.86–1.19)	1.00 (0.84–1.18)
NRTI pair				
AZT/3TC	10,964	3671 (33)	1	1
D4T/3TC	3468	994 (29)	0.80 (0.73–0.87)	0.69 (0.63–0.76)
D4T/DDI	1716	581 (34)	1.02 (0.91–1.13)	1.02 (0.91–1.15)
Other	1518	577 (38)	1.22 (1.09–1.36)	1.22 (1.08–1.38)
Overall	17,666	5823 (33)	…	…

NOTE. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; EFV, efavirenz; IDV, idinavir; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir.

[a] Adjusted for age, injection drug use, clinical stage, CD4 cell count, HIV-1 RNA level, and year of starting HAART.

We evaluated patterns of survival after 6 months of therapy, accounting for the initial response to HAART. The adjusted model controlled for CDC clinical stage, CD4 cell count, and HIV-1 RNA level at 6 months as well as age, IDU status, and clinical stage at initiation of HAART. At 6 months, compared with EFV, elevated crude HRs for mortality were observed for RTV (1.73 [95% CI, 1.02–2.91]) and for RTV-boosted PI regimens (1.76 [95% CI, 1.02–3.01]). However, these HRs were attenuated in the multivariable analysis, to 1.09 (95% CI, 0.64–1.87) for RTV and to 1.00 (95% CI, 0.58–1.73) for boosted regimens, suggesting that the higher HRs resulted from poor immunological and virological response during the first 6 months. The corresponding crude HR for NVP was 1.57 (95% CI, 0.97–2.54), which was attenuated to 1.33 (95% CI, 0.81–2.18). Therefore, the excess deaths in those who started with NVP, compared with deaths in those who started with EFV, might not have been the result of poor initial response. Among those who subsequently died, the mean CD4 cell count mea-

Table 7. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the end point of death from any cause, comparing nevirapine with other third drugs in models including interactions with sex, CD4 cell count, injection drug use (IDU), and hepatitis C virus (HCV) infection status.

Interaction	Adjustments	Subgroup	Patients, no.	Deaths, no.	HR (95% CI)	*P* for interaction
All patients						
Sex	IDU, age, CD4, HIV-1 RNA, clinical stage, NRTI pair	Overall	17,666	895	1.47 (1.16–1.87)	.54
		Male	13,326	727	1.42 (1.08–1.86)	
		Female	4340	168	1.65 (1.06–2.57)	
CD4 cell count	IDU, age, sex, HIV-1 RNA, clinical stage, NRTI pair	Overall	17,666	895	1.40 (1.10–1.78)	.13
		<350 cells/μL	12,633	776	1.28 (0.97–1.68)	
		$\geqslant$350 cells/μL	5033	119	1.89 (1.22–2.94)	
IDU	Age, sex, CD4, HIV-1 RNA, clinical stage, NRTI pair	Overall	17,666	895	1.47 (1.16–1.87)	.18
		Non-IDU	14,751	626	1.63 (1.24–2.14)	
		IDU	2915	269	0.72 (0.44–1.17)	
Patients with HCV status						
IDU	Age, sex, CD4, HIV-1 RNA, clinical stage, NRTI pair	Overall	6096	315	1.71 (1.11–2.64)	.63
		Non-IDU	4640	188	1.86 (1.08–3.18)	
		IDU	1456	127	1.52 (0.79–2.92)	
IDU controlling for HCV	HCV, age, sex, CD4, HIV-1 RNA, clinical stage, NRTI pair	Overall	6096	315	1.72 (1.11–2.65)	.75
		Non-IDU	4640	188	1.81 (1.06–3.11)	
		IDU	1456	127	1.59 (0.83–3.03)	
HCV	IDU, age, sex, CD4, HIV-1 RNA, clinical stage, NRTI pair	Overall	6096	315	1.72 (1.11–2.65)	.27
		HCV negative	3968	153	1.29 (0.65–2.57)	
		HCV positive	2128	162	2.05 (1.22–3.44)	

NOTE. NRTI, nucleoside reverse-transcriptase inhibitor.

Table 8. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the end point of death from any cause and for the combined end point of AIDS or death (AIDS/death), from sensitivity analyses for all patients but with follow-up censored at 2 years after starting highly active antiretroviral therapy (HAART) and restricted to patients without a history of injection drug use (IDU), patients with a history of IDU, patients starting HAART after 1 January 1998, and patients with a CD4 cell count >200 cells/μL at initiation of HAART.

The table is available in its entirety in the online edition of *The Journal of Infectious Diseases*

sured at 6 months was 403 cells/μL for those who started with NVP, compared with 294 cells/μL for those who started with other drugs, showing that the deaths of those who started with NVP occurred in less immunologically suppressed individuals.

We examined whether the effects of drug regimens differed according to whether patients' presumed transmission was via IDU. Models including and excluding the interaction between each third drug and IDU status were compared using likelihood ratio tests. In analyses that used separate models for IDU and non-IDU, the HRs for the third drugs were generally attenuated for non-IDU and increased for IDU. There was evidence only of an interaction between the third drug and IDU for NVP ($P = .05$). Results from analyses restricted to patients with a history of IDU, patients without a history of IDU, patients with a baseline CD4 cell count >200 cells/μL, and patients who started HAART after 1 January 1998 and for all patients but with follow-up censored at 2 years after starting HAART are presented in table 8. Censoring at 2 years did not affect estimates substantially. The HR for NVP was increased to 1.43 (95% CI, 0.97–2.10) in patients with a CD4 cell count >200 cells/μL at initiation of HAART. When the analysis was restricted to those starting HAART after 1 January 1998, the HR for RTV was increased to 1.41 (95% CI, 0.96–2.08).

DISCUSSION

Thanks to a collaborative effort involving 12 different studies, the prognosis of HIV infection in patients initiating HAART could be elucidated for several initial regimens. We found that the choice of drugs used in the initial regimen was associated with the probability of viral suppression and with the sustained use of this regimen 6 months after starting HAART. We observed few differences in the rates of mortality between regimens, and these rates were much lower than were those in the pre-HAART era [21]. EFV performed the best of the third drugs, but several other drugs had similar effectiveness. Compared with EFV, the highest mortality risk was for patients who initiated HAART by receiving NVP.

In the absence of large trials, the present observational study provides important information on potential differences between regimens. Because all patients involved were treatment naive, our results were not confounded by previous ART and are relevant to many patients starting HAART. Data were combined across continents and countries, and our results should, therefore, be generalizable. Confounding is an important issue, because prognostic factors differed between groups of patients starting different regimens. Additional, unmeasured confounding factors could have distorted our results. Cox models were stratified both by cohort and by calendar year, and the results should not, therefore, be biased by between-cohort differences in treatment choices or by secular changes in the risk of the end points. AIDS diagnoses were not centrally reviewed or verified, which may have introduced bias due to misclassification. However, all cohorts used the same CDC criteria for the prospective diagnosis of AIDS-defining events, and study clinics are based in specialized centers with extensive expertise in HIV medicine. Some patients may have participated in clinical trials comparing different initial regimens, but it is likely that the proportion of such patients was small, and enrollment in the cohorts was independent of participation in trials.

HRs changed after adjustments were made for prognostic factors in multivariable models. In all cases except for NVP-based regimens, effects were attenuated. For example, in the unadjusted analysis, PI regimens boosted with RTV were associated with a 2-fold higher rate of AIDS/death (HR, 2.07), but this effect was considerably smaller after adjustments were made for prognostic factors (HR, 1.45), because these combinations were more likely to be prescribed to patients with more-advanced disease. Prognostic factors will have been subject to measurement error, and, therefore, it is possible that, because of residual confounding, the adjusted HR continues to be an overestimate of the true risk associated with boosted PI regimens. The opposite was the case for NVP-based therapies: patients at lower risk of progression were more likely to have received these regimens, and adjustment for prognostic factors at baseline, therefore, increased the HR for progression to AIDS/death, from 1.04 to 1.28. It is, therefore, possible that, because of residual confounding, the adjusted HR underestimates the true increase in the risk of progression associated with NVP.

Differences in outcome between EFV and NVP might have been the result of confounding by indication if patients with a poorer propensity to adhere tended to be prescribed NVP in preference to EFV. To distinguish this possibility from differences in discontinuation rates due to differences in efficacy or toxicity would require data both on reasons for choice of drug regimen and on reasons for discontinuation, which are difficult to collect. It is also important to consider whether observed differences could have been the result of differences in socioeconomic status [22, 23]. However, except for the United States,

our patient populations came from countries where all individuals (with the possible exception of migrants of sub-Saharan African origin, who are not always legal migrants) had similar low-cost access to HAART and laboratory monitoring.

Our analyses did not account for adherence to treatment, because this information was not available. Formally, adherence to treatment cannot confound the effect of initial regimen, because it occurs subsequent to the choice of regimen. Rather, failure to adhere to treatment is likely to modify the effect of treatment, because poor adherence has been shown in previous studies to be associated with poor CD4 cell count and HIV-1 RNA response as well as mortality [24–27]. However, choice of initial regimen might be affected by physicians' perception of the extent to which the patient is likely to adhere to treatment [25, 28, 29], because different HAART regimens have clear differences in pill burden [28, 30]. This is reflected, for example, in the fact that presumed mode of transmission is associated with initial regimen. Unmeasured patient characteristics that affect propensity to adhere and also predict choice of regimen could confound our results.

Although our analyses were conducted on the basis of intent to continue initial regimen, 27% of patients were no longer receiving their initial regimen at 6 months after initiation. Those patients initially receiving RTV (46%) or RTV-boosted PIs (40%) were particularly likely to change regimens. To estimate the effect of initial regimen accounting for regimen change would be difficult, since regimen-specific factors (such as toxicities) will themselves be associated with regimen change.

Large variations in therapeutic responses by initial regimen have been observed previously. A recent meta-analysis of clinical trials comparing HAART regimens among persons with extensive ART experience demonstrated that unboosted PI regimens were clearly superior to NNRTI regimens based on NVP or delavirdine [31]. In particular, CD4 cell count response and the suppression of viral replication was found to be less for NNRTI regimens than for PI regimens. In contrast, a systematic review of trials evaluating HAART regimens in treatment-naive HIV-infected adults demonstrated that boosted PI and NNRTI regimens provided superior virological suppression than did PI and triple nucleoside-containing regimens [32]. However, boosted PI regimens showed the greatest increase in CD4 cell counts, compared with the other 3 regimen types.

Our results do not confirm the main findings from the 2NN trial [2], although a sensitivity analysis in the 2NN trial, which included only those participants who received at least 1 dose of drugs, did find a significant benefit of EFV [2, 33, 34]. In our analysis, EFV appears to be more efficacious than any other third drug in a HAART regimen. These differences could be attributed to the superiority of EFV or might reflect underlying unmeasured differences in the ways in which physicians prescribe and patients use EFV, compared with other third drugs [28, 35–37]. Other observational studies have also suggested that EFV may be more efficacious than NVP with regard to CD4 cell count gain and virological efficacy [38, 39]. Of note, in our study, differences in viral load response were not generally associated with differences in rates of mortality, and differences in rates of mortality between EFV and NVP were associated with deaths that occurred during the first 6 months. These deaths could have been the result of either drug-induced toxicities or other factors not related to toxicity or therapeutic response [40]. The 2NN trial lacked the power to demonstrate, or to exclude with certainty, smaller differences in rates of mortality.

The present study arose from the need to characterize differences in response and survival by initial HAART regimen. No previous observational study has examined this issue with such a large patient population or large number of regimen types. Some of the third drugs analyzed here are no longer being prescribed in most settings, and there is a need for future work to examine regimens that have been prescribed in more recent years, once sufficient numbers of patients and follow-up time have accrued. The long-term impact of initial regimen choice may not be evident after 3 years of follow-up. It is not possible to simultaneously compare recently prescribed drug regimens and long-term effects—our approach represents a compromise between these 2 competing requirements.

In conclusion, the choice of drugs used in the initial HAART regimen is associated with the probability of viral suppression and with the sustained use of this regimen 6 months after the start of HAART. However, poorer response and higher rate of regimen change do not necessarily indicate subsequent differences in mortality. We cannot rule out confounding, rather than differences in drug effectiveness, as an explanation for our findings. Large clinical trials that are powered to assess differences in clinical outcomes are required to produce a more-definitive answer, and we strongly urge funding bodies to support such large, long-term trials in the future.

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References

1. Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada, and Australia Study. JAMA **1998**; 279:930–7.
2. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet **2004**; 363:1253–63.
3. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). Antivir Ther **2002**; 7:81–90.
4. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med **2003**; 349:2293–303.
5. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med **2003**; 349:2304–15.
6. Lange JM. Efficacy and durability of nevirapine in antiretroviral drug naive patients. J Acquir Immune Defic Syndr **2003**; 34(Suppl 1):S40–52.
7. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. AIDS **2003**; 17:987–99.
8. Yeni PG, Hammer SM, Hirsch MS, et al. Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society–USA Panel. JAMA **2004**; 292:251–65.
9. Wood E, Hogg RS, Heath KV, et al. Provider bias in the selection of non-nucleoside reverse transcriptase inhibitor and protease inhibitor-based highly active antiretroviral therapy and HIV treatment outcomes in observational studies. AIDS **2003**; 17:2629–34.
10. Keiser P, Nassar N, Yazdani B, Armas L, Moreno S. Comparison of efficacy of efavirenz and nevirapine: lessons learned for cohort analysis in light of the 2NN Study. HIV Clin Trials **2003**; 4:358–60.
11. Phillips AN, Ledergerber B, Horban A, et al. Rate of viral rebound according to specific drugs in the regimen in 2120 patients with HIV suppression. AIDS **2004**; 18:1795–804.
12. Harrigan PR, Hertogs K, Verbiest W, et al. Modest decreases in NNRTI susceptibility do not influence virological outcome in patients receiving initial NNRTI-containing triple therapy. Antivir Ther **2003**; 8:395–402.
13. Olsen CH, Gatell J, Ledergerber B, et al. Risk of AIDS and death at given HIV-RNA and CD4 cell count, in relation to specific antiretroviral drugs in the regimen. AIDS **2005**; 19:319–30.
14. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet **2002**; 360:119–29.
15. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet **2003**; 362:679–86.
16. May M, Royston P, Egger M, Justice AC, Sterne JA. Development and validation of a prognostic model for survival time data: application to prognosis of HIV positive patients treated with antiretroviral therapy. Stat Med **2004**; 23:2375–98.
17. d'Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. Arch Intern Med **2005**; 165:416–23.
18. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep **1992**; 41: 1–19.
19. Cox DR. Regression models and life tables (with discussion). J Roy Stat Soc (Series B) **1972**; 187–20.
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ **2003**; 327:557–60.
21. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet **1998**; 352:1725–30.
22. Wood E, Montaner JS, Chan K, et al. Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. AIDS **2002**;16: 2065–72.
23. Schechter MT, Hogg RS, Aylward B, Craib KJ, Le TN, Montaner JS. Higher socioeconomic status is associated with slower progression of HIV infection independent of access to health care. J Clin Epidemiol **1994**; 47:59–67.
24. Alexander CS, Asselin JJ, Ting LS, et al. Antiretroviral concentrations in untimed plasma samples predict therapy outcome in a population with advanced disease. J Infect Dis **2003**; 188:541–8.
25. Castillo E, Palepu A, Beardsell A, et al. Outpatient pharmacy care and HIV viral load response among patients on HAART. AIDS Care **2004**; 16:446–57.
26. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. J Acquir Immune Defic Syndr **2000**; 23:360–1.
27. Hogg RS, Heath K, Bangsberg D, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. AIDS **2002**; 16:1051–8.
28. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. Antivir Ther **2003**; 8:471–8.
29. Murri R, Ammassari A, Trotta MP, et al. Patient-reported and physician-estimated adherence to HAART: social and clinic center-related factors are associated with discordance. J Gen Intern Med **2004**; 19: 1104–10.
30. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. AIDS **2001**; 15:1369–77.
31. Yazdanpanah Y, Sissoko D, Egger M, Mouton Y, Zwahlen M, Chene

G. Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors: indirect comparison of controlled trials. BMJ **2004**; 328:249.
32. Bartlett J, DeMasi MF, Quinn J, Hermes A, Rousseau F. An updated meta-analysis of triple combination therapy in antiretroviral-naive HIV-infected adults (abstract 586). In: Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections (Boston, MA). Alexandria, VA: Foundation for Retrovirology and Human Health, **2005**.
33. van Leth F, Phanuphak P, Stroes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. PLOS Med **2004**; 1:e19.
34. Ananworanich J, Moor Z, Siangphoe U, et al. Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs. AIDS **2005**; 19:185–92.
35. Montaner JS, Hogg RS, Heath KV, et al. Heterogeneity of physician agreement with recommended therapeutic guidelines for the management of HIV-associated disease. Antivir Ther **1996**; 1:157–66.
36. Justice AC, Chang CH, Rabeneck L, Zackin R. Clinical importance of provider-reported HIV symptoms compared with patient-report. Med Care **2001**; 39:397–408.
37. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? AIDS **2003**; 17:711–20.
38. Phillips AN, Pradier C, Lazzarin A, et al. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients. AIDS **2001**; 15:2385–95.
39. Matthews GV, Sabin CA, Mandalia S, et al. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. AIDS **2002**; 16:53–61.
40. Becker S. Liver toxicity in epidemiological cohorts. Clin Infect Dis **2004**; 38(Suppl 2):S49–55.