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ORIGINAL RESEARCH

History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change*

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Objectives

HIV-infected persons experience different patterns of viral suppression after initiating combination antiretroviral therapy (cART). The relationship between such differences and risk of virological failure after starting a new antiretroviral could help with patient monitoring strategies.

Methods

A total of 1827 patients on cART starting at least one new antiretroviral from 1 January 2000 while maintaining a suppressed viral load were included in the analysis. Poisson regression analysis identified factors predictive of virological failure after baseline in addition to traditional demographic variables. Baseline was defined as the date of starting new antiretrovirals.

Results

Four hundred and fifty-one patients (24.7%) experienced virological failure, with an incidence rate (IR) of 7.3 per 100 person-years of follow-up (PYFU) [95% confidence interval (CI) 6.7–8.0]. After adjustment, patients who had rebounded in the year prior to baseline had a 2.4-times higher rate of virological failure after baseline (95% CI 1.77–3.26; $P<.0001$), while there was no increased incidence in patients whose last viral rebound was >3 years prior to baseline [Incidence rate ratio (IRR) 1.06; 95% CI 0.75–1.50; $P=0.73$] compared with patients who had never virally rebounded. Patients had an 86% (95% CI 1.36–2.55; $P<.0001$), 53% (95% CI 1.06–2.04; $P=0.02$) and 5% (95% CI 0.80–1.38; $P=0.72$) higher virological failure rate after baseline if they were virally suppressed $<50\%$, 50–70% and 70–90% of the time they were on cART prior to baseline, respectively, compared with those virally suppressed $>90\%$ of the time.

Discussion

Intensive monitoring after a treatment switch is required in patients who have rebounded recently or have a low percentage of time suppressed while on cART. Consideration should be given to increasing the provision of adherence counselling.

Keywords: virological failure, antiretroviral therapy, virological suppression, viral rebound

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Introduction

Treatment guidelines for HIV-1 infection state that suppression of viral load below the level of quantification (normally 50 HIV-1 RNA copies/mL) is one of the key goals of combination antiretroviral therapy (cART) and should be one of the deciding factors when planning a patient's treatment strategy [1–4]. However, a substantial number of patients fail to achieve viral suppression in the first 6

months after starting cART [5] and many others go on to experience viral rebound at some time thereafter [6]. With increasing numbers of episodes of viral failure, the goal of viral suppression becomes harder to achieve [7].

Patients experience different immunological and virological responses after initiating cART [5,8,9]. In clinical practice, earlier studies found that around 70–80% of patients starting cART achieve an undetectable viral load [10]. This proportion has increased in recent years [11–13]; however, viral replication is still not fully controlled in all patients at all times. Previous analyses have found that a patient is most likely to fail in the first few months after initial viral suppression [14], that increasing time with viral suppression decreases the risk of rebound [15,16], and that treatment interruptions with detectable viral load [17] increase the risk of rebound, as does pre-cART exposure to nucleoside reverse transcriptase inhibitor (NRTI) regimens [15,18]. Additionally, low CD4 cell counts, high viral load, a slow virological response to cART and prior AIDS diagnosis were linked to lack of durable viral load undetectability [19,20].

Patients who are more adherent to treatment are more likely to achieve sustained viral suppression [21,22] and are less likely to show signs of disease progression [21,23–25]. Poor adherence has been linked to an increased risk of the development of resistance [26]. However, certain regimens may be more susceptible to development of resistance than others at differing levels of adherence [27]. The choice of a new regimen can therefore impact on a patient's risk of future virological failure if patients have some resistance to the regimen chosen, which may lead to a higher risk of virological failure.

As patients are living longer and are exposed for extended periods of time to more antiretrovirals (ARVs), they may experience different periods and patterns of suppression. The aim of this study was therefore to investigate whether a patient's viral suppression history while on cART, such as prior number of viral rebounds or the size of the viral rebound while on cART, was a predictor of future virological failure after a change in regimen in addition to traditional predictors.

Patients

EuroSIDA is a large prospective study with more than 100 centres across Europe (and also in Israel and Argentina). Details of the study have been published previously [28]. At each follow-up visit, all CD4 cell counts and HIV RNA measurements since last follow-up are recorded, as well as the date of starting or stopping any ARV drug, the use of any prophylaxis against opportunistic infections, the date of development and type of any AIDS-defining illnesses, non-AIDS-defining illness and opportunistic infections, and death. Data are collected from the centres through follow-up forms at 6-monthly intervals and the database is updated accordingly. The follow-up forms contain information on all data accrued on individual patients seen as required at the clinical centre in the previous 6 months. This analysis includes follow-up data to a median date of November 2008.

All patients in EuroSIDA who were on cART and started any new ARVs, regardless of the reason for change (excluding recycling ARVs or a change in formulation), on or after 1 January 2000 with some prospective follow-up were included in the analysis, providing that they had been on cART for >6 months prior to starting the new ARVs. Baseline was defined as the date on which new ARVs were first started on or after 1 January 2000. cART was defined as a treatment regimen of at least two NRTIs and a nonnucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI) or a PI boosted with ritonavir. All patients were required to have a suppressed viral load, defined as a viral load ≤ 500 copies/mL, at baseline. Patients were excluded if there was no viral load measurement in the 6 months after baseline.

Virological failure was defined as a viral load >500 copies/mL measured at least 4 months after baseline. Patient follow-up was measured from baseline to date of virological failure or date of last viral load measurement. Poisson regression analysis was used to identify viral load response prior to baseline associated with virological failure after starting new ARVs. Potential explanatory variables included age, gender, year of starting cART, ARV exposure status at cART initiation (ARV-naïve or ARV-experienced), risk group, ethnicity, region of Europe, baseline CD4 cell count, CD4 nadir, peak viral load, previous AIDS diagnosis, time on cART, current treatment regimen, number of previous treatment regimens, time spent on cART prior to baseline, number of ARVs to which the patient was previously exposed and the reason reported for starting the new ARV.

In addition to the traditional explanatory variables investigated above, variables that summarized the history of viral suppression after cART initiation prior to baseline were investigated. The variables used to summarize the history of viral suppression after cART initiation were as follows.

1. Months to initial suppression (HIV RNA ≤ 500 copies/mL) after starting cART.
2. Number of viral rebounds after initial suppression.
3. Size of the highest viral rebound (none, 500–1000, 1000–10 000 and $>10\,000$ copies/mL).
4. Time since most recent viral rebound.

5. Proportion of time spent with a viral load ≤ 500 copies/mL while receiving cART.

Viral suppression was defined as a measurement of HIV RNA ≤ 500 copies/mL. Viral rebound was defined as a viral load > 500 copies/mL measured after a period of suppression prior to the regimen change. For variable 5, any period of time when the patient was off cART and the first 4 months after starting a new cART regimen were excluded. Thus, only periods during which the patient was on cART and should have been virally suppressed were included.

Any variable that was significant at the 10% level in the univariate model was then included in a multivariate model.

The sensitivity analysis considered confirmed virological failure after baseline (i.e. two consecutive viral load measurements above 500 copies/mL) and, in the subgroup of patients who had viral load measured using an assay with a lower limit of detection of 50 copies/mL, virological failure after baseline defined as a viral load above 50 copies/mL. Analyses were also repeated taking account of HIV drug resistance at baseline in the subset of patients with resistance data, using genotypic sensitivity scores (GSS) calculated using the REGA algorithm, version 7.1 [29].

Results

A total of 1827 patients (67%) were included in the analysis. Table 1 describes the characteristics of the patients included in the analysis. Eight hundred and seventy-eight patients (48%) were treatment naïve at cART initiation. Median CD4 count at baseline was 500 cells/μL [interquartile range (IQR) 350–690 cells/μL]. Patients had been on cART for a median of 4.4 years prior to baseline. The majority of patients (1029; 56.3%) were on an NNRTI-based cART regimen after starting new ARVs at baseline. The main reason reported for starting new ARVs was toxicity or patient/physician choice. Nine hundred and thirty-two patients (51%) only started one new ARV and 349 (19%) started a completely new cART regimen (at least three ARVs).

Patients had a median viral load of 4.54 $\log_{10}$ copies/mL when they started cART. The median time to first viral suppression after cART initiation was 3.0 months (IQR 1.3–7.4 months). Five hundred and eighty-nine patients (68%) experienced at least one viral rebound prior to baseline after cART initiation. Of those patients who had rebounded prior to baseline, 206 (35%) had experienced a viral rebound to $> 10\,000$ copies/mL and 137 patients (23.2%) had experienced a viral rebound in the year prior to baseline. Overall, patients had spent a median of 98% (IQR 86–100%) of the time on cART virally suppressed (viral load < 500 copies/mL) after cART initiation.

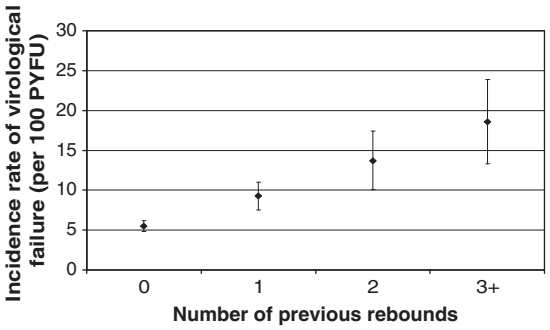
Table 1 Baseline characteristics

Total [*n* (%)]	1827 (67.1)
Gender [*n* (%)]	
Male	1394 (68.6)
Race [*n* (%)]	
White	246 (13.5)
Exposure group [*n* (%)]	
Homosexual	841 (46.0)
IDU	315 (17.2)
Heterosexual	550 (30.1)
Other	121 (6.6)
Region of Europe [*n* (%)]	
South	433 (23.7)
Central	438 (24.0)
North	739 (40.5)
East	217 (11.9)
Hepatitis B status [*n* (%)]	
HBV-negative	1505 (82.4)
HBV-positive	123 (6.7)
Unknown	199 (10.9)
Hepatitis C status [*n* (%)]	
HCV-negative	1197 (65.5)
HCV-positive	373 (20.4)
Unknown	257 (14.1)
Naïve [*n* (%)]	
Yes	878 (48.1)
Previous AIDS [*n* (%)]	
Yes	517 (28.3)
Number of new antiretrovirals started [*n* (%)]	
1	932 (51.0)
2	546 (29.9)
3	295 (16.1)
4	54 (3.0)
Reason for treatment change [*n* (%)]	
Addition	374 (20.5)
TF	61 (3.3)
TOXPC	959 (52.5)
Other/unknown	433 (23.7)
Age (years) [median (IQR)]	42 (37–50)
CD4 count (cells/μL) [median (IQR)]	500 (350–690)
cART CD4 count (cells/μL) [median (IQR)]	220 (102–335)
cART viral load ($\log_{10}$ copies/mL) [median (IQR)]	4.54 (3.60–5.20)
CD4 count nadir (cells/μL) [median (IQR)]	142 (54–238)
Peak viral load ($\log_{10}$ copies/mL) [median (IQR)]	4.94 (4.34–5.42)
Number of ARVs taken prior to baseline [median (IQR)]	5 (4–7)
Time since started cART (years) [median (IQR)]	4.4 (2.5–6.2)
Baseline date (month/year) [median (IQR)]	12/03 (04/02–10/05)

Baseline was defined as date of starting one or more new antiretrovirals (ARVs) after 1 January 2000 with a viral load ≤ 500 copies/mL. Regions of Europe: South: Spain, Portugal, Italy and Greece, plus Israel and Argentina; Central: France, Belgium, south Germany, Luxembourg, Switzerland and Austria; North: UK, Ireland, the Netherlands, north Germany, Denmark, Sweden, Norway and Finland; East: Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Croatia, Serbia, Estonia, Latvia, Lithuania, Belarus, Ukraine and Russia.
cART, combination antiretroviral therapy; IDU, injecting drug use; IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; TF, reported treatment failure (virological, immunological or clinical); TOXPC, toxicity or patient/physician choice.

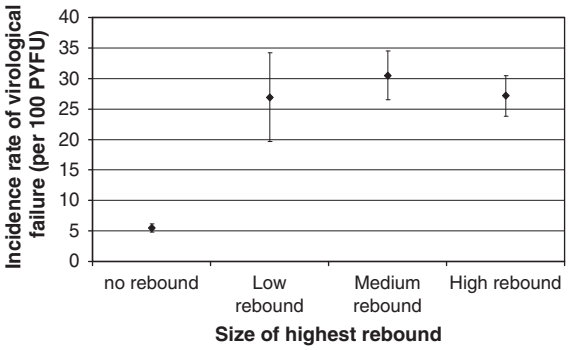
Incidence of virological failure after starting a new ARV(s)

After starting a new ARV(s), 451 patients (24.7%) experienced virological failure, with an incidence rate



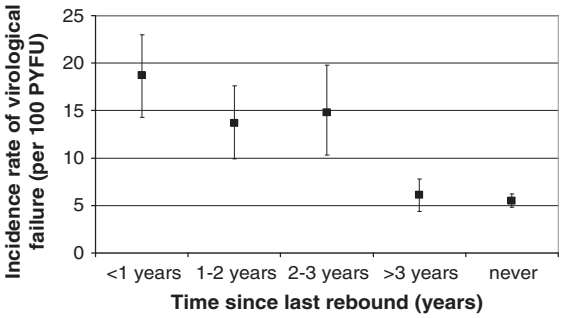
Number of rebounds prior to baseline	0	1	2	3+
Number virologically failed after baseline	238	111	54	48
PYFU	4305	1199	393	258

Fig. 1 Rate of virological failure after baseline by the number of rebounds experienced after combination antiretroviral therapy (cART) initiation and prior to baseline. PYFU, person-years of follow-up.



Size of highest rebound	No rebound	Low rebound	Medium rebound	High rebound
Number virologically failed after baseline	238	53	221	252
PYFU	4305	197	725	928

Fig. 2 Rate of virological failure after baseline by the size of the highest rebound experienced after combination antiretroviral therapy (cART) initiation prior to baseline. PYFU, person-years of follow-up.



Time since last rebound (years)	<1	1-2	2-3	>3	Never
Number virologically failed after baseline	22	49	42	50	238
PYFU	386	357	284	823	4305

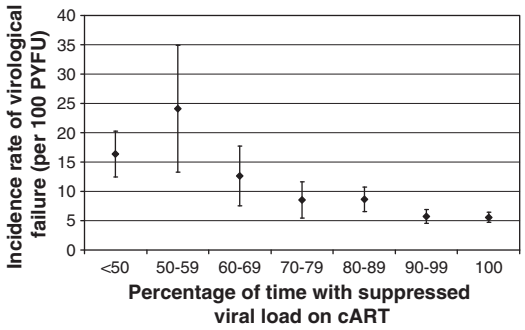
Fig. 3 Rate of virological failure after baseline by time since last rebound after combination antiretroviral therapy (cART) initiation prior to baseline. PYFU, person-years of follow-up.

(IR) of 7.3 per 100 person-years of follow-up (PYFU) [95% confidence interval (CI) 6.7–8.0].

Patients who took longer to achieve initial viral suppression after cART initiation had an increased rate of virological failure after baseline (IRR 1.04 per 6 months longer to achieve suppression; 95% CI 0.99–1.09); however, this difference was not statistically significant ($P = 0.14$). Figure 1 shows the rate of virological failure after baseline by the number of viral rebounds the patient had experienced prior to baseline. There was a 41% increased rate of virological failure after baseline for each viral rebound experienced prior to baseline (IRR 1.41; 95% CI 1.31–1.51). Patients who had a low viral rebound prior to baseline (501–1000 copies/mL) had a 30% lower rate of virological failure after baseline (IRR 0.70; 95% CI 0.49–1.01; $P = 0.06$) and those who had a medium viral rebound (1001–10 000 copies/mL) had an 18% lower rate (IRR 0.82; 95% CI 0.60–1.10; $P = 0.19$) compared with patients who had experienced a high viral rebound (> 10 000 copies/mL) prior to baseline (Fig. 2). There was a higher rate of virological failure in patients who had virally rebounded more recently before baseline (Fig. 3). For example, patients who had virally rebounded in the year prior to baseline had a 3.4-times higher rate of virological failure compared with patients who had never virally rebounded (IRR 3.37; 95% CI 2.59–4.39; $P < .0001$), whereas there was no significant difference in the rate of virological failure between patients whose last viral rebound was more than 3 years prior and those who had never rebounded (IRR 1.10; 95% CI 0.81–1.49; $P = 0.54$). There was an increased risk of virological failure with decreasing percentage of time a patient had spent with a suppressed viral load while on cART prior to baseline (Fig. 4). Patients who were virally suppressed for < 50% of the time they were on cART had almost a 3-times higher rate of virological failure compared with patients who were virally suppressed for > 90% of the time they were on cART (IRR 2.91; 95% CI 2.23–3.81; $P < .0001$).

Factors predictive of virological failure after starting a new ARV(s)

In addition to the variables describing the patients' history of viral suppression prior to baseline, demographic variables found in univariate analysis to be associated with rate of virological failure after baseline were gender, age, HIV exposure group, region of Europe, hepatitis C status, ARV exposure status (naïve or experienced) at cART



Percentage of time with suppressed viral load on cART	<50	50-59	60-69	70-79	80-89	90-99	100
Number virologically failed after baseline	68	19	24	29	65	87	159
PYFU	416	79	190	341	751	1520	2858

Fig. 4 Rate of virological failure by percentage of time spent on combination antiretroviral therapy (cART) with a suppressed viral load (<500 copies/mL) prior to baseline. PYFU, person-years of follow-up.

initiation, whether AIDS had been diagnosed previously, CD4 nadir, time on cART prior to baseline, number of ARVs to which the patient was exposed prior to baseline, date of baseline, treatment regimen at baseline, the reason for the switch in treatment at baseline and the number of new drugs started.

After adjustment (Table 2), there was no significant difference in the rate of virological failure between patients whose last viral rebound was more than 3 years prior to baseline and patients who had never rebounded (IRR 1.06; 95% CI 0.75–1.50; $P = 0.73$), whereas patients who had virally rebounded in the year prior to baseline had a 2.4-times higher rate of virological failure after baseline than patients who had never rebounded (IRR 2.40; 95% CI 1.77–3.26; $P < 0.0001$). The lower the percentage of time a patient had spent virally suppressed prior to baseline, the higher the rate of virological failure; patients who had spent <50% of the time they were on cART prior to baseline with a suppressed viral load had an 86% (IRR 1.86, 95% CI 1.36–2.55; $P < .0001$) higher rate of virological failure after baseline compared with patients who were suppressed >90% of the time they were on cART. Older patients had a lower rate of virological failure (IRR 0.84 per 10 years older; 95% CI 0.75–0.94; $P = 0.0003$). Patients with a higher CD4 nadir had an increased rate of virological failure (IRR 1.13 per two-fold increase; 95% CI 1.03–1.22; $P = 0.0009$). In addition, the more ARVs a patient had been exposed to prior to baseline, the higher the rate of virological failure (IRR 1.06 per drug; 95% CI 1.01–1.12; $P = 0.03$). Patients on a boosted PI-containing cART regimen had a 24% lower rate of virological failure (IRR 0.76; 95% CI 0.57–1.01; $P = 0.06$) and patients on an NNRTI regimen had a 31% lower rate of virological failure (IRR 0.69; 95% CI 0.53–0.90; $P = 0.007$) compared with patients on a nonboosted PI regimen.

Sensitivity analysis

The analyses were repeated with virological failure defined as two consecutive viral load measurements > 500 copies/mL. Two hundred and seventy-eight patients (15%) experienced confirmed virological failure after baseline, with an IR of 4.2 per 100 PYFU (95% CI 3.7–4.7). After adjustment, patients who were virally suppressed <50% of the time they were on cART had a 2.4-times higher rate of virological failure (95% CI 1.58–3.53; $P > 0.0001$) compared with those who were virally suppressed >90% of the time, and those who had virally rebounded in the year prior to baseline had a 3.1-times higher rate of virological failure compared with patients who had never virally rebounded (95% CI 1.84–5.25; $P < .0001$). The analyses were also repeated using a lower limit of detection for viral load of 50 copies/mL; 901 patients were included in the analysis and 41% experienced virological failure (defined as a viral load >50 copies/mL), with an IR of 14.3 per 100 PYFU (95% CI 12.8–15.8). Those who had virally rebounded in the year prior to baseline had an 84% higher rate of virological failure compared with patients who had never virally rebounded (95% CI 1.33–2.57; $P = 0.0003$) and patients who were virally suppressed <50% of the time they were on cART had a 13% higher rate of virological failure (95% CI 0.79–1.64; $P = 0.50$) compared with those who were virally suppressed >90% of the time, although this was not statistically significant after adjustment. Five hundred and forty-four patients (29%) had some resistance data available at baseline. Four hundred and five patients (75%) had a GSS ≥ 3 for their baseline cART regimen; there was no significant difference in rate of virological failure in patients with a GSS <3 compared with those with a GSS ≥ 3 (IRR 1.41; 95% CI 0.89–2.23; $P = 0.14$) after adjustment for all demographic variables, percentage of time suppressed and time since last rebound.

Discussion

A patient's history of viral suppression can provide important information about the risk of viral failure after a change in ARVs. The variables describing the history of viral suppression after cART initiation but before a change in regimen were highly predictive of future virological failure, in addition to the traditional baseline predictors. The most important factors were the percentage of time spent with suppressed viral load since starting cART prior to baseline and time since last viral rebound. After adjustment for these factors, none of the other markers of

Table 2 Predictors of virological failure after a treatment switch

	Univariate			Multivariate		
	IRR	**95% CI**	***P*-value**	**IRR**	**95% CI**	***P*-value**
Gender						
Male	1.00		<0.0001	1.00	–	–
Female	1.54	1.26–1.88		1.05	0.82–1.34	0.72
Exposure group						
Homosexual	1.00		<0.0001	1.00	–	–
IDU	2.34	1.84–2.97		1.21	0.87–1.70	0.26
Heterosexual	1.74	1.40–2.17		1.51	1.15–1.97	0.003
Other	0.99	0.64–1.53		0.98	0.62–1.55	0.93
Region						
South	1.00		<0.0001	1.00	–	–
West	0.55	0.43–0.71		0.70	0.54–0.91	0.007
North	0.40	0.32–0.51		0.61	0.48–0.78	<0.0001
East	0.46	0.32–0.67		0.58	0.39–0.86	0.006
Hepatitis C status						
Negative	1.00		<0.0001	1.00	–	–
Positive	2.05	1.66–2.52		1.55	1.15–2.09	0.004
Unknown	0.57	0.43–0.76		0.65	0.46–0.91	0.01
Naïve						
No	1.00		0.0003	1.00	–	–
Yes	0.71	0.58–0.85		1.05	0.83–1.32	0.70
Prior AIDS diagnosis						
No	1.00		0.04	1.00	–	–
Yes	0.80	0.64–0.98		0.90	0.71–1.134	0.39
Regimen						
PI	1.00		0.002	1.00	–	–
Boosted PI	0.74	0.56–0.98		0.76	0.57–1.01	0.06
NNRTI	0.62	0.48–0.81		0.69	0.53–0.90	0.007
Reason for treatment						
Addition	1.00		0.05	1.00	–	–
TF	1.47	0.91–2.36		1.06	0.64–1.75	0.83
TOXPC	0.95	0.74–1.21		0.96	0.73–1.24	0.74
Other/unknown	1.25	0.95–1.64		1.08	0.79–1.46	0.60
Time since last rebound						
Never	1.00		<0.0001	1.00	–	–
<1 year	3.37	2.59–4.39		2.40	1.77–3.26	<0.0001
1–2 years	2.48	1.82–3.37		1.72	1.21–2.43	0.002
2–3 years	2.68	1.93–3.72		2.21	1.54–3.18	<0.0001
>3 years	1.10	0.81–1.49		1.06	0.75–1.50	0.73
Proportion of time suppressed						
>90%	1.00	–	<0.0001	1.00	–	–
89–70%	1.53	1.21–1.94		1.05	0.80–1.38	0.72
69–50%	2.85	2.07–3.94		1.53	1.06–2.04	0.02
<50%	2.91	2.23–3.81		1.86	1.36–2.55	<0.0001
Age	0.76	0.69–0.84	<0.0001	0.84	0.75–0.94	0.003
CD4 nadir	1.15	1.08–1.23	<0.0001	1.13	1.05–1.22	0.0009
Baseline date	0.90	0.85–0.95	0.0002	0.95	0.89–1.01	0.11
Time on cART	0.96	0.92–1.00	0.07	0.98	0.93–1.04	0.51
Number of new drugs started	1.10	0.99–1.22	0.07	0.97	0.87–1.09	0.59
Number of drugs exposed to	1.10	1.06–1.14	<0.0001	1.06	1.01–1.12	0.03

cART, combination antiretroviral therapy; CI, confidence interval; IDU, injecting drug use; IRR, incidence rate ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TF, reported treatment failure (virological, immunological or clinical); TOXPC, toxicity or patient/physician choice.

previous patterns of suppression was a significant predictor of virological failure after baseline.

There was a clear inverse relationship between time suppressed and risk of future virological failure. Patients with viral suppression <50% of the time prior to baseline had almost double the rate of virological failure compared with those with viral suppression >90% of the time. A study in patients with CD4 counts >200 cells/μL found that time with undetectable viraemia was a significant predictor of clinical progression [30]. In addition, previous

studies have found that patients with a history of persistent low-level viraemia (51–1000 copies/mL) were more likely to experience virological failure [31], as were those with intermittent viraemia above 400 copies/mL, compared with those who sustained an undetectable viral load [32]. However, some studies have shown that, although moderate viraemia and viral rebounds may increase your risk of future rebounds, this may not translate into an increased risk of clinical disease progression [33,34].

After adjustment, time since last viral rebound was highly predictive of virological failure after starting new ARVs, consistent with findings from other studies. For example, Benzie *et al.* [16] reported that up to 4 years of sustained viral suppression was necessary in patients with previous treatment failures for them to achieve rebound rates similar to those of patients with no prior treatment failures. The greatest risk of viral rebound has been shown to be in the first few months after initial suppression [14], and therefore it follows that increasing time since last virological rebound decreased the risk of virological failure after baseline. This could be attributable to problems associated with starting a new regimen, such as tolerability [35].

In contrast to previous findings [19], the size of each viral rebound prior to baseline was not significant after adjustment. The number of previous viral rebounds before baseline was important; however, after adjustment for the percentage of time a patient had spent virally suppressed and the time since last rebound, this variable added very little additional information. These analyses suggest that a patient with three or more viral rebounds prior to baseline would have a very high rate of viral rebound. Palella *et al.* [36] found that successive cART regimens were progressively less effective in suppressing viral load and were generally shorter in duration. Our results highlight the need for patients to be placed on a suitable regimen when initiating cART, emphasize the importance of adherence, and suggest that consideration should also be given to future treatment strategies in order to decrease the risk of future viral rebounds.

As with all cohorts studies there are a number of limitations to this study. One such limitation is that viral load suppression was defined using a viral load cut-off of 500 copies/mL for the main analysis. In current clinical practice, a viral load of <50 copies/mL is the aim [2,3]) but assays to such low levels were not consistently available from all the centres over the period of analysis covered. However, the sensitivity analysis in patients with available data where viral suppression was defined as a viral load <50 copies/mL produced results consistent with those of the main analysis. Resistance data were available in a minority of patients; however, 70% of those with data available were predicted to be on a fully active regimen. The patients' resistance profile at baseline was not independently associated with the risk of future virological failure. However, some resistance tests were performed several years prior to baseline and these patients could have acquired new mutations. This analysis may also be limited by power, or it is also possible that the variables that were significant in our main analysis captured information that was also captured by the availability of resistance data. Adherence to antiretroviral therapy remains a very important issue. Without adequate adherence ARVs are not maintained at a sufficient concentration to suppress HIV replication in infected cells and to lower plasma viral load [26]. Patients who are more adherent to treatment are more likely to achieve sustained viral suppression [21,22] and are less likely to show signs of disease progression [23]. Patients have been found to take on average 70–75% of their prescribed medication [24,25]. Paterson *et al.* [21] found that adherence of 95% or more was necessary to achieve optimal viral suppression; however, other studies on disease progression have found that even adherence of 50% significantly decreases a patient's risk of progression to AIDS [23,24]. EuroSIDA has only recently begun collecting data on adherence and the data are still very limited. However, the portion of time a patient has spent with an undetectable viral load since starting cART could serve as an indicator of a patient's adherence, as the initial 4 months after starting or changing a cART regimen, when the viral load would not be expected to be undetectable, was excluded from analyses. Thus patients who are suppressed for longer must be adherent to their therapy and those with a poor history of viral suppression are those with poor adherence.

To summarize, when deciding on future treatment options, the previous response to cART regimens may provide an indication of the risk of future virological failure. Patients making a change to their cART regimen while maintaining a suppressed viral load have an increased risk of virological failure if they have spent a low percentage of time on cART with suppressed viral load or experienced a viral rebound close to the time of the treatment switch. Patients with a low percentage of time virally suppressed while on cART and those who have recently rebounded may require more intensive monitoring after a switch and consideration should also be given to increasing the provision of adherence counselling. The history of patterns of viral response to cART regimens should be taken into account when making decisions on monitoring strategies and adherence counselling for patients whenever a change in cART is made.

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Conflict of interest

All authors have stated that they have no competing interests to declare.

Ethics approval

Ethical approval for each participating centre is sought according to local regulations.

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Appendix

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