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## **Primary prophylaxis of disseminated histoplasmosis in HIV patients in French Guiana: a cost effectiveness study**

Mathieu Nacher, Antoine Adenis, Celia Basurko, Vincent Vantilcke, Denis Blanchet, Christine Aznar, Bernard Carme, Pierre Couppié

### **Abstract**

Histoplasmosis is the first cause of AIDS and AIDS-related deaths in French Guiana. Cohort data was used to determine whether primary prophylaxis with 100mg itraconazole for patients with CD4 counts  $<150/\text{mm}^3$  was cost effective with different scenarios. For a scenario where 12% of patients die, 60% are aware of their HIV infection and adherence is only 50%, primary prophylaxis would prevent 1 death and 9 cases of histoplasmosis for a cost of 36 792 euros per averted death, 1533 per life year saved, 4415 euros per averted case, when only counting the costs of itraconazole prophylaxis. Taking into account the total costs of hospitalisation showed that primary prophylaxis would allow to save 185 178 euros per year. Even in a scenario of low adherence primary prophylaxis would be cost-effective in French Guiana, and presumably in the rest of the Guianas and the Amazon.

### **Introduction**

French Guiana is a French territory located in South America between Suriname and Brazil. It has a French health system and follows French HIV expert recommendations. However, French Guiana differs in many ways with metropolitan France. One of the striking ways it differs is in what are the main AIDS-defining illnesses in the context of Amazonian pathogens. Disseminated histoplasmosis (DH) is the first cause of AIDS in French Guiana and presumably one of the most frequent ones in South America<sup>1</sup>. Disseminated histoplasmosis has also been the main cause of death in French Guiana. Recent studies showed that the incidence of histoplasmosis among HIV-patients had a seasonal pattern, suggesting that a significant proportion of the infections were acute and recently acquired.<sup>2</sup> This has raised the question of the use of primary prophylaxis among severely immunocompromised patients. The infectious diseases society of America has recommended that primary prophylaxis be given in persons with CD4 counts  $<150$  per  $\text{mm}^3$  when the annual incidence of histoplasmosis exceeded 10 per 100 person-years<sup>3</sup>.

In this perspective, we decided to look at the burden of disease associated with histoplasmosis and the expected cost effectiveness of primary prophylaxis against DH in HIV patients with CD4 counts  $<150$  per  $\text{mm}^3$  in the context of French Guiana using the available data from the French hospital database on HIV.

### **Methods**

The data from French Guiana included in the French hospital data base on HIV was analyzed to look at the evolution of the incidence rate of disseminated histoplasmosis according to the level of immunodepression. The French Hospital database is a national data base that combines data from all regional coordinations of the fight against HIV (COREVIH). It has been approved by the Commission Nationale Informatique et Libertés, the regulatory authority.

The total number of patients and the incidence rate of histoplasmosis were used to calculate the number of incident cases. The death rate of histoplasmosis (40% at one month in our database) was then used to calculate the number of expected deaths. The mean hospital stay was multiplied by the number of cases of histoplasmosis to calculate the cost due to hospital stays. In France the cost of a day in the hospital is a fixed cost that covers all treatments and paraclinical explorations. It was 821 euros at the time of the study. However, for some very expensive drugs, such as liposomal amphotericin there is an added cost. Here we factored an average of 7 days treatment at 3mg/kg/day at 152 euros per 50mg vial, which amounts to an

extra  $7 \times 608 = 4760$  Euros per patient on liposomal amphotericin. Since in our historical database 43% percent of patients with DH receive liposomal amphotericine B, we proportionally added that cost to hospital costs. Because not all patients know their HIV serostatus when they are admitted we multiplied the number of expected cases by 60%, the proportion of patients that are aware of their HIV diagnosis on admission. The cost of prophylaxis was obtained by multiplying the cost of Sporanox® (itraconazole) in France for two 100mg tablets per day (1.68 euros/day) given for a year assuming that they would also receive antiretroviral treatment, which would restore immunity beyond the 150 CD4 threshold by the end of the year.

Life years saved (LYS) were calculated by subtracting the mean age at death (40 years) to the expected life expectancy at 40, which is 39.7 for men and 45.7 for women,<sup>4,5</sup> and in treated patients starting treatment at less than 200 CD4 cells is reduced by 18 years<sup>6</sup>. The sex ratio was 2 men for one woman as observed in our historical database. This proportion was incorporated in the calculations of life years lost.

Given that treated histoplasmosis can reverse symptoms in a matter of days or weeks, the disability associated was a negligible quantity of years lived with disability relative to the >40 years of life lost. We thus used Life Years Saved (LYS) and not DALYs. The number of patients requiring prophylaxis was obtained by multiplying the total number of patients by the proportion with CD4 counts below 150, which was 18% in our cohort.

The number of patients receiving prophylaxis to prevent one case was calculated, and the cost of prophylaxis to prevent one case was calculated. The same calculation was performed to obtain the number of patients receiving prophylaxis to prevent 1 death and then one life year for different scenarios.

## Results

Figure 1 shows that the incidence of histoplasmosis increases with the level of incidence and exceeded 10% in the most immunodepressed patients.

Table 1 shows the numbers used in the calculations presented in table 2. The details of the costs in lost life and morbidity, the financial cost of hospitalizations, and the cost of giving prophylaxis using itraconazole 200mg per day for a year at French prices. The expected results are adapted according to the proportion of patients that are immunodepressed, according to the proportion of patients that are aware of their diagnosis, according to the death rate that has improved in the past years because of improvement of diagnosis and early presumptive treatment. The different scenarios all suggested that primary prophylaxis was cost effective.

## Discussion

A randomized trial in the context of the USA has shown that primary prophylaxis against fungal infections for patients with CD4 counts <150 per mm<sup>3</sup> reduced incidence but did not improve survival<sup>7</sup>. In the context of French Guiana and Amazonian South America, with larger patient numbers, it is arguable that this could improve survival. The present simulations suggest that, given various plausible scenarios, primary prophylaxis was a life saving and cost effective strategy. It is arguable though that patients presenting with disseminated histoplasmosis are often a very particular group of patients. In our experience, 60% of the patients were known HIV patients with histoplasmosis. Thus they had the opportunity to obtain antiretroviral treatment that would have rapidly raised their immunity above the dangerous thresholds for histoplasmosis and should not have developed histoplasmosis. This

implies that 60% of the patients had severe adherence problems and that the others had waited until very late in the course of the HIV infection to get tested, which arguably may not predict perfect adherence to future treatments. Thus, primary prophylaxis would not be effective if patients do not take it, then why bother? Nevertheless, a scenario where only 50% of the patients would be adherent still showed its advantage. And there may be room for improvement with early testing and therapeutic education which, on paper, could avoid histoplasmosis in some of these patients.

The cost of primary prophylaxis was very affordable for the health system of France. Moreover, these costs only included the cost of prophylaxis. However, when subtracting the costs avoided by preventing patients from getting DH (expensive hospital stays and liposomal amphotericin B) primary prophylaxis was a very interesting measure saving lives, suffering, and money in all scenarios including the low adherence scenario. Arguably, since incidence increases in the most immunodepressed patients, the number of patients treated could be reduced, thus the cost could also be even lower by targeting patients with lower CD4 counts. The world bank specified 500 USD per DALY as attractive for middle income countries and 100 USD as highly attractive<sup>8</sup>. Here when calculating the cost per life year saved in Suriname using rates from French Guiana and patient numbers and costs from Suriname, the cost was 89 Euros which is near the super attractive range of costs per life year saved, for the World Bank. However, these “back of the envelope” calculations are crude estimates using incidence rates from the neighbouring French Guiana. They should thus be refined and verified with using prospective data measuring the incidence of this disease in Suriname, and the proportion of histoplasmosis cases that were aware of their HIV status. When looking at Brazil alone, if there are 600 000 patients with a comparable incidence of 1 case per 100 patient years the potential number of lives saved could be tremendous, with substantial cost savings. Again, given the scarcity of precise data, prospective studies should measure the incidence of histoplasmosis in northern Brazil.

These findings suggest that it is important to give primary prophylaxis against DH in immunodepressed HIV patients living in endemic areas. This reemphasizes the need for simple, affordable diagnostic tools in order to precise the true burden of HIV-associated histoplasmosis in the Amazon region<sup>1</sup>.

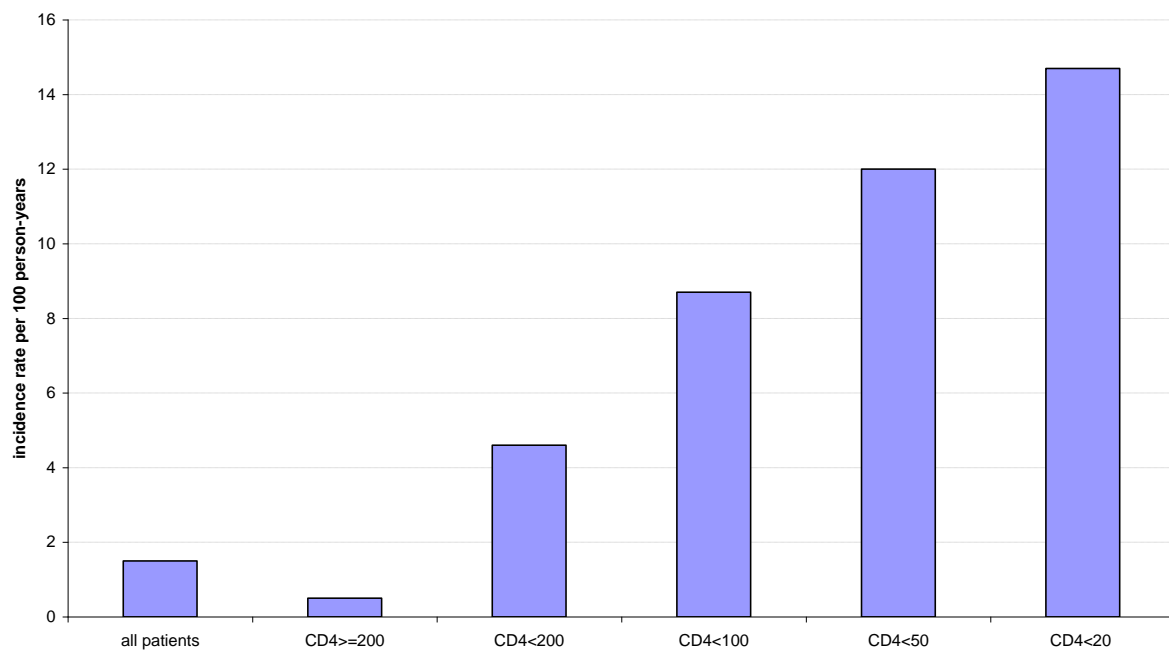
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Incidence rate of histoplasmosis according to CD4 counts in French Guiana



<b>Hypothesis</b>	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
	<b>Historical</b>	<b>Current optimistic</b>	<b>Current pessimistic</b>	<b>Ideal</b>
Total number of patients		2000	2000	2000
Number of patients requiring prophylaxis (CD4<150)		360	360	360
Incidence of histoplasmosis		1,5	1,5	1,5
Proportion of patients with histoplasmosis aware of their HIV status		0,6	0,6	0,6
Proportion of deaths		0,4	0,12	0,12
Adherence level (%)		100	100	50
Average duration of hospitalisation		28,5	28,5	28,5

- if only patients <50 CD4 8.7% of total
- if only patients <100 CD4 (8.7+6.7 ) % of total

A : Historical scenario, French Guiana, historical rate 40%

B: Optimistic scenario, French Guiana, current rate 12%, adherence 100%

C: Current pessimistic scenario, French Guiana, mortality 12%, adherence 50%

D: Ideal scenario, French Guiana, mortality 12%, HIV testing improved to 80% of patients with DH previously aware of HIV diagnosis

**Figure 2. The predicted number of cases and deaths from histoplasmosis, and the expected benefits of primary prophylaxis Given different scenarios.**

<b>Outcome</b>	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>
	<b>Historical</b>	<b>Current optimistic</b>	<b>Current pessimistic</b>	<b>Ideal</b>
Number of predicted cases of DH annually	30	30	30	30
Cases of DH averted annually	18	18	9	24
Annual deaths from DH expected	12	3,6	3,6	3,6
Expected life years lost	284	85	85	85
Annual Deaths from DH averted	7,2	2,2	1,1	2,9
Life years saved (years)	182,	55	27	73

\* Life years approximated to nearest decimal.

**Fig 3. Costs of primary prophylaxis vs hospitalisation for disseminated histoplasmosis, and cost effectiveness of primary prophylaxis for different scenarios.**

<i>Outcome</i>	<i>A</i> <i>Historical</i>	<i>B</i> <i>Current</i> <i>optimistic</i>	<i>C</i> <i>Current</i> <i>pessimistic</i>	<i>D</i> <i>Ideal</i>
1-Prophylaxis cost per year for patients with CD4<150 (Euro)	39 735	39 735	39 735	39 735
2-Cost per averted DH case (Euro)	2 207	2 207	4 415	1 655
3-Average of total annual costs of hospitalizations of DH (Euro)	763 359	763 359	763 359	763 359
4-Average of total annual Costs in DH hospitalization averted (Euro)	435 500	435 500	224 914	575 891
5-Cost per DH death averted (Euro)	5 518	18 396	36 792	13 797
6-Cost per life year saved (Euro)	229	766	1 533	574
7-Total cost saved per year (Euro) [4-1]	395 765	395 765	185 178	536 156