BACKGROUND
The incidence and risk of ADEs at CD4 <200/mm³ 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/mm³. Identification of a possible threshold of immunodeficiency above 500/mm³ has important implications for patient management.

AIMS
• Describe the incidence of specific ADEs at a CD4 of 200/mm³ or higher
• Determine the factors associated with developing a new ADE at a CD4 of 500/mm³ or higher
• Investigate the potential threshold at which no further increases in CD4 reduce the risk of ADEs

METHODS
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 requires a large sample size. Baseline was defined as the first CD4 ≥200/mm³ measured after 1/1/1998. PYFU were allocated to CD4 strata (200-349, 350-499, 500-749, 750-999 and >1000/mm³) 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/mm³. Baseline for this analysis was the first CD4 count ≥500/mm³ measured after 1/1/98.

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/mm³.

12135 ADEs were diagnosed at a CD4 count ≥200/mm³ (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=1253, 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/mm³ to 4.1 per 1000 PYFU (95% CI 3.6 – 4.4) in patients with a current CD4 >1000/mm³.

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/mm³ are shown in Table 2. Compared to patients with a CD4 of 750-999/mm³, those with a current CD4 of 500-749/mm³ had a significantly higher rate of new ADEs (aIRR 1.22; 95% CI 1.11-1.33) while those with a CD4 of ≤400/mm³ had a similar rate.

Among patients with a current CD4 between 500-749/mm³, a 50/mm³ 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/mm³, and ≥1000/mm³, there was no evidence that a lower CD4 within these strata was associated with an increased rate (aIRR 1.00 and 1.03 respectively).

Results of various sensitivity analyses are shown in Table 2. In an analysis limited to those with only definitive diagnoses, there was a 2% increased rate in those with a current CD4 of 500-749/mm³. 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/mm³ to 750-999/mm³. 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/mm³ and was generally low among all patients at higher CD4. Compared to those with a current CD4 of 750-999/mm³, the rate was significantly increased in those with a current CD4 of 500-749/mm³ and was similar in those with a current CD4 of ≥1000/mm³.

Within CD4 count strata 750-999 and ≥1000/mm³, 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/mm³.