

Mycobacterium kansasii in HIV patients: clarithromycin and antiretroviral effects

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SUMMARY

SETTING: Charity Hospital New Orleans, Louisiana, USA.

OBJECTIVE: To define the differences between the pre-HAART (highly active anti-retroviral treatment) and HAART eras in patients co-infected with *Mycobacterium kansasii* and the human immunodeficiency virus (HIV).

DESIGN: A retrospective chart review revealed 82 patients with HIV and *M. kansasii* during the 6-year period from 1 July 1991 to 30 June 1997 (pre-HAART era), while the 6-year period from 1 July 1997 to 30 June 2003 (HAART era) revealed 55 cases.

RESULTS: Among all patients with *M. kansasii* and HIV, 47 (34%) had an additional, concurrent mycobacterial infection and two had triple mycobacterial species isolation.

More patients (17/82, 21%) had disseminated mycobacterial disease in the pre-HAART era than in the HAART era (3/55, 5%; $P = 0.045$). Pre-HAART patients treated without clarithromycin (CLM) survived a median of 2 months vs. 10 months for pre-HAART patients treated with CLM ($P = 0.05$). Those treated without CLM had a median survival of 2 months in the pre-HAART era ($n = 19$) vs. 10.5 months in the HAART era ($n = 12$, $P < 0.02$).

CONCLUSION: CLM use in treatment of *M. kansasii* in HIV-co-infected patients is associated with significantly longer survival.

KEY WORDS: *Mycobacterium kansasii*; HIV; HAART; atypical mycobacteria; NTM; CLM; AIDS; environmental mycobacteria

MYCOBACTERIUM KANSASII is the second most common non-tuberculous mycobacterium after *M. avium* complex (MAC) to cause disease in human immunodeficiency virus (HIV) infected individuals.¹ Disseminated disease due to *M. kansasii* is an acquired immune-deficiency syndrome (AIDS) defining diagnosis.² Since a prior study from New Orleans that included a summary of all previously reported cases in the world,³ there have been other reports of *M. kansasii* disease in HIV-infected individuals.⁴⁻³² The New Orleans study included 38 *M. kansasii* and HIV co-infected patients from Charity Hospital in the 3-year period from 1 July 1988 to 30 June 1991.³ The present paper follows the earlier New Orleans experience by retrospectively studying 137 HIV-infected patients with *M. kansasii* isolates at Charity Hospital from 1 July 1991 to 30 June 2003.

PATIENTS AND METHODS

Charity Hospital is a public tertiary care medical facility located in central New Orleans. Charity Hospital, along with Bellevue Hospital in New York City, is the oldest continuously operating hospital in the USA

(both hospitals date from 1736), but suffered severe damage in the 2005 New Orleans flood that resulted from multiple levee breaks after Hurricane Katrina had passed.

After approval had been obtained from the Tulane Institutional Review Board, all mycobacterial cultures in the 12-year study period that yielded *M. kansasii* isolates were reviewed. An examination of available laboratory data identified which patients with *M. kansasii* isolates were HIV-infected.

M. kansasii infections were defined as either pulmonary or disseminated (extra-pulmonary). Disseminated disease required isolation of *M. kansasii* from blood, bone marrow, or organs other than lung, lymph nodes, or skin. Pulmonary disease was defined as *M. kansasii* isolation from the lung in association with pulmonary symptoms and an abnormal chest radiograph (CXR), or in association with persisting clinical and radiograph abnormalities after treatment of another pulmonary infection. Colonization with *M. kansasii* was defined as lack of association with clinical symptoms, a normal CXR, or if follow-up sputum cultures demonstrated spontaneous *M. kansasii* absence (without specific antibiotic therapy).

A dual or triple mycobacterial infection was defined as concurrent isolation of *M. kansasii* with another species of mycobacterium from the same patient specimen or from subsequently submitted specimens within the same hospital admission (defined as within 2 weeks).

M. kansasii isolates were identified by standard biochemical methods after growth in BACTEC media and subculture on Löwenstein-Jensen (LJ) media. If more than one mycobacterial species from a specimen was suspected by variable colony morphology on LJ media, a subculture of each colony to Middlebrook 7H10 media was performed to identify each species separately. Dual or triple mycobacterial isolates from one patient specimen could thus be identified.

Drug susceptibility testing was evaluated using the BACTEC radiometric method.³³ After April 1997, susceptibility testing was performed for rifampicin (RMP) alone, unless otherwise requested.

Treatment was defined as a combination of at least two antimycobacterial drugs for at least 1 month, with the treatment endpoint being drug hypersensitivity, death, or completion of an 18-month course.

The 12-year study period was divided into equal pre- highly active anti-retroviral treatment (HAART) and HAART time periods, corresponding to the history of HAART use in New Orleans. Although HAART became available in 1996, it was not until 1997 that three-drug HAART regimens became the clinical practice standard for the Charity Hospital HIV out-patient clinic. Therefore, 1 July 1991–30 June 1997 is referred to as the pre-HAART era and 1 July 1997–30 June 2003 as the HAART era.

The two-tailed *t*-test and 95% confidence intervals (CIs) were used to determine statistical significance of observed differences between mean values of the study subgroups.

RESULTS

Demography

Review of mycobacterial culture data yielded *M. kansasii* isolates from 261 patients. Laboratory review identified 137 (52.5%) patients as HIV-infected and 124 as either HIV-negative or not tested. The 137 HIV-infected patients had a total of 377 *M. kansasii* isolates (mean 2.75 isolates).

Of the 137 HIV-infected patients with *M. kansasii* isolates, 115 were male and 22 female. The mean age was 39 years (range 21–61). Most patients (127, or 93%) had New Orleans zip codes. Ninety-seven (71%) had a history of inhaling recreational toxins: 77 smoked cigarettes, 24 smoked cigarettes and crack cocaine, and 6 smoked just crack cocaine. Two patients had occupational lung disease: one due to sand blasting and one due to cutting sugar cane. The demographics of pre-HAART and HAART groups regarding age (mean 37 vs. 42 years), sex (69 male/13 female vs. 46

male/9 female), postal (zip) codes (almost all had New Orleans zip codes, except for 4 pre-HAART and 6 HAART patients), smoking status (66% vs. 78% smokers), did not differ significantly.

Clinical and radiological findings

Of the 137 HIV-infected patients, 117 had pulmonary *M. kansasii* isolates and 20 had disseminated *M. kansasii* disease. Of those with *M. kansasii* dissemination, 13 had growth of *M. kansasii* from blood culture, 2 from bone marrow, 2 from blood culture and bone marrow, 1 from the spleen (in addition to the lung), one from blood and sputum, and one from blood and skin. Significantly more patients (17/82, 21%) had disseminated mycobacterial disease in the pre-HAART era than in the HAART era (3/55, 5%; $P = 0.045$).

Clinical and radiographic data were available for 129 of the 137 HIV-infected patients with *M. kansasii* isolates (Table 1). Only 15 patients had a normal CXR: three of these had disseminated *M. kansasii* infections and were treated, and four had multiple pulmonary *M. kansasii* isolates and were treated. Another patient had only one *M. kansasii* isolate and lived for 30 months without being treated (this patient had a CD4 count of 183/mm³ at the time of isolation, but repeat testing was not performed, making it impossible to rule out progression of *M. kansasii* to infection before death). Of the remaining seven patients with normal CXRs, two were colonized and did well without treatment (one had documented sputum culture conversion and one was cured with HAART therapy and immune reconstitution); two died within 2 months from unrelated causes, although whether *M. kansasii* played a role is uncertain; and of the three remaining patients, two were lost to follow-up, and the third was clinically and radiographically stable for 6 months then had ethambutol (EMB) and clarithromycin (CLM) prescribed for disseminated MAC infection. Therefore, as many as 8 of 137 patients (6.6%) had *M. kansasii* isolates found without clear evidence of disease. A more conservative estimate is that only three (2%) of the above patients were clearly colonized and never ill from *M. kansasii*.

Mycobacteria concurrently isolated with *M. kansasii*

Fifty-nine (43%) of the patients were found to have other concurrent pathogenic isolates within 2 weeks of when *M. kansasii* was initially isolated. Non-mycobacterial pulmonary co-isolates included *Pneumocystis jirovecii* (4 patients), *Pseudomonas aeruginosa* (2 patients), cytomegalovirus (2 patients), *Histoplasma capsulatum* (two patients), and 1 each with *Streptococcus pneumoniae*, *Cryptococcus neoformans*, community-acquired pneumonia of unspecified etiology, and pneumonia attributed to both *C. neoformans* and community-acquired pneumonia.

Forty-seven (34%) patients were found to have other concurrent mycobacterial isolates (Table 2). Of

Table 1 Signs, symptoms and radiography of *M. kansasii* and HIV co-infected patients

	Pre-HAART (n = 82) %	HAART (n = 55) %	Fisher's exact test, 2 tailed comparing pre-HAART and HAART cohorts
Symptoms			
Fever	55	49	NS
Diarrhea	17	87	<i>P</i> < 0.001
Weight loss	44	45	NS
Dyspnea	44	40	NS
Productive cough	33	44	NS
Cough	29	65	<i>P</i> < 0.01
Night sweats	26	33	NS
Chills	20	22	NS
Fatigue	18	18	NS
Nausea or vomiting	12	18	NS
Hemoptysis	10	9	NS
Signs			
Fever	54	36	NS
Crackles	27	30	NS
Wheezes	16	4	<i>P</i> = 0.05
Hepatomegaly	2	2	NS
Splenomegaly	1	0	NS
Lymphadenopathy	0	13	NS
CXR findings			
Interstitial infiltrates	45	49	NS
Alveolar infiltrates	28	18	NS
Cavitation	17	18	NS
Mass lesions	7	13	NS
Fibrosis	4	5	NS
Pleural effusion	2	5	NS
Hilar lymphadenopathy	0	15	NS
Bilateral distribution	49	36	NS
Unilateral distribution	21	22	NS
Apical distribution	34	51	NS
Mid-lung distribution	24	40	NS
Lower distribution	20	40	NS
Normal CXR	5	13	NS

HIV = human immunodeficiency virus; HAART = highly active anti-retroviral treatment; NS = not significant; CXR = chest radiograph.

note are two cases of concurrent triple mycobacterial pulmonary isolation. The patient with *M. kansasii*, MAC, and *M. fortuitum* was given azithromycin 1.2 g weekly after mycobacterial isolation. He was readmitted 5 months later with clinical and CXR deterioration, but had negative mycobacterial cultures from bronchoalveolar lavage, and was released for hospice care. The patient with *M. kansasii*, *M. chelonae*, and *M. fortuitum* died from combined respiratory and hepatic failure

4 months after mycobacterial isolation, never having received any mycobacterial-specific therapy.

CD4 (T-cell count) and mycobacterial culture data

CD4 counts were available for 113 patients at the time of *M. kansasii* isolation; 107 had CD4 counts <200/mm³. The overall median CD4 count was 17/mm³ (range 0–495/mm³). However, the pre-HAART group's median CD4 count was 13/mm³ vs. 31/mm³ for the

Table 2 Mycobacteria co-isolated with *Mycobacterium kansasii*

	Pre-HAART era cases (n = 82) <i>n</i>	HAART era cases (n = 55) <i>n</i>	Total cases for both periods <i>n</i>	Total cases (n = 137) %	<i>P</i> value
<i>M. kansasii</i> co-mycobacterial isolates					
Pulmonary <i>M. kansasii</i> and MAC	10	10	20	15	NS
Pulmonary <i>M. kansasii</i> and <i>M. fortuitum</i>	0	2	2	1.5	NS
Pulmonary <i>M. kansasii</i> , MAC and <i>M. fortuitum</i>	0	1	1	<1	NS
Pulmonary <i>M. kansasii</i> , <i>M. chelonae</i> , and <i>M. fortuitum</i>	0	1	1	<1	NS
Pulmonary <i>M. kansasii</i> and disseminated MAC	8	2	10	7.3	NS
Pulmonary <i>M. kansasii</i> and disseminated <i>M. tuberculosis</i>	2	0	2	1.5	NS
Disseminated <i>M. kansasii</i> and disseminated MAC	7	3	10	7.3	NS
Disseminated <i>M. kansasii</i> and pulmonary <i>M. tuberculosis</i>	1	0	1	<1	NS
Total			47	34	

HAART = highly active anti-retroviral treatment; MAC = *Mycobacterium avium* complex; NS = not significant.

HAART era ($P < 0.002$ for comparison of medians). The median CD4 count was $18.5/\text{mm}^3$ for patients with pulmonary *M. kansasii* isolates, as opposed to $8.5/\text{mm}^3$ for those with disseminated *M. kansasii* disease ($P < 0.03$).

Laboratory culture data revealed that 96 of the 137 patients (70%) had more than one *M. kansasii* isolate (range 2–14 isolates). Of 119 patients, 69 (58%) with pulmonary *M. kansasii* isolates had positive acid-fast smears of sputum at the time of isolation, 44 were negative, and six results were missing. Of the 41 patients with only one *M. kansasii* isolate, 5 had disseminated *M. kansasii* bacteremia, and 7 died at the time of *M. kansasii* isolation. Of the remaining 29 patients with only one isolate, only 5 had negative CXRs and were not treated, 13 were treated, and 10 were not treated (one patient had missing treatment data).

The antimicrobial susceptibilities of the *M. kansasii* isolates from the HIV-co-infected group were available from 117 isolates. In April 1998, the 1995 National Committee for Clinical and Laboratory Standards provisional guidelines were instituted.³⁴ These stated that routine testing for *M. kansasii* should be for RMP only, as clinical outcomes are worse with RMP resistance. Most isolates (115/117) were susceptible to RMP at a cut-off of $1 \mu\text{g}/\text{ml}$. Seventy-seven other isolates were tested against other agents: 11/77 (14%) were susceptible to high-dose isoniazid (INH) at a cut-off of $1.0 \mu\text{g}/\text{ml}$, and only 2/77 isolates (3%) were completely susceptible to INH at a cut-off of $0.2 \mu\text{g}/\text{ml}$. EMB susceptibility was 20/77 isolates (26%), at a cut-off of $5 \mu\text{g}/\text{ml}$, but 55/77 (71%) isolates were susceptible at a cut-off of $10 \mu\text{g}/\text{ml}$. Streptomycin (SM) susceptibility was high, with 75/77 (97%) susceptible at a cut-off of $2 \mu\text{g}/\text{ml}$ and 77/77 (100%) susceptible at a cut-off of $10 \mu\text{g}/\text{ml}$.

Prophylaxis and treatment

During the pre-HAART period, one patient each (2.4%) had received rifabutin or a macrolide drug

prophylaxis against MAC. This is very different for the HAART period, when 17 of 55 patients received MAC prophylaxis (31%, $P < 0.0001$).

Treatment data were available for the 137 HIV-infected patients with *M. kansasii* isolates (Table 3). The only two significant results center upon the use of CLM, with or without antiretrovirals, in treatment regimens. Between the pre-HAART and HAART patients, the only significant difference was a survival of only 2 months in 19 pre-HAART patients treated without a CLM-containing regimen versus a survival of 10.5 months in 12 HAART patients treated without a CLM-containing regimen ($P < 0.02$). Moreover, when the pre-HAART patients treated with CLM ($n = 19$ with median survival 10 months) are compared with the pre-HAART patients treated without CLM ($n = 19$ with median survival 2 months), the 2-tailed *t*-test yields a result equal to $P = 0.05$. This result straddles the border of statistical significance.

The most common *M. kansasii* treatment regimen used was RMP, EMB, CLM, and INH (despite the poor susceptibility profile of INH). Treatment regimens did not differ significantly between the pre-HAART and HAART era. All five patients receiving a fluoroquinolone were also in the CLM-based treatment group. Other medications used in select cases included SM, azithromycin, clofazamine, ethionamide, and pyrazinamide (PZA).

DISCUSSION

The results of this study are generally consistent with our previous clinical experience in HIV-infected individuals.³ Patients usually present when they are significantly immunocompromised, and most (94%) have a CD4 count $<200/\text{mm}^3$. Patients with disseminated *M. kansasii* have lower median CD4 counts than those with pulmonary *M. kansasii* (13 vs. $31/\text{mm}^3$, $P < 0.03$).

The most striking observed difference is the survival advantage attributable to using CLM in an *M.*

Table 3 Treatment outcome data for *M. kansasii* and HIV co-infected patients

<i>M. kansasii</i> treatment category	Pre-HAART ($n = 82$) n/N (%)	HAART ($n = 55$) n/N (%)	<i>P</i> value (2-tailed <i>t</i> -test)
Patients on MAC prophylaxis	2/82 (2.4)	17/55 (36)	$P < 0.0001$
Patients with disseminated disease, treated or untreated	17/82 (21)	3/55 (5)	$P < 0.045$
Patients treated for <i>M. kansasii</i> , disseminated	12/17 (71)	2/3 (67)	NS
Patients treated for <i>M. kansasii</i> , pulmonary	47/58 (81)	27/54 (50)	NS
CLM-based treatment	37/59 (62)	16/28 (57)	NS
Median survival, months			
Disseminated <i>M. kansasii</i> , treated	10	<1	NA
Disseminated <i>M. kansasii</i> , untreated	3	16	NA
Pulmonary <i>M. kansasii</i> , treated	7	10.5	NS
Pulmonary <i>M. kansasii</i> , untreated	6	4.5	NS
Disseminated or pulmonary <i>M. kansasii</i> , treated with CLM	10	10	NS
Disseminated or pulmonary <i>M. kansasii</i> , treated without CLM	2	10.5	$P < 0.02$

HIV = human immunodeficiency virus; HAART = highly active anti-retroviral treatment; MAC = *Mycobacterium avium* complex; NS = not significant; NA = not applicable; CLM = clarithromycin.

kansasii treatment regimen before the availability of HAART. Specifically, the 19 pre-HAART patients who used CLM survived a median of 10 months vs. only 2 months for the 19 pre-HAART patients who did not use CLM ($P = 0.05$). The poor median survival of only 2 months is improved by using HAART: this 2-month median survival is compared with a 10.5-month median survival in 12 HAART patients treated without CLM ($P < 0.02$). An explanation for these two findings could be that the positive effect of CLM on treatment survival is masked by the known effects of immune reconstitution with HAART.

The HAART cohort had no statistically significant survival advantage detected between patients treated for pulmonary *M. kansasii* (median survival 10.5 months for 28 patients) and those not treated for *M. kansasii* (median survival 4.5 months for 26 patients, $P > 0.2$ for the comparison). A possible explanation for this is that the study was small. Another factor involved may be that the immune reconstitution seen with HAART makes the outcome attributable to treating *M. kansasii* harder to detect. Another possible confounding variable was the emerging standard of care of prophylaxis for disseminated MAC infection for those with CD4 counts of $\leq 50/\text{mm}^3$.

A lower percentage of patients in the pre-HAART study group had disseminated *M. kansasii* (21%) than in the previous New Orleans study (35%).³ Furthermore, the HAART group had a rate of disseminated *M. kansasii* of only 5.5%. One explanation may be because a higher percentage of pre-HAART pulmonary cases in the present study (81%) were treated than in the older study (63%); therefore, the pulmonary cases may not have had a chance to disseminate. Another reason for the dramatic decrease in observed disseminated cases may be progress in the antiretroviral treatment used against HIV over time. As only 2–6.6% of patients were estimated to be colonized with *M. kansasii*, we agree with Rooney et al. and Marras et al. that *M. kansasii* isolates should be treated aggressively with triple antibiotic regimens when encountered in HIV-infected patients.^{21,25}

The paucity of MAC prophylaxis in the pre-HAART study patients was striking, and the trend of only 55 HIV-*M. kansasii* co-infections in the HAART era versus the 82 HIV-*M. kansasii* co-infections in the pre-HAART era suggests that patients who received a macrolide (CLM or azithromycin) or rifabutin for prophylaxis may have avoided *M. kansasii* infection. The effect of macrolide MAC prophylaxis on *M. kansasii* disease epidemiology cannot be separated from HAART use, as both became the standard of care at around the same time in the New Orleans community.

Concurrent infection with other mycobacteria in addition to *M. kansasii* can obfuscate the clinical picture. It is often not possible to determine which mycobacterium is dominant, i.e., responsible for most of the pathological processes. We believe that *M. kan-*

sasii should be treated in all dual mycobacterial isolations to avoid the possibility of dissemination.

Limitations of the study are primarily based on its observational nature. As a retrospective case series with an imposed comparison of the times before and after HAART, opportunities for bias exist. In particular, the collection of clinical specimens for mycobacterium culture was not standardized. Historical controls may be unreliable; however, the fact that HAART became the recognized and practiced standard of care in New Orleans in 1997 makes the comparison useful.

The drug regimens used by physicians for *M. kansasii* disease in HIV-infected patients at Charity Hospital were consistent, but can be improved. RMP resistance as encountered elsewhere was not found to be significant.¹⁴ SM was underused, and both INH (which has frequent high-level resistance) and PZA (which has no activity against *M. kansasii*) were overused. CLM has excellent in vitro activity against *M. kansasii*,^{35,36} and may confer a survival benefit when used in combination with the standard agents (RMP, EMB, or INH), as shown for the first time in this study. To confirm this observation, further research with prospective randomization would be useful; however, this research may not be feasible due to the fact that modern HAART regimens are now the standard of care for CD4 $< 200/\text{mm}^3$ (when most *M. kansasii* infections appear), making the difference between CLM and non-CLM regimens extremely difficult to detect without a very large study population.

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R É S U M É

CONTEXTE : Hôpital de la Charité, New Orleans, Louisiane, USA.

OBJECTIF : Définir les différences entre les ères pré-HAART (thérapie antirétrovirale hautement active) et HAART chez les patients co-infectés par *Mycobacterium kansasii* et par le virus de l'immunodéficience humaine (VIH).

SCHÉMA : Revue rétrospective des dossiers révélant 82 patients infectés par le VIH et *M. kansasii* pendant une période de 6 ans s'étalant du 1^{er} juillet 1991 au 30 juin 1997 (ère pré-HAART) et 55 cas pendant la période de 6 ans du 1^{er} juillet 1997 au 30 juin 2003 (ère HAART).

RÉSULTATS : Chez tous les patients infectés par VIH et *M. kansasii*, 47 (34%) étaient atteints d'une infection mycobactérienne simultanée supplémentaire et chez deux

on a isolé trois espèces mycobactériennes. Un plus grand nombre de patients souffraient d'une maladie mycobactérienne disséminée (17/82, soit 21%) dans la période pré-HAART que pendant l'ère HAART (3/55, soit 5% ; $P = 0,045$). Les patients de l'ère pré-HAART traités sans clarithromycine (CLM) ont survécu pendant une période médiane de 2 mois contre 10 mois pour les patients pré-HAART traités avec CLM ($P = 0,05$). Ceux traités sans CLM ont eu une survie médiane de 2 mois dans l'ère pré-HAART contre 10,5 mois dans l'ère HAART ($n = 12$; $P < 0,02$).

CONCLUSION : Un traitement à la CLM chez les patients co-infectés par *M. kansasii* et VIH est en association avec une prolongation significative de la survie.

R E S U M E N

MARCO DE REFERENCIA : El Charity Hospital en Nueva Orleans, Luisiana, Estados Unidos.

OBJETIVO : Definir las diferencias entre la época previa al tratamiento antirretrovírico de gran actividad (TARGA) y la época del TARGA, en pacientes coinfectados por *Mycobacterium kansasii* y por el virus de la inmunodeficiencia humana (VIH).

MÉTODO : En un estudio retrospectivo de historias clínicas se encontraron 82 pacientes con coinfección por VIH y *M. kansasii* durante un período de 6 años entre el 1^o de julio de 1991 y el 30 de junio de 1997 (época pre-TARGA) y 55 casos entre el 1^o de julio de 1997 y el 30 de junio de 2003 (época del TARGA).

RESULTADOS : De todos los pacientes coinfectados por VIH y *M. kansasii*, 47 (34%) presentaron una infección adicional por micobacterias y en dos casos se aislaron tres

especies de micobacterias. La enfermedad diseminada causada por micobacterias fue más frecuente durante la época pre-TARGA (17/82 ó 21%) que durante la época del TARGA (3/55 ó 5% ; $P = 0,045$). En la era pre-TARGA, la mediana de supervivencia de los pacientes tratados sin claritromicina (CLM) fue 2 meses y la de los pacientes que sí la recibieron fue 10 meses ($P = 0,05$). Comparando ambas épocas, la mediana de supervivencia de los pacientes tratados sin CLM en la era pre-TARGA fue 2 meses ($n = 19$) y en la era del TARGA fue 10,5 meses ($n = 12$; $P < 0,02$).

CONCLUSIÓN : El uso de CLM en el tratamiento de pacientes coinfectados por *M. kansasii* y VIH se asocia en forma estadísticamente significativa con una mayor supervivencia.