УДК 616.9:612.017.1: 615.281-07-036.8

D. G. Zhyvytsia
State Institute "Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine"

PREDICTORS OF MORTALITY IN HIV/TB-INFECTED PATIENTS INITIATING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

Background: There is little information from Ukraine about the effect of Highly active antiretroviral therapy (HAART) on survival of HIV/TB-infected patients. Our objective was to identify predictors of mortality in HIV/TB-infected patients initiating HAART at the Zaporizhzhya AIDS Center, Ukraine.

Materials and methods: Prospective cohort study of HIV/TB-infected patients from January 2005 to December 2006 in a Zaporizhzhya AIDS Center, and were tracked for 60 months after start HAART. univariate and multivariate analysis and constructed Kaplan-Meier curves to assess predictors. To identify predictors of mortality were used to build a regression Cox proportional hazards model.

Results: Ninty four patients were studied (mean age 34 years, 20% female, median CD4 count 80 cell/μL). In 60 months of HAART 18 patients died. The probability of survival was 81%. Univariate analysis revealed that a baseline CD4 cell count <100/μL was a significant predictor of mortality (HR 5,6;95% CI 1,6–20,1, p=0,02). Patients who died had a mean pre-ART CD4 cell count of 77 (43–95) μL compared with 130 (65–213) μL for those who were alive at the conclusion of the study. Also, in univariate analysis, patients with extrapulmonary tuberculosis had an increased mortality risk (HR 2,4; 95% CI 1,2–10,4, p=0,032). In multivariate analysis, patients with a CD4 cell count <100 μL had a 5-fold higher risk of mortality (HR 5,2;95% CI 1,4–19,4) and those with extrapulmonary tuberculosis a 2,2-fold increased risk (HR 2,2, 95% CI 1,1–8,3).

Conclusions: HAART significantly increased probability of survival and reduced the risk of death for HIV/TB-infected patients in Ukraine. Simple clinical and laboratory data independently predict mortality and allow for risk stratification in HIV/TB-infected patients in Ukraine.

Keywords: TB, HIV, AIDS, HAART, predictors of mortality.

The HIV and tuberculosis (TB) epidemics overlap to a great degree in Eastern Europe countries, including Ukraine. The risk of TB is dramatically increased in HIV-infected patients as a result of a higher probability of either primary progression or reactivation of latent infection. [1–3] In Ukraine tuberculosis is the most frequent major opportunistic infection (OI) and the leading cause of mortality among HIV-infected patients. In developed countries, prior to the introduction of highly active antiretroviral therapy (HAART), a wide range of survival times in people with TB-HIV was reported [4, 5]. In the HAART era morbidity and mortality of people living with HIV and AIDS has been reduced significantly, in both industrialized and less developed regions [6, 7]. Further, in settings of widespread use, HAART appears to have been responsible for a significant reduction in the incidence of TB, even in places with high prevalence of this disease [8, 9]. There is also increasing evidence about the efficacy or effectiveness of HAART when used together with anti-TB therapy [10].

To date, there have been limited clinical data regarding survival rates among HIV/TB-infected patients and the impact of HAART on clinical outcomes in Ukraine. Previous studies showed associations between immunosuppression, history of AIDS and TB location with risk of death. Also the factors that have predicted mortality in studies evaluating patients prior to initiation of ART include high HIV RNA, mild to severe anaemia, low body mass index, elevated aspartate aminotransferase (AST), a history of opportunistic infections, and depression [5, 6].

Zaporizhzhya AIDS Center (The Clinic of Infection Diseases Department of Zaporizhzhya Medical Academy of Postgraduate Education) has offered HAART to patients since 2005. Since then, rapid scale-up has occurred and over 1500 patients are receiving HAART at that site. As more patients begin treatment, it is important to identify factors that predict a higher risk of mortality so that they can be more closely monitored.

Our objective was to identify predictors of mortality in HIV/TB-infected patients initiating HAART at the Zaporizhzhya AIDS Center, Ukraine.

Materials and methods

We conducted a prospective cohort study of HIV/TB-infected patients who started HAART at

Zaporizhzhya AIDS Center from January 2005 to December 2008.

In study we included HIV-infected patients older than 18 years. A total of 94 patients who met the inclusion criteria were identified. Time of follow-up was 60 months. Mean age at initial presentation was 34 years (range 23–54 years). Nineteen patients (20%) were female. The median (IQR) CD4 cell count was 80 μL (47–172). Fifty-four patients (57%) had an initial CD4 cell count <100/ μL, 24 (26%) a count of 100–200/μL, 16 (17%) a count of >200/μL.

The median initial HIV RNA was 5,2 $\log_{10}$ copies/ ml (4,6–5,5 $\log_{10}$ copies/ml) or 90 572 copies/ ml, although these results were only available for 31 patients (26%). Injection drug use was the most common route (65%) of HIV transmission. The number of patients co-infected with the hepatitis C virus (HCV) was 69 (73%). The baseline demographic and clinical characteristics are provided in Table 1.

TB diagnosis was confirmed by direct (positive Ziehl-Nielsen in sputum smear) or pathological (typical granuloma in biopsy) examination.

Pulmonary TB was the one with positive sputum or positive culture of sputum or bronchial aspirate, without clinical or radiological evidence of extra-pulmonary extension. Extra-pulmonary TB was considered when there was clinical evidence and positive Ziehl-Nielsen in biopsy from at least one extra-pulmonary location, with or without pulmonary TB.

In general anti-TB therapy was standard according to the World Health Organization (WHO). All patients included in the study received antituberculosis medications as directly observed therapy and in accordance with standard regimens.

All patients initiating HAART met WHO criteria for the use of antiretrovirals in resource-limited settings. The HAART regimens prescribed at Zaporizhzhya AIDS Center consisted of three-drug therapy using combinations listed by the WHO as approved first-line regimens. Most patients were prescribed nonnucleoside reverse transcriptase inhibitors (NNRTIs) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). Prophylactic regimens against opportunistic infections were provided in accordance with national Ukrainian guidelines during all time of the study.

Data from paper medical records were reviewed using a standardised data collection instrument. Records were reviewed for variables at initial presentation, follow-up and death (if applicable). We collected data in the following domains: demographics, opportunistic infection history, clinical, and laboratory. For patients who died while taking ART, date of death and time from diagnosis to death were recorded.

Statistical analysis were performed using STATISTICA 6.0. Median (interquartile range, IQR), and frequencies (%) were used to describe patients' characteristics in each group. The Kaplan-Meier test was used to estimate the probability of death and the median time to death. To compare survival by baseline immunological status, the Kaplan-Meier analysis was further stratified by baseline CD4 count (<100, 100–200, and >200 cells/μL) The hazard ratio (HR) and its 95% confidence interval (CI) derived from univariate and multivariate Cox proportional hazards models. A P value less than 0,05 was considered statistically significant.

Table 1

Baseline characteristics of patients with HIV/TB-infection who initiated HAART

No. of patients	94
Mortality rate (N(%))	18 (19)
Mean age (min-max)	34 (23–54)
Gender (N (%))	
Male	75 (80)
Female	19 (20)
Route of HIV transmission (N (%))	
IDU	61 (65)
Heterosexual	33 (35)
Pulmonary TB location (N (%))	33 (35)
HIV RNA (median (IQR)) ($\log_{10}$ copies/ml)	5,2 (4,6–5,5)
CD4 T-lymphocyte count (cells/μL)	
(median (IQR))	80 (47–172)
<100 cells/μL (N(%))	54 (57)
100–200 cells/μL (N(%))	24 (26)
>200 cells/μL (N(%))	16 (17)

Results and discussion

The probability of survival after start HAART estimated by the Kaplan-Meier method at 1, 2, 3, 4 and 5 years were 94%, 91%, 85%, 84%, and 81%. Among 18 patients who died, 14 patients (77%) died during the first 36 months of HAART. Five of the 14 patients who died had CD4 counts less than 50 cells/μL. The causes of death were TB (12 cases), primary CNS lymphoma and cryptococal meningitis (one case for each). Among the 5 patients with HIV-related deaths that occurred during the first 12 months of HAART, we identified 4 in whom death could be attributed to IRIS (3 case of tuberculosis meningitis).

Univariate analysis revealed that a baseline CD4 cell count <100/μL was a significant predictor of mortality (HR 5,6; 95% CI 1,6–20,1, p=0,02) (Table 2). Patients who died had a mean pre-ART CD4 cell count of 77 (43–95) μL compared with 130 (65–213) μL for those who were alive at the conclusion of the study. Also, in univariate analysis, patients with extrapulmonary tuberculosis had an increased mortality risk (HR 2,4; 95% CI 1,2–10,4, p=0,032).

In multivariate analysis, patients with a CD4 cell count <100 μL had a 5-fold higher risk of mortality (HR 5,2; 95% CI 1,4–19,4,p<0,05) and those with extrapulmonary tuberculosis a 2,2-fold increased risk (HR 2,2, 95% CI 1,1–8,3, p<0,05) (Table 2). Age, gender, route of HIV transmission were not predictive of mortality.

To date, HAART has been widely used for the treatment for HIV/TB-infected patients in the world. A plenty of studies precisely demonstrate the impact of ART on the survival outcomes among HIV-infected patients with successful immune restoration and reductions in morbidity and mortality [11–12]. However, the data regarding survival rates among HIV/TB-coinfected patients and the impact of HAART on clinical outcomes in Ukraine are still limited.

For HIV/TB-infected patients who did not receive ART, approximately half of them died within 1 year after TB diagnosis. As known, the simultaneous use of HAART with anti-TB therapy in patients with TB-HIV significantly reduces the risk of death in the short and long term compared with the risk of death for those receiving only anti-TB therapy [13–14].

We determine the factors prior to HAART initiation that were most predictive of mortality in HIV/TB-infected patients after they started HAART. Two factors were found to be the strongest predictors of mortality in these patients: a CD4 cell count <100 μL and a extrapulmonary form of tuberculosis.

Mortality differences based on initial CD4 cell count have been documented in previous studies in sub-Saharan Africa [8]. This study was consistent with those findings. Badri et al. [9] have shown that survival time was shorter in HIV-infected patients with extrapulmonary TB. This finding may be explained by the fact that patients with extrapulmonary TB have a higher bacterial load of M.tuberculosis and much more severe immunodeficiency status.

Most patients in the present study died of TB-related conditions. The previous studies have demonstrated that death within the first few months of TB treatment may be related to TB, whereas late deaths are attributable to HIV disease progression.

Initiation of HAART and immunological restitution may "unmask" extrapulmonary sites of TB explains the high mortality in first 6 months of HAART. We observed 4 deaths that could be attributed to IRIS, of which 3 were attributable to cen-

Table 2

Cox proportional hazards for baseline predictors of HIV/TB- patients

Variable	Category	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age	>34	1,8 (0,6–5,2)	1,4 (0,4–4,4)
	<34	1	1
Gender	Female	0,5 (0,16–1,6)	0,4 (0,13–1,4)
	Male	1	1
TB location	Extrapulmonary	2,4 (1,2–10,4)	2,2 (1,1–8,3)
	Pulmonary	1	1
Route of HIV transmission	IDU	1,2 (0,3–3,2)	1,1 (0,4–3,1)
	non IDU	1	1
CD4 count	< 100 cells/uL	5,6 (1,6–20,1)	5,2 (1,4–19,4)
	> 100 cells/uL	1	1

HR-Cox proportional hazards ratio: 95% CI=95% confidence interval.
Unadjusted-Cox proportional hazards ratio comparing group 1 v. group 2 in a univariate model with only one risk factor included.
Adjusted-Cox proportional hazards ratio estimated in a multivariate model including age. gender, TB location, route of HIV transmission, CD4 cell count

tral nervous system syndromes. The IRIS deaths primarily involved the central nervous system, suggesting that central nervous system manifestations may not be as well tolerated as manifestations in other body compartments and may require more-urgent attention.

This study demonstrates that simple laboratory and clinical data, available to health care providers prior to HAART initiation, can predict which patients are at increased risk of death when they start therapy. Interventions enabling more patients to be identified before they develop these clinical markers and earlier initiation of HAART will help ensure maximum benefits of therapy.

Conclusions

1. The probability of survival HIV/TB-infected after 60 months of HAART was 81% in Zaporizhzhya AIDS Center, Ukraine.

2. The baseline CD4 cell count <100/ μL in HIV/TB-infected patients was a significant predictor of mortality in univariate analysis (HR 5,6; 95% CI 1,6–20,1, p=0,02) and multivariate analysis (HR 5,2; 95% CI 1,4–19,4, p<0,05).

3. In HIV/TB-infected patients who start HAART extrapulmonary tuberculosis had an increased mortality risk in univariate analysis (HR 2,4; 95% CI 1,2–10,4, p=0,032) and multivariate analysis (HR 2,2, 95% CI 1,1–8,3, p<0,05).

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Стаття надійшла до редакції 25.03.2014 р.

Д. Г. Живиця
ДЗ «Запорізька медична академія післядипломної освіти МОЗ України»

ПРЕДИКТОРИ СМЕРТНОСТІ У ПАЦІЄНТІВ З ВІЛ/ТБ-ІНФЕКЦІЄЮ НА ФОНІ ВИСОКОАКТИВНОЇ АНТИРЕТРОВІРУСНОЇ ТЕРАПІЇ

В наш час відносно мало інформації про вплив високоактивної антиретровирусной терапії (ВААРТ) на виживання ВІЛ/ТБ-інфікованих хворих в Україні. Мета нашого дослідження полягала у виявленні предикторів смертності у пацієнтів з ВІЛ/ТБ, що почали ВААРТ у Запорізькому Центрі СНІДу, Україна.

Методи: У проспективне когортне дослідження були включені пацієнти з ВІЛ/ ТБ інфекцією, які почали ВААРТ із січня 2005 року по грудень 2006 року в Запорізькому Центрі СНІДу. Тривалість

спостереження склала 60 місяців після початку ВААРТ. Для виявлення предикторів смертності використовувалася побудова регресійної моделі пропорційних ризиків Коксу.

Результати: У дослідження були включені 94 пацієнта (середній вік 34 роки, 20% жінки, середній рівень CD4 80 мкл$^{-1}$). Через 60 місяців ВААРТ 18 пацієнтів померли. Імовірність виживання склала 81% . Одномірний аналіз показав, що рівень CD4<100 мкл$^{-1}$ був значимим предиктором смертності (ВР 5,6; 95% ДІ 1,6–20,1; p=0,02). Пацієнти, які померли, мали середній рівень CD4 до початку ВААРТ 77 (43–95) мкл$^{-1}$, у порівнянні з 130 (65–213) мкл$^{-1}$ у тих, хто був живий у момент завершення дослідження. Крім того, в одномірному аналізі, пацієнти із позалегеневим туберкульозом, мали підвищений ризик смертності (ВР 2,4; 95% ДІ 1,2–10,4; p=0032). При багатофакторному аналізі, пацієнти із числом лімфоцитів CD4<100 мкл мали в 5 разів вище ризик смерті (ВР 5,2; 95% ДІ 1,4–19,4), а із позалегеневим туберкульозом в 2,2 рази вище (ВР 2,2; 95% ДІ 1,1–8,3).

Висновки: ВААРТ значно збільшує ймовірність виживання і знижує ризик смерті для ВІЛ/ТБ-інфікованих пацієнтів в Україні. Прості клінічні і лабораторні дані можуть прогнозувати результат і дозволяють стратифікувати ризик смерті у хворих з ВІЛ/ТБ-інфекцією.

Ключові слова: туберкульоз, ВІЛ, СНІД, ВААРТ, предиктори смертності.

Д. Г. Живица
ГЗ «Запорожская медицинская академия последипломного образования МЗ Украины»

ПРЕДИКТОРЫ СМЕРТНОСТИ У ПАЦИЕНТОВ С ВИЧ/ТБ-ИНФЕКЦИЕЙ НА ФОНЕ ВЫСОКОАКТИВНОЙ АНТИРЕТРОВИРУСНОЙ ТЕРАПИИ

В настоящее время относительно мало информации о влиянии высокоактивной антиретровирусной терапии (ВААРТ) на выживание ВИЧ/ТБ-инфицированных больных в Украине. Цель нашего исследования заключалась в выявлении предикторов смертности у пациентов с ВИЧ/ТБ, начавших ВААРТ в Запорожском Центре СПИДа, Украина.

Методы: В проспективное когортное исследование были включены пациенты с ВИЧ/ ТБ инфекцией, которые начали ВААРТ с января 2005 года по декабрь 2006 года в Запорожском Центре СПИДа. Длительность наблюдения составила 60 месяцев после начала ВААРТ. Для выявления предикторов смертности использовалось построение регрессионной модели пропорциональных рисков Кокса.

Результаты: В исследование были включены 94 пациента (средний возраст 34 года, 20% женщины, средний уровень CD4 80 мкл$^{-1}$). Через 60 месяцев ВААРТ 18 пациентов умерли. Вероятность выживания составила 81% . Одномерный анализ показал, что уровень CD4<100 мкл$^{-1}$ был значимым предиктором смертности (ОР 5,6; 95% ДИ 1,6–20,1; p=0,02). Пациенты, которые умерли, имели средний уровень CD4 до начала ВААРТ 77 (43–95) мкл$^{-1}$, по сравнению с 130 (65–213) мкл$^{-1}$ у тех, кто был жив в момент завершения исследования. Кроме того, в одномерном анализе, пациенты с внелегочным туберкулезом, имели повышенный риск смертности (ОР 2,4; 95% ДИ 1,2–10,4; p=0032). При многофакторном анализе , пациенты с числом лимфоцитов CD4<100 мкл имели в 5 раз выше риск смерти (ОР 5,2; 95% ДИ 1,4–19,4) и с внелегочным туберкулезом в 2,2 раза выше (ОР 2,2; 95% ДИ 1,1–8,3).

Выводы: ВААРТ значительно увеличивает вероятность выживания и снижает риск смерти для ВИЧ/ТБ-инфицированных пациентов в Украине. Простые клинические и лабораторные данные могут прогнозировать исход и позволяют стратифицировать риск смерти у больных с ВИЧ/ТБ-инфекцией.

Ключевые слова: туберкулез, ВИЧ, СПИД, ВААРТ, предикторы смертности.