

Antiretroviral changes after viral load rebound in the UK Collaborative HIV Cohort (CHIC) Study

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Background

- Due to the potential for drug resistance, UK guidelines recommend that HAART regimens should be switched rapidly in those experiencing virological failure
- Second-line regimens should contain 2, preferably 3, new drugs, ideally with a drug from a new class
- Little is known about treatment changes in clinical practice, nor the impact of these guidelines
- Recent BHIVA audit suggested that there was often a delay between viral load (VL) rebound and a change in treatment

Aims

Among ARV-naïve individuals starting HAART for the first time:

- To determine the time until first treatment switch after reaching the recommended time for switching according to treatment guidelines
- To investigate the proportion of patients making a switch in line with current guidelines
- To determine the factors that influence more rapid switching, and to assess whether practice has changed over time

Patients and methods

- ARV-naïve individuals in UK CHIC who achieved VL suppression (<400 copies/ml) within 6 months of start of HAART (1998-2005)
- Changes for toxicity and viral rebounds in the first 6 months were ignored
- Confirmed VL rebound: 2 consecutive $VL > 400$ copies/ml within 6 months
- Patient follow-up during treatment interruptions (or in 6 months after re-initiation of HAART) was excluded

The UK CHIC Study

- Collaboration of some of the largest HIV clinics in the UK
- Centres provide routinely collected data on all patients aged >16 years seen for care at since 1996
- Data collected include information on demographics, AIDS events, deaths, antiretroviral use, CD4 counts and HIV RNA levels
- Current dataset includes information on 25,274 patients seen at 10 clinical centres up to the end of 2005



Statistical methods

- Time to treatment change described using Kaplan-Meier methods with follow-up censored if patients experienced re-suppression of VL (<400 copies/ml)
- Factors associated with treatment change were identified using proportional hazards regression
- Among those who did switch treatment, logistic regression was used to identify factors associated with whether or not the switch was made in line with guidelines

Results

- 7,931 antiretroviral-naïve patients in UK CHIC started a first HAART regimen between 1998 and 2005
- Of these, 6,480 patients achieved VL suppression within 6 months of starting HAART
- 694 (10.7%) patients experienced a confirmed VL rebound a median of 1.4 years after start of HAART

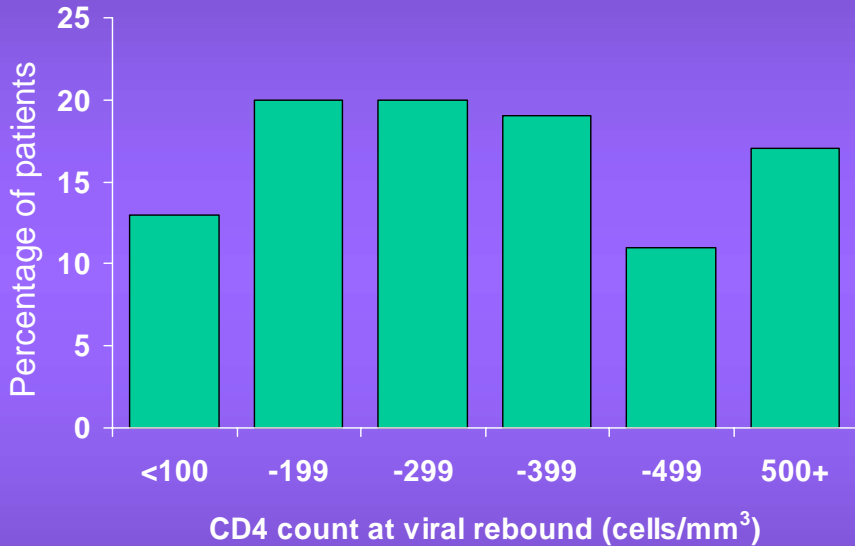
Characteristics of patients with confirmed VL rebound

Total number of patients		694	100
Sex:	Male	493	71.0
Risk group:	Homo/bisexual	309	44.5
	IDU	30	4.3
	Heterosexual	318	45.8
	Other/not known	37	5.3
Age:		37	(32, 41)
Calendar year:	1998-1999	75	10.8
	2000-2002	316	45.5
	2003 or later	303	43.7
ART regimen:	NNRTI	368	53.0
	PI	223	32.1
	Other	103	14.8
≥ 4 drugs in regimen		60	8.6

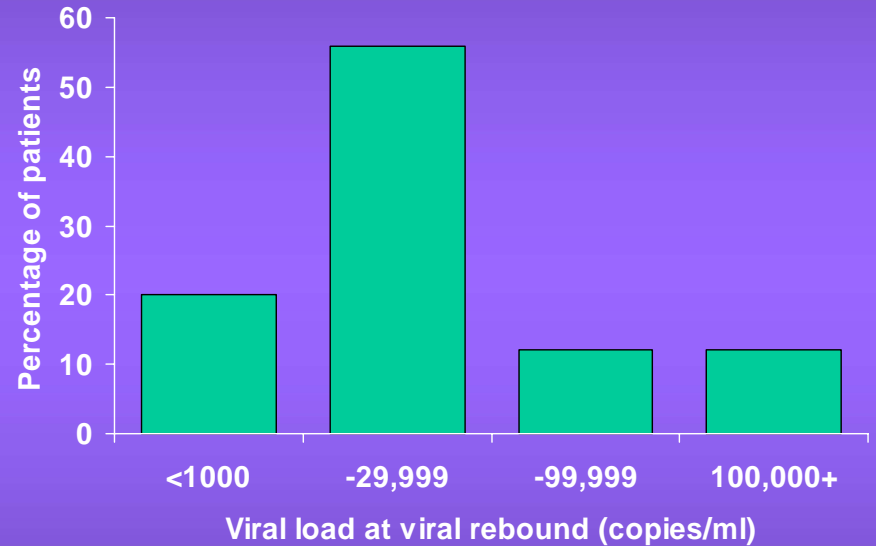
Entries are n (%) or median (IQR) as appropriate



CD4 count and HIV RNA at time of confirmed VL rebound



Median (IQR):
286 (170, 433) cells/mm³



Median (IQR):
3.7 (3.11, 4.47) log₁₀ copies/ml

Changes made to treatment regimen

	n	%
Total number with VL rebound	694	100.0
Next change to regimen		
No change by end of follow-up	198	28.5
Added only recycled drugs	36	5.2
1 new drug	145	20.9
2 new drugs	118	17.0
≥ 3 new drugs	197	28.4
Total making change*	496	71.5

* Includes 30 patients (4.3%) who made a change to their regimen after the first VL >400 copies/ml

Outcomes up to two years after confirmed VL rebound

Proportion:	Status by:		
	6 months	1 year	2 years
Switching	42%	53%	63%
Re-suppressing	22%	25%	27%
On a failing regimen	36%	21%	10%

Predictors of switch after viral rebound

	HR*	95% CI	P-value
Age at rebound (/5 years older)	1.06	0.99-1.13	0.09
Latest CD4 (/100 cells/mm ³ higher)	0.83	0.78-0.89	<0.001
Latest VL (/log ₁₀ copies/ml higher)	1.28	1.14-1.44	<0.001
Calendar year			
	1997-1999	1	0.84
	2000-2002	1.08	0.82-1.43
	2003-2005	1.08	0.79-1.49

*Obtained from a cause-specific proportional hazards model with follow-up censored at time of VL re-suppression

Factors NOT associated with switch were sex, risk group, current ART regimen, number of drugs in current regimen, and previous substitution of drugs



Treatment change in line with guidelines?

	n	%
Number making a treatment change	496	100.0
In line with guidelines	242	48.8
Not in line with guidelines	254	51.2
<i><2 new drugs</i>	46	9.3
<i>No new class</i>	73	14.7
<i><2 new drugs AND no new class</i>	135	27.2

Predictors of making switch in line with guidelines

	Odds ratio*	95% CI	P-value
CD4 at rebound (/100 cells/mm ³ higher)	0.86	0.76- 0.97	0.02
VL at rebound (/log ₁₀ cps/ml higher)	0.52	0.38- 0.71	<0.001
Current ART regimen			
PI	1	-	
NNRTI	2.25	1.31-3.84	<0.001
Other	0.59	0.28-1.27	
Previous drug substitution	0.20	0.12-0.33	<0.001
Calendar year			
1998-2000	1	-	0.24
2001-2003	0.60	0.27-1.31	
2004-2005	0.49	0.21-1.12	

* Results from logistic regression model including all patients who made a switch. Other factors NOT associated with appropriate switch were age, sex, risk group and number of drugs in current regimen



Discussion (1)

- A substantial proportion of patients/clinicians delay changing HAART regimen after confirmed VL rebound
- This proportion has not changed over time, although changes in clinical practice may only become apparent with longer follow-up
- Our results suggest that clinicians may monitor the patient's VL/CD4 count and may change therapy if and when these deteriorate (a 'wait and see' approach)
- Fewer than half of changes made were in line with current guidelines, with most patients adding <2 new drugs and/or no drug from a new class



Discussion (2)

- **Given the limited information collected as part of most cohorts, it is difficult to interpret these findings within a clinical context**
- **Possible explanations for our findings may include:**
 - Patient choice
 - Uncertainty around the significance of low-level viraemia/‘blips’
 - The results from resistance tests to support treatment decisions
 - The availability of new boosted PIs with limited cross-resistance to other PIs
- **The long-term implications of these treatment decisions remain to be investigated**



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