Long-term virological response to multiple sequential regimens of highly active antiretroviral therapy for HIV infection

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Objective: Information about the virological response to sequential highly active antiretroviral therapy (HAART) for HIV infection is limited. The virological response to four consecutive therapies was evaluated in the Swiss HIV Cohort.

Design: Retrospective analysis in an observational cohort.

Methods: 1140 individuals receiving uninterrupted HAART for 4.8 ±0.6 years were included. The virological response was classified as success (<400 copies/ml), low-level (LF: 400–5000 copies/ml) or high-level failure (HF: >5000 copies/ml). Potential determinants of the virological response, including patient demographics, treatment history and virological response to previous HAART regimens were analysed using survival and logistic regression analyses.

Results: 40.1% failed virologically on the first (22.0% LF; 18.1% HF), 35.1% on the second (14.2% LF; 20.9% HF), 34.2% on the third (9.9% LF; 24.3% HF) and 32.7% on the fourth HAART regimen (9% LF; 23.7% HF). Nucleoside pre-treatment (OR: 2.34; 95% CI: 1.67–3.29) and low baseline CD4 T-cell count (OR: 0.79/100 cells rise; 95% CI: 0.72–0.88) increased the risk of HF on the first HAART. Virological failure on HAART with HIV-1 RNA levels exceeding 1000 copies/ml predicted a poor virological response to subsequent HAART regimens. A switch from a protease inhibitor- to a non-nucleoside reverse transcriptase inhibitor-containing regimen significantly reduced the risk of HF. Multiple switches of HAART did not affect the recovery of CD4 T lymphocytes.

Conclusion: Multiple sequential HAART regimens do not per se reduce the likelihood of long-term virological suppression and immunological recovery. However, early virological failure increases significantly the risk of subsequent unfavourable virological responses. The choice of a potent initial antiretroviral drug regimen is therefore critical.

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Introduction

A major goal of highly antiretroviral therapy (HAART) is the reduction of plasma HIV-1 viraemia to values below the threshold of detection [1–3]. In observational studies the proportion of treated HIV-1-infected individuals suppressing plasma HIV-1 RNA to levels below 400 copies/ml barely reaches 50–60% despite a continuously growing number of antiretroviral drugs, targeting distinct phases of the HIV-1 life cycle [4–6]. The risk of virological failure on HAART is higher in individuals with low CD4 T-cell count and high plasma HIV-1 RNA at baseline [7–9]. In addition, pre-treatment with nucleoside analogue mono- or dual-therapy for a short duration of 2 months may suffice to reduce the likelihood of sustained reduction in plasma HIV-1 RNA significantly, because of the rapid selection of drug resistance mutations [10–13]. Once resistance mutations have emerged, the virological response to salvage regimens remains poor because of the broad intra-class cross resistance [14–17]. A different situation may arise in individuals changing drug regimens only due to adverse events. It is unknown whether multiple

changes of HAART favour the emergence of drug resistance in this specific patient population.

We studied the consequences of changing HAART regimens up to four times in 1140 individuals of the Swiss HIV Cohort Study, with regard to the durability of the virological response and CD4 T-cell recovery. We formulated the hypothesis that multiple changes of antiretroviral therapy for reasons other than virological failure do not negatively influence virological and immunological responses to HAART.

Methods

Patients

We included all participants of the Swiss HIV Cohort Study who commenced HAART between January 1996 and December 1998, and continued therapy without interruption. The Swiss HIV Cohort Study is a prospective observational multicentre study described in detail elsewhere [5]. Data collected until August 2002 were considered in this retrospective analysis. HAART was defined as a drug regimen containing: (a) two nucleoside analogue reverse transcriptase inhibitors (NRTIs) in combination with a protease inhibitor (PI) or a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI); (b) two PIs in combination with at least one NRTI; (c) a combination of a PI and a NNRTI with at least one NRTI; or (d) a combination of three NRTIs.

Of 2037 individuals meeting these criteria, 613 (30.1%) were excluded because of intermittent switches to non-HAART regimens, eight (0.4%) because of a short follow up (<3 years), and 276 (13.5%) with missing baseline CD4 or CD8 T-cell count, or missing baseline plasma HIV-1 RNA values before initiation of HAART.

Data of 1140 individuals were included in the final analysis, consisting of patient demographics, treatment history, longitudinal CD4 and CD8 T-cell counts, and plasma HIV-1 RNA levels. T-lymphocyte counts and plasma HIV-1 RNA were determined at irregular time intervals, ranging from 1 to 6 months. Monthly values were calculated by linear interpolation.

The mean follow-up was 4.8 ±0.6 years. Most study participants were male (74.7%) and Caucasian (87.5%). Nearly a third (30.9%) had acquired HIV infection through heterosexual and 42.9% through homosexual intercourse. 21.9% were intravenous drug users. At baseline, the mean age was 38.8 ±9.2 years, and based on the first positive documented HIV-1 serology the estimated median duration of HIV-1 infection was 4.8 years (IQR: 1.0–9.1). 21% of patients were in CDC stage C and 608 individuals (53.3%) were pre-treated with non-HAART regimens when they commenced HAART (Table 1).

Statistical analysis

Primary end-points included the virological response and CD4 T-cell recovery. Four virological outcomes were defined: (i) individuals with virological success reduced plasma HIV-1 RNA to levels <400 copies/ml at all visits 6 months after initiation of HAART; (ii) low-level virological failure (LF) was defined as at least one plasma HIV-1 RNA value reaching 400–5000 copies/ml 6 months after initiation of HAART; (iii) high-level virological failure (HF) was characterized by at least one plasma HIV-1 RNA level exceeding 5000 copies/ml; (iv) individuals receiving HAART regimens for at least 3, but fewer than 6 months had to demonstrate a reduction of ≥1 $\log_{10}$ copies/ml of plasma HIV-1 RNA to meet the criteria of a successful virological responder. HF anf LF were mutually exclusive. The virological outcome could not be conclusively stratified in individuals receiving a HAART regimen for fewer than 3 months. Data of these individuals were not considered for statistical evaluation.

The impact of multiple treatment changes on CD4 T-cell recovery was judged according to the absolute CD4 T-cell-increase after 4 years of HAART.

A number of determinants of the virological and immunological responses to HAART were studied, including gender, age, HIV transmission group, CDC stage, duration of HIV-1 infection, previous treatment history, and baseline HIV-1 RNA, CD4 and CD8 T-cell count. In addition, the effect of elevated plasma HIV-1 RNA levels during previous HAART regimens and switches to distinct antiretroviral drug classes were analysed.

Data were statistically evaluated using logistic regression and Cox proportional hazards models. A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS release 11.0 (SPSS, inc., Chicago, Ill., USA).

Results

Characteristics of patients changing the first HAART regimen

During the mean observation period of 4.8 years, 289 individuals (25.4%) received one HAART regimen. 426 individuals (37.4%) changed the drug regimen once, 242 (21.2%) twice, and 183 (16.1%) three or more times (Figure 1). The proportion of PI-containing therapies declined over time. In 97.3%, PIs were part of the first, in 71.2% part of the second, in 61.6% part of the third and in 54.5% part of the fourth HAART regimen. The number of patients on NNRTI-containing regimens and triple nucleoside therapy increased during the observation period (Table 2).

Intravenous drug users changed the first HAART regimen less frequently than patients who had acquired

Table 1. Baseline characteristics

	All subjects (*n*=1140)	No switch (*n*=289)	One switch (*n*=426)	Two switches (*n*=242)	Three or more switches (*n*=183)
Gender (%)					
Male	852 (74.7)	208 (72.0)	333 (78.2)	173 (71.5)	138 (75.4)
Female	288 (25.3)	81 (28.0)	93 (21.8)	69 (28.5)	45 (24.6)
Age (years)	38.8 ±9.2	38.0 ±9.1	38.8 ±8.9	38.9 ±9.6	40.0 ±9.4
Ethnicity (%)					
Caucasian	583 (87.5)	153 (87.4)	234 (87.0	109 (87.2)	153 (87.4)
Black	48 (7.2)	12 (6.9)	21 (7.9)	10(8.0)	12 (6.9)
Hispanic	12 (1.8)	2 (1.1)	5 (1.9)	4 (3.2)	2 (1.1)
Asian	23 (3.5)	8 (4.6)	9 (3.3)	2 (1.6)	8 (4.6)
No information	474	114	157	117	114
HIV transmission category (%)					
Heterosexual	352 (30.9)	86 (29.8)	133 (31.2)	78 (32.3)	55 (30.1)
Homosexual	489 (42.9)	103 (35.6)	191 (44.8)	99 (40.9)	96 (52.5)
IV drug use	250 (21.9)	87 (30.1)	84 (19.7)	53 (21.9)	26 (14.2)
Other/unknown	49 (4.3)	13 (4.5)	18 (4.2)	12 (5.0)	6 (3.3)
Duration of HIV-1 infection (years)	4.8 (1.0–9.1)	5.0 (0.9–10.0)	4.3 (0.8–8.9)	4.8 (1.6–8.5)	4.9 (1.5–9.5)
CDC stage					
A (%)	43.9	50.0	45.9	37.8	38.4
B (%)	35.1	34.8	32.3	38.9	36.2
C (%)	21.0	15.2	21.8	23.3	25.4
Pre-treated (%)	608 (53.3)	136 (47.1)	210 (49.3)	147 (60.7)	115 (62.8)
Nucleoside analogues	581(95.6)	131 (96.3)	197 (93.8)	143 (96.6)	111 (96.5)
PI	26 (4.3)	5 (3.7)	12 (5.7)	5 (3.4)	4 (3.5)
NNRTI	1 (0.2)	0 (0)	1 (0.5)	0 (0)	0 (0)
Baseline HIV-1 RNA (log_{10} copies/ml)	4.6 (3.8–5.2)	4.5 (3.7–5.1)	4.6 (3.9–5.3)	4.5 (3.8–5.2)	4.9 (4.1–5.3)
Baseline CD4 count (cells/µl)	195 (83–334)	225 (91–355)	195 (88–340)	187 (84–318)	160 (50–311)
Baseline CD8 count (cells/µl)	733 (467–1064)	767 (467–1093)	710 (476–1027)	740 (417–1025)	731 (455–1110)

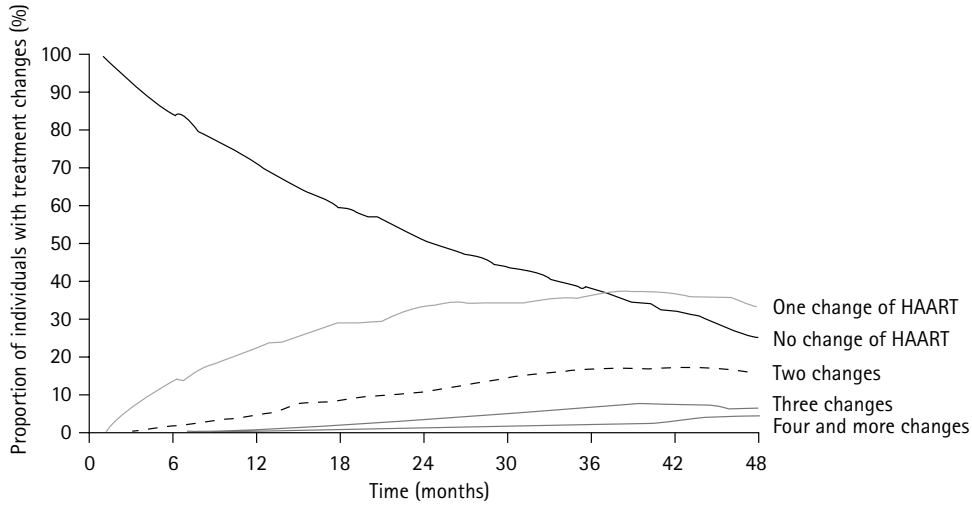
Age is given as mean and standard deviation. All other data are shown as numbers and proportions or medians, 25th and 75th percentiles.
PI, protease inhibitor; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor.

HIV-1 infection through homosexual or heterosexual intercourse (65.2 vs 78.9%; *P*<0.001; 65.2 vs 75.6; *P*=0.006; Table 3). A larger proportion of treatment-experienced patients changed HAART as compared with treatment-naive individuals (77.6 vs 71.2%; *P*=0.014). In addition, individuals who commenced nelfinavir-containing drug regimens changed the first therapy less frequently during the observation period than patients who initiated HAART that included saquinavir, ritonavir or indinavir (51.6% vs 92.3%, 78.8% and 85.8%; *P*<0.001 for all comparisons). The numbers of individuals commencing NNRTI-containing regimens (*n*=9) or triple NRTI therapies (*n*=37) were too small to study the effect of these drug regimens on the likelihood of switching HAART. Low baseline CD4 T-cell count represented a further risk factor of changing HAART [hazard ratio (HR): 0.96 per 100 cells increase; 95% CI: 0.92–0.99; *P*=0.028]. Gender, the duration of HIV-1 infection, baseline CD8 T-cell count and plasma HIV-1 RNA did not significantly affect the risk of changing HAART. In a Cox model adjusted for potentially confounding variables, intravenous drug users were less likely to change HAART (adjusted HR: 0.69; 95% CI: 0.57–0.83), whereas pre-treatment increased the risk of changing therapy (adjusted HR: 1.21; 95% CI: 1.06–1.39). In contrast, baseline CD4 T-cell count and the initial PI were not independent predictors of changing HAART. In a subgroup of individuals who changed therapy because of adverse events or inconvenience and not due to virological failure (HIV-1 RNA <400 copies/ml at the time of treatment change), intravenous drug use was the only factor significantly associated with a reduced likelihood of switching HAART (HR: 0.75; 95% CI: 0.57–0.97).

Virological response to HAART during the observation period

Low- or high-level virological failure as defined by viral rebound to levels above 400 copies/ml during the observation period was more frequently observed in individuals with CDC stage C (adjusted HR: 1.40; 95% CI: 1.08–1.81), pre-treatment with NRTIs (adjusted HR: 1.96; 95% CI: 1.64–2.35), low baseline CD4 T-cell count (adjusted HR: 0.88 per 100 cells increase; 95% CI: 0.83–0.92) and high baseline HIV-1

Figure 1. Proportion of patients receiving one, two, three, or four and more HAART regimens



RNA levels (adjusted HR: 1.15 per 1 $\log_{10}$ increase; 95% CI: 1.05–1.25) (Table 4).

The risk of only high-level virological failure (HF) as defined by viral rebound to ≥5000 copies/ml was elevated in individuals with low baseline CD4 T-cell count (adjusted HR: 0.83 per 100 cells increase; 95% CI: 0.76–0.90), high baseline plasma HIV-1 RNA (adjusted HR: 1.23 per 1 $\log_{10}$ increase; 95% CI: 1.07–1.41), CDC stage C (adjusted HR: 1.50; 95% CI: 1.04–2.18) and pre-treatment with NRTIs (adjusted HR: 2.70; 95% CI: 2.05–3.54), but it was reduced in women (adjusted HR: 0.71; 95% CI: 0.52–0.97).

Virological response to the first and second HAART regimen

The median duration of the first HAART was 24 months (IQR: 10–48). A total of 417 individuals (40.1%) experienced low- (22.0%) or high-level virological failure (18.1%). Individuals with high-level virological failure were more frequently pre-treated with nucleoside analogues (68.6 vs 49.5%; adjusted OR: 2.34; 95% CI: 1.67–3.29) and had lower CD4 T-cell counts (135 vs 212 cells/μl; adjusted OR: 0.79 per 100 cells increase; 95% CI: 0.72–0.88) than individuals with virological success (Figure 2A).

851 individuals (74.6%) received a second HAART regimen for a median time of 20 months (IQR: 8–35). 65.6% of these patients received one, 17.9% two and 16.3% three or more new antiretroviral drugs. In 57.3%, the new drug regimen included at least one new PI and in 19.3% a new NNRTI. In 50.3% one or more new NRTIs were prescribed.

35% failed on the second therapy (14.2% LF; 20.9% HF). The virological response strongly depended on the response to the initial HAART regimen. 26.9% of patients, responding well to the first HAART regimen, failed on the second therapy (16.6% HF; 10.3% LF). A slightly higher proportion of 33.3% that had experienced low-level virological failure during the first antiretroviral drug regimen did not succeed on the second HAART (13.6% HF; 19.7% LF; P=0.43). The proportion of virological failures was significantly higher in individuals with high-level virological failure on the first HAART (58.7%, consisting of 42.8% HF; 15.9% LF; P<0.001). In an analysis adjusted for potentially confounding variables, higher mean plasma HIV-1 RNA levels during the previous

Table 2. Antiretroviral drug regimens

	First therapy (%)	Second therapy (%)	Third therapy (%)	Fourth therapy (%)
PI + ≥2 nucleoside analogues	87.9	48.3	36.8	25.1
NNRTI + ≥2 nucleoside analogues	0.7	17.0	28.3	29.9
PI+NNRTI + ≥1 nucleoside analogue	0.4	1.7	4.5	7.8
Double PI + ≥1 nucleoside analogue	8.9	21.2	20.3	21.6
Triple nucleoside analogues	2.0	11.8	10.3	15.6

PI, protease inhibitor; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor.

Table 3. Predictors of changing HAART in all individuals (*n*=1140) and in subjects, maintaining plasma HIV-1 RNA <400 copies/ml (*n*=640)

Parameter	All subjects			Controlling viral load at <400 copies/ml		
	Proportion with change of HAART (%)	Hazard ratio (95% CI) ǂ	*P*-value	Proportion with change of HAART (%)	Hazard ratio (95% CI)	*P*-value
Gender						
Male	75.6	1.00		71.4	1.00	
Female	71.9	0.99 (0.83–1.19)	0.937	67.4	0.91 (0.73–1.12)	0.348
Age (years)*		1.03 (0.95–1.11)	0.455		1.09 (0.99–1.20)	0.094
<35	72.4			70.0		
35–42	74.1			66.8		
>42	78.2			74.6		
Homosexual risk	78.9	1.00		73.7	1.00	
Heterosexual risk	75.6	0.93 (0.79–1.08)	0.328	70.0	0.91 (0.74–1.13)	0.406
Intravenous drug use	65.2	0.69 (0.57–0.83)	<0.001	61.2	0.75 (0.57–0.97)	0.027
Duration of HIV-1 infection (years)*		0.93 (0.76–1.13)	0.454		0.93 (0.74–1.17)	0.523
<2.1	72.6			68.3		
2.1–7.7	76.7			71.2		
>7.7	71.7			68.1		
CDC stage						
A	70.3	1.00		68.6	1.00	
B	74.1	1.00 (0.83–1.21)	0.985	66.0	0.87 (0.68–1.12)	0.285
C	81.1	1.17 (0.94–1.45)	0.168	72.0	1.05 (0.77–1.43)	0.770
Pre-treated						
No	71.2	1.00		71.1	1.00	
Yes	77.6	1.21 (1.06–1.39)	0.006	69.3	0.91 (0.76–1.10)	0.343
Baseline CD4 count † (cells/µl)		0.96 (0.92–0.99)	0.028		1.02 (0.98–1.07)	0.309
<117	77.9			67.7		
117–285	73.9			71.4		
>285	72.1			71.4		
Baseline CD8 count † (cells/µl)		1.00 (0.99–1.02)	0.570		1.01 (0.99–1.03)	0.429
<556	75.8			68.1		
556–933	75.2			73.1		
>933	72.0			67.1		
Baseline HIV-1 RNA § (log_{10} copies/ml)		1.06 (0.99–1.13)	0.093		1.03 (0.95–1.12)	0.453
<4.16	73.1			71.8		
4.16–5.04	72.9			65.9		
>5.04	78.0			73.3		

A Cox proportional hazards model was applied to analyse the risk of changing the first HAART regimen in all individuals and in individuals who changed therapy for reasons other than virological failure such as drug intolerance and inconvenience (plasma HIV-1 RNA levels <400 copies/ml at the time of switch).
*Per 10 years increase; † per 100 cells/µl increase; § per 1 log_{10} increase in plasma HIV-1 RNA; ǂ adjusted for pre-treatment, mode of HIV-1 transmission and baseline CD4 T-cell count.

HAART regimen (adjusted OR: 1.42 per 1 log_{10} increase; 95% CI: 1.13–1.79) and high-level virological failure (adjusted OR: 2.26; 95% CI: 1.29–3.94) best predicted a poorer response to the second HAART regimen (Figure 2B).

A mean plasma HIV-1 RNA value, ranging from 3 to 4 log_{10} copies/ml increased the risk of high-level virological failure to subsequent HAART regimens 2.8-fold (95% CI: 1.7–4.6), whereas HIV-1 RNA levels >4 log_{10} copies/ml were associated with a 4.3-times higher risk of high-level virological failure (95% CI: 2.6–7.0; Figure 2C). Of note, mean plasma HIV-1 RNA levels >400 and <1000 copies/ml did not significantly increase the risk of high-level virological failure (OR: 1.3; 95% CI: 0.8–2.2).

Switching from a PI to a NNRTI improved the virological response (adjusted OR: 0.30; 95% CI: 0.14–0.64; Figure 2D), whereas a switch to a triple

Table 4. Predictors of virological failure during the observation period

Parameter	Low-level failure or high-level failure			High-level failure		
	Proportion of subjects with failure	Adjusted analysis ∫ Hazard ratio (95% CI)	*P*-value	Proportion of subjects with failure	Adjusted analysis ¶ Hazard ratio (95% CI)	*P*-value
Gender						
Male	50.6	1.00		24.9	1.00	
Female	45.1	0.91 (0.75–1.10)	0.331	17.4	0.71 (0.52–0.97)	0.031
Age (years)*		0.97 (0.89–1.07)	0.566		0.94 (0.82–1.08)	0.382
<35	46.6			22.1		
35–42	50.8			23.2		
>42	49.6			23.9		
Homosexual risk	49.9	1.00		24.7	1.00	
Heterosexual risk	44.9	0.91 (0.74–1.10)	0.327	19.3	0.95 (0.68–1.32)	0.744
Intravenous drug use	54.4	0.99 (0.80–1.22)	0.919	26.0	1.03 (0.75–1.42)	0.851
Duration of HIV-1 infection* (years)		0.95 (0.76–1.19)	0.652		1.09 (0.79–1.51)	0.588
<2.1	41.6			16.1		
2.1–7.7	55.0			28.7		
>7.7	49.7			23.8		
CDC stage						
A	43.8	1.00		17.8	1.00	
B	54.5	1.09 (0.87–1.37)	0.442	27.2	1.24 (0.88–1.72)	0.216
C	66.7	1.40 (1.08–1.81)	0.012	36.7	1.50 (1.04–2.18)	0.031
Pre-treated						
No	39.1	1.00		14.7	1.00	
Yes	58.1	1.96 (1.64–2.35)	<0.001	30.3	2.69 (2.05–3.54)	<0.001
Baseline CD4 count † (cells/µl)		0.88 (0.83–0.92)	<0.001		0.83 (0.76–0.90)	<0.001
<117	57.4			30.3		
117–285	52.4			24.7		
>285	37.9			13.9		
Baseline CD8 count † (cells/µl)		1.01 (0.99–1.02)	0.502		1.02 (0.99–1.04)	0.223
<556	50.0			23.1		
556–933	53.4			25.6		
>933	45.7			21.5		
Baseline HIV-1 RNA ǂ (log_{10} copies/ml)		1.15 (1.05–1.25)	0.002		1.23 (1.07–1.41)	0.003
<4.16	43.3			16.6		
4.16–5.04	50.0			24.5		
>5.04	54.4			27.9		

A Cox proportional hazards model was used for this analysis.*Per 10 years increase; † per 100 cells/µl increase; ǂ per 1 log_{10} increase in plasma HIV-1 RNA; ∫ adjusted for pre-treatment, baseline plasma HIV-1 RNA and baseline CD4 T-cell count; ¶ adjusted for pre-treatment, baseline plasma HIV-1 RNA, baseline CD4 T-cell count and gender. CI, confidence interval; PI, protease inhibitor; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor.

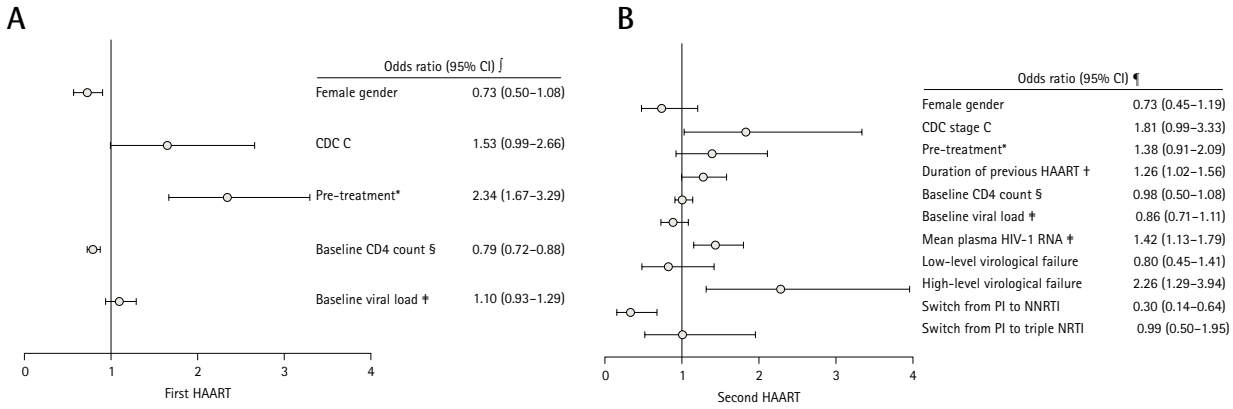
NRTI regimen was not significantly associated with high-level virological failure.

Patients receiving multiple sequential HAART regimens

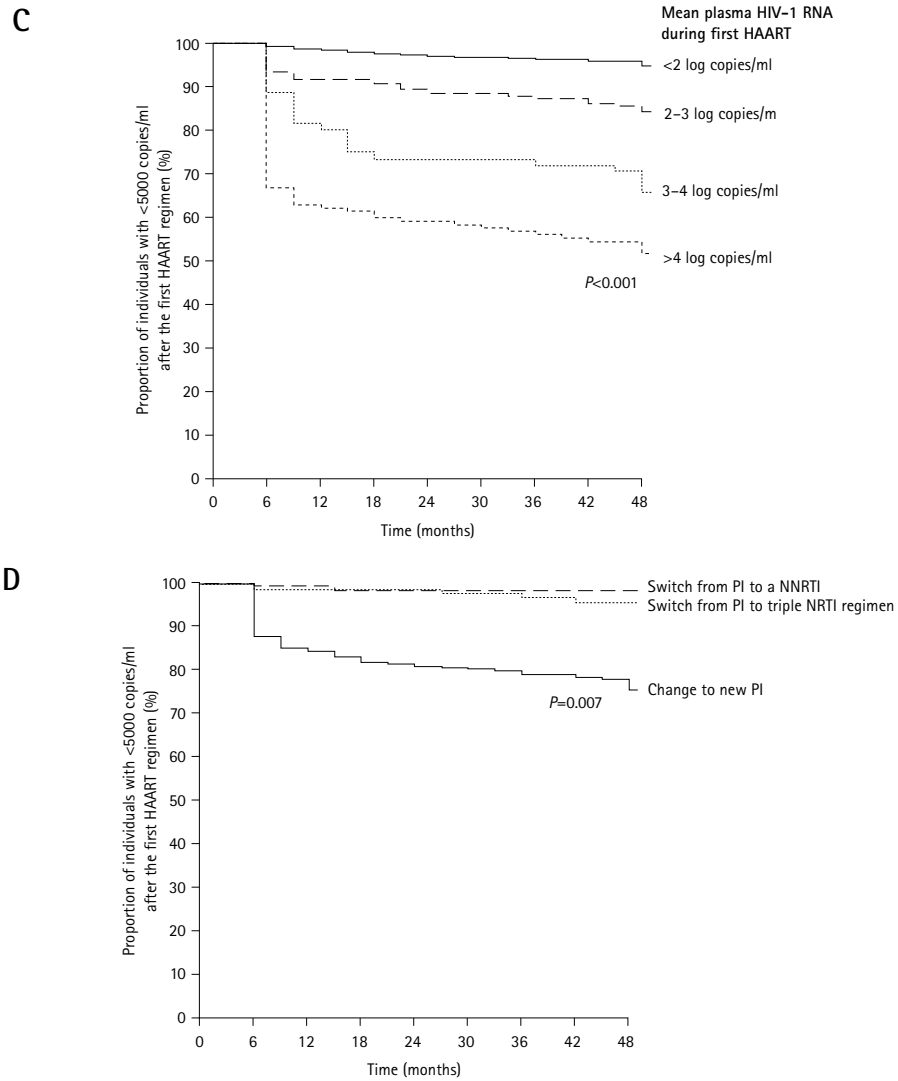
37% of individuals (*n*=425) were treated with a third HAART regimen for a median time of 15 months (IQR: 6–29). 55.2% of these individuals received one, 16.0% two and 15.5% three and more new antiretroviral drugs. The remaining patients reduced the number of drugs. In 41.9% the new antiretroviral drug regimen consisted of at least one new PI. In 30.0% a new NNRTI and in 44.3% at least one new NRTI were added.

34% of patients experienced virological failure on the third HAART regimen (9.9% LF; 24.3% HF). Similar to previous results, the virological response depended on the degree of viral suppression during previous therapy. 19% of virological responders to the second HAART regimen failed (15.3% HF; 4.3% LF), whereas 41% with low- and 45.8% with high-level

Figure 2. Predictors of high-level virological failure (HF; >5000 copies/ml) during the first (**A**) and second (**B**) HAART regimen



Percentage of individuals suppressing plasma HIV-1 RNA to levels <5000 copies/ml after initiation of the second HAART regimen, stratified by mean plasma HIV-1 RNA levels during the initial HAART (**C**) or switch of classes of drugs (**D**)



A multivariate logistic regression model was used for this analysis. * Pre-treatment with an antiretroviral drug combination not meeting HAART criteria; † per year increase; § per 100 cells/µl increase; ǂ per 1 $\log_{10}$ increase of plasma HIV-1 RNA; ∫ adjusted for pre-treatment with non-HAART regimens and baseline CD4 T-cell count; ¶ adjusted for mean plasma HIV-1 RNA levels on previous HAART, switch of drug classes and high-level virological failure on previous HAART.

virological failure during the second drug regimen responded poorly to the third drug regimen (20.5% HF; 20.5% LF and 33.0% HF; 12.8% LF, respectively; P=0.491; P=0.002). Higher mean plasma HIV-1 RNA during the second HAART regimen predicted a poorer response to the third HAART regimen (OR: 1.77 per 1 $\log_{10}$ increase of HIV-1 RNA; 95% CI: 1.40–2.24). The risk of high-level virological failure could be significantly reduced by a switch from a PI- to a NNRTI-containing regimen (OR: 0.13; 95% CI: 0.04–0.44), but not by a switch to triple NRTI therapy (Figure 3A).

A small number of individuals (n=73) received a fourth HAART regimen for a median time of 14 months (IQR: 6–24). Of these individuals, 62.8% added one, 16.9% two and 14.8% three and more new antiretroviral drugs. In 42.7%, the new antiretroviral drug regimen consisted of at least one new PI and in 29.5% of a new NNRTI, whereas 50.9% received at least one new NRTI.

33% experienced virological failure on the fourth antiretroviral drug regimen (9% LF; 23.7% HF). The proportion of virological failures was higher in individuals with low- and high-level virological failure during the third HAART regimen than in virological responders to the third therapy (44% and 46.7% vs 17%). The mean plasma HIV-1 RNA value during the third HAART regimen was significantly associated with the risk of high-level virological failure on the fourth HAART regimen (OR: 1.78 per 1 $\log_{10}$ increase of HIV-1 RNA; 95% CI: 1.35–2.36; Figure 3B).

Effect of multiple virological failures and successes

Individuals who did not change HAART due to virological failure (plasma HIV-1 RNA <400 copies/ml at the time of switch) responded well to subsequent HAART regimens. 291 (73.1%) of the virological responders to the first HAART regimen suppressed plasma HIV-1 RNA to values <400 copies/ml on the second HAART regimen, of whom 72 (82.8%) responded well to the third and all of these (n=14) responded well to the fourth HAART regimen.

In contrast, 130 (45.6%) of the patients responding poorly to the first HAART regimen, failed on the second HAART regimen. Thirty-two (45%) of these patients failed on the third drug regimen, and seven (53.9%) of these individuals failed on the fourth drug regimen.

The probability of virological failure of the second HAART regimen doubled in virological non-responders to the first HAART regimen as compared with individuals succeeding on the first therapy (adjusted OR: 2.26; 95% CI: 1.29–3.94). Patients with two subsequent virological failures showed after adjustment for a change of antiretroviral drug classes a 6.27-times increased risk of further poor virological responses (adjusted OR: 6.27; 95% CI: 2.36–16.67). Treatment changes per se do not affect CD4.

T-cell recovery

In the whole cohort, median CD4 T-cell count increased from 195 (83–334) to 493 (346–715) cells/µl. In a subgroup of individuals who permanently controlled HIV-1 viraemia at levels <400 copies/ml (n=640), the increase of CD4 T-lymphocytes was not related to the number of therapy changes (Figure 4).

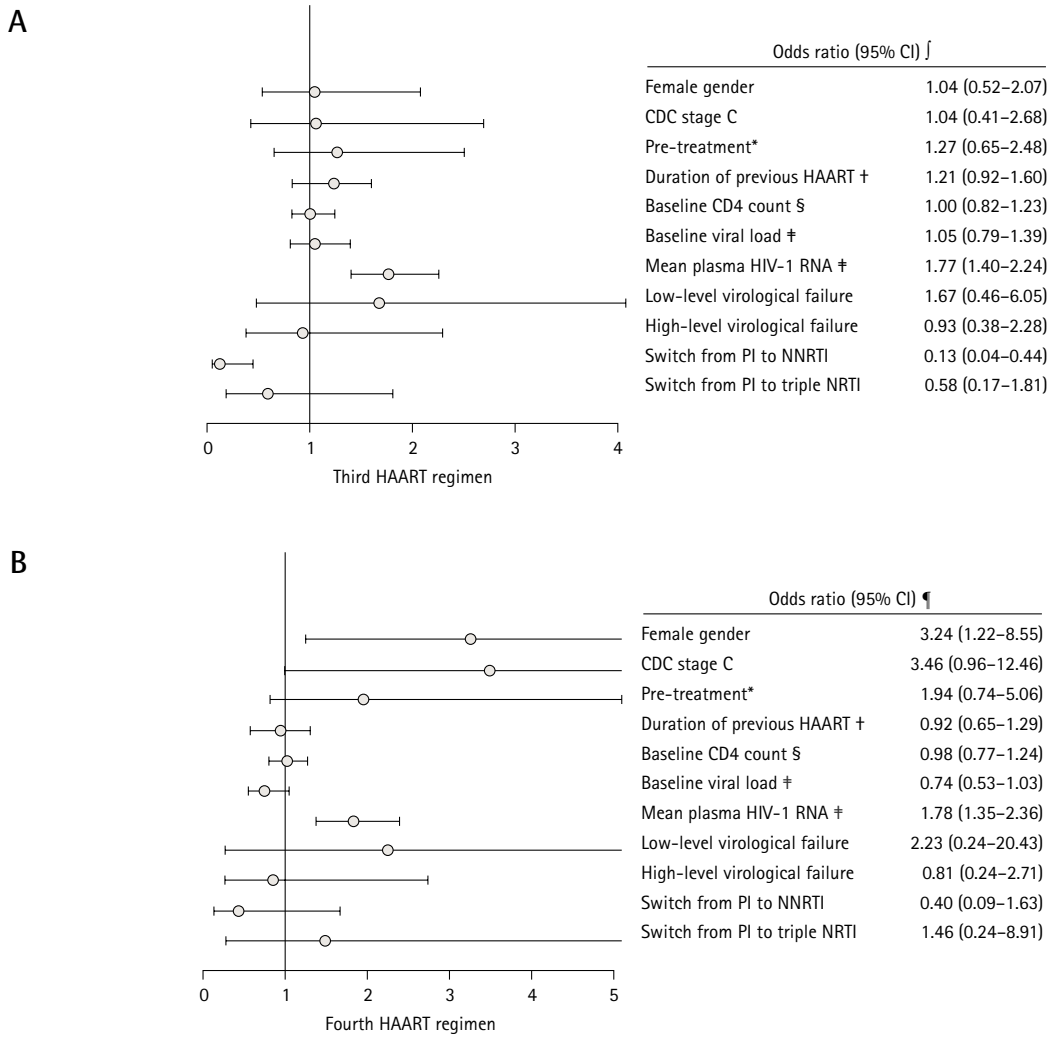
Discussion

We studied the important clinical issue of multiple sequential changes of potent antiretroviral drug therapy in a large cohort of 1140 patients of the Swiss HIV Cohort. From a theoretical point of view, sequencing HAART may potentially increase the probability of multidrug resistance and ultimately limit the number of antiretroviral agents that remain available for salvage regimens. HAART regimens had been changed very often, but multiple sequential therapies per se did not increase the risk of virological or immunological failure. The frequent modifications of HAART were partly the consequence of the high incidence of adverse events and partly the result of virological failure [18–20]. Almost half of all treated participants of the Swiss HIV Cohort suffer from clinical adverse events and three-quarters experience clinical and/or laboratory side effects [21]. In fact, 52.9% of patients who changed HAART during the observation period had low plasma HIV-1 RNA levels below the threshold of 400 copies/ml.

Individuals who were pre-treated with NRTIs showed a 1.2-fold increased likelihood of changing HAART, presumably due to the increased risk of virological failure in this patient group. In individuals changing HAART regimens because of reasons other than virological failure, NRTI pre-treatment was not a risk factor of switching therapy. Of note, HIV-1-related factors such as CD4 T-cell count or plasma HIV-1 RNA levels did not significantly alter the risk of changing HAART as well. Interestingly, intravenous drug users stayed more frequently on the initial HAART regimen than individuals who had acquired HIV-1 infection through homosexual or heterosexual intercourse. The reluctance to change HAART in intravenous drug users may reflect the prevailing opinion of physicians that this patient group adheres poorly to the drug regimen [22,23]. In addition, a switch to a NNRTI-containing HAART regimen may have been considered unsuitable for intravenous drug users because of CNS side effects and increased liver toxicity [24].

The risk factors for low- and high-level virological failure during the entire observation period were similar

Figure 3. Predictors of high-level virological failure (>5000 copies/ml) during the third (**A**) and fourth (**B**) HAART regimen



A multivariate logistic regression model was used for this analysis. *Pre-treatment with an antiretroviral drug combination not meeting HAART criteria; † per year increase; § per 100 cells/µl increase; ǂ per 1 $\log_{10}$ plasma HIV-1 RNA increase; ∫ adjusted for mean plasma HIV-1 RNA during previous HAART and switch of classes of drugs; ¶ adjusted for mean plasma HIV-1 RNA during previous therapy.

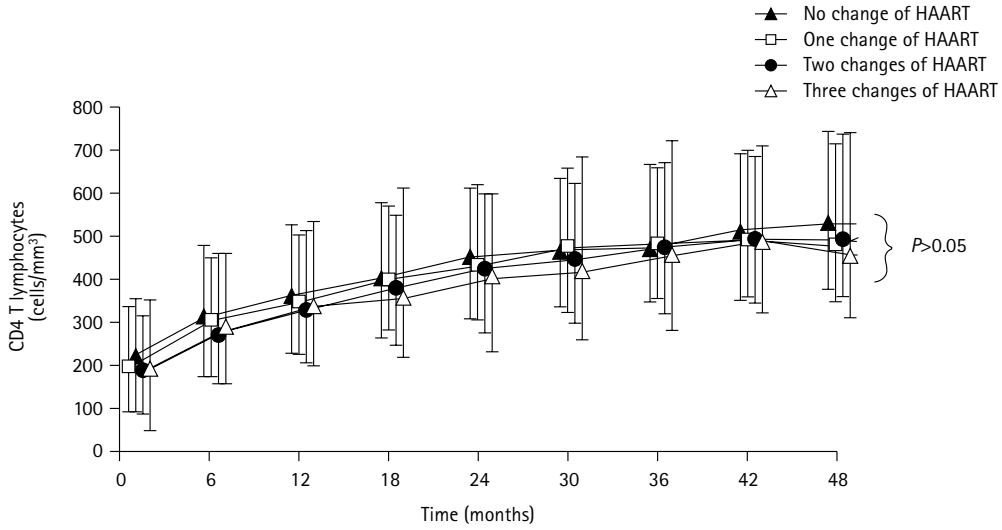
and included low baseline CD4 T-cell count, advanced CDC stage C, high baseline plasma HIV-1 RNA and pre-treatment with NRTIs. These results are in good agreement with reports from others [6,7,12,25–30].

The initial virological response to HAART strongly predicted the virological response to subsequent antiretroviral therapies [26,31–33]. Mean HIV-1 RNA levels during the first HAART exceeding 1000 copies/ml reduced the probability of a favourable virological response, but not plasma HIV-1 RNA levels ranging from 400 to 1000 copies/ml. These findings support the conclusions of two other studies, demonstrating that transitory low-level viraemia is not necessarily associated with virological failure [11,34].

A switch from a PI- to a NNRTI-containing regimen reduced the likelihood of high-level virological failure by 60–70%. Most patients were switched to efavirenz and only a minority to nevirapine. The positive effect of changing classes of antiretroviral drugs in combination with a new nucleoside regimen has been previously reported and should be seriously considered in individuals with high-level virological failure [24,35,36].

Changing HAART regimens in individuals at the time when HIV-1 viraemia was below 400 copies/ml had no negative impact on the virological response, but even appeared to result in a long-term benefit, extending the durability of viral suppression. It is conceivable that the emergence of drug resistance on long-term HAART can be partly prevented by switching antiretroviral drug regimens after 1 or 2 years of antiretroviral therapy. Indeed, a recent

Figure 4. Time course of CD4 T lymphocytes according to the number of treatment changes during the observation period in individuals who suppressed plasma HIV-1 RNA levels below 400 copies/ml



prospective study showed that alternating antiretroviral drug regimens in 3 monthly intervals improved the virological response [37]. On the other hand, consecutive virological failures in our study appeared to have a particularly unfavourable prognostic value. One virological failure doubled the probability of future virological failures, whereas two subsequent unfavourable virological responses increased the risk almost sevenfold.

A limitation of our study was the lack of sufficient information regarding the reason for switching HAART. Nevertheless, patients could be roughly stratified into two groups 'virological failure' or 'adverse events' according to the plasma HIV-1 RNA level when therapy was switched. Unfortunately, adherence and resistance data were not readily available that may have allowed a more detailed analysis of patients with elevated plasma HIV-1 RNA at the time of switching therapy. Hence, individuals with poor adherence may have been misjudged as virological non-responders.

In summary, most treated HIV-1-infected individuals in the Swiss HIV cohort switched HAART regimen at least once in 4 years. Individuals changing HAART regimens only because of intolerance or inconvenience showed no increased risk of subsequent virological failure. In contrast, long-term virological control is less likely in individuals, experiencing early virological failure during the first HAART. This observation suggests that the choice of the initial HAART regimen is critical for durable virological suppression.

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References

1. Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hirsch MS, Jacobsen DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schechter M, Schooley RT, Thompson MA, Vella S & Volberding PA. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002; **288:**222–235.
2. Raboud JM, Montaner JS, Conway B, Rae S, Reiss P, Vella S, Cooper D, Lange J, Harris M, Wainberg MA, Robinson P, Myers M & Hall D. Suppression of plasma viral load below 20 copies/ml is required to achieve a long-term response to therapy. *AIDS* 1998; **12:**1619–1624.

3. Wood E, Yip B, Hogg RS, Sherlock CH, Jahnke N, Harrigan RP, O'Shaughnessy MV & Montaner JS. Full suppression of viral load is needed to achieve an optimal CD4 cell count response among patients on triple drug antiretroviral therapy. *AIDS* 2000; **14:**1955–1960.
4. Fatkenheuer G, Theisen A, Rockstroh J, Grabow T, Wicke C, Becker K, Wieland U, Pfister H, Reiser M, Hegener P, Franzen C, Schwenk A & Salzberger B. Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients. *AIDS* 1997; **11:**F113–F116.
5. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, Vernazza P, Sudre P, Flepp M, Furrer H, Francioli P & Weber R. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 1999; **353:**863–868.
6. Lucas GM, Chaisson RE & Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Annals of Internal Medicine* 1999; **131:**81–87.
7. Staszewski S, Miller V, Sabin C, Carlebach A, Berger AM, Weidmann E, Helm EB, Hill A & Phillips A. Virological response to protease inhibitor therapy in an HIV clinic cohort. *AIDS* 1999; **13:**367–373.
8. Casado JL, Perez-Elias MJ, Antela A, Sabido R, Marti-Belda P, Dronda F, Blazquez J & Quereda C. Predictors of long-term response to protease inhibitor therapy in a cohort of HIV-infected patients. *AIDS* 1998; **12:**F131–F135.
9. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, Costagliola D, D'Arminio Monforte A, de Wolf F, Reiss P, Lundgren JD, Justice AC, Staszewski S, Leport C, Hogg RS, Sabin CA, Gill MJ, Salzberger B & Sterne JA. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; **360:**119–129.
10. Romano L, Venturi G, Giomi S, Pippi L, Valensin PE & Zazzi M. Development and significance of resistance to protease inhibitors in HIV-1-infected adults under triple-drug therapy in clinical practice. *Journal of Medical Virology* 2002; **66:**143–150.
11. Cohen Stuart JW, Wensing AM, Kovacs C, Righart M, de Jong D, Kaye S, Schuurman R, Visser CJ & Boucher CA. Transient relapses (blips) of plasma HIV RNA levels during HAART are associated with drug resistance. *Journal of Acquired Immune Deficiency Syndromes* 2001; **28:**105–113.
12. Phillips AN, Staszewski S, Lampe F, Youle MS, Klauke S, Bickel M, Sabin CA, Doerr HW, Johnson MA, Loveday C & Miller V. Human immunodeficiency virus rebound after suppression to <400 copies/ml during initial highly active antiretroviral therapy regimens, according to prior nucleoside experience and duration of suppression. *Journal of Infectious Diseases* 2002; **186:**1086–1091.
13. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, Jonas L, Meibohm A, Holder D, Schleif WA, Condra JH, Emini EA, Isaacs R, Chodakewitz JA & Richman DD. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection: 100-week follow-up. *Journal of the American Medical Association* 1998; **280:**35–41.
14. Tsuchiya K, Matsuoka S, Hachiya A, Yasuoka A, Tachikawa N, Kikuchi Y, Genka I, Teruya K, Kimura S & Oka S. Accumulation of lopinavir resistance-associated mutations over 3 years follow-up of patients on highly active antiretroviral therapy: implication in salvage therapy. *AIDS* 2001;**15:**1183–1184.
15. Harrigan PR & Larder BA. Extent of cross-resistance between agents used to treat human immunodeficiency virus type 1 infection in clinically derived isolates. *Antimicrobial Agents & Chemotherapy* 2002; **46:**909–912.
16. Casado JL, Moreno A, Hertogs K, Dronda F & Moreno S. Extent and importance of cross-resistance to efavirenz after nevirapine failure. *AIDS Research & Human Retroviruses* 2002; **18:**771–775.
17. Khanna N, Klimkait T, Schiffer V, Irigoyen J, Telenti A, Hirschel B & Battegay M. Salvage therapy with abacavir plus a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor in heavily pre–treated HIV-1 infected patients. Swiss HIV Cohort Study. *AIDS* 2000; **14:**791–799.
18. Carr A & Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; **356:**1423–1430.
19. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ & Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353:**2093–2099.
20. Mocroft A, Youle M, Moore A, Sabin CA, Madge S, Lepri AC, Tyrer M, Chaloner C, Wilson D, Loveday C, Johnson MA & Phillips AN. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS* 2001; **15:**185–194.
21. Fellay J, Boubaker K, Ledergerber B, Bernasconi E, Furrer H, Battegay M, Hirschel B, Vernazza P, Francioli P, Greub G, Flepp M & Telenti A. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001; **358:**1322–1327.
22. Carrieri MP, Chesney MA, Spire B, Loundou A, Sobel A, Lepeu G & Moatti JP. Failure to maintain adherence to HAART in a Cohort of French HIV-Positive Injecting Drug Users. *International Journal of Behavioral Medicine* 2003; **10:**1–14.
23. Bouhnik AD, Chesney M, Carrieri P, Gallais H, Moreau J, Moatti JP, Obadia Y & Spire B. Nonadherence among HIV-infected injecting drug users: the impact of social instability. *Journal of Acquired Immune Deficiency Syndromes* 2002; **31**(**Suppl. 3**)**:**S149–S153.
24. Hirschel B, Flepp M, Bucher HC, Zellweger C, Telenti A, Wagels T, Bernasconi E & Ledergerber B. Switching from protease inhibitors to efavirenz: differences in efficacy and tolerance among risk groups: a case-control study from the Swiss HIV Cohort. *AIDS* 2002; **16:**381–385.
25. Mocroft A, Gill MJ, Davidson W & Phillips AN. Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor. *AIDS* 1998; **12:**2161–2167.
26. Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, van Lunzen J, Katzenstein TL, Antunes F, Lundgren JD & Clotet B. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Archives of Internal Medicine* 2000; **160:**1123–1132.
27. Skowron G, Street JC & Obee EM. Baseline CD4(+) cell count, not viral load, correlates with virologic suppression induced by potent antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes* 2001; **28:**313–319.
28. Kempf DJ, Rode RA, Xu Y, Sun E, Heath-Chiozzi ME, Valdes J, Japour AJ, Danner S, Boucher C, Molla A & Leonard JM. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS* 1998; **12:**F9–F14.
29. Miller V, Staszewski S, Sabin C, Carlebach A, Rottmann C, Weidmann E, Rabenau H, Hill A, Lepri AC & Phillips AN. CD4 lymphocyte count as a predictor of the duration of highly active antiretroviral therapy-induced suppression of human immunodeficiency virus load. *Journal of Infectious Diseases* 1999; **180:**530–533.
30. Raboud JM, Rae S, Woods R, Harris M & Montaner JS. Consecutive rebounds in plasma viral load are associated with virological failure at 52 weeks among HIV-infected patients. *AIDS* 2002; **16:**1627–1632.
31. Bini T, Testa L, Chiesa E, Adorni F, Abeli C, Castelnuovo B, Melzi S, Sollima S, Bongiovanni M & d'Arminio Monforte A. Outcome of a second-line protease inhibitor-containing regimen in patients failing or intolerant of a first highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes* 2000; **24:**115–122.

32. Mocroft A, Phillips AN, Miller V, Gatell J, van Lunzen J, Parkin JM, Weber R, Roge B, Lazzarin A & Lundgren JD. The use of and response to second-line protease inhibitor regimens: results from the EuroSIDA study. *AIDS* 2001; **15:**201–209.

33. Paris D, Ledergerber B, Weber R, Jost J, Flepp M, Opravil M, Ruef C & Zimmerli S. Incidence and predictors of virologic failure of antiretroviral triple-drug therapy in a community-based cohort. *AIDS Research & Retrovirology* 1999; **15:**1631–1638.

34. Havlir DV, Bassett R, Levitan D, Gilbert P, Tebas P, Collier AC, Hirsch MS, Ignacio C, Condra J, Gunthard HF, Richman DD & Wong JK. Prevalence and predictive value of intermittent viremia with combination HIV therapy. *Journal of the American Medical Association* 2001; **286:**171–179.

35. Drechsler H & Powderly WG. Switching effective antiretroviral therapy: a review. *Clinical Infectious Diseases* 2002; **35**:1219–1230.

36. Negredo E, Cruz L, Paredes R, Ruiz L, Fumaz CR, Bonjoch A, Gel S, Tuldra A, Balague M, Johnston S, Arno A, Jou A, Tural C, Sirera G, Romeu J & Clotet B. Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting viral suppression. *Clinical Infectious Diseases* 2002; **34:**504–510.

37. Martinez-Picado J, Negredo E, Ruiz L, Shintani A, Fumaz CR, Zala C, Domingo P, Vilaro J, Llibre JM, Viciana P, Hertogs K, Boucher C, D'Aquila RT & Clotet B. Alternation of antiretroviral drug regimens for HIV infection. A randomized, controlled trial. *Annals of Internal Medicine* 2003; **139:**81–89.

38. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, Hirschel B, Ledergerber B, Vernazza P, Bernasconi E, Rickenbach M, Egger M & Battegay M. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Archives of Internal Medicine* 2003; **163:**2187–2195.

39. Kaufmann GR, Bloch M, Finlayson R, Zaunders J, Smith D & Cooper DA. The extent of HIV-1-related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy. *AIDS* 2002; **16:**359–367.

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