Treatment switches after viral rebound in HIV-infected adults starting antiretroviral therapy: multicentre cohort study

The United Kingdom Collaborative HIV Cohort (CHIC) Study*

Objective: To describe the time from first viral rebound on highly active antiretroviral therapy to first treatment change, identify factors associated with more rapid switching, and investigate whether treatment changes are in line with treatment guidelines.

Design and setting: A multicentre cohort study.

Methods: We described the time to first treatment switch among individuals experiencing confirmed virological rebound after initiating highly active antiretroviral therapy; factors associated with more rapid switching were identified using proportional hazards regression and predictors of a switch in line with guidelines were identified using logistic regression.

Results: Thirty-four percent of the 694 patients experiencing virological rebound remained on a failing regimen for more than 6 months. Factors associated with more rapid switching were lower CD4 cell count (hazard ratio, 0.84/100 cells/μl higher, $P < 0.001$), higher viral load (1.29/$\log_{10}$ copies/ml higher, $P < 0.001$), older age (1.06/5 years older, $P = 0.07$), and changing/adding drugs to the regimen prior to rebound (1.16, $P = 0.16$). Two hundred and eighteen of the 394 treatment changes (55%) were in line with guidelines; those receiving nonnucleoside reverse transcriptase inhibitor-containing regimens were more likely to make changes in line with guidelines (adjusted odds ratio, 2.80, $P < 0.001$), whereas those who had previously added drugs to their regimen were less likely to make changes in line with guidelines (0.15, $P = 0.001$).

Conclusion: A substantial minority of patients remain on a failing highly active antiretroviral therapy regimen for periods of 6 months or longer without adding new drugs. Changes made are often not in line with treatment guidelines, raising concerns about the development of resistance and long-term clinical outcomes in these individuals.

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Keywords: clinical practice, guidelines, highly active antiretroviral therapy, HIV, treatment switching, viral load rebound

Introduction

Although the majority of HIV-infected individuals who start highly active antiretroviral therapy (HAART) will experience a rapid and sustained virological response to therapy, a minority will fail to achieve a virological response to HAART or will experience virological rebound after a period of viral suppression [1,2]. The

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weight of evidence [3–5] suggests that continued exposure to failing HAART regimens will rapidly lead to the development of HIV strains that are resistant to drugs in the failing regimen and possibly to those that may be required in the future. Resistance is associated with suboptimal responses to subsequent HAART regimens and poorer clinical outcomes [6–8]. Consequently, most HIV treatment guidelines recommend that HAART regimens are changed rapidly in patients experiencing virological failure [9,10].

In the UK, it is currently recommended that any new regimen should contain at least three active drugs (in which the determination of an 'active' drug is based on the results from resistance tests or treatment history or both), preferably including one from a new class [9]. However, little is known about what actually happens in clinical practice; in particular, there is little information on either the time to or determinants of switching following virological rebound, or whether the switches that are made follow these guidelines. A national audit from the UK, conducted in 2004 [11], revealed that over a third of individuals who had experienced viral rebound and then switched had delayed switching for more than 6 months from the time of their first detectable viral load; furthermore, around a fifth of patients with virological failure switched only one drug, and many did not include a drug from a new class. However, this audit only included patients who actually switched regimens; thus, it does not enable us to obtain a complete picture of how long patients remain with a detectable viral load before switching.

The UK Collaborative HIV Cohort (CHIC) Study provides an opportunity to explore this issue in more detail in a large representative patient cohort, including those who switch following viral rebound and those who do not. In the present study, we describe the time from an individual experiencing confirmed viral rebound after starting HAART to their first treatment change, identify factors that influence more rapid switching in this situation, and investigate whether treatment changes made are broadly in line with treatment guidelines.

Methods

UK CHIC is a multicentre cohort of HIV-infected patients aged 16 years or above receiving care at some of the largest HIV treatment centres in the UK since 1996. The analyses in this report are based on data reported to UK CHIC from 10 clinical centres to June 2006, with complete data to the end of 2005. The design of the UK CHIC Study has been described in detail elsewhere [12]. The UK CHIC Study has received approval from the West Midlands Research Ethics Committee.

Eligible patients for the present study were antiretroviral-naive individuals who initiated HAART from 1998 onwards. HAART was defined as any regimen containing at least three drugs from at least two classes [from nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (Pls) or nonnucleoside reverse transcriptase inhibitors (NNRTIs)], or triple NRTI regimens including tenofovir or abacavir. Analysis was restricted to patients reaching virological suppression of less than 400 copies/ml within 26 weeks of HAART initiation who subsequently experienced confirmed virological rebound, defined as the second of two consecutive (within 6 months) HIV-1 RNA measurements of more than 400 copies/ml more than 26 weeks after HAART initiation. This period was chosen as most patients would be expected to have experienced an initial response to treatment by this time, and a viral load threshold of 400 copies/ml was chosen to allow for the changing use of viral load assays and guideline recommendations over time. Viral load measurements during a treatment break or within 26 weeks of restarting HAART after a break were ignored to allow time for the viral load to be resuppressed. Treatment changes prior to rebound were ignored as these were expected to be for toxicity; thus, although all patients in this analysis had started HAART for the first time, some may not have remained on their initial regimen until the time of viral rebound.

We investigated the characteristics of patients at viral rebound and describe the first switch to the regimen after rebound, classified as the addition of at least one (either new or 'recycled') drug to the regimen. CD4 cell count and viral load at the time of rebound and at the time of regimen change are the closest measurements up to 3 months before or 1 month after the event.

Competing risk analysis was used to estimate the time from viral load rebound to treatment switch to allow for the fact that some patients resuppressed ($\leq$400 copies/ml) before changing treatment. However, in the analysis of risk factors for time to switch we considered the cause-specific hazard of switching, that is, follow-up on patients who resuppressed (<400 copies/ml) before changing treatment was right censored on the date of resuppresssion. A competing risk analysis gave similar results so only the results from the cause-specific models are presented [13]. Cox modelling was used to assess potential risk factors for faster switch including: sex; HIV exposure group; age at rebound; receiving a Pl- or NNRTI-containing regimen; being on at least four drugs; having previously added a new drug to the regimen before rebound (all as fixed covariates at the time of rebound); calendar year; latest CD4 cell count; and latest viral load (as time-dependent covariates). A sensitivity analysis was also carried out defining suppression as achieving viral load of less than 50 copies/ml, and rebound as confirmed viral load of

more than 50 copies/ml. In all analyses, ritonavir was not counted as a separate drug when used in combination with another PI, as it was assumed that this was a boosting dose (dosage was not recorded).

Finally, we considered whether changes that were made were broadly in line with current UK guidelines. As the guidelines have changed over time, we used a pragmatic definition that required the addition of at least two drugs with the inclusion of at least one drug from a new class. Potential predictors of a switch made in line with this definition (sex, age and HIV exposure group, CD4 cell count and viral load at the time of switch, being on a PI or NNRTI-containing regimen, being on at least four drugs, having previously added a new drug to the regimen and calendar year at the time of rebound) were assessed using univariate and multivariable logistic regression models. To ensure that all patients were included, the small number of missing CD4 values at the time of rebound (4% of patients) were imputed using chained estimation with 10 imputations from multivariable models [14].

Results

Of the 25 274 patients in UK CHIC, 8512 antiretroviral-naïve patients started HAART between 1998 and 2005. Six thousand four hundred and eighty of these patients experienced virological suppression within 26 weeks, of whom 694 (11%) experienced a confirmed viral load rebound a median of 1.4 years after viral suppression and were included in this analysis (Table 1). Four hundred and ninety-three patients (71%) were men and 309 (45%) were homosexual. The median (IQR) age, CD4 cell count and viral load at rebound were 37 years (32–41), 286 cells/μl (170–433) and 5562 copies/ml (1300–29300), respectively, with an average post-rebound follow-up of 1.4 years (range 0.5–6.9). Three hundred and fifty-six patients (57%) had already added at least one new drug to their regimen prior to viral load rebound.

One hundred and eighty-two of the 694 patients with virological rebound (26%) experienced viral resuppression of less than 400 copies/ml prior to changing their regimen (Table 2), after a median (IQR) 0.21 years (0.11–0.36), with 30 patients (4%) changing their regimen between their first and second detectable viral load (15 of whom subsequently resuppressed and 15 who did not). Three hundred and ninety-four of the 512 patients who did not resuppress (77%) switched their regimen after virological rebound. The median (IQR) CD4 cell count and viral load at the time of switching were 240 cells/μl (121–380) and 16 100 copies/ml (2503–71 500), respectively. Of note, 78 of 394 patients switching before resuppression (20%) had a treatment interruption for 14 or more days prior to switching.

Table 1. Characteristics of patients at confirmed viral rebound of more than 400 copies/ml.

	All patients rebounding ($n = 694$)
Male sex, *n* (%)	493 (71)
Exposure, *n* (%)	
Men who have sex with men	309 (45)
Heterosexual	318 (46)
Injection drug user	30 (4)
Other/unknown	37 (5)
Median (IQR) age (years)	37 (32–41)
Calendar year, *n* (%)	
1998–1999	75 (11)
2000–2002	316 (46)
2003 onwards	303 (44)
Median (IQR) years from HAART initiation to rebound	1.4 (0.9–2.6)
Median (IQR) days between the first and second viral load more than 400 copies/ml[a]	47 (26–84)
Median (IQR) viral load ($\log_{10}$ copies/ml)[b]	3.7 (3.1–4.5)
Median (IQR) CD4 cell count (cells/μl) ($n = 665$)	286 (170–433)
Antiretroviral regimen at the time of rebound, *n* (%)	
PI and NRTI	223 (33)
NNRTI and NRTI	368 (53)
PI and NNRTI and NRTI	16 (2)
Other combination	87 (13)
Previous addition of new drugs to initial HAART regimen prior to viral load rebound, *n* (%)	356 (57)
Number of drugs in regimen, *n* (%)	
Three or less	634 (91)
At least four	60 (9)

HAART, highly active antiretroviral therapy; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. [a]Time difference between two viral load of more than 400 copies/ml is less than 183 days by definition. [b]Viral loads assumed to be the midpoint between zero and the lower limit of detection if undetectable and calculated using the conditional mean of the log viral load if above the limit of detection.

Table 2. Summary of first switch after confirmed viral rebound.

	Number of patients	(%)
Patients experiencing viral rebound	694	
Patients experiencing viral rebound but not resuppressing viral load to less than 400 copies/ml	512	100
Patients adding at least one drug to their regimen	394	77
Number of drugs added to regimen[a]		
Zero	28	7
One	104	26
Two	96	24
At least three	166	42
Treatment switch made in line with treatment guidelines[a]		
Yes	218	55
No, did not include two new drugs	43	11
No, did not include a new class	44	11
No, did not include two new drugs nor a new class	89	23

[a]Denominator is the total number of patients who added at least one drug to their regimen ($n = 394$).

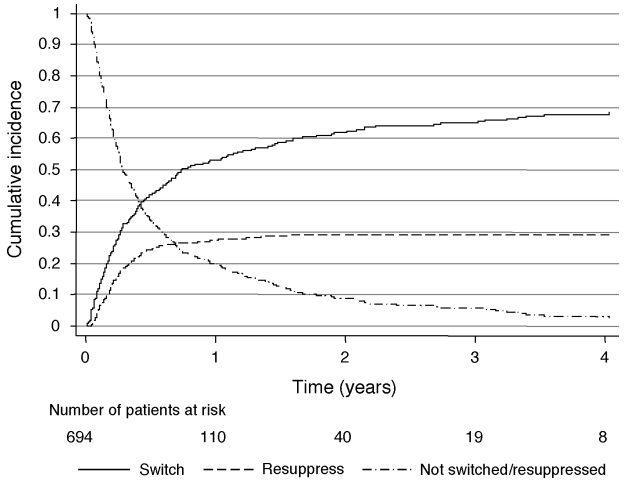

Fig. 1. Cumulative incidence of switching or resuppressing after virological rebound (defining suppression as <400 copies/ml and rebound as >400 copies/ml).

An estimated 34% of patients [95% confidence interval (CI) 30–37%] remained on a failing regimen, having not switched or resuppressed, for more than 6 months after virological rebound of more than 400 copies/ml, falling to 20% (95% CI 17–23%) and 9% (95% CI 7–11%) at 1 and 2 years after rebound, respectively (Fig. 1). Classifying suppression as less than 50 copies/ml and rebound as more than 50 copies/ml, 46% of patients were still on a failing regimen 6 months after rebound, falling to 31% (95% CI 27–34%) and 15% (95% CI 12–18%) after 1 and 2 years. Patients with lower current CD4 cell count [adjusted hazard ratio, 0.84 /100 CD4 cells/μl higher (95% CI 0.79–0.89), $P < 0.001$] and higher current viral load [adjusted hazard ratio, 1.29 /$\log_{10}$ copies/ml higher (95% CI 1.14–1.46), $P < 0.001$] changed their regimen sooner (Table 3). There was also a trend towards older patients [adjusted hazard ratio, 1.06 per 5 years older (95% CI 0.99–1.13), $P = 0.07$], and patients who had changed or added drugs to their regimen prior to rebound [adjusted hazard ratio, 1.16 compared with those who had not added drugs previously (95% CI 0.94–1.43), $P = 0.16$] switching their regimen more rapidly. There was no difference in time to regimen change over calendar time, with adjusted hazard ratio, 1.08 (95% CI 0.78–1.48) for 2004–2006 compared to 1998–2000 ($P = 0.65$, global $P = 0.90$).

Of patients who did not resuppress and did change treatments, 28 (7%) added only recycled drugs, with 104 (26%), 96 (24%) and 166 (42%) adding one, two and at least three new drugs respectively (Table 2). Two hundred and eighteen of the 394 post-rebound changes (55%) were in line with treatment guidelines; of the remaining 176 changes made, 44 did not include a new drug class, 43 changed fewer than two drugs and 89 did neither. Patients on an NNRTI-containing regimen at the time of rebound were more likely to switch in line with treatment guidelines [adjusted odds ratio (OR) 2.80, (95% CI 1.52–5.15) compared with patients on a Pl-containing regimen, $P = 0.001$, global $P < 0.001$), whereas patients who had added drugs prior to the rebound were less likely to switch in line with treatment guidelines (adjusted OR, 0.15 (95% CI 0.09–0.24) compared with those who had

Table 3. Results from univariate and multivariable Cox regression model to identify factors associated with the rate of switching after viral load rebound of more than 400 copies/ml; follow-up on patients who resuppressed without any change in treatment was censored at the time of resuppression.

	Univariate models			Full multivariable model		
	HR	95% CI	*P*	HR	95% CI	*P*
Age at rebound (/5 years)	1.08	1.02–1.15	0.01	1.06	0.99–1.13	0.07
Sex (female vs. male)	0.98	0.79–1.22	0.87	1.06	0.79–1.43	0.68
Latest CD4 (/100 cells/μl higher)	0.80	0.75–0.85	<0.001	0.84	0.79–0.89	<0.001
Latest viral load (/$\log_{10}$ copies/ml higher)	1.44	1.28–1.61	<0.001	1.29	1.14–1.46	<0.001
Exposure group			0.62			0.58
MSM	1			1		
Heterosexual	1.06	0.87–1.32		0.95	0.72–1.26	
Injection drug user	0.81	0.48–1.37		0.78	0.45–1.33	
Other/unknown	0.85	0.52–1.38		0.74	0.44–1.24	
ART regimen at rebound			0.23			0.54
PI only	1			1		
NNRTI only	0.92	0.74–1.16		0.98	0.78–1.24	
PI and NNRTI	1.00	0.41–2.46		0.77	0.29–1.99	
Neither	1.27	0.92–1.74		1.21	0.87–1.68	
On more than four drugs at rebound	1.11	0.76–1.63	0.58	1.06	0.70–1.59	0.79
Added drugs previously	1.30	1.07–1.59	0.01	1.16	0.94–1.43	0.16
Calendar year			0.68			0.90
1998–2000	1			1		
2001–2003	1.08	0.83–1.40		1.05	0.80–1.39	
2004–2006	1.15	0.85–1.55		1.08	0.78–1.48	

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 4. Results from univariate and multivariable logistic regression models to identify factors associated with a treatment switch in line with treatment guidelines; patients not switching, or those who resuppressed before switching are excluded from these analyses ($n = 394$[a]).

	Univariate models			Full multivariable model		
	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Age at rebound (/5 years)	0.96	0.85–1.07	0.45	1.04	0.91–1.20	0.54
Sex (female vs. male)	0.81	0.52–1.26	0.35	0.76	0.39–1.50	0.43
CD4 at rebound (/100 cells/μl higher)	0.99	0.90–1.10	0.88	0.95	0.83–1.08	0.44
Viral load at rebound (/$\log_{10}$ copies/ml higher)	0.91	0.74–1.12	0.36	0.90	0.70–1.16	0.42
Exposure group			0.52			0.31
MSM	1			1		
Heterosexual	0.93	0.61–1.42		1.24	0.64–2.38	
Injection drug user	0.53	0.18–1.52		0.44	0.12–1.57	
Other/unknown	0.60	0.23–1.59		0.59	0.19–1.87	
ART regimen at rebound[a]			<0.001			<0.001
PI only	1			1		
NNRTI only	2.15	1.28–3.62		2.80	1.52–5.15	
Neither	0.70	0.42–1.19		0.91	0.49–1.69	
On more than four drugs	0.48	0.21–1.13	0.09	0.82	0.30–2.24	0.61
Added drugs previously	0.15	0.10–0.24	<0.001	0.15	0.09–0.24	<0.001
Calendar year at the time of rebound			0.009			0.06
1998–2000	1			1		
2001–2003	0.64	0.27–1.52		0.83	0.31–2.22	
2004–2006	0.37	0.16–0.87		0.47	0.18–1.27	

ART, antiretroviral therapy; CI, confidence interval; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor. [a]Only three patients were on both PIs and NNRTIs at the time of virological rebound; these three patients have been excluded from any analyses that included this covariate.

not added drugs previously, $P < 0.001$) (Table 4). Interestingly, there was a trend for patients rebounding in later calendar years to be less likely to switch in line with treatment guidelines [adjusted OR, 0.83 (95% CI 0.31–2.22) and 0.47 (95% CI 0.18–1.27) for 2001–2003 and 2004–2006 compared with 1998–2000 respectively, global $P = 0.06$).

Discussion

Using data from a large multicenter cohort in the UK, we report that although most patients change their HAART regimen soon after viral load rebound, around 20% remain on a failing regimen for a year or longer before adding any new drugs. Many of the changes that are made do not appear to be in line with UK treatment guidelines, with only around a half adding at least two new drugs and a drug from a new class to their failing regimen. Of some concern, given the possible implications for subsequent response to therapy and clinical outcomes [15,16], was the finding that around a fifth of patients who switched drugs had taken a treatment interruption of a least 14 days prior to switching.

Careful reflection on treatment practices is an essential part of patient care as it ensures that any deficiencies in current practice can be identified and rectified. Furthermore, an increased awareness of the degree to which treatment guidelines are followed is important when interpreting the results of research studies conducted in this setting or when assessing the potential impact of different antiretroviral treatment strategies for the prevention of onward transmission of HIV. Our findings are consistent with those from a recent audit conducted in the UK [11], in which a substantial delay in switching was also reported, as was the finding that fewer than half of patients switched to regimens that included three or more new drugs. Our study provides additional information to this audit on a larger sample of patients experiencing viral load rebound over the period 1998–2005, thus allowing us to additionally consider trends over time.

Although our results appear to be disappointing, there are several possible reasons why treatment practices may deviate from guidelines in the UK. First, clinicians may be prepared to delay the decision to switch treatments in those with high CD4 cell count. Instead, they may monitor these measurements closely and may recommend switching only if these measurements start to deteriorate. This hypothesis is supported by our finding of a lower CD4 cell count in those who switched rapidly. Second, the decision to switch treatments is made jointly between the clinician and patient. Some patients may be keener to switch treatments sooner than others, and this may explain our finding of more rapid switching in older individuals, a group who have also been documented to have better adherence to therapy [17,18]. Third, where poor adherence is suspected as a possible cause of viral rebound, the clinician may attempt to address any adherence issues before recommending a treatment change. Of note, a relatively high proportion of patients (26%) did experience viral resuppression despite not

making any changes to their HAART regimen. Although some of these episodes of viraemia may have been viral 'blips', which resolve without any intervention [19], it is likely that many of these patients had an improvement in adherence that led to resuppression. Unfortunately, we do not collect information on adherence from all clinics participating in UK CHIC and so cannot quantify this. Finally, given the increased availability of resistance testing, it is possible that clinicians may wait for the results of a resistance test, either to inform the choice of the next regimen [9] or, in some cases, to rule out nonadherence as a cause of viral rebound. We did not incorporate resistance testing into our analyses. However, among patients with viral rebound, only 46% had a resistance test performed after rebound and prior to any change in therapy; the median time from requesting a resistance test to the result being available was only 4 weeks, suggesting that this was unlikely to explain any delay seen.

There may also be explanations as to why treatment switches that were made were not always in line with recommendations. Resistance testing, if performed, may have revealed that other drugs from the same class as the failing regimen remained active and this may remove the necessity to add a drug from a new class to the regimen. This is particularly true of the PI class, in which newer drugs in this class [9,20] or the availability of boosted PI regimens or both may mean that it is acceptable to switch drugs within the PI class. In contrast, individuals on a failing NNRTI regimen would be more likely to make a change in line with treatment guidelines given the strong potential for cross-resistance and the low genetic barrier [21] of this class (of note, our study preceded the availability of etravirine in the UK). Finally, if a known toxicity is thought to be the cause of viral rebound, then clinicians may prefer to switch a single drug to allow this toxicity to resolve before changing other drugs in the regimen.

Our review covered a long period from 1998 to 2005 which allowed us to investigate whether there have been any changes in clinical behaviour over time given an increased awareness of the implications of incomplete viral suppression for long-term outcomes [22,23]. The lack of such trends suggests that our results can be generalized to the current 'norm'. However, the long time-span of our study also introduces analytical challenges, as treatment guidelines have evolved over time [9,24–27]. With this in mind, we tried to follow the spirit of the guidelines to determine whether treatment changes were made appropriately, both in terms of the viral load threshold for change ($<$400 copies/ml) and the drugs in the regimen ($\geq$2 new drugs, with at least one from a new class). For pragmatic reasons, we only included the first change to the regimen, although in a handful of cases, further drugs were changed in the subsequent weeks. We did not check whether all drugs in the new regimen, including those from a new class, remained active. Furthermore, because of the lack of clear guidelines for switching treatments in patients who do not achieve an initial response to therapy, we focussed only on those who did achieve an initial response and who then experienced viral load rebound. Guidelines for switching are also very different in patients who are experiencing viral load failure of later lines of therapy, in which limited treatment options are available and the goals of antiretroviral therapy may be different [6,28]. Thus, our results are only generalizable to patients experiencing their first viral load rebound after initial suppression. Of note, although this study included patients starting HAART for the first time, a substantial proportion had already switched at least one drug in their regimen prior to viral load rebound, presumably for toxicity or intensification purposes. Thus, not all patients remained on first-line HAART at the time of viral rebound.

There is increasing evidence to suggest that individuals who are maintained on a failing HAART regimen are at increased risk of resistance development, viral load failure and clinical progression [8,22,29]. However, despite our findings of a delay in switching from a failing regimen, other studies from the UK [30,31] suggest that long-term outcomes of HAART in this country are extremely good. Given the increased number of HAART regimens that are now available, most people experiencing viral load failure on first-line HAART regimens will have several alternative options for active regimens in the future, and rapid treatment switching may now be perceived to be of less importance than in the past. Thus, it may be appropriate to question whether prescriptive guidelines for switching are necessary in patients with first-line viral failure. Although we are unable to address this question directly (we have no information on the switching that would have occurred in the absence of such guidelines), ongoing analyses from this cohort will permit us to investigate the rate of development of resistance, CD4 responses and progression to AIDS and death in those who delay switching compared with those who switch rapidly after treatment failure.

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