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## The incidence of AIDS-defining illnesses at a current CD4 count 200 cells/ L in the post-combination antiretroviral therapy era

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**Abstract:** **BACKGROUND:** Few studies consider the incidence of individual AIDS-defining illnesses (ADIs) at higher CD4 counts, relevant on a population level for monitoring and resource allocation. **METHODS:** Individuals from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) aged 14 years with 1 CD4 count of 200  $\mu$ L between 1998 and 2010 were included. Incidence rates (per 1000 person-years of follow-up [PYFU]) were calculated for each ADI within different CD4 strata; Poisson regression, using generalized estimating equations and robust standard errors, was used to model rates of ADIs with current CD4 500/ $\mu$ L. **RESULTS:** A total of 12 135 ADIs occurred at a CD4 count of 200 cells/ $\mu$ L among 207 539 persons with 1 154 803 PYFU. Incidence rates declined from 20.5 per 1000 PYFU (95% confidence interval [CI], 20.0-21.1 per 1000 PYFU) with current CD4 200-349 cells/ $\mu$ L to 4.1 per 1000 PYFU (95% CI, 3.6-4.6 per 1000 PYFU) with current CD4 1000 cells/ $\mu$ L. Persons with a current CD4 of 500-749 cells/ $\mu$ L had a significantly higher rate of ADIs (adjusted incidence rate ratio [aIRR], 1.20; 95% CI, 1.10-1.32), whereas those with a current CD4 of 1000 cells/ $\mu$ L had a similar rate (aIRR, 0.92; 95% CI, .79-1.07), compared to a current CD4 of 750-999 cells/ $\mu$ L. Results were consistent in persons with high or low viral load. Findings were stronger for malignant ADIs (aIRR, 1.52; 95% CI, 1.25-1.86) than for nonmalignant ADIs (aIRR, 1.12; 95% CI, 1.01-1.25), comparing persons with a current CD4 of 500-749 cells/ $\mu$ L to 750-999 cells/ $\mu$ L. **DISCUSSION:** The incidence of ADIs was higher in individuals with a current CD4 count of 500-749 cells/ $\mu$ L compared to those with a CD4 count of 750-999 cells/ $\mu$ L, but did not decrease further at higher CD4 counts. Results were similar in patients virologically suppressed on combination antiretroviral therapy, suggesting that immune reconstitution is not complete until the CD4 increases to >750 cells/ $\mu$ L.

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# The Incidence of AIDS-Defining Illnesses at a Current CD4 Count $\geq 200$ Cells/ $\mu\text{L}$ in the Post-Combination Antiretroviral Therapy Era

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(See the HIV/AIDS Major Article by Lesko et al on pages 1027–37 and the Editorial Commentary by Lange on pages 1048–50.)

**Background.** Few studies consider the incidence of individual AIDS-defining illnesses (ADIs) at higher CD4 counts, relevant on a population level for monitoring and resource allocation.

**Methods.** Individuals from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) aged  $\geq 14$  years with  $\geq 1$  CD4 count of  $\geq 200$   $\mu\text{L}$  between 1998 and 2010 were included. Incidence rates (per 1000 person-years of follow-up [PYFU]) were calculated for each ADI within different CD4 strata; Poisson regression, using generalized estimating equations and robust standard errors, was used to model rates of ADIs with current CD4  $\geq 500$   $\mu\text{L}$ .

**Results.** A total of 12 135 ADIs occurred at a CD4 count of  $\geq 200$  cells/ $\mu\text{L}$  among 207 539 persons with 1 154 803 PYFU. Incidence rates declined from 20.5 per 1000 PYFU (95% confidence interval [CI], 20.0–21.1 per 1000 PYFU) with current CD4 200–349 cells/ $\mu\text{L}$  to 4.1 per 1000 PYFU (95% CI, 3.6–4.6 per 1000 PYFU) with current CD4  $\geq 1000$  cells/ $\mu\text{L}$ . Persons with a current CD4 of 500–749 cells/ $\mu\text{L}$  had a significantly higher rate of ADIs (adjusted incidence rate ratio [aIRR], 1.20; 95% CI, 1.10–1.32), whereas those with a current CD4 of  $\geq 1000$

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<sup>a</sup>Members of the study group are listed in the Appendix.

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cells/ $\mu\text{L}$  had a similar rate (aIRR, 0.92; 95% CI, .79–1.07), compared to a current CD4 of 750–999 cells/ $\mu\text{L}$ . Results were consistent in persons with high or low viral load. Findings were stronger for malignant ADIs (aIRR, 1.52; 95% CI, 1.25–1.86) than for nonmalignant ADIs (aIRR, 1.12; 95% CI, 1.01–1.25), comparing persons with a current CD4 of 500–749 cells/ $\mu\text{L}$  to 750–999 cells/ $\mu\text{L}$ .

**Discussion.** The incidence of ADIs was higher in individuals with a current CD4 count of 500–749 cells/ $\mu\text{L}$  compared to those with a CD4 count of 750–999 cells/ $\mu\text{L}$ , but did not decrease further at higher CD4 counts. Results were similar in patients virologically suppressed on combination antiretroviral therapy, suggesting that immune reconstitution is not complete until the CD4 increases to  $>750$  cells/ $\mu\text{L}$ .

**Keywords.** CD4; virologic suppression; cART; AIDS defining illnesses; immune reconstitution.

The decline in AIDS-defining illnesses (ADIs) and deaths following the introduction of combination antiretroviral therapy (cART) in 1996–1997 has been well documented [1–3]. Studies have also described the decline in individual ADIs, such as non-Hodgkin lymphoma, *Pneumocystis jirovecii* pneumonia, *Mycobacterium avium* complex, Kaposi sarcoma, tuberculosis, and cytomegalovirus infections [1, 4–7]. Prior to the introduction of cART, and in antiretroviral-naïve patients, the incidence of ADIs according to current CD4 count has been described [8, 9]. There is preliminary evidence that the risk of ADIs continues to decrease as CD4 count increases, even at CD4 counts  $>500$  cells/ $\mu\text{L}$  [9, 10], but, to our knowledge, there are few studies that have specifically considered the incidence of individual ADIs at higher CD4 counts [10, 11]. Previous work from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) has shown that the risk of a new ADI or death continued to decrease in patients with virological suppression where the current CD4 count was  $>500$  cells/ $\mu\text{L}$ , but the study did not report the incidence of individual ADIs or investigate whether there was an additional decrease at higher CD4 counts [12]. Approximately 80% of persons on cART are virologically suppressed [13], but it is also relevant to determine the incidence of ADIs overall and for specific diagnoses on a population level, both for monitoring and for resource allocation. Knowledge of the risk of a specific ADI at a given CD4 lymphocyte count and the identification of a possible threshold of immunodeficiency have important implications for patient management, as well as providing an important reference for the incidence of a wide range of ADIs at higher CD4 counts.

The aims of this study were to describe the incidence of specific ADIs at CD4 counts of  $\geq 200$  cells/ $\mu\text{L}$ , according to the latest CD4 count across a wide range of CD4 counts using data from COHERE, a European collaboration of HIV cohort studies. Our second objective was to determine the factors associated with developing a new ADI at a CD4 count of  $\geq 500$  cells/ $\mu\text{L}$ .

## METHODS

### Patients

COHERE is a collaboration of 33 cohorts from across Europe. COHERE was established in 2005 and merges data from

already established cohorts to conduct epidemiological research on the prognosis of HIV-positive persons where the individual contributing cohorts are not adequately powered. Local ethical committee and/or other regulatory approval were obtained as applicable according to local and/or national regulations in all cohorts unless no such requirement applied to observational studies according to national regulations. Each cohort submits information using the standardized HIV Collaboration Data Exchange Protocol (HICDEP; [14]) to coordinating centers at the Copenhagen HIV Programme (CHIP), Copenhagen, Denmark, or the Institut de Santé Publique d'Épidémiologie et de Développement (ISPED), Bordeaux, France. Data collected and analyzed herein were part of the 2011 merger, and included data from the period 1998–2010. Data collected include information on patient demographics, use of cART, CD4 cell counts, ADIs, and deaths. ADIs were diagnosed using the 1993 classification from the Centers for Disease Control and Prevention [15]. COHERE is part of EuroCOORD, a network of excellence established in 2010 (<http://www.eurocoord.net/>). Further details about COHERE can be found at [www.cphiv.dk](http://www.cphiv.dk) and <http://etudes.isped.u-bordeaux2.fr/cohere/>. All individuals in COHERE aged  $\geq 14$  years with at least 1 CD4 count of  $\geq 200$  cells/ $\mu\text{L}$  measured after 1 January 1998 with some prospective follow-up were included in the analyses, regardless of their current antiretroviral treatment or treatment history.

### Statistical Methods

Baseline was defined as the first recorded CD4 count  $\geq 200$  cells/ $\mu\text{L}$  measured after 1 January 1998 (corresponding to the widespread availability of cART); person-years of follow-up (PYFU) were allocated to CD4 count strata (200–349, 350–499, 500–749, 750–999, and  $\geq 1000$  cells/ $\mu\text{L}$ ) and the individual ADIs allocated to the stratum they occurred in. Follow-up was censored when the CD4 count fell below 200 cells/ $\mu\text{L}$  (and was subsequently reentered into the analysis if the CD4 count rose to  $\geq 200$  cells/ $\mu\text{L}$ ) or at last CD4 count. Incidence rates were calculated for each individual ADI occurring in  $>50$  individuals, and other diagnoses were combined to create an “other” category. Recurrences of the same ADI were excluded but persons could contribute  $>1$  event to the analysis and moved through CD4 count categories according to their current CD4 count.

Poisson regression, using generalized estimating equations and robust standard errors, were used to model rates of a new ADI in persons with a current CD4  $\geq 500$  cells/ $\mu\text{L}$ . Baseline for this analysis was the first CD4 count  $\geq 500$  cells/ $\mu\text{L}$  measured after January 1998. Standard adjustments for other factors included age, sex, HIV transmission group, ethnic origin, HIV RNA load, duration of immune suppression (proportion of follow-up time with CD4 count  $\leq 200$  cells/ $\mu\text{L}$ , including prior to baseline for this analysis) or of controlled viremia (viral load [VL]  $< 400$  copies/mL including time prior to baseline), and starting cART. Within each CD4 count stratum, the current CD4 count was included as a continuous variable to see if there was a trend of an increasing rate of new ADIs at lower CD4 counts within CD4 stratum.

We performed a number of sensitivity analyses to investigate if our results were robust in different populations. We excluded the first 6 months of follow-up to see if patients presenting with ADIs were biasing our findings, and also limited analyses to those with a definitive diagnosis, defined by cohorts according to the 1993 guidelines [15] and follow-up where the current CD4 count had been measured within the previous 6 months. We also repeated the analysis in antiretroviral-naive persons by right-censoring at starting cART, in those with VL  $< 400$  copies/mL or  $> 400$  copies/mL, and in follow-up limited to the first 6 months after initiation of cART. We also considered new malignant ADIs (cervical cancer, Kaposi sarcoma, non-Hodgkin lymphoma) and nonmalignant disease (all other ADIs) separately, as well as pulmonary and extrapulmonary tuberculosis. A subset of individuals had information available on CD8 count and CD4 and CD8 percentages; additional models investigated whether adjusting for these immunological markers, or ratios of these, further explained our findings.

All analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

Of 250 553 individuals included in participating cohorts in COHERE, 24 481 were excluded because they had no CD4 counts recorded of  $\geq 200$  cells/ $\mu\text{L}$ ; a further 218 were excluded because sex or information on date of birth was missing; 1930 were excluded because they were aged  $< 14$  years; and 16 385 were excluded because they had no prospective follow-up, leaving 207 539 persons included in the analysis. Characteristics at baseline are shown in Table 1; 149 730 persons were included in the analysis focused on those with CD4 counts  $\geq 500$  cells/ $\mu\text{L}$ . The most common HIV transmission group was men who have sex with men (MSM). The median CD4 at baseline was 378 cells/ $\mu\text{L}$  (interquartile range [IQR], 264–548 cells/ $\mu\text{L}$ ), and 39 968 (19.3%) had a prior AIDS diagnosis.

A total of 12 135 of the ADIs observed occurred at a CD4 count of  $\geq 200$  cells/ $\mu\text{L}$ . The most common ADI was esophageal candidiasis ( $n = 1629$  [13.4%]), followed by Kaposi sarcoma ( $n = 1323$  [10.9%]) and pulmonary tuberculosis ( $n = 1263$  [10.4%]). The median CD4 count at diagnosis ranged from 314 cells/ $\mu\text{L}$  (IQR, 252–450 cells/ $\mu\text{L}$ ) in persons diagnosed with disseminated *Mycobacterium avium* complex to 416 cells/ $\mu\text{L}$  (IQR, 310–574 cells/ $\mu\text{L}$ ) in persons diagnosed with recurrent herpes infections. Incidence rates of new ADIs declined from 20.5 per 1000 PYFU (95% confidence interval [CI], 20.0–21.1 per 1000 PYFU) in those with a current CD4 count of 200–349 cells/ $\mu\text{L}$  to 4.1 per 1000 PYFU (95% CI, 3.6–4.6 per 1000 PYFU) where current CD4 count was  $\geq 1000$  cells/ $\mu\text{L}$ . The number of events, PYFU, and event rates within each CD4 count stratum are shown for each ADI in Table 2, ordered from the highest overall incidence to the lowest. Four ADIs—esophageal candidiasis (1.4 [95% CI, 1.3–1.5]), Kaposi sarcoma (1.2 [95% CI, 1.1–1.2]), pulmonary tuberculosis (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 ADI at a current CD4 count of  $\geq 500$  cells/ $\mu\text{L}$  are shown in Table 3. Male and female intravenous drug users had an increased rate of developing a new ADI, whereas male and female heterosexuals had a lower rate. Persons with a current VL  $> 10\,000$  copies/mL had a higher rate, as did older individuals and those with a higher proportion of follow-up time with a CD4 count  $< 200$  cells/ $\mu\text{L}$ . A higher proportion of follow-up time with VL  $< 400$  copies/mL was associated with a lower rate of new ADIs. Compared to persons with a CD4 count of 750–999 cells/ $\mu\text{L}$ , those with a current CD4 count of 500–749 cells/ $\mu\text{L}$  had a significantly higher rate of new ADIs (adjusted incidence rate ratio [aIRR], 1.20 [95% CI, 1.10–1.32],  $P < .0001$ ), whereas those with a CD4 count of  $\geq 1000$  cells/ $\mu\text{L}$  had a similar rate (aIRR, 0.92 [95% CI, .79–1.07],  $P = .26$ ). Among persons with a current CD4 of 500–749 cells/ $\mu\text{L}$ , a 50-cells/ $\mu\text{L}$ -lower CD4 count was associated with a 6% increased rate of a new ADI (aIRR, 1.06 [95% CI, 1.02–1.10],  $P < .0001$ ), whereas in those with a CD4 count of 750–999 cells/ $\mu\text{L}$ , there was no evidence that a lower CD4 count within this stratum was associated with an increased rate (aIRR, 1.01 [95% CI, .96–1.07],  $P = .72$ ), or in those with a current CD4 of  $\geq 1000$  cells/ $\mu\text{L}$  (aIRR, 1.00 [95% CI, .98–1.03],  $P = .86$ ).

We performed several sensitivity analyses; those considering viral suppression or antiretroviral treatment are shown in Figure 1. Results were consistent in antiretroviral-naive patients. There was no evidence that the relationship between current CD4 and ADIs differed according to level of viral suppression ( $P = .49$ , test for interaction). Compared to patients with a current CD4 count of 750–999 cells/ $\mu\text{L}$ , those with a CD4 count of 500–749 cells/ $\mu\text{L}$  had significantly higher rates of new ADIs after adjustment in those with a low ( $< 400$  copies/mL)

**Table 1. Characteristics of Included Persons at Baseline; Collaboration of Observational HIV Epidemiological Research Europe (COHERE), 1998–2010<sup>a</sup>**

Characteristic	CD4 Count $\geq 200$ Cells/ $\mu$ L		CD4 Count $\geq 500$ Cells/ $\mu$ L	
	No.	%	No.	%
All	207 539	100	149 730	100
HIV transmission group				
MSM	83 831	40.4	64 929	43.4
Male IDU	21 973	10.6	14 247	9.5
Female IDU	8526	4.1	6066	4.1
Male heterosexual	31 913	15.4	20 763	13.9
Female heterosexual	41 682	20.1	30 546	20.4
Male other	13 300	6.4	8823	5.9
Female other	6314	3.0	4356	2.9
Country of origin				
Developed country	86 445	41.7	65 037	43.4
Africa	20 425	9.8	13 018	8.7
Other	9498	4.6	6445	4.3
Unknown	91 171	43.9	65 230	43.6
Ethnic origin				
White	68 127	32.8	51 939	34.7
Other	18 250	8.8	12 036	8.0
Unknown	121 162	58.4	85 755	57.3
Prior AIDS at baseline	39 968	19.3	26 931	18.0
VL $< 400$ copies/mL <sup>b</sup> at baseline	66 370	33.1	76 989	52.9
On cART at baseline	92 103	44.4	86 198	57.5
ART naive at baseline	94 339	45.5	50 055	33.4
Measurements at Baseline	Median	IQR	Median	IQR
CD4	378	265–548	580	530–680
VL <sup>b</sup>	3.30	2.55–4.44	2.60	1.70–3.74
Baseline date (month/year)	12/2001	7/1998–11/2005	12/2002	7/1999–7/2006
Age	37	31–43	37	32–44

Abbreviations: ART, antiretroviral therapy; cART, combination ART; HIV, human immunodeficiency virus; IDU, intravenous drug user; IQR, interquartile range; MSM, men who have sex with men; VL, viral load.

<sup>a</sup> Baseline defined as first CD4  $\geq 200$  cells/ $\mu$ L (or  $\geq 500$  cells/ $\mu$ L) after 1 January 1998.

<sup>b</sup> Viral load data available for 200 827 (96.7%) of those with baseline CD4 count  $\geq 200$  cells/ $\mu$ L and 145 529 (97.2%) of those with baseline CD4 count  $\geq 500$  cells/ $\mu$ L at baseline, respectively.

or high viral load ( $> 400$  copies/mL; Figure 1). During the first 6 months of cART, slightly different results were found (Figure 1). After adjustment, compared to patients with a current CD4 of 750–999 cells/ $\mu$ L, there was no increased rate of a new ADI in those with either lower (500–749 cells/ $\mu$ L) or higher current CD4 counts ( $> 1000$  cells/ $\mu$ L). Additional sensitivity analyses are shown in Table 4. We removed the first 6 months of follow-up for each individual due to concerns that a significant number of new ADIs might be diagnosed at, or soon after, initial presentation, and found a 19% increased incidence of a new ADI in those with a current CD4 count of 500–749 cells/ $\mu$ L compared to those with a current CD4 count of 750–999 cells/ $\mu$ L (aIRR, 1.19 [95% CI, 1.08–1.32]). In an analysis limited to those with only definitive diagnoses, there was a 22%

increased rate in those with a current CD4 count of 500–749 cells/ $\mu$ L (aIRR, 1.22 [95% CI, 1.05–1.41]). This increased rate was somewhat higher for malignant ADIs (aIRR, 1.52 [95% CI, 1.25–1.86]) than for nonmalignant ADIs (aIRR, 1.12 [95% CI, 1.01–1.25]). Adjusting additionally for CD8, missing for approximately 20% of persons, did not alter our findings (Table 4), but CD8 was a predictor of a new ADI; a CD8 count  $> 1000$  cells/ $\mu$ L was associated with a higher rate of new ADIs (aIRR, 1.16 [95% CI, 1.06–1.27],  $P = .0009$ ).

## DISCUSSION

This analysis included  $> 200\ 000$  HIV-infected individuals with 1 154 803 PYFU while at a current CD4 count of  $\geq 200$  cells/ $\mu$ L,

**Table 2. Crude Incidence Rates (Per 1000 Person-years of Follow-up) of AIDS-Defining Illnesses in CD4-Specific Strata**

ADI	Stratum (Cells/ $\mu$ L)					
	All	200–349	350–499	500–749	750–999	$\geq$ 1000
PYFU	1 154 803	274 441	324 134	354 069	138 039	64 120
Events	12 135	5632	3319	2271	648	265
Rate (95% CI)	10.5 (10.3–10.7)	20.5 (20.0–21.1)	10.2 (9.9–10.6)	6.4 (6.2–6.7)	4.7 (4.3–5.1)	4.1 (3.6–4.6)
AIDS defining illness						
Esophageal candidiasis	1629/1.4/1.3–1.5	823/3.0/2.8–3.2	418/1.3/1.2–1.4	263/0.7/0.7–.8	96/0.7/0.6–.8	29/0.5/0.3–.6
Kaposi's sarcoma	1323/1.2/1.1–1.2	560/2.0/1.9–2.2	423/1.3/1.2–1.4	261/0.7/0.7–.8	57/0.4/0.3–.5	22/0.3/0.2–.5
Pulmonary tuberculosis	1263/1.1/1.0–1.1	576/2.1/1.9–2.3	351/1.1/1.0–1.2	230/0.7/0.6–.7	68/0.5/0.4–.6	38/0.6/0.4–.8
Non-Hodgkins lymphoma	1236/1.1/1.0–1.1	574/2.1/1.9–2.3	345/1.1/1.0–1.2	235/0.7/0.6–.8	51/0.4/0.3–.5	31/0.5/0.3–.7
Extrapulmonary tuberculosis	997/0.9/0.8–.9	491/1.8/1.6–2.0	282/0.9/0.8–1.0	158/0.5/0.4–.5	48/0.4/0.3–.5	18/0.3/0.2–.4
Bacterial pneumonia	898/0.8/0.7–.8	384/1.4/1.3–1.5	264/0.8/0.7–.9	174/0.5/0.4–.6	58/0.4/0.3–.5	18/0.3/0.2–.4
<i>Pneumocystis jirovecii</i> pneumonia	840/0.7/0.7–.8	507/1.9/1.7–2.0	196/0.6/0.5–.7	112/0.3/0.3–.4	18/0.1/0.1–.2	7/0.1/0.0–.2
Recurrent herpes simplex	778/0.7/0.6–.7	274/1.0/0.9–1.1	222/0.7/0.6–.8	212/0.6/0.5–.7	58/0.4/0.3–.5	12/0.2/0.1–.3
HIV dementia	750/0.7/0.6–.7	314/1.1/1.0–1.3	196/0.6/0.5–.7	166/0.5/0.4–.5	56/0.4/0.3–.5	18/0.3/0.2–.4
Cervical cancer <sup>a</sup>	190/0.6/0.5–.7	71/0.9/0.7–1.2	53/0.6/0.4–.8	44/0.5/0.3–.6	14/0.4/0.2–.6	8/0.5/0.2–.9
Other ADIs occurring in <50 persons	495/0.4/0.4–.5	196/0.7/0.6–.8	135/0.4/0.4–.5	115/0.3/0.3–.4	35/0.3/0.2–.3	14/0.2/0.1–.4
HIV wasting syndrome	374/0.3/0.3–.4	183/0.7/0.6–.8	102/0.3/0.3–.4	62/0.2/0.1–.2	18/0.1/0.1–.2	9/0.1/0.1–.3
Progressive multifocal leukoencephalopathy	307/0.3/0.2–.3	167/0.6/0.5–.7	78/0.2/0.2–.3	50/0.1/0.1–.2	8/0.1/0.0–.1	4/0.1/0.0–.2
Toxoplasmosis of brain	299/0.3/0.2–.3	169/0.6/0.5–.7	74/0.2/0.2–.3	44/0.1/0.1–.2	9/0.1/0.0–.1	3/0.1/0.0–.1
Cytomegalovirus (nonretinitis)	273/0.2/0.2–.3	113/0.4/0.3–.5	53/0.2/0.1–.2	56/0.2/0.1–.2	30/0.2/0.1–.3	21/0.3/0.2–.5
Cryptosporidiosis	174/0.2/0.1–.2	66/0.2/0.2–.3	54/0.2/0.1–.2	37/0.1/0.1–.1	8/0.1/0.0–.1	9/0.1/0.1–.3
<i>Mycobacterium avium</i> complex	127/0.1/0.1–.1	78/0.3/0.2–.4	24/0.1/0.0–.1	15/0.0/0.0–.1	8/0.1/0.0–.1	2/0.0/0.0–.1
Cytomegalovirus retinitis	95/0.1/0.1–.1	45/0.2/0.1–.2	27/0.1/0.1–.1	16/0.1/0.0–.1	6/0.0/0.0–.1	1/0.0/0.0–.1
Cryptococcosis	87/0.1/0.1–.1	41/0.2/0.1–.2	22/0.1/0.0–.1	21/0.1/0.0–.1	2/0.0/0.0–.1	1/0.0/0.0–.1

Data are presented as events/rate/95% CI for the rate.

Abbreviations: ADI, AIDS-defining illness; CI, confidence interval; HIV, human immunodeficiency virus; PYFU, person-years of follow-up.

<sup>a</sup> PYFU totaled 313 010 in females; 75 173, 88 209, 94 734, 37 084, and 17 811 in the CD4 count strata 200–349, 350–499, 500–749, 750–999, and  $\geq$ 1000 cells/ $\mu$ L, respectively.

including almost 150 000 persons and >550 000 PYFU with a current CD4 count of  $\geq$ 500 cells/ $\mu$ L, and described the incidence of the 18 most commonly occurring ADIs in European HIV Cohort studies, across a range of current CD4 stratum, up to and including CD4 counts >1000/ $\mu$ L. Compared to patients with a current CD4 count of 750–999 cells/ $\mu$ L, those with a CD4 count of 500–749 cells/ $\mu$ L had a significantly higher rate of new ADIs, whereas those with current CD4 counts of >1000 cells/ $\mu$ L had a similar incidence. Within CD4 count strata 750–999 cells/ $\mu$ L and  $\geq$ 1000 cells  $\mu$ L, there was no evidence of a decreasing incidence of new ADIs within the strata. Highly consistent results were found across a wide range of sensitivity analyses.

The overall rate of new ADIs was low at current CD4 counts  $\geq$ 500 cells/ $\mu$ L, <6 per 1000 PYFU, compared to a rate of >1000 per 1000 PYFU at current CD4 counts <50 cells/ $\mu$ L [9]. We found an increased rate of new ADIs at a current CD4 count of 500–749 cells/ $\mu$ L compared to 750–999 cells/ $\mu$ L or higher

but no evidence of any association between CD4 count and incidence of new ADIs within the 750–999 cells/ $\mu$ L or  $\geq$ 1000 cells/ $\mu$ L category, with quite narrow confidence intervals, suggesting that HIV-infected patients with a CD4 count  $\geq$ 750 cells/ $\mu$ L have no further reduction in risk of new ADIs with higher CD4 counts. We adjusted for other markers of immunological function, such as CD8, CD4 percentage, and CD8 percentage, in the subset of individuals with data, with consistent results (data not shown). There are a number of studies that have shown that having a current CD4 count  $\geq$ 500 cells/ $\mu$ L is beneficial in terms of a combined endpoint of a new ADI and death [9, 10, 12, 16], although these studies have been more limited by power and have not split CD4 count stratum  $\geq$ 500 cells/ $\mu$ L as in this current analysis.

Our results were consistent across a range of sensitivity analyses, and were similar between antiretroviral-naive persons and those who were or were not virologically suppressed, although we were unable to say whether the ADIs experienced were

**Table 3. Factors Associated With a New AIDS-Defining Illness With CD4 Count  $\geq$ 500 Cells/ $\mu$ L**

Factor	Univariate Analysis			Multivariate Analysis		
	IRR	95% CI	PValue	IRR	95% CI	PValue
<b>Current CD4, cells/<math>\mu</math>L</b>						
<750	1.33	1.22–1.46	<.0001	1.20	1.10–1.32	<.0001
750–999	1.00	...	...	1.00	...	...
$\geq$ 1000	0.85	.74–.98	.029	0.92	.79–1.07	.26
<b>HIV transmission group</b>						
MSM	1.00	...	...	1.00	...	...
Male IDU	1.13	.99–1.28	.066	1.24	1.09–1.40	.0009
Female IDU	1.50	1.28–1.77	<.0001	1.61	1.37–1.89	<.0001
Male heterosexual	0.86	.76–.97	.015	0.88	.78–.99	.037
Female heterosexual	0.86	.77–.95	.0043	0.88	.79–.97	.019
Male other	0.87	.72–1.04	.13	0.97	.82–1.14	.71
Female other	1.14	.90–1.43	.28	1.19	.95–1.48	.13
<b>Country of origin</b>						
Developed	1.00	...	...	1.00	...	...
Africa	1.02	.88–1.19	.76	1.26	1.07–1.47	.0047
Other	0.97	.79–1.19	.76	1.13	.92–1.39	.24
Unknown	1.03	.95–1.12	.49	1.10	1.01–1.19	.026
<b>Ethnic origin</b>						
White	1.00	...	...	1.00	...	...
Other	1.02	.88–1.15	.83	1.08	.92–1.26	.37
Unknown	0.85	.78–.92	<.0001	0.85	.78–.92	<.0001
<b>Current VL, copies/mL</b>						
<400	1.00	...	...	1.00	...	...
400–10 000	1.28	1.16–1.42	<.0001	0.94	.82–1.07	.34
>10 000	2.60	2.36–2.85	<.0001	1.68	1.46–1.92	<.0001
<b>Baseline AIDS</b>						
Yes vs no	1.32	1.20–1.45	<.0001	1.57	1.42–1.74	<.0001
<b>Baseline</b>						
Per year later	1.04	1.03–1.06	<.0001	1.04	1.03–1.05	<.0001
<b>Baseline cART</b>						
Yes vs no	0.88	.82–.95	.006	1.24	1.13–1.36	<.0001
<b>Age</b>						
Per 10 y older	1.03	.99–1.08	.13	1.14	1.09–1.18	<.0001
<b>Follow-up CD4 <math>\leq</math> 200<sup>a</sup></b>						
Per 10% longer	1.22	1.14–1.31	<.0001	1.17	1.09–1.25	<.0001
<b>Follow-up VL &lt; 400<sup>a</sup></b>						
Per 10% longer	0.91	.90–0.92	<.0001	0.92	.90–.93	<.0001

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IDU, intravenous drug user; IRR, incidence rate ratio; MSM, men who have sex with men; VL, viral load.

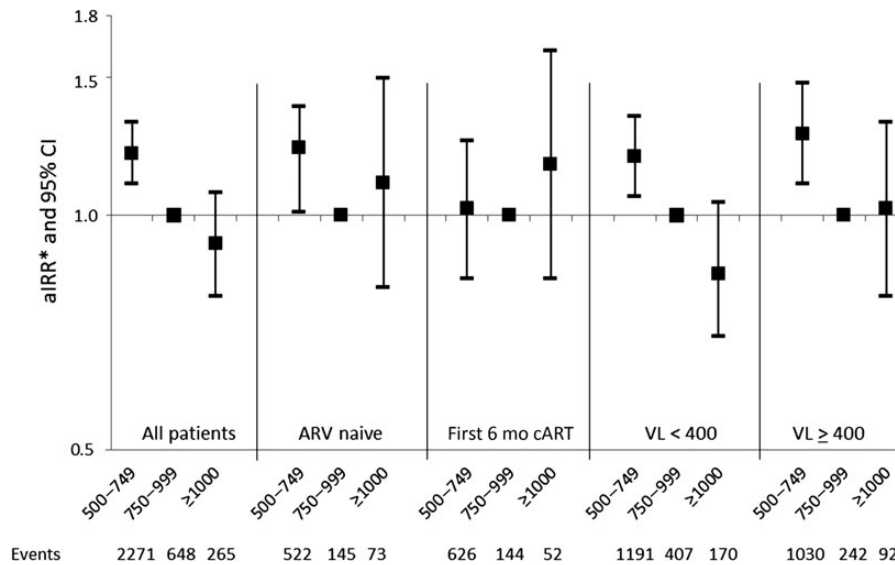
<sup>a</sup> Included as time-updated variable and includes follow-up time prior to baseline.

similar between those on and off cART or with and without virologic suppression. The relationship between current CD4 and ADIs differed slightly during the first 6 months of cART, with no increased rate seen in those with a current CD4 count of 500–749 cells/ $\mu$ L compared to 750–999 cells/ $\mu$ L. The reasons for this are unclear, but could reflect the increased rate of ADIs

in relation to high viremia irrespective of CD4 count during the initial period after starting cART, compared to patients who have been on cART for longer [6].

Our findings were stronger for malignant compared to non-malignant ADIs. The strength of the association was similar for Kaposi sarcoma and non-Hodgkin lymphoma (data not





**Figure 1.** Relationship between current CD4 and AIDS-defining illness with a CD4 count  $\geq 500$  cells/ $\mu\text{L}$ : relationship with current viral load and antiretroviral treatment. \*Adjusted for human immunodeficiency virus transmission category, region of origin, region of presentation, age, baseline date, on combination antiretroviral therapy at baseline, AIDS diagnosis at baseline, CD4 nadir, proportion of follow-up time with CD4 count  $\leq 200$  cells/ $\mu\text{L}$ , and proportion of follow-up time with viral load  $< 400$  copies/mL. Overall model also adjusts for current viral load ( $<$  or  $\geq 400$  copies/mL). Abbreviations: aIRR, adjusted incidence rate ratio; ARV, antiretroviral; cART, combination antiretroviral therapy; CI, confidence interval; VL, viral load.

shown) while the model for cervical cancer did not converge due to insufficient numbers. Kaposi sarcoma is diagnosed across a wide range of CD4 counts independent of CD4 nadir [17]. Most persons in this study had started cART at low CD4 count levels [18], and the onset of non-Hodgkin lymphoma soon after cART initiation might be indicative of immune reconstitution syndrome [19] or subclinical disease. COHERE is an observational study, and confounding by indication is likely to play a significant role. Our findings should not therefore be extrapolated to the “when to start cART” question. In time, the randomized clinical trial START (Strategic Timing of Initiation of Antiretroviral Therapy), with both AIDS and non-AIDS clinical endpoints, will provide unbiased estimates of whether cART is of net clinical benefit to persons commencing therapy at higher CD4 counts. The clinical benefits of cART at higher CD4 counts, where the reduction in risk is statistically but not necessarily clinically significant, need to be balanced against the long-term potential costs and risks of antiretroviral therapy, such as resistance development and adverse events including cardiovascular and renal disease, and malignancies that may add to other comorbidities associated with aging, immune activation, and HIV-related inflammation [20–22].

Other predictors of a new ADI included HIV transmission group and HIV load, as previously reported [23–25]. Both proportion of follow-up time with advanced immunodeficiency (CD4 count  $\leq 200$  cells/ $\mu\text{L}$ ) and with controlled viremia ( $< 400$  copies/mL) were independent predictors of a new ADI. Viremia

copy-years, a different way of measuring exposure to replicating virus, has been shown to predict mortality independent of current CD4 counts among those on cART [26]. This supports findings from the SMART trial, which also showed that the proportion of follow-up time with detectable viremia was, as expected, higher in persons who interrupted vs continued cART, and that the group that interrupted cART had an increased risk of both ADI as well as various types of organ disease [27]. One explanation is that cumulative exposure to uncontrolled HIV replication is a surrogate for cumulative immune system activation, inflammation, and depletion of lymphoid organs from central memory and naive CD4<sup>+</sup> T cells exhausting the immune system [26, 28, 29]. Duration of immune deficiency as a marker of disease progression has been investigated in previous studies with varying degrees of immunodeficiency, endpoints, and results [30–32]. It is likely that circulating CD4 cells are a good but not a perfect marker of the immune capacity in HIV infection. In addition, duration of immunodeficiency likely captures extra data not measured through the CD4 count due to its variability [33] or differences in frequency of measurement between persons.

This study has a number of limitations. We were not able to adjust for hepatitis B or C status, or prior use of disease-specific prophylaxis, as the data were quite limited. The incidence of new ADIs at higher CD4 counts was extremely low, and our results provide some evidence that there is a small increased risk of a new ADI at CD4 counts of 500–750 cells/ $\mu\text{L}$ , but not

**Table 4. Relationship Between Current CD4 and AIDS-Defining Illness With CD4 Count  $\geq 500$  Cells/ $\mu\text{L}$ —Sensitivity Analyses**

CD4 Count	Crude Data				Multivariate Model <sup>a</sup>		
	Events	PYFU	Rate <sup>b</sup>	95% CI	aIRR	95% CI	P Value
Excluding first 6 mo of follow-up for each person							
500–749 cells/ $\mu\text{L}$	1962	334 388	5.9	5.6–6.1	1.19	1.08–1.32	.0004
750–999 cells/ $\mu\text{L}$	583	131 730	4.4	4.1–4.8	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	234	62 016	3.8	3.3–4.3	0.92	.78–1.07	.27
Total	2779	528 133	5.3	5.1–5.5			
Including definitive diagnoses only							
500–749 cells/ $\mu\text{L}$	857	354 069	2.4	2.3–2.6	1.22	1.05–1.41	.011
750–999 cells/ $\mu\text{L}$	261	138 039	1.9	1.7–2.1	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	96	64 120	2.2	2.1–2.3	0.88	.71–1.09	.15
Total	1214	556 228					
CD4 current for 6 mo only							
500–749 cells/ $\mu\text{L}$	2017	308 191	6.5	6.3–6.8	1.20	1.09–1.32	.0003
750–999 cells/ $\mu\text{L}$	587	119 864	4.9	4.5–5.3	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	235	55 487	4.2	3.7–4.8	0.93	.80–1.10	.41
Total	2839	483 541	5.9	5.7–6.1			
Malignant ADIs							
500–749 cells/ $\mu\text{L}$	555	354 069	1.7	1.5–1.8	1.52	1.25–1.86	<.0001
750–999 cells/ $\mu\text{L}$	129	138 039	1.0	.8–1.2	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	61	64 120	1.1	.7–1.2	1.07	.78–1.47	.67
Total	745	556 228	1.4	1.3–1.5			
Nonmalignant ADIs							
500–749 cells/ $\mu\text{L}$	1745	354 069	5.2	5.0–5.5	1.12	1.01–1.25	.026
750–999 cells/ $\mu\text{L}$	542	138 039	4.1	3.8–4.5	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	206	64 120	3.3	2.9–3.8	0.88	.74–1.04	.13
Total	2493	556 228	4.7	4.5–4.9			
Tuberculosis-related ADIs (pulmonary and extrapulmonary)							
500–749 cells/ $\mu\text{L}$	395	354 069	1.2	1.1–1.3	1.12	.90–1.39	.30
750–999 cells/ $\mu\text{L}$	120	138 039	0.9	.8–1.1	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	56	64 120	0.9	.7–1.1	1.05	.75–1.47	.76
Total	571	556 228	1.1	1.0–1.2			
With CD8 values available <sup>c</sup>							
500–749 cells/ $\mu\text{L}$	1662	278 438	6.0	5.7–6.3	1.17	1.05–1.31	.0033
750–999 cells/ $\mu\text{L}$	498	108 793	4.6	4.2–5.0	1.00	...	...
$\geq 1000$ cells/ $\mu\text{L}$	192	50 670	3.8	3.3–4.3	.88	.74–1.05	.16
Total	2352	437 901	5.4	5.2–5.6			

Abbreviations: ADI, AIDS-defining illness; aIRR, adjusted incidence rate ratio; CI, confidence interval; PYFU, person-years of follow-up.

<sup>a</sup> Adjusted for HIV transmission category, region of origin, region of presentation, current viral load, age, baseline date, on combination antiretroviral therapy at baseline, AIDS diagnosis at baseline, CD4 nadir, proportion of follow-up time with CD4  $\leq 200$  cells/ $\mu\text{L}$ , and proportion of follow-up time with viral load  $< 400$  copies/mL.

<sup>b</sup> Rate per 1000 PYFU.

<sup>c</sup> Adjusted additionally for CD8 count ( $\leq 1000$  cells/ $\mu\text{L}$  and  $> 1000$  cells/ $\mu\text{L}$ ).

above this level. Although COHERE includes many of the European observational cohorts, some regions, such as Eastern Europe, are not well represented [18] and the incidence of specific ADIs in these regions may well differ from that presented here [34]. In addition, cohorts have a range of quality assurance systems, and we did not use case verification for any ADIs.

Even small differences in reporting of ADIs could change the incidence rates in these rare events considerably. COHERE does not have complete information on non-AIDS events, and we were unable to assess the relationship between non-AIDS events and high CD4 counts, which form a significant proportion of morbidity and mortality in HIV-positive persons [35].

In conclusion, the incidence of specific ADIs varied widely among persons with current CD4 counts 200–499 cells/ $\mu$ L and was generally low among all persons at higher CD4 counts. Despite this low rate of new ADIs at current CD4 counts  $\geq$ 500 cells/ $\mu$ L, the rate was increased by 20% when compared to those with a current CD4 of 750–999 cells/ $\mu$ L, whereas there were no further significant reductions in ADIs at higher CD4 counts. Results were similar in those with viral suppression and stronger for malignant than nonmalignant events, suggesting that immune-mediated mechanisms other than those induced by HIV replication alone are responsible for this increased rate. Persons with HIV infection are not fully immune reconstituted until the CD4 count increases to  $>$ 750 cells/ $\mu$ L.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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## Appendix

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