

ORIGINAL CONTRIBUTIONS

Decline in Esophageal Candidiasis and Use of Antimycotics in European Patients with HIV

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BACKGROUND: Esophageal candidiasis (EC) remains one of the most common AIDS defining illnesses in patients with human immunodeficiency virus (HIV) in the era of highly active antiretroviral therapy (HAART), but little is known about factors associated with EC after starting HAART.

OBJECTIVES: To describe changes in the use of antimycotic medication, the incidence of EC and factors associated with EC before and after starting HAART.

METHODS: Patients from EuroSIDA, a pan-European longitudinal, prospective observational study. Generalized linear models and poisson regression models were used to investigate the relationships.

RESULTS: A total of 9,873 patients did not have EC at recruitment, subsequently 537 (15.8%) developed EC. The proportion of patients taking any antimycotic dropped from 18% at January 1995 to 2% at January 2004 ($p < 0.0001$); the duration of treatment declined from 10 to 3 months over the same period ($p < 0.0001$). There was a 32% annual decline in the incidence of EC (95% CI 30–35%, $p < 0.0001$). There was a significant annual decline in the incidence of EC pre-HAART in time-updated, adjusted models, (incidence rate ratio (IRR) 0.80, 95% CI 0.76–0.85, $p < 0.0001$) but not post-HAART (IRR 0.97; 95% CI 0.90–1.06, $p = 0.54$). Older patients and those with low CD4 counts had the greatest incidence of EC in the post-HAART era.

CONCLUSIONS: There has been a marked decline in the incidence of EC between 1994 and 2004. This was accompanied by a decline in markers associated with fungal disease, including use of antimycotics and a decline in duration of treatment.

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INTRODUCTION

Esophageal candidiasis (EC) is one of the most common AIDS defining illnesses in patients infected with the human immunodeficiency virus (HIV). It occurs in 10–15% of patients with AIDS and presents most commonly with dysphagia, odynophagia, and retrosternal chest pain (1–4). Typically diagnosed at higher CD4 counts (5), EC was associated with longer survival (3, 6, 7) compared to other AIDS defining illnesses. It is commonly treated with antimycotic systemic treatment, such as fluconazole, itraconazole, ketoconazole, and amphotericin. The goal of therapy is relief of symptoms and prevention of relapse as eradication of the infection is

rare (1). Despite a rapid response to antimycotic treatment, patients with AIDS were at high risk of symptomatic recurrences of EC (8, 9). Studies have suggested that the average disease-free interval was less than 2 months and the frequency of relapses was related to immunosuppression (10, 11). Routine primary prophylaxis is not currently recommended (12), due to the effectiveness of antimycotic medication, the low mortality associated with the disease, and the potential for resistant *Candida* organisms to develop (12).

The rapid and widespread use of highly active antiretroviral therapy (HAART) in patients with HIV led to a decline in the incidence of all AIDS defining illnesses (13, 14). In the post-HAART era, EC remains one of the most common AIDS defining illnesses (13, 15). Several studies have reported a reduced incidence of EC since the introduction of HAART (15, 16). Studies tend to be limited

* Members of the study group are listed in the Appendix.

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to patients within a single clinic or country, without extended follow-up of patients and often lacking data on the use of antimycotic medication. There are few investigations considering the factors associated with EC after starting HAART.

The aims of this study were therefore, to describe the changes across Europe in the use of antimycotic medication, the incidence of EC, and to determine the factors associated with EC among patients who have started HAART.

PATIENTS AND METHODS

The EuroSIDA study is a prospective, European study of patients with HIV-1 infection in 82 centers across Europe (including Israel—see Appendix) and now including Argentina. Details of the study have been published (17). In brief, the centers provided data on consecutive patients seen in the outpatient clinic since May 2, 1994, until a predefined number of patients were enrolled from each center. This cohort of 3,118 patients was defined as the EuroSIDA I cohort. A further five cohorts have been added over time. Current follow-up is up to November 2004. Demographic and clinical information is collected at recruitment, together with a complete antiretroviral history and the eight most recent CD4 counts and viral load measurements. Details on all CD4 lymphocyte counts measured since last follow-up and viral load measurements were collected at each follow-up visit, as was the date of starting and stopping each antiretroviral drug. HAART was defined as a minimum of three drugs, of which at least two were nucleosides, and one was a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or abacavir. Also collected was the use of drugs for prophylaxis against opportunistic infections. Information on date of starting and stopping systemic antimycotic medication (amphotericin B, itraconazole, ketoconazole, and fluconazole) was available. Specific data on which drug was used against which pathogen was not available. Dates of diagnosis of all AIDS defining illnesses (including those made subsequent to the first diagnosis) have been recorded using the 1993 clinical definition of AIDS from the Centers for Disease Control. EC was diagnosed definitively or at autopsy (gross inspection by endoscopy/autopsy or by microscopy [histology]) or presumptively (recent onset of retrosternal pain on swallowing and confirmed oral or pharyngeal candidiasis). Specific details on diagnostic criteria, medication, or data collected can be found at <http://www.cphiv.dk>.

Members of the coordinating office visited all centers to ensure correct patient selection and that accurate data were provided by checking the information provided against case notes for all reported clinical events and a random sample of 10% of all other patients.

Patients were included in these analyses if they had not been diagnosed with EC prior to recruitment to EuroSIDA, had a CD4 lymphocyte count measured at or before recruitment and had some prospective follow-up.

Statistical Methods

The characteristics at the recruitment of patients who developed EC were compared to those who did not using χ^2 tests for proportions and Wilcoxon tests for continuous variables. The use of antimycotic medication was determined at January each year for patients under follow-up. Patients were defined as under follow-up if they had a follow-up visit in the period from 6 months before to 6 months after 1 January. The proportion using any antimycotic treatment was determined overall, in patients with a CD4 count of $200/\text{mm}^3$, with EC diagnosed prior to the date in question, and those who had started HAART. Generalized linear models were used to test for changes over time in the proportion of patients using any antimycotic medication using a binomial distribution. Changes in the duration of antimycotic treatment were tested using a similar methodology and a normal distribution. Multivariate analyses adjusted for calendar date, CD4 lymphocyte count, region of Europe, age, diagnosis of fungal disease (EC or cryptococcosis), diagnosis of any other AIDS defining illness, exposure group, gender, use of HAART, and age.

The incidence of EC was calculated according to calendar year and treatment era (pre-HAART—1994–1995, early-HAART—1996–1997, late-HAART—1998 and later). Changes in incidence were tested by poisson regression. Patients were followed up from the date of recruitment until the first of the development of EC or last follow-up.

The incidence of EC was calculated in patients not exposed to HAART. The years 1999–2004 were combined because of the small number of events and limited follow-up. In this analysis, any follow-up or diagnoses of EC that occurred after starting HAART were excluded. Similarly, the incidence was calculated after starting HAART, and the years before 1998 were combined because of the small number of events and limited follow-up. This allows a patient recruited in 1994, starting HAART in 1998 and developing EC in 2001 to contribute person-years of follow-up (PYFU) to both analyses. Both analyses were intent-to-treat and no adjustments were made for patients modifying their HAART regimen. The factors associated with development of EC in patients before and after HAART were determined using poisson regression. Before HAART, factors investigated included gender, ethnic origin, exposure group, region of Europe, age, prior AIDS diagnoses, hepatitis B and C status, use of antimycotics, antiretroviral treatment started, and CD4 count. It was not possible to include viral load in this model because routine viral load testing was not introduced until 1997. The same variables were considered after starting HAART, but additional variables, such as viral load, treatment prior to HAART, date of starting HAART regimen started, and time since started HAART (as a continuous or categorical variable) were included. Factors significant in either of the univariate analysis ($p < 0.10$) were included in multivariate analyses.

All analyses were performed using SAS (Statistical Analysis Software, version 8.2).

RESULTS

A total of 9,873 patients recruited to the EuroSIDA study had not developed EC at or before recruitment to the EuroSIDA study and 537 patients (15.8%) subsequently developed OC. There were some differences in their characteristics, as shown in Table 1. Approximately 16% of those who developed EC were female, compared to 23% of those who did not ($p < 0.0001$). Patients who developed EC had significantly lower CD4 counts at recruitment (medians of $111/\text{mm}^3$ vs $272/\text{mm}^3$, $p < 0.0001$), lower CD4 count nadirs (83 vs $175/\text{mm}^3$), and were recruited to EuroSIDA earlier (median June 1994 vs March 1997, $p < 0.0001$). A lower proportion of patients who developed EC had ever taken HAART at/before recruitment (10.2 vs 37.4% , $p < 0.0001$),

and a significantly higher proportion of patients were taking any antimycotic medication at the date of recruitment (18.1 vs 6.5% , $p < 0.0001$). In addition, a higher proportion of patients who developed EC had previously been diagnosed with AIDS (32.6 vs 23.9% , $p < 0.0001$).

The use of antimycotic medication is shown in Figure 1, together with the number of patients under follow-up. The proportion of patients taking any antimycotic dropped from 18% at January 1995 to 2% at January 2004. The proportion of patients taking any antimycotic drug was estimated to decrease by 25% per year (95% CI 24–28%, $p < 0.0001$). After adjustment for region of Europe, gender, exposure group, CD4 count, time spent with a CD4 count of less than $50/\text{mm}^3$ or $200/\text{mm}^3$, concomitant use of HAART, age, diagnosis of EC or cryptococcosis, or any other AIDS

Table 1. Characteristics of 9,873 Patients without Esophageal Candidiasis at Recruitment to EuroSIDA

	Disease Free During Follow-Up		Develop Esophageal Candidiasis		<i>p</i> *
	N	%	N	%	
All	9,336	94.6	537	15.8	
Gender					
Male	7,155	76.6	452	84.2	<0.0001
Female	2,181	23.4	85	15.8	
Exposure Group					
Homosexual	4,101	43.9	255	47.5	<0.0001
IDU	2,194	23.5	150	27.9	
Heterosexual	2,419	25.9	92	17.9	
Other	622	6.7	40	17.5	
Ethnic Origin					
White	8,009	85.8	466	86.8	0.52
Other	1,327	14.2	71	13.2	
Region					
South/Argentina	2,813	30.1	157	29.2	<0.0001
Central West	2,517	27.0	148	27.6	
North	2,851	30.5	216	40.2	
Central East/East	1,155	12.4	16	3.0	
Prior AIDS					
Yes	2,227	23.9	175	32.6	<0.0001
ARV Treatment					
None	1,767	18.9	98	18.3	<0.0001
At/Before					
ART	4,075	43.7	384	71.5	
Recruitment					
HAART	3,494	37.4	55	10.2	
Antifungals					
On at recruitment	602	6.5	97	18.1	<0.0001
	Median	IQR	Median	IQR	
CD4					
At recruitment	272	140–414	111	39–220	<0.0001
CD4 nadir					
At recruitment	170	65–290	83	21–167	<0.0001
Viral Load ¹					
At recruitment	3.03	2.29–4.33	4.31	3.10–5.11	<0.0001
Age					
At recruitment	36.3	31.3–43.6	36.9	31.3–43.0	0.60
Date					
Of recruitment	3/97	7/94–6/99	6/94	5/94–12/95	<0.0001

**p* value was from testing differences between those who developed or did not develop EC during follow-up.

¹Data available for 5,529 patients who did not develop esophageal candidiasis (59.2%) and for 94 who did (17.5%, $p < 0.0001$, χ^2 test).

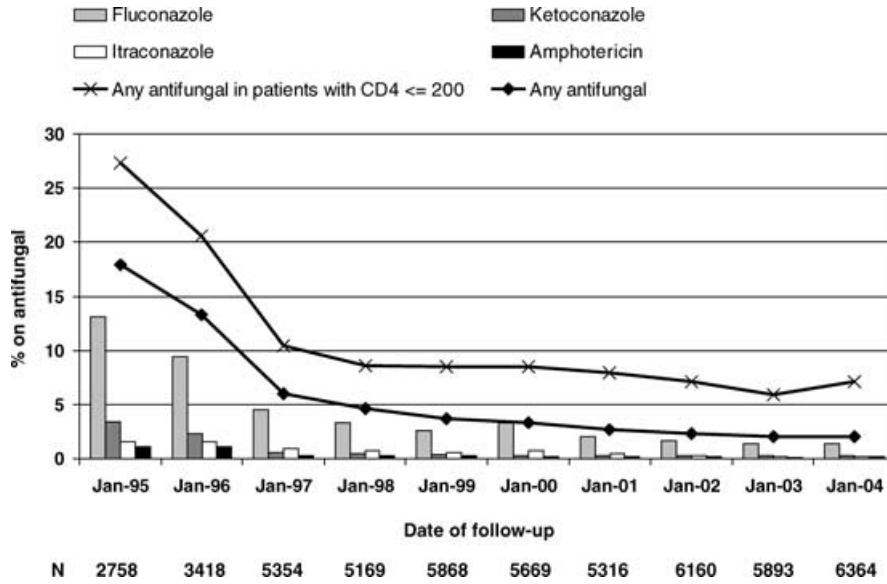


Figure 1. Use of antimycotic treatment in EuroSIDA 1994–2004.

defining illness, there was an estimated 24% decrease in the proportion of patients taking antimycotic drugs per year (95% CI 20 – 27%, $p < 0.0001$). Use of each antimycotic has also decreased over time (Fig. 1). For example, the proportion of patients using fluconazole decreased from 13% at January 1995 to 1.4% at January 2004. Fluconazole remained the most commonly used antimycotic, used by approximately 75% of patients taking any antimycotic medication. The use of antimycotic medication among patients with a CD4 count of $200/\text{mm}^3$ or below decreased from 27% at January 1995 to 7% at January 2004. The proportion of patients using any antimycotic treatment after starting HAART was very similar to the overall proportion taking any antimycotic medication after 1997 (data not shown).

There was a significant decline over time in the proportion starting ketoconazole and an increase in the proportion start-

ing fluconazole (Fig. 2, $p = 0.021$, χ^2 test). There has been a significant decline over time in the duration of treatment (Fig. 2), from a median of 10 months (interquartile range (IQR): 4–22 months) in patients starting antimycotic medication in 1994 to 3 months (IQR: 1–9 months) in patients who started antimycotic medication during 2003 or 2004 ($p < 0.0001$). There was a 7% decline in duration of antimycotic treatment per year before adjustment (95% CI 5–9%, $p < 0.0001$). After adjustment, there was an estimated 10% annual decline in the duration of antimycotic treatment (95% CI 7–14%, $p < 0.0001$).

There was a 32% annual decline in the incidence of EC (95% CI 30–35%, $p < 0.0001$, poisson regression). The incidence dropped from 6.2 per 100 PYFU in 1994 to under 0.5 per 100 PYFU after 1999 (Fig. 3). The incidence of EC in the late-HAART treatment era (Table 2) was consistent

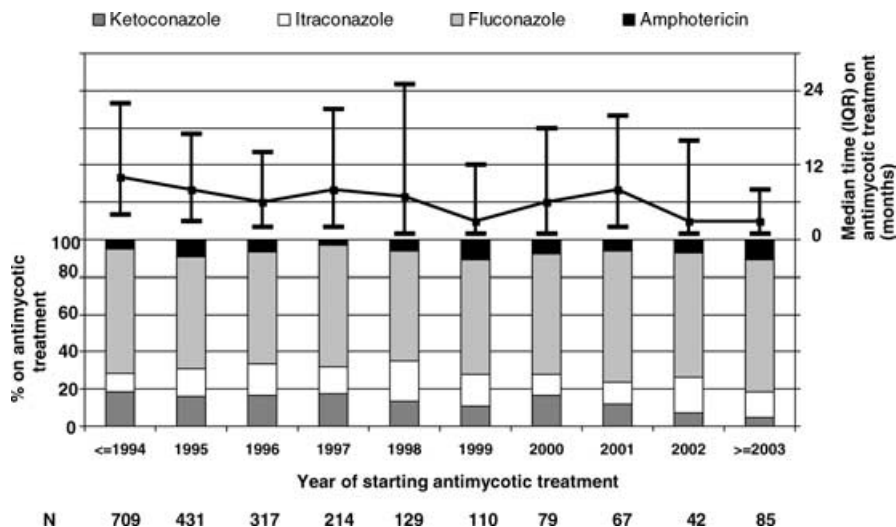


Figure 2. Use of and time on antimycotic treatment among patients taking antimycotics in EuroSIDA 1994–2004.

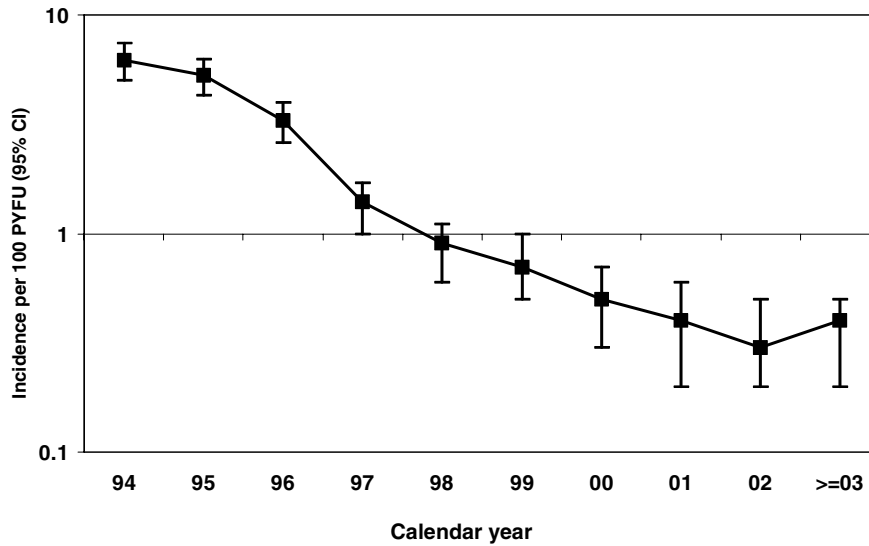


Figure 3. Incidence of esophageal candidiasis in EuroSIDA 1994–2004.

with Figure 2, at 0.5 per 100 PYFU (95% CI 0.4–0.6). The median CD4 count at diagnosis increased from 30/mm³ in the pre-HAART era to 84/mm³ in the late-HAART treatment era ($p < 0.0001$, Wilcoxon test).

The factors associated with EC before and after HAART are shown in Table 3. There are two multivariate models, the first including only factors known at baseline and the second including time-updated variables. The incidence of EC declined from 6.2 per 100 PYFU in 1994 (95% CI 5.0–7.4) to 0.5 per 100 PYFU (95% CI 0.3–0.7) for all years at/after 1999 before patients started HAART. This was an estimated annual decline of 31% (95% CI 27–35%, $p < 0.0001$). Heterosexual patients had a reduced incidence rate of EC compared to all other exposure groups combined (incidence rate ratio (IRR) 0.69, 95% CI 0.51–0.95, $p = 0.022$) after adjustment for factors known at baseline. In the same analysis, patients with a higher CD4 count had a reduced incidence, while patients taking antimycotic medication had an increased incidence. Of note, there was a significant decrease over time in the incidence of EC (IRR per 12 months 0.75; 95% CI 0.71–0.79 $p < 0.0001$). The updated multivariate analysis showed similar results, except that the development of an AIDS defining

illness after recruitment was associated with an increased incidence of EC (IRR 1.35, 95% CI 1.04–1.74, $p = 0.023$).

There was a smaller, but statistically significant decline in the incidence of EC after patients started HAART, from 1.4 per 100 PYFU in/before 1997 (95% CI 0.9–1.8) to 0.3 per 100 PYFU (95% CI 0.2–0.5) in/after 2003. This was an estimated annual decline of 25% (95% CI 18–30%, $p < 0.0001$). Slightly different factors were associated with EC after starting HAART (Table 3). The incidence of EC among heterosexual patients was not reduced, while the incidence of EC was increased in older patients in the multivariate model adjusted for factors known at baseline. In the same model, viral load at starting HAART was not associated with the incidence of EC. In addition, there was a significant decline in EC over calendar time (IRR 0.87, 95% CI 0.79–0.97, $p = 0.0096$). However, in the time-updated model the effect of calendar time was no longer significant (IRR 0.97, 95% CI 0.90–1.06, $p = 0.54$). In the same model, use of antimycotic medication was associated with an increased incidence of EC as was latest viral load. A sensitivity analysis which only included patients starting HAART after recruitment to EuroSIDA showed similar results (data not shown).

Table 2. Incidence Rates and Values at Diagnosis of EC According to Treatment Era

	Pre-HAART 1994–1995	Early-HAART 1996–1997	Late-HAART 1998 and Later	<i>p</i>
PYFU	3768.7	7054.4	33337.3	
Events	214	151	172	
Incidence per 100 PYFU	5.7	2.1	0.5	<0.0001
95% CI	4.6–6.4	1.8–2.5	0.4–0.6	
Median CD4 at diagnosis (IQR)	30 (10–83)	56 (18–143)	84 (24–215)	<0.0001
Median VL at diagnosis (IQR)	–	4.78 (3.51–5.34)	4.87 (3.82–5.44)	0.92
Initial AIDS diagnosis, N (%)	113 (52.8)	76 (50.3)	107 (62.2)	0.40
Presumptive diagnosis, N (%)	125 (58.4)	79 (52.3)	107 (62.2)	0.20
On HAART at diagnosis, N (%)	0 (0)	36 (23.8)	128 (74.4)	<0.0001

Table 3. Factors Associated with Esophageal Candidiasis Before and After HAART

	Univariate			Multivariate—fixed			Multivariate—updated		
	IRR	95% CI	p Value	IRR	95% CI	p Value	IRR	95% CI	p Value
Pre-HAART									
Gender									
Female vs. Male	0.69	0.65–0.73	<0.0001	0.78	0.57–1.08	0.14	0.84	0.61–1.16	0.29
Exposure group									
Hetero vs. other	0.51	0.38–0.66	<0.0001	0.69	0.51–0.95	0.022	0.72	0.53–0.99	0.045
Age									
Per 10-yr older	1.07	0.97–1.19	0.19	1.05	0.94–1.18	0.37	1.05	0.94–1.18	0.37
AIDS ¹	2.18	1.76–2.72	<0.0001	0.92	0.71–1.18	0.50	1.35	1.04–1.74	0.023
CD4 ¹									
Per 50% higher	0.68	0.65–0.71	<0.0001	0.74	0.70–0.77	<0.0001	0.70	0.67–0.73	<0.0001
Treatment ¹									
Any vs. None	1.45	1.13–1.85	0.0031	0.95	0.74–1.22	0.67	0.74	0.56–0.98	0.033
Any antimycotic ¹	3.12	2.42–4.03	<0.0001	1.39	1.06–1.83	0.018	1.47	1.16–1.85	0.0011
Calendar year									
Per 12 months	0.69	0.65–0.73	<0.0001	0.75	0.71–0.79	<0.0001	0.80	0.76–0.85	<0.0001
Post-HAART									
Gender									
Female vs. Male	0.82	0.55–1.23	0.34	1.36	0.79–2.36	0.26	1.30	0.82–2.05	0.27
Exposure group									
Hetero	1.15	0.79–1.67	0.48	0.93	0.56–1.52	0.76	1.25	0.82–1.92	0.30
Age									
Per 10-yr older	1.17	1.00–1.37	0.056	1.29	1.06–1.58	0.013	1.33	1.13–1.57	0.0007
AIDS ¹	2.65	1.93–3.63	<0.0001	1.37	0.86–2.18	0.18	1.20	0.77–1.87	0.42
CD4 ¹									
Per 50% higher	0.75	0.70–0.80	<0.0001	0.79	0.71–0.88	<0.0001	0.63	0.58–0.68	<0.0001
VL ¹									
Per log higher	1.37	1.11–1.67	0.0036	1.18	0.95–1.47	0.13	1.74	1.51–2.00	<0.0001
Date started HAART									
Per 12 months later	0.61	0.50–0.75	<0.0001	0.90	0.73–1.10	0.30	0.91	0.76–1.09	0.29
Any antimycotic ¹	2.82	1.94–4.09	<0.0001	1.54	0.91–2.62	0.11	1.74	1.22–2.49	0.0025
Calendar year									
Per 12 months	0.75	0.70–0.82	<0.0001	0.87	0.79–0.97	0.0096	0.97	0.90–1.06	0.54

¹The univariate IRR is for the fixed variable at baseline (date of recruitment or date of starting HAART).

DISCUSSION

There has been a marked decline in the incidence of EC in patients with HIV between 1994 and 2004 in almost 10,000 patients from across Europe, accompanied by a decline in markers associated with fungal disease. Patients with a low CD4 count and who were older had the highest incidence of EC after starting HAART. The improvement in CD4 count after starting HAART explained the decline in EC over time since starting HAART.

There was a decline over time in the proportion of patients using antimycotic treatment in patients with low CD4 counts, a diagnosis of EC or those starting HAART. Our results were consistent with Detels *et al.* (16), where EC prophylaxis dropped from 10% in 1995 to less than 5% of all patients in 1999, and from 60 to 30% in patients with AIDS. This decline was consistent for all antimycotic drugs, and could not be explained by higher CD4 counts, the increasing proportion starting HAART, the lower incidence of EC, or other fungal diseases such as cryptococcosis. One possible reason is the significant decrease in the prevalence of oral candida in patients with HIV (18–20), leading to less antimycotic medication. We were unable to adjust for this, as we do

not have data on oral candida. It is unlikely to explain all of the reduction, previously attributed to improvements in CD4 count (20), which we have adjusted for. Reporting errors are unlikely to account for the decline, as data monitoring procedures have been in place since the outset of the study. It is possible that antimycotics were over used in the period prior to HAART becoming widely available, or that we cannot completely capture the improvement in health by adjusting for CD4 count and other markers of disease progression. Few other studies have considered the changing treatment for EC in the era of HAART, and none have demonstrated that the duration of treatment has also declined. The decreased cost of antimycotics, both in terms of the proportion of patients requiring medication and the duration of treatment, can be offset against the costs of HAART.

The incidence of EC declined by over 90% between 1994 and 2004 and was below 1 per 100 PYFU at/after 2003. This is consistent with reports from other cohorts of HIV-infected patients (21–25), and the decline in EC was similar to that observed for other AIDS defining illnesses in the EuroSIDA study (26, 27). There was no change over time in the proportion of EC diagnoses made as an initial AIDS-defining illness, or in the proportion of diagnoses made as a definitive

diagnosis. We did observe an increase in the CD4 lymphocyte count at diagnosis of EC. Several studies have reported an increase in CD4 lymphocyte count at diagnosis of AIDS since the introduction of HAART (13, 28, 29). This could suggest a change in the natural history of HIV infection following the introduction of HAART, with implications for monitoring and disease-specific prophylaxis. However, it is more likely to reflect the large number of patients surviving on HAART with higher CD4 counts. The immediate risk of any AIDS defining illness for a given CD4 count has been shown to be much later in recent years (13).

Before the introduction of HAART, patients with low CD4 counts (at recruitment or during follow-up) had a higher incidence of EC. There was a strong relationship with calendar year, which could not be explained by any of the variables adjusted for. Patients with HIV who develop oral candida are at an increased risk of EC (30), and guidelines for the initiation of HAART have consistently suggested starting HAART in patients with recurrent mucosal candidiasis (31, 32). It is likely that patients with oral candida were started on HAART prior to invasion of the oesophagus. This would have increased their CD4 count and subsequently reduced the incidence of EC prior to starting HAART. If the disease progressed to the esophagus in such patients, it would then occur after starting HAART. There was a decrease in the incidence of EC in later calendar years after starting HAART when factors known at starting HAART were adjusted for, but not after adjustment for the current CD4 count. This suggests that improvements in CD4 count occurring after HAART explain the decreased incidence of EC. Cassone *et al.* (33) showed that PI's directly inhibit the growth of the candida protease enzyme called secreted aspartic proteinases (SAP), and that the lower incidence of EC seen in patients starting HAART was not solely due to the improved immune status but also due to the PI-inhibiting candida protease. We found no relationship between the incidence of EC and regimens, which did or did not include a PI in this study (data not shown).

There are several limitations to this study. Firstly, the extent to which the EuroSIDA population is representative of patients with HIV in general. Although there are many centers across Europe represented in the EuroSIDA study, nonparticipating centers may be different in terms of physician experience or availability of antimycotic or HAART regimens. Treatment decisions are made at a center level for individual patients and may not be uniform across Europe. However, due to the large number of clinics and patients involved, EuroSIDA is arguably more representative than any one single clinic cohort. Information on diagnosis of oral candida was not available, which may help explain some of our findings. In addition, use of antimycotics was limited to four main systemic treatments. It is possible that other antimycotic drugs, or topical antimycotics, have been used across Europe during the 10-yr period of EuroSIDA. The duration of the antimycotic treatment should be regarded as a maximum as only the date of first starting and last stopping each antimycotic drug was recorded, and treatment interruptions have not been

recorded. We used antimycotics as a marker for oral candida, and it was not possible to validate the extent to which all patients using oral antimycotics had oral candida or vice versa. However, it is highly likely that there is substantial overlap between the use of antimycotics and the diagnosis of oral candida, and our estimate of the relative hazard associated with antimycotics was highly consistent with the relative hazard associated with oral candida (12).

In conclusion, there has been a 95% decline in the incidence of EC among patients infected with HIV across Europe between 1994 and 2004, and a decline in the use of antimycotic treatment and in the duration of treatment. The decline in EC seen prior to starting HAART may reflect a decrease in the prevalence of oral candida, whereby patients with oral candida were started on HAART before progressing to esophageal candidiasis, in line with treatment guidelines.

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APPENDIX

The multicenter study group on EuroSIDA (national coordinators in parenthesis).

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