

Risk of AIDS and death at given HIV-RNA and CD4 cell counts, in relation to specific antiretroviral drugs in the regimen

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Background: It is unknown whether the relationship between the HIV-RNA/CD4 cell count and risk of clinical disease continues to hold true for newer antiretroviral drugs approved without data from clinical endpoint trials.

Objective: To determine and compare whether rate ratios of AIDS and death at given, latest HIV-RNA and CD4 cell counts levels were similar, regardless of which nucleoside pair and specific third drugs patients received as antiretroviral therapy.

Design: EuroSIDA observational cohort. A total of 9802 prospectively followed patients.

Methods: Analysis included patients taking combination antiretroviral therapy (CART) regimens containing two non-abacavir nucleosides plus a 'third drug' of a non-nucleoside reverse transcriptase inhibitor, a (possibly ritonavir boosted) protease inhibitor or abacavir.

Results: A total of 6814 patients contributed a total of 22 766.6 person-years of follow up. Median latest CD4 cell count was 353×10^6 cells/l, HIV-RNA 199 copies/ml. A total of 900 events of new AIDS or death were observed. AIDS/death rates for any given CD4 or HIV-RNA category were similar regardless of specific drugs being used. Adjusted rate ratios (RR) for individual drugs compared with indinavir (for which clinical endpoint trials are available) were all close to 1 and with relatively narrow 95% confidence intervals (CI); for example, nelfinavir RR, 0.99 (95% CI, 0.76–1.28); efavirenz RR, 0.83 (95% CI, 0.57–1.20); abacavir RR, 1.01 (95% CI, 0.64–1.60). Results were similar for different nucleoside pairs.

Conclusions: The results indicate that AIDS/death rates for given CD4 cell count and HIV-RNA categories are similar, regardless of CART regimen being taken and provide reassurance that HIV-RNA and CD4 cell counts in individual patients receiving newer drugs have the same meaning, in terms of AIDS/death risk, regardless of specific antiretroviral regimen.

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regimen. For each month of follow up we assigned the current CD4 cell count (and HIV-RNA) for that month to be the first measured in that month or (if there were none in that month) the most recently measured previous value. The nucleoside backbone treatment was classified as the three most frequently used combinations: zidovudine/lamivudine (ZDV/3TC), stavudine/didanosine (d4t/ddI), stavudine/lamivudine (d4t/3TC) and other. The third (and possible fourth) drug(s) in the regimen were saquinavir, ritonavir, ritonavir-boosted saquinavir, indinavir or lopinavir, nelfinavir, efavirenz, nevirapine or abacavir. For all other third drugs there were insufficient person-years of experience available (< 500). Person-time in which patients were not taking one of the specified regimens was not included, so for example, if a person was taking zidovudine/lamivudine/efavirenz but then switched to stavudine/didanosine/amprenavir, the person time on the first regimen was included, but not that on the second (even in the analysis of nucleoside backbones). Person time was attributed to the current drug regimen only, not to any previous drug regimen.

As a sensitivity analysis we restricted person-time to that where the current regimen had been used for at least 6 months, to exclude any residual effects of the previous regimen, which might remain during this period. It is important to emphasize that when we are assessing the rate of AIDS and death associated with a specific drug we only include person time spent on that drug, not any previous time since the start of CART but before starting the drug.

Several sensitivity analyses were performed, including such that restricted analyses to (1) person time in which a given drug had been used for at least 6 months, in order to test if the effect measured by the surrogate marker can be attributed to a certain drug and not, for example, a delay in the effect of the previously used third drug; (2) person months where CD4 cell and HIV-RNA were known within at most the past 3 months, to be sure that results did not change when insisting that the 'current' CD4 cell count and viral load were recently measured; (3) person time with a $> 50 \text{ mm}^3$ increase attained on the third drug to ensure that results were robust also when ensuring that the specific drug had contributed to the attainment of the current CD4 cell level; and (4) to person time where the specific third drug had been started when the HIV-RNA was < 500 copies/ml, to be sure that results were consistent also looking at the group where the specific third drug had been started in virologically suppressed patients. Furthermore, AIDS/death rates for patients with CD4 cell counts between 200 and 350×10^6 cells/l were considered separately.

The HIV-RNA values below the assay quantification limit were assigned a value of 1 copy/ml below the assay limit; that is, values of 49 represent a value of < 50 copies/ml

using an assay with 50 copies/ml as the lower limit. Thus, the median decrease in HIV-RNA from start of CART will be underestimated.

Poisson regression models (fitted using PROC GENMOD in SAS 8.2; SAS Institute, Cary, North Carolina, USA) were used to assess rate ratios comparing these specific drugs and combinations of drugs after adjusting for: the latest CD4 cell count and HIV-RNA, risk group, age, prior AIDS, calendar year, time from starting CART and time on current combination. GEE estimation was used with Poisson regression models to ensure that standard errors accounted for the clustering of multiple AIDS/death events in each person [33].

Results

A total of 6814 patients contributed observation time to the analysis, representing 94% of all those that had started CART. Those not contributing were exclusively taking various regimens other than those we focused on. Of the total 1478 (22%) were female. Exposure categories were male sex with another male (MSM) 3130 (46%), injection drug use (IDU) 1469 (22%), heterosexual 1697 (25%) and other/unknown 518 (8%). Median date of starting CART was March 1997 and median age 36.8 years [interquartile range (IQR), 32.1, 43.8]. A total of 4773 (70%) had used nucleoside monotherapy or dual therapy before starting CART. The median (IQR) current CD4 cell count and HIV-RNA at the start of CART were 184×10^6 cells/l (78–315) and 26 000 copies/ml (3100–129 000), respectively.

There were a total of 22 766.6 person-years of follow up. For 79 and 81% of this time the CD4 cell count and HIV-RNA, respectively, were known in the past 3 months. The latest median CD4 cell count (taking a median over all CD4 cell counts for all months of follow up) was 353×10^6 cells/l (IQR, 206, 539) and similarly the latest median HIV-RNA was 199 copies/ml (IQR, 49, 1900). The median amount (over all person-months of follow up) by which the CD4 cell count was above that at start of CART was 137×10^6 cells/l (12, 290). For HIV-RNA, the median decrease from start of CART was 1.68 \log_{10} copies/ml (0.34, 2.83).

Table 1 shows details relating to use of specific third drugs. As might be expected, the protease inhibitors, which were introduced in 1995/1996, namely saquinavir, indinavir and ritonavir, were generally started as part of the initial CART regimen and when CD4 cell counts were relatively low (around $150\text{--}160 \times 10^6$ cells/l). In contrast, ritonavir-boosted indinavir or saquinavir, nelfinavir, lopinavir, nevirapine, efavirenz and abacavir, tended to be initiated some time after CART was started and at higher CD4 cell counts. This was particularly the case for efavirenz,

Table 1. Total number of subjects taking the drug, total person-years on drug and median [interquartile range (IQR)] time (in months) (i) from start of combination antiretroviral therapy (CART) to initiation of drug, (ii) from initiation of drug, (iii) CD4 cell count at start of drug and (iv) current change in CD4 cell count since initiation of drug, for specific third drugs. For (i) and (iii) median (IQR) is over all subjects who took the drug, whereas for (ii) and (iv) median (IQR) is over all person-months of use of the drug.

	Total person-years	Months from CART to initiation (i)	Months from initiation (ii)	CD4 cell count at initiation (iii)	Change in CD4 cell count since initiation (iv)
Indinavir (<i>n</i> = 3338)	6729.1	0 (0, 4)	16 (7,29)	167 (67,296)	+98 (0, +240)
Ritonavir (<i>n</i> = 1231)	1705.4	0 (0, 4)	14 (5,29)	148 (56,264)	+86 (0, +242)
Saquinavir (<i>n</i> = 1257)	1441.9	0 (0, 0)	8 (3,17)	160 (68,270)	+0 (0, +102)
Nelfinavir (<i>n</i> = 1705)	3194.5	12 (0, 24)	15 (6,29)	265 (137,401)	+70 (0, +196)
IDV/r or SQV/r (<i>n</i> = 1649)	2637.8	12 (0, 29)	18 (7,34)	218 (100,382)	+100 (0, +240)
Lopinavir / r (<i>n</i> = 675)	773.9	51 (37,59)	9 (4,15)	251 (132,420)	+46 (0, +149)
Abacavir ^a (<i>n</i> = 765)	1217.8	34 (20,50)	14 (6,25)	377 (222,578)	+35 (-12,+149)
Nevirapine (<i>n</i> = 1423)	2629.6	18 (0,35)	16 (7,29)	325 (200,469)	+62 (0, +179)
Efavirenz (<i>n</i> = 1465)	2436.5	29 (5,43)	13 (6,24)	342 (195,524)	+50 (0, +166)

^aCounted only when third drug.

IDV, indinavir; SQV, saquinavir; x / r means drug x boosted with ritonavir.

nevirapine and abacavir, which were started at median CD4 cell counts between 325×10^6 cells/l (nevirapine) and 377×10^6 cells/l (abacavir). The median degree of CD4 cell count increase experienced while taking each drug also varied, with lower increases for the drugs such as efavirenz, nevirapine and abacavir, which were introduced when the CD4 cell count was already relatively high. For saquinavir, the median increase was zero.

During the observation time there were a total of 779 occurrences of AIDS diseases and 125 deaths (900 events for the endpoint of AIDS or death). Person-years of observation, numbers of AIDS events and deaths, and AIDS/death rates according to specific nucleoside backbone pairs and specific third drugs and latest CD4 cell count are given in Table 2 and summarized in Fig. 1. As seen, while AIDS/death rates differ markedly according to the latest CD4 cell count, there is no evidence that the rates differ between specific drugs within CD4 cell count strata. Table 3 shows similar results by HIV-RNA instead of CD4 count; that is, AIDS/death rates are higher in patients with higher HIV-RNAs, but no significant difference in rate ratios could be shown within the HIV-RNA groups for different CART regimens.

Table 4 shows results from a Poisson regression model of the incidence of AIDS/death on CD4 group, HIV-RNA group, age, HIV exposure group nucleoside combination and third drug. Rate ratios for third drugs are compared with indinavir, a drug for which there is some evidence of efficacy from clinical endpoint trials. While the univariable rate ratios differ between drugs, after adjustment for factors including latest CD4 cell count and HIV-RNA these differences disappear and all rate ratio estimates are close to one, consistent with the results in Tables 2 and 3 and Fig. 1.

Due to concern that the AIDS/death rate that we have ascribed to use of a given third drug at a given point in

time could instead relate to the effects of drugs which have recently been stopped, we fitted a similar Poisson model to that described above, but restricted to person time in which the third drug had been used for at least 6 months. The results were similar, with no rate ratio estimate for any drug (relative to indinavir) showing a significant ($P < 0.05$) difference from one. This was also the case when we instead restricted to: (1) person time in which at least a 50×10^6 cells/l increase had been attained on the current third drug; to (2) person months where CD4 cell and HIV-RNA were known within at most the past 3 months; and to (3) person time for which the initial HIV-RNA value on the current third drug was < 500 copies/ml (i.e. persons switched to the drug while virally suppressed). We also considered rates of AIDS/death separately for those who had a CD4 cell count below 200×10^6 cells/l at the time of the start of CART and a latest CD4 cell count of above 350×10^6 cells/l. Rates were: indinavir 1.00 per 100 person-years [95% confidence interval (CI) 0.48–1.84; 10 AIDS/death events in 998.8 person-years], ritonavir 1.12 (95% CI, 0.23–3.25; 3/267.3), saquinavir 1.31 (95% CI, 0.03–7.33; 1/76.4), nelfinavir 1.30 (95% CI, 0.48–2.81; 6/462.8), indinavir/ritonavir or saquinavir/ritonavir 0.81 (95% CI, 0.26–1.90; 5/615.4), lopinavir/ritonavir 0.55 (95% CI, 0.01–3.11; 1/180.3), abacavir 0.00 (95% CI, 0.00–1.45; 0/255.6), nevirapine 0.44 (95% CI, 0.05–1.60; 2/450.3) and efavirenz 0.71 (95% CI, 0.19–1.81; 4/562.3).

Discussion

No trials exist which directly demonstrate the clinical benefit of regimens containing commonly used drugs such as efavirenz, abacavir and nelfinavir, because they have been licensed after changes in the drug approval process, which meant that evidence from trials with clinical endpoints was no longer required. Indeed, even

Table 2. Numbers of occurrences of AIDS, death and AIDS or death (i) person-years of observation (ii) AIDS/death rates (iii) with 95% confidence intervals (iv) at latest given CD4 cell count groups according to (a) specific nucleoside pairs and (b) specific third drugs.

	CD4 cell count (× 10 ⁶ cells/l) group					
	< 50	50–99	100–199	200–349	350–499	≥ 500
(a) Nucleoside pair						
ZDV / 3TC						
(i)	121 / 12 / 132	59 / 4 / 63	68 / 7 / 75	39 / 4 / 43	14 / 4 / 18	9 / 4 / 13
(ii)	364.4	436.1	1251.2	2160.5	1854.4	2613.6
(iii)	36.2	14.4	6.0	2.0	1.0	0.5
(iv)	(29.9–42.5)	(10.8–18.0)	(4.6–7.4)	(1.4–2.6)	(0.6–1.5)	(0.3–0.9)
d4T / ddl						
(i)	28 / 2 / 29	10 / 4 / 14	14 / 3 / 17	8 / 3 / 11	7 / 4 / 11	3 / 2 / 5
(ii)	75.3	122.2	338.3	640.2	539.1	656.8
(iii)	38.5	11.5	5.0	1.7	2.0	0.8
(iv)	(24.2–52.8)	(6.3–19.2)	(2.9–8.0)	(0.9–3.1)	(1.0–3.7)	(0.2–1.8)
d4T / 3TC						
(i)	106 / 18 / 124	61 / 5 / 66	54 / 15 / 68	40 / 7 / 47	20 / 3 / 23	21 / 9 / 29
(ii)	392.8	432.4	1257.3	2194.5	1862.3	2602.0
(iii)	31.6	15.3	5.4	2.1	1.2	1.1
(iv)	(25.9–37.3)	(11.5–19.1)	(4.1–6.7)	(1.5–2.7)	(0.7–1.7)	(0.7–1.5)
Other						
(i)	37 / 7 / 44	24 / 0 / 24	16 / 3 / 19	12 / 2 / 14	4 / 1 / 5	4 / 2 / 6
(ii)	154.4	173.2	409.8	796.5	603.1	836.3
(iii)	28.5	13.9	4.6	1.8	0.8	0.7
(iv)	(24.2–32.8)	(8.2–19.6)	(2.9–7.3)	(1.0–3.0)	(0.3–1.9)	(0.3–1.6)
(b) Third/fourth drug						
Indinavir						
(i)	121 / 9 / 130	59 / 2 / 61	70 / 10 / 80	36 / 6 / 42	11 / 3 / 14	7 / 2 / 8
(ii)	396.2	454.6	1200.3	1812.3	1324.4	1541.3
(iii)	32.8	13.4	6.7	2.3	1.1	0.5
(iv)	(27.0–38.6)	(10.0–16.8)	(5.2–8.2)	(1.6–4.0)	(0.6–1.8)	(0.2–1.0)
Ritonavir						
(i)	36 / 6 / 42	12 / 2 / 14	13 / 4 / 17	5 / 0 / 5	4 / 1 / 5	4 / 0 / 4
(ii)	141.0	150.5	301.0	441.7	319.7	351.6
(iii)	29.8	9.3	5.6	1.1	1.6	1.1
(iv)	(20.6–39.0)	(5.1–15.6)	(3.3–9.0)	(0.4–2.6)	(0.5–3.7)	(0.3–2.9)
Saquinavir						
(i)	54 / 7 / 60	27 / 4 / 31	13 / 0 / 13	14 / 2 / 16	7 / 0 / 7	3 / 1 / 4
(ii)	128.6	139.6	308.8	434.7	232.2	198.1
(iii)	46.7	22.2	4.2	3.7	3.0	2.0
(iv)	(34.7–58.7)	(14.2–30.2)	(2.2–7.2)	(2.0–6.0)	(1.2–6.2)	(0.6–5.1)
Nelfinavir						
(i)	30 / 4 / 33	25 / 1 / 26	15 / 3 / 18	6 / 4 / 10	9 / 2 / 11	9 / 2 / 11
(ii)	90.7	116.3	399.3	814.5	725.3	1048.4
(iii)	36.4	22.4	4.5	1.2	1.5	1.0
(iv)	(23.7–49.1)	(13.6–31.2)	(2.7–7.1)	(0.6–2.3)	(0.8–2.8)	(0.5–1.9)
IDV / r or SQV / r						
(i)	20 / 2 / 22	10 / 0 / 10	15 / 2 / 16	9 / 2 / 11	3 / 2 / 5	4 / 1 / 5
(ii)	94.8	112.6	345.0	662.1	609.4	814.0
(iii)	23.2	8.9	4.6	1.7	0.8	0.6
(iv)	(13.3–33.1)	(4.2–16.3)	(2.6–7.5)	(0.8–3.0)	(0.3–1.9)	(0.2–1.4)
Lopinavir / r						
(i)	9 / 4 / 13	5 / 0 / 5	5 / 1 / 6	3 / 1 / 4	2 / 1 / 3	2 / 1 / 3
(ii)	31.8	38.5	125.5	206.9	158.8	212.4
(iii)	40.9	13.0	4.8	1.9	1.9	1.4
(iv)	(21.7–69.8)	(4.2–30.4)	(1.7–10.4)	(0.5–4.9)	(0.4–5.5)	(0.3–4.1)
Abacavir ^a						
(i)	8 / 2 / 10	1 / 1 / 2	2 / 1 / 3	8 / 0 / 8	1 / 0 / 1	1 / 2 / 3
(ii)	26.7	28.4	80.7	237.6	312.3	532.3
(iii)	37.5	7.0	3.7	3.4	0.3	0.6
(iv)	(18.0–68.9)	(0.8–25.4)	(0.7–10.9)	(1.5–6.6)	(0.0–1.8)	(0.1–1.7)
Nevirapine						
(i)	5 / 3 / 8	10 / 1 / 11	8 / 3 / 11	8 / 1 / 9	5 / 2 / 7	6 / 3 / 9
(ii)	31.1	69.3	259.3	646.4	640.5	983.0
(iii)	25.7	15.9	4.2	1.4	1.1	0.9
(iv)	(11.1–50.8)	(7.9–28.4)	(2.1–7.7)	(0.6–2.6)	(0.4–2.2)	(0.4–1.7)

(continued overleaf)

Table 2. (continued)

	CD4 cell count (× 10 ⁶ cells/l) group					
	< 50	50–99	100–199	200–349	350–499	≥ 500
Efavirenz						
(i)	9 / 2 / 11	5 / 2 / 7	11 / 4 / 15	10 / 0 / 10	3 / 1 / 4	1 / 5 / 6
(ii)	46.2	54.0	236.7	535.6	536.4	1027.7
(iii)	23.8	13.0	6.3	1.9	0.7	0.6
(iv)	(11.9–42.8)	(5.1–26.7)	(3.5–10.4)	(0.9–3.4)	(0.2–1.9)	(0.2–1.3)

^aCounted only when third drug.

IDV, indinavir; SQV, saquinavir; 3TC, lamivudine; d4T, stavudine; ddl, didanosine; ZDV, zidovudine; x / r means drug x boosted with ritonavir.

Note: The numbers in Table 2 should be read as follows:

(i) Observed number of events of AIDS / death / AIDS or death

(ii) Person-years of follow up (PYFU)

(iii) Incidence rate (IR) of AIDS or death per 100 PYFU

(iv) 95% confidence intervals (95%CI) for the IR above.

Example given below using the first group in Table 2, namely the nucleoside pair ZDV / 3TC.

We observed 121 AIDS events and 12 deaths, and a total of 132 AIDS or deaths (one patient was diagnosed with AIDS at time of death) during 364.4 person-years of follow up resulting in an IR of 36.2 per 100 PYFU with a 95% CI of (29.9–42.5).

for d4T, approved before 1997, there is no such clinical evidence. We therefore conducted an analysis to test the assumption which is implicitly made in both clinical and research settings, namely that the risk of a clinical AIDS event or death for a patient on CART with a given HIV-RNA and CD4 cell count is the same, regardless of which specific drugs are being used in the current regimen. Our results are based on over 22 000 person-years of observation and represent some of the first substantial body of data on risk of clinical endpoints for patients taking several of the key drugs in current clinical use, most notably efavirenz (51 AIDS/death events in 2436.5 person-years of experience) and lopinavir (34 AIDS/death events in 773.9 person-years of experience), which are currently among the most widely recommended drugs of their class for initial therapy.

Reassuringly, we found that rates of disease and death for a given latest (i.e. the most recent measurement) HIV-RNA/CD4 cell count do not appear to differ between drugs for which there is some direct evidence of clinical efficacy (zidovudine [34], didanosine [35,36], lamivudine [37], indinavir [38], ritonavir [39], saquinavir [40]), and those newer drugs which are currently widely used, for which there is no such evidence. This remained the case when we restricted our analysis to person time in which the third drug had been used for at least 6 months, to person time in which at least a 50 × 10⁶ cells/l increase had been attained on the current third drug and to person time for which the initial HIV-RNA value on the current third drug was < 500 copies/ml. We also found similar results when we restricted to person-years when the CD4 cell count was below 200 × 10⁶ cells/l at the time of the

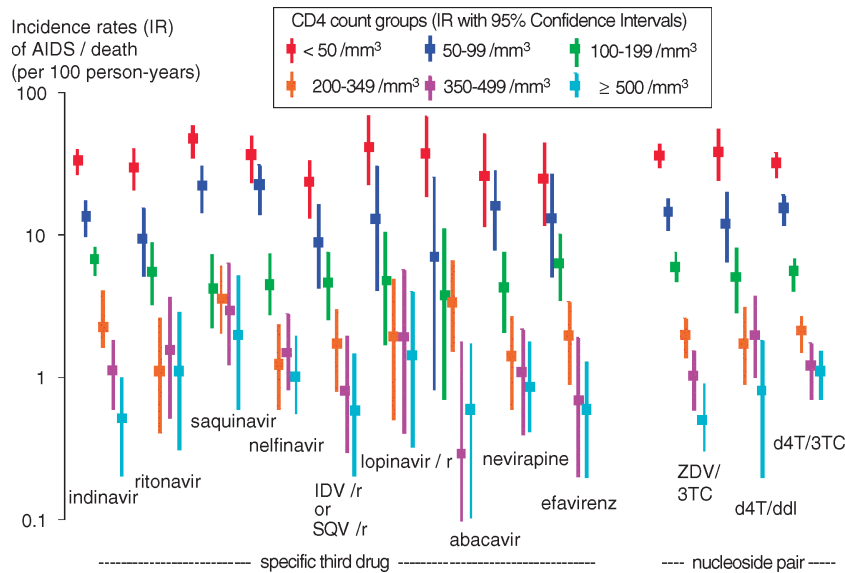


Fig. 1. Rates of AIDS/death according to latest CD4 count and specific drugs used. The nucleoside backbone combinations are shown in the right part and the third (and fourth) drugs in the regimens are shown in the left part. IDV, indinavir; SQV, saquinavir; RTV, ritonavir; 3TC, lamivudine; d4T, stavudine; ddl, didanosine; ZDV, zidovudine; x / r means drug x boosted with ritonavir.

Table 3. Numbers of occurrences of AIDS, death and AIDS or death (i) person-years of observation (ii) together with AIDS/death rates (iii) with 95% confidence intervals (iv) at latest given CD4 cell count groups according to (a) specific nucleoside pairs and (b) specific third drugs.

	HIV-RNA (copies/ml) group				
	< 500	500–4999	5000–49 999	50 000–499 999	≥ 500 000
(a) Nucleoside pair					
ZDV / 3TC					
(i)	46 / 13 / 59	31 / 3 / 34	36 / 7 / 43	93 / 7 / 99	36 / 2 / 38
(ii)	5745.4	1073.9	746.9	534.9	111.8
(iii)	1.0	3.2	5.8	18.5	34.0
(iv)	(0.7–1.3)	(2.1–4.3)	(4.0–7.6)	(14.8–22.2)	(23.0–45.0)
d4T / ddl					
(i)	12 / 6 / 18	10 / 3 / 13	10 / 4 / 14	16 / 2 / 18	11 / 3 / 13
(ii)	1286.3	410.6	361.3	192.8	34.2
(iii)	1.4	3.2	3.9	9.3	38.0
(iv)	(0.8–2.2)	(1.7–5.4)	(2.1–6.5)	(5.5–14.8)	(20.2–64.9)
d4T / 3TC					
(i)	71 / 21 / 92	48 / 11 / 57	38 / 10 / 48	59 / 8 / 67	26 / 1 / 27
(ii)	5329.5	1361.0	1013.3	537.0	87.9
(iii)	1.7	4.2	4.7	12.5	30.7
(iv)	(1.3–2.1)	(3.3–5.3)	(3.3–6.1)	(11.0–14.0)	(28.9–42.5)
Other					
(i)	10 / 4 / 14	7 / 2 / 9	18 / 1 / 19	18 / 5 / 23	9 / 2 / 11
(ii)	1747.8	395.6	307.8	201.5	31.1
(iii)	0.8	2.3	6.2	11.4	35.4
(iv)	(0.4–1.3)	(1.0–4.3)	(3.7–9.6)	(6.6–16.2)	(17.7–63.3)
(b) Third/fourth drug					
Indinavir					
(i)	58 / 10 / 68	42 / 7 / 48	45 / 5 / 50	64 / 5 / 69	27 / 1 / 28
(ii)	3837.8	1062.1	761.6	460.3	93.4
(iii)	1.8	4.5	6.6	15.0	30.0
(iv)	(1.4–2.2)	(3.2–5.8)	(4.7–8.5)	(11.4–18.6)	(18.7–41.3)
Ritonavir					
(i)	7 / 2 / 9	8 / 1 / 9	6 / 1 / 7	22 / 5 / 27	4 / 1 / 5
(ii)	903.1	252.0	181.8	131.9	21.7
(iii)	1.0	3.6	3.9	20.4	23.0
(iv)	(0.5–1.9)	(1.6–6.8)	(1.5–7.9)	(22.5–28.3)	(7.3–53.9)
Saquinavir					
(i)	4 / 3 / 7	13 / 3 / 16	13 / 1 / 14	25 / 3 / 27	7 / 1 / 8
(ii)	379.6	312.6	262.0	143.0	24.3
(iii)	1.8	5.1	5.3	18.9	32.9
(iv)	(0.7–3.8)	(2.9–8.3)	(2.9–9.0)	(11.6–26.2)	(14.4–65.0)
Nelfinavir					
(i)	23 / 5 / 28	12 / 3 / 15	10 / 3 / 13	24 / 2 / 26	16 / 3 / 18
(ii)	2041.4	476.9	359.3	216.7	36.4
(iii)	1.4	3.5	3.6	12.0	49.5
(iv)	(0.9–1.9)	(1.8–5.3)	(1.9–6.2)	(7.3–16.7)	(29.4–78.3)
IDV / r or SQV / r					
(i)	10 / 4 / 14	6 / 3 / 8	8 / 0 / 8	19 / 2 / 21	10 / 0 / 10
(ii)	1786.1	336.3	253.6	171.7	27.3
(iii)	0.8	2.4	3.2	12.2	36.6
(iv)	(0.4–1.3)	(1.0–4.7)	(1.4–6.2)	(6.9–17.5)	(17.6–67.4)
Lopinavir / r					
(i)	5 / 2 / 7	5 / 0 / 5	5 / 3 / 8	6 / 2 / 8	4 / 1 / 5
(ii)	496.8	101.6	96.5	64.8	11.1
(iii)	1.4	4.9	8.3	12.3	45.0
(iv)	(0.6–2.9)	(1.6–11.6)	(3.6–16.4)	(5.4–24.4)	(14.4–105.4)
Abacavir [#]					
(i)	10 / 2 / 12	1 / 1 / 2	3 / 1 / 4	4 / 1 / 5	3 / 1 / 4
(ii)	907.6	145.6	99.7	49.1	9.7
(iii)	1.3	1.4	4.0	10.2	41.2
(iv)	(0.7–2.3)	(0.2–4.9)	(1.1–10.2)	(3.2–23.8)	(11.3–105.2)
Nevirapine					
(i)	12 / 7 / 19	5 / 1 / 6	9 / 5 / 14	10 / 0 / 10	4 / 0 / 4
(ii)	1840.8	357.2	259.3	114.6	16.4
(iii)	1.0	1.7	5.4	8.7	24.4
(iv)	(0.6–1.6)	(0.6–3.6)	(3.0–9.0)	(4.2–16.1)	(6.7–62.2)

(continued overleaf)

Table 3. (continued)

	HIV-RNA (copies/ml) group				
	< 500	500–4999	5000–49 999	50 000–499 999	≥ 500 000
Efavirenz					
(i)	10 / 9 / 19	4 / 0 / 4	3 / 3 / 6	12 / 2 / 14	7 / 0 / 7
(ii)	1915.8	196.8	155.4	114.2	24.8
(iii)	1.0	2.0	3.9	12.3	28.2
(iv)	(0.6–1.6)	(0.6–5.2)	(1.4–8.5)	(6.8–20.6)	(11.3–58.1)

^aCounted only when third drug.

IDV, indinavir; SQV, saquinavir; 3TC, lamivudine; d4T, stavudine; ddl, didanosine; ZDV, zidovudine; x / r means drug x boosted with ritonavir.

Note: The numbers in Table 3 should be read as follows:

(i) Observed number of events of AIDS / death / AIDS or death

(ii) Person-years of follow up (PYFU)

(iii) Incidence rate (IR) of AIDS or death per 100 PYFU

(iv) 95% confidence intervals (95%CI) for the IR above.

Example given below using the first group in Table 3, namely the nucleoside pair ZDV / 3TC. We observed 46 AIDS events, 13 deaths, and a total of 59 AIDS or deaths during 5745.4 person-years of follow up resulting in an incidence rate (IR) of 1.0 of AIDS or death per 100 PYFU with a 95% confidence interval of (0.7–1.3).

Table 4. Crude and adjusted rate ratios for occurrence of AIDS disease or death from a Poisson regression model.

	Univariable		Multivariable	
	Rate ratio (95% CI)	P-value	Rate ratio (95% CI)	P-value
Latest CD4 cell count (× 10 ⁶ cells/l)				
< 50	37.7 (28.2–49.9)	P < 0.0001	13.7 (9.39–19.9)	P < 0.0001
50–99	15.8 (11.7–21.5)	P < 0.0001	7.39 (5.10–10.6)	P < 0.0001
100–199	6.23 (4.66–8.41)	P < 0.0001	3.39 (2.41–4.76)	P < 0.0001
200–349	2.23 (1.62–3.06)	P < 0.0001	1.57 (1.12–2.20)	P = 0.01
350–499	1.43 (1.01–2.03)	P = 0.04	1.17 (0.80–1.72)	P = 0.40
≥ 500	1		1	
Latest HIV-RNA (copies/ml)				
< 500	0.05 (0.03–0.06)	P < 0.0001	0.22 (0.16–0.30)	P < 0.0001
500–4999	0.12 (0.08–0.17)	P < 0.0001	0.36 (0.27–0.49)	P < 0.0001
5000–49 999	0.17 (0.12–0.24)	P < 0.0001	0.41 (0.31–0.55)	P < 0.0001
50 000–499 999	0.47 (0.35–0.64)	P < 0.0001	0.61 (0.47–0.79)	P = 0.0002
> 500 000	1		1	
Previous AIDS diagnosis	2.12 (1.84–2.46)	P < 0.0001	1.02 (0.85–1.21)	P = 0.84
Exposure group				
MSM	0.82 (0.63–1.08)	P = 0.16	1.08 (0.80–1.45)	P = 0.63
IDU	0.77 (0.57–1.05)	P = 0.10	0.90 (0.65–1.26)	P = 0.55
Heterosexual	0.89 (0.66–1.20)	P = 0.44	1.13 (0.83–1.54)	P = 0.46
Other/unknown	1		1	
Age (per 10 years older)	1.42 (0.60–0.83)	P < 0.0001	1.17 (1.07–1.26)	P = 0.0001
Calendar year ^a	0.65 (0.62–0.69)	P < 0.0001	1.10 (1.02–1.18)	P = 0.009
Time from start of CART ^a	0.56 (0.52–0.61)	P < 0.0001	0.86 (0.80–0.93)	P = 0.0002
Time on current third drug ^a	0.33 (0.26–0.42)	P < 0.0001	0.69 (0.60–0.80)	P < 0.0001
Nucleoside pair				
ZDV / 3TC	1.05 (0.84–1.34)	P = 0.66	1.21 (0.93–1.58)	P = 0.15
d4T / ddl	1.08 (0.86–1.36)	P = 0.49	1.26 (0.97–1.62)	P = 0.08
d4T / 3TC	0.98 (0.72–1.32)	P = 0.87	1.15 (0.84–1.58)	P = 0.38
Other	1		1	
Third drug				
Indinavir	1		1	
Ritonavir	1.14 (0.84–1.54)	P = 0.41	0.88 (0.66–1.17)	P = 0.39
Saquinavir	1.80 (1.36–2.41)	P < 0.0001	1.04 (0.78–1.38)	P = 0.80
Nelfinavir	0.78 (0.59–1.02)	P = 0.069	0.99 (0.76–1.28)	P = 0.92
IDV/r or SQV/r	0.56 (0.41–0.77)	P = 0.0004	0.79 (0.59–1.05)	P = 0.10
Lopinavir / r	1.04 (0.69–1.57)	P = 0.83	1.08 (0.65–1.82)	P = 0.76
Abacavir ^b	0.72 (0.49–1.05)	P = 0.09	1.01 (0.64–1.60)	P = 0.97
Nevirapine	0.57 (0.42–0.78)	P = 0.0004	0.91 (0.65–1.28)	P = 0.59
Efavirenz	0.62 (0.46–0.84)	P = 0.002	0.83 (0.57–1.20)	P = 0.31

^aRate ratio per extra year.

^bCounted only when third drug.

CI, confidence interval; MSM, men who have sex with men; IDU, injecting drug users; CART, combination drug therapy; IDV, indinavir; SQV, saquinavir; RTV, ritonavir; 3TC, lamivudine; d4T, stavudine; ddl, didanosine; ZDV, AZT, zidovudine; x / r means drug x boosted with ritonavir.

start of CART and the latest CD4 cell count above 350×10^6 cells/l. The overall median responses to CART that we observed (a rise of 137×10^6 cells/l in CD4 cell count and a decline of 1.68 log copies/ml in viral load) may appear relatively modest. This probably largely reflects the fact that the person time we included was distributed such that most occurred in patients who had started CART within the past 2 to 3 years, but it also reflects the slightly poorer responses to therapy observed in unselected cohorts, compared with randomized trials.

It has been suggested that antiretroviral drugs might have adverse or perhaps even positive effects on risk of AIDS and/or death, which are not mediated by the effect of the drugs on HIV-RNA and CD4 cell count [17,18,41]. Such effects would generally be missed by trials designed to examine the short-term effects of drugs on HIV-RNA and CD4 cell count, both due to inadequate size and insufficient length of follow up. Even in a large follow-up study like this, where surrogate markers, namely CD4 cell count and HIV-RNA, are correlated to effect markers, namely clinical AIDS events or death, there is a possibility of overlooking moderately large additional effects of drugs due to random chance given the width of confidence intervals for the rate ratios comparing drugs. However, our results suggest that for a given CD4 cell count, HIV-RNA and time from start of the drug (plus the other factors that we adjusted for in our model) the risk of AIDS or death is the same, regardless of the specific antiretroviral drug being used. It is important to note that these results do not suggest that the regimens assessed have equal clinical efficacy. Several published randomized clinical trials have shown that different regimens have different capacities to decrease the HIV-RNA and raise the CD4 cell count and this will lead to a difference in clinical efficacy for different drug regimens.

Complete reliance on the ability of surrogate endpoints to evaluate treatment effect has led to adverse clinical outcome in other disease areas; one example being anti-arrhythmia drugs [42]. Therefore it is imperative to revisit and validate historical assumptions on a regular basis, especially in the case of new drug regimens [1].

To be an ideal surrogate, two basic conditions should be satisfied, namely that the surrogate marker is a correlate of the clinical outcome being the only causal pathway of the disease process, and that the intervention's entire effect on the clinical outcome is mediated through its effect on the surrogate [18,43]. The use of surrogate markers such as HIV-RNA and CD4 cell counts do not always provide a true estimate of the treatment effect on clinical progression of HIV disease [4,44]. Previous analyses from the EuroSIDA study have suggested an effect of ART over and above the effect mediated via CD4 cell count and HIV-RNA [45,46]. This could imply that the predictive values of CD4/HIV-RNA is different in patients off rather than on therapy [47], or that there are

benefits of ART, which are mediated via other mechanisms [41,48–50]. However, residual confounding due to measurement error in the current CD4 cell count and HIV-RNA is another, more mundane potential explanation.

Even so these markers are among the best available at the present time and have been shown to be good and independent predictors of the clinical progression of AIDS events and HIV-related death and to be of clinical use to assess the efficacy of antiretroviral drugs [8,12,45,51–53]. However, the above-mentioned references suggest that also in the field of HIV, it is necessary to validate surrogate markers against effect markers regularly to evaluate the true treatment effect of drugs and the predictive ability of surrogate markers on clinical progression. The relevance of these type of analyses is evident, knowing that complete reliance have been made on the virologic and immunologic markers to measure treatment effect of drugs released after 1997, even though the relative proportion of non-AIDS-related death has increased during the period of combination and highly active antiretroviral therapy, and treatment effects and regimens have changed dramatically since the release of these newer drugs [43,54].

In conclusion, the AIDS/death rate ratios do not appear to differ significantly for various regimens for patients having the same CD4 cell count or HIV-RNA levels. This implies that the markers currently used for gauging patients' risk of clinical progression can be interpreted similarly, regardless of which regimen the patient is receiving.

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Appendix

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