Rates of AIDS-defining opportunistic illnesses (OIs) and CD4 cell counts at OI diagnosis in a cohort of US patients (1994-2006)

Buchacz K[1], Baker RK[2], Palella FJ[3], Lichtenstein KA[4], Wood KC[2], Brooks JT[1], and the HOPS Investigators

[1] Centers for Disease Control and Prevention, [2] Cerner Corporation; [3] Northwestern University; [4] University of Colorado Health Sciences Center

Introduction

- Highly active antiretroviral therapy (HAART) and antimicrobial prophylaxis have dramatically reduced the rates of OIs among HIV-infected persons
- However, it is not clear if the rates of OIs have continued to decline or have stabilized in recent years, and if the spectrum of OI diagnoses has changed over time
- Anecdotal reports suggest that some OIs are increasingly diagnosed at higher CD4 cell counts, which may have implications for OI prophylaxis

Objectives

- To examine rates of OIs among HOPS patients during 1994-2006
- To describe the predominant OIs in the current HAART era (2002-2006)
- To describe trends in median CD4 cell counts at OI diagnoses

Methods

HIV Outpatient Study (HOPS) is a prospective open cohort chart-abstraction study of HIV-infected patients seen at 10 HIV clinics (public and private) in seven cities in the United States.

Study population for OI analyses (N=7825). Patients having at least 2 clinical encounters during 1994-2006 at HOPS sites.

Analysis methods

- Annual incidence rates per 1000 person-years (py) with 95% confidence intervals (CIs) based on Poisson distribution for the first occurrence of most frequent OIs in our cohort.
- Stratified, multivariable Poisson regression models (adjusting for sex, race, HIV risk category, with and without current CD4 cell count), to estimate annual percent changes in the incidence rate of OIs within three periods: 1994-1997 (pre-HAART), 1998-2001 (early HAART), 2002-2006 (contemporary HAART).

Observation time for calculating annual rates of OIs (1994-2006)

- Require patient had an encounter with a HOPS site in a given year to be in the denominator.
- Start of observation for the year: January 1 of that year (if patient already followed in the cohort) or date of first HOPS encounter during that year.
- End of observation for the year: December 31 of that year (if patients continues in the cohort) or the earliest of: OI diagnosis or last contact (including physician/clinic visit, hospitalization, home nursing visit, laboratory result or telephone contact).

PCP - *Pneumocystis jirovecii* pneumonia
MAC - *Mycobacterium avium* complex
CMV disease - cytomegalovirus disease (including retinitis)
KS - Kaposi's sarcoma
NHL - non-Hodgkin's lymphoma
PML - Progressive multifocal leukoencephalopathy

Results

- We observed 7,825 persons (median age = 38 years) of whom 81% were male, 57% were white, and 58% were MSM (Table 1). During 1994-2006, the proportion of women and person with heterosexual risk for HIV increased, as did the median age of the cohort.
- Rates of OIs fell precipitously during 1994-1997 (Table 2, Figures 1,2,3) with continued declines for MAC, esophageal candidiasis, and NHL during 1998-2001 (Table 2). The combined category of OI maligancies and MAC continued to decline during 2002-2006.
- The median CD4 cell count at OI diagnosis increased significantly over time for KS, NHL, and HIV encephalopathy (Table 3). A trend toward an increase in CD4 was observed for CMV disease, and esophageal candidiasis (Table 3). The findings for KS and HIV encephalopathy persisted in the analyses limited to patients on HAART.
- The five most frequent OIs in the 1994 HOPS population were (in order of incidence rate, Table 2) CMV disease, PCP, MAC, KS, and esophageal candidiasis; whereas, in 2006 they were esophageal candidiasis, PCP, CMV disease, NHL, and HIV encephalopathy.
- Adjusting for patients' increasing current CD4 cell count, which is an important risk factor for OIs but also an outcome related to HAART, attenuated the estimated changes in the rates of OIs over time. In these analyses, CMV disease was the only OI which showed a trend toward an increase in the contemporary HAART era.
- The absolute rates and trends in rates of OIs did not change substantially when OIs diagosed at death within 60 days of last patient contact were included in analyses (only 1% of OIs were first detected at death in HOPS patients, data not shown).

Table 1.
Characteristics of HOPS patients included in analysis from 1994-2006

	1994-1997		1998-2001		2002-2006		Overall	
Pt Characteristic	N	%	N	%	N	%	N	%
Total	4228		4401		4476		7825	
Age* group (years)								
< 30	578	**14**	452	**10**	332	**7**	1018	**13**
30-49	3262	**77**	3381	**77**	3280	**73**	5904	**75**
50+	388	**9**	568	**13**	864	**19**	903	**12**
median age (years)		*37*		*39*		*41*		*38*
Male gender	3493	**83**	3480	**79**	3532	**79**	6305	**81**
Race/ethnicity								
White	2692	**64**	2425	**55**	2365	**53**	4424	**57**
African American	1051	**25**	1369	**31**	1437	**32**	2354	**30**
Hispanic	389	**9**	484	**11**	547	**12**	838	**11**
Oth/unk	96	**2**	123	**3**	127	**3**	209	**3**
HIV risk group								
MSM	2574	**61**	2513	**57**	2578	**58**	4550	**58**
Hetrosexual	770	**18**	1091	**25**	1180	**26**	1788	**23**
IDU	661	**16**	598	**14**	496	**11**	1075	**14**
Other	117	**3**	99	**2**	104	**2**	195	**2**
Unknown	106	**3**	100	**2**	118	**3**	217	**3**
Baseline CD4 cell count (cell/mm³) *								
0-49	621	**15**	390	**9**	254	**6**	1015	**13**
50-199	858	**20**	754	**17**	544	**12**	1461	**19**
200-349	785	**19**	895	**20**	850	**19**	1480	**19**
350+	1330	**31**	1941	**44**	2399	**54**	2946	**38**
Unknown	634	**15**	421	**10**	429	**10**	923	**12**
median count		*257*		*339*		*415*		*295*
Used HAART*	521	**12**	2699	**61**	2857	**64**	2230	**28**
Observation time in period (yrs)								
median (IQR)	1.3 (0.6-2.8)		3.3 (1.4-5.3)		5.5 (2.5-9.0)		2.9 (1.1-6.7)	

* As of beginning of observation in the period (within 6 months prior to 3 months after for HAART and CD4 cell)

Table 2.
Incidence rates per 1000 py and adjusted annual changes in the rates of first occurrence of each OI among HOPS patients, 1994-2006

Category	Incidence rate (95% CI) 1994	Incidence rate (95% CI) 2006	Adjusted estimates of annual percent change in incidence rate during period (95% CI)* 1994–1997	1998–2001	2002–2006
OI malignancies†	40.6 (29.5, 54.5)	2.6 (0.9, 5.6)	-37 (-44, -28) -34 (-44, -23)	-24 (-41, -1) -19 (-34, -1)	-19 (-34, -1) -17 (-31, -1)
OI infections‡	111.2 (91.1, 134.5)	13.6 (8.9, 19.9)	-27 (-36, -18) -23 (-30, -15)	-19 (-27, -10) -18 (-28, -6)	-9 (-20, 3) -5 (-16, 7)
CMV disease	46.2 (34.4, 60.7)	2.9 (1.2. 6.1)	-37 (-49, -21) -32 (-42, -21)	-27 (-47, 1) -22 (-39, 0)	-19 (-12, 60) 32 (0, 65)
PCP	36.4 (25.8, 50.0)	4.2 (1.9, 7.9)	-30 (-41, -17) -27 (-38, -15)	-14 (-29, 4) -9 (-26, 10)	-12 (-26, 9) -9 (-26, 9)
MAC	33.9 (24.0, 46.5)	1.3 (0.3, 3.7)	-23 (-34, -10) -17 (-30, -3)	-23 (-37, -7) -20 (-35, -3)	-27 (-43, -6) -19 (-32, -3)
KS	30.2 (20.8, 42.4)	0.8 (0.1, 3.1)	-39 (-47, -29) -37 (-47, -25)	-26 (-47, 3) -23 (-40, 0)	-10 (-33, 21) -7 (-24, 16)
Esophageal candidiasis	18.7 (11.6, 28.6)	5.6 (3.0, 9.5)	-18 (-33, 1) -14 (-28, 2)	-24 (-34, -12) -20 (-34, -4)	-4 (-22, 17) 1 (-14, 20)
Tuberculosis	5.3 (1.9, 11.5)	0.0 (0.0, 1.5)	-30 (-48, -5) -28 (-46, -3)	7 (-24, 51) 10 (-15, 43)	-29 (-51, 3) -27 (-45, -4)
NHL	9.6 (4.8, 17.3)	1.7 (0.5, 4.2)	-37 (-50, -19) -35 (-50, -17)	-29 (-49, -1) -25 (-42, -3)	-26 (-46, 0) -25 (-40, -7)
HIV encephalopathy	6.1 (2.5, 12.6)	1.7 (0.5, 4.2)	-13 (-35, 16) -7 (-27, 18)	0 (-33, 47) 3 (-25, 40)	-1 (-28, 34) 3 (-18, 29)

* Estimates derived from the multivariable Poisson regression models. Top estimate adjusted for sex, race, HIV risk category. Bottom estimate further adjusted for current CD4 cell count (closest to start of observation in a given year, measured within 6 months prior to 3 months after start of observation)
† Includes KS, non-Hodgkin's lymphoma and CNS lymphoma.
‡ Includes all AIDS-defining opportunistic infections, except recurrent pneumonia (because unable to distinguish viral from bacterial pneumonia in the database) and salmonella septicemia (because only one case).

Figure 1.
Incidence rates of HIGH FREQUENCY infectious OIs in the HOPS, 1994-2006

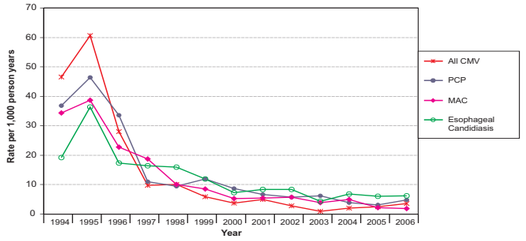

Figure 2.
Incidence rates of LOW FREQUENCY infectious OIs in the HOPS, 1994-2006

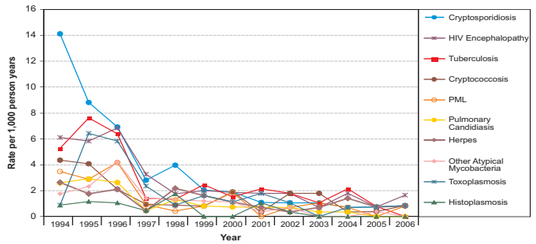

Figure 3.
Incidence rates of malignant OIs in the HOPS, 1994-2006

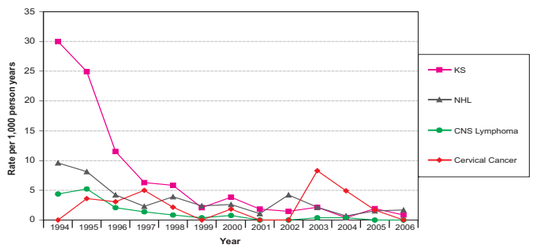

Table 3.
Median CD4 cell counts at OI diagnosis, HOPS 1994-2006

	Median CD4 cell count (cells/mm³) (IQR) 1994-1997 N†	n	Median	1998-2001 N	n	Median	2002-2006 N	n	Median	P value* for trend
CMV disease‡	219 27	172 25	20 (9-50) 29 (13-71)	54 30	52 29	29 (10-111) 35 (15-126)	23 14	21 13	41 (12-67) 23 (12-62)	0.09 0.66
PCP	185 23	164 20	55 (17-145) 28 (7-191)	77 26	71 25	49 (14-143) 60 (14-143)	50 23	45 22	76 (34-187) 69 (19-216)	0.47 0.33
MAC	181 27	132 19	22 (9-57) 13 (5-100)	65 28	54 23	32 (11-65) 48 (11-120)	42 20	39 18	20 (6-90) 34 (21-100)	0.48 0.89
KS	108 12	97 11	38 (13-120) 25 (10-120)	33 15	31 15	107 (21-247) 111 (23-236)	18 9	17 8	143 (38-299) 201 (54-320)	<0.001 0.03
Esophageal candidasis	145 28	123 26	43 (14-120) 34 (14-96)	99 41	89 37	44 (15-154) 60 (18-166)	75 31	70 31	89 (20-200) 100 (23-243)	0.09 0.09
Tuberculosis	34 4	27 4	168 (60-457) 159 (121-227)	19 5	16 5	269 (151-400) 261 (190-271)	16 16	12 12	207 (98-669) 207(112-376)	0.34 0.35
NHL	38 5	30 5	73 (17-123) 96 (17-123)	25 18	24 17	164 (83-334) 152 (79-309)	28 14	25 13	243 (139-375) 219 (135-380)	0.0001 0.17
HIV encephalopathy	37 8	30 8	43 (12-126) 73 (10-148)	19 13	17 12	210 (21-292) 226 (136-337)	18 8	17 7	233 (25-275) 273 (223-450)	0.03 0.01

* Trend in CD4 counts by time period evaluated by Jonckheere-Terpstra non-parametric test.
† N is total number of patients diagnosed with an OI; n is number with available CD4 cell count at OI diagnosis
‡ For each OI, the first row presents data for all cases, the second row presents data for the cases diagnosed on HAART.

Limitations

- Low incidence of OIs, particularly in the current HAART era
  - Imprecise estimates of modeled changes in OI rates
  - Precluded analyses of OI trends stratified by gender and other sociodemographics

Conclusions

- We found no statistically significant changes in the rates of key OIs in the current HAART era (2002-2006), except for decreases in MAC and combined category of OI malignancies.
- While the rates of all OIs fell dramatically between 1994 and 2006, three of the five OIs most common in 1994 remained the most common in 2006.
- The increases in median CD4 cell count at diagnosis of KS, NHL, and HIV encephalopathy may signal a shift in the epidemiology of these OIs in the HAART era warranting further investigation.

Appendix

The HIV Outpatient Study (HOPS) Investigators, September 2007– present

The HOPS Investigators include the following investigators and sites: John T. Brooks, Kate Buchacz, Tony Tong, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention (NCHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, GA; Kathleen C. Wood, Rose K. Baker, James T. Richardson, Darlene Hankerson, and Carl Armon, Cerner Corporation, Vienna, VA; Frank J. Palella, Joan S. Chmiel, Aditya Chawla, and Onyinye Enyia, Feinberg School of Medicine, Northwestern University, Chicago, IL; Kenneth A. Lichtenstein and Cheryl Stewart, National Jewish Medical and Research Center Denver, CO; John Hammer, Benjamin Young, Kenneth S. Greenberg, Barbara Widick, and Joslyn D. Axinn, Rose Medical Center, Denver, CO; Bienvenido G. Yangco and Kalliope Halkias, Infectious Disease Research Institute, Tampa, FL; Douglas J. Ward and Charles A. Fiorentino, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian and Faye Ruley, Temple University School of Medicine, Philadelphia, PA; Richard M. Novak and Andrea Wendrow, University of Illinois at Chicago, Chicago, IL.