AIDS-Related Opportunistic Illnesses Occurring After Initiation of Potent Antiretroviral Therapy

The Swiss HIV Cohort Study

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Context Acquired immunodeficiency syndrome–related opportunistic illnesses (OIs) continue to occur after initiation of potent antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection. Risk factors for clinical progression to OIs during potent therapy are not well defined.

Objective To examine the incidence of and risk factors for OIs among patients treated with potent antiretroviral therapy in a population-based study.

Design The Swiss HIV Cohort Study, a prospective cohort study of adult HIV-infected persons.

Setting Seven study centers throughout Switzerland.

Patients A total of 2410 cohort study participants with a potential follow-up of at least 15 months after starting potent therapy between September 1995 and December 1997.

Main Outcome Measures Disease-specific incidence of OIs during the 6 months preceding potent antiretroviral therapy and at 3 intervals after initiating therapy; risk factors for development of OIs during therapy.

Results Of the 2410 participants, 143 developed 186 OIs after initiation of potent antiretroviral therapy. Incidence of any OI decreased from 15.1 per 100 person-years in the 6 months before therapy to 7.7 in the first 3 months after starting treatment, 2.6 in the following 6 months, and 2.2 per 100 person-years between 9 and 15 months. Reductions in incidence ranged from 38% per month for Kaposi sarcoma ($P<.001$) to 5% per month for non-Hodgkin lymphoma ($P = .31$). Baseline CD4 cell count continued to predict the risk of disease progression after initiating potent therapy. Compared with CD4 cell counts above 200×10^6/L, the hazard ratio for developing OIs was 2.5 (95% confidence interval [CI], 1.4-4.5) for counts between 51 and 200×10^6/L and 5.8 (95% CI, 3.2-10.5) for counts below 51×10^6/L at baseline. Independent of baseline CD4 cell count, a rise in CD4 cell count by 50×10^6/L or more and undetectable HIV-1 RNA in plasma (<400 copies/mL) by 6 months reduced risk of subsequent events, with hazard ratios of 0.32 (95% CI, 0.20-0.52) and 0.39 (0.24-0.65), respectively.

Conclusions Our data indicate that the risk of developing an OI for a person receiving potent antiretroviral therapy is highest during the initial months of therapy. Baseline CD4 cell count and immunologic and virologic response to treatment were strong predictors of disease progression in patients receiving potent therapy. Individuals with CD4 cell counts of 50×10^6/L or below may need close clinical surveillance after initiation of potent therapy.

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POTENT ANTIRETROVIRAL TREATMENT has led to a dramatic decrease in human immunodeficiency virus (HIV)-associated morbidity and mortality.[1-3] However, acquired immunodeficiency syndrome (AIDS)-related opportunistic illnesses (OIs) continue to occur,[4] and risk factors for clinical progression during potent therapy are ill-defined at present.

Treatment is followed by progressive recovery of memory and naive CD4 T-lymphocyte subpopulations and of proliferative responses to various bacterial and viral antigens; however, normalization may require years.[5-7] There is thus a period of uncertain immune function, particularly for persons with advanced disease who are starting therapy. Also, initiation of potent therapy may be accompanied by inflammatory reactions to opportunistic pathogens,[8-12] probably because of rapid

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immune response recovery, which may alter clinical presentation.[13]

We examined the Swiss HIV Cohort Study database to identify incidence patterns and risk factors for developing OIs among patients treated with potent antiretroviral therapy.

PARTICIPANTS AND METHODS

The Swiss HIV Cohort Study

The Swiss HIV Cohort Study enrolls HIV-infected persons aged 16 years or older.[14] Patients are followed up in 1 of 7 study centers (Basel, Bern, Geneva, Lausanne, Lugano, St Gall, Zurich). Enrollment is independent of disease stage or degree of immunosuppression and data are collected according to standardized criteria on structured forms at registration and at follow-up visits scheduled at 6-month intervals. Medications are registered by month of initiation and discontinuation. We measured CD4 cell counts with flow cytometry and viral load with the Roche Amplicor Monitor assay (Roche Diagnostics, Basel, Switzerland, level of detection, 400 copies/mL). AIDS was defined according to category C clinical conditions of the Centers for Disease Control and Prevention classification system for HIV infection revised in 1993.[15] Ethics committees in the 7 centers approved the study, and informed consent was obtained from all participants.

Inclusion Criteria

We included all participants of the Swiss HIV Cohort Study who started potent antiretroviral therapy between September 1, 1995, and December 31, 1997; had a CD4 cell count and viral load measurement during the 3 months before starting; and made at least 1 follow-up visit more than 1 month after starting potent therapy. The database included data up to March 1999. All patients had a potential follow-up of at least 15 months after starting potent therapy. Potent antiretroviral therapy was defined as combination treatment with at least 3 drugs, including at least 1 protease inhibitor.

We excluded patients receiving regimens for which saquinavir hard gel capsules were the only form of protease inhibitor used because of reduced probability of reaching undetectable viremia[2] (probably explained by inferior bioavailability of saquinavir in hard gel formulation).[16]

Incidence Patterns and Risk Factors

We calculated disease-specific incidence for the 6 months preceding potent antiretroviral therapy, and months 1 to 3, 4 to 9, and 10 to 15 after initiating potent therapy. These intervals were chosen a priori. Incidences were calculated by dividing the number of patients developing an event by the number of person-years at risk. In patients developing the event of interest, follow-up was censored at the date the diagnosis was made, but subjects were followed up for all possible OIs as long as they survived. We used the Poisson distribution to calculate confidence intervals (CIs). We used Poisson regression to estimate slopes of incidence trends, coding time points as 0 for the period preceding start of potent therapy; 1.5, covering the first 3 months; 6, months 4 to 9, and 12, months 10 to 15.

We analyzed the risk of progression to an OI at any time during follow-up, including events occurring more than 15 months after initiating potent therapy, by means of Kaplan-Meier lifetable methods and Cox proportional hazards regression. We measured time from initiating potent therapy either to the OI diagnosis date or the date of the most recent follow-up visit. We considered the importance of treatment response in analyses excluding the first 6 months (to allow adequate assessment of treatment outcome) after starting potent therapy; however, all patients were included in the analysis.

Proportional hazards assumptions were based on Schoenfeld residuals.[17] Results are presented as odds ratios or hazard ratios, with 95% CIs. Analyses were conducted using SAS (version 6.12; SAS Institute, Cary, NC) and Stata software (version 6.0; Stata Corporation, College Station, Tex).

RESULTS

Between September 1995 and December 1997, 2867 (66.2%) of 4328 patients seen in the Swiss HIV Cohort Study started protease inhibitor–containing regimens with at least 3 antiretroviral drugs. We excluded 61 patients (2.1%) having saquinavir (hard gel capsule formulation) as the only protease inhibitor, 98 patients (3.4%) who were not seen since initiating treatment, and 298 patients (10.4%) with missing baseline viral load or CD4 cell count. The analysis was thus based on 2410 patients (84.1%) contributing 3974 person-years of follow-up. The mean number of visits per patient was 7.9 (range, 1-29); 642 patients (26.6%) were female. Categories of HIV transmission included men having sex with men (n = 925, 38.4%), injectable drug use (n = 701, 29.1%), heterosexual intercourse (n = 689, 28.6%), and transmission via blood products or an unclear route (n = 95, 3.9%). Indinavir was used in 1284 patients (53.3%), ritonavir in 619 (25.7%), nelfinavir in 305 (12.7%), a saquinavir-ritonavir combination in 167 (6.9%), and other combinations in 35 (1.4%). A total of 919 patients (38.1%) were treatment-naive prior to initiation of potent antiretroviral therapy. In comparing the 6-month period before starting potent therapy with the subsequent 6 months, no significant ($P>.25$) changes were noted for primary and secondary prophylaxis of *Pneumocystis carinii* pneumonia and cerebral toxoplasmosis, antifungal or antimycobacterial drugs, therapy for cytomegalovirus disease, or anticancer treatment.

During the same period, 1522 patients seen in a study clinic did not start potent therapy. Compared with patients starting potent therapy, median CD4 cell counts were higher (303 vs 188 $\times 10^6$/L, $P<.0001$) and median viral load lower (3.94 vs 4.49 log RNA copies/mL, $P<.001$) among those not starting therapy.

Incidence Patterns

Incidence trends across the 4 time periods before and after initiating potent antiretroviral therapy are shown in FIGURE 1

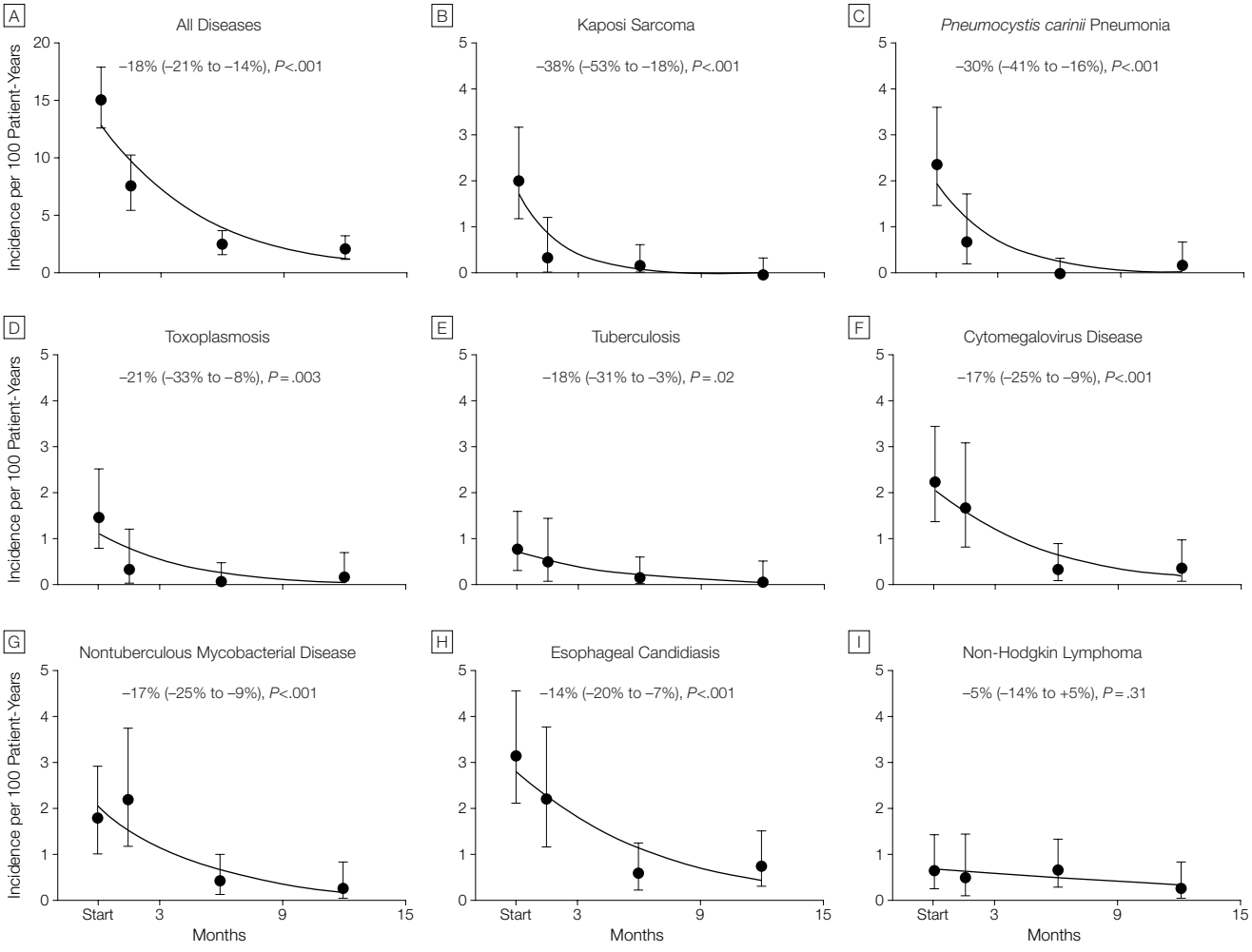
for all OIs combined and for individual diseases diagnosed in 10 or more patients. The incidence of 15.1 new OIs per 100 person-years during the 6 months preceding potent therapy was similar to that of 15.7 per 100 person-years observed in the entire cohort from 1992 to 1994, before potent therapies were available.[18] Incidence of any OI decreased to 7.7 per 100 person-years in the first 3 months after starting treatment, 2.6 in the following 6 months, and to 2.2 per 100 person-years between 9 and 15 months. Incidences of individual diseases generally followed a similar pattern, although the decline appeared to be more pronounced for some diseases than others. This was further examined in regression analyses. The decline was described by a log linear relationship. Incidence of all OIs combined decreased by an estimated 18% per month ($P<.001$). The reduction in incidence ranged from 38% per month for Kaposi sarcoma ($P<.001$) to 5% per month for non-Hodgkin lymphoma ($P = .31$). A formal test for heterogeneity indicated that this variation in slopes was unlikely to be due to chance ($\chi^2_7 = 15.9$; $P = .03$).

Incidence rates and selected characteristics of events are shown in TABLE 1 for 6 months before and 15 months after initiating potent therapy. No significant difference was observed between the 2 periods for CD4 cell count at diagnosis. Prior to initiation of potent therapy, 9.2% of events (10/109) occurred at CD4 cell counts greater than 200×10^6/L vs 12.6% (13/103) during the 15 months after start of therapy ($P = .42$ by χ^2 test). With potent therapy, significantly more events ($P<.001$) occurred at undetectable viral load levels: 28.4% (29/102) vs 7.1% (7/98).

Risk of Progression to OIs With Potent Antiretroviral Therapy

Overall, 143 participants developed 186 OIs at any time after starting potent an-

Figure 1. Incidences of All Opportunistic Illnesses Combined and for Individual Diseases Diagnosed in 10 or More Patients Before and After Introduction of Potent Antiretroviral Therapy



Incidences given at the start of potent therapy represent the 6 months prior to potent therapy. The percentages in each graph (with 95% confidence intervals) indicate percentage reduction in incidence per month and correspond to the slope of the log linear regression line (solid line).

Table 1. AIDS-Related Opportunistic Illnesses in Individuals Taking Potent Antiretroviral Therapy*

Illness	Events Within 6 Months Before Start of Potent Antiretroviral Therapy			Events Within 15 Months After Start of Potent Antiretroviral Therapy			
	No. of Patients (n = 131)	Incidence per 100 Person-Years†	CD4 at Event, $\times 10^6$/L, Median (Range)	No. of Patients (n = 92)	Incidence per 100 Person-Years†	CD4 at Event, $\times 10^6$/L, Median (Range)	No. (%) Within First 3 Months
Esophageal candidiasis	28	3.14	28 (0-194)	28	1.02	50 (2-516)	14 (50)
Nontuberculous mycobacteria	16	1.79	16 (0-151)	21	0.76	77 (1-286)	13 (62)
Cytomegalovirus disease	20	2.24	28 (0-230)	18	0.65	30 (3-90)	10 (56)
Non-Hodgkin lymphoma	6	0.67	175.5 (13-222)	14	0.50	122.5 (16-602)	3 (21)
Mycobacterium tuberculosis	7	0.78	6 (3-41)	6	0.22	97.5 (58-137)	3 (50)
Pneumocystis carinii pneumonia	21	2.35	28 (2-460)	6	0.22	139 (6-220)	4 (67)
Toxoplasmosis	13	1.45	10 (0-207)	5	0.18	42 (8-203)	2 (40)
Kaposi sarcoma	18	2.02	48 (2-292)	4	0.14	56.5 (10-150)	2 (50)
Progressive multifocal leukoencephalopathy	2	0.22	102 (52-152)	4	0.14	116.5 (74-164)	3 (75)
Other	19	2.13	54 (2-250)	12	0.43	125.5 (6-242)	6 (50)
All	**150**	15.10	26 (0-460)‡	**118**	3.57	60 (1-602)§	**60** (51)

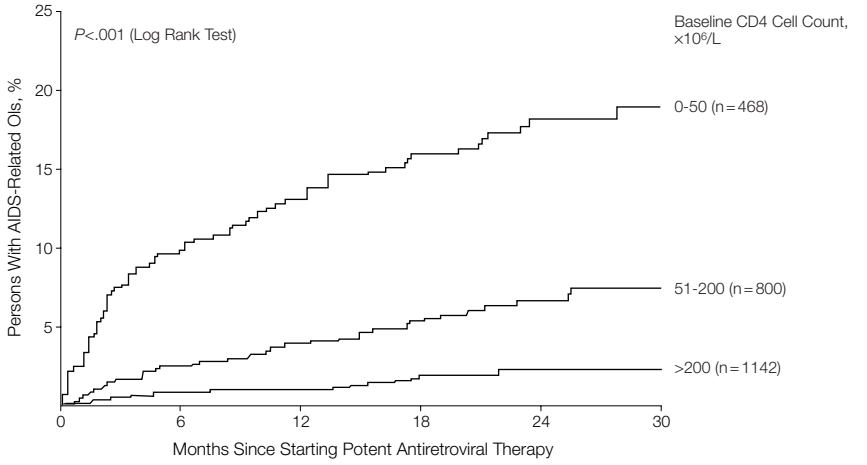
*AIDS indicates acquired immunodeficiency syndrome; other, cryptococcosis, isosporiasis, cryptosporidiosis, recurrent bacterial pneumonia, and primary lymphoma of the central nervous system.
†Calculation of incidence is based on the first event in each patient.
‡Missing for 41 events.
§Missing for 15 events.

Table 2. Risk of AIDS-Related Opportunistic Illnesses*

	Hazard Ratio (95% CI)†	*P* Value
CD4 cell count at baseline, $\times 10^6$/L		
≤50	5.79 (3.21-10.46)	<.001
51-200	2.51 (1.42-4.45)	
>200	1.00	
Viral load at baseline, copies/mL		
>100 000	2.02 (1.12-3.67)	.02
5000-100 000	1.40 (0.77-2.53)	
<5000	1.00	
Age, per 10-y increase	0.80 (0.65-0.99)	.045
Sex (female vs male)	1.29 (0.89-1.85)	.18
Clinical stage at baseline‡		
C	1.52 (1.02-2.26)	.008
B	1.38 (0.81-2.35)	
A	1.00	

*AIDS indicates acquired immunodeficiency syndrome; CI, confidence interval.
†Hazard ratios are determined from Cox regression models. Analysis is based on 2410 patients and 143 events. Estimates are adjusted for all variables listed.
‡Stages defined according to the Centers for Disease Control and Prevention classification system.[15]

Figure 2. Cumulative Probability of Developing an Acquired Immunodeficiency Syndrome (AIDS)–Related Opportunistic Illness (OI) After Starting Potent Antiretroviral Therapy With Stratification by CD4 Cell Count at Baseline



tiretroviral therapy. Esophageal candidiasis was the most frequent OI (n = 49), followed by nontuberculous mycobacterial infections (n = 29), cytomegalovirus disease (n = 27), non-Hodgkin lymphoma (n = 15), toxoplasmosis (n = 13), *P carinii* pneumonia (n = 11), tuberculosis (n = 9), progressive multifocal leukoencephalopathy (n = 8), Kaposi sarcoma (n = 6), and other (n = 19). A new event occurred in 125 patients and 18 patients suffered a relapse of a previous condition. At baseline, there were no differences between subjects developing and not developing OIs in age and sex distribution, HIV transmission group, history of antiretroviral therapy, or type of potent therapy.

In multivariate Cox regression analyses, baseline CD4 cell count was the best predictor of disease progression risk in the setting of potent therapy. Compared with CD4 cell counts above 200 × 10^6/L, the hazard ratio for developing OIs was 2.5 (95% CI, 1.4-4.5) for counts of 51 to 200 × 10^6/L, and 5.8 (3.2-10.5) for counts of 50 × 10^6/L or below. Baseline viral load, clinical stage, and age were also independent predictors of progression risk (TABLE 2). Kaplan-Meier estimates, stratified by baseline CD4 cell count, are shown in FIGURE 2. At 30 months of follow-up, the estimated cumulative risk of devel-

oping an OI was 18.8% (95% CI, 14.8%-22.8%) in patients with a baseline CD4 cell count below 50 × 10^6/L, vs 7.3% (95% CI, 5.1%-9.5%) in patients at 50 to 200 × 10^6/L, and 2.1% (95% CI, 1.1%-3.2%) in patients with a CD4 cell count above 200 × 10^6/L.

Risk of Progression After the Initial 6 Months of Potent Antiretroviral Therapy

We analyzed the risk factors for developing OIs after the initial 6 months of potent antiretroviral therapy (TABLE 3). In Cox regression, baseline CD4 cell count, but not baseline viral load, continued to predict the ongoing risk of clinical progression. In addition, both a rise in CD4 cell count by 50 × 10^6/L or more and reaching undetectable viremia by 6 months reduced risk of subsequent events. This protective effect was also present for subjects with advanced disease (CD4 cell count ≤50 × 10^6/L) since there was no evidence of an interaction between effects associated with values at baseline and at 6 months. Kaplan-Meier estimates of OIs stratified by CD4 cell count and viral load at 6 months are shown in FIGURE 3. The cumulative incidence of OIs at 30 months was 16.6% (95% CI, 11.3%-21.8%) among participants with 200 × 10^6/L or fewer CD4 cells and detectable viremia at 6 months, whereas rates of 5% or less were observed among patients with CD4 cell counts above 200 × 10^6/L or with viremia below level of detection at 6 months.

Table 3. Risk of an AIDS-Related Opportunistic Illness After 6 Months of Potent Antiretroviral Therapy*

	Hazard Ratio (95% CI)†	*P* Value
CD4 cell count at baseline, ×10^6/L		
≤50	5.66 (2.40-13.34)	<.001
51-200	2.68 (1.17-6.16)	
>200	1.00	
CD4 cell count at 6 months ≥50 × 10^6/L increase from baseline	0.32 (0.20-0.52)	<.001
Viral load at baseline, copies/mL		
>100 000	1.69 (0.71-4.00)	.45
5000-100 000	1.42 (0.61-3.20)	
<5000	1.00	
Viral load at 6 months below 400 copies/mL	0.39 (0.24-0.65)	<.001
Age, per 10-y increase	0.78 (0.58-1.06)	.11
Sex (female vs male)	1.42 (0.85-2.36)	.18
Clinical stage at baseline‡		
C	1.52 (0.88-2.63)	.16
B	1.24 (0.55-2.78)	
A	1.00	

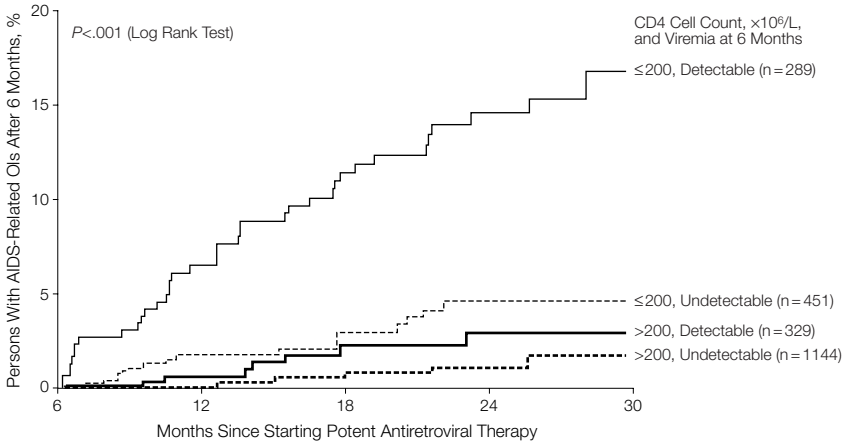
*AIDS indicates acquired immunodeficiency syndrome; CI, confidence interval.
†The analysis is based on all patients, including those having an opportunistic illness in the first 6 months. Hazard ratios are determined from Cox regression models. Analysis is based on 2213 patients and 72 events. Estimates are adjusted for all variables listed.
‡Stages defined according to the Centers for Disease Control and Prevention classification system.[15]

COMMENT

We analyzed AIDS-related OIs before and after initiation of potent antiretroviral therapy in a large HIV cohort. Our results indicate that decline in the incidence of OIs takes place soon after starting potent therapy and is not explained by concomitant changes in the use of drugs for OI prevention. The risk of developing an OI while receiving potent therapy is highest during the initial months of therapy and thus patients should be followed up closely during this critical period. However, the decline varies between diseases. Early reductions in incidence were less pronounced for cytomegalovirus disease, nontuberculous mycobacterial disease, and esophageal candidiasis. Continued immunodeficiency as well as inflammatory reactions accompanying the restoration of immune function[10-12] may have contributed to this trend.[9]

Clinical manifestations that were suggestive of immune restoration disease included uveitis and vitritis in 2 patients with cytomegalovirus retinitis, diffuse adenopathy and cutaneous bullous reaction in a patient with disseminated *Mycobacterium bovis* infection, and necrotizing intra-abdominal adenopathies in 2 patients with *M avium* who were treated with antimycobacterial drugs. In the latter cases, mycobacteria were observed microscopically but could not be cultured. We also observed 1 patient with rapid development of multiple cerebral lesions compatible with progressive multifocal leukoencephalopathy followed by spontaneous improvement and 2 patients with Kaposi sarcoma having a rapid worsening of skin lesions. The incidence of herpes zoster infection may also increase following initiation of potent therapy.[19] The occurrence of some OIs at higher CD4 cell counts further supports the notion that a number of early events may have been triggered

Figure 3. Cumulative Probability of Developing an Acquired Immunodeficiency Syndrome (AIDS)–Related Opportunistic Illness (OI) After 6 Months of Potent Antiretroviral Therapy With Stratification by CD4 Cell Count and Viral Load



by potent therapy. Adjuvant treatment with corticosteroids has been shown to be useful in controlling some of these manifestations such as tuberculosis[20] and ocular cystoid macular edema.[13] Such treatment was successful in our patients with Kaposi sarcoma and symptomatic intra-abdominal adenopathies due to *M avium* disease. Controlled trials are required to define the role of corticosteroids in management of immune restoration disease after initiation of potent therapy.

Patients ceased to be at risk of developing Kaposi sarcoma once immune function had been improved, whereas they appeared to continue to be at risk for non-Hodgkin lymphoma, despite potent therapy. Numbers were small and results should therefore be interpreted with caution. However, the discrepant trends in the incidence of the 2 HIV-related malignancies were also evident in analyses comparing the years when potent antiretroviral therapy was introduced with previous periods.[18] One could speculate that the causal link with an infectious agent (human herpesvirus 8) makes Kaposi sarcoma more amenable to control through recovery of specific immunity than the process of malignant transformation in non-Hodgkin lymphoma.

The CD4 cell count at the time of initiation of potent therapy was a strong predictor for development of OIs in ensuing months. Similar findings were reported for the EuroSIDA study.[21] Furthermore, in our study, risk beyond the first 6 months was reduced substantially if the CD4 cell count increased by at least 50×10^6/L and undetectable viremia was reached. A therapy-induced CD4 cell count of 200×10^6/L at 6 months continued to distinguish more profound from moderate immunodeficiency, as only a small percentage of all observed events occurred above that threshold. This observation is relevant to the current discussion about the pace of immune recovery for patients receiving potent therapy and to the question of whether primary or secondary OI prophylaxis can be stopped.[22] A number of studies suggest that it is safe to stop primary prophylaxis against *P carinii* pneumonia in patients who experience a sustained rise of their CD4 cell count to 200×10^6/L or above.[23-25]

Low rates of disease progression were seen among patients reaching a CD4 cell count of 200×10^6/L or more even in the presence of virological failure, which confirmed the results of an earlier analysis of the database.[2] However, it is unclear how long these CD4 cell counts can be maintained in the presence of uncontrolled viremia.[26,27] In a minority of patients, OIs developed despite satisfactory control of viremia. In some patients, the recovery of immune reactivity triggering clinical symptoms can be invoked as a plausible explanation. Other patients have a slow CD4 cell recovery despite optimal control of viremia.[28] These patients remain at risk, and would likely benefit from continuation of prophylactic interventions and possibly additional treatments aimed at accelerating immune recovery, for example, with interleukin 2.[29]

The pattern of OIs seen in the present study reflects the impact of potent therapy in a population of HIV-infected persons living in a country with nearly universal health insurance coverage. The reasons for initiating or not initiating potent therapy in the Swiss HIV Cohort Study have been analyzed.[30] Patients were treated with regimens that conform to current guidelines regarding use of potent antiretroviral therapies.[31] Unfortunately, adherence to treatment was not recorded in this study. A measure of adherence has only recently been introduced.

In conclusion, our results should contribute to clinical decision making in the era of potent antiretroviral therapy.[32] Clearly, a thorough understanding of the natural history of AIDS-related OIs and a comprehensive analysis of the pace and quality of immune recovery in each patient is required for optimal clinical management.

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—Barbara W. Tuchman (1912-1989)