

# The Incidence of AIDS Defining Events (ADEs) at a Current CD4 Count ≥ 200/mm<sup>3</sup> in the Post Combination Antiretroviral Therapy Era

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COHERE is a collaboration of 33 cohorts from across Europe, established in 2005 with the aim of conducting epidemiological research on the prognosis and outcome of HIV-positive persons that require a large sample size. Baseline was defined as the first CD4 ≥200/mm<sup>3</sup> measured after 1/1/1998; PYFU were allocated to CD4 strata (200-349, 350-499, 500-749, 750-999 and >1000/mm<sup>3</sup>) and the individual ADEs allocated to the stratum they occurred in. Recurrences of the same ADE were excluded. Poisson regression was used to model risk of a new ADE in patients with a current CD4 ≥500/mm<sup>3</sup>. Baseline for this analysis was the first CD4 count ≥500/mm<sup>3</sup> measured after 1/1/98.

### BACKGROUND

The incidence and risk of ADEs at CD4 <200/mm<sup>3</sup> is well described, less information is available about the incidence or risk of ADEs at a higher CD4; specifically whether the risk continues to decrease at CD4 >500/mm<sup>3</sup>. Identification of a possible threshold of immunodeficiency above 500/mm<sup>3</sup> has important implications for patient management.

### AIMS

- Describe the incidence of specific ADEs at a CD4 of 200/mm<sup>3</sup> or higher
- Determine the factors associated with developing a new ADEs at a CD4 of 500/mm<sup>3</sup> or higher
- Investigate the potential threshold at which no further increases in CD4 reduce the risk of ADEs

### METHODS

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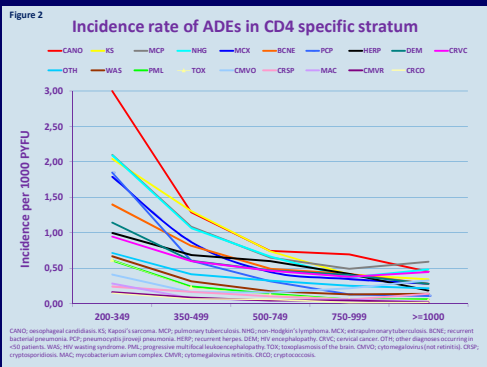
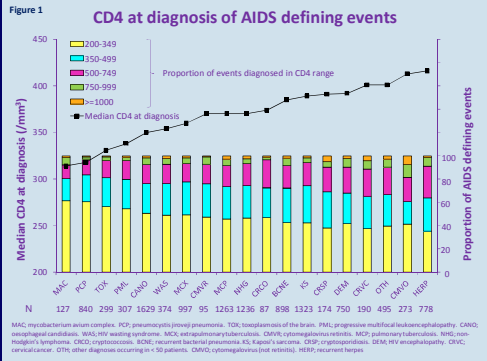
### RESULTS

Characteristics at baseline of 207539 included patients are shown in **Table 1**; 149730 patients were included in the analysis focused on patients with CD4 ≥500/mm<sup>3</sup>.

12135 ADEs were diagnosed at a CD4 count ≥200/mm<sup>3</sup> (**Figure 1**). The most common ADE was oesophageal candidiasis (n=1629, 13.4%), followed by Kaposi's sarcoma (n=1323, 10.9%) and pulmonary tuberculosis (n=1263, 10.4%).

Incidence rates of new ADEs declined from 20.5 per 1000 PYFU, 95% CI 20.0 – 21.1 in patients with a current CD4 200-349/mm<sup>3</sup> to 4.1 per 1000 PYFU (95% CI 3.6 – 4.6) in patients with a current CD4 ≥1000/mm<sup>3</sup>.

Table 1 Patient characteristics at baseline; COHERE collaboration 1998-2010*					
All	(N, %)	CD4<200/mm <sup>3</sup>		CD4≥200/mm <sup>3</sup>	
		N	%	N	%
HIV transmission					
Group					
Male IDU	21973	10.6	14247	9.5	
Female IDU	8526	4.1	6886	4.1	
Male heterosexual	31913	15.4	20763	13.9	
Female heterosexual	41862	20.1	30546	20.4	
Male other	13300	6.4	8923	5.9	
Female other	6314	3.0	4356	2.9	
Prior AIDS	39968	19.3	28911	18.0	
VL < 400*	64370	31.1	70989	52.9	
On cART at baseline	92053	44.4	86322	57.5	
CD4					
Median IQR					
Viral load†					
Median IQR					
Age					
Median IQR					



The number of events, PYFU and event rates within CD4 strata are shown for each ADE in **Figure 2**. Four ADEs, oesophageal candidiasis (1.4; 95% CI 1.3 – 1.5), Kaposi's sarcoma (1.2; 95% CI 1.1 – 1.2), pulmonary (1.1; 95% CI 1.0 – 1.2) and extrapulmonary tuberculosis (1.1; 95% CI 1.0 – 1.1) had overall incidence rates >1 per 1000 PYFU.

Factors associated with the development of a new ADE at a current CD4 ≥500/mm<sup>3</sup> are shown in **Table 2**. Compared to patients with a CD4 of 750-999/mm<sup>3</sup>, those with a current CD4 of 500-749/mm<sup>3</sup> had a significantly higher rate of new ADEs (aIRR 1.22; 95% CI 1.11-1.35) while those with a CD4 of ≥1000/mm<sup>3</sup> had a similar rate.

Among patients with a current CD4 between 500-749/mm<sup>3</sup>, a 50/mm<sup>3</sup> lower CD4 was associated with a 5% increased rate of a new ADE (aIRR 1.05; 95% CI 1.02–1.09, p=0.0013), while in those with a CD4 of 750-999/mm<sup>3</sup>, and ≥1000/mm<sup>3</sup>, there was no evidence that a lower CD4 within these strata was associated with an increased rate (aIRR 1.00 and 1.01 respectively).

Results of various sensitivity analyses are shown in **Table 3**. In an analysis limited to those with only definitive diagnoses, there was a 25% increased rate in those with a current CD4 of 500-749/mm<sup>3</sup>. In patients on cART and with a current viral load < 400 copies/ml, there was a 22% increased rate comparing those with current CD4 of 500-749/mm<sup>3</sup> to 750-999/mm<sup>3</sup>. This increased rate was somewhat higher for malignant ADEs than for non-malignant ADEs.

### CONCLUSIONS

The incidence of specific ADEs varied widely among patients with current CD4 200-499/mm<sup>3</sup> and was generally low among all patients at higher CD4. Compared to those with a current CD4 of 750-999/mm<sup>3</sup>, the rate was significantly increased in those with a CD4 500-749/mm<sup>3</sup> and was similar in those with a current CD4 of ≥1000/mm<sup>3</sup>.

Within CD4 count strata 750-999 and >1000/mm<sup>3</sup>, there was no evidence of a decreasing incidence rate of new ADEs as CD4 increased within the strata.

Results were similar in those on cART with viral suppression and for malignant and non-malignant events, suggesting immune mediated mechanisms rather than HIV replication are responsible for this increased rate and that persons with HIV infection are not fully immune reconstituted until the CD4 increases above 750/mm<sup>3</sup>.

Table 2 Factors associated with a new ADE while CD4 ≥ 500/mm <sup>3</sup>						
Current CD4	Events	PYFU	Univariate		Multivariate	
			aIRR	95% CI	aIRR	95% CI
500-749/mm <sup>3</sup>	117	13039	1.26	1.23-1.29	1.22	1.11-1.35
750-999/mm <sup>3</sup>	250	13839	1.00	-	1.00	-
≥1000/mm <sup>3</sup>	113	64120	0.95	0.82-1.10	0.96	0.86-1.16
<b>HIV transmission</b>						
Group	Male IDU	1.13	0.99-1.28	0.86	1.21	1.06-1.38
Female IDU	1.50	1.28-1.77	<0.001	1.62	1.37-1.92	<0.001
Male heterosexual	0.86	0.76-0.97	0.015	0.94	0.74-0.96	0.0002
Female heterosexual	0.86	0.77-0.95	0.0043	0.90	0.80-1.01	0.076
Male other	0.87	0.72-1.04	0.13	0.88	0.73-1.06	0.16
Female other	1.14	0.90-1.43	0.28	1.23	0.97-1.54	0.086
<b>Current VL</b>						
<400	1.00	-	-	-	1.00	-
400 - 10000	1.28	1.16-1.42	<0.001	0.91	0.78-1.05	0.19
>10000	2.60	2.36-2.85	<0.001	1.68	1.45-1.95	<0.001
<b>Age</b>						
Per 10 yr older	1.03	0.99-1.08	0.13	1.15	1.10-1.20	<0.001
FU CD4 < 200*	1.22	1.14-1.31	<0.001	1.18	1.11-1.27	<0.001
FU VL < 400*	0.91	0.90-0.92	<0.001	0.92	0.90-0.93	<0.001

Table 3 Factors associated with a new ADE event while CD4 ≥ 500/mm <sup>3</sup>						
Including definitive diagnoses only	Events	PYFU	Sensitivity analyses		Multivariate model†	
			aIRR	95% CI	aIRR	95% CI
500-749/mm <sup>3</sup>	117	13039	1.26	1.23-1.29	1.25	1.07-1.45
750-999/mm <sup>3</sup>	250	13839	1.00	-	1.00	-
≥1000/mm <sup>3</sup>	113	64120	1.00	-	1.00	-
<b>Viral load &lt; 400 on combination antiretroviral therapy</b>						
500-749/mm <sup>3</sup>	106	23058	1.00	-	1.22	1.07-1.38
750-999/mm <sup>3</sup>	330	88750	1.7	3.3-4.1	1.00	-
≥1000/mm <sup>3</sup>	152	48085	1.3	2.8-3.8	0.89	0.74-1.09
<b>Malignant ADEs</b>						
500-749/mm <sup>3</sup>	540	354069	1.5	1.4-1.7	1.57	1.29-1.92
750-999/mm <sup>3</sup>	122	13839	1.0	0.7-1.0	1.00	-
≥1000/mm <sup>3</sup>	61	64120	1.0	0.7-1.2	1.26	0.94-1.65
<b>Non-malignant ADEs</b>						
500-749/mm <sup>3</sup>	1731	354069	4.9	4.7-5.1	1.15	1.03-1.27
750-999/mm <sup>3</sup>	526	13839	3.8	3.5-4.1	1.00	-
≥1000/mm <sup>3</sup>	204	64120	3.2	2.7-3.6	0.94	0.80-1.10

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