INT J TUBERC LUNG DIS 17(2):198–206

http://dx.doi.org/10.5588/ijtld.12.0224

Health care index score and risk of death following tuberculosis diagnosis in HIV-positive patients

D. N. Podlekareva,* D. Grint,† F. A. Post,‡ A. Mocroft,† A. M. Panteleev,§ R. F. Miller,¶ J. M. Miro,# M. Bruyand,**,†† H. Furrer,‡‡ V. Riekstina,§§ E. Girardi,¶¶ M. H. Losso,## J. A. Caylá,*** E. A. Malashenkov,††† N. Obel,‡‡‡ A. M. Skrahina,§§§ J. D. Lundgren,*,‡‡‡ O. Kirk;*,‡‡‡ HIV-TB Study Group

*Copenhagen HIV Programme, University of Copenhagen, Denmark; †University College London, London, ‡King's College London School of Medicine, London, UK; §TB Hospital #2, St Petersburg, Russia; ¶Centre for Sexual Health and HIV Research, University College London, London, UK; #Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; **Centre Inserm U897-Epidemiologie-Biostatistique, Université Bordeaux, Institut de Santé Publique, d'Epidémiologie et de Developpement (ISPED), Bordeaux, ††Centre Inserm U897-Epidemiologie-Biostatistique, Institut National de la Santé et de la Recherche Médicale, ISPED, Bordeaux, France; ‡‡Clinic for Infectious Diseases, Berne University Hospital and University of Berne, Berne, Switzerland; §§Infectology Centre of Latvia, Tuberculosis and Lung Diseases Clinic, Riga, Latvia; ¶¶Instituto Nazionale Malattie Infettive L Spallanzani, Rome, Italy; ##Hospital JM Ramos Mejia, Servicio de Immunocomprometidos, Buenos Aires, Argentina; ***Servicio de Epidemiología, Agencia de Salud Pública de Barcelona, CIBER Epidemiología y Salud Pública, Barcelona, Spain; †††Botkin Hospital of Infectious Diseases, St Petersburg, Russia; ‡‡‡Rigshospitalet, Copenhagen, Denmark; §§§Research Institute of Pulmonology and Pulmonary Tuberculosis, Minsk, Belarus

SUMMARY

OBJECTIVES: To assess health care utilisation for patients co-infected with TB and HIV (TB-HIV), and to develop a weighted health care index (HCI) score based on commonly used interventions and compare it with patient outcome.

METHODS: A total of 1061 HIV patients diagnosed with TB in four regions, Central/Northern, Southern and Eastern Europe and Argentina, between January 2004 and December 2006 were enrolled in the TB-HIV study. A weighted HCI score (range 0–5), based on independent prognostic factors identified in multivariable Cox models and the final score, included performance of TB drug susceptibility testing (DST), an initial TB regimen containing a rifamycin, isoniazid and pyrazinamide, and start of combination antiretroviral treatment (cART).

RESULTS: The mean HCI score was highest in Central/Northern Europe (3.2, 95%CI 3.1–3.3) and lowest in Eastern Europe (1.6, 95%CI 1.5–1.7). The cumulative probability of death 1 year after TB diagnosis decreased from 39% (95%CI 31–48) among patients with an HCI score of 0, to 9% (95%CI 6–13) among those with a score of ⩾4. In an adjusted Cox model, a 1-unit increase in the HCI score was associated with 27% reduced mortality (relative hazard 0.73, 95%CI 0.64–0.84).

CONCLUSIONS: Our results suggest that DST, standard anti-tuberculosis treatment and early cART may improve outcome for TB-HIV patients. The proposed HCI score provides a tool for future research and monitoring of the management of TB-HIV patients. The highest HCI score may serve as a benchmark to assess TB-HIV management, encouraging continuous health care improvement.

KEY WORDS: TB-HIV co-infection; health care index score; outcome of TB-HIV patients; TB-HIV health care utilisation

TUBERCULOSIS (TB) in human immunodeficiency virus (HIV) positive persons remains a great challenge for physicians globally. Survival rates of HIV-positive persons with active TB (TB-HIV patients) vary substantially around the world and depend on several factors relating to the management of both HIV infection and TB disease. Among such factors, the most important are prompt and proper diagnosis of TB, including culture and drug susceptibility testing (DST), timely initiation of adequate anti-tuberculosis treatment, as well as assessment of a patient's immune status and timely initiation of combination antiretroviral treatment (cART).[1,2] These factors are mainly related to, and depend on, the local level of health care and the availability of resources. Incidence rates of TB among HIV-infected persons would naturally be higher in regions with a high prevalence of *Mycobacterium tuberculosis* infection in the general population, while mortality rates are likely to be higher in settings with a high prevalence of multidrug-resistant

Correspondence to: Daria Podlekareva, Copenhagen HIV Programme, University of Copenhagen, The Panum Institute, Building 21.1, Blegdamsvej 3B, 2200 Copenhagen N, Denmark. Tel: (+45) 35 45 57 57. Fax: (+45) 35 45 57 58. e-mail: dpo@cphiv.dk

Article submitted 22 March 2012. Final version accepted 28 August 2012.

TB (MDR-TB).[3–7] However, even in resource-limited settings with a high prevalence of TB it is possible to achieve a significant reduction in TB-associated mortality among TB-HIV patients.[8,9]

We previously reported that a number of patient characteristics related to both HIV (i.e., acquired immune-deficiency syndrome [AIDS] or poor immune status) and TB (i.e., disseminated or rifamycin-resistant disease) were associated with an increased risk of death. In addition, some aspects related to patient care, such as not including a rifamycin in first-line anti-tuberculosis treatment or not commencing cART, were independent predictors of death.[6] These factors, however, could only partially explain regional differences in mortality, suggesting that other patient or health care-associated factors may differ between the geographic regions.

The purpose of the current analysis was to evaluate the extent of appropriate health care provided to TB-HIV patients across different geographic regions by establishing a health care index (HCI), and to use this HCI to generate a TB-HIV HCI score that reflects health care utilisation. We then analysed the cumulative probability of death in patients stratified by HCI score and regional differences in hazards of death in multivariable models incorporating the HCI score.

METHODS

Patient cohort

The TB-HIV study is an international cohort of HIV-positive patients consecutively diagnosed with TB who initiated anti-tuberculosis treatment between January 2004 and December 2006 at one of the 52 participating clinics in Europe and Argentina. The present analysis is based on 1061 TB-HIV patients whose HIV infection was diagnosed before or up to 1 month after TB diagnosis, to avoid bias when assessing HIV management. Details of the study have been published elsewhere.[6] Briefly, information was collected retrospectively on standardised case report forms (CRF), and included demographic and clinical characteristics of the TB disease, details of smear tests, culture and DST performed, drug regimens used and TB outcomes. Information on underlying HIV infection was collected on a separate CRF, and included all available CD4 cell count and HIV-RNA measurements, use of antiretroviral drugs, presence of non-TB AIDS-defining illnesses and use of chemoprophylaxis.[10]

The study was approved by the ethics committees of the participating clinics, as per local and national regulations. Patients had to sign informed consent where requested by local regulations.

Health care index

To evaluate aspects of TB and HIV health care, we chose a number of the most important health care parameters that reflected the actual care provided to patients rather than disease-specific characteristics (e.g., 'having a culture or DST performed' rather than 'having MDR-TB'). These parameters were combined in an HCI, for which the following components were a priori considered to be based on the guidelines for management of TB-HIV patients:[1,2]

1 World Health Organization (WHO) defined definite diagnosis of TB: culture-confirmed disease due to *M. tuberculosis* and/or at least one sputum smear examination positive for acid-fast bacilli (AFB);[11]
2 Performance of DST for *M. tuberculosis*;
3 Inclusion of a rifamycin (R), isoniazid (H, INH) and pyrazinamide (Z, PZA) in the initial anti-tuberculosis treatment regimen;
4 Availability of at least one CD4 cell count measurement between 6 months before and 1 month after TB diagnosis;
5 Initiation of cART (a combination of at least three antiretroviral drugs from any class) before or up to 1 month after TB diagnosis.

The 1-month cut-off for CD4 cell counts and use of cART was chosen to reduce survival bias, as substantial early mortality was observed. In sensitivity analyses, we assessed the effects of initiation of cART within 3, 6, 3–9 and >9 months of TB diagnosis, and CD4 cell count measurements obtained within 2, 3 and 6 months of TB diagnosis.

Statistical analysis

The study population was divided into four geographic regions according to country of residence: Eastern Europe (n = 573), Central/Northern Europe (n = 166), Southern Europe (n = 208) and Argentina (n = 114).* Descriptive statistics were used to compare patient characteristics and the HCI components across regions. The HCI components were considered as quantitative discrete variables (yes/no), and were given a score of zero if no information was available for a given patient. The proportion of patients to whom each HCI component applied was calculated and compared by region. Follow-up was from the date of TB diagnosis until the last clinic visit (or date of loss to follow-up), date of death or 1 year after TB diagnosis, whichever occurred first. TB was classified as pulmonary if disease was limited to the lungs and/or pleura; extra-pulmonary if TB was limited to any other single organ system; or disseminated if it was miliary TB, TB in at least two organ systems, or if *M. tuberculosis* had been isolated from blood or bone marrow.

To establish an HCI score, the relative hazard (RH) of death for each HCI component was calculated using a multivariable Cox model incorporating all five HCI components. A weighted score was then

*Eastern Europe: Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe: Denmark, France, Switzerland, United Kingdom; Southern Europe: Italy, Spain.

assigned to each significant HCI component based on the natural logarithm of its RH of death. The mean HCI score was calculated for each region and compared to the proportion of patients who died within 12 months of TB diagnosis and to those with successful TB outcomes (cure/treatment completion).

Kaplan-Meier survival analysis was used to estimate the probability of death within 12 months of TB diagnosis among patients stratified by HCI score. Cox proportional hazard models were used to analyse the effect of the HCI score on mortality. Other factors included in the Cox model were those that were previously shown to be associated with mortality, and included sex, CD4 cell count at TB diagnosis, previous AIDS diagnosis, previous TB diagnosis, TB rifamycin resistance and site of TB.[6]

RESULTS

Patient population

A total of 1061 TB-HIV patients were included in the analysis. Patient characteristics are presented in Table 1. As reported previously, patients from Eastern Europe were younger and more often had a history of injection drug use (IDU) and/or hepatitis C coinfection.[6] Approximately half of all patients had disseminated TB, and the majority of patients had established HIV infection at the time of TB diagnosis. Patients from Argentina had more profound immunodeficiency, while patients from Eastern Europe had less advanced HIV infection.

The proportion of patients with positive values for each HCI component differed significantly by geographic region (Table 1). Fewer patients in Eastern Europe had a definite TB diagnosis, initiated RHZ-containing anti-tuberculosis treatment or received cART. Patients in Eastern Europe and Argentina were less likely to undergo DST for *M. tuberculosis* and have CD4 cell counts performed.

Health care index score

To develop an HCI score, the five selected components were included in a Cox model, with death as the dependent variable (Table 2). Use of cART, RHZ-containing initial anti-tuberculosis treatment and undergoing DST were associated with a reduced hazard of death in both univariable and multivariable models. The availability of a CD4 cell count and a definite TB

Table 1 Baseline characteristics and health care index components in TB-HIV patients stratified by geographic region*

	Eastern Europe† (n = 573) n (%)	Southern Europe† (n = 208) n (%)	Central/Northern Europe† (n = 166) n (%)	Argentina (n = 114) n (%)	P value
Patient characteristics					
Male sex	410 (71.6)	160 (76.9)	78 (47.0)	73 (64.0)	<0.0001
IDU (as risk factor for TB)‡	409 (71.9)	63 (34.6)	19 (13.0)	30 (26.6)	<0.0001
Hepatitis C antibody-positive§	268 (46.9)	53 (25.5)	15 (9.0)	15 (13.2)	<0.0001
Disseminated TB¶	349 (60.9)	104 (50.0)	86 (51.8)	57 (50.0)	<0.0001
Rifamycin-resistant TB#	121 (45.8)	5 (3.5)	5 (4.5)	6 (16.2)	<0.0001
Prior AIDS**	79 (13.8)	42 (20.2)	22 (13.3)	63 (55.3)	<0.0001
Age, years, median [IQR]	30.2 [26.2–35.0]	37.7 [31.8–43.5]	37.4 [31.6–44.2]	35.5 [30.2–41.7]	<0.0001
CD4 cell count, cells/μl, median [IQR]††	210 [85–463]	132.5 [46–291]	140 [50.5–293.5]	92 [40–233.5]	<0.0001
HIV-RNA, $\log_{10}$ copies/ml, median [IQR]‡‡	5.1 [4.3–5.7]	4.9 [3.5–5.6]	4.9 [3.4–5.6]	4.6 [3.5–5.4]	0.023
Health Care Index components					
Definite TB diagnosis	389 (67.9)	167 (80.3)	136 (81.9)	82 (71.9)	0.0002
DST performed§§	264 (84.9)	141 (87.6)	111 (85.4)	37 (69.8)	<0.0001
RHZ-containing initial anti-tuberculosis treatment	258 (45.0)	163 (78.4)	146 (88.0)	96 (84.2)	<0.0001
CD4 cell count measurement performed from 6 months before to 1 month after TB diagnosis	316 (55.2)	161 (77.4)	126 (75.9)	67 (58.8)	<0.0001
cART started before or within 1 month of TB diagnosis	98 (17.1)	112 (53.9)	87 (52.4)	54 (47.4)	<0.0001

*Baseline defined as the date of TB diagnosis.
†Eastern Europe: Belarus, Latvia, Romania, Russia, Ukraine; Central/Northern Europe: France, Denmark, Switzerland, United Kingdom; Southern Europe: Italy, Spain.
‡TB risk factor was unknown for 51 patients: Eastern Europe 4 (7.8%), Southern Europe 26 (51.0%), Central/Northern Europe 20 (39.2%), Argentina 1 (2.0%); $P < 0.0001$.
§Unknown for 528 patients. No significant differences comparing the proportions with unknown HCV antibody status across the regions; $P = 0.13$.
¶TB involving more than one organ system, miliary TB or *Mycobacterium tuberculosis* isolated from blood or bone marrow.
#Proportion of those with DST performed.
**AIDS defined using the 1993 Centers for Disease Control and Prevention clinical case definitions (category C).
††Unknown for 208 patients: Eastern Europe 146 (25.5%), Southern Europe: 14 (6.7%), Central/Northern Europe 22 (13.3%), Argentina 26 (22.8%); $P < 0.0001$.
‡‡Unknown for 547 patients: Eastern Europe 467 (81.5%), Southern Europe 23 (11.1%), Central/Northern Europe 11 (6.6%), Argentina 46 (40.4%); $P < 0.0001$.
§§Proportion of those with positive culture for *M. tuberculosis* (culture-confirmed TB respectively 311, 161, 130 and 53 in Eastern Europe, Southern Europe, Central/Northern Europe and Argentina).
TB = tuberculosis; HIV = human immunodeficiency virus; IDU = injection drug use; AIDS = acquired immune-deficiency syndrome; IQR = interquartile range; DST = drug susceptibility testing; RHZ = rifamycin+isoniazid+pyrazinamide; cART = combination antiretroviral therapy; HCV = hepatitis C virus.

Table 2 Cox proportional hazard model used to calculate the weighted HCI score*

HCI component	Univariable			Multivariable			Final			Ln RH†	HCI score weighting
	RH	95%CI	*P* value	RH	95%CI	*P* value	RH	95%CI	*P* value		
Definite diagnosis	0.76	0.54–1.05	0.097	1.18	0.79–1.78	0.42					0
DST performed	0.63	0.47–0.86	0.0031	0.65	0.45–0.95	0.025	0.71	0.53–0.97	0.031	−0.34	1
Initial TB treatment with RHZ	0.37	0.28–0.51	<0.0001	0.41	0.30–0.57	<0.0001	0.43	0.31–0.58	<0.0001	−0.85	2
CD4 measured from 6 months before or up to 1 month after TB diagnosis	0.90	0.66–1.23	0.50	1.22	0.89–1.68	0.21					0
cART started before or up to 1 month after TB diagnosis	0.32	0.21–0.48	<0.0001	0.35	0.23–0.53	<0.0001	0.36	0.24–0.55	<0.0001	−1.02	2

*Absence of an HCI component yielded a zero score. The HCI score was calculated for each patient as the sum of each of the HCI components.
†Ln RH is calculated from the RHs of death obtained in the final model.
HCI = health care index; RH = relative hazard; CI = confidence interval; Ln = natural logarithm; TB = tuberculosis; RHZ = rifamycin+isoniazid+pyrazinamide; cART = combination antiretroviral therapy.

diagnosis were not associated with a reduced hazard of death in either univariable or multivariable analysis (Table 2). These two components were therefore not included in the final HCI score. Similar results were obtained when using different time windows for CD4 cell count measurements or cART initiation (data not shown). Of note, having a culture-based definitive TB diagnosis (i.e., excluding patients with only positive smear tests) was highly correlated with undergoing DST ($R = 82\%$, $P < 0.0001$). Including smear-positive tests in the definitive diagnosis reduced this correlation to 62%, and reduced the association between definitive diagnosis and the risk of death to a non-insignificant level.

The natural logarithms of the three RHs of death were used to weigh the components that make up the HCI score. As the effects of initial treatment with RHZ and use of cART were approximately double the magnitude of the effect of DST, DST was assigned 1 point and the use of RHZ-containing initial antituberculosis treatment and use of cART 2 points each. The HCI score could thus range from 0 to 5, with a higher score being indicative of more intensive health care utilisation (Table 2).

An HCI score was calculated for each patient. The distribution of HCI scores for each region is shown in Figure 1. The majority (54–82%) of patients from Central/Northern Europe, Southern Europe and Argentina had HCI scores ⩾3, compared with only 29% of patients from Eastern Europe ($P < 0.0001$), whereas 28% of those in Eastern Europe had an HCI score of 0. The mean HCI score was highest in Central/Northern Europe (3.2, 95% confidence interval [CI] 3.1–3.3), followed by Southern Europe

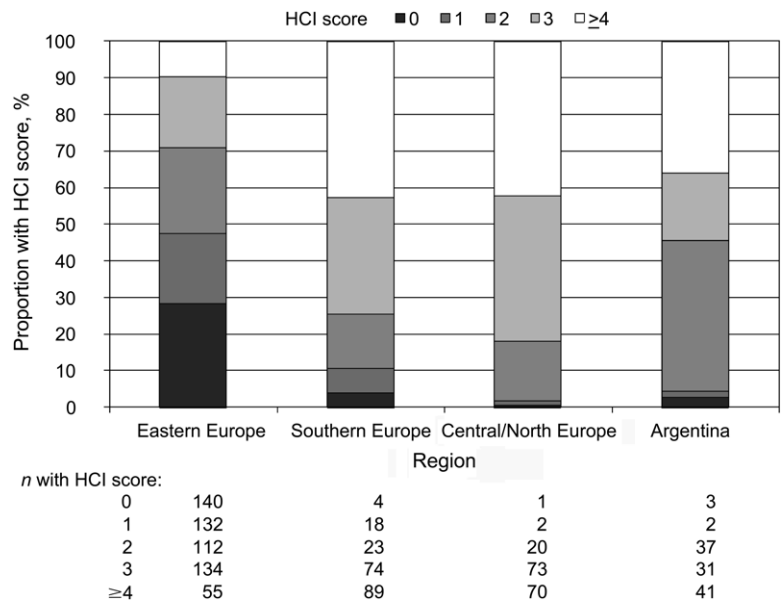

Figure 1 Distribution of patients according to HCI score and region of residence. HCI = health care index.

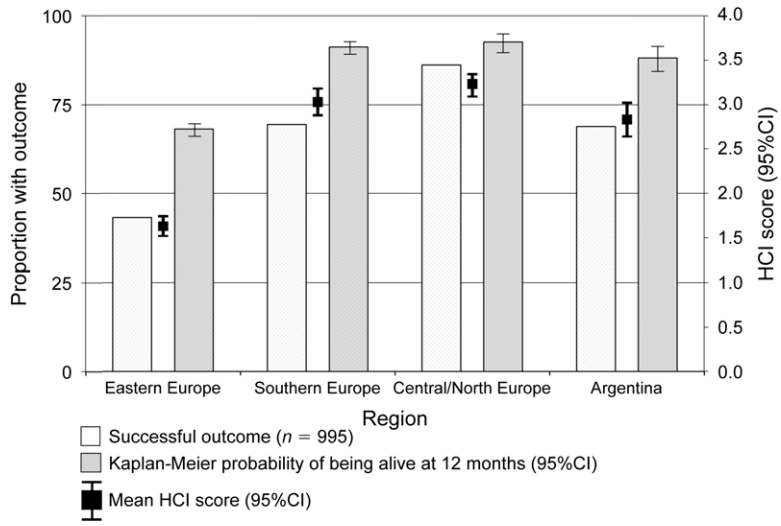

Figure 2 Mean HCI score and outcomes in TB-HIV patients stratified by region of residence. Mean HCI score (95%CI): Eastern Europe 1.63 (1.52–1.74); Southern Europe 3.03 (2.88–3.18); Central/Northern Europe 3.22 (3.09–3.34); Argentina 2.83 (2.64–3.02). HCI = health care index; CI = confidence interval; TB = tuberculosis; HIV = human immunodeficiency virus.

(3.0, 95%CI 2.9–3.2) and Argentina (2.9, 95%CI 2.6–3.0); it was lowest in Eastern Europe (1.6, 95%CI 1.5–1.7, $P < 0.0001$).

Health care index score and anti-tuberculosis treatment outcome

Information on treatment outcome was available for 995 (98%) patients. Overall, a successful treatment outcome was reported for 578 patients (58%), and was most common in those regions with the highest HCI scores. Similarly, Kaplan-Meier estimates of being alive at 12 months were highest in regions with the highest HCI scores (Figure 2). A progressive decrease was observed in 12-month cumulative mortality, from 39% (95%CI 31–48) for patients with HCI = 0, to 9% (95%CI 6–13) for those with HCI ⩾ 4 ($P < 0.0001$; Figure 3). When the HCI score was incorporated into unadjusted Cox models of death within 12 months of TB diagnosis, a 38% decrease in mortality for each unit increase in HCI score was observed (RH 0.62, 95%CI 0.56–0.70, $P < 0.0001$; Table 3). This association remained significant (RH 0.73, 95%CI 0.64–0.84) after adjustment for other factors that could potentially affect the prognosis of TB-HIV patients (sex, CD4 cell count at TB diagnosis, previous TB or AIDS diagnosis, rifamycin resistance and site of TB; Table 3). However, despite the significant predictive value of the HCI score, patients

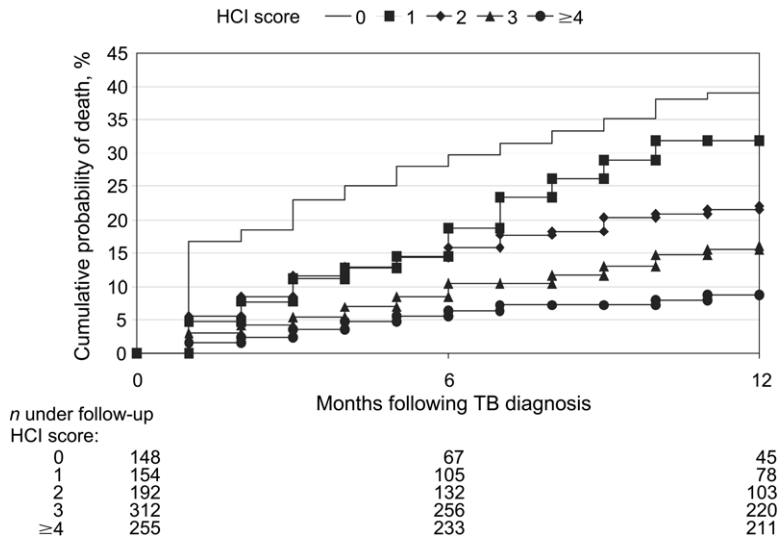

Figure 3 Kaplan-Meier probability of death in patients stratified according to their HCI score. HCI = health care index; TB = tuberculosis.

Table 3 Univariable and multivariable* RH of death within 12 months of TB diagnosis

	Univariable		Multivariable			
			Not including HCI score		Including HCI score	
	RH (95%CI)	*P* value	RH (95%CI)	*P* value	RH (95%CI)	*P* value
HCI score (per 1 unit increase)	0.62 (0.56–0.70)	<0.0001			0.73 (0.64–0.84)	<0.0001
Region						
Eastern Europe	1.00		1.00		1.00	
Southern Europe	0.14 (0.07–0.28)	<0.0001	0.13 (0.06–0.25)	<0.0001	0.19 (0.09–0.39)	<0.0001
Central/Northern Europe	0.16 (0.08–0.32)	<0.0001	0.17 (0.08–0.35)	<0.0001	0.27 (0.13–0.58)	0.0007
Argentina	0.28 (0.14–0.54)	0.0002	0.22 (0.11–0.45)	<0.0001	0.31 (0.25–0.64)	0.0015
Sensitivity analyses						
Patient with pan-susceptible TB (n = 337)	0.70 (0.50–0.97)	<0.032			0.73 (0.50–1.07)	0.10
Injection drug users (n = 521)	0.69 (0.60–0.80)	<0.0001			0.76 (0.66–0.87)	0.0004
Patients from Eastern Europe (n = 573)	0.76 (0.67–0.87)	<0.0001			0.73 (0.64–0.84)	<0.0001
Only including TB- and AIDS-related deaths	0.83 (0.73–0.94)	0.0044			0.85 (0.73–0.99)	0.042
Score						
0	1.00				1.00	
1	0.70 (0.45–1.10)	0.12			0.55 (0.35–0.86)	0.0082
2	0.50 (0.33–0.76)	0.0010			0.57 (0.38–0.85)	0.0064
3	0.33 (0.21–0.50)	<0.0001			0.40 (0.25–0.63)	0.0001
⩾4	0.09 (0.05–0.19)	<0.0001			0.28 (0.16–0.49)	<0.0001

*Multivariable model adjusted also for sex, CD4 cell count at TB diagnosis (< or > 200 cells/mm^3), previous AIDS, previous diagnosis of TB, presence of *Mycobacterium* strains resistant to at least a rifamycin, location of TB (pulmonary, extra-pulmonary, disseminated).
RH = relative hazard; TB = tuberculosis; CI = confidence interval; HCI = health care index; AIDS = acquired immune-deficiency syndrome.

from Eastern Europe remained at an approximately three-fold increased risk of death compared with the other regions, after adjustment for HCI score.

Sensitivity analyses

A number of sensitivity analyses were performed (Table 3) to test the performance of the score in various subpopulations. Overall, the results of these analyses were consistent with the main finding that the HCI score was a significant predictor of 1-year mortality in TB-HIV patients. For example, when restricting the analysis to IDU patients (n = 521) or patients from Eastern Europe (n = 573), a 1-unit increase in HCI score was associated with respectively 24% and 27% decreases in mortality. In analysis restricted to patients with pan-susceptible TB (n = 337), a 1-unit increase in HCI score was associated with a 27% decrease in mortality, although this was insignificant in the multivariable model, likely due to the small sample size. Furthermore, when restricting endpoints to only TB- and AIDS-related deaths (excluding deaths from any other causes), a 1-unit increase in HCI score reduced mortality by 15%. Finally, when the HCI score was included in the model as a categorical variable, 1-year mortality was 45% lower in patients with an HCI score of 1 and 72% lower in those with HCI scores of 4/5 compared with patients with an HCI score of 0 (Table 3).

DISCUSSION

In this study, we assessed and compared health care utilisation for TB-HIV patients by using a number of health care parameters. These parameters were further used to generate an HCI score as a measure of health care utilisation. The final HCI score, which was based on the use of TB DST, RHZ-based antituberculosis treatment and early cART, was predictive of mortality in TB-HIV patients: a 1-unit increase was independently associated with a 27% reduced risk of death within the first year of TB diagnosis. However, the observed regional differences in mortality among TB-HIV patients in Europe and Argentina were only partly explained by differences in health care utilisation. While implementation of the health care parameters included in the HCI score would be a priority to improve patient outcome, further research is required to explain the profound regional differences in HIV and TB outcomes and propose additional measures to harmonise these outcomes.

The HCI score presented here can be implemented and used for two main purposes: evaluating and comparing health care utilisation for TB-HIV patients, and predicting patients' prognosis. It can be implemented and assessed by health care authorities at various levels, from a single clinic to programme, country and region. Further, it can contribute to the establishment of a benchmark of health care utilisation for TB-HIV patients by identifying a best performing facility. The advantage of this HCI score is that it includes a set of three simple, widely used diagnostic and treatment procedures, which should be available in both high- and low-income settings. Our HCI score is based on health care parameters that have previously been found to be independently associated with the outcome of TB-HIV patients.[5,6,12] The predictive value of

the HCI score remained highly significant when the model was adjusted for other factors that might play a role in patient outcome (Table 3), suggesting that this association is not a result of confounding.

Optimal management of TB includes early case detection and initiation of effective anti-tuberculosis treatment. Increased frequency of sputum smear negativity in HIV patients requires culture, which has been shown to be more sensitive in TB-HIV patients.[13,14] Culture and DST are essential in TB diagnosis to ensure that effective treatment is administered, particularly in settings with high MDR-TB prevalence.[15,16] Conventional culture and DST are disadvantaged by the need for sophisticated laboratory equipment and long incubation time. Early detection of resistant *M. tuberculosis* strains is critical, particularly in high MDR-TB prevalent settings, to adjust treatment regimens and prevent transmission of drug-resistant strains. There is thus a critical need for the diagnosis of TB to be more rapid and reliable and less costly than is currently the case in many resource-limited settings.[17–19] Rapid tests for simultaneous molecular detection of *M. tuberculosis* and drug-resistant strains should be widely implemented and used.[17]

As approximately 50% of our patients had disseminated TB, relying solely on sputum samples may not be sufficient to make a definite TB diagnosis, and culture or molecular diagnostics of lymph node aspirates, blood or bone marrow may need to be more widely undertaken to obtain *M. tuberculosis* isolates for DST, thus fulfilling this HCI component.[20,21]

Successful outcome of anti-tuberculosis treatment relies on a treatment regimen of high-quality drugs to which the *M. tuberculosis* isolate is susceptible, given at the correct dose and for a sufficient duration.[1,21] The WHO recommends that empiric anti-tuberculosis treatment should include at least a rifamycin, INH and PZA (i.e., RHZ-based), with the addition of 2–3 second-line anti-tuberculosis drugs if resistance is suspected.[22] When the DST results become available, the regimen should be adjusted accordingly. In our study, the use of RHZ-based regimens as initial TB treatment and outcome were strongly correlated, even after adjustment for region of residence.[6] While this may reflect clinicians' decisions to avoid RHZ in patients with poor outcome, such as those with significant liver injury (i.e., hepatitis C virus co-infected),[23] universal implementation of RHZ-based regimens to treat TB-HIV in Eastern Europe is an inexpensive measure to improve patient outcome. More importantly, if second-line anti-tuberculosis drugs are added while awaiting the DST results, amplification of TB drug resistance in partially resistant *M. tuberculosis* isolates may be avoided and transmission of drug-resistant TB reduced. Further research is needed to investigate underlying reasons for not initiating RHZ-based treatment in Eastern Europe.

Three recent studies have addressed the timing of cART in TB-HIV patients.[24–27] Both studies provided evidence for early cART initiation in patients with CD4 cell counts < 50 cells/mm^3. In addition, the SAPiT (Starting ART at 3 Points in TB) study showed benefit from cART use during treatment rather than deferral until completion of anti-tuberculosis treatment, even in patients with CD4 cell counts > 200 cells/mm^3. We observed that few patients were receiving cART before TB diagnosis or up to 1 month after TB diagnosis, irrespective of region of residence, and many of our patients did not commence cART during anti-tuberculosis treatment. Our HCI model suggests that there are benefits from early cART use in TB-HIV patients, which is consistent with the results of the above clinical trials and provides support for the notion that all TB-HIV patients should start cART while still receiving anti-tuberculosis treatment. For most patients, cART may be safely deferred until the end of the intensive phase of anti-tuberculosis treatment, although patients with low CD4 cell counts or other evidence of immunosuppression, and possibly those infected with MDR-TB, should start cART at the earliest opportunity (i.e., within 2 weeks of starting anti-tuberculosis treatment).[25,26] In Eastern Europe especially, this will require improved access to cART for marginal population groups (i.e., IDUs, prisoners, alcohol addicts, etc.) and adherence support for those who start cART.[28] Finally, when making the decision to initiate cART in TB-HIV patients, the benefits and risks should be carefully weighed for each individual patient, considering the potential toxicities and drug-drug interactions, the probability of immune reconstitution inflammatory *syndrome*, adherence issues, etc.

There are some limitations to this study. Due to the retrospective design, some data could have been missed or were not available for collection. To ensure the completeness of data collection, an extensive quality assurance programme was performed, which included queries to the sites and monitoring visits. We were able to define the HCI score using variables measured within the study; however, there may be other variables that we were not able to capture. Although we included health care parameters known to be associated with patient outcome,[5,6,12] other factors, including prevalence of primary MDR-TB, use of second-line anti-tuberculosis drugs, presence of integrated HIV and TB services, etc., may affect outcomes. Future studies designed around these factors are needed to enable measures to be identified that may further improve TB-HIV outcomes, particularly in Eastern Europe. Experience from South Africa has shown that integration of HIV and TB services helps to improve patient management, and thus survival.[29] Health care infrastructure differs in Eastern Europe, and is characterised by separate management of HIV and TB in different hospitals by different specialists, where collaboration and data exchange may not be well developed. A sensitivity analysis including only

patients from Eastern Europe showed results consistent with the main analysis: a higher HCI score was associated with improved survival. The HCI score also did not change when the models were stratified by an individual centre or country (data not shown). The HCI score needs to be validated in independent cohorts of TB-HIV patients in Europe and elsewhere, including low-income countries. Validation of the HCI score is also planned in a prospective extension of the TB-HIV study, which has now been initiated (http://www.cphiv.dk).

Based on our HCI score, and in line with previous publications, TB-HIV programmes in the developing world are encouraged to implement DST, standard anti-tuberculosis treatment and early cART initiation in TB-HIV patients.[30] The HCI score presented here may serve as a tool to predict the benefits of such interventions. Further refinement of the health care parameters, for example by adding additional components, such as TB-HIV service integration, duration of anti-tuberculosis treatment, treatment changes according to DST patterns, use of directly observed treatment, use of cotrimoxazole prophylaxis and treatment adherence, may enhance its clinical usefulness.

CONCLUSIONS

We have developed an HCI score that reflects health care utilisation in TB-HIV patients and predicts outcome. The HCI is easy to apply in both high- and low-income settings and, if validated in other populations, may assist in the planning of programmatic interventions. Our results suggest that the outcome of TB-HIV patients may be improved by implementing several simple measures, including *M. tuberculosis* DST, use of RHZ-based anti-tuberculosis treatment and early use of cART.

Acknowledgements

Data collection in Eastern Europe (Belarus, Latvia, Russia, Ukraine) and Argentina was funded by the Copenhagen HIV Programme and the EuroSIDA study.* Data collection in Western Europe was self-funded by the participating cohorts: Aquitaine Cohort, France; Danish HIV Cohort, Denmark; Mortimer Market Hospital and King's College Hospital in London, UK. In Rome, Italy, the Istituto Nazionale per le Malattie Infettive L. Spallanzani cohort was supported in part by the Ministry of Health AIDS Project (grant no. 49H79). In Spain, the study was funded in part by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Spanish Network for the AIDS Research (RD06/006), Madrid, Spain, and Agencia de Salud Pública de Barcelona, and a personal Intensification Research Grant to JMM in 2011 from the Instituto de Salud Carlos III, Madrid, and the Departament de Salut de la Generalitat de Catalunya, Barcelona (INT10/219; I3SNS and PRICS programmes). In Switzerland, the study has been financed under the Swiss HIV Cohort Study (http://www.shcs.ch), supported by the Swiss National Science Foundation (grant # 33CS30_134277). DNP was financed through the Post Doc Scholarship from the The Danish Council for Independent Research, Denmark.

Conflict of interest: none declared.

TB-HIV Study Group

Argentina, Buenos Aires—M H Losso (Principal Investigator); Project Manager: J J Toibaro; Hospital Interzonal General de Agudos Dr D Proissien: E Warley, N Tamayo, M Cristina Ortiz; Hospital General de Agudos Donación F Santojanni: P Scapelatto, E Bottaro; Hospital Provincial Petrona V de Cordero San Fernando: F Murano; Hospital San Juan de Dios, La Plata: M Miachans, J Contarelli, L Massera; Hospital Interzonal HIGA Oscar Alende, Mar del Plata: J Corral, M Hualde, C Miglioranza; Hospital de Infecciosas Francisco Muñiz: M Corti, H Metta; Hospital General de Agudos Dr T Álvarez: A Casiró, R Cuini; Hospital Posadas: H Laplume; Hospital Rawson, Cordoba: D David, C Marson; Instituto CAICI: S Lupo, L Trape; Hospital Piñero: O Garcia Messina, O Gear; Hospital General de Agudos J M Ramos Mejía: J J Toibaro, J M Bruguera.

Belarus, Minsk—University Hospital of Infectious Diseases: I Karpov (Principal Investigator), A Vasilenko; Republican Research and Practical Center for Pulmonology and Phthisiology: E Skrahina, A Skrahin; Gomel: University Hospital of Infectious Diseases: V Mitsura, E Kozorez; University Hospital of Tuberculosis: D Ruzanov, V Bondarenko; Svetlogorsk: Gomel Region AIDS Centre: O Suetnov, D Paduto.

Denmark—Danish HIV Cohort: N Obel (cohort Principal Investigator and TB-HIV Study Principal Investigator).

France—Aquitaine Cohort: F Dabis (cohort Principal Investigator); M Bruyand (TB-HIV Study PI, Epidemiology Group).

Italy—Brescia: Institute of Infectious and Tropical Diseases, University of Brescia: A Matteelli, A C Carvalho, R Basché; Division of Infectious Diseases, Spedali Civili: I E Hamad, B A Ricci, Bergamo:F Maggiolo, V Ravasio; Modena: Clinica di Malattie Infettive: C Mussini, F Prati, S Castelletti; Rome: Istituto Nazionale per le Malattie Infettive: L Spallanzani, A Antinori, G Antonucci, C Bibbolino, G Bove, E Busi Rizzi, S Cicalini, A Conte, G Cuzzi, P De Mori, A Festa, E Girardi (Principal Investigator), D Goletti, S Grisetti, G Gualano, F N Lauria, R Maddaluno, P Migliorisi Ramazzini, P Narciso, L Parracino, F Palmieri (coordinator), N Petrosillo, L Pucillo, V Puro, P Vanacore, R Urso; ICONA Cohort: A d'Arminio Monforte (cohort Principal Investigator); E Girardi (TB-HIV Study Principal Investigator); wwwfondazioneicona org/

Latvia, Riga—State Agency of TB and Lung Diseases: V Riekstina (Principal Investigator); Infectology Centre of Latvia: P Aldins, I Zeltina.

Romania, Bucharest—Spitalul de Boli Infectioase si Tropicale: D Duiculescu (Principal Investigator).

Russia, St Petersburg—Botkin Hospital of Infectious Diseases: A Rakhmanova (Principal Investigator), E Malashenkov, A Kozlov; St Petersburg City TB Hospital No. 2: A Panteleev; Novgorod City AIDS Centre: S Buzunova.

Spain—Barcelona: Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona: J M Miro (Principal Investigator), C Manzardo, J F García-Goez, A Moreno-Camacho, J A Martínez, J González, F García-Alcaide, I Pérez, J M Gatell; Hospital del Mar: P Sánchez, J L López-Colomes Mutua de Terrassa: X Martínez-Lacasa; Hospital Universitari Vall d'Hebrón: V Falcó A Imaz, I Ocaña, R Vidal; Hospital Universitari de Sant Pau: M A Sambeat; Agencia de Salud Pública de Barcelona: J Caylà, A Moreno-Martínez, J P Millet, L Fina, L del Baño, A Orcau.

Switzerland—Swiss HIV Cohort (SHCS): J Barth, M Battegay, E Bernasconi, J Böni, H C Bucher, C Burton-Jeangros, A Calmy, M Cavassini, C Cellerai, M Egger, L Elzi, J Fehr, J Fellay, M Flepp, H Furrer (TB-HIV Study Principal Investigator, Chairman of the

*Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773) and the 6th Framework (LSHP-CT-2006-018632) programmes. Current support also includes unrestricted grants from Bristol-Myers Squibb, Glaxo-SmithKline, Roche, Gilead, Pfizer, Merck and Co., Tibotec and Boehringer-Ingelheim.

Clinical and Laboratory Committee), C A Fux, M Gorgievski, H Günthard (President of the SHCS), D Haerry (deputy of 'Positive Council'), B Hasse, H H Hirsch, B Hirschel, I Hösli, C Kahlert, L Kaiser, O Keiser, C Kind, T Klimkait, H Kovari, B Ledergerber, G Martinetti, B Martinez de Tejada, K Metzner, N Müller, D Nadal, G Pantaleo, A Rauch (Chairman of the Scientific Board), S Regenass, M Rickenbach (Head of Data Center), C Rudin (Chairman of the Mother & Child Substudy), P Schmid, D Schultze, F Schöni-Affolter, J Schüpbach, R Speck, P Taffé, P Tarr, A Telenti, A Trkola, P Vernazza, R Weber, S Yerly.

United Kingdom—London: King's Hospital: F Post (Principal Investigator), L Campbell; Mortimer Market Centre: R Miller, A Arenas-Pinto.

Ukraine—Kiev City AIDS Centre: N Chentsova (Principal Investigator).

EuroSIDA cohort: J D Lundgren (TB-HIV Study Principal Investigator); http://www.cphivdk

Coordinating centre (CHIP): D Podlekareva, O Kirk, A Mocroft, J Kjær, M Ellefson.

Steering Committee: N Chentsova, D Duiculesku, H Furrer, E Girardi, M Bruyand, M H Losso, J D Lundgren, A Panteleev, R Miller, JM Miro, N Obel, F Post, V Riekstina, A Skrahin, J J Toibaro.

References

1 Kaplan J E, Benson C, Holmes K H, Brooks J T, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009; 58 (RR-4): 1–207.

2 Pozniak A L, Coyne K M, Miller R F, Lipman M C, Freedman A R, Ormerod L P. British HIV Association guidelines for the treatment of TB/HIV co-infection 2011. London, UK: BHIVA, 2012. http://www.bhiva.org/documents/Guidelines/TB/hiv_954_online_final.pdf Accessed October 2012.

3 World Health Organization. Global tuberculosis control: epidemiology, strategy, financing. WHO report 2009. WHO/HTM/TB/2009.411. Geneva, Switzerland: WHO, 2009. http://www.who.int/tb/publications/global_report/2009/en/index.html Accessed October 2012.

4 Gandhi N R, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010; 375: 1830–1843.

5 Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet 2010; 375: 1798–1807.

6 Podlekareva D N, Mocroft A, Post F A, et al. Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. AIDS 2009; 23: 2485–2495.

7 Dye C, Espinal M A, Watt C J, Mbiaga C, Williams B G. Worldwide incidence of multidrug-resistant tuberculosis. J Infect Dis 2002; 185: 1197–1202.

8 Seung K J, Omatayo D B, Keshavjee S, Furin J J, Farmer P E, Satti H. Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in southern Africa. PLoS ONE 2009; 4: e7186.

9 Mulissa Z, Jerene D, Lindtjorn B. Patients present earlier and survival has improved, but pre-ART attrition is high in a six-year HIV cohort data from Ethiopia. PLoS ONE 2010; 5: e13268.

10 Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992; 41 (RR-17): 1–19.

11 Rieder H L, Watson J M, Raviglione M C, et al. Surveillance of tuberculosis in Europe. Recommendations of a Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting on tuberculosis cases. Eur Respir J 1996; 9: 1097–1104.

12 Worodria W, Massinga-Loembe M, Mazakpwe D, et al. Incidence and predictors of mortality and the effect of tuberculosis immune reconstitution inflammatory syndrome in a cohort of TB/HIV patients commencing antiretroviral therapy. J Acquir Immune Defic Syndr 2011; 58: 32–37.

13 Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet 2007; 369: 2042–2049.

14 Hudson C P, Wood R, Maartens G. Diagnosing HIV-associated tuberculosis: reducing costs and diagnostic delay. Int J Tuberc Lung Dis 2000; 4: 240–245.

15 Monkongdee P, McCarthy K D, Cain K P, et al. Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. Am J Respir Crit Care Med 2009; 180: 903–908.

16 Colebunders R, Bastian I. A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. Int J Tuberc Lung Dis 2000; 4: 97–107.

17 Boehme C C, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010; 363: 1005–1015.

18 Helb D, Jones M, Story E, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol 2010; 48: 229–237.

19 Blakemore R, Story E, Helb D, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. J Clin Microbiol 2010; 48: 2495–2501.

20 Wilson D, Nachega J B, Chaisson R E, Maartens G. Diagnostic yield of peripheral lymph node needle-core biopsies in HIV-infected adults with suspected smear-negative tuberculosis. Int J Tuberc Lung Dis 2005; 9: 220–222.

21 von Reyn C F. The significance of bacteremic tuberculosis among persons with HIV infection in developing countries. AIDS 1999; 13: 2193–2195.

22 World Health Organization. Treatment of tuberculosis: guidelines. 4th ed. WHO/HTM/TB/2009.420. Geneva, Switzerland: WHO, 2009. http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf Accessed October 2012.

23 Saukkonen J J, Cohn D L, Jasmer R M, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935–952.

24 Abdool Karim S S, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010; 362: 697–706.

25 Abdool Karim S S, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011; 365: 1492-1501.

26 Havlir D V, Kendall M A, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 2011; 365: 1482–1491.

27 Blanc F X, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011; 365: 1471–1481.

28 Donoghoe M C, Bollerup A R, Lazarus J V, Nielsen S, Matic S. Access to highly active antiretroviral therapy (HAART) for injecting drug users in the WHO European Region 2002–2004. Int J Drug Policy 2007; 18: 271–280.

29 Lawn S D, Harries A D, Wood R. Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings. Curr Opin HIV AIDS 2010; 5: 18–26.

30 Havlir D V, Getahun H, Sanne I, Nunn P. Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. JAMA 2008; 300: 423–430.

RÉSUMÉ

OBJECTIFS : Evaluer l'utilisation des soins de santé chez les patients co-infectés par le virus de l'immunodéficience humaine et la tuberculose (TB-HIV) et élaborer un score d'index pondéré de soins de santé (HCI) basé sur les interventions couramment utilisées, et le comparer avec les résultats chez les patients.

MÉTHODES : On a enrôlé dans l'étude TB-HIV 1061 patients VIH où le diagnostic de TB a été porté entre janvier 2004 et décembre 2006. Ces patients provenaient de quatre régions : Europe Centrale et du Nord, Europe du Sud, Europe de l'Est et Argentine. Un score pondéré HCI (limite 0,5) a été établi en se basant sur les facteurs indépendants de pronostic identifiés dans les modèles multivariés de Cox ; le score final a comporté les performances dans les tests de sensibilité aux médicaments antituberculeux (DST), un régime TB initial comportant une rifamycine, l'isoniazide et le pyrazinamide ainsi que la mise en route du traitement antirétroviral combiné (cART).

RÉSULTATS : Le score HCI moyen est le plus élevé en Europe centrale et du Nord (3,2 ; IC95% 3,1–3,3) et le plus bas en Europe de l'Est (1,6 ; IC95% 1,5–1,7). La probabilité cumulative de décès un an après le diagnostic de TB est passée de 39% (IC95% 31–48) parmi les patients dont le score HCI est de zéro, à 9% (IC95% 6–13) chez ceux dont le score est ⩾4. Dans un modèle ajusté de Cox, l'augmentation d'une unité dans le score HCI est en association avec une réduction de 27% de la mortalité (RH 0,73 ; IC95% 0,64–0,84).

CONCLUSIONS : Nos résultats suggèrent que le DST, un traitement standard antituberculeux et un cART précoce peuvent améliorer les résultats chez les patients TB-HIV. Le score HCI proposé constitue un outil pour des recherches ultérieures et la prise en charge du suivi des patients TB-HIV. Le score HCI le plus élevé peut servir de référence pour évaluer la qualité de la prise en charge du TB-HIV et encourager une amélioration continue des soins de santé.

RESUMEN

OBJETIVOS: Analizar la utilización de los servicios de atención de salud por parte de los pacientes coinfectados por el virus de la inmunodeficiencia humana y la tuberculosis (TB-HIV) y establecir un índice ponderado de atención sanitaria (HCI), con base en las intervenciones frecuentes y en función del desenlace clínico de los pacientes.

MÉTODOS: Entre enero del 2004 y diciembre del 2006, participaron en el estudio sobre TB-HIV 1061 pacientes tuberculosos provenientes de las siguientes regiones: Europa central y del norte, Europa del sur, Europa del este y Argentina. Se estableció un HCI (entre 0 y 5), con base en los factores pronósticos independientes definidos por los modelos multifactoriales de Cox; en la puntuación final intervinieron los siguientes elementos: el rendimiento diagnóstico de las pruebas de sensibilidad (DST) a los medicamentos antituberculosos, el régimen terapéutico inicial con una rifamicina, isoniazida y pirazinamida y el comienzo de un tratamiento antirretrovírico combinado (cART).

RESULTADOS: El promedio del HCI fue más alto en Europa central y del norte (3,2; IC95% 3,1–3,3) y más bajo en Europa del este (1,6; IC95% 1,5–1,7). La mortalidad acumulada en un año a partir del diagnóstico de TB disminuyó de 39% (de 31% a 48%) en los pacientes con HCI = 0, hasta 9% (IC95% de 6% a 13%) en los pacientes con una puntuación ⩾ 4. En un modelo de Cox ajustado, cada incremento de una unidad en la puntuación del HCI se asoció con una disminución de 27% de la mortalidad (RH 0,73; IC95% 0,64–0,84).

CONCLUSIÓN: Estos resultados indican que la DST, un régimen normalizado de tratamiento antituberculoso y el comienzo temprano del cART podrían mejorar el desenlace clínico de los pacientes coinfectados por el TB-HIV. La escala que se propone del HCI ofrece una herramienta a las investigaciones futuras y a la supervisión del manejo de los pacientes que sufren esta coinfección. La puntuación más alta en la escala podría servir como el criterio de referencia en la evaluación del tratamiento de la coinfección por el TB-HIV, que estimule el mejoramiento continuo de la atención de salud.