Genotype of 88 *Toxoplasma gondii* Isolates Associated with Toxoplasmosis in Immunocompromised Patients and Correlation with Clinical Findings

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We report the genotyping analysis of *Toxoplasma gondii* isolates in samples collected from 88 immunocompromised patients, along with clinical and epidemiological data. Most of these samples were collected in France during the current decade by the *Toxoplasma* Biological Resource Center. Lack of specific anti-*Toxoplasma* treatment, pulmonary toxoplasmosis, and involvement of multiple organs were the 3 main risk factors associated with death for this patient group. Genotyping results with 6 microsatellite markers showed that type II isolates were predominant among patients who acquired toxoplasmic infection in Europe. Non–type II isolates included 13 different genotypes and were mainly collected from patients who acquired toxoplasmosis outside Europe. Type III was the second most common genotype recovered from patients, whereas type I was rare in our population. Three nonarchetypal genotypes were repeatedly recovered from different patients who acquired the infection in sub-Saharan Africa (genotypes Africa 1 and Africa 2) and in the French West Indies (genotype Caribbean 1). The distribution of genotypes (type II vs. non–type II) was not significantly different when patients were stratified by underlying cause of immunosuppression, site of infection, or outcome. We conclude that in immunocompromised patients, host factors are much more involved than parasite factors in patients' resistance or susceptibility to toxoplasmosis.

In immunocompetent patients, toxoplasmosis is usually asymptomatic or benign, but severe outcomes have been described in tropical areas such as French Guiana and the Republic of Suriname [1, 2] for cases that involved wild strains of *Toxoplasma gondii* [3]. In immunocompromised patients, *T. gondii* is an opportunistic parasite

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that may induce life-threatening disease. In patients with AIDS, those with hematological malignancies, and those who undergo hematopoietic stem cell transplantation (HSCT), toxoplasmosis mainly occurs after reactivation of latent infection, rarely during a primary infection. In patients who have undergone solid-organ transplantation, *T. gondii* is mainly transmitted via a graft from a donor who is seropositive for *Toxoplasma* to a recipient who is seronegative for *Toxoplasma*. Toxoplasmic encephalitis is considered to be the most frequent clinical presentation, especially in patients with AIDS [4], and the lung is the second most common site of disease due to *T. gondii* in immunocompromised patients [5]. The involvement of other organs, such as the eye, heart, peritoneum, liver, spleen, kidney, muscle, and bone marrow have also been described, albeit infrequently [6]. In fact, multiple-organ involvement is rarely found clinically but is a frequent finding at autopsy [7].

Toxoplasmic encephalitis is one of the major opportunistic infections that occur in patients with AIDS. Although its incidence has been reduced by three-quarters as a result of highly active antiretroviral therapy (HAART) and primary prophylaxis [8], toxoplasmic encephalitis remains the most prevalent cause of neurological opportunistic infection in HIV-infected patients in Europe [9]. In France, toxoplasmic encephalitis was the fourth most frequent AIDS-indicative disease in 2005–2006 [10]. Toxoplasmosis-associated deaths have dramatically decreased among HIV-infected persons in the United States, reflecting the effectiveness of anti-*Toxoplasma* treatment and primary prophylaxis, as well as HAART [11]. However, because toxoplasmic encephalitis is associated with a high probability of early death, survival analysis shows that the occurrence of toxoplasmic encephalitis remains associated with a poor prognosis in the natural history of HIV-infected persons, even in the era of HAART [9].

In contrast to patients with AIDS, toxoplasmosis is considered to be a rare opportunistic infection in patients who are immunosuppressed because of other causes, such as recipients of HSCT or solid-organ transplants [12, 13], and in patients with lymphoproliferative or myelopoietic malignancies [6]. The highest incidences of toxoplasmosis are observed in patients who have undergone allogeneic HSCT and heart transplantation [14, 15]. In patients whose immunosuppression is not caused by HIV infection, toxoplasmosis is considered to have a poor prognosis [12], and starting appropriate anti-*Toxoplasma* therapy as soon as possible is considered to be the main factor involved in survival [16]. Among heart transplant recipients, this disease and disseminated aspergillosis are associated with the highest mortality rates attributable to an infectious complication [15].

During the past decade, on the basis of a limited sample of strains from domestic animals and humans from North America and western Europe, *T. gondii* was considered to have a clonal population structure and low genetic diversity, with >95% of strains belonging to 3 clonal lineages, which were named types I, II, and III [17]. Recent studies that used multiple markers and collected samples from Brazil and French Guiana [3, 18–20] showed that, at least in the tropical part of South America, *Toxoplasma* strains show genetic diversity that is absent in strains from North America and Europe. In North America, the clonal types predominate [20], but recent works suggest greater genetic diversity than was initially recognized [21–23]. In Europe, mainly in France, various studies conducted in animals and humans showed a tremendous predominance (>95%) of only 1 genotype, type II [24–27]. Few data concerning the genetic diversity and population structure of this parasite are available for Africa [28, 29] and Asia [30, 31], where 75% of the human population currently lives. The influence of genotype on the clinical presentation or outcome of the disease is poorly reported for immunocompromised patients [32–34].

The *Toxoplasma* Biological Resource Center was created in 2003 in France. To date, this network of French parasitologists has collected 462 *Toxoplasma* isolates from patients with toxoplasmosis, together with clinical and epidemiological data for these patients. All these isolates have been genotyped with microsatellite markers. We report the genotyping analysis of *T. gondii* in samples collected from 88 immunocompromised patients—52 patients with AIDS and 36 patients whose immunosuppression was not due to HIV infection—and the correlation of genotypes with clinical findings. Most of these samples were collected in France during the current decade by the *Toxoplasma* Biological Resource Center.

MATERIALS AND METHODS

Patients. Epidemiological and clinical data for the 88 immunocompromised patients are reported in table 1. The serological findings (data not shown) permitted us to know the geographical origin of toxoplasmic infection (i.e., the country of residence during the infection) for 6 patients with recent primary infection . For 72 patients with reactivated infection, we assumed that toxoplasmic infection occurred in the country from which the patients originated. For 9 patients, the geographical origin of infection was unknown because of insufficient data or because of *Toxoplasma* transmission via the graft in patients who underwent solid-organ transplantation. For 1 patient, despite the absence of serological data, we assumed that toxoplasmic infection occurred in France because this case involved a 6-year-old child with no history of travel outside France. Infection was presumed to have originated in Europe for 52 patients (48 in France, 2 in Portugal, 1 in Germany, and 1 in Austria) and to have originated outside Europe for 27 patients (17 in sub-Saharan Africa, 4 in the French West Indies, 3 in South America, 1 in Central America, 1 in Maghreb, and 1 on Reunion Island).

The underlying causes of immunosuppression were as follows: 52 patients had AIDS; of the 36 patients negative for HIV infection, 27 had undergone transplantation (12 received bone

marrow transplants, 4 received cord blood cell transplants, and 11 received solid-organ transplants), 4 had lymphoma, 3 had leukemia, 1 had IgA nephropathy (i.e., Berger disease), and 1 had iatrogenous aplasia. All but 1 of the patients were adults.

Data on the clinical features of toxoplasmosis were available for all 88 patients. The most frequent site of infection was the brain (49 patients with toxoplasmic encephalitis), followed by the lung (39 patients with pulmonary toxoplasmosis), bone marrow (7 patients with medullar toxoplasmosis), peritoneum (4 patients with peritoneal toxoplasmosis), and heart (3 patients with myocardial toxoplasmosis). Other locations (e.g., the liver, kidney, pancreas, eye, lymph node, and spinal cord) occurred rarely. Toxoplasmosis involved a single organ in 67 patients and ⩾2 noncontiguous organs (hereafter, "multiple organ") in 21 patients.

For 76 of 88 patients, we could determine whether specific anti-*Toxoplasma* drug therapy was given. The outcome was available for 84 patients. A total of 45 patients died; for 35 of these patients, death was caused by toxoplasmosis. Of the 35 patients who died of toxoplasmosis, 9 did not receive specific anti-*Toxoplasma* therapy because of the rapid, fatal progression of the disease.

Toxoplasma isolates and DNA extracts. DNA extraction for genotyping analysis was performed directly on clinical samples for 56 patients and indirectly on infected mouse tissue (brain or ascitic fluid) or infected cell cultures after inoculation of clinical samples for 32 patients (table 1). The following 25 isolates or DNA extracts were collected before the creation of the *Toxoplasma* Biological Resource Center, from 1985 to 2001: in France, MAN-NJA, LGE-1998–1, SUR, LGE-2001–6, BOU, ELG, DIJ-1996-BAC, RMS-2000-MER, BIL, LGE-2001–5, DAM, LGE-2001–3, BRE-1997-PERR, DIJ-1998-COL, LEG-NJA, COR, DPHT, FOU, DIJ-2000-LEC and LIL-2000-BRI; in Austria, HG; in Germany, NTE and BU/GER/01; in Portugal, HIV; and in Uruguay, ATIH. The remaining 63 isolates or DNA extracts were collected in France from 2002 to 2007 by the different laboratories of the *Toxoplasma* Biological Resource Center.

Genotyping analysis. Strain typing was performed by using the length polymorphism of 6 microsatellite markers in a modified multiplex assay. Elsewhere, we described a multiplex polymerase chain reaction (PCR) for typing strains of *T. gondii* by use of 5 microsatellite markers (*TUB2, W35, TgM-A, B18,* and *B17*) [35]. For this study, we added a sixth microsatellite marker to the multiplex assay, *M33,* which is located on chromosome IV. The primer sequences of the microsatellite marker *M33* were described elsewhere [36]. For this modified multiplex assay, the forward primer of *M33* was 5'-end labeled with 2,7',8'-benzo-5'-fluoro-2',4,7-trichloro-5-carboxyfluorescein (NED). Primers were synthesized by Applied Biosystems. For PCR, we used the Qiagen Multiplex PCR kit (Qiagen) with 2× Qiagen Multiplex PCR Master Mix (final concentration, 1×), 0.04 μmol/L of each primer, 5.5 μL of distilled water and 4 μL of DNA in a total volume of 25 μL. Amplifications were carried out in a GeneAmp PCR System 2700 Thermal Cycler (Applied Biosystems), as follows: 15 min at 95°C, followed by 40 cycles consisting of 94°C for 30 s, 61°C for 3 min, and 72°C for 60 s. The last extension step was performed at 60°C for 30 min. Electrophoresis of PCR products was carried out on an ABI Prism 310 genetic analyzer (Applied Biosystems), and the data were stored and analyzed with GeneScan analysis software (version 3.1; Applied Biosystems).

Statistical analysis. The following variables were analyzed: underlying cause of immunosuppression (AIDS vs. non-HIV), site of infection (cerebral vs. noncerebral, pulmonary vs. nonpulmonary, and single vs. multiple-organ), geographical origin of infection (Europe vs. outside Europe), outcome (death due to toxoplasmosis vs. survival), receipt of specific anti-*Toxoplasma* therapy (yes vs. no), genotype (type II strain vs. non–type II strain), and $CD4^+$ cell count at time of diagnosis of toxoplasmosis for patients with AIDS. Nine patients for whom the geographical origin of infection was unknown and 12 patients for whom no information about treatment was available were excluded from the analysis of those variables. Fourteen patients were excluded from the analysis of the outcome variable, including 10 patients whose death was not due to toxoplasmosis and 4 patients for whom no outcome data was available. Of the 52 patients with AIDS, 8 did not have $CD4^+$ cell count data. The results for this quantitative variable were expressed as median and interquartile range. The comparison of this quantitative variable between 2 groups was performed with the Mann-Whitney *U* test. The results for the qualitative variables were expressed as percentages. The comparison of qualitative variables between 2 groups was performed with the χ^2 test or Fisher's exact test, depending on the sample size. Multivariate logistic regression analysis was performed to adjust for the potential effect of geographical origin of infection (Europe vs. outside Europe) on the observed differences in site of infection, underlying cause of immunosuppression, outcome, and genotype. All *P* values ⩽.05 were considered to be statistically significant. Statistical analysis was performed using SAS software (version 9.1.3; SAS Institute) and Epi Info (version 6.04; French Institute for Public Health Surveillance).

RESULTS

Clinical and epidemiological data. As shown in table 2, toxoplasmic infection acquired outside Europe was observed significantly more frequently in patients with AIDS than in patients whose immunosuppression was not caused by HIV infection. Our study found a significantly higher rate of cerebral localization in patients with AIDS than in patients whose immunosuppression was not caused by HIV infection, whereas pulmonary localization was significantly more common in patients whose immunosuppression was not caused by HIV infection than in

Table 1. Epidemiological and clinical data for 88 immunocompromised patients with toxoplasmosis.

Patient number	Isolate	Sample (typing method)	Geographical origin of infection (mechanism)	Underlying cause of immunosuppression ($CD4^+$ cell count, cells/μL)[a]	Clinical finding(s)	Receipt of specific anti-*Toxoplasma* treatment	Outcome	Isolate genotype
1	MAN-NJA	Bronchoalveolar lavage fluid (S)	France (R)	AIDS (3)	Pulmonary toxoplasmosis[b]	Yes	Death due to toxoplasmosis	Type II
2	CRL-2005-YOU	Cerebral biopsy (D)	France (R)	AIDS (1)	Toxoplasmic encephalitis, pulmonary toxoplasmosis	Yes	Survived	Type II
3	SLS-2006-SMA	Bronchoalveolar lavage fluid (D)	France (P)	AIDS (10)	Toxoplasmic encephalitis, pulmonary toxoplasmosis	Yes	Survived	Type II
4	LGE-1998–1	Cerebral biopsy (S)	France (R)	AIDS (106)	Toxoplasmic encephalitis	Yes	Death due to other causes	Type II
5	RMS-2006-BEA	Cerebral biopsy (D)	France (R)	AIDS (11)	Toxoplasmic encephalitis	Yes	Death due to toxoplasmosis	Type II
6	SUR	Bone marrow (S)	France (R)	AIDS (140)	Medullar toxoplasmosis	Yes	Death due to toxoplasmosis	Type II
7	CCH-2007-GIO	Cerebrospinal fluid (D)	France (R)	AIDS (2)	Toxoplasmic encephalitis	Yes	Survived	Type II
8	STE-2005-MAL	Bronchoalveolar lavage fluid (S)	France (R)	AIDS (22)	Pulmonary toxoplasmosis	Yes	Death due to other causes	Type II
9	PTR-2006-DOC	Cerebral biopsy (D)	France (R)	AIDS (24)	Toxoplasmic encephalitis	Yes	Survived	Type II
10	DIJ-2004-KNA	Cerebral biopsy (D)	France (R)	AIDS (25)	Toxoplasmic encephalitis	Yes	Survived	Type II
11	DIJ-2004-MAR	Cerebral biopsy (D)	France (R)	AIDS (264)	Toxoplasmic encephalitis	Yes	Survived	Type II
12	CCH-2004-KAN	Bronchoalveolar lavage fluid (D)	France (R)	AIDS (30)	Toxoplasmic encephalitis, pulmonary toxoplasmosis	Yes	Survived	Type II
13	TOU-2006-FLO	Cerebrospinal fluid (D)	France (R)	AIDS (348)	Toxoplasmic encephalitis	Yes	Survived	Type II
14	LGE-2001–6	Cerebral biopsy (D)	France (R)	AIDS (57)	Toxoplasmic encephalitis	Yes	Death due to other causes	Type II
15	SLS-2006-SPA	Cerebral biopsy (D)	France (R)	AIDS (60)	Toxoplasmic encephalitis	Yes	Survived	Type II
16	MAR-2005-POR	Bronchoalveolar lavage fluid (D)	France (R)	AIDS (70)	Pulmonary toxoplasmosis	Yes	Survived	Type II
17	REN-2006-GAU	Cerebrospinal fluid (D)	France (R)	AIDS (79)	Toxoplasmic encephalitis	Yes	Survived	Type II
18	BOU	Cerebral biopsy (S)	France (R)	AIDS (NR)	Toxoplasmic encephalitis	NR	Death due to toxoplasmosis	Type II
19	LPN-2004-ROU	Cerebral biopsy (S)	Cameroon (R)	AIDS (24)	Toxoplasmic encephalitis	Yes	Survived	Type II
20	PSP-2006-BLA	Cerebral biopsy (D)	Reunion (R)	AIDS (4)	Toxoplasmic encephalitis	Yes	Survived	Type II
21	FDF-2007-ANG	Bronchoalveolar lavage fluid, bone marrow, blood (D)	Martinique (R)	AIDS (64)	Pulmonary toxoplasmosis, medullar toxoplasmosis	Yes	Survived	Type II
22	TOU-2006-PER	Blood (D)	Portugal (R)	AIDS (9)	Pulmonary toxoplasmosis	Yes	Survived	Type II
23	HG	Brain (S)	Austria (R)	AIDS (NR)	Toxoplasmic encephalitis at autopsy	NR	Death due to toxoplasmosis	Type II
24	NTE	Brain (S)	Germany (R)	AIDS (NR)	Toxoplasmic encephalitis at autopsy	NR	Death due to toxoplasmosis	Type II

(continued)

Table 1. ***(Continued.)***

Patient number	Isolate	Sample (typing method)	Geographical origin of infection (mechanism)	Underlying cause of immunosuppression ($CD4^+$ cell count, cells/μL)[a]	Clinical finding(s)	Receipt of specific anti-*Toxoplasma* treatment	Outcome	Isolate genotype
25	ELG	Cerebral biopsy (S)	Tunisia (R)	AIDS (NR)	Toxoplasmic encephalitis	No	Death due to toxoplasmosis	Type II
26	TOU-2007-MEL	Cerebrospinal fluid (D)	Unknown[c]	AIDS (4)	Toxoplasmic encephalitis	Yes	Survived	Type II
27	CCH-2007-SOU	Blood (D)	Unknown[c]	AIDS (7)	Pulmonary toxoplasmosis, disseminated toxoplasmosis, multiple organ failure	No	Death due to toxoplasmosis	Type II
28	DIJ-2005-HAN	Cerebrospinal fluid (D)	Unknown[c]	AIDS (NR)	Toxoplasmic encephalitis	NR	NR	Type II
29	DIJ-1996-BAC	Ascitic fluid (D)	France (R)	Acute myelogenous leukemia	Peritoneal toxoplasmosis	Yes	Survived	Type II
30	GRE-2005-BRA	Bronchoalveolar lavage fluid, blood (D)	France (R)	Bone marrow transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type II
31	MAR-2004-JEA	Expectoration, blood (D)	France (R)	Bone marrow transplant	Pulmonary toxoplasmosis	Yes	Survived	Type II
32	CCH-2006-MAR	Bronchoalveolar lavage fluid (S)	France[d]	Bone marrow transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type II
33	BDX-2006-HIL	Bronchoalveolar lavage fluid, blood (D)	France (R)	Bone marrow transplant	Pulmonary toxoplasmosis	No	Death due to toxoplasmosis	Type II
34	LGE-2007-VAN	Ascitic fluid (D)	France (R)	Bone marrow transplant	Peritoneal toxoplasmosis	Yes	Death due to other causes	Type II
35	DIJ-2006-BAZ	Cerebrospinal fluid (D)	France (R)	Bone marrow transplant	Toxoplasmic encephalitis	Yes	Death due to other causes	Type II
36	RMS-2000-MER	Cerebrospinal fluid (S)	France (R)	Bone marrow transplant	Toxoplasmic encephalitis	Yes	Survived	Type II
37	BDX-2007-PAS	Bronchoalveolar lavage fluid (D)	France (R)	Bone marrow transplant	Pulmonary toxoplasmosis	No	Death due to toxoplasmosis	Type II
38	DIJ-2006-COU	Cerebrospinal fluid (D)	France (R)	Bone marrow transplant	Toxoplasmic encephalitis	Yes	Death due to toxoplasmosis	Type II
39	BIL	Bronchoalveolar lavage fluid (S)	France (R)	Cardiopulmonary transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type II
40	SLS-2002-GOR	Blood (D)	France (R)	Cord blood cell transplant	Toxoplasmic encephalitis	Yes	Death due to other causes	Type II
41	NAN-2007-NOB	Pleural fluid, cerebrospinal fluid (D)	France (R)	Cord blood cell transplant	Toxoplasmic encephalitis, Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type II
42	LPN-2007-BAL	Bronchoalveolar lavage fluid, pleural fluid, blood (D)	France (R)	Hepatic transplant	Pulmonary toxoplasmosis	Yes	Survived	Type II
43	LGE-2001–5	Cerebral biopsy (D)	France (R)	Hodgkin lymphoma	Toxoplasmic encephalitis	NR	Survived	Type II
44	DAM	Bone marrow, blood (S)	France (P)	Iatrogenous aplasia	Pulmonary toxoplasmosis, medullar toxoplasmosis	Yes	Death due to toxoplasmosis	Type II

(continued)

Table 1. ***(Continued.)***

Patient number	Isolate	Sample (typing method)	Geographical origin of infection (mechanism)	Underlying cause of immunosuppression ($CD4^+$ cell count, cells/μL)[a]	Clinical finding(s)	Receipt of specific anti-*Toxoplasma* treatment	Outcome	Isolate genotype
45	LGE-2001–3	Blood (S)	France (R)	Leukemia	Pulmonary toxoplasmosis	NR	Death due to toxoplasmosis	Type II
46	LGE-2007-DEB	Bronchoalveolar lavage fluid (D)	France (R)	Non-Hodgkin lymphoma	Pulmonary toxoplasmosis	Yes	Survived	Type II
47	BRE-2006-DOR	Bronchoalveolar lavage fluid, bone marrow (D)	France (R)	Prolymphocytic leukemia	Toxoplasmic encephalitis, pulmonary toxoplasmosis, medullar toxoplasmosis	Yes	Survived	Type II
48	BRE-1997-PERR	Bone marrow, blood (S)	France (P)	Renal transplant	Pulmonary toxoplasmosis, medullar toxoplasmosis	No	Death due to toxoplasmosis	Type II
49	DIJ-1998-COL	Cerebral biopsy (D)	France (R)	Renal transplant	Toxoplasmic encephalitis	Yes	Death due to other causes	Type II
50	LPN-2003-TRE	Pleural fluid (D)	France (R)	T cell lymphoma	Pulmonary toxoplasmosis	NR	Death due to toxoplasmosis	Type II
51	TRS-2003-DUB	Blood (S)	Unknown[e]	Cardiac transplant	Fever, asthenia	Yes	Survived	Type II
52	PSP-2004-CON	Pleural fluid (S)	Unknown[e]	Cardiac transplant	Pulmonary toxoplasmosis	Yes	Survived	Type II
53	BU/GER/01	Lung, myocardial biopsy (S)	Unknown[c]	Cardiac transplant	Toxoplasmic encephalitis, Pulmonary toxoplasmosis, myocardial toxoplasmosis at autopsy	NR	Death due to toxoplasmosis	Type II
54	CCH-2005-MES	Bronchoalveolar lavage fluid (D)	Portugal (R)	Hepatic transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type II
55	HIV	Cerebral biopsy (S)	Unknown[c]	AIDS (NR)	Toxoplasmic encephalitis	NR	NR	Type I
56	ATIH	Blood (S)	Uruguay (R)	AIDS (25)	Toxoplasmic encephalitis, Pulmonary toxoplasmosis	NR	Death due to toxoplasmosis	Type I
57	PSP-2004-SAM	Cerebral biopsy (S)	Central African Republic (R)	AIDS (30)	Toxoplasmic encephalitis	Yes	Survived	Type III
58	SLS-2005-LAK	Expectoration (D)	Côte d'Ivoire (R)	AIDS (1)	Pulmonary toxoplasmosis, hepatic toxoplasmosis	Yes	Survived	Type III
59	PSP-2005-MUP	Cerebral biopsy (S)	Democratic Republic of the Congo (R)	AIDS (NR)	Toxoplasmic encephalitis	Yes	Survived	Type III
60	PTR-2007-FAB	Cerebral biopsy (D)	French Guiana (R)	AIDS (8)	Toxoplasmic encephalitis	Yes	Survived	Type III
61	LPN-2005-LUM	Bone marrow (D)	France (R)	AIDS (39)	Septic shock	No	Death due to toxoplasmosis	Type III
62	LGE-2003-BOU	Cerebral biopsy (D)	France (R)	AIDS (35)	Toxoplasmic encephalitis	Yes	Survived	Type III
63	LEG-NJA	Bronchoalveolar lavage fluid (S)	France (R)	AIDS (48)	Pulmonary toxoplasmosis[f]	Yes	Death due to toxoplasmosis	Type III
64	LIL-2003-LAM	Bronchoalveolar lavage fluid (D)	France (R)	Bone marrow transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type III
65	LPN-2002-SEE	Bronchoalveolar lavage fluid, pleural fluid (S)	France (R)	Cord blood cell transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Type III
66	COR	Blood, ascitic fluid (S)	France (R)	Non-Hodgkin lymphoma	Peritoneal toxoplasmosis	NR	Death due to toxoplasmosis	Type III

(continued)

Table 1. ***(Continued.)***

Patient number	Isolate	Sample (typing method)	Geographical origin of infection (mechanism)	Underlying cause of immunosuppression ($CD4^+$ cell count, cells/μL)[a]	Clinical finding(s)	Receipt of specific anti-*Toxoplasma* treatment	Outcome	Isolate genotype
67	MAR-2005-ABB	Cerebral biopsy (D)	Ghana (R)	AIDS (10)	Toxoplasmic encephalitis, ocular toxoplasmosis	Yes	Death due to other causes	Africa 1
68	RMS-2003-DJO	Cerebral biopsy (S)	Benin (R)	AIDS (141)	Toxoplasmic encephalitis	Yes	Survived	Africa 1
69	SLS-2002-MOU	Spinal cord abscess (D)	Côte d'Ivoire (R)	AIDS (222)	Toxoplasmic spinal cord abscess	Yes	NR	Africa 1
70	RMS-2006-GUE	Cerebral biopsy (D)	Côte d'Ivoire (R)	AIDS (398)	Toxoplasmic encephalitis	Yes	Survived	Africa 1
71	PSP-2006-BAY	Cerebrospinal fluid (D)	Cameroon (R)	AIDS (5)	Toxoplasmic encephalitis	Yes	Survived	Africa 1
72	SBX-2007-ADD	Cerebral biopsy (D)	Uganda (R)	AIDS (7)	Toxoplasmic encephalitis	Yes	Survived	Africa 1
73	IPP-2003-KAN	Blood (D)	Senegal (P)	IgA nephropathy	Fever, hepatic cytolysis, Pancreatitis	NR	NR	Africa 1
74	DPHT	Myocardial biopsy (S)	Guinea (P)	Renal transplant	Myocardial toxoplasmosis	Yes	Death due to other causes	Africa 1
75	FOU	Bone marrow, myocardium (S)	Unknown[e]	Renal transplant	Medullar toxoplasmosis, myocardial toxoplasmosis at autopsy	No	Death due to toxoplasmosis	Africa 1
76	CCH-2006-NGO	Brain (D)	Cameroon (R)	AIDS (4)	Toxoplasmic encephalitis, disseminated toxoplasmosis at autopsy	No	Death due to toxoplasmosis	Africa 2
77	CCH-2004-NIA	Bronchoalveolar lavage fluid (S)	Senegal (R)	AIDS (NR)	Pulmonary toxoplasmosis, hepatic cytolysis, Renal insufficiency	No	Death due to toxoplasmosis	Africa 2
78	FDF-2007-HEN	Brain (D)	Martinique (R)	AIDS (38)	Toxoplasmic encephalitis at autopsy	Yes	Death due to other causes	Caribbean 1
79	PSP-2003-ERO	Lymphadenopathy (S)	Guadeloupe (R)	AIDS (686)	Toxoplasmic lymphadenopathy[g]	Yes	Survived	Caribbean 1
80	CCH-2005-REN	Blood (S)	Guadeloupe (R)	Bone marrow transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Caribbean 1
81	PSP-2003-KOM	Cerebral biopsy (S)	Cameroon (R)	AIDS (100)	Toxoplasmic encephalitis	Yes	Survived	Unique 1
82	CRL-2004-MOT	Cerebral biopsy (D)	Cameroon (R)	AIDS (50)	Toxoplasmic encephalitis[h]	Yes	Survived	Unique 2
83	CCH-2004-JOS	Bronchoalveolar lavage fluid (D)	French Guiana (R)	AIDS (13)	Pulmonary toxoplasmosis	Yes	Survived	Unique 3
84	NEC-2006-OUA	Blood (D)	Côte d'Ivoire[i]	AIDS (532)	Toxoplasmic encephalitis, Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Unique 4
85	DIJ-2000-LEC	Bronchoalveolar lavage fluid (D)	France (P)	AIDS (1)	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Unique 5
86	LIL-2000-BRI	Bronchoalveolar lavage fluid, Blood (D)	France (R)	Cord blood cell transplant	Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Unique 6
87	REN-2007-VAL	Bronchoalveolar lavage fluid (D)	Guatemala (R)	Bone marrow transplant	Pulmonary toxoplasmosis	Yes	Survived	Unique 7
88	CCH-2002-BAO	Cerebral biopsy (D)	Unknown[c]	Cardiac transplant	Toxoplasmic encephalitis, Pulmonary toxoplasmosis	Yes	Death due to toxoplasmosis	Unique 8

NOTE. D, direct typing from the clinical sample; NR, not reported; P, primary infection; R, reactivation; S, typing of the strain isolated in mouse tissue or cell culture after inoculation of the clinical sample.

[a] $CD4^+$ cell count at the time acute toxoplasmosis was diagnosed.

[b] Pulmonary toxoplasmosis with recovery but relapse 2 months later with toxoplasmic encephalitis.

[c] Insufficient data.

[d] A 6-year-old child with no history of travel.

[e] *Toxoplasma* transmission by graft (donor of unknown origin seropositive for *Toxoplasma* and recipient seronegative for *Toxoplasma*).

[f] Pulmonary toxoplasmosis with recovery but relapse 3 months later with toxoplasmic encephalitis, medullar toxoplasmosis, and peritoneal toxoplasmosis.

[g] Inguinal lymphadenopathy 3 months after discontinuation of secondary prophylaxis and 21 months after toxoplasmic encephalitis (see [33]).

[h] Relapse 3 months after initial toxoplasmic encephalitis.

[i] Congenital transmission of HIV and *Toxoplasma gondii* after reactivation in the mother during pregnancy.

Table 2. Geographical origin and site of toxoplasmic infection for patients with AIDS and patients whose immunosuppression was not caused by HIV infection.

Characteristic	Patients with AIDS, no. (%)	Patients with immunosuppression not due to HIV infection, no. (%)	*P*	Adjusted *P*[a]
Geographical origin of infection				
Europe ($n = 52$)	25 (52.1)	27 (87.1)	.001	ND
Outside Europe ($n = 27$)	23 (47.9)	4 (12.9)		
Site of infection				
Cerebral ($n = 49$)	39 (75.0) [OE, 17; E, 19; NR, 3]	10 (27.8) [OE, 0; E, 8; NR, 2]	<.001	<.001
Noncerebral ($n = 39$)	13 (25.0) [OE, 6; E, 6; NR, 1]	26 (72.2) [OE, 4; E, 19; NR, 3]		
Pulmonary ($n = 39$)	16 (30.8) [OE, 6; E, 9; NR, 1]	23 (63.9) [OE, 2; E, 18; NR, 3]	.002	.018
Nonpulmonary ($n = 49$)	36 (69.2) [OE, 17; E, 16; NR, 3]	13 (36.1) [OE, 2; E, 9; NR, 2]		
Single organ ($n = 67$)	39 (75.0) [OE, 17; E, 19; NR, 3]	28 (77.8) [OE, 3; E, 23; NR, 2]	.763	.454
Multiple organ ($n = 21$)	13 (25.0) [OE, 6; E, 6; NR, 1]	8 (22.2) [OE, 1; E, 4; NR, 3]		

NOTE. Geographical origin of infection is reported in square brackets. Data on geographical origin was not available for all patients (see Methods for details). E, Europe; NR, not reported; ND, not done; OE, outside Europe.

[a] Adjusted for geographical origin of infection (Europe vs. outside Europe) by multivariate logistic regression analysis.

patients with AIDS . There was no statistical difference between patients with AIDS and patients whose immunosuppression was not caused by HIV infection with respect to the occurrence of single or multiple-organ localization. These results were unchanged when adjusted for the geographical origin of infection.

Our results in table 3 suggest that the prognosis of toxoplasmosis (death due to toxoplasmosis vs. survival) in immunocompromised patients was significantly linked to the underlying cause of immunosuppression, site of infection, and the receipt of specific anti-*Toxoplasma* treatment. Patients with AIDS were less likely to die than those whose immunosuppression was not due to HIV infection. Patients whose infection was cerebral had a better outcome than those whose infection was noncerebral, whereas pulmonary involvement was more frequently associated with death than was nonpulmonary localization. Patients with multiple-organ involvement had a worse prognosis than those with single-organ localization. These results were unchanged by multivariate logistic regression analysis, though it is worth noting that the rate of death among patients whose immunosuppression was not caused by HIV infection and in patients with multiple organ involvement reached borderline statistical significance when adjusted for the geographical origin of infection ($P = .054$). Patients who did not receive specific anti-*Toxoplasma* therapy were more likely to die than those who received it.

Table 3. Underlying cause of immunosuppression, site of toxoplasmic infection, and receipt of specific anti-*Toxoplasma* treatment for patients with toxoplasmosis, according to outcome.

Characteristic	Patients, no. (%)		*P*	Adjusted *P*[a]
	Died of toxoplasmosis	Survived		
Underlying cause of immunosuppression				
AIDS ($n = 44$)	15 (42.9) [OE, 5; E, 9; NR, 1]	29 (74.4) [OE, 15; E, 13; NR, 1]	.005	.054
Immunosuppression not due to HIV infection ($n = 30$)	20 (57.1) [OE, 1; E, 16; NR, 3]	10 (25.6) [OE, 1; E, 7; NR, 2]		
Site of infection				
Cerebral ($n = 40$)	14 (40.0) [OE, 4; E, 8; NR, 2]	26 (66.6) [OE, 11; E, 14; NR, 1]	.002	.018
Noncerebral ($n = 34$)	21 (60.0) [OE, 2; E, 17; NR, 2]	13 (33.4) [OE, 5; E, 6; NR, 2]		
Pulmonary ($n = 38$)	24 (68.6) [OE, 4; E, 17; NR, 3]	14 (35.9) [OE, 4; E, 9; NR, 1]	.005	.016
Nonpulmonary ($n = 36$)	11 (31.4) [OE, 2; E, 8; NR, 1]	25 (64.1) [OE, 12; E, 11; NR, 2]		
Single organ ($n = 54$)	21 (60.0) [OE, 2; E, 19; NR, 0]	33 (84.6) [OE, 14; E, 16; NR, 3]	.017	.054
Multiple organ ($n = 20$)	14 (40.0) [OE, 4; E, 6; NR, 4]	6 (15.4) [OE, 2; E, 4; NR, 0]		
Specific anti-*Toxoplasma* treatment received				
Yes ($n = 56$)	18 (66.7)	38 (100)	<.001	ND
No ($n = 9$)	9 (33.3)	0 (0)		

NOTE. Geographical origin of infection is reported in square brackets. E, Europe; ND, Not done; NR, not reported; OE, outside Europe.

[a] Adjusted for geographical origin of infection (Europe vs. outside Europe) by multivariate logistic regression analysis.

Table 4. Allelic combinations for the 14 genotypes identified in isolates obtained from 88 immunocompromised patients with toxoplasmosis.

Genotype	Isolates, no. (%)	Alleles					
		TUB2	*W35*	*TgM-A*	*B18*	*B17*	*M33*
Type II							
All	54 (61.4)	2 or 3	2 or 3	2	2	2 or 3	1 or 2
Non–type II							
All	34 (38.6)						
Type I	2 (2.3)	1	1	1	1 or 3	1	1 or 2
Type III	10 (11.4)	2 or 3	2 or 3	3	1 or 3	2 or 3	3
Africa 1	9 (10.2)	1	1	3	1 or 3	1	3
Africa 2	2 (2.3)	2 or 3	1	3	1 or 3	2 or 3	3
Caribbean 1	3 (3.4)	1	2 or 3	3	4	1	3
Unique 1	1 (1.1)	1	6	3	1 or 3	1	3
Unique 2	1 (1.1)	1	1	3	1 or 3	2 or 3	3
Unique 3	1 (1.1)	2 or 3	2 or 3	3	4	2 or 3	3
Unique 4	1 (1.1)	2 or 3	2 or 3	3	1 or 3	2 or 3	1 or 2
Unique 5	1 (1.1)	2 or 3	2 or 3	2	1 or 3	2 or 3	1 or 2
Unique 6	1 (1.1)	2 or 3	2 or 3	5	1 or 3	2 or 3	1 or 2
Unique 7	1 (1.1)	1	2 or 3	3	1 or 3	2 or 3	3
Unique 8	1 (1.1)	1	2 or 3	4	4	2 or 3	1 or 2

Genotyping analysis. Genotyping results for the 88 isolates are reported in table 1. By use of 6 microsatellite markers, we identified the 14 different genotypes listed in table 4. One genotype, type II, was predominant; it was observed in 54 isolates (61.4%) . Non–type II strains accounted for 34 isolates (38.6%) and included the 13 remaining genotypes. Type III was the second most common genotype; infection due to isolates of this type was acquired in France for 6 patients, sub-Saharan Africa for 3 patients, and French Guiana for 1 patient. Type I isolates were recovered from 2 patients, including 1 who acquired toxoplasmosis in Uruguay. Three genotypes (Africa 1, Africa 2, and Caribbean 1), which are different from the archetypal genotypes I, II, and III, were recovered from several patients. The most common nonarchetypal genotype, Africa 1, was recovered from 9 patients: 6 who had a reactivated toxoplasmic infection and came from sub-Saharan African countries, 2 who had a primary infection acquired in Guinea and Senegal, respectively, and 1 who underwent renal transplantation that involved *Toxoplasma* transmission from the graft (donor of unknown origin). The Africa 2 genotype was recovered from 2 patients from Cameroon and Senegal, respectively, whereas the Caribbean 1 genotype was recovered from 3 patients from 2 islands in the French West Indies (Guadeloupe and Martinique). The 8 remaining genotypes, named Unique 1–8, were recovered from 1 patient each.

Correlation between genotypes and toxoplasmosis. As shown in table 5, the genotype of *Toxoplasma* strains was strongly linked to the presumed geographical origin of infection. Type II strain were more commonly recovered from patients with infections acquired in Europe than from those who acquired their infections outside Europe, and consequently non–type II strains were more commonly recovered from patients with infections acquired outside Europe than from those who acquired their infections in Europe ($P < .001$). Type II strains were predominant, regardless of the underlying cause of immunosuppression, site of infection, or outcome. There was no statistical difference between the rate at which type II strains and non–type II strains were recovered from patients with AIDS and patients whose immunosuppression was not caused by HIV infection; similarly, there was no statistical difference in this regard between patients with cerebral toxoplasmosis and those with noncerebral toxoplasmosis, between patients with pulmonary toxoplasmosis and those with nonpulmonary toxoplasmosis, between patients with a single site of infection and those with multiple organ localizations, or between patients with toxoplasmosis who died of toxoplasmosis and those who survived. These results were unchanged when adjusted for the geographical origin of infection. There was no statistical difference between the median $CD4^+$ cell count of patients with AIDS who were infected by type II strains and those infected by non–type II strains (24 vs. 35 cells/μL, respectively).

DISCUSSION

Of 52 patients with AIDS, 39 (75.0%) had toxoplasmosis with cerebral involvement, whereas 16 (30.8%) had toxoplasmosis with pulmonary involvement. This confirms the predominance of toxoplasmic encephalitis in patients with AIDS [4], but also underscores the fact that pulmonary toxoplasmosis is relatively common. Of 36 patients whose immunosuppression was not due to HIV infection, 23 (63.9%) had toxoplasmosis with pul-

Table 5. Correlations between isolate genotype and geographical origin of infection, underlying cause of immunosuppression, site of toxoplasmic infection, outcome, and median CD4$^+$ cell count.

Characteristic	Type II	Non–type II	*P*	Adjusted *P*[a]
Geographical origin of infection				
Europe ($n = 52$)	44 (91.7)	8 (25.8)	<.001	ND
Outside Europe ($n = 27$)	4 (8.3)	23 (74.2)		
Underlying cause of immunosuppression				
AIDS ($n = 52$)	28 (51.9) [OE, 4; E, 21; NR, 3]	24 (70.6) [OE, 19; E, 4; NR, 1]	.081	.56
Immunosuppression not due to HIV infection ($n = 36$)	26 (48.1) [OE, 0; E, 23; NR, 3]	10 (29.4) [OE, 4; E, 4; NR, 2]		
Site of infection				
Cerebral ($n = 49$)	31 (57.4) [OE, 3; E, 25; NR, 3]	18 (52.9) [OE, 14; E, 2; NR, 2]	.681	.165
Noncerebral ($n = 39$)	23 (42.6) [OE, 1; E, 19; NR, 3]	16 (47.1) [OE, 9; E, 6; NR, 1]		
Pulmonary ($n = 39$)	26 (48.1) [OE, 1; E, 22; NR, 3]	13 (38.2) [OE, 7; E, 5; NR, 1]	.362	.589
Nonpulmonary ($n = 49$)	28 (51.9) [OE, 3; E, 22; NR, 3]	21 (61.8) [OE, 16; E, 3; NR, 2]		
Single organ ($n = 67$)	43 (79.6) [OE, 3; E, 36; NR, 4]	24 (70.6) [OE, 17; E, 6; NR, 1]	.333	.815
Multiple organ ($n = 21$)	11 (20.4) [OE, 1; E, 8; NR, 2]	10 (29.4) [OE, 6; E, 2; NR, 2]		
Outcome				
Death ($n = 35$)	21 (45.7) [OE, 1; E, 18; NR, 2]	14 (50.0) [OE, 5; E, 7; NR, 2]	.716	.150
Survival ($n = 39$)	25 (54.3) [OE, 3; E, 19; NR, 3]	14 (50.0) [OE, 13; E, 1; NR, 0]		
CD4$^+$ cell count			.600	ND
Median cells/μL (IQR)	24 (7–70)	35 (8–100)		
Range	1–348	1–686		

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Geographical origin of infection is reported in square brackets. E, Europe; IQR, interquartile range; ND, not done; NR, not reported; OE, outside Europe.

[a] Adjusted for geographical origin of infection (Europe vs. outside Europe) by multivariate logistic regression analysis.

monary involvement, whereas 10 (27.8%) had toxoplasmosis with cerebral involvement. These results were unexpected because studies and reviews from the past decade or earlier reported the brain as the main site of the disease in patients who have undergone HSCT [12, 16] and in patients with cancer [6]. The higher rate of pulmonary toxoplasmosis observed in our study is likely the consequence of the general accessibility and optimization of more sensitive diagnostic procedures in the current decade, such as PCR techniques, especially for bronchoalveolar lavage fluid samples. The number of organs involved (1 vs. $\geqslant$2) did not differ significantly between patients with AIDS and patients whose immunosuppression was not caused by HIV infection. Patients who acquired *Toxoplasma* infection outside Europe were predominantly persons with AIDS. This reflects the geographical and ethnic specificity of HIV epidemiology in France. In 2006, the median rate of positive HIV test results per million inhabitants was 178 in France but this rate was considerably higher in the 3 French overseas departments of America: 2077 in French Guiana, 861 in Guadeloupe, and 409 in Martinique [10]. Moreover, nearly 30% of newly diagnosed HIV infections in France occur among the migrant population from sub-Saharan African countries [10]. In our study, of the 46 patients with AIDS who also had reactivated toxoplasmosis, 23 originated from areas outside Europe, including 15 from sub-Saharan African countries, and 6 from French overseas departments.

The most important factors influencing outcome were the receipt of specific anti-*Toxoplasma* therapy, the site of infection, and the number of organs involved. No receipt of specific treatment, pulmonary toxoplasmosis, and the involvement of $\geqslant$2 noncontiguous organs (i.e., disseminated toxoplasmosis) were the risk factors associated with the worst prognosis, which is in accordance with other published data [16, 37]. All 9 patients who did not receive specific treatment died of toxoplasmosis, and 6 of them had multiple-organ involvement. Of the 18 patients who died of toxoplasmosis despite receiving specific therapy, 15 had pulmonary involvement, which shows that the lung is frequently involved in fatal cases of toxoplasmosis. The worse outcome observed for patients whose immunosuppression was not caused by HIV infection is explained by the increased frequency of pulmonary toxoplasmosis in these patients, compared with persons with AIDS, who predominantly had cerebral involvement.

Because AIDS is the main risk factor for developing severe toxoplasmosis, and toxoplasmic encephalitis is the most common infection for this group, previous genetic studies on *Toxoplasma* isolates focused only [38–40] or mainly [41, 42] on patients with AIDS who had toxoplasmic encephalitis, neglecting both patients with toxoplasmosis whose immunosuppression was not due to HIV infection and other clinical presentations of toxoplasmosis. No information about the outcome of the disease was available in these studies.

As previously reported in a large study that used a single marker to genotype 71 isolates obtained from immunocompromised patients in France [32], we confirmed that the distribution of *Toxoplasma* genotypes (type II vs. non–type II) was not significantly different between patients with AIDS and patients whose immunosuppression was not caused by HIV infection, nor was it significantly different for different sites of infection. Our study provides new data on the distribution of genotypes according to outcome and the geographical origin of toxoplasmic infection in immunocompromised patients. We observed that the distribution of type II and non–type II strains was highly similar for both patients who died of toxoplasmosis and those who survived, leading to the conclusion that the genotype of the strain was probably not a major factor in the outcome. However, the low number of isolates with different genotypes observed among the non–type II strains did not allow analysis of the outcome associated with each of these genotypes. We observed a clear difference in distribution of genotypes, according to the presumed geographical origin of infection. Of 48 patients infected by type II strains, 44 (91.7%) acquired toxoplasmosis in Europe; of 31 patients infected by non–type II strains, 23 (74.2%) acquired toxoplasmosis outside Europe. These results in immunocompromised patients are in accordance with observations regarding the geographical distribution of *Toxoplasma* genotypes worldwide, which shows an overwhelming predominance of type II strains in France and very likely in other European countries, whatever the host (humans and domestic or wild animals) or the clinical findings (asymptomatic and congenital toxoplasmosis in humans) [24, 26, 27, 43–45].

Type II seems endemic only in Europe and North America, and our results confirm the widespread distribution of type III that has already been described in North and South America, Europe, Africa, and Asia [17, 26, 29, 30, 46]. The rarity of type I in our population contrasts with the overrepresentation of this genotype in other studies [38–42]. This may be explained by true epidemiological differences between our population and the Brazilian population studied by Ferreira et al. [40] or by misidentification of type I in studies that used a single marker [32, 39, 41, 42]. With multilocus typing, conflicting results can be observed when clinical or epidemiological data about the geographical origins of patients are lacking or when the size of clinical samples is too small. For these reasons, it is difficult to know whether type II [17] or type I [38] strains predominate in immunocompromised patients in the United States.

Certain nonarchetypal genotypes were repeatedly recovered from different patients who acquired the infection in sub-Saharan Africa (genotypes Africa 1 and 2) and in the French West Indies (genotype Caribbean 1). The Africa 1 genotype is the most common in patients who acquired infection in western and central African countries. Since the Africa genotype 1 has been collected in various and distant areas (from Senegal to Uganda) and at different time, this genotype is a candidate for an African clonal lineage. Although recovered from few patients, the Africa 2 and Caribbean 1 genotypes could also be representative of other clonal lineages in Africa and in the Caribbean. Further population genetics analyses with more isolates from different hosts in these areas are needed to confirm these results. These presumed clonal lineages, together with the recovery of 8 unique genotypes from immunocompromised patients, confirm that the genetic diversity of *T. gondii* is greater than was initially thought. Recent studies in which isolates were collected from chickens in several African countries [28, 29] showed a predominance of archetypal types I, II and III lineages in these areas, which contrasts with the higher proportion of nonarchetypal genotypes (e.g., Africa 1 and 2) recovered from African patients in this study. These differences may suggest a correlation of specific genotypes with clinical toxoplasmosis in immunocompromised patients in Africa, but they must be confirmed by greater sampling of isolates both in patients and animals in Africa.

The influence of the *Toxoplasma* genotype in human toxoplasmosis remains unclear because other parasite factors (life-cycle stage and inoculum size) and, above all, host factors (immune status and genetic background) play a key role in the natural course of toxoplasmosis [47, 48]. If some data suggest a possible correlation between severe toxoplasmosis and atypical genotypes in immunocompetent patients [1, 2, 49] and in cases of congenital toxoplasmosis [27], this seems not to be the case in immunocompromised patients who reactivate a type II strain (if acquired in Europe) or a non–type II strain (if acquired in Africa or South America). A larger number of samples are needed to better understand the influence of the different non–type II genotypes in immunocompromised patients. Further investigations that combine parasite genotyping and analysis of host factors, such as cytokine activation and regulation by genes of the major histocompatibility complex [50], are necessary to better understand host resistance and susceptibility to toxoplasmosis in immunocompromised patients.

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