IMPACT OF ANTIRETROVIRAL THERAPY ON SURVIVAL IN HIV INFECTED PATIENTS

Manuela Arbune, MD
Infectious Diseases Hospital, Galati, Romania

ABSTRACT

The main objective of the study is to compare the survival time on antiretroviral treated HIV patients (TG) versus untreated group (NTG). Medical records of confirmed HIV patients between 1990 -2008 in Galati County were retrospectively studied. From 600 cases 279 died, 255 are living and 71 are censored. The mean survival time after HIV diagnostic data was 84.82 months, with the higher risk of death on 23-24 months. Median surviving time was significantly higher ($p<0.001$) on TG (96 months) vs. NTG (24 months). The survival probability on 228 months after HIV diagnostic is 2.4 higher on TG vs. First line therapy was mono/ bi-therapy with INRT (63 patients) or HAART with either INNRT (91) or PI (123). The influence of HAART on surviving time is meaningfully on HIV patients diagnosed before 1998 ($p<0.001$) without influence of sex, AIDS stage or types of HAART (INNRT/PI). The durability of the first line HAART was 28 months on INNRT vs. 25 months on PI. Conclusions: The surviving chance on 228 months after HIV diagnostic is significantly improved by HAART. Durability of the first HAART line was similar for combination with INNRT and PI.

Key words: HIV, HAART, survival

BACKGROUND

Nowadays triple drug highly active antiretroviral therapy (HAART) dramatically improved the life expectancy of the patients with HIV/AIDS (Human Immunodeficiency Virus infection/Acquired Immune Deficiency Syndrome). Due to the success of antiretroviral therapy since 1996, as well as improvements in the prevention and treatment HIV complications, over 80% of patients are now alive 10 years after sero-conversion [May MT, 2006]. Deaths from opportunistic infections have declined while mortality from other co-morbidities has become more common [Bhaskaran K, 2008].

A systematic review and meta-analysis of 54 antiretroviral clinical trials has demonstrated reduced progression to AIDS or death by 30% against placebo if one antiretroviral is used, by 40% against one antiretroviral if two antiretrovirals are used and by 40% against two antiretrovirals if three antiretrovirals are used [Jordan R, 2002].

A randomised controlled trial known as CHER, compared the evolution of HIV infection on infants with HAART early after diagnostic versus those with delayed treatment until declined CD4 count or evidenced of clinical AIDS signs. 16% of the infants in the delayed group died versus 4% of the immediately treated infants. Early HIV diagnosis and early antiretroviral therapy reduced early infant mortality by 76% and HIV progression by 75%. [Violari A, 2008].

The risk of progression to AIDS or death for patients on HAART in the Swiss Cohort was 14% of patients not on HAART [Sterne J, 2005].

The EuroSIDA study of over 9 000 patients showed the decline in deaths and AIDS as a result of the introduction of HAART. Incidence of AIDS was about 50% lower in late-HAART (after 1998) than in early-HAART (1996-1997). In multivariate Cox's models, with early-HAART as the reference, there was an increased risk of AIDS (relative hazard 1.39; 95% CI 1.16-1.67, $p=0.0004$) and all deaths (1.29; 1.08-1.56, $p=0.0065$) in the pre-HAART era, and a reduced risk of AIDS (0.62; 0.50-0.77, $p<0.0001$) and all deaths (0.66; 0.53-0.82, $p=0.0002$) in the late-HAART era [Mocroft A, 2003].

Adresa de corespondență:
Dr. Manuela Arbune, Spitalul de Boli Infecțioase, Str. Traian, Nr. 393, Cod poştal 800179, Galați, România

The EuroSIDA risk-score for clinical progression or death is available now by developping of an algorithm calculation, based on current values of CD4 cell count, viral load, level of anaemia, body mass index (BMI) and rate of CD4 cell change. A patient with a EuroSIDA risk-score of < 1.5 had a 1 in 801 chance of disease progression within the next 3 months, compared with a chance of 1 in 17 for a patient whose EuroSIDA risk-score was > 4.5 [Mussini C, 2008].

Actually, HIV therapy is a continuous challenge. The future strategies of HIV management should consider the regional natural history of HIV epidemics and the characteristics of target population.

OBJECTIVES

The objectives of the study are:

1. To estimate the survival time from HIV diagnostic of treated group patients (TG) comparative to no treated group (NTG).
2. To estimate the durability of the first line of HAART.
3. To characterize the features of the HIV survivors on December 2008.

MATERIAL AND METHODS

Medical records of the patients confirmed with HIV infection between 1990 -2008 in Galati County were retrospectively studied.

The study sample was based on 600 subjects. The diagnostic date was considered as the analyze baseline because the moment of HIV infection was uncertain for most of the patients. Follow up continued at least 12 months after HIV diagnostic. Lost from evidence or incomplete data were censored. Patients with initial mono or bi-therapy were censored for the durability estimation of first line HAART.

Primary endpoint in this analysis was death. Deaths occurring during the follow up period were identified on a continuous basis. The end of the study was 31 December 2008.

Cumulative mortality rates, comparative mortality of TG vs. NTG and durability of first line HAART were estimated by Kaplan-Meier methods. XL-STAT-LIFE software was used for statistical analysis.

RESULTS

From 600 HIV patients recorded in Galați County 11,33% (71) were censored, 46,16% (276) died and 42,50% (255) survived until 31 December 2008 (table 1). Most of the deaths were recorded on pediatric age, before 1998 (fig.1).

TABLE 1: *Distribution by sex of HIV survivors and deaths patients*

	Male	Female	Total
Deaths	179	98	277
Survivors	135	120	255
Censored	36	32	68
Total	350	250	600

First line therapy available in Galați County was mono/ bi-therapy with nucleoside reverse transcrip-

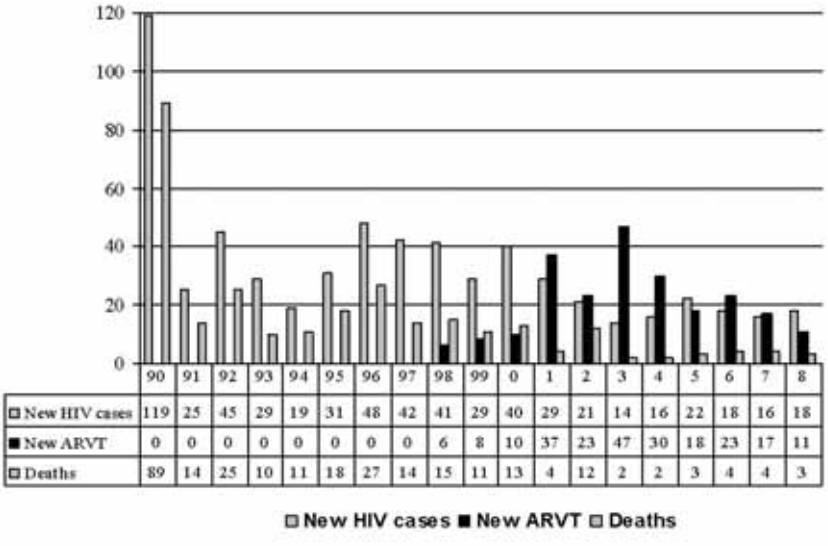


Fig. 1: *Comparative distribution of yearly new HIV cases, deaths and new HAART on naive HIV patients*

tase inhibitors (NRTI) on 63 patients during 1996-1998 and HAART after 1998. A number of 91 first HAART line contained non-nucleoside reverse transcriptase inhibitors (NRTI) and 123 protease inhibitors (PI).

The average of survival time from HIV diagnostic data of NTG was 84.852 months (CI [78.71; 90.95]), with the higher risk of death on 23-24 months. Surviving time was improved by HAART to 147 months (CI [137-158]; p<0.001). No influence of sex, AIDS stage or type of HAART (INNRT/PI) was found for surviving time (fig. 2).

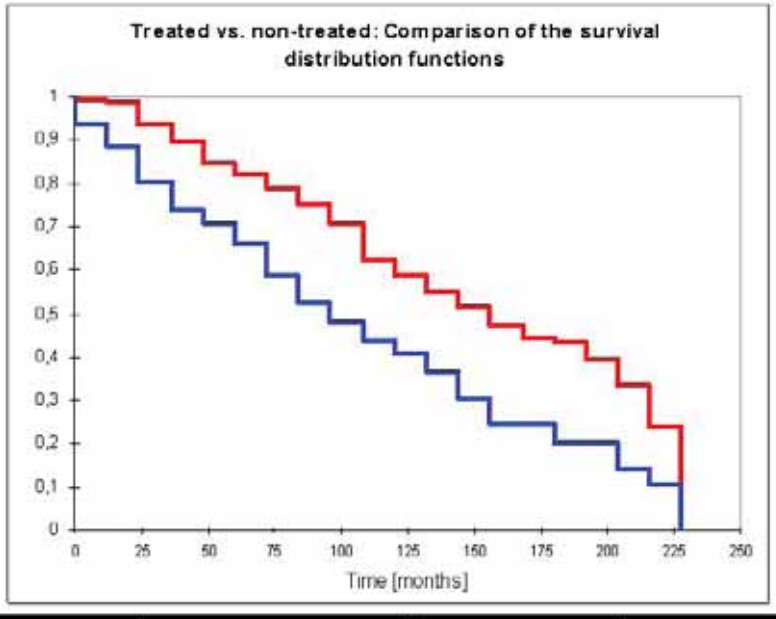
The durability of the first line HAART was 28 months on INNRT vs. 25 months on PI, but without statistical significance (table 2). 150 HIV patients who received HAART as first line at least 12 months are living at the end of the study.

TABLE 2: *Influence of first line HAART on regimen durability and on surviving time*

	IP	INNRT	Wilcoxon Statistical Test
Number	123	91	
Median durability	25,02	28,19	P=0,105
Median surviving	119,02	107,94	P=0,043

Median surviving time was significantly higher on TG (96 months) vs. NTG (24 months): OR=32.12; CI [21.69-48.91]; p<0.001. The survival probability on 120 months after HIV diagnostic was 0.41 NTG vs. 0.59 TG. The chance of surviving on 228 months is more than twice for TG (0,24) vs. NTG (0,10). The influence of HAART on surviving time is meaningfully, especially on HIV patients diagnosed before 1998 (OR 74.215; CI [39.52-139.36]; p<0.001), but the median time until the death was similar (24 months) before and after 1998 (fig. 3).

On the end of the study they are 255 living patients with median age 21 years old and 1.1 sex ratio M/F. AIDS stage was considered in 82%. Previous or current TB co-infection was AIDS defining disease in 33%. As HIV associated diseases, HBV co-infection represents 39% and lipo-distrophy 61%. Median time of antiretroviral treatment was 72 months, including median 3 experienced therapeutic combinations. Immunological status on the end of the study is described by median 542/mm3 CD4 count (table 3).



	Survival Time Average	Standard Deviation	Lower Bound 95%	Upper Bound 95%
TG	147,75	5,308	137,341	158,149
NTG	84,853	3,134	78,710	90,995

Fig. 2: *Kaplan Meyer survival of treated (+) vs. no treated (-) HIV patients*

TABLE 3: *Characteristics of HIV survivors on December 2008*

Median age	21 years old
Sex ratio M/F	1,1
AIDS stage	82%
Median CD4	542/mm3
Median length of ARVT	72 months
Median number of ARV lines	3

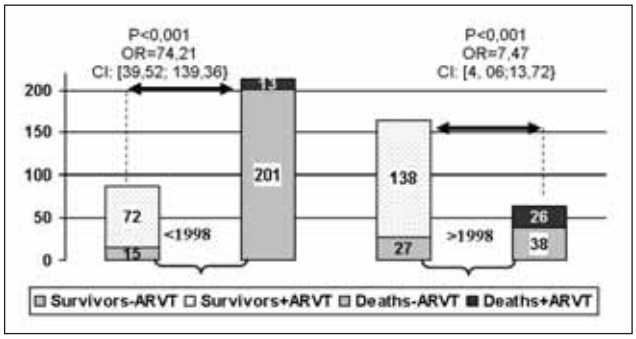


FIGURA 3. *Comparative results of ARVT on patients with HIV diagnostic before and after 1998*

DISCUSSION

HIV test was available in Galati – Romania since 1990. According to few previous studies, the most frequent HIV-1 isolate in Romanian pediatric epidemic is subtype F, characterized by a high diversity of strains.

Peculiarity of Romanian HIV epidemic is the joint of a slow growing adult epidemic and a pediatric epidemic, prevailed by a cohort born between 1988 -1990, horizontally infected and a high number of long time survivors. The pattern of HIV transmission was: 81% horizontal (nosocomial or unknown), 5% vertical and 14% sexual. The highest rate of deaths in 1990 is explained by very small age of the patients and the rapid progression to AIDS occurred in the absence of treatment.

The limitation of the study is high proportion of HIV patients without immunologic and virologic data, because the evaluation of immunity and HIV-viral load was available in Galaţi after 2000. Euro-SIDA risk score was not feasible because of meagrely recorded data.

Meta-analysis evidenced that increasing numbers of drugs in antiretroviral combination therapy reduce the AIDS deaths. Hereby in the present study, the surviving time of patients with mono/bi-therapy was inferior comparative to HAART first line therapy. These patients were HIV diagnosed before 1998 and were considered as treated group. Consequently, the surviving difference between TG and NTG is weakening and require stratification of TG in HAART and mono/bi-therapy.

Long surviving of pediatric Romanian HIV cohort until adult age, early aging related to HIV, high effectiveness of HAART balanced by complex associated events, are continuing to change the life and death perspectives on HIV. A prospective study aimed on HAART era will be helpful to up-to-date the survival rate of HIV/AIDS in Galaţi County.

CONCLUSIONS

1. HAART improved with 62,147 months the life expectancy of HIV patients on 228 months after diagnostic.
2. Durability of the first HAART line was similar for combination with INNRT (28 months) and PI (25 months).
3. Antiretroviral multi-experience and complex co-morbidities are new challenges for the treatment of survived HIV patients.

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