MAJOR ARTICLE

The Rate of Viral Rebound after Attainment of an HIV Load <50 Copies/mL According to Specific Antiretroviral Drugs in Use: Results from a Multicenter Cohort Study

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Background. Relatively few data are available on the association between the use of specific antiretroviral drugs and the rate of viral rebound in those attaining a viral load (VL) <50 copies/mL while receiving highly active antiretroviral therapy (HAART).

Methods. Patients achieving a VL <50 copies/mL for the first time while receiving HAART were followed until viral rebound (2 consecutive VLs >500 copies/mL). Pre-HAART antiretroviral-naive patients were analyzed separately from those with nucleoside reverse transcriptase inhibitor (NRTI) experience.

Results. Of 3565 suppressed antiretroviral-naive patients, 381 experienced viral rebound (rate, 6.26 events/100 person-years of follow-up [pyrs] [95% confidence interval {CI}, 5.63–6.89 events/100 pyrs]). For those receiving efavirenz, the rate was 4.08 (95% CI, 3.16–5.01) events/pyrs. Compared with this, the rebound rate for those receiving indinavir was 1.52 times higher (rate ratio [RR], 1.52 [95% CI, 0.82–2.84]). RRs (95% CIs) for other drugs were: soft-gel saquinavir, 0.54 (0.07–3.97); nelfinavir, 2.44 (1.68–3.54); indinavir/ritonavir, 1.96 (1.02–3.77); saquinavir/ritonavir, 1.12 (0.48–2.61); lopinavir/ritonavir, 1.23 (0.58–2.59); nevirapine, 1.53 (1.11–2.10); and abacavir, 2.03 (1.26–3.25). Of 810 NRTI-exposed patients, 145 experienced viral rebound (rate, 8.29 [95% CI, 6.94–9.64] events/pyrs). For those receiving efavirenz, the rate was 5.25 (95% CI, 3.11–8.30) events/pyrs. Compared with this, the RRs (95% CIs) were: indinavir, 1.75 (0.82–3.73); hard-gel saquinavir, 3.48 (0.36–33.37); nelfinavir, 2.64 (1.37–5.08); indinavir/ritonavir, 0.32 (0.04–2.49); saquinavir/ritonavir, 0.64 (0.23–1.80); nevirapine, 1.65 (0.90–3.02); and abacavir, 1.82 (0.73–4.52).

Conclusions. We must make comparisons of antiretroviral outcomes in observational data with caution; however, our results suggest that, in those with VLs <50 copies/mL, certain drugs may be associated with higher rebound rates than others.

The aim of highly active antiretroviral therapy (HAART) is to achieve and maintain suppression of HIV in plasma to levels below quantification, because this leads to the greatest potential for immune reconstitution [1]. It is important for those who have achieved virological suppression to maintain this, because, once virological failure has occurred, resistant viruses may be selected, reducing the chance of successfully achieving and maintaining a

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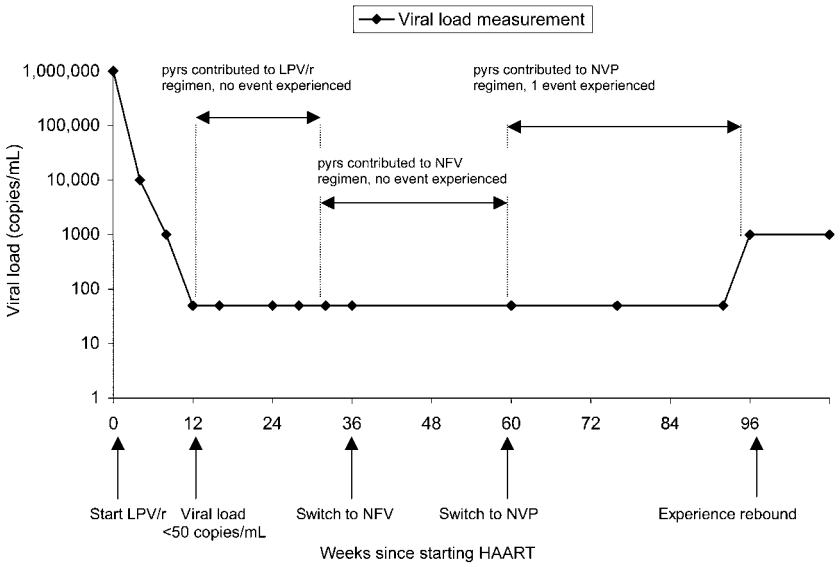

Figure 1. Example of allocation of person-years of follow-up (pyrs) for a hypothetical individual. LPV/r, ritonavir-boosted lopinavir; NFV, nelfinavir; NVP, nevirapine.

suppressed viral load on subsequent attempts [2] and often resulting in immunological deterioration [3].

Randomized trials have investigated whether specific antiretroviral drugs are associated with different rates of viral rebound among those who initially achieve virological suppression [4–10]. Because allocation to drugs is random, the likelihood of bias in comparing outcomes of drug regimens in these trials is small. However, most have not been sufficiently long or large enough to precisely estimate differences in rebound rates between specific drugs. Furthermore, only certain drug comparisons have been made. Observational cohort studies have also studied this issue [11–18]. Here, allocation to treatments is not random, so there is a risk of bias, because those who are receiving any specific drug may tend to have different characteristics than do those receiving other drugs, including prognosis. Conversely, observational cohort studies tend to follow large numbers of patients. Thus, more-precise estimates can generally be obtained, although these estimates are not necessarily unbiased. The EuroSIDA study group [11] recently reported no strong evidence that any particular nucleoside reverse transcriptase inhibitor (NRTI) pair was associated with a higher rate of virological rebound than were zidovudine (ZDV) and lamivudine (3TC), and, among those who were naive before starting HAART, there was no evidence of different viral rebound rates in patients receiving triple nucleosides, including abacavir (ABA), compared with 2 nucleosides plus efavirenz (EFV). However, the confidence intervals (CIs) for these comparisons were wide. Likewise, at present there are relatively few available data on virological rebound rates in patients receiving ritonavir-boosted protease inhibitor regimens. Furthermore, it is important to understand whether the length of time that a patient has had a suppressed viral load influences their risk of rebound, because there have been conflicting results and because these studies were limited by small numbers [2, 19]. We aimed to investigate these issues in a cohort of HIV-positive patients in the United Kingdom.

PATIENTS, MATERIALS, AND METHODS

The source of data for our analyses was the United Kingdom Collaborative HIV Cohort (CHIC) study [20]. This is a collaboration of large clinical HIV centers, 6 of which have currently contributed data—5 in London (Chelsea and Westminster Hospital, St. Mary's NHS Trust, King's College Hospital, the Mortimer Market Centre, and the Royal Free Hospital) and 1 in Brighton (Brighton and Sussex University Hospital). The inclusion criteria for the UK CHIC study are that a person be HIV positive, be >16 years old, and have attended at least 1 of the participating centers for HIV care at any time from 1996 onward. Each center provides data on demographics, AIDS diagnoses, laboratory findings, and ART history. An extensive data-checking process exists, and every effort is taken to merge the records of individuals who have attended >1 participating center. Viral load is measured approximately every 3 months, although this may differ according to center. All viral loads measured at each center are included in the database. The project was approved by a multicenter research ethics committee and by local ethics committees.

For the present study, all individuals in the UK CHIC study who had attained at least 1 viral load <50 copies/mL while receiving HAART (defined as a regimen containing at least 3 antiretrovirals) were considered for inclusion. Before achieving

Table 1. Demographics of the patients included in the study.

Category, parameter	ART naive	ART experienced
Total	3565 (100.0)	810 (100.0)
Sex, male	2824 (79.2)	680 (84.0)
Ethnicity		
White	2003 (56.2)	531 (65.6)
Black	968 (27.2)	135 (16.7)
Other/mixed	287 (8.1)	70 (8.6)
Not known	307 (8.6)	74 (9.1)
Risk group		
Homosexual	2197 (61.6)	596 (73.6)
Injection drug use	99 (2.8)	29 (3.6)
Heterosexual	1150 (32.3)	165 (20.4)
Other/not known	119 (3.3)	20 (2.5)
Age at the time of achieving a viral load <50 copies/mL, median (IQR), years	35.8 (31.4–41.6)	37.0 (32.7–44.1)
CD4 cell count, median (IQR), cells/mm^3		
At the time of achieving a viral load <50 copies/mL	307 (185–465)	340 (225–484)
At start of HAART	187 (87–290)	195 (90–303)
Viral load at start of HAART, median (IQR), log_{10} copies/mL	4.9 (4.4–5.4)	4.3 (3.1–5.1)
Year of starting HAART		
1996/1997	467 (13.1)	411 (50.7)
1998	552 (15.5)	184 (13.0)
1999	684 (19.2)	105 (6.1)
2000	689 (19.3)	49 (4.8)
2001	679 (19.1)	39 (2.6)
2002/2003	494 (13.9)	22 (0.1)
"Third" drug received at the time of achieving a viral load <50 copies/mL		
IDV	260 (7.3)	178 (22.0)
SQV	51 (1.5)	22 (2.7)
NFV	433 (12.2)	99 (12.2)
IDV/r	94 (2.6)	14 (1.7)
SQV/r	81 (2.3)	59 (7.3)
LPV/r	135 (3.8)	3 (0.4)
NVP	991 (27.8)	205 (25.3)
EFV	1172 (32.9)	116 (14.3)
ABA	171 (4.8)	27 (3.3)
Other[a]	177 (5.0)	87 (10.7)
NRTI combination received at the time of achieving a viral load <50 copies/mL		
ZDV/3TC	1963 (55.1)	200 (24.7)
ZDV/ddI	151 (4.2)	32 (4.0)
d4T/3TC	817 (22.9)	338 (41.7)
d4T/ddI	368 (10.3)	122 (15.1)
Other	266 (7.5)	118 (14.6)
Previous nucleosides received before initial HAART regimen		
ZDV	…	654 (80.7)
ddI	…	328 (40.5)
3TC	…	343 (42.4)
ddC	…	157 (19.4)
d4T	…	242 (29.9)
New ART drugs received in initial HAART regimen, median (IQR), no.	…	2 (1–2)
Length of exposure to prior NRTIs before initial HAART regimen, median (IQR), days	…	385 (104–968)

NOTE. Data are no. (%) of patients, unless otherwise noted. 3TC, lamivudine; ABA, abacavir; ART, antiretroviral therapy; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; EFV, efavirenz; HAART, highly active antiretroviral therapy; IDV, indinavir; IDV/r, ritonavir-boosted IDV; IQR, interquartile range; LPV, lopinavir; LPV/r, ritonavir-boosted LPV; NFV, nelfinavir; RTV, ritonavir; NVP, nevirapine; NRTI, nucleoside reverse transcriptase inhibitor; SQV, saquinavir; SQV/r, ritonavir-boosted SQV; ZDV, zidovudine.

[a] These patients were not receiving eligible HAART regimens at the time of achieving a viral load <50 copies/mL; they became eligible for inclusion in the analysis when they subsequently switched to a different antiretroviral regimen.

Table 2. Person-years of follow-up (pyrs) and no. of virological rebounds according to exposure to nucleoside reverse transcriptase inhibitor (NRTIs).

NRTI combination	Naive patients			Experienced patients		
	pyrs	No. of virological rebounds	Rebound rate (95% CI), events/100 pyrs	pyrs	No. of virological rebounds	Rebound rate (95% CI), events/100 pyrs
ZDV/3TC	3467.4	197	5.68 (4.89–6.48)	580.0	44	7.59 (5.35–9.83)
ZDV/ddI	347.4	28	8.06 (5.08–11.05)	82.5	9	10.91 (4.99–20.71)
d4T/3TC	1573.5	89	5.66 (4.48–6.83)	787.2	57	7.24 (5.36–9.12)
d4T/ddI	552.2	52	9.42 (6.86–11.98)	223.6	26	11.63 (7.16–16.10)
Other	147.8	15	10.15 (5.68–16.74)	75.3	9	11.95 (5.47–22.70)
Total	6088.2	381	6.26 (5.63–6.89)	1748.7	145	8.29 (6.94–9.64)

NOTE. Confidence intervals (CIs) for the incidence rates were calculated by the exact Poisson method where the no. of events is <20 and by the normal approximation otherwise. 3TC, lamivudine; ddI, didanosine; d4T, stavudine; ZDV, zidovudine.

a viral load <50 copies/mL, patients were required to never have had a viral load >1000 copies/mL after having received HAART for >6 months, because we wished to include individuals who had never failed a HAART regimen. We felt that if an individual had experienced a viral load >1000 copies/mL >6 months after starting HAART, then that person had most likely experienced virological failure of their first HAART regimen. Furthermore, we believed that this criterion would ensure that those who started HAART before the introduction of assays with a lower limit of detection of 50 copies/mL had never experienced virological failure of a HAART regimen before inclusion in the study. Patients were either antiretroviral naive at the time of starting HAART or were experienced with NRTIs only, and these 2 groups of patients were analyzed separately.

The date of viral rebound was defined as the date of the first of 2 consecutive viral loads >500 copies/mL (or the date of a single value if this was the last viral load measured). We considered for each patient the person-years of follow-up (pyrs) over which he or she was receiving 2 NRTIs (including tenofovir) plus 1 of the following "third" antiretrovirals: EFV, nevirapine (NVP), ABA, indinavir (IDV), ritonavir-boosted IDV (IDV/r), ritonavir-boosted saquinavir (SQV/r), nelfinavir (NFV), ritonavir-boosted lopinavir (LPV/r), or SQV alone (either hard-gel capsule [HGC] or soft-gel capsule). These antiretrovirals were chosen because they are currently in relatively common use. We did not include pyrs when patients were receiving regimens other than these. Therefore, for example, a patient may have started HAART and achieved a viral load <50 copies/mL with a drug regimen of LPV/r, EFV, 3TC, and ZDV and later (before experiencing viral rebound) switched to a 3-drug regimen including NFV and 2 NRTIs. Here, the time spent receiving the LPV/r and EFV regimen would not contribute to our analysis, because it is not one of the "included" antiretroviral combinations described above. However, the time spent receiving the NFV regimen would contribute to the analysis. Similarly, patients were also allowed to contribute pyrs to >1 drug/regimen if they switched from one eligible regimen to another while maintaining a viral load <50 copies/mL. For each specific drug, individuals were followed from the date of attaining a viral load <50 copies/mL while receiving the regimen containing the specific drug or, for those who switched to the drug after reaching a viral load <50 copies/mL, the date of switching to the drug. Follow-up for the specific drug was until viral rebound, stopping the drug (whether switching to another one or stopping all drugs), or last available viral load, whichever occurred first. The allocation of pyrs is explained further in figure 1. This person-time was used as the denominator for calculating the rate of viral rebound according to the specific drug that a person was currently receiving. These rates were calculated by dividing the number of viral rebounds experienced by patients receiving a particular drug by the total pyrs accumulated while receiving that drug. Ninety-five percent CIs for the rate of viral rebound were calculated by the exact Poisson method where the number of events was <20 and by the normal approximation otherwise. If the 95% CIs for the rate of rebound for 2 different antiretrovirals did not overlap, then the difference in the incidence of viral rebound between the 2 drugs is significant at the 5% level in an unadjusted analysis. The NRTI combination received was divided into the following categories: ZDV/3TC, ZDV/didanosine (ZDV/ddI), stavudine/3TC (d4T/3TC), d4T/ddI, and other NRTI combinations.

We used Poisson regression to compare rates of viral rebound according to use of specific drugs after adjusting for other potential confounding variables. We obtained rate ratios (RRs) from these models, which give an estimate of the relative rate of viral rebound, compared with the reference group. A RR is significant at the 5% level if the 95% CI of the estimate does not include 1. Analyses were adjusted for the following other potentially relevant factors: calendar year, whether the third drug had been switched since the first viral load <50 copies/mL, time since attaining a viral load <50 copies/mL, pre-HAART CD4 cell count and viral load, age, ethnicity, sex, and risk group. Analyses of the pre-HAART nucleoside–experienced group were also adjusted for the number of new NRTIs introduced

Table 3. Person years of follow-up (pyrs) and no. of virological rebounds according to exposure to the "third" drug.

	Naive patients			Experienced patients		
Third drug	pyrs	No. of virological rebounds	Rebound rate (95% CI), events/100 pyrs	pyrs	No. of virological rebounds	Rebound rate (95% CI), events/100 pyrs
EFV	1837.5	75	4.08 (3.16–5.01)	342.8	18	5.25 (3.11–8.30)
NVP	1993.3	138	6.92 (5.77–8.08)	526.5	46	8.74 (6.21–11.26)
IDV	416.3	16	3.84 (2.20–6.24)	291.5	27	9.26 (5.77–12.76)
SQV-HGC	11.3	0	0.00 (0.00–32.65)	8.0	2	25.00 (3.03–90.31)
SQV-SGC	49.2	1	2.03 (0.05–11.33)	23.9	0	0.00 (0.00–15.44)
NFV	862.1	85	9.86 (7.76–11.96)	212.8	31	14.57 (9.44–19.69)
IDV/r	181.5	12	6.61 (3.42–11.55)	74.4	2	2.69 (0.33–9.71)
SQV/r	151.9	11	7.24 (3.62–12.96)	149.9	11	7.34 (3.66–13.13)
LPV/r	156.1	9	5.77 (2.64–10.95)	37.8	0	0.00 (0.00–9.76)
ABA	428.9	34	7.93 (5.26–10.59)	81.1	8	9.87 (4.26–19.44)
Total	6088.2	381	6.26 (5.63–6.89)	1748.7	145	8.29 (6.94–9.64)

NOTE. Confidence intervals (CIs) for the incidence rates were calculated by the exact Poisson method where the no. of events is <20 and by the normal approximation otherwise. ABA, abacavir; EFV, efavirenz; IDV, indinavir; IDV/r, ritonavir-boosted IDV; LPV/r, ritonavir-boosted lopinavir; NFV, nelfinavir; NVP, nevirapine; SQV-HGC, saquinavir hard-gel formulation; SQV/r, ritonavir-boosted saquinavir; SQV-SGC, saquinavir soft-gel formulation.

to the HAART regimen (not counting d4T in people with previous ZDV use [18]), the NRTIs previously used, and the total pre-HAART exposure time to NRTIs.

RESULTS

Previously antiretroviral-naive patients. Of 5896 previously antiretroviral-naive individuals starting HAART, 486 (8.2%) had no eligible follow-up, 1219 (20.7%) had not yet had a viral load <50 copies/mL, and 626 (10.6%) had a viral load >1000 copies/mL >6 months after starting HAART. Thus, 3565 individuals were included in the analyses. Most (2824 [79.2%]) were male, 2197 (61.6%) had a homosexual risk, and 2003 (56.2%) were of white ethnicity. When starting HAART, the median (interquartile range [IQR]) CD4 cell count and viral load were 187 (87–290) cells/mm^3 and 4.9 (4.4–5.4) $\log_{10}$ copies/mL, respectively. When first achieving a viral load <50 copies/mL, the median (IQR) CD4 cell count was 307 (185–465) cells/mm^3 (table 1). Follow-up on the first individual to be included in the study started in November 1999, and the last individual's follow-up ceased in July 2003. Those who were excluded from the study had characteristics that were similar to those who were included (data not shown).

In 6088.2 pyrs, 381 patients experienced virological rebound, corresponding to a rate of viral rebound of 6.26 (95% CI, 5.63–6.89) events/100 pyrs. The unadjusted rates of viral rebound were broadly similar regardless of the NRTI combination received (table 2), although those receiving d4T/ddI appeared to have an increased rate (9.42 [95% CI, 6.86–11.98] events/100 pyrs), and those receiving other NRTI combinations had a rate of 10.15 (95% CI, 5.68–16.74) events/100 pyrs. However, there was more variation in the rate of viral rebound according to the third drug included in the HAART regimen (table 3). The highest rates of rebound were observed among those receiving NFV (9.86 [95% CI, 7.76–11.96] events/100 pyrs), ABA (7.93 [95% CI, 5.26–10.59] events/100 pyrs) and SQV/r (7.24 [95% CI, 3.62–12.96] events/100 pyrs). The lowest unadjusted rates were observed among individuals receiving IDV (3.84 [95% CI, 2.20–6.24] events/100 pyrs), EFV (4.08 [95% CI, 3.16–5.01] events/100 pyrs), and LPV/r (5.77 [95% CI, 2.64–10.95] events/100 pyrs).

In a Poisson regression model, compared with those receiving ZDV/3TC, there was a statistically significant higher rate of viral rebound among those receiving ZDV/ddI, those receiving d4T/ddI, and those receiving other NRTI combinations (table 4). Those receiving ZDV/ddI had a 69% increase in the rate of viral rebound (RR, 1.69 [95% CI, 1.10–2.61]); those receiving d4T/ddI had a 77% increase in the rate (RR, 1.77 [95% CI, 1.25–2.49]), and those receiving other NRTI combinations had more than twice the rate (RR, 2.34 [95% CI, 1.29–4.27]). Compared with those receiving EFV, those receiving NFV (RR, 2.44 [95% CI, 1.68–3.54), IDV/r (RR, 1.96 [95% CI, 1.02–3.77]), NVP (RR, 1.53 [95% CI, 1.11–2.10]), and ABA (RR, 2.03 [95% CI 1.26–3.25]) had statistically significant increased rates of virological rebound.

We found associations significant at the 5% level between the rate of viral rebound and ethnicity, risk group, and age (table 4). Those of black ethnicity had a 74% increase in the rate of viral rebound, compared with those of white ethnicity (RR, 1.74 [95% CI, 1.24–2.44]). Those with a heterosexual (RR, 1.23 [95% CI, 0.84–1.80]) or other (RR, 1.96 [95% CI, 1.31–2.93]) risk had increased rates of rebound, compared with those with a homosexual risk. For every 10-year increase in age, the

Table 4. Poisson regression results of factors associated with virological rebound.

	Naive patients				Experienced patients			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Category, parameter	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
NRTI combination								
ZDV/3TC	1.00	.0047	1.00	.0012	1.00	.20	1.00	.21
ZDV/ddI	1.42 (0.95–2.11)		1.69 (1.10–2.61)		1.43 (0.70–2.93)		1.90 (0.88–4.11)	
d4T/3TC	1.00 (0.78–1.28)		1.08 (0.80–1.45)		0.97 (0.65–1.44)		1.11 (0.69–1.79)	
d4T/ddI	1.66 (1.21–2.25)		1.77 (1.25–2.49)		1.56 (0.96–2.54)		1.73 (0.98–3.04)	
Other	1.79 (1.06–3.02)		2.34 (1.29–4.27)		1.61 (0.79–3.30)		1.71 (0.67–4.35)	
"Third" drug								
EFV	1.00	<.0001	1.00	.0005	1.00	.0086	1.00	.0096
NVP	1.70 (1.28–2.25)		1.53 (1.11–2.10)		1.66 (0.96–2.87)		1.65 (0.90–3.02)	
IDV	0.94 (0.55 1.62)		1.52 (0.82–2.84)		1.75 (0.96–3.17)		1.75 (0.82–3.73)	
SQV-HGC	…		…		4.78 (1.11–20.61)		3.48 (0.36–33.37)	
SQV-SGC	0.50 (0.07–3.58)		0.54 (0.07–3.97)		…		…	
NFV	2.42 (1.77–3.30)		2.44 (1.68–3.54)		2.77 (1.55–4.96)		2.64 (1.37–5.08)	
IDV/r	1.62 (0.88–2.98)		1.96 (1.02–3.77)		0.51 (0.12–2.21)		0.32 (0.04–2.49)	
SQV/r	1.77 (0.94–3.34)		1.12 (0.48–2.61)		1.40 (0.66–2.96)		0.64 (0.23–1.80)	
LPV/r	1.41 (0.71–2.82)		1.23 (0.58–2.59)		…		…	
ABA	1.94 (1.30–2.91)		2.03 (1.26–3.25)		1.88 (0.82–4.32)		1.82 (0.73–4.52)	
Year								
1998 and before	1.29 (0.68–2.42)	.76	1.47 (0.73–2.97)	.28	0.81 (0.43–1.53)	.094	0.96 (0.45–2.04)	.54
1999	1.00		1.00		1.00		1.00	
2000	0.89 (0.62–1.27)		1.07 (0.71–1.61)		0.60 (0.38–0.95)		0.68 (0.40–1.16)	
2001	0.88 (0.62–1.24)		1.18 (0.78–1.79)		0.53 (0.33–0.87)		0.58 (0.30–1.14)	
2002/2003	0.93 (0.67–1.29)		1.47 (0.94–2.29)		0.72 (0.45–1.13)		0.63 (0.28–1.46)	

Switched third drug since viral load <50 copies/mL	0.89 (0.68–1.16)	.038	1.03 (0.74–1.44)	.87	0.82 (0.55–1.23)	.34	1.22 (0.74–2.01)	.43
Time spent with viral load <50 copies/mL per 1 year longer	0.90 (0.81–0.99)	.030	0.88 (0.77–1.00)	.057	0.91 (0.79–1.04)	.17	1.05 (0.79–1.40)	.72
CD4 cell count at HAART per 100 cells/mm^3 increase	0.98 (0.92–1.05)	.62	0.99 (0.92–1.07)	.79	1.01 (0.91–1.12)	.86	0.98 (0.86–1.11)	.72
Viral load at HAART per 1 log copy/mL increase	0.89 (0.80–0.98)	.026	0.96 (0.85–1.07)	.45	0.93 (0.81–1.08)	.35	0.99 (0.83–1.17)	.87
Age per 10-year increase	0.70 (0.61–0.80)	<.0001	0.72 (0.62–0.84)	<.0001	0.69 (0.56–0.84)	.0001	0.72 (0.56–0.92)	.0055
Ethnicity								
Black	2.15 (1.74–2.67)	<.0001	1.74 (1.24–2.44)	.0016	2.29 (1.59–3.29)	<.0001	2.23 (1.18–4.20)	.0003
Other	0.97 (0.70–1.33)		0.91 (0.64–1.29)		0.56 (0.31–1.00)		0.45 (0.22–0.92)	
White	1.00		1.00		1.00		1.00	
Sex								
Female	1.50 (1.19–1.89)	.001	0.73 (0.52–1.03)	.075	1.59 (1.07–2.36)	.029	0.99 (0.49–1.98)	.98
Male	1.00		1.00		1.00		1.00	
Risk group								
Heterosexual	1.72 (1.39–2.14)		1.23 (0.84–1.80)	.009	1.50 (1.03–2.19)	.11	0.59 (0.27–1.30)	.40
Other	2.22 (1.57–3.14)	<.0001	1.96 (1.31–2.93)		1.22 (0.62–2.41)		0.85 (0.34–2.16)	
Homosexual	1.00		1.00		1.00		1.00	
Total pre-HAART exposure to NRTIs per 1 year longer	…	…	…	…	1.08 (1.00–1.15)	.050	1.15 (1.05–1.26)	.003
No. of new NRTIs per 1 NRTI extra	…	…	…	…	0.98 (0.76–1.26)	.89	1.27 (0.91–1.78)	.16
Previous exposure to								
ZDV	…	…	…	…	0.92 (0.50–1.68)	.79	0.61 (0.30–1.24)	.17
ddC	…	…	…	…	0.68 (0.42–1.10)	.10	0.65 (0.35–1.20)	.17
ddI	…	…	…	…	1.60 (1.06–2.41)	.02	1.87 (1.16–3.01)	.01
d4T	…	…	…	…	0.71 (0.42–1.20)	.19	0.51 (0.28–0.93)	.03
3TC	…	…	…	…	1.90 (1.25–2.89)	.002	2.95 (1.71–5.07)	<.0001

NOTE. Rate ratios (RRs) were calculated by Poisson regression models. 3TC, lamivudine; ABA, abacavir; CI, confidence interval; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; EFV, efavirenz; HAART, highly active antiretroviral therapy; IDV, indinavir; IDV/r, ritonavir-boosted IDV; LPV/r, ritonavir-boosted lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RTV, ritonavir; SQV-HGC, saquinavir hard-gel formulation; SQV/r, ritonavir-boosted saquinavir; SQV-SGC, saquinavir soft-gel formulation; ZDV, zidovudine.

rate of rebound decreased by 28% (RR, 0.72 [95% CI, 0.62–0.84]). There was also some evidence of an association between decreased rates of rebound and women (RR compared with men, 0.73 [95% CI, 0.52–1.03]) and longer time spent with a viral load <50 copies/mL (RR, 0.88 [95% CI, 0.77–1.00] per year longer).

Previously NRTI-experienced patients. Of 2756 patients starting HAART with previous NRTI experience, 285 (10.3%) had no eligible follow-up, 648 (23.5%) had not yet had a viral load <50 copies/mL, and 1013 (36.8%) had a viral load >1000 copies/mL >6 months after starting HAART. Thus, 810 individuals were included in the analyses. The majority (680 [84.0%]) were male, with a homosexual risk (596 [73.6%]) and white ethnicity (531 [65.6%]). At the time of starting HAART, the median (IQR) viral load and CD4 cell count were 195 (90–303) cells/mm^3 and 4.3 (3.1–5.1) $\log_{10}$ copies/mL, respectively. At the time of achieving a viral load <50 copies/mL, the median (IQR) CD4 cell count was 340 (225–484) cells/mm^3. The median length of exposure to NRTIs before HAART was 385 (IQR, 104–968) days (table 1). Follow-up on the first individual to be included in the study started in November 1996, and the last individual's follow-up ceased in July 2003. Those who were excluded from the study had characteristics that were similar to those who were included (data not shown).

In 1748.7 pyrs, 145 patients experienced a virological rebound, giving a rate of 8.29 (95% CI, 6.94–9.64) events/100 pyrs. The unadjusted rate of viral rebound was lower among those receiving ZDV/3TC (7.59 [95% CI, 5.35–9.83] events/100 pyrs) and d4T/3TC (7.24 [95% CI, 5.36–9.12] events/100 pyrs) and was higher among those receiving ZDV/ddI (10.91 [95% CI, 4.99–20.71] events/100 pyrs), d4T/ddI (11.63 [95% CI, 7.16–16.10] events/100 pyrs) and other NRTI combinations (11.95 [95% CI, 5.47–22.70] events/100 pyrs) (table 2). When looking at the unadjusted rates of viral rebound according to the third drug in the regimen (table 3), the highest rates were observed among those receiving NFV (14.57 [95% CI, 9.44–19.69] events/100 pyrs) and SQV-HGC (25.00 [95% CI, 3.03–90.31] events/100 pyrs). The lowest rates were observed among individuals receiving IDV/r (2.69 [95% CI, 0.33–9.71] events/100 pyrs) and EFV (5.25 [95% CI, 3.11–8.30] events/100 pyrs).

In a multivariate Poisson regression analysis (table 4), there was little difference in the rates of viral rebound according to the NRTI combination received ($P = .21$). Compared with those receiving EFV, those receiving NFV had >2.5 the rate of viral rebound, corresponding to a RR of 2.64 (95% CI, 1.37–5.08). Those receiving IDV (RR, 1.75 [95% CI, 0.82–3.73]), SQV-HGC (RR, 3.48 [95% CI, 0.36–33.37]), and NVP (RR, 1.65 [95% CI, 0.90–3.02]) experienced a trend toward increased rates of virological rebound.

Other factors associated with an increased rate of viral rebound were ethnicity, age, and length of exposure to NRTIs (table 4). Those of black ethnicity had more than twice the rate of viral rebound, compared with those of white ethnicity (RR, 2.23 [95% CI, 1.18–4.20]), and for every 10-year increase in age the rate of viral rebound decreased by 28% (RR, 0.72 [95% CI, 0.56–0.92]). For every 1-year increase in exposure to NRTIs before starting HAART, the rate of virological rebound increased by 15% (RR, 1.15 [95% CI, 1.05–1.26]).

Sensitivity analyses. We performed 3 sensitivity analyses. The first did not include a single viral load >500 copies/mL as a viral rebound when it was the last recorded viral load. The second included those who switched or intensified their HAART regimen after a single viral load >500 copies/mL and before their next viral load measurement as virological failures. Both analyses led to results consistent with those presented above. The third sensitivity analysis divided each individual's follow-up data according to whether it took place during the first year after achieving a viral load <50 copies/mL or subsequently. During the first year after achieving a viral load <50 copies/mL, the RRs (95% CI), compared with EFV in previously antiretroviral-naive patients, were as follows: IDV, 1.85 (0.80–4.29); NFV, 3.25 (1.94–5.43); IDV/r, 1.74 (0.61–5.00); SQV/r, 2.19 (0.84–5.71); LPV/r, 0.60 (0.14–2.51); NVP, 2.02 (1.31–3.12); and ABA, 2.12 (1.05–4.26). Compared with EFV, when only including pyrs after an individual had maintained a viral load <50 copies/mL for at least 1 year, the RRs of viral rebound were as follows: IDV, 1.32 (0.52–3.35); SQV-HGC, 1.28 (0.17–9.60); NFV, 1.89 (1.10–3.25); IDV/r, 2.11 (0.90–4.93); SQV/r, 0.33 (0.05–2.42); LPV/r, 1.87 (0.75–4.66); NVP, 1.17 (0.73–1.85); and ABA, 1.88 (0.98–3.61).

DISCUSSION

Our analysis has shown that there is generally a low rate of virological rebound in this cohort, with a rate of 6.26 events/100 pyrs in previously antiretroviral-naive patients and a rate of 8.29 events/100 pyrs in NRTI-experienced patients. These are consistent with those found in other studies [4, 6, 11] and confirm results showing that virological rebound rates are higher among those exposed to NRTIs before starting HAART [2, 21–24]. However, even though there is a low overall rate of virological rebound in our cohort, rates appears to differ according to the use of different antiretrovirals.

To date, few other studies [11] have investigated the rate of virological rebound associated with ritonavir-boosted regimens, because they are relatively new and long periods of follow-up are not always available. Our study suggests that there appears to be an increased rate of viral rebound in regimens containing IDV/r in previously antiretroviral-naive patients, with the rate of rebound being approximately twice that seen with EFV. In NRTI-experienced patients, the reverse was true. However, both of these estimates had wide CIs and so must be interpreted with caution. Regimens containing SQV/r and LPV/r appeared

to be associated with rates of viral rebound that are similar to those observed among patients receiving EFV.

Our results also indicate that those receiving ABA are at a greater risk of virological failure, compared with those receiving EFV. This is consistent with the results of some studies [5, 6, 10] but not of the EuroSIDA study previously mentioned [11]. The simpler tablet requirements of an ABA-containing regimen make it an attractive option and potentially useful for simplification after initial virological suppression has been achieved. However, in our sensitivity analysis that considered only follow-up of patients after they had maintained an undetectable viral load for >1 year, we found that those receiving ABA still had a higher rate of viral rebound than did those receiving EFV. It may still be that those patients switching to ABA may have done so because of adherence problems, and so any differences observed in the rates of viral rebound between ABA and other antiretrovirals may be for this reason.

Both previously antiretroviral-naive and NRTI-experienced patients receiving NFV were at an increased risk of virological failure, compared with those receiving EFV, confirming the findings of other studies [11, 25]. We also found a trend toward higher rates of virological rebound in previously NRTI-experienced individuals receiving SQV-HGC [12, 26, 27]. However, very few previously-naive individuals had received SQV-HGC, and the use of NFV had decreased in later years (data not shown).

Our data suggest that, when the 2 main NNRTIs are compared, EFV is associated with a lower rate of virological rebound than NVP. Other studies have also found EFV to be associated with higher rates of virological suppression [28–31] and lower viral rebound rates [11, 15]. However, this result was not replicated in 2NN, a large, randomized trial comparing the 2 antiretrovirals [32], although the results in the trial did significantly favor EFV when the analysis was restricted to those who took at least 1 dose of the trial drug. Any discrepancy with 2NN may be the result of unmeasured confounding factors present in observational data or may reflect genuine differences in outcome between a trial and routine clinic setting.

No NRTI combination was associated with an increased rate of virological rebound among NRTI-experienced patients. However, the rate of rebound in previously antiretroviral-naive individuals was significantly higher in those receiving ddI/d4T and in those receiving other NRTI combinations [27]. Follow-up of individuals receiving other NRTI combinations included a variety of different NRTIs, including older NRTIs such as zalcitabine and newer drugs such as tenofovir, and as such it is difficult to interpret exactly what this result means. Ethnicity was associated with viral rebound, with those of black ethnicity being at increased risk [33]. We also found that those in the non–heterosexual risk and non-homosexual risk group (a group including injection drug users, blood product recipients, other, and unknown) had a higher rate of viral rebound [33, 34]. The reasons for these associations are not clear. One possible explanation is that these groups had lower levels of adherence [33–37]. However, because all individuals in the present study had achieved at least 1 viral load <50 copies/mL, one might expect some of this effect to be removed. We also found a trend toward a decreasing rate of viral rebound with increased length of time that a patient had had a viral load <50 copies/mL, although this was not significant at the 5% level, confirming the results of one [2], but not another [38], study.

Comparisons of antiretrovirals made on observational data such as these must be made with caution, because one cannot rule out the possibility that any observed differences could be the result of residual confounding rather than differences in drug effectiveness. For example, if patients who have lower adherence rates are more likely to receive a particular antiretroviral regimen, this regimen may appear to result in higher rates of rebound than other drug regimens purely because individuals receiving this regimen had a higher likelihood of experiencing viral rebound, regardless of the antiretroviral regimen received (although, because all individuals had to achieve a viral load <50 copies/mL, some of this adherence effect may have been removed). Although we have attempted to adjust for potential confounding variables in our analyses, there are likely to be other unmeasured confounding variables that are hard to quantify. Furthermore, the present analysis included only individuals who achieved a viral load <50 copies/mL while receiving their first HAART regimen. Conversely, there are also benefits to the use of observational data to address questions such as these, because large patient numbers and long follow-up periods can be accrued. Additionally, observational data such as these can compare several different antiretroviral drugs rather than just 1 or 2, as would be expected in a randomized trial.

In summary, although it is important to make comparisons in observational data with extreme caution, our study provides evidence suggesting that the specific antiretroviral drug received may be associated with differences in the rate of virological rebound among patients with a viral load <50 copies/mL who have never failed a HAART regimen.

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