Epidemiology of Human Immunodeficiency Virus–Associated Opportunistic Infections in the United States in the Era of Highly Active Antiretroviral Therapy

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The incidence of nearly all AIDS-defining opportunistic infections (OIs) decreased significantly in the United States during 1992–1998; decreases in the most common OIs (*Pneumocystis carinii* pneumonia [PCP], esophageal candidiasis, and disseminated *Mycobacterium avium* complex [MAC] disease) were more pronounced in 1996–1998, during which time highly active antiretroviral therapy (HAART) was introduced into medical care. Those OIs that continue to occur do so at low $CD4^+$ T lymphocyte counts, and persons whose $CD4^+$ counts have increased in response to HAART are at low risk for OIs, a circumstance that suggests a high degree of immune reconstitution associated with HAART. PCP, the most common serious OI, continues to occur primarily in persons not previously receiving medical care. The most profound effect on survival of patients with AIDS is conferred by HAART, but specific OI prevention measures (prophylaxis against PCP and MAC and vaccination against *Streptococcus pneumoniae*) are associated with a survival benefit, even when they coincide with the administration of HAART. Continued monitoring of incidence trends and detection of new syndromes associated with HAART are important priorities in the HAART era.

The natural history of HIV infection has changed dramatically in the era of highly active antiretroviral therapy (HAART) in the areas of the world that are able to afford these therapies. The incidence of HIV-associated opportunistic infections (OIs), including those for which specific preventive measures are not available, has decreased, as have hospitalizations and inpatient costs [1–6]. AIDS-associated deaths have dropped precipitously [1–4]. These observations are highly encouraging yet raise many questions that concern access to HAART, the spectrum and incidence of HIV-associated OIs in the HAART era, the $CD4^+$ T lymphocyte counts at which patients develop OIs, the use of specific OI preventive measures, and the impact of OI preventive measures in the HAART era.

Each of these issues is relevant to the 1999 US Public Health Service/Infectious Diseases Society of America guidelines for prevention of OIs in persons infected with HIV, which appear in this issue of *Clinical Infectious Diseases* [7]. This article summarizes information concerning the epidemiology of OIs in the era of HAART, primarily from the Centers for Disease Control and Prevention's (CDC's) Adult and Adolescent Spectrum of Disease (ASD) Project. Information from this project has been updated with data collected through September 1999, to the extent that this was possible at the time of writing (October 1999). New information pertaining to the incidence of OIs in HIV-infected children is also presented.

The ASD Project

Information on the occurrence of OIs is best obtained from large databases on HIV-infected persons in care; a number of these are available in the United States [1, 8–10], Canada [3], and Western Europe [4]. In the United States, the largest of these is the CDC's ASD Project, a medical record review/surveillance project initiated in 1990 in collaboration with local and state public health departments in 11 cities in the United States. The methods of the ASD project have been described in detail elsewhere [8].

In brief, HIV-infected persons aged ⩾13 years are enrolled in the study when they enter into care in participating health care facilities in Atlanta, Dallas, Denver, Detroit, Los Angeles, New York City, San Antonio, Seattle, Houston, New Orleans, and Bayamon, Puerto Rico. At enrollment, their medical records are reviewed for demographic information, HIV exposure mode, and history of AIDS-defining illnesses. From the 1-year period before enrollment, information on other illnesses, medications, and laboratory tests is recorded. Medical record reviews are repeated at 6-month intervals until loss to follow-up or death.

As of September 1999, >49,000 persons had been enrolled in the ASD Project from >100 medical facilities in the 11 US cities. Approximately 80% were men and 20% were women; 38% white, 41% black, and 19% Hispanic; 46% men who have sex

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with men; 19% injection drug users; 10% both men who have sex with men and injection drug users; 10% heterosexual contact cases; and 15% with other or unknown HIV risk exposures. The median age was 34 years.

Incidence Trends for OIs, 1992–1998

Incidence trends for OIs in 1992–1998 were examined in the ASD Project by assessing incidence of AIDS-defining conditions in cases per 100 person-years [10]. The data were standardized to the population of persons reported with AIDS nationally in 1992–1998, by age, sex, race, HIV exposure mode, country of origin, and $CD4^+$ T lymphocyte count [11, 12]. The incidence was computed in this way so that the data would be as representative as possible of persons with AIDS in the United States, despite the fact that the ASD Project is limited to the 11 cities listed above and therefore does not include all cities with significant rates of AIDS or AIDS-defining OIs (e.g., histoplasmosis and coccidioidomycosis) that occur in limited geographic areas in the United States. The Cochran-Mantel-Haenszel statistic was used to test for trend during this 7-year period.

The incidence of nearly all AIDS-defining illnesses decreased significantly in 1992–1998; trends for the most commonly occurring OIs are depicted in figure 1 (adapted and updated from [11]). Additional analyses comparing the decreases in incidence of *Pneumocystis carinii* pneumonia (PCP), disseminated *Mycobacterium avium* complex (MAC) disease, and candidal esophagitis in 1996–1998 (during which time HAART was increasingly used in the United States) with the decreases in incidence of these diseases in 1992–1995 indicated significantly steeper declines in the later period.

The incidence of PCP declined 21.5% per year in 1996–1998, compared with 3.4% per year in 1992–1995 (difference in rates of decline, $P < .001$). The incidence of MAC disease declined 39.9% per year in 1996–1998, compared with 4.7% per year in 1992–1995 ($P < .001$), and the incidence of candidal esophagitis declined 16.7% per year in 1996–1998, compared with 0.2% per year in 1992–1995 ($P < .001$).

Such declines in morbidity due to HIV have been reported in other cohorts of HIV-infected persons in the United States [1], Canada [3], and Western Europe [4]. These observations have been attributed to improvement in the general care of HIV-infected persons, to specific OI prevention measures, and, most recently, to the availability of HAART [1]. A specific link between declining OI incidence and HAART has been established by other investigators [13, 14]. Particularly encouraging is the observation that the incidence of most OIs has decreased, including that of many for which specific OI preventive measures have not been available or recommended, such as cytomegalovirus disease, cryptosporidiosis, and Kaposi's sarcoma.

It is also noteworthy that in this analysis, incidence data were standardized to reported AIDS cases by $CD4^+$ T lymphocyte count; hence, they do not take into account potential increases in $CD4^+$ counts in the HIV-infected population and the declines in incidence of OIs that accompany such increases, changes

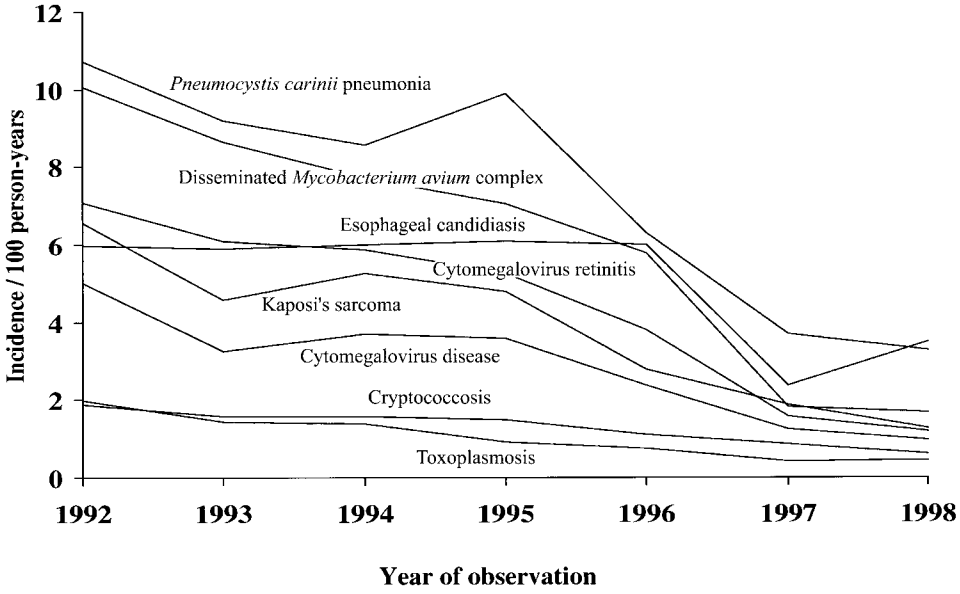

Figure 1. Trends for opportunistic infections in HIV-infected adults and adolescents, ASD (Adult and Adolescent Spectrum of Disease) Project, 1992–1998. Data are standardized to the population of AIDS cases reported nationally in the same years by age, sex, race, HIV exposure mode, country of origin, and $CD4^+$ T lymphocyte count. Since the median $CD4^+$ T lymphocyte count of reported patients with AIDS is between 100 and 110/μL, rates indicate the incidence of OIs among persons with $CD4^+$ counts in this range. Nos. of subjects included in the analysis are 10,441, 11,589, 11,276, 10,048, 9250, 8897, and 8074, respectively, for the years 1992–1998. Figure is adapted and updated from [11].

that routinely occur among persons who respond to HAART [15–21].

Incidence of OIs, 1996–1998

With the decreasing incidence of OIs since 1992 and particularly in the era of HAART (1996–1998), it is reasonable to assess the spectrum of diseases still observed in the latter era. The incidence of OIs was examined in the ASD Project database specifically for 1996–1998. Data were standardized to the population of AIDS cases reported nationally in the same years; thus, these data represent the incidence of OIs in a population with the $CD4^+$ T lymphocyte profile of reported AIDS cases (median $CD4^+$ count between 100 and 110/μL). OIs with the highest incidence were PCP (4.7 cases/100 person-years), candidal esophagitis (4.3 cases/100 person-years), and disseminated MAC disease (3.4 cases/100 person-years). The incidence of any AIDS-defining OI in this population was 16 cases/100 person-years (adapted and updated from [11]).

Some differences in incidence rates in 1996–1998 were observed by sex and by HIV exposure mode (figure 2*A* and 2*B*). The incidence rates of esophageal candidiasis, tuberculosis, cryptosporidiosis, and chronic mucocutaneous herpes simplex virus disease were significantly higher among women, whereas Kaposi's sarcoma was more frequent among men (figure 2*A*). By HIV exposure mode, among men, Kaposi's sarcoma was more frequent among men who have sex with men, whereas esophageal candidiasis, recurrent pneumonia, tuberculosis, and toxoplasmosis were more frequent among injection drug users (figure 2*B*).

Therefore, despite declining OI incidence, the data for 1996–1998 clearly indicate that OIs continue to occur, with an appreciable incidence in persons with $CD4^+$ T lymphocyte counts in the range of those reported with AIDS in the United States. It is also noteworthy that the spectrum of disease and the relative frequencies of OIs have not changed appreciably since earlier in the AIDS epidemic. PCP, candidal esophagitis, and MAC disease continue to be the most common OIs; these data are in agreement with data reported by others [1, 3, 4, 10].

It is also noteworthy that differences in incidence by sex and HIV exposure mode are present and are consistent with results reported by others [22, 23]; the most notable of these concerns Kaposi's sarcoma, which is clearly most common among men who have sex with men. The latter observation is consistent with the likelihood that the causative agent of Kaposi's sarcoma, human herpesvirus type 8, is transmitted sexually in this population [24].

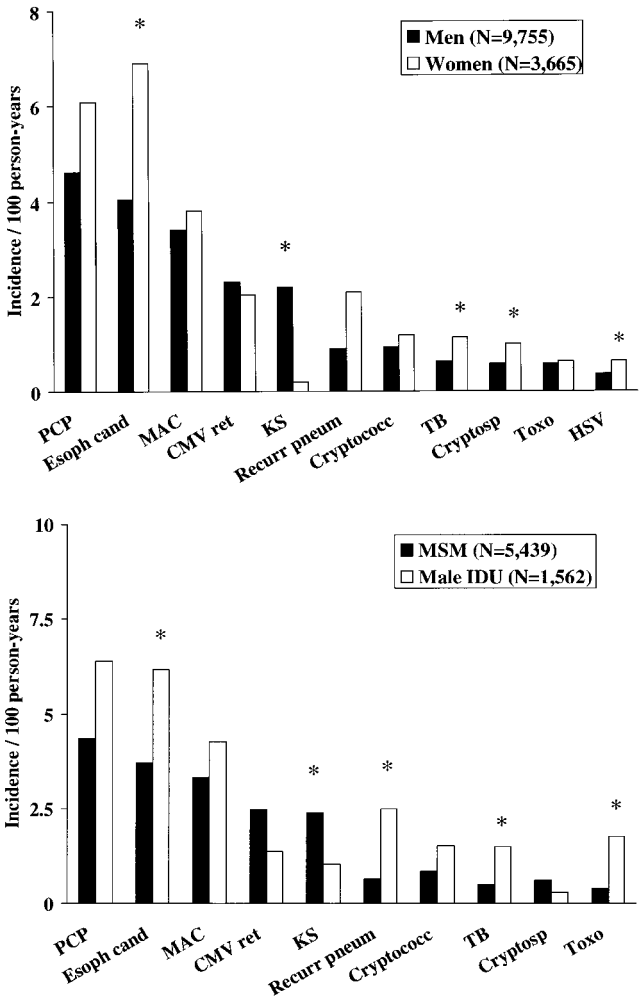

Figure 2. Incidence of AIDS-defining opportunistic infections in *(A)* men vs. women and *(B)* men who have sex with men *(MSM)* vs. men who are injection-drug users *(IDUs)*, from the ASD Project, 1996–1998. Data are standardized to the population of AIDS cases reported nationally in the same years by age, race, country of origin, and $CD4^+$ T lymphocyte count. CMV ret, cytomegalovirus retinitis; Cryptococc, cryptococcosis; Cryptosp, cryptosporidiosis; Esoph cand, esophageal candidiasis; HSV, herpes simplex virus disease; KS, Kaposi's sarcoma; MAC, disseminated disease due to *Mycobacterium avium* complex; PCP, *Pneumocystis carinii* pneumonia; Recurr pneum, recurrent pneumonia; TB, tuberculosis; Toxo, toxoplasmic encephalitis; and *, statistically significant differences. Figure is adapted and updated from [11].

At What $CD4^+$ T Lymphocyte Counts Do Patients Develop OIs in the HAART Era?

Since HAART frequently results in increases in the $CD4^+$ T lymphocyte count of 100–250/μL, it is reasonable to assess whether OIs continue to occur at these higher $CD4^+$ counts, or whether the increased $CD4^+$ T lymphocyte counts confer immunologic reconstitution, such that those OIs that occur do so primarily at low $CD4^+$ counts. This question was addressed with regard to the ASD Project database by analyzing incident OIs during 1994–1997 [24]. Among persons whose lowest previous $CD4^+$ T lymphocyte counts were <200/μL, the estimated median $CD4^+$ count at which OIs occurred in persons receiving

Table 1. Estimated $CD4^+$ T lymphocyte count at AIDS diagnosis, as related to antiretroviral therapy (ART) regimen at time of diagnosis, for persons with a $CD4^+$ T lymphocyte nadir <200/μL (ASD Project, 1994–1997).

AIDS-defining illness	No. of cases	$CD4^+$ T lymphocytes/μL (95% CI)[a]			
		No ART	Mono ART	Dual ART	HAART
Initial AIDS-defining illness[b]	2453	22 (19–25)	28 (25–32)	33 (29–38)	45 (31–66)
Pneumocystis carinii pneumonia	1208	13 (11–16)	20 (16–24)	28 (21–37)	29 (15–55)
Candidiasis	1118	13 (10–16)	22 (18–28)	20 (15–26)	24 (11–52)
Extrapulmonary mycobacteriosis	1288	8 (7–10)	11 (9–14)	11 (8–14)	19 (9–42)
Cytomegalovirus retinitis	821	6 (5–8)	10 (8–13)	11 (7–15)	22 (8–61)
Kaposi's sarcoma	527	19 (15–25)	19 (13–27)	24 (17–36)	21 (9–50)
Recurrent pneumonia	472	14 (10–20)	18 (14–24)	20 (13–30)	66 (24–184)
Cytomegalovirus disease	503	7 (5–10)	10 (7–15)	10 (6–18)	12 (4–38)
Tuberculosis	271	27 (19–39)	20 (13–30)	30 (17–52)	62 (15–261)
Extrapulmonary cryptococcosis	282	19 (14–26)	18 (13–24)	23 (15–35)	19 (7–55)
Toxoplasmosis of brain	306	17 (11–26)	14 (8–22)	17 (9–31)	12 (3–42)

NOTE. HAART, highly active antiretroviral therapy (2 nucleoside reverse-transcriptase inhibitors plus a nonnucleoside reverse-transcriptase inhibitor or a protease inhibitor).

[a] $CD4^+$ T lymphocyte counts were estimated from a linear regression model including $CD4^+$ T lymphocyte nadir (lowest count before that associated with OI diagnosis) and ART regimen as dependent variables. Missing $CD4^+$ data were augmented from multiple imputations.

[b] Nos. of initial AIDS-defining illness cases per therapy category were as follows: No ART, 1111; Mono ART, 784; Dual ART, 495; and HAART, 63.

HAART (defined as 2 nucleoside reverse-transcriptase inhibitors plus a nonnucleoside reverse-transcriptase inhibitor or a protease inhibitor) was somewhat higher than that at which OIs occurred in persons not receiving antiretroviral therapy (e.g., for PCP, 29/μL vs. 13/μL; for candidiasis [esophagitis or pneumonia], 24/μL vs. 13/μL; and for nontuberculous mycobacteriosis, 19/μL vs. 8/μL [table 1]) [25]. Although these differences were statistically significant and suggest incomplete immune reconstitution, these $CD4^+$ T lymphocyte counts were low and the differences are of questionable clinical significance.

The issue of immune reconstitution was also examined by determining the risk of PCP and MAC disease among persons whose $CD4^+$ T lymphocyte counts had increased from below to above thresholds recommended for chemoprophylaxis (200/μL for PCP and 50/μL for MAC disease) and for whom prophylaxis had been discontinued, compared with the risk for persons whose $CD4^+$ counts had never dropped below these thresholds [21]. The risks were similar but substantially lower than for subjects whose $CD4^+$ T lymphocyte counts were below threshold values but who had never been prescribed prophylaxis [21]. Other investigators have also reported very low risk of PCP [15–21] and MAC disease [21, 26] among patients whose $CD4^+$ counts have increased to above prophylaxis thresholds. These observations suggest that HIV-infected persons are at substantially lower risk for most OIs when their $CD4^+$ T lymphocyte counts increase significantly in response to HAART.

Why Do HIV-Infected Persons Continue to Get PCP?

Since PCP continues to be the most common incident OI, a separate analysis was conducted to determine the reasons why HIV-infected adults in the ASD Project population continue to develop this disease. Cases of PCP occurring in 1996–1998 were categorized as involving persons not previously receiving medical care, if they had no history of a positive HIV test result, a $CD4^+$ T lymphocyte count determination, or an AIDS-defining illness before diagnosis of PCP. Cases involving persons who were in care but had not been prescribed prophylaxis before illness were defined as those who had been enrolled in the ASD Project and had at least 1 $CD4^+$ T lymphocyte count recorded but had not been prescribed trimethoprim-sulfamethoxazole, dapsone, or aerosolized pentamidine prior to illness.

These persons in turn were categorized as (1) having met the criteria for PCP prophylaxis ($CD4^+$ T lymphocyte count <200/μL or history of thrush or unexplained fever) and therefore should have been prescribed prophylaxis or (2) not having met these criteria and therefore not expected to have had prophylaxis prescribed. Finally, persons with PCP were deemed to have developed PCP during prescribed prophylaxis if any of the 3 drugs mentioned above had been prescribed before diagnosis. The data in this analysis were weighted by age, sex, race, and HIV exposure mode to AIDS cases diagnosed in 1996–1998, so that the results would be as representative as possible of AIDS patients in the United States.

The results of this analysis are shown in figure 3 (updated from [27]). Nearly half (46%) of PCP cases involved persons not previously in medical care. Twenty-three percent involved persons who were in care but who had not been prescribed prophylaxis; of these, 16% met the criteria for prophylaxis (and therefore should have been prescribed prophylaxis) and 7% did not meet the criteria. Thirty-two percent of cases involved persons who had been prescribed prophylaxis.

The PCP data indicate the importance of identifying HIV infection early and getting people into care. Of the estimated 650,000–900,000 HIV-infected persons in the United States [28], ~500,000 are aware of their HIV infection [29], and an esti-

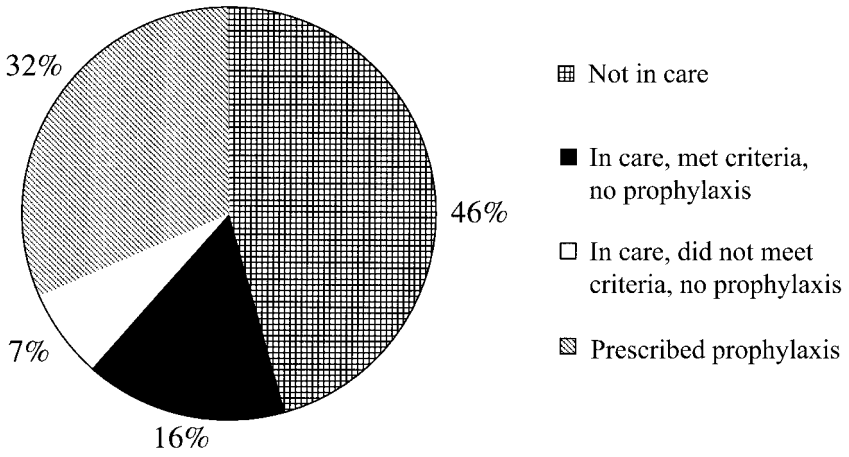

Figure 3. Reasons why persons developed *Pneumocystis carinii* pneumonia, from the ASD Project, 1996–1998 (n = 1837). See text for description of categories. Figure is updated from [27].

mated 335,000, or approximately half of those infected, are receiving medical care [30]. Clearly, improved efforts to identify such persons and to get them into care is important for their own health as well as others', since behavioral counseling may reduce transmission of HIV. The data also indicate that a significant proportion of cases of PCP involve persons prescribed prophylaxis; possible reasons include poor adherence, lower efficacy at very low $CD4^+$ T lymphocyte counts, and antimicrobial resistance [27]. These possible causes could not be differentiated in this analysis, although an earlier analysis documented very low $CD4^+$ T lymphocyte counts to be a risk factor for PCP in this group [31].

Prevalence of Prescription of Antiretroviral Therapy and Specific OI Prophylaxis

The annual rates of prescription of antiretroviral therapy and prophylaxis for PCP and MAC disease among persons for whom these therapies are recommended by current guidelines [7] in the ASD Project are shown in figure 4*A*, 4*B*, and 4*C*. Among persons with a $CD4^+$ T lymphocyte count $<500/\mu L$, 58% were prescribed HAART (2 nucleoside reverse-transcriptase inhibitors plus either a nonnucleoside reverse-transcriptase inhibitor or a protease inhibitor) by the end of 1998; among eligible persons, 76% and 54% were prescribed prophylaxis for PCP and MAC disease, respectively (updated from [11]).

The data regarding prescription of therapies are encouraging because the prescription of HAART among persons with $CD4^+$ T lymphocyte counts $<500/\mu L$ has increased rapidly since 1996. However, the frequency of prescription of HAART and of prophylaxis for both PCP and MAC is still suboptimal. Prescriptions of these therapies have been shown by various investigators to differ by sex, race, HIV exposure mode, type of health care facility, method of payment, and expertise of the health care provider [32–36].

Impact of OI Prophylaxis in the HAART Era

The impact of HAART and specific OI prevention measures on the survival of patients with AIDS was evaluated in an analysis of the effects of these measures on survival in an extended multivariate Cox model, by use of data from the period 1990–1997 [37]. The most profound effect on survival was associated with HAART (RR, 0.15; 95% CI, 0.12–0.17); lesser but highly significant effects were associated with double antiretroviral therapy (RR, 0.24; 95% CI, 0.22–0.26) and monotherapy (RR, 0.38; 95% CI, 0.36–0.4; figure 5, adapted from [37]). Prophylaxis for PCP and MAC disease and pneumococcal vaccination conferred increases in survival time, although of lesser magnitude (RR, 0.79, 95% CI, 0.7–0.89; RR, 0.76, 95% CI, 0.68–0.86; and RR, 0.96, 95% CI, 0.92–1, respectively; figure 5) [37].

The survival data clearly indicate that antiretroviral therapy, specifically HAART, is associated with the most profound effect on the survival among AIDS patients in the ASD Project population; the data also indicate that specific OI prevention measures are still important in the HAART era and would be expected to be particularly important for those who do not have access to HAART, are not willing to take HAART, are poorly adherent to HAART, or are infected with resistant strains of HIV. The latter problem is likely to increase in the next few years.

Incidence Trends of OIs in HIV-Infected Children

Dramatic declines in the incidence of pediatric AIDS have occurred as a result of successful implementation of the 1994 US Public Health Service guidelines for the use of zidovudine during pregnancy and the neonatal period [38] and guidelines for universal, routine HIV counseling and voluntary testing of

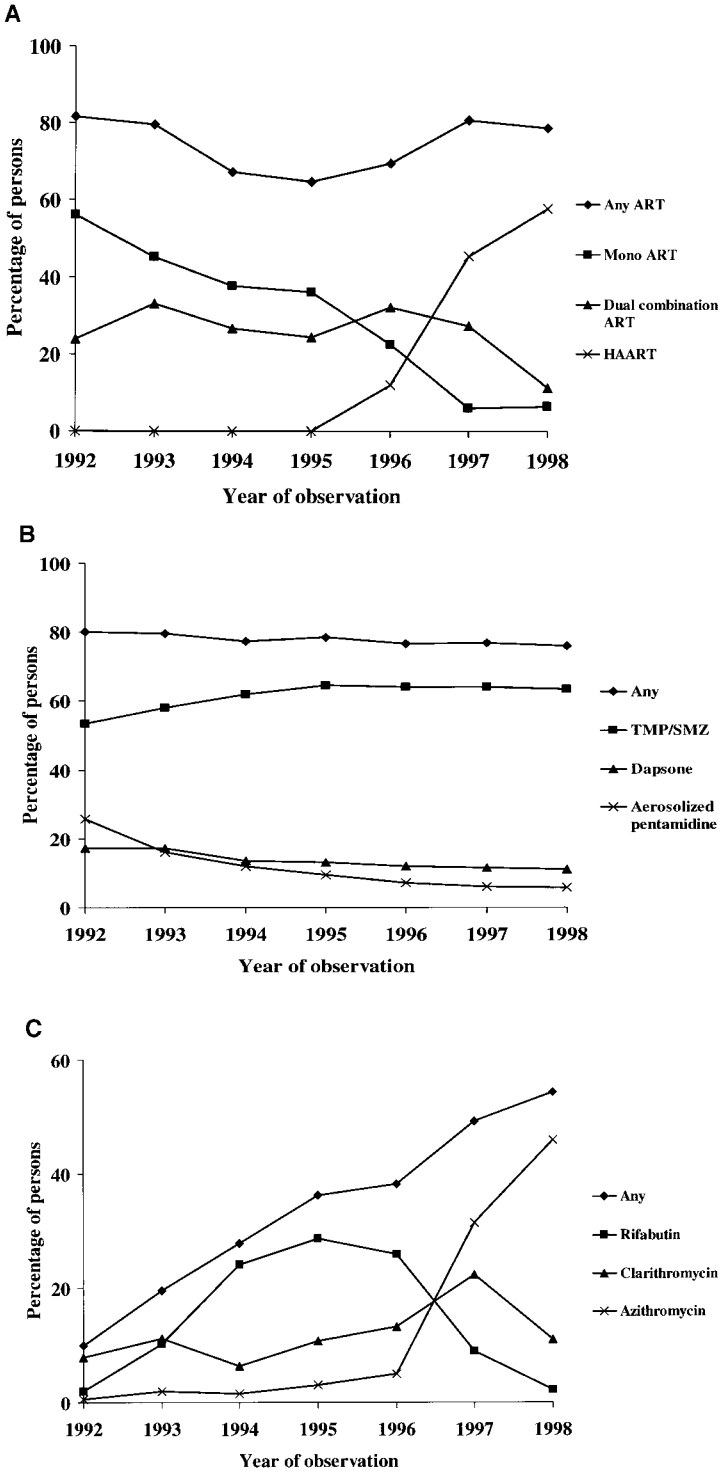

Figure 4. From ASD Project data (1992–1998), trends in *(A)* prescribed use of antiretroviral therapy (ART) among persons with $CD4^+$ T lymphocyte counts <500/μL; *(B)* prophylaxis for *Pneumocystis carinii* pneumonia among persons with $CD4^+$ T lymphocyte counts <200/μL; and *(C)* prophylaxis for disseminated *Mycobacterium avium* complex disease among persons with $CD4^+$ T lymphocyte counts <50/μL. ART, antiretroviral therapy; HAART, highly active antiretroviral therapy (2 nucleoside reverse-transcriptase inhibitors plus a nonnucleoside reverse-transcriptase inhibitor or a protease inhibitor); and TMP-SMZ, trimethoprim-sulfamethoxazole. Figure is adapted and updated from [11].

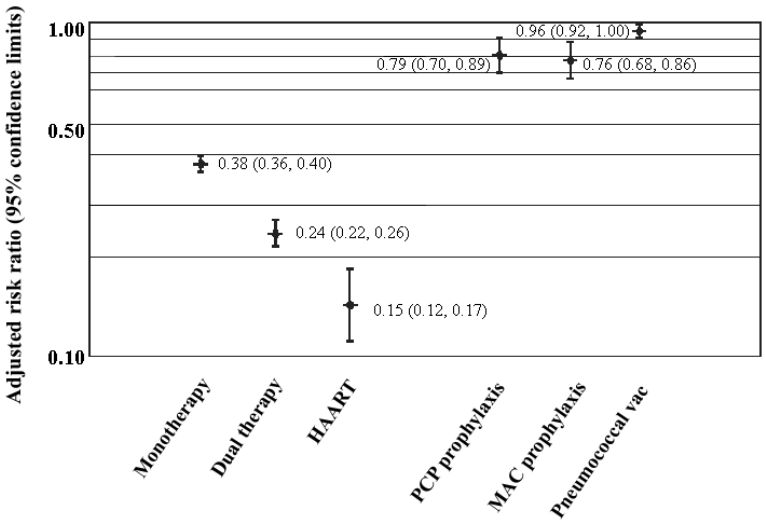

Figure 5. Effects of antiretroviral therapy and prophylaxis for opportunistic infection on survival after diagnosis of AIDS, from the ASD Project, 1990–1997. HAART, highly active antiretroviral therapy (2 nucleoside reverse-transcriptase inhibitors plus a nonnucleoside reverse-transcriptase inhibitor or a protease inhibitor); MAC, disease due to *Mycobacterium avium* complex; PCP, *Pneumocystis carinii* pneumonia; vac, vaccination. Figure is adapted from [37].

pregnant women [39]. From 1992 through 1997, the overall incidence of AIDS among children declined 67% [40].

Among children who are HIV-infected, trends for OIs were examined in the CDC's Pediatric Spectrum of Disease Project, which monitored trends for 7 OIs during 1992–1997 among 3971 HIV-infected children who were enrolled in 8 sites in the United States [41]. Incidence rates were estimated per 100 children alive in each year and who had not had the OI of interest diagnosed before that year. Rates were adjusted for age because age is a significant risk factor for OIs in HIV-infected children [41] and because the mean age of the cohort studied has increased from 1992 through 1997. Because the slope of the trend in incidence rates did not change significantly over the study period, a Poisson regression model, which assumes a linear trend in OI rates from 1992 through 1997, was used for the age adjustment.

Average age-adjusted incidence rates for the period were highest for PCP, disseminated MAC disease, esophageal candidiasis, and recurrent bacterial infection, but annual incidence rates for each of these OIs declined from 1992 through 1997 (figure 6). Average age-adjusted rates for the period were lower for cytomegalovirus disease, cryptosporidiosis, and candidiasis of the bronchi, trachea, or lung, but annual rates for these OIs also declined during the period (figure 6). Therefore, declining incidence was observed for all 7 OIs. Although there was a trend toward a sharper decline in all OI rates after 1995, when HAART became available for children [42], the change in slope was not significant. Since the introduction of HAART for children is a relatively more recent phenomenon than that for adults, evaluation of OI trends for subsequent years will be necessary to fully evaluate the impact of HAART in HIV-infected children.

For those OIs that continue to occur in HIV-infected children, national AIDS surveillance data indicate that the relative frequencies of AIDS-defining conditions are similar to those observed in earlier years of the epidemic, as is the case with data for HIV-infected adults. For instance, in 1997, PCP, recurrent bacterial infection, and candidal esophagitis were the conditions most frequently associated with reported AIDS cases [43], similar to the distribution observed in cases reported cumulatively (CDC, unpublished data).

The Future of OIs

The declining incidence of HIV-associated OIs in both adults and children in the United States raises questions about the occurrence of OIs in the next few years. Will incidence rates continue to decline? For what OIs (or other conditions) will patients be hospitalized? Will new OIs emerge?

The declining incidence of OIs, hospitalizations, and deaths in the United States is tempered by the facts that complete suppression of HIV plasma RNA is not maintained in most patients receiving HAART [44], that loss of viral suppression is associated with resistance to antiretroviral drugs [45], and that transmission of HIV-resistant strains is occurring [46]. Furthermore, the declines in AIDS incidence and AIDS-related deaths have shown signs of slowing in 1998 [47], as have incidence rates of specific OIs, as shown here and by other in-

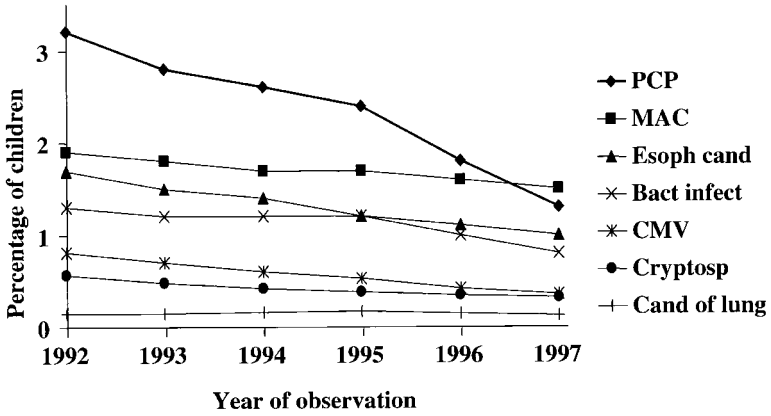

Figure 6. Trends of opportunistic infections in HIV-infected children, from the Centers for Disease Control and Prevention's Pediatric Spectrum of Disease Project, 1992–1997. Incidence rates were estimated per 100 children alive in each year and were age-adjusted in a Poisson regression model. Bact infect, recurrent bacterial infection; Cand of lung, candidiasis of the bronchi, trachea, or lung; CMV, cytomegalovirus disease; Cryptosp, cryptosporidiosis; Esoph cand, esophageal candidiasis; MAC, disease due to *Mycobacterium avium* complex; and PCP, *Pneumocystis carinii* pneumonia.

vestigators ([48] and Frank Palella, M.D., personal communication). We hope that the incidence of OIs will remain relatively low, despite incomplete viral suppression in many patients, or that new therapies and simpler, more convenient regimens that facilitate adherence to HAART will allow these trends to continue. However, the future is uncertain in this regard.

In the meantime, the OIs that continue to occur appear to be doing so with approximately the same relative frequency as in the pre-HAART era, and other reasons for hospitalization do not yet appear to be epidemiologically significant. For example, in New York City, although the hospital census of HIV-infected patients has sharply declined [5], the percentage of hospitalized HIV-infected patients who have OIs has remained stable in the HAART era [49].

However, not all HIV-associated conditions are diminishing in the HAART era. For example, accumulating evidence suggests that successful suppression of HIV RNA does not translate into decreased replication of hepatitis C virus (HCV) [50] and, worse, with antiretroviral therapy, inflammation and fibrosis from HCV coinfection may become manifest [51, 52]. Since HCV coinfection is common among HIV-infected persons, it is possible that hospitalizations for chronic liver disease may increase. Similarly, although the incidence of Kaposi's sarcoma is decreasing, incidence rates of other neoplasms, such as immunoblastic lymphoma, invasive cervical cancer, Hodgkin's lymphoma, and Burkitt's lymphoma, are not [53]. These findings suggest that the neoplastic complications of HIV disease may become relatively more frequent in the future.

Several new syndromes have been described that occur in the first 2 months after the initiation of HAART; these include cytomegalovirus vitritis [54], MAC lymphadenitis [55], paradoxical responses to treatment for tuberculosis [56], and exacerbation of cryptococcosis [57]. These syndromes, which have been termed "reversal syndromes," frequently occur in the setting of increasing $CD4^+$ T lymphocyte counts, and it has been hypothesized that they represent an unmasking of an undiagnosed OI, or an exacerbation of a diagnosed OI in the setting of improved immune function that contributes to the pathogenesis of the OI. Some of these syndromes respond to symptomatic treatment [56]. Although the epidemiology of these syndromes has not been clearly defined, they may occur with significant frequency, according to some reports [58, 59], and may contribute to the epidemiology of OIs in the future. Thus, one of the many challenges in this era of expanding therapeutic options for HIV disease will be to maintain surveillance for all OIs and to monitor "emerging" OIs, to assess their incidence, risk factors, and modes of prevention and treatment.

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