

# Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000–2010

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(See the editorial commentary by Furrer on pages 830–1.)

**Background.** There are few recent data on the rates of AIDS-defining opportunistic infections (OIs) among human immunodeficiency virus (HIV)-infected patients in care in the United States and Canada.

**Methods.** We studied HIV-infected participants in 16 cohorts in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) during 2000–2010. After excluding 16 737 (21%) with any AIDS-defining clinical events documented before NA-ACCORD enrollment, we analyzed incident OIs among the remaining 63 541 persons, most of whom received antiretroviral therapy during the observation. We calculated incidence rates per 100 person-years of observation (hereafter, “person-years”) with 95% confidence intervals (CIs) for the first occurrence of any OI and select individual OIs during 2000–2003, 2004–2007, and 2008–2010.

**Results.** A total of 63 541 persons contributed 261 573 person-years, of whom 5836 (9%) developed at least 1 OI. The incidence rate of any first OI decreased over the 3 observation periods, with 3.0 cases, 2.4 cases, and 1.5 cases per 100 person-years of observation during 2000–2003, 2004–2007, and 2008–2010, respectively ( $P_{\text{trend}} < .001$ ); the rates of most individual OIs decreased as well. During 2008–2010, the leading OIs included *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, and disseminated *Mycobacterium avium* complex or *Mycobacterium kansasii* infection.

**Conclusions.** For HIV-infected persons in care during 2000–2010, rates of first OI were relatively low and generally declined over this time.

**Keywords.** AIDS-related opportunistic infections; HIV cohort studies; incidence; prophylaxis; combination antiretroviral therapy; CD4<sup>+</sup> T-lymphocyte count; epidemiology.

Despite declines in the incidence of AIDS-defining opportunistic infections (OIs) following the advent of effective combination antiretroviral therapy (ART) [1–5], OIs remain prominent causes of hospitalization [6, 7] and death [8–11] among human immunodeficiency virus (HIV)-infected persons in the United States and other high-income countries. Concurrent HIV infection and AIDS diagnoses in the United States are common, with few signs of nationwide improvement in recent years among individuals who receive a diagnosis

during late-stage disease [12, 13]. OIs continue to be frequently documented in persons presenting with late-stage HIV disease and may be the sentinel events prompting initial diagnosis [14–17]; however, there are few robust recent data on their incidence rates and types among North American patients in HIV care [3, 4]. The National HIV Surveillance System in the United States and the HIV and AIDS surveillance maintained by the Public Health Agency of Canada are deemed no longer suitable for monitoring OIs rates because of increasing reliance on CD4<sup>+</sup> T-cell count criteria alone for classification of AIDS and resultant substantial OI underreporting [18–20].

OIs continue to occur among patients prescribed ART and at relatively high CD4<sup>+</sup> T-cell counts in both European [5, 21–24] and US [3] cohorts. Their occurrence varies by plasma HIV-1 RNA level [21, 25] and other clinical and demographic factors [1], which may correlate with level of engagement in HIV care. Characterizing the key OIs that continue to occur among North

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American patients in the contemporary ART era, and the CD4<sup>+</sup> T-cell counts at which they occur, provides important data for informing opportunistic illness screening, prophylaxis, and management guidelines [16, 26], and other aspects of HIV care and treatment [27] to reduce OI-associated mortality and morbidity [10, 25]. It is of particular interest and epidemiologic value to characterize the rates of first OIs among patients who have no history of prior AIDS-defining clinical events, not only because such patients compose a well-defined study population, but also because, on average, they better represent the leading edge of the HIV epidemic, namely, contemporary patients with more-recent HIV infections and less extensive treatment histories.

In this report, we focus on incident AIDS-defining infections in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD); rates of AIDS-defining malignancies have been described separately [28]. We sought to assess whether incidence rates of first OIs have continued to decline or have stabilized over the last decade among such HIV-infected patients in care and to describe risk factors for and the epidemiology of these OIs in the recent ART era.

## METHODS

### Study Population

The NA-ACCORD is the largest collaboration of longitudinal HIV cohort studies in North America and has compiled data from >100 clinical sites in the United States and Canada [12, 29]. Briefly, at scheduled intervals, participating HIV cohorts submit data regarding enrolled participants' demographic characteristics, vital status, prescribed antiretrovirals, clinical diagnoses, and dates and results of laboratory tests including HIV load and CD4<sup>+</sup> T-cell count. These clinical data are obtained from routine chart abstractions or scheduled study visits, depending on the cohort. Among clinical cohorts, only persons with  $\geq 2$  clinical visits within 12 months are enrolled into the NA-ACCORD. Death is ascertained by each contributing cohort by using a variety of methods, including the National Death Index, the Social Security Death Index, and state, provincial, and local sources, such as death certificates and electronic medical records. NA-ACCORD data undergo extensive quality control for completeness and accuracy per a standardized protocol before they are combined into harmonized data files at the NA-ACCORD's Data Management Center (University of Washington, Seattle, Washington). The data are reviewed again, organized into analytic files, and analyzed at the NA-ACCORD Epidemiology and Biostatistics Core (Johns Hopkins University, Baltimore, Maryland). The human subjects research activities of the NA-ACCORD and each of the participating cohort studies have been reviewed and approved by their respective local institutional review boards and by the Johns Hopkins School of Medicine.

We analyzed data from HIV-infected persons followed in 16 participating cohorts in NA-ACCORD in the United States and

Canada, listed at the end of the text, during 2000–2010; each cohort agreed to participate and had available OI data for this analysis. Because the protocols for collection and validation of OIs varied across participating cohorts, if a given cohort contributed no OI events of a specific type (eg, cryptococcal meningitis and disseminated coccidioidomycosis) during any one of the 3 analysis periods (2000–2003, 2004–2007, and 2008–2010), that cohort was excluded entirely from analyses of that specific OI during that particular period, to avoid underestimating OI incidence rates. Sensitivity analyses without this exclusion were performed (see below). We further restricted analyses to persons who had no history of any clinical AIDS events at the start of their observation but imposed no restrictions on their CD4<sup>+</sup> T-cell count, HIV load, or prescription of ART at baseline. We analyzed data from 1 January 2000 or the date the participating cohort began contributing data (cohort entry date), whichever came later. The start of observation for each patient (baseline) was the later of the patient's enrollment date in the participating cohort or 1 January 2000. The end of follow-up for each patient was the earliest of the following: the patient's last CD4<sup>+</sup> T-cell count or last HIV load date plus 6 months, the date of the event being analyzed (ie, either the first occurrence of any OI diagnosis or the first occurrence of a specific OI of interest, regardless of prior occurrence of other OIs), the date of death, or the end of the study period (31 December 2010). We defined 3 calendar periods for analyses: 2000–2003 (early period), 2004–2007 (middle period), and 2008–2010 (contemporary ART period). The participating cohorts relied on standard definitions for ART and for prophylaxis to prevent *Pneumocystis pneumonia* (PCP) and disseminated *Mycobacterium avium* complex (MAC) infection [26, 27]. We studied all OIs listed in the Centers for Disease Control (CDC) 2014 surveillance case definition for HIV infection [18, 19, 26], with a few exceptions, as noted in the Appendix. OI events were defined solely on the basis of diagnoses recorded by the participating cohorts.

The CD4<sup>+</sup> T-cell counts and HIV loads at the beginning of each period were those measured nearest to the start of observation in the period (from 6 months before up to 6 months after). We also examined the CD4<sup>+</sup> T-cell count and HIV load closest to incident OI diagnoses (from 6 months before up to 3 months after). Finally, the CD4<sup>+</sup> T-cell count and HIV load at ART initiation were the nearest measurements from 6 months before through the date of ART initiation.

### Statistical Methods

We calculated incidence rates of OI diagnoses per 100 person-years with 95% Poisson confidence intervals (CIs) for the first occurrence of any OI and for the first occurrence of select OIs that were uniformly ascertained in the participating cohorts. Incidence rate estimates for selected OIs were calculated by ignoring the occurrence of other OIs prior to the first occurrence of

the OI of interest. For each OI, we summed the total observation time across participating patients from the start of observation to the end of follow-up for each patient. The incidence of individual OIs was estimated on an event-by-event basis. For example, in the analyses of incident tuberculosis, if during follow-up a person received a diagnosis of another OI, such as candidiasis, before receiving a diagnosis of tuberculosis, they still contributed all available observation time up to the date of tuberculosis diagnosis to the tuberculosis incidence rate calculation. Tests of temporal trends in OI rates were assessed using Poisson regression models.

We also quantified the incidence rates of any OI in a subset of persons who initiated ART during 2000–2010. We estimated the time to any first OI with the Kaplan–Meier method; as a sensitivity analysis, we accounted for the competing risk of death [30, 31], thus providing an overall estimate of the cumulative incidence of the OI event occurring prior to death according to calendar period or CD4<sup>+</sup> T-cell count at ART initiation.

Using Poisson regression, we further explored the clinical and sociodemographic risk factors for select high-incidence OIs, adjusting for the following factors at the start of observation in each calendar period: age, sex, race/ethnicity, CD4<sup>+</sup> T-cell count, HIV load, and cohort. A patient may have contributed observation time to multiple calendar periods. We explored additional modeling strategies by including a variable for whether or not a patient used ART at the start of observation for each calendar period, but we omitted this variable from the final models because of its strong dependence on CD4<sup>+</sup> T-cell count at the start of the period and calendar period. We report incidence rate ratios (IRRs) and 95% CIs. We performed analyses using SAS, version 9.3 (Cary, North Carolina).

## RESULTS

We identified 80 278 HIV-infected persons followed in 16 participating cohorts in NA-ACCORD in the United States and Canada during 2000–2010. After excluding 16 737 persons (21%) with any history of documented AIDS-defining conditions at baseline (see the Appendix for details), we analyzed incident OIs among the remaining 63 541 persons, regardless of their baseline immunologic status or ART use.

### Persons at Risk for Development of OIs

Of persons studied, median age at baseline was 40 years (interquartile range, 34–47 years), 78% were men, 40% were white, 37% were black, 41% were men who have sex with men (MSM), 19% were persons who had injection drug use (IDU) as an HIV risk factor; and 12% were Canadian (Table 1). Median CD4<sup>+</sup> T-cell count at baseline was 360 cells/mm<sup>3</sup> (IQR, 196–557 cells/mm<sup>3</sup>), about one third had a baseline HIV load of <500 copies/mL, and 43% had any documented ART prescription at the start of observation for this analysis. The subset of persons who were antiretroviral naive at baseline and initiated

ART sometime during their observation had largely similar demographic characteristics to those of all persons in our study population (Table 1).

During 2000–2010, 63 541 persons contributed 261 573 person-years of observation, and 5836 developed at least 1 OI. The 27 500 persons who started ART during the period of analysis

**Table 1. Baseline Characteristics of Patients at Risk of Incident Opportunistic Infections, NA-ACCORD, 2000–2010, United States and Canada**

Characteristic	All Persons at Risk (n = 63 541)	Persons Starting ART (n = 27 500)
<b>Age, y</b>		
<35	18 202 (29)	8208 (30)
35–44	24 863 (39)	10 254 (37)
≥45	20 476 (32)	9038 (33)
Median (IQR)	40 (34–47)	40 (33–47)
<b>Sex</b>		
Male	49 483 (78)	21 363 (78)
Female	14 058 (22)	6137 (22)
<b>Race/ethnicity</b>		
White	25 354 (40)	9930 (36)
Black/African American	23 248 (37)	10 207 (37)
Hispanic/Latino	8880 (14)	4064 (15)
Other	2927 (5)	1378 (5)
Missing	3132 (5)	1921 (7)
<b>HIV risk group</b>		
MSM	26 289 (41)	11 285 (41)
IDU	11 803 (19)	4485 (16)
Heterosexual	16 440 (26)	7733 (28)
Other/unknown	9009 (14)	3997 (15)
<b>Country of cohort</b>		
US	56 131 (88)	23 235 (84)
Canada	7410 (12)	4265 (16)
<b>CD4<sup>+</sup> T-cell count, cells/mm<sup>3a</sup></b>		
<200	15 434 (24)	9978 (36)
200–349	13 907 (22)	8642 (31)
350–499	12 310 (19)	4219 (15)
500+	18 932 (30)	3478 (13)
Missing	2958 (5)	1183 (4)
Median (Q1, Q3)	360 (196–557)	252 (134–376)
<b>HIV load, copies/mL<sup>a</sup></b>		
<500	19 619 (31)	3941 (14)
500–9999	11 984 (19)	3573 (13)
10 000–99 999	17 251 (27)	9569 (35)
≥100 000	11 092 (17)	8046 (29)
Missing	3595 (6)	2371 (9)
Median (IQR)	7485 (200–61 787)	41 576 (5300–122 576)
<b>Ever used ART at start of observation</b>		
Yes	27 310 (43)	NA
No	36 231 (57)	NA

Data are no. (%) of patients, unless otherwise indicated. Baseline was defined as the later of the patient's enrollment date in the participating cohort or 1 January 2000.

Abbreviations: ART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IDU, persons who inject drugs; IQR, interquartile; MSM, men who have sex with men; NA, not applicable.

<sup>a</sup> CD4<sup>+</sup> T-cell count and HIV load measurements were as follows: for all persons at risk, nearest measurement to baseline date from 6 months before to 6 months after; for persons starting ART, nearest measurement within 6 months before or on the date of ART start.

contributed 107 875 person-years of observation, and 1843 developed at least 1 OI.

### Trends in Rates of OIs

The incidence rates of the first OI decreased over time, with values of 2.96 events/100 person-years for 2000–2003, 2.36 events/100 person-years for 2004–2007, and 1.45 events/100 person-years for 2008–2010 ( $P < .001$ , by the test for trend; Table 2). These decreases coincided with temporal improvements in clinical status and care of the entire study population: increases in the percentage of observation time during which ART was received, median CD4<sup>+</sup> T-cell counts, and frequency with HIV loads of <500 copies/mL ( $P < .001$  for comparisons; Table 2). The incidence rates of key high-frequency OIs declined significantly over time ( $P < .05$ ; Figure 1), as did the rates of most other OIs (Table 3), except for the less-frequent OIs, such as isosporiasis, coccidioidomycosis, and histoplasmosis, as well as toxoplasmosis and CMV infection, for which no significant declines were noted ( $P \geq .05$ ). During 2008–2010, the leading OIs included PCP, esophageal candidiasis, and disseminated MAC or *M. kansasii* infection.

In sensitivity analyses of OI incidence rates that included person-years of observation for cohorts that did not report any OIs of a given type during the calendar period(s), we found somewhat lower rates for some OIs (Supplementary Table 1), but the overall first OI rates and the statistical inferences regarding temporal trends were similar.

### Risk Factors for OIs

In multivariable Poisson regression models (Supplementary Table 2) that included variables for age, sex, race, HIV risk category, CD4<sup>+</sup> T-cell count, and HIV load at the start of the calendar period, and the calendar period, factors independently ( $P < .05$ ) associated with occurrence of any first incident OI included African American/black race or Hispanic/Latino ethnicity (IRR, 1.11 and 1.12, respectively, compared with white), IDU and heterosexual HIV transmission risk group (IRR, 1.21 and 1.15, respectively, compared with MSM), lower CD4<sup>+</sup> T-cell count categories (IRRs of 5.17 and 1.65, respectively, for CD4<sup>+</sup> T-cell counts of <200 and 200–349 cells/mm<sup>3</sup>, compared with  $\geq 500$  cells/mm<sup>3</sup>), higher HIV load (IRR, 1.50 per 1 log<sub>10</sub> copies/mL), and later calendar periods (IRR, 0.94 and 0.68, respectively for 2004–2007 and 2008–2010, compared with 2000–2003). For most individual OIs, the incidence rates were consistently and markedly increased among persons with low CD4<sup>+</sup> T-cell counts and elevated HIV loads, and some associations with sex, race/ethnicity, and HIV risk status were noted (Supplementary Table 2).

### Occurrence of OIs Among Persons Starting ART

Among a subset of persons initiating ART, the incidence rate of any first OI declined over the 3 calendar periods (Table 2) in a similar pattern as for all persons studied. Overall, by 2 years after initiating ART, approximately 4% of persons experienced a first OI, and that percentage was 3% for persons starting ART in

**Table 2. Incidence Rates and Other Descriptive Information for Patients Followed for Incident AIDS-Defining Opportunistic Infections (OIs) Overall and During 3 Observation Periods, NA-ACCORD, 2000–2010, United States and Canada**

Variable	Overall	2000–2003	2004–2007	2008–2010
Unique persons contributing observation time, no.	63 541	34 497	40 567	39 316
Person-years, no.	261 573	80 031	102 281	79 260
Any first OI				
Events, no.	5836	2329	2368	1139
Incidence <sup>a</sup> (95% CI)	2.27 (2.21–2.33)	2.96 (2.84–3.08)	2.36 (2.27–2.46)	1.45 (1.37–1.54)
Death at any time				
Events, no.	1076	427	382	267
Incidence <sup>a</sup> (95% CI)	0.41 (0.39–0.44)	0.54 (0.49–0.59)	0.38 (0.34–0.42)	0.34 (0.30–0.38)
Any first OI among persons initiating ART				
Events, no.	1843	519	826	498
Incidence <sup>a,b</sup> (95% CI)	2.01 (1.92–2.10)	3.24 (2.97–3.53)	2.21 (2.07–2.37)	1.29 (1.19–1.41)
Person-years during which ART was received, % of total	82	79	81	86
CD4 <sup>+</sup> T-cell count, cells/mm <sup>3</sup>				
Midpoint of the observation period, median	417	400	419	466
Entire observation period, mean of means	440	433	446	492
HIV load measurements <500 copies/mL, % of total				
Midpoint of the observation period	58	51	57	73
Entire observation period, mean	69	67	74	83

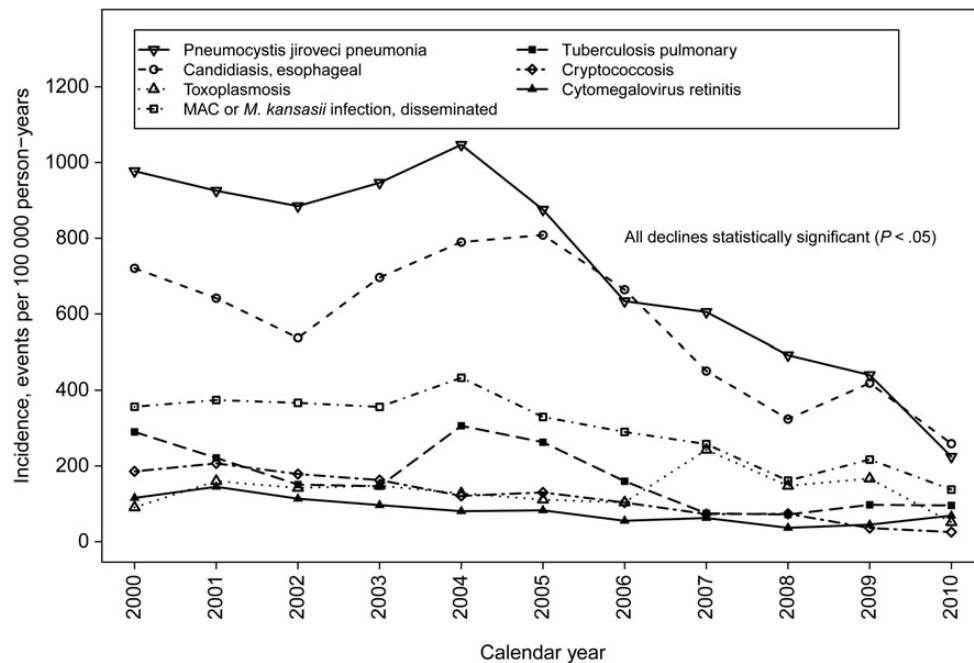
Analysis entry (baseline) date is the later of the patient's enrollment date in NA-ACCORD or 1 January 2000.

Abbreviations: ART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus.

<sup>a</sup> Incidence data denote the number of events per 100 person-years of observation. The start of observation for incidence calculations in a given period is the later of the beginning date for that period or the patient's start of observation in that period if patient is still OI free. The end of observation for incidence calculations is the first of the following dates: death date, OI diagnosis date, last CD4<sup>+</sup> T-cell count or HIV load measurement plus 6 months, and 31 December 2010. If OI cases for any participating cohort over the whole calendar period numbered 0, that given cohort was dropped from the analysis for that particular OI in that period. See Supplementary Table 1 for results without such cohort exclusions.

<sup>b</sup> Calculated after the start of ART only.





**Figure 1.** The incidence of select opportunistic infections among all 63 541 patients, NA-ACCORD, 2000–2010, United States and Canada. Abbreviations: MAC, *Mycobacterium avium* complex; *M. kansasii*, *Mycobacterium kansasii*.

2008–2010, compared with 5% for those starting ART in 2000–2003 (Figure 2A). Furthermore, the incidence rate of any first OI was highly elevated among persons starting ART with CD4<sup>+</sup> T-cell counts of <200 cells/mm<sup>3</sup>, compared with others (Figure 2B). In subset analyses for persons who started ART in 2008–2010, the 2-year probabilities of developing a first OI were 7.2%, 1.2%, 1.0%, and 1.0% when the CD4<sup>+</sup> T-cell count at the start of ART was <200, 200–349, 350–499, and ≥500 cells/mm<sup>3</sup>, respectively. In further analyses incorporating competing risk of death, the results were similar (Supplementary Figure 1).

#### Trends in CD4<sup>+</sup> T-Cell Counts at OI Diagnosis

The CD4<sup>+</sup> T-cell count was available for 5465 of 5836 OI diagnoses (94%) and was measured a median of 2 days before the OI diagnosis (IQR, 18 days before to 7 days after the OI diagnosis). A substantial percentage of OIs occurred among patients with CD4<sup>+</sup> T-cell counts of ≥200 cells/mm<sup>3</sup>: 34% (705 of 2055) during 2000–2003, 34% (755 of 2243) during 2004–2007, and 42% (486 of 1167) during 2008–2010 ( $P < .001$ , by the univariate test for trend). The corresponding median CD4<sup>+</sup> T-cell counts at OI diagnosis, by calendar period of diagnosis, were 101, 101, and 145 cells/mm<sup>3</sup>, respectively. The increase in median CD4<sup>+</sup> T-cell count for OI cases corresponded with an increase in the median CD4<sup>+</sup> T-cell count of the entire at-risk population (Table 2).

The median CD4<sup>+</sup> T-cell count was above or close to 200 cells/mm<sup>3</sup> for tuberculosis and isosporiasis and was <100 cells/mm<sup>3</sup> for most other OIs, including candidiasis, PCP, CMV infection, and MAC infection (Figure 3). The

range of CD4<sup>+</sup> T-cell counts (defined as the 5th–95th percentile) at diagnosis was wide for many OIs. Most persons who had OIs documented at relatively high CD4<sup>+</sup> T-cell counts also had a high CD4<sup>+</sup> T-cell percentage measurement (data not shown). Notably, most OIs occurred among persons prescribed ART, a substantial fraction of whom had virological suppression (<500 copies/mL) proximal to OI diagnosis (Figure 3). Although it is possible that some of these events were consistent with immune reconstitution inflammatory syndrome [32, 33], we observed no marked increase in risk of any first OI diagnosis within 6 months of ART initiation (Figure 2A).

#### DISCUSSION

In our large and demographically diverse cohort of HIV-infected persons in care in the United States and Canada, we observed persistent reductions in incidence rates of first OIs during 2000–2010, which coincided with the improvements in viral suppression and immune status of our study population receiving increasingly potent and tolerable newer ART regimens [12]. We found that, on average, among contemporary North American patients with no history of an AIDS-defining event, fewer than 2 in 100 developed any OI per year. Among a subset of persons starting ART during 2008–2010, the probability of developing a new OI within the next 2 years was about 7% when the initial CD4<sup>+</sup> T-cell count was <200 cells/mm<sup>3</sup> and 1% when the initial CD4<sup>+</sup> T-cell count was ≥500 cells/mm<sup>3</sup>.

Although direct comparisons of our observed OI rates to those reported from other cohorts are not appropriate because

**Table 3. Incidence Rates of Select AIDS-Defining Opportunistic Infections (OIs) Overall and During 3 Observation Periods, NA-ACCORD, United States and Canada, 2000–2010**

OI Diagnosis, Variable <sup>a</sup>	Observation Period				P Value
	Overall	2000–2003	2004–2007	2008–2010	
<i>Pneumocystis pneumonia</i>					
Events	1828	733	786	309	
Person-years	260 278	79 609	101 601	79 068	
Incidence (95% CI)	0.70 (.67–.74)	0.92 (.86–.99)	0.77 (.72–.83)	0.39 (.35–.44)	<.0001
Candidiasis					
Events	1348	466	625	257	
Person-years	260 672	79 787	101 795	79 090	
Incidence (95% CI)	0.52 (.49–.55)	0.58 (.53–.64)	0.61 (.57–.66)	0.32 (.29–.37)	<.0001
Candidiasis, esophageal					
Events	1163	403	547	213	
Person-years	208 913	63 142	82 284	63 487	
Incidence (95% CI)	0.56 (.53–.59)	0.64 (.58–.70)	0.66 (.61–.72)	0.34 (.29–.38)	<.0001
<i>M. avium</i> complex or <i>M. kansasii</i> infection					
Events	669	251	293	125	
Person-years	234 188	70 054	91 614	72 520	
Incidence (95% CI)	0.29 (.26–.31)	0.36 (.32–.41)	0.32 (.29–.36)	0.17 (.14–.21)	<.0001
CMV infection					
Events	631	202	249	180	
Person-years	261 281	79 950	102 138	79 194	
Incidence (95% CI)	0.24 (.22–.26)	0.25 (.22–.29)	0.24 (.22–.28)	0.23 (.20–.26)	.3023
CMV retinitis					
Events	156	70	55	31	
Person-years	205 053	61 098	80 375	63 580	
Incidence (95% CI)	0.08 (.07–.09)	0.11 (.09–.14)	0.07 (.05–.09)	0.05 (.03–.07)	<.0001
Tuberculosis, any					
Events	624	222	290	112	
Person-years	261 070	79 874	102 007	79 189	
Incidence (95% CI)	0.24 (.22–.26)	0.28 (.24–.32)	0.28 (.25–.32)	0.14 (.12–.17)	<.0001
Tuberculosis, pulmonary					
Events	339	121	162	56	
Person-years	211 046	63 352	83 465	64 229	
Incidence (95% CI)	0.16 (.14–.18)	0.19 (.16–.23)	0.19 (.17–.23)	0.09 (.07–.11)	<.0001
Toxoplasmosis					
Events	340	103	141	96	
Person-years	251 709	76 441	97 746	77 523	
Incidence (95% CI)	0.14 (.12–.15)	0.13 (.11–.16)	0.14 (.12–.17)	0.12 (.10–.15)	.5487
Cryptococcosis					
Events	285	143	106	36	
Person-years	261 378	79 967	102 180	79 231	
Incidence (95% CI)	0.11 (.1–.12)	0.18 (.15–.21)	0.10 (.09–.13)	0.05 (.03–.06)	<.0001
Cryptococcal meningitis					
Events	202	101	77	24	
Person-years	208 665	63 223	82 501	62 942	
Incidence (95% CI)	0.10 (.08–.11)	0.16 (.13–.19)	0.09 (.07–.12)	0.04 (.03–.06)	<.0001
Cryptosporidiosis <sup>b</sup>					
Events	185	83	66	36	
Person-years	224 649	66 552	87 246	70 850	
Incidence (95% CI)	0.08 (.07–.10)	0.12 (.10–.15)	0.08 (.06–.10)	0.05 (.04–.07)	<.0001
Histoplasmosis <sup>c</sup>					
Events	159	38	71	50	
Person-years	252 914	77 839	99 117	75 959	
Incidence (95% CI)	0.06 (.05–.07)	0.05 (.04–.07)	0.07 (.06–.09)	0.07 (.05–.09)	.1598

Table 3 continued.

OI Diagnosis, Variable <sup>a</sup>	Observation Period				P Value
	Overall	2000–2003	2004–2007	2008–2010	
<b>PML</b>					
Events	143	59	57	27	
Person-years	234 895	70 217	91 695	72 983	
Incidence (95% CI)	0.06 (.05–.07)	0.08 (.07–.11)	0.06 (.05–.08)	0.04 (.03–.05)	.0003
<b>Coccidioidomycosis<sup>c</sup></b>					
Events	31	10	12	9	
Person-years	163 657	52 090	63 891	47 675	
Incidence (95% CI)	0.02 (.01–.03)	0.02 (.01–.04)	0.02 (.01–.03)	0.02 (.01–.04)	.9700
<b>Isosporiasis<sup>b</sup></b>					
Events	11	5	4	2	
Person-years	135 421	42 342	53 811	39 267	
Incidence (95% CI)	0.01 (0–.01)	0.01 (0–.03)	0.01 (0–.02)	0.01 (0–.02)	.2950
<b>Any first OI<sup>d</sup></b>					
Events	5836	2329	2368	1139	
Person-years	257 466	78 708	100 172	78 586	
Incidence (95% CI)	2.27 (2.21–2.33)	2.96 (2.84–3.08)	2.36 (2.27–2.46)	1.45 (1.37–1.54)	<.0001
<b>Death</b>					
<b>Before first OI</b>					
Events	1055	419	374	262	
Person-years	261 573	80 031	102 281	79 260	
Incidence (95% CI)	0.40 (.38–.43)	0.52 (.48–.58)	0.37 (.33–.4)	0.33 (.29–.37)	<.0001
<b>Any time</b>					
Events	1076	427	382	267	
Person-years	260 195	79 399	101 641	79 155	
Incidence (95% CI)	0.41 (.39–.44)	0.54 (.49–.59)	0.38 (.34–.42)	0.34 (.30–.38)	<.0001

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; *M. avium* complex, *Mycobacterium avium* complex; *M. kansasii*, *Mycobacterium kansasii*; PML, progressive multifocal leukoencephalopathy.

<sup>a</sup> Person-years data denote the number of person-years of observation. Incidence data denote the number of events per 100 person-years of observation. If the number of individual OI events reported over the whole calendar period was 0 for a participating cohort, that cohort was dropped from the analysis (numerator and denominator) for that particular OI for that period, to guard against underestimates of OI rates due to nonascertainment. See [Supplementary Table 1](#) for results without such cohort exclusions.

<sup>b</sup> Chronic intestinal.

<sup>c</sup> Disseminated or extrapulmonary.

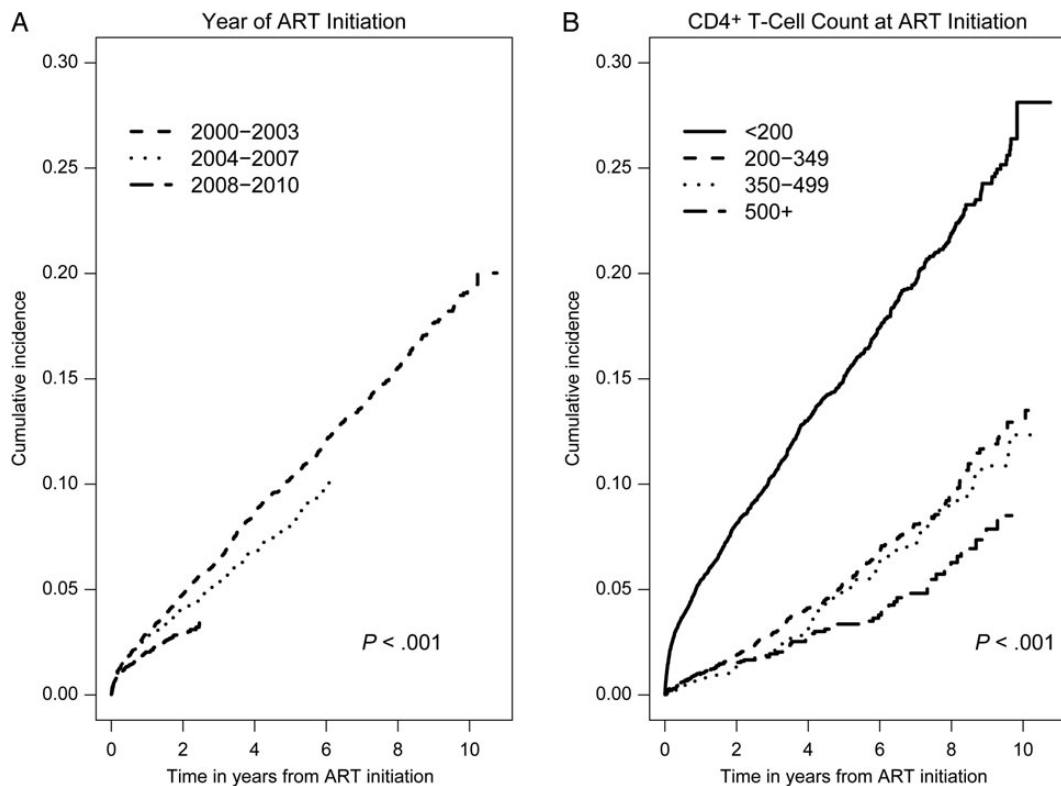
<sup>d</sup> Excluding recurrent pneumonia, *Salmonella* septicemia, and herpes simplex.

of multiple cross-cohort differences, including degree of immunosuppression and differences in analytic methods, our absolute OI incidence rates were generally of the same magnitude as in other studies of OIs during the ART era [3–5]. Higher HIV loads and lower CD4<sup>+</sup> T-cell counts remained associated with OIs among patients, corroborating earlier analyses [1, 21, 24, 34]. Since most persons in our analyses were ART recipients, these findings could reflect patients with more-recent ART initiation, suboptimal responses to ART, or medication nonadherence. In addition, as in prior studies, we found that certain demographic factors increased the risk for specific OIs [3, 5, 35, 36], including older age, male sex, and HIV transmission risk behavior (eg, IDU and male-male sex for a variety of opportunistic infections [5, 35]).

A considerable variability in CD4<sup>+</sup> T-cell counts at diagnosis of OIs has been documented before and after introduction of ART, with some patients experiencing OIs at relatively high CD4<sup>+</sup> T-cell counts [3, 5, 24]. Two principal hypotheses exist

to explain observed trends [1, 37, 38]. First, the increase in median CD4<sup>+</sup> T-cell count at diagnosis, for the few OI events that still occur, likely reflects the increased CD4<sup>+</sup> T-cell counts of the entire NA-ACCORD population followed after introduction of ART (Table 1). Second, ART-associated immune restoration is functionally incomplete, particularly among persons who had experienced profound CD4<sup>+</sup> T-cell depletion, resulting in OI occurrence at higher CD4<sup>+</sup> T-cell counts.

In this analysis, we investigated incidence rates for the first occurrence of any OI and of individual OIs. It is difficult to accurately assess the prevalence or total burden of OIs in a population at any point in time, for at least 2 reasons: (1) some viral OIs are chronic, and their historical documentation since the date of initial onset is likely incompletely recorded across many participating cohorts in NA-ACCORD; and (2) some OIs may occur more than once, and the dates of their onset, resolution, and recurrence may not be well recorded. Our approach to focus on first incident OIs among patients without any



**Figure 2.** Time from initiation of antiretroviral therapy (ART) to the first incident opportunistic infection, NA-ACCORD, 2000–2010, United States and Canada, by period of ART initiation (A) and CD4<sup>+</sup> T-cell count at the start of ART (B). Analyses do not consider competing risk of death.

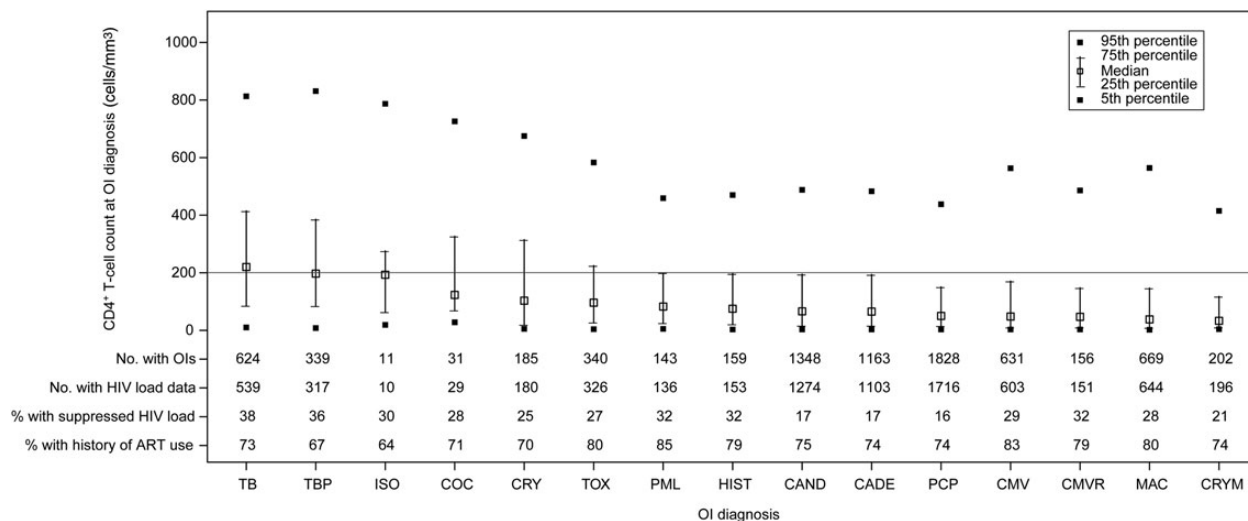
preexisting OIs (ie, no clinical AIDS) as per their available medical history results in our study population being, on average, more reflective of patients with less advanced HIV disease and more-recently diagnosed HIV infection; we also examined OI rates among persons newly starting ART.

Our study has several limitations. We relied on the standardized study protocols of 16 participating cohorts for ascertaining OIs without reviewing original medical records to conduct centralized NA-ACCORD event validation. Although most OIs present acutely and thereby bring affected patients into clinical care, some OIs might have gone undetected because of presentation and care provided outside of the participating NA-ACCORD facilities or subclinical presentation or incomplete screening (eg, tuberculosis); we do not suspect this possible underascertainment to differ over time, but it could result in underestimation of OI incidence. To guard against underreporting bias, for each analysis period we excluded from incidence calculations any cohort reporting no OI events of that type in the period (eg, this occurred when a cohort could report all candidiasis cases without differentiating esophageal candidiasis); we chose this approach because we believed that underascertainment of OIs posed a greater threat to the validity of our results than potentially inflating OI rates (by removing observation time when no events were recorded). In sensitivity analyses, which considered all available person-time whether or not a

cohort reported any OI events of a given type, the individual OI rates were somewhat lower, but the inferences regarding decreasing or level trends in incidence of OIs over time were similar (Supplementary Table 1). Overestimation of first OI incidence rates could have also resulted from inadvertent inclusion of patients with preexisting OI histories that were not documented in available medical records and because some patients may have had latent infections or bacterial colonization, as well as immune-compromising conditions beyond HIV infection, that could lead to OI misdiagnoses [39]. Conversely, our report excludes some OIs, chiefly recurrent bacterial pneumonia, because neither recurrence nor differentiation between bacterial and viral pneumonia was systematically documented in most cohorts; thus, our overall incidence rate of any first OI may be lower than had these diagnoses been included. We assessed temporal trends and use of ART in a descriptive, ecological fashion and did not quantify the precise reductions in incidence of given OIs attributable to ART use, which was not the primary goal of our analysis and would have required accounting for confounding by indication [40]. Finally, ascertainment of ART prescriptions, particularly before and at enrollment into participating NA-ACCORD cohorts, may be incomplete, depending on the available patient medical records.

In conclusion, in our large and diverse cohort of HIV-infected patients in North America, rates of first OIs in the ART era have





**Figure 3.** CD4<sup>+</sup> T-cell counts, viral load data, and history of antiretroviral therapy (ART) use among 5836 patients experiencing any first opportunistic infections (OIs), NA-ACCORD, 2000–2010, United States and Canada. Abbreviations: CADE, candidiasis, esophageal; CAND, candidiasis; CMV, cytomegalovirus; CMVR, CMV retinitis; COC, coccidioidomycosis; CRY, cryptosporidiosis; CRYM, cryptococcal meningitis; HIST, histoplasmosis disseminated; HIV, human immunodeficiency virus; ISO, isosporiasis, chronic intestinal; MAC, *Mycobacterium avium* complex or *Mycobacterium kansasii* infection, disseminated; PCP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; TB, tuberculosis; TBP, tuberculosis, pulmonary; TOX, toxoplasmosis.

continued to decline during 2000–2010. OIs that predominated in the pre-ART period in prior US-based analyses [1, 4, 35], such as PCP and esophageal candidiasis, have remained prominent in the contemporary ART period. A significant minority of patients have OIs diagnosed at higher-than-expected CD4<sup>+</sup> T-cell counts and possibly while experiencing virological suppression, highlighting that healthcare providers need to remain vigilant for incident opportunistic illnesses in all HIV-infected patients and reduce OI-associated morbidity and mortality. Early HIV diagnosis and prompt linkage of HIV-infected patients to care with immediate offer of ART [27, 41] are also key to achieve further gains in OI prevention.

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## Supplementary Data

Supplementary materials are available at <http://jid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

## Notes

**Disclaimer.** The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH).

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**Potential conflicts of interest.** K. N. A. has served on a medical advisory board for Gilead Sciences in the last 3 years. G. B. has received grant support from Amgen and Bristol-Myers Squibb and has served as a consultant for Definicare. K. G. has served on the scientific advisory board for Tibotec and has received grant funding from Tibotec. M. J. G. has served on the HIV advisory boards of Abbvie, Merck, Janssen, Gilead, and ViiV Health. K. H. has received research funding from Gilead, ViiV/GSK, Janssen, and Merck. A. R. has served on the medical advisory boards of Merck, ViiV, Gilead, and Janssen over the past 3 years and has received research grants for clinical trials from Merck, ViiV, Gilead, and Janssen. M. J. S. is an employee of Kaiser Permanente, which has received research grant funding from Pfizer and Merck (none of these potential conflicts are directly related to this work). J. E. T. has served on medical advisory boards for AbbVie, Mallinckrodt, and XOMA; has been a consultant to Gilead; and has received grant support from NEI and Allergan (none of these potential conflicts are related to the current work). All other authors report no potential 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

### AIDS-Defining Opportunistic Infections (OIs) Included and Excluded From Analyses

The OI diagnoses included in the analyses of the incidence of any first OI are as follows: *Pneumocystis pneumonia* (PCP); candidiasis; candidiasis, esophageal; *Mycobacterium avium* complex or *M. kansasii* infection, disseminated or extrapulmonary; cytomegalovirus (CMV) infection; CMV retinitis; tuberculosis, any; tuberculosis, pulmonary; toxoplasmosis; cryptococcosis; cryptococcal meningitis; cryptosporidiosis, chronic intestinal; histoplasmosis, disseminated or extrapulmonary; progressive multifocal

leukoencephalopathy; coccidioidomycosis, disseminated or extrapulmonary; and isosporiasis, chronic intestinal.

Notably, we excluded the following 3 OI diagnoses: recurrent bacterial pneumonia, because we were unable to distinguish viral from bacterial pneumonia in most cases; recurrent *Salmonella* septicemia, because recurrence versus treatment failure was not systematically documented; and herpes simplex virus (HSV) disease, because in most cohorts HSV-related illness was not systematically documented as chronic ulcers, bronchitis, pneumonitis, or esophagitis. As aforementioned, our analysis excluded all AIDS-defining cancers. Two AIDS-defining conditions were also omitted: HIV encephalopathy, because it had no clear infectious etiology beyond HIV itself; and HIV wasting, because it lacked specificity and systematic corroborating information in our database (eg, information on weight loss not available in most participating cohorts).

Among 16 737 persons who were excluded from analyses of incidence rates of any first OI event because they had a history of any documented AIDS-defining condition at baseline, 13 807 were excluded for having at least 1 OI event of interest in this study, and the remaining 2930 were excluded chiefly on account of AIDS-defining malignancies. In descending order of frequency, we excluded 6584 cases of PCP, 2692 cases of candidiasis (mostly esophageal), 1725 cases of CMV infection, and 1591 cases of disseminated or extrapulmonary *M. avium* complex or *M. kansasii* infection, and 1193 cases of tuberculosis; the remaining OI events each numbered <850.

These prior OI events were diagnosed either before or after patients' enrollment into the HIV cohorts participating in NA-ACCORD; some events were abstracted from historical records, if available. Of 16 737 OI diagnoses, about 60% were made in the 1990s, well before inception of NA-ACCORD. Because we had no data to inform denominators (ie, patients in follow-up at the participating sites at the time) and because we suspect incomplete counts for numerators (historic OI cases), we focused on analyzing incident OI rates and did not analyze the prevalence of OIs.