Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study

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Summary

Background Data on adverse events to antiretroviral treatment have been recorded in clinical trials, post-marketing analyses, and anecdotal reports. Such data might not be an up-to-date or comprehensive assessment of all possible treatment combinations defined as potent antiretroviral treatment.

Methods Using a standard clinical and laboratory method, we assessed prevalence of adverse events in 1160 patients who were receiving antiretroviral treatment. We measured the toxic effects associated with the drug regimen (protease inhibitor [PI], non-nucleoside and nucleoside analogue reverse transcriptase inhibitor) and specific compounds using multivariate analyses.

Findings 47% (545 of 1160) of patients presented with clinical and 27% (194 of 712) with laboratory adverse events probably or definitely attributed to antiretroviral treatment. Among these, 9% (47 of 545) and 16% (30 of 194), respectively, were graded as serious or severe. Single-PI and PI-sparing-antiretroviral treatment were associated with a comparable prevalence of adverse events. Compared with single-PI treatment, use of dual-PI-antiretroviral treatment and three-class-antiretroviral treatment was associated with higher prevalence of adverse events (odds ratio [OR] 2·0 [95% CI 1·0–4·0], and 3·9 [1·2–12·9], respectively). Compound specific associations were identified for zidovudine, lamivudine, stavudine, didanosine, abacavir, ritonavir, saquinavir, indinavir, nelfinavir, efavirenz, and nevirapine.

Interpretation We recorded a high prevalence of toxic effects attributed to antiretroviral treatment for HIV-1. Such data provides a reference for regimen-specific and compound-specific adverse events and could be useful in postmarketing analyses of toxic effects.

Lancet 2001; **358:** 1322–27

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Introduction

Because so many retroviral agents are available, clinicians need a precise understanding of the efficacy and toxic effects of the various drug combinations. When efficacy is similar, the choice of combination will be affected by the toxic effects of the drugs. Adverse reactions have been recorded anecdotally and in randomised clinical trials,[1–3] but, little information is available about prevalence and severity of adverse events in routine clinical practice. To describe the pattern of clinical and laboratory abnormalities potentially associated with antiretroviral treatment, and to compare the prevalence of adverse events between drug regimens and for various antiretroviral agents, we have done a cross-sectional, observational study of 1160 patients who were receiving potent antiretroviral treatment.

We did two types of analyses. First, we did a structured interview and laboratory analysis to identify and describe all potential adverse events attributed to treatment according to standard definitions. Second, we identified independent associations using logistic regression analysis that excluded the investigator's assessment. This approach could be a useful strategy in postmarketing analysis of the toxic effects of drugs used in multidrug treatments.

Methods

Patients

The Swiss HIV Cohort Study is a prospective cohort study of individuals with HIV-1 who are aged 16 years or older.[4] Patients were followed up in one of seven outpatient clinics (Basel, Bern, Geneva, Lausanne, Lugano, St-Gallen, Zürich). Potent antiretroviral treatment is defined as a combination that includes at least three agents—a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor, or a nucleoside analogue reverse transcriptase inhibitor. Drug regimens were defined as single-PI-antiretroviral treatment (contains one PI and no non-nucleoside reverse transcriptase inhibitors), PI-sparing-antiretroviral treatment (contains no PIs and one non-nucleoside reverse transcriptase inhibitor, or triple nucleoside analogue reverse transcriptase inhibitors including abacavir), dual-PI-antiretroviral treatment (contains two PIs and no non-nucleoside reverse transcriptase inhibitor), and three-class-antiretroviral treatment (contains nucleoside analogue reverse transcriptase, PI, and non-nucleoside reverse transcriptase inhibitors). In patients receiving dual-PI-antiretroviral treatment, no pharmacokinetic boosting with low-dose ritonavir was recorded.

We did a cross-sectional study over 4 weeks (August, 1999, to September, 1999) that included all participants in the Swiss HIV Cohort Study who were receiving potent antiretroviral treatment. We excluded patients who had started or changed regimens within the previous 30 days. During an outpatient visit, physicians completed a questionnaire about adverse events. The questionnaire was based on classification used by the

AIDS Clinical Trials Group (http://aactg.s-3.com). Physicians explicitly asked patients if symptoms listed in the questionnaire had arisen within the 30 days preceding the visit. Lipodystrophy was described according to Carr and colleagues.[5] Potential adverse events were scored according to severity (1=mild, 2=moderate, 3=severe, 4=serious) and the likelihood of resulting from antiretroviral treatment (unlikely, possible, probable, and certain), after the definition of the World Health Organisation (http://www.who-umc.org/defs.html).

Procedures

Blood concentrations of haemoglobin, creatinine, urate, transaminases, alkaline phosphatase, bilirubin, amylase, creatine phosphokinase, lactate, glucose, triglyceride, and cholesterol were measured. We also recorded the number of blood neutrophils and platelets, and the concentration of protein in the urine. Blood lactate concentration was measured after the tourniquet was removed, in tubes containing sodium fluoride. Glucose and triglyceride concentrations were assessed according to whether or not the patient was fasting at the time of blood sampling. Normal limits were defined as the interval between the 2·5 and 97·5 percentiles of healthy people. CD4 cell count was measured by flow cytometry, and viral loads were ascertained with the Roche Amplicor Monitor assay (Roche Diagnostic, Basel, Switzerland), which could detect 400 or more copies RNA/mL. Laboratory analyses were done at or immediately before (<10 days) the outpatient visit.

Statistical analysis

We investigated associations between clinical and laboratory abnormalities and different antiretroviral treatment regimens, and between such abnormalities and specific drugs using multiple logistic regression. Variables included in the basic model were age, sex, body mass index, intravenous drug use, last CD4 cell count, last viral load, and concomitant medication (trimethoprim-sulfamethoxazol, antimycobacterial, antitoxoplasmosis, and anticytomegalovirus treatment). We also did a subgroup analysis of drugs that are commonly coprescribed (>80% coadministration; zidovudine with lamivudine, didanosine with stavudine, indinavir with lamivudine), to improve the power of the logistic model to separate associations. For analysis of long-term toxic effects (lipodystrophy, paraesthesia, and neuromotor disorders), the model included type and duration of previous antiretroviral drug exposure as covariables. For analysis of liver-specific laboratory abnormalities, the model included hepatitis C and B serostatus. Analysis of regimen-specific toxic effects used single-PI-antiroviral treatment as reference. We used STATA version 7.0 for statistical analysis.

Results

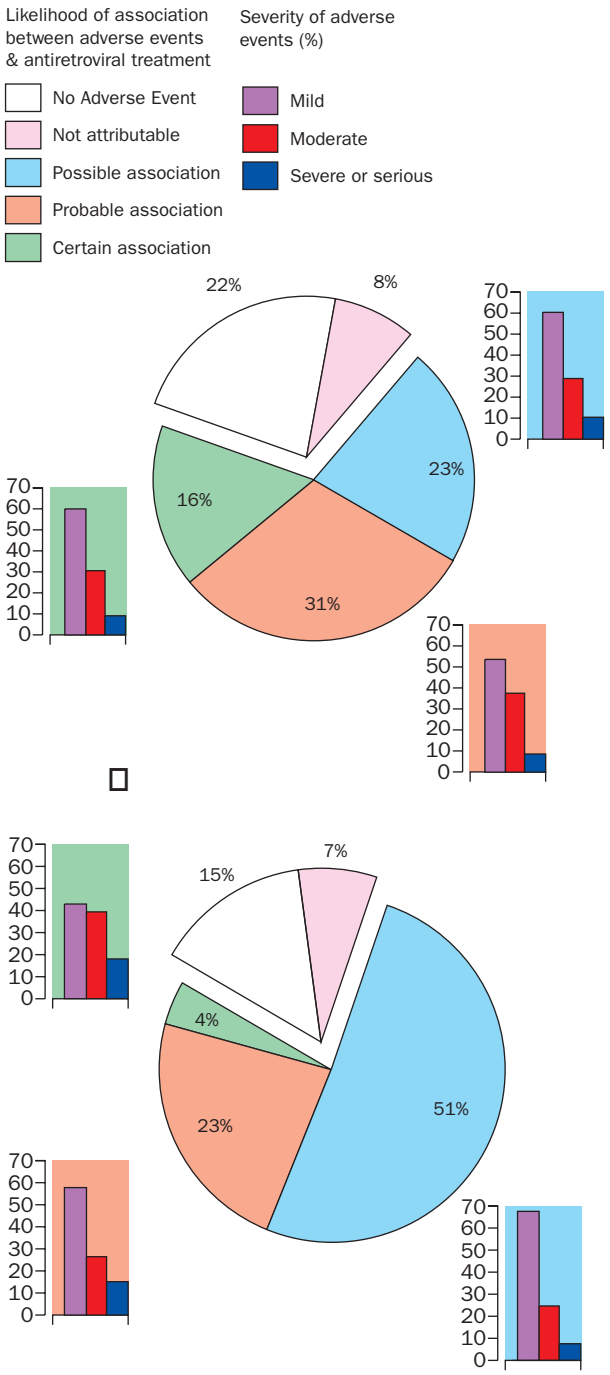
Table 1 summarises demographic and HIV-related characteristics of the 1160 participants. 60% of patients were receiving single PI-antiretroviral treatment, 15% each PI-sparing-antiretroviral treatment or dual-PI-antiretroviral treatment, and 10% three-class-antiretroviral treatment (table 1). Patients on three-class-antiretroviral treatment tended to have a lower CD4 cell count and more instances of suboptimum viral suppression (and thus more advanced disease) than those in the other three treatment groups (p=0·0001, p=0·045, respectively). Intravenous drug users (23% of participants) were less likely to be on PI-sparing-antiretroviral treatment than non-users (p=0·023). Agents for treatment or prophylaxis of opportunistic infections were used by 354 (30·5%) patients. 36 patients (3%) were receiving lipid-lowering drugs and 12 (1%) antidiabetic agents. We did not gather data on other comedication. More men who have sex with men (42% *vs* 36%; p=0·0001), and fewer intravenous drug users (24% *vs* 28%; p=0·001) were recorded in our study compared with 2225 Swiss HIV Cohort Study patients on antiretroviral treatment examined in 1999, but not included in this study. Patients in our cohort had lower CD4 concentrations (20% *vs* 16% had <200 cells/mL; p=0·004), and a greater number of visits (4 *vs* 3, p<0·0001) than those in the 1999 cohort. No differences in the type of antiretroviral treatment were recorded between patients who were included and those who were not.

The figure shows the severity of adverse events and the likelihood that they would be caused by antiretroviral

	n	Age (median [IQR], years)	Men	Body-mass index (Median [IQR], kg/m²)	Intravenous drug user	CD4 (median [IQR], cells/μL)	Viral load <400 copies/mL
Treatment							
All	1160	38·9 (34·4–46·3)	848 (73%)	22·6 (20·5–24·5)	278 (24%)	376 (232–574)	835 (72%)
Single PI-ART	698 (60%)	38·8 (34·2–45·6)	510 (73%)	22·8 (20·6–24·7)	188 (27%)	405 (259–599)	510 (74%)
PI-sparing-ART	172 (15%)	38·2 (33·6–48·2)	120 (70%)	22·6 (20·7–24·9)	28 (16%)	425 (252–652)	132 (77%)
Dual PI-ART	174 (15%)	39·7 (35·2–45·3)	132 (76%)	22·4 (20·2–24·5)	37 (21%)	358 (203–528)	115 (66%)
Three-class-ART	116 (10%)	39·3 (35·2–48·0)	87 (75 %)	21·9 (20·0–23·7)	24 (21%)	258 (131–411)	63 (54%)
NRTI*							
Zidovudine	444 (38%)	39·0 (34·2–47·4)	319 (72%)	22·8 (20·7–24·9)	111 (25%)	390 (244–607)	346 (78%)
Lamivudine	791 (68%)	38·9 (34·4–46·6)	567 (72%)	22·8 (20·8–24·8)	198 (25%)	407 (261–611)	617 (78%)
Stavudine	653 (56%)	38·5 (34·1–44·6)	479 (73 %)	22·5 (20·4–24·3)	157 (24%)	379 (243–575)	464 (71%)
Didanosine	213 (18%)	38·7 (33·8–44·6)	164 (77 %)	22·3 (20·2–24·0)	45 (21%)	312 (204–480)	130 (61%)
Abacavir	130 (11%)	40·3 (35·0–50·2)	102 (79%)	22·2 (19·9–24·0)	29 (22%)	359 (175–585)	86 (66%)
PI†							
Ritonavir	236 (20%)	39·0 (34·8–46·1)	180 (76%)	22·5 (20·2–24·3)	52 (22%)	367 (213–559)	163 (69%)
Saquinavir mesilate	180 (16%)	39·2 (34·9–45·5)	130 (72%)	21·8 (19·9–24·1)	36 (20%)	335 (198–516)	113 (63%)
Indinavir	235 (20%)	40·5 (36·2–47·8)	184 (78%)	23·3 (20·9–25·0)	59 (25%)	434 (285–585)	179 (76%)
Nelfinavir mesilate	530 (46%)	38·3 (33·9–44·6)	377 (71%)	22·5 (20·4–24·5)	143 (27%)	333 (202–529)	366 (69%)
APV	13 (1%)	39·3 (37·1–44·1)	11 (85%)	21·5 (19·1–23·2)	2 (15%)	262 (120–396)	4 (31%)
NNRTI‡							
Efavirenz	184 (16%)	38·6 (34·2–48·4)	133 (73%)	22·3 (20·3–24·3)	26 (14%)	299 (175–497)	120 (65%)
Nevirapine	59 (5%)	38·7 (34·4–47·5)	41 (69%)	22·1 (20·1–23·8)	18 (31%)	300 (197–470)	32 (54%)

ART=antiretroviral treatment. *NRTI=nucleoside analogue reverse transcriptase inhibitor. †PI =protease inhibitor, ‡NNRTI=non-nucleoside analogue reverse transcriptase inhibitor.

Table 1: **Characteristics of patients**



Prevalence, severity, and likelihood of adverse events resulting from antiretroviral treatment

(Top) Clinical adverse events. (Bottom) Laboratory adverse events.

treatment. Clinical and laboratory abnormalities were recorded in 78% (306 of 1160) and 85% (620 of 725 for which all data were available) of patients respectively, but, most laboratory abnormalities were only possibly attributed to treatment (figure). Overall, most adverse events were mild or moderate (grade 1 or 2). However, for patients with probable or certain adverse events, 9% (46 of 535) presented clinical and 16% (31 of 194) with laboratory adverse events that were defined as severe or serious (grade 3 or 4). 6% of outpatient visits were specifically triggered by an adverse event. Eight (0·6%) patients were admitted to hospital during the study period, four of whom had an adverse event probably or definitely attributed to antiretroviral treatment (nephrolithiasis, severe thrombopaenia, renal dysfunction with grade 4 creatinine increase, or grade 4 fatigue).

Table 2 shows the adverse events attributed to different antiretroviral treatment combinations. In a multivariate analysis that accounted for stage of disease as measured by CD4 cell count, viraemia concentration, and use of comedication for opportunistic illnesses, single-PI-antiretroviral treatment and PI-sparing-antiretroviral treatment had closely similar prevalence of adverse events. Compared with single-PI-antiretroviral treatment, use of dual-PI-antiretroviral treatment and three-class-antiretroviral treatment were associated with higher prevalence of adverse events (OR 2·0 [95% CI 1·0–4·0] and 3·9 [1·2–12·9], respectively).

Table 2 lists all associations identified in the logistic analysis. Compared with single-PI-antiretroviral treatment, use of three-class-antiretroviral treatment was associated with greater risk of diarrhoea, and increased concentrations of cholesterol, triglyceride, alkaline phosphatase, and lactate. Use of dual-PI-antiretroviral treatment was associated with greater risk of fever and diarrhoea, and increased concentrations of cholesterol, triglyceride, and alkaline phosphatase. Use of PI-sparing-antiretroviral treatment was associated with greater risk of vomiting, mood and sleep disorders, and increased concentrations of amylase; but reduced risk of diarrhoea, and increased concentrations of bilirubin and urate.

Table 3 lists all adverse events attributed to specific antiretroviral treatment by logistic analysis. In patients taking nucleoside reverse transcriptase inhibitors, lamivudine was independently associated with mood disorders and lipodystrophy; stavudine with headache, lipodystrophy, and rise in serum concentrations of urate, creatine phosphokinase, lactate, cholesterol, and triglyceride; didanosine with increase in urate and lactate concentrations; and abacavir with vomiting and increase in creatine phosphokinase concentrations. There was a trend towards an association between zidovudine and anaemia. Use of zidovudine and lamivudine in combination was associated with neutropenia. In patients on PI, ritonavir was independently associated with diarrhoea, hyperbilirubinaemia, and increases in cholesterol and triglyceride concentrations; saquinavir with diarrhoea and thrombocytopenia; indinavir with nephrolithiasis, rash, and hyperbilirubinaemia; and nelfinavir with diarrhoea. Since only 13 patients received amprenavir, we were unable to analyse this group. In patients on non-nucleoside reverse transcriptase inhibitors, efavirenz was associated with mood and sleep disorders, and nevirapine with rise in serum transaminase concentrations.

The logistic regression model identified several associations with clinical symptoms or laboratory abnormalities that were not from antiretroviral treatment. Fatigue was associated with higher viral load; paraesthesiae and neuromotor disorders (polyneuropathy) with older age and higher viral load; lipodystrophy with older age; and nausea and vomiting with intravenous drug use. Pancytopenia was associated with lower CD4 cell count; hyperlipidaemia and hyperglycaemia with higher body mass index and older age. High concentrations of creatine phosphokinase were not associated with use of statins. Drugs used for treatment or prophylaxis of opportunistic illnesses were associated with neutropenia and raised lactate and creatine phosphokinase concentrations.

Adverse events	PI-sparing-ART	p	dual PI-ART	p	Three-class-ART	p
Clinical						
Fever	1·7 (0·7–4·1)	NS	2·6 (1·2–5·7)	0·016*	2·1 (0·8–5·4)	NS
Headache	1·2 (0·8–1·7)	NS	0·8 (0·5–1·2)	NS	0·8 (0·5–1·3)	NS
Fatigue	0·9 (0·7–1·4)	NS	1·1 (0·8–1·6)	NS	1·0 (0·7–1·6)	NS
Nausea	1·1 (0·7–1·8)	NS	0·9 (0·6–1·4)	NS	1·3 (0·8–2·1)	NS
Vomiting	1·9 (1·1–3·4)	0·023*	0·5 (0·2–1·1)	NS	1·1 (0·5–2·2)	NS
Diarrhoea	0·3 (0·2–0·5)	<0·0001†	1·6 (1·2–2·3)	0·004*	2·0 (1·3–3·0)	NS
Mood disorders	1·8 (1·2–2·5)	0·003*	1·2 (0·8–1·7)	NS	1·4 (0·9–2·2)	NS
Sleep disorders	2·3 (1·5–3·3)	0·001*	1·1 (0·7–1·7)	NS	1·4 (0·9–2·4)	NS
Rash	1·3 (0·7–2·3)	NS	1·0 (0·6–1·9)	NS	0·6 (0·2–1·3)	NS
Myositis	1·7 (0·5–5·7)	NS	0·7 (0·1–3·2)	NS	1·6 (0·4–5·5)	NS
Nephrolithiasis	0·4 (0·1–4·0)	NS	1·6 (0·3–7·9)	NS	1·4 (0·2–12·8)	NS
Paraesthesia	0·7 (0·4–1·1)	NS	1·2 (0·8–1·9)	NS	1·7 (0·9–2·8)	NS
Neuro-motor disorders	1·0 (0·5–2·4)	NS	0·9 (0·4–1·9)	NS	1·1 (0·5–2·5)	NS
Lipodystrophy	1·0 (0·7–1·4)	NS	1·0 (0·7–1·4)	NS	0·8 (0·5–1·2)	NS
Laboratory						
Anaemia	0·4 (0·1–2·0)	NS	0·7 (0·2–2·6)	NS	1·1 (0·3–3·2)	NS
Neutropenia	1·6 (0·6–3·9)	NS	1·1 (0·5–2·7)	NS	0·7 (0·2–1·9)	NS
Thrombopenia	0·7 (0·2–2·3)	NS	1·9 (0·9–4·1)	NS	1·9 (0·8–4·4)	NS
Aspartate aminotransferase	0·9 (0·1–9·4)	NS	2·5 (0·9–11·6)	NS	2·2 (0·5–9·5)	NS
Alanine aminotransferase	0·4 (0·1–1·9)	NS	1·6 (0·7–3·7)	NS	2·0 (0·7–5·9)	NS
Alkaline phosphatase	1·8 (0·3–9·0)	NS	5·6 (2·1–15·1)	0·001*	5·9 (1·6–21·5)	0·007*
Bilirubin	0·2 (0·1–0·9)	0·032†	0·8 (0·2–3·0)	NS	0·5 (0·1–4·9)	NS
Amylase	2·5 (1·2–5·3)	0·014*	0·9 (0·3–2·4)	NS	1·9 (0·8–4·6)	NS
Creatinine	0·6 (0·2–2·2)	NS	0·5 (0·2–1·9)	NS	1·4 (0·5–3·9)	NS
Proteinuria	1·3 (0·7–2·5)	NS	0·8 (0·4–1·7)	NS	1·5 (0·7–3·1)	NS
Urate	0·4 (0·2–0·8)	0·004†	1·2 (0·8–1·9)	NS	0·7 (0·4–1·3)	NS
Creatine phosphokinase	1·2 (0·6–2·4)	NS	1·1 (0·6–2·3)	NS	0·9 (0·4–2·3)	NS
Lactate	1·7 (0·9–3·2)	NS	1·0 (0·5–2·1)	NS	2·0 (1·0–3·9)	NS
Glucose	1·9 (0·8–4·5)	NS	1·5 (0·6–3·8)	NS	1·6 (0·6–4·5)	NS
Cholesterol	0·9 (0·6–1·3)	NS	1·7 (1·2–2·4)	0·009*	2·3 (1·5–3·6)	0·0004*
Triglyceride	0·9 (0·6–1·2)	NS	2·2 (1·1–2·6)	0·001*	1·7 (1·1–2·6)	0·016*

Odds ratios (ORs) were estimated from the basic model using single-protease inhibitor-antiretroviral treatment as reference. PI=protease inhibitor. ART=antiretroviral treatment. NS=not significant. *Significant (p<0·05) independent positive association. †Significant independent negative association.

Table 2: **Logistic regression analysis of clinical and laboratory adverse events attributed to antiretroviral treatment regimens**

Discussion

We have investigated the complex issue of attributing toxic effects to drug regimens, or to agents used in multi-drug combinations. In view of the high prevalence of adverse events associated with antiretroviral treatment, such information is essential for management of patients with HIV-1. In the outpatient population included in this analysis, more than two thirds of patients presented one or more clinical or laboratory adverse events which could have been due to antiretroviral treatment. A significant proportion of adverse events was classified as severe (grade 3) or serious (grade 4). Four of eight admissions of patients followed up during the study were attributed to severe toxic effects. However, since patients included in the study were more frequently examined during 1999 in outpatient clinics, and 6% of visits were specifically due to an adverse event, our data could overestimate the actual prevalence of adverse events.

Patients were asked point by point which symptoms of potential toxic effects described in the standard AIDS Clinical Trials Group questionnaire they had had. In a first assessment, the likelihood of association was defined by the investigator, and thereafter, analysis was completed with a logistic regression model that disregarded the investigator's assessment. Thus, bias incurred through attributing specific toxic effects to a particular drug or drug regimen from pre-existing knowledge of particular toxic effect profiles was kept to a minimum. Prevalence of attributed adverse events was highest in three-class-antiretroviral treatment and in dual-PI-antiretroviral treatment than in single-PI-antiretroviral treatment or PI-sparing-antiretroviral treatment.

In a randomised controlled study,[6] fatigue and headache were reported by 10–20% of patients taking placebo,[6] but in our population, fatigue was reported by 37% and headache by 22% of patients, irrespective of the treatment taken. Lipodystrophy was strongly associated with use of stavudine but not with use of PIs. Such an association has been recorded in three other investigations.[7–9] Some of the unexpected toxic effects, such as thrombocytopenia with saquinavir or mood disorders with lamivudine, could have been missed by previous studies (saquinavir being almost always used in dual PI combination, which generates higher plasma drug concentrations) or be spurious. By contrast with earlier reports,[10] there was only a trend towards more anaemia with use of zidovudine as compared with other agents, and high creatine phosphokinase concentration was more frequently seen in association with stavudine and abacavir. The improved tolerability of zidovudine could be accounted for by the decrease in the recommended dose from 1500 mg/day to 500–600 mg/day in the early 1990s.[10] In our study, as in others,[8,11] both didanosine and stavudine were associated with a high frequency of hyperlactataemia. Symptomless increase in urate concentrations has also been described in patients on didanosine,[12,13] but not, as we recorded, in those taking stavudine. Unconjugated hyper-bilirubinaemia has been associated with use of indinavir,[14] and was also associated with use of ritonavir in our study. One-fifth of all patients had high concentrations of transaminases. But, after including infection with hepatitis B and hepatitis C in the model, only nevirapine was associated with a rise in transaminase concentrations. This correlates with reports about severe toxic effects in the liver as a result of treatment with nevirapine.[15]

We have described clinical and laboratory disorders associated with a wide variety of treatment combinations. As in all cohort analyses, patients were

Adverse effects	Nucleoside analogue reverse transcriptase inhibitors					Protease inhibitors				Non-nucleoside reverse transcriptase inhibitors	
	Zidovudine	Lamivudine	Stavudine	Didanosine	Abacavir	Ritonavir	Saquinavir	Indinavir	Nelfinavir	Efavirenz	Nevirapine
Clinical											
Fever	0·6 (0·3–1·2)	1·0 (0·5–2·0)	1·8 (0·9–3·7)	0·6 (0·2–1·5)	2·2 (0·9–5·7)	1·3 (0·5–3·2)	1·5 (0·6–4·1)	1·1 (0·5–2·5)	0·8 (0·4–1·4)	1·1 (0·5–2·6)	0·8 (0·2–3·5)
Headache	1·0 (0·7–1·3)	1·3 (0·9–1·9)	1·3 (1·0–1·9)	0·7 (0·5–1·0)	1·6 (0·9–2·6)	0·8 (0·5–1·2)	1·0 (0·6–1·7)	1·1 (0·8–1·5)	1·0 (0·8–1·3)	1·1 (0·7–1·7)	1·1 (0·6–2·1)
Fatigue	1·0 (0·8–1·3)	1·2 (0·9–1·7)	1·0 (0·8–1·3)	0·7 (0·5–0·9)	1·0 (0·6–1·5)	0·9 (0·6–1·3)	1·3 (0·8–2·0)	1·0 (0·7–1·3)	1·1 (0·9–1·5)	1·1 (0·8–1·6)	0·9 (0·5–1·6)
Nausea	1·3 (0·9–1·7)	0·9 (0·6–1·4)	0·9 (0·6–1·2)	0·8 (0·6–1·3)	1·4 (0·9–2·3)	1·1 (0·7–1·7)	1·0 (0·5–1·7)	1·3 (0·9–1·9)	0·8 (0·6–1·1)	1·2 (0·8–1·9)	1·4 (0·8–2·7)
Vomiting	1·4 (0·9–2·1)	1·1 (0·6–1·4)	0·7 (0·4–1·1)	1·0 (0·6–1·8)	2·3 (1·2–4·4)	1·1 (0·5–2·1)	0·5 (0·2–1·2)	1·0 (0·6–1·8)	0·7 (0·5–1·1)	1·3 (0·7–2·3)	1·6 (0·7–3·7)
Diarrhoea	0·8 (0·6–1·1)	0·5 (0·4–0·7)	0·9 (0·7–1·2)	1·3 (0·9–1·7)	0·5 (0·3–0·8)	2·4 (1·5–3·7)	2·1 (1·4–3·3)	0·5 (0·1–0·9)	3·1 (2·4–4·1)	0·9 (0·6–1·3)	1·0 (0·6–1·9)
Mood disorders	1·1 (0·8–1·4)	1·7 (1·2–2·5)	1·0 (0·8–1·4)	0·5 (0·4–0·8)	1·0 (0·6–1·6)	0·9 (0·6–1·3)	1·4 (0·8–2·2)	1·1 (0·8–1·5)	0·8 (0·6–1·0)	1·5 (1·0–2·2)	1·6 (0·9–2·8)
Sleep disorders	0·9 (0·7–1·2)	0·9 (0·6–1·3)	1·1 (0·8–1·5)	0·9 (0·6–1·4)	1·4 (0·9–2·3)	0·8 (0·5–1·3)	0·9 (0·5–1·5)	0·9 (0·6–1·3)	0·8 (0·6–1·1)	2·1 (1·4–3·2)	1·0 (0·5–1·9)
Rash	0·8 (0·5–1·2)	1·2 (0·7–2·0)	1·4 (0·9–2·3)	1·1 (0·7–2·0)	0·9 (0·4–2·0)	0·6 (0·3–1·3)	1·2 (0·6–2·7)	2·0 (1·2–3·3)	0·7 (0·5–1·1)	1·0 (0·5–1·8)	0·9 (0·3–2·7)
Myositis	0·4 (0·2–1·2)	1·2 (0·4–3·3)	2·9 (0·9–8·7)	1·1 (0·4–3·3)	2·8 (0·7–11·1)	0·7 (0·1–3·7)	0·3 (0·1–2·5)	0·8 (0·2–2·9)	1·2 (0·5–3·1)	3·0 (0·9–9·5)	.. ..
Nephro-lithiasis	0·4 (0·1–1·6)	2·6 (0·3–23·9)	2·1 (0·9–3·8)	.. ..	.. ..	1·2 (0·2–8·0)	1·1 (0·1–15·0)	11·3 (2·9–45·0)	0·2 (0·1–1·0)	1·2 (0·2–3·0)	.. ..
Paresthesia	1·1 (0·8–1·5)	0·9 0·9 (0·6–1·3)	0·9 (0·6–1·2)	0·7 (0·4–1·1)	1·4 (0·8–2·3)	1·2 (0·8–2·0)	1·0 (0·6–1·8)	1·0 (0·7–1·5)	1·1 (0·8–1·5)	0·8 (0·5–1·2)	1·2 (0·8–3·0)
Neuromotor disorders	1·2 (0·7–2·0)	1·1 (0·6–2·2)	1·0 (0·6–1·7)	0·8 (0·4–1·5)	1·7 (0·8–3·9)	1·2 (0·6–2·5)	0·7 (0·3–1·8)	1·3 (0·7–2·5)	0·8 (0·5–1·4)	1·2 (0·6–2·4)	0·6 (0·2–2·2)
Lipody-strophy	0·8 (0·6–1·2)	1·6 (1·2–2·2)	1·8 (1·4–2·4)	1·0 (0·7–1·4)	0·7 (0·4–1·1)	1·0 (0·6–1·3)	1·4 (0·9–2·2)	1·2 (0·9–1·6)	0·9 (0·7–1·2)	0·7 (0·5–1·1)	1·7 (0·9–2·9)
Laboratory											
Anaemia	2·3 (0·9–5·3)	0·8 (0·3–2·4)	0·4 (0·1–1·0)	0·7 (0·2–2·1)	2·1 (0·6–7·9)	1·4 (0·4–4·8)	1·7 (0·5–6·5)	0·4 (0·1–1·9)	1·1 (0·5–2·6)	0·4 (0·1–1·4)	2·2 (0·6–7·1)
Neutropenia	2·4 (1·1–5·6)	2·4 (1·1–5·6)	0·4 (0·2–0·9)	0·5 (0·2–1·3)	0·7 (0·2–2·3)	0·4 (0·1–1·1)	2·8 (0·9–5·4)	0·3 (0·1–1·0)	1·5 (0·8–2·9)	1·4 (0·5–3·4)	0·8 (0·2–2·9)
Thrombo-penia	0·6 (0·3–1·2)	1·1 (0·5–2·2)	1·8 (0·9–3·5)	0·6 (0·2–1·4)	1·0 (0·3–3·2)	0·5 (0·2–1·3)	4·9 (2·0–12·6)	0·9 (0·4–1·9)	0·9 (0·5–1·6)	1·0 (0·4–2·5)	1·7 (0·6–5·0)
Aspartate aminotrans-ferase	0·6 (0·3–1·2)	0·5 (0·3–0·9)	1·2 (0·8–2·0)	1·5 (0·8–2·6)	0·5 (0·2–1·3)	1·0 (0·5–1·9)	1·3 (0·6–2·6)	0·4 (0·2–0·8)	1·3 (0·8–2·1)	1·6 (0·8–3·1)	1·4 (0·6–3·6)
Alanine aminotrans-ferase	0·8 (0·6–1·2)	0·6 (0·4–0·9)	0·9 (0·7–1·3)	1·1 (0·8–1·7)	0·7 (0·4–1·3)	0·9 (0·5–1·4)	1·4 (0·8–2·5)	0·8 (0·3–1·0)	1·3 (0·9–1·8)	1·0 (0·6–1·6)	2·2 (1·1–4·2)
Alk. Phos-phatase	0·5 (0·3–0·9)	0·6 (0·4–1·0)	0·9 (0·6–1·5)	1·3 (0·8–2·2)	1·0 (0·5–2·1)	1·5 (0·9–2·8)	1·4 (0·7–2·8)	0·5 (0·3–1·0)	0·6 (0·4–1·0)	1·5 (0·9–2·6)	1·6 (0·7–3·5)
Bilirubin	0·7 (0·5–1·2)	0·9 (0·4–1·8)	1·3 (0·8–2·0)	0·7 (0·4–1·5)	0·3 (0·1–0·9)	2·5 (1·4–4·4)	0·3 (0·1–0·8)	18·3 (9·7–31·3)	0·2 (0·1–0·7)	0·4 (0·2–1·0)	.. ..
Amylase	0·7 (0·4–1·4)	0·7 (0·3–1·3)	0·8 (0·4–1·5)	1·3 (0·7–2·7)	2·1 (0·9–4·8)	0·3 (0·1–0·9)	1·5 (0·5–4·5)	1·2 (0·6–2·6)	0·8 (0·4–1·5)	1·7 (0·8–3·7)	0·9 (0·3–3·2)
Creatinine	1·0 (0·5–2·1)	2·2 (0·8–5·7)	0·9 (0·4–1·9)	0·5 (0·2–1·5)	1·0 (0·3–3·3)	0·8 (0·2–2·7)	1·6 (0·4–5·6)	1·7 (0·8–3·6)	1·2 (0·6–2·4)	1·4 (0·5–3·8)	1·6 (0·4–5·8)
Proteinuria	1·0 (0·6–1·6)	1·6 (0·9–2·8)	1·2 (0·7–2·0)	0·5 (0·3–1·0)	1·0 (0·5–2·3)	1·0 (0·5–2·1)	1·5 (0·6–3·6)	1·4 (0·8–2·4)	0·6 (0·4–1·0)	1·6 (0·8–3·1)	1·8 (0·7–4·5)
Urate	0·4 (0·3–0·6)	0·5 (0·4–0·8)	2·1 (1·5–3·1)	3·2 (2·2–4·6)	0·9 (0·4–1·6)	0·8 (0·5–1·3)	1·2 (0·7–2·2)	0·9 (0·6–1·4)	1·3 (0·9–1·8)	0·6 (0·3–1·0)	0·3 (0·1–1·0)
CPK	0·6 (0·4–1·1)	1·4 (0·8–2·6)	1·8 (1·0–3·1)	0·8 (0·4–1·5)	2·9 (1·4–6·0)	1·6 (0·8–3·3)	0·4 (0·2–1·2)	1·4 (0·8–2·5)	0·9 (0·5–1·5)	1·3 (0·6–2·8)	0·5 (0·5–2·1)
Lactate	0·5 (0·3–0·8)	0·8 (0·5–1·3)	1·7 (1·1–2·9)	1·8 (1·1–3·1)	0·8 (0·3–1·8)	0·9 (0·5–1·9)	0·7 (0·3–1·7)	0·8 (0·5–1·5)	1·0 (0·7–1·6)	1·6 (0·8–3·0)	2·0 (0·9–3·7)
Glucose	0·9 (0·7–1·2)	1·0 (0·7–1·3)	0·9 (0·7–1·2)	0·6 (0·4–0·8)	1·6 (0·9–2·6)	0·6 (0·4–1·0)	1·2 (0·8–1·9)	1·9 (0·9–3·9)	1·0 (0·7–1·2)	1·6 (0·9–2·3)	0·9 (0·5–1·5)
Cholesterol	0·6 (0·4–0·7)	1·0 (0·8–1·4)	1·8 (1·4–2·4)	1·0 (0·7–1·3)	1·0 (0·6–1·5)	2·0 (1·3–2·9)	0·7 (0·4–1·1)	1·0 (0·7–1·3)	1·0 (0·8–1·3)	1·3 (0·9–1·9)	0·8 (0·5–1·4)
Triglyceride	0·6 (0·5–0·7)	1·1 (0·8–1·6)	1·5 (1·1–1·9)	0·9 (0·6–1·2)	0·9 (0·6–1·4)	2·4 (1·6–3·5)	1·1 (0·6–1·7)	1·0 (0·7–1·3)	0·7 (0·6–1·0)	0·8 (0·6–1·2)	0·7 (0·4–1·3)

Odds ratios (OR) were estimated from the basic model including all drugs as covariables. Values in boxes are significant at p<0·05. CPK=creatine phosphokinase.

Table 3: **Logistic regression analysis of adverse events attributed to specific antiretroviral treatment agents**

not randomly allocated to treatment. Allocation of treatment could have been biased since patients with more advanced disease would have been given three-class antiretroviral treatment, and since intravenous drug users were less likely to receive PI-sparing-antiretroviral treatment. Data from the Swiss HIV Cohort Study suggest that patients taking methadone have significant rates of abandoning antiretroviral treatment if it contains efavirenz, probably because of pharmacological interaction leading to reduced methadone concentrations and withdrawal symptoms.

Furthermore, cross-sectional use of the AIDS Clinical

Trial Group questionnaire excludes disorders that are being treated but were not bothersome during the study visit (such as neuropathy controlled with analgesics, diarrhoea or nausea controlled by medication). Another potential restriction of the study is that we did not analyse early toxic effects such as hypersensitivity reactions that arose soon after initiation of antiretroviral treatment, since patients had to be on stable treatment. We also did not include data on treatment interruption and rechallenge, which would have provided stronger evidence for causality. An additional challenge is the assessment of toxic effects that have persisted from previous treatments. Patients were on the same regimen for the 30 days preceding the study, which should have allowed recovery from most observed adverse events resulting from a previously used medication. For analysis of long-term toxic effects, we included previous drug use in the model, thereby avoiding attribution of cumulative toxic effects such as abnormal fat distribution or neurotoxicity to medications such as nevirapine or abacavir that are used to prevent continuous evolution of these adverse events. While a longer study could give a more precise understanding of cumulative toxic effects, it would also be more complex in view of the treatment modification and intercurrent illnesses expected during an extended follow up.

Finally, identification of specific associations of adverse events to particular drug regimens can be challenged due to the overwhelming use of single-PI-antiretroviral treatment during the study. Nelfinavir was the most frequently used PI, and efavirenz the most common PI-sparing-antiretroviral treatment used at the time in Switzerland (August, 1999, to September, 1999). Thus, toxic effects attributed to a particular antiretroviral treatment regimen (PI-antiretroviral treatment, PI-sparing-antiretroviral treatment) will reflect actual use of particular agents as components of the various regimens. Change in relative use of a particular agent will modify the weight of its drug-specific toxic effects to its class.

Various antiretroviral treatment regimens have comparable efficacy in controlling HIV-1 infection, therefore toxic effects, as well as pill number, pill size, cost, previous medication history, or drug interactions will drive the choice of treatment, in particular when patients suffer from co-morbidity, or from previous treatment-induced adverse effects. It should be underscored that more than two-thirds of patients might have complaints if precisely questioned and that adverse events have an effect on adherence and on development of viral resistance, which might lead to treatment discontinuation or failure.[16] Yearly surveys using the proposed cross-sectional analysis could help to assess changes in prevalence of specific toxic effects and in overall well-being of patients receiving antiretroviral treatment. Postmarketing surveillance of drug toxic effects is essential for development of treatment guidelines, and tolerability of anti-HIV-1 treatment needs to be improved.

Contributors

A Telenti and K Boubaker designed the study. J Fellay, G Greub, B Ledergerber, and K Boubaker did the analysis. E Bernasconi, H Furrer, M Battegay, B Hirschel, P Vernazza, and M Flepp were responsible for patient recruitment and clinical assessment. P Francioli directs the Swiss HIV Cohort Study. J Fellay and A Telenti wrote the report, assisted by all coauthors.

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Acknowledgments

This study has been financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation. (Grant 3345-062041).

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