Predictors of death in Malaysian HIV-infected patients on anti-retroviral therapy

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Abstract

Objective. To determine the predictors of death in Malaysian HIV-infected patients undergoing antiretroviral therapy (ART).

Methods. Data from 845 HIV-infected patients aged ≥20 years on ART in a large teaching hospital in Malaysia from 1989 to 2009 were analyzed using Kaplan–Meier and Cox regression analyses.

Results. 72.7% of the patients survived. Multivariate Cox regression showed that significant predictors of death were age ≥50 years (HR 1.76; 95% CI 1.18–2.64), secondary education (HR 3.57; 95% CI 1.12–11.37), tertiary education (HR 3.57; 95% CI 1.09–11.70), being unemployed (HR 1.49; 95% CI 1.07–2.09), AIDS on initial presentation (HR 5.75; 95% CI 3.29–10.07), single-drug ART (HR 1.84; 95% CI 1.27, 2.66), double-drug ART (HR 1.65; 95% CI 1.19–2.25) and inability to achieve viral load ≤50 copies/ml (HR 10.22; 95% CI 7.26–14.37).

Conclusion. Every effort needs to be made to ensure that all HIV patients have access to triple drug ART, to lower viral load to ≤50 copies/ml and to treat HIV patients before they progress to AIDS as these are significant modifiable predictors of death in Malaysian HIV patients.

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Introduction

Anti-retroviral therapy (ART) has been shown to increase the survival of HIV-infected patients (Taiwo et al., 2009) but most studies have been conducted in developed countries (Walensky et al., 2010). A study done in Hong Kong showed increased median survival in the triple drug ART era compared to the single or double drug ART era (Wong et al., 2004). In Malaysia, the first AIDS case was reported in 1986 (Goh et al., 1987) and ART has been available since 1989 (MOH, 2001). There is a lack of scientific research on ART and survival of HIV-infected Malaysian patients. The aim of this study was to determine the predictors of death in Malaysian HIV-infected patients undergoing antiretroviral therapy.

Methods

This is a cohort study which was started in 2007 in a large teaching hospital in Malaysia. Patient medical records were retrospectively traced back to 1989. These same patients were prospectively followed up until 2009. All 845 HIV-infected patients during this period who were aged ≥20 years, had baseline CD4 levels and baseline viral load (VL) levels and were receiving ART in the hospital were included in the analysis. Survival time was measured from the date of starting ART until the date of the patient’s death or the end of the study. The sample size was calculated using the PS Power and Sample software. The minimum sample size calculated based on a power of 80%, a hazard ratio of 0.6 (Pezzotti et al., 1999), a median survival time of 70 months (Wong et al., 2004), a ratio of control to experimental groups of 1:1, an accrual time of 36 months and a follow-up time of 3 months was 270. Allowing for a 20% follow-up loss, 324 patients were required. The sample size obtained was 845 patients, which is more than the minimum required sample size. Data for the study were mainly taken from the patients’ medical records. Follow-up of these patients was carried out every 3 months as part of the treatment by the infectious disease team. Collected data included socio-demographic data, lab tests, clinical information, type of ART therapy and opportunistic infections (OI). Mortality data were obtained from the National Registration Department. Analysis was carried out using Kaplan–Meier (KM) and Cox proportional hazards regression with forward selection. Variables which had at least a p-value of 0.2 in the univariate Cox analysis were selected for multivariate analysis. Proportional hazard assumptions were checked using log negative log survival and hazard function plots. Multi-collinearity and interaction between predictors were also checked and excluded. SPSS version 15.0 software was used for analysis. Ethical approval was obtained from the hospital’s Medical Ethics Committee (reference number 565.22), which is an independent review board. The ethical approval included approval to use mortality data from the National Registration Department.

Results

A total of 845 HIV-infected patients aged ≥20 were included for analysis. The median age of the patients was 34.1 years (IQR 13.1). Most (70.4%) were aged between 20 and 39 years, were male (78.2%) and were Chinese (67.3%) while 48.5% were married, 67.5% had at least secondary education, 49.2% were professional or non-manual workers,
42.5% earned between RM 1000 to RM 3000 per month, 73.3% had CD4 < 200 cells/μl, 55.5% had viral load (VL) ≥ 100,000 copies/ml. 59.5% had initial HB ≥ 12 g/dl, 74.2% contracted HIV via the heterosexual route, 62.0% presented with AIDS, and 65.1% had positive opportunistic infection. Anti-retroviral therapy with triple drugs or more (2 NRTI+1 NNRTI) was initiated in 74.1% of the patients. A total of 64.5% achieved VL ≤ 50 copies/ml and at the end of the study, 72.7% of the patients survived.

**Median survival time of HIV infected patients on ART**

The mean survival time was 130.9 (95% CI 123.4, 138.3) months. The median survival time could not be calculated because the cumulative survival was still high (>50%). The 5 and 10-year survival rates were 70.6% (95% CI 67.1, 74.1) and 62.3% (95% CI 57.4, 67.2), respectively. Significant variables affecting survival from the Kaplan–Meier analysis are summarized in Table 1.

Table 2 displays the final Cox regression model (predictors of death in HIV-infected patients on ART). Significant independent predictors of death in HIV-infected patients on ART were an age of ≥ 50 years, having at least secondary and tertiary education, unemployment, initial presentation of AIDS, starting ART with single or double drugs and inability to achieve VL ≤ 50 copies/ml.

**Discussion**

The highest risks of death in older patients (aged 50 years and above, those who initially presented with AIDS, started ART with only 1 or 2 drugs and were unable to achieve VL ≤ 50 copies/ml) reflect the findings in developed countries (Bonnet et al., 2005; Egger et al., 1997; Geretti et al., 2008; Hanna et al., 2006; Li et al., 2000; Schwarz et al., 2000). Increasing age and AIDS are associated with a diminished immune response with consequent high viral load and increased probability of opportunistic infections so it is not surprising that these factors increase the risk of death of HIV-infected patients. Initial ART with single drug and double drugs was common in the pre-HAART (highly active anti-retroviral therapy) era i.e., before 1997 and has proven less effective than the triple drugs of HAART (1997 and later) in reducing VL to ≤ 50 copies/ml (Geretti et al., 2008; Schwarz et al., 2000). It is difficult to explain why better educated patients had a higher risk of death unlike the findings of other researchers (Borrell et al., 2006; McFarland et al., 2003; Rapiti et al., 2000) but one possible explanation could be the late presentation of these patients due to the stigma attached to HIV infection in Malaysia. More research is needed to explain this apparent discordant finding but it is not difficult to explain why unemployed patients with no independent source of income would have a higher risk of death as similar results have been found elsewhere (Desilva et al., 2008).

**Strengths and limitations**

The strengths of this study were the cohort design, large sample size, large number of variables and our ability to accurately crosscheck with mortality records of the National Registration Department. Limitations included the reliance in part on medical records which contained missing data and uncertainty about prior ART elsewhere before patients...
presented for treatment in this hospital. The participants did not repre-
sent the actual situation in Malaysia since most of the patients were of
Chinese ethnicity and were infected via the heterosexual route whereas
most HIV patients in Malaysia are Malays and are infected by the intra-
venous drug user (IDU) route.

Conclusion

Every effort needs to be made to ensure patient accessibility to tri-
ple drug ART, to lower viral load to ≤50 copies/ml and to treat HIV
patients before they progress to AIDS as these are significant modifi-
able predictors of death in Malaysian HIV patients.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Acknowledgments

This work is part of the IDM project (StEMM Programme) supported
by the University of Malaya/Ministry of Higher Education (UM/MOHE)
High Impact Research Grant (grant number E000010-20001) and the
Fundamental Research Grant Scheme (FRGS) from the Ministry of
Higher Education, Malaysia (grant FP080/2006A).

References

Bonnet, F., Thiébaut, R., Chêne, G., et al., 2005. Determinants of clinical progression in
antiretroviral-naïve HIV-infected patients starting highly active antiretroviral

Borrell, C., Rodríguez-Sanz, M., Pasarín, M.I., et al., 2006. AIDS mortality before and after
the introduction of highly active antiretroviral therapy: does it vary with socioeco-
nomic group in a country with a National Health System? Eur. J. Public Health 16

Desilva, M.B., Merry, S.P., Fischer, P.R., Rohrer, J.E., Isichei, C.O., Cha, S.S., 2008. Youth, un-
employment, and male gender predict mortality in AIDS patients started on HAART

tion therapies in HIV infected patients in Switzerland: prospective multicentre

successful viral load suppression in first-line highly active antiretroviral therapy.
Antivir. Ther. 13 (7), 927–936.

syndrome — report of the first case in Malaysia. Medical Journal of Malaysia (42),
58–60.

sis Increases the Risk of HIV-related Death Among Persons Newly Diagnosed with
AIDS in New York City, 2002–2004. New York City Dept. of Health and Mental
Hygiene, New York, NY, USA.

Li, Y., McDonald, A.M., Dore, G.J., Kaldor, J.M., Committee, f. t. N. H. S., 2000. Improving

is associated with a higher rate of death in the era of highly active antiretroviral
therapy. San Francisco. JAIDS Journal of Acquired Immune Deficiency Syndromes
33 (1), 96–103.

MOH, 2001. Malaysian Society of Infectious Disease and Chemotherapy: Consensus on
Antiretroviral Treatment. 2nd ed. Malaysia Ministry of Health, Kuala Lumpur.

Italy: the role of new combination antiretroviral therapies. AIDS 13 (2), 249–255.

Socioeconomic status and survival of persons with AIDS before and after the
introduction of highly active antiretroviral therapy. Epidemiology 11 (5),
496–501.

and other antiretroviral treatments on acquired immunodeficiency syndrome sur-
http://dx.doi.org/10.1093/aje/152.2.178.

Taiwo, B.O., Li, X., Palella, F., et al., 2009. Higher risk of AIDS or death in patients with
lower CD4 cell counts after virally suppressive HAART. HIV Med. 10 (10), 657–660.
http://dx.doi.org/10.1111/j.1468-1293.2009.00739.x (HIV739 [pii]).

Walensky, R.P., Wood, R., Ciaranello, A.L., et al., 2010. Scaling up the 2010 World Health Or-
ganization HIV Treatment Guidelines in resource-limited settings: a model-based anal-

Hong Kong cohort of patients with advanced HIV type 1 disease during the era of