

CAUSES AND PATTERN OF MORTALITY IN HIV-INFECTED, HOSPITALIZED PATIENTS IN A TERTIARY CARE HOSPITAL: A FOURTEEN YEAR STUDY

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ABSTRACT

BACKGROUND: The introduction of highly active antiRetroviral therapy (HAART) in several centers in India has raised the expectation that many human immunodeficiency virus (HIV)-infected individuals will live longer. However, as most infected individuals remain undiagnosed till the late stage of infection; several continue to succumb to this infection even in the era of HAART. **MATERIALS AND METHODS:** A retrospective study was conducted over a 14 year period on 2,050 HIV-infected, hospitalized patients to evaluate the pattern of mortality and to determine proportion, risk factors and causes of death. **RESULTS:** A total of 145 deaths among HIV-infected patients were documented during hospitalization, with an overall mortality rate of 8.15%: 2.94% in the pre HAART era (1992-1996), 7.29% in the early HAART era (1997-2000) and 9.73% in the present HAART era (2001-2005). 11.7% (17/145) of deceased patients were aware of their HIV-infected status before getting admitted. Only five patients were on any antiretroviral treatment prior to admission. Ninety (62.07%) deaths were HIV-related (AIDS-defining conditions) and 55 (37.93%) were nonHIV-related. **DISCUSSION:** Our study stresses the importance of early diagnosis of HIV infection to curb adult mortality, which will continue to rise unless effective treatment interventions are introduced.

Key words: Antiretroviral, highly active antiretroviral therapy, mortality rate, World Health Organization clinical stage

Latest estimates show that 39.5 million people were living with the human immunodeficiency virus (HIV) infection in 2006.^[1] Acquired immunodeficiency syndrome (AIDS) has claimed 25 million lives since it was discovered 26 years ago. India, the second most populous

country in the world, with 5.2 million HIV-infected people is in the grip of an HIV epidemic.^[2] According to the United Nations Acquired Immunodeficiency Syndrome/World Health Organization (UNAIDS/WHO), 270,000-680,000 Indians died of AIDS in 2006.^[1]

With the introduction of highly active anti retroviral therapy (HAART) in 1996, morbidity and mortality due to HIV/AIDS have declined^[3-5] and the general perception of HIV infection has changed from that of a deadly disease to a chronic disease. HAART is being scaled up

in many developing countries like India and especially in our State of Andhra Pradesh, where 10% of India's total HIV-infected individuals (0.51 million) are located. The Andhra Pradesh State AIDS Control Society (APSACS) in collaboration with the National AIDS Control Organization (NACO) and WHO, has been providing ART free of cost under WHO's 3 by 5 ARV Phase-I Program at select Government Medical Hospitals of Andhra Pradesh since April 2004. This initiative, which meant to treat three million people by the year 2005, has helped many infected people, especially low-income people, to improve their immune status and control their viral loads. Many HIV-infected individuals continue to succumb to this infection in the era of HAART due to delays in HIV diagnosis.

It is hard to clearly demonstrate the impact of AIDS on mortality in India, as death registration and HIV/AIDS reporting systems are usually incomplete. Even though several studies have been conducted internationally,^[6-13] to date, no such large-scale study of the mortality rates in HIV-infected individuals from India has been performed. Thus, the extent to which the management of HIV-infected patients could be suitably modified remains unknown. Since no such study is available from our State of Andhra Pradesh, we took a retrospective study in our Institute to evaluate patterns of mortality and to determine the proportion of hospitalised HIV-infected patients who died and their causes of death.

MATERIALS AND METHODS

A retrospective study was conducted over a 14 year period from 1992 to 2005, on 2,050 HIV-infected patients, hospitalized under

various units in the Nizam's Institute of Medical Sciences, a tertiary care hospital and University in Hyderabad, Andhra Pradesh. Our Institute is not a free antiretroviral therapy (ARV) centre and thus represents all the patients who are or are not on ARV treatment. Since our Institute does not have any separate ward for HIV-infected patients, the bias of inclusion of terminally ill referral cases from other hospitals also does not exist. The study period was divided into preHAART (1992-1996), early HAART (1997-2000) (when it was not readily available to all) and present HAART (2001-2005) periods (when ART is easily accessible to many), to study the effect of HAART on mortality rates. Of the 2,050 admitted cases, medical records of 1,780 were available for review. All deaths that occurred among these patients were noted and reviewed for demographic, clinical and diagnostic information. Causes of death were then coded as HIV-related or nonHIV-related. When the underlying cause of death was due to WHO stage 3 or 4 conditions, it was considered HIV-related and all other causes were classified as nonHIV-related.

CD4 testing in our Institute was started in August 1999 using the fluorescence-activated cell sorting (FACS) Count (Becton and Dickinson) system, courtesy of the National AIDS Control Organization (NACO), Government of India.

RESULTS

A total of 145 deaths (8.2%) were documented among HIV-infected patients during their hospitalization during the study period. There has been a considerable rise in the mortality among HIV-infected, hospitalized patients

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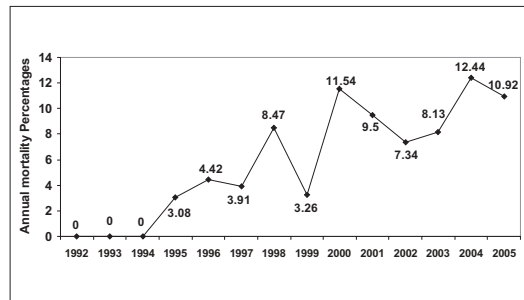


Figure 1: Annual mortality rates among HIV-infected, hospitalized patients

over the years [Figure 1]. This proportion was 2.9% in the preHAART era (1992-1996), which then increased to 7.3% in the early HAART era (1997-2000) and was then highest in the present HAART era (2001-2005) with 9.7% mortality rate ((27/217) 12.4% in 2004).

The majority (75.9%) of the deaths among HIV-infected hospitalized patients had occurred in males and the median age was 43 years (range 16-69 years). Seventeen out of 145 (11.7%) of the deceased patients were aware of their HIV-positive status before getting admitted into our institute. However, almost half of them had come to know of it just within one week before

hospitalization and were referred to our Institute for further management. Except for five of these HIV-infected individuals, no other patient was on any ARV therapy before admission.

Ninety (62.1%) deaths were HIV-related (AIDS-defining conditions) and 55 (37.9%) were nonHIV-related [Table 1]. The most common causes of HIV-related death were pulmonary or other respiratory tract infections (RTI) (44.4%), meningitis (41.1%), mycobacterial infections (40.0%) and AIDS-related malignancies (4.4%); affecting the HIV-infected individual as a single manifestation or in association with other infections [Figure 2]. The frequent causes of nonHIV-related deaths were hepatic failure (41.8%), trauma mostly resulting from road traffic accidents (RTA) (27.3%), cardiac failure (16.4%), malignancies (7.3%) and septicemia (7.3%).

CD4 cell counts of 86 cases from the study cohort (all 145 deaths) were available for analysis, which accounted for 62/90 (68.9%) of HIV-related deaths and 24/55 (43.6%) of nonHIV-related deaths [Table 2]. Symptomatic

Table 1: Causes of death among human immunodeficiency virus-infected hospitalized patients (n = 145)

Mortality causes	1992-1996	1997-2000	2001-2005	Total
HIV - Related causes of mortality				
TB	1	-	1	2
Meningitis	2	3	4	9
Pneumonia and other RTI	1	7	3	11
TB + Meningitis	1	4	14	19
TB + RTI	1	4	13	18
TB/Meningitis/RTI + Acute GE	-	1	15	15
TB/Meningitis/RTI + Septicemia	-	2	10	12
AIDS-related malignancies	-	1	3	4
Total	6	22	62	90
Non HIV - Related causes of mortality				
Hepatic failure	-	5	18	23
Trauma (RTA or other causes)	-	5	10	15
Cardiac failure	-	1	8	9
NonAIDS-related malignancies	-	2	2	4
Other unidentified causes	1	1	2	4
Total	1	14	40	55

RTI - Respiratory tract infection; GE - Gastroenteritis; RTA - Road traffic accident, HIV - Human immunodeficiency virus

Table 2: Symptomatic classification of CD4 counts of human immunodeficiency virus-infected, hospitalized, deceased patients as per the WHO clinical staging system (n = 86)

CD4 cell counts		Clinical categories of HIV infection (applicable only to HRa)								Total (Total HR ^a)
		1		2		3		4		
		Asymptomatic		Mild		Moderate		Severe		
		HRa	HURb	HRa	HURb	HRa	HURb	HRa	HURb	
CD4 test not done		-	14	1	7	5	4	26	2	59
A	> 500 cells/μL	-	17	-	2	-	-	-	-	32 (HR ^a)
										19
B	200-499 cells/μL	-	4	2	-	2	-	2	-	-- (HR ^a)
										10
C	< 200 cells/μL	-	-	-	-	4	-	52	1	6 (HR ^a)
										57
Total		-	35	3	9	11	4	80	3	56 (HR ^a)
										145
										94 (HR ^a)

HRa - HIV-related deaths, HURb -HIV-unrelated deaths

classification of these CD4 counts as per the WHO clinical staging system reveals that 19/86 (22.0%) of the patients had CD4 cell counts > 500 cells/ μ L at the time of death and that all these deaths were nonHIV-related. Only 10/86 (11.6%) cases had their cell counts between 200 and 499 cells/ μ L of which four deaths were nonHIV-related. The remaining 57/86 (66.3%) patients had CD4 counts of < 200 cells/ μ L and only one of these was a nonHIV-related death.

DISCUSSION

Due to the global HIV/AIDS epidemic, the last decade has seen a shift in mortality in the older generation to the younger generation, the complete opposite of what is normally expected.

Since 1996, while mortality rates among HIV-infected individuals have fallen with the use of highly active antiretroviral therapy (HAART) in developed nations, our institute continues to record increasing number of deaths among HIV-infected, hospitalized patients. The study period was divided into three eras according to the use of HAART. While we expected the

number of HIV-related deaths to decline in the HAART era, it was observed to rise even in the present HAART era. Considering that 88.28% of deceased patients were not even aware of their HIV-infected status before getting admitted into our institute, it is not surprising to note that the a higher number of patients are dying before their HIV diagnosis. As our Institute has not yet been recognized as a free ART center by the Government of India, most of the HIV-infected patients are not provided with free ART here. Importantly, another reason for the deaths of HIV-infected individuals is the diagnosis of HIV late in the course of infection, which results in the late initiation of HAART. Based on these and another observation that 96.6% of patients had never been treated for their HIV-infection, this study advocates methodical screening for the early diagnosis of HIV-infected individuals. With the scaling up of ART centers by the Government of India in Andhra Pradesh from three centers in 2004 to 24 in 2007, most of these infected patients, if diagnosed earlier, could have been provided with free ART that might have reduced the number of HIV-related deaths.

Contrary to general belief, due to late diagnosis and noninitiation of HAART in our study, a high number of deaths (60.8%) in the present HAART era were still due to many opportunistic infections. However, the overall number of HIV-related deaths had declined from 85.7% in the preHAART era to 61.1% in the early HAART era to 60.8% in the present HAART era. It was observed from our study that there was a high incidence of TB and pneumonia among HIV-infected, deceased patients. Even in this present HAART era, it was observed that deaths were mainly due to occurrence of more than one opportunistic infection. Thus, this study underlines the HIV-related mortality pattern and highlights the leading role of meningeal, mycobacterial and HIV-related respiratory tract infections as the causes of death.

Similar to findings from other studies,^[11-12] there has also been a considerable increase in the proportion of nonHIV-related causes of death, from 14.3% in the preHAART era to 38.9% in the early HAART era to 39.2% in the present HAART era. Increase in deaths due to hepatic disorders among nonHIV-related causes was distinct, from no case in the preHAART era to 45% in the present HAART era. This was mostly attributable to the progression of liver disease due to hepatitis B virus (HBV) or hepatitis C virus (HCV) over time (7.6%), direct liver toxicity of long-term usage of anti-tuberculosis treatment (ATT) (6.9%) or some other factor. This higher prevalence of hepatitis viral infections in the HIV-infected patients stresses the need of screening this population for HCV and HBV markers for improved clinical and therapeutic management of these coinfecting patients. Our study has shown that

trauma, especially due to road traffic accidents, which was already one of the main causes of death in the preHAART era, remains the second major cause of mortality in the era of HAART.

WHO classification of these deaths has shown that a great number of deaths among these HIV-infected, deceased patients was mainly attributable to WHO clinical stage 4 in case of HIV-related deaths. On the other hand, most of the nonHIV-related deaths were in the clinically asymptomatic stage 1 of WHO classification. Deaths during all the three eras were proportionally more often attributable to HIV-related causes and thus unlike other studies, this study has shown that AIDS-defining illnesses still continue to cause death. Even though WHO clinical stage 4 was the strongest risk factor for death, most of the nonHIV-related deaths in our study were either directly or indirectly linked to HIV infection, even if they were not classified as being due to an AIDS-defining event according to the WHO classification.

Since our study was a retrospective one, several limitations could not be avoided. Cause of death could not be verified by autopsy and since the study was a hospital-based one, deaths among HIV-infected, individuals after their discharge from the hospital could not be traced.

Due to incomplete death registration and HIV/AIDS reporting systems in India, the actual number of deaths occurring due to HIV infection is difficult to determine. Further the statistics for AIDS cases may be a poor guide to the severity of the epidemic, as in many

situations a patient will die without HIV having been diagnosed and mostly with the cause of death attributed to an opportunistic infection, such as tuberculosis.

Our study, which was taken up specifically to collect data on mortality among HIV-infected, hospitalized patients over the last 14 years, presents that opportunistic infections remain the most common cause of death even in the HAART era, suggesting that HIV-related causes will continue to be important in the future. We also report that over the years, nonHIV-related deaths of HIV-infected patients is also on the rise. Adult mortality will continue to rise unless effective treatment interventions are introduced. Our study stresses the need for early diagnosis of HIV infection in exposed persons to avoid delayed diagnosis at the AIDS stage, to develop new antiretroviral therapeutic strategies to diminish the incidence of opportunistic infections, unnecessary drug exposure and related adverse events. Furthermore, similar kinds of mortality studies need to be continuously investigated in order to identify emerging causes of death and to improve the epidemiological surveillance and case management of HIV-infected patients in the era of HAART.

REFERENCES

1. UNAIDS. Report on the Global AIDS Epidemic. Geneva; 2006. [Last accessed on 2007 Apr 2]. Available from: http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.
2. National AIDS Control Organization: HIV/AIDS epidemiological Surveillance and Estimation Report for the Year 2005. 2006. New Delhi:

Ministry of Health and Family Welfare, Government of India. [Last accessed on 2007 Apr 2]. Available from: <http://www.nacoonline.org/fnlapi06rprt.pdf>.

3. CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet* 2000;355:1158-9.
4. Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, *et al.* AIDS across Europe, 1994-98: the Euro SIDA study. *Lancet* 2000;356:291-6.
5. Lewden C, Salmon D, Morlat P, Bevilacqua S, Jouglu E, Bonnet F, *et al.* Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: Emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol* 2005;34:121-30.
6. Sani MU, Mohammed AZ, Adamu B, Yusuf SM, Samaila AA, Borodo MM. AIDS mortality in a tertiary health institution: A four-year review. *J Natl Med Assoc* 2006;98:862-6.
7. Krentz HB, Kliever G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Med* 2005;6:99-106.
8. Bane A, Yohannes AG, Fekade D. Morbidity and mortality of adult patients with HIV/AIDS at Tikur Anbessa Teaching Hospital, Addis Ababa, Ethiopia. *Ethiop Med J* 2003;41:131-40.
9. Ogun SA, Adelowo OO, Familoni OB, Adefuye OB, Alebiosu C, Jaiyesimi AE, *et al.* Spectrum and outcome of clinical diseases in adults living with AIDS at the Ogun State University Teaching Hospital. *East Afr Med J* 2003;80:513-7.
10. Groenewald P, Nannan N, Bourne D, Laubscher R, Bradshaw D. Identifying deaths from AIDS in South Africa. *AIDS* 2005;19:193-201.
11. Cohen MH, French AL, Benning L, Kovacs A, Anastos K, Young M, *et al.* Causes of death among women with human immunodeficiency virus

infection in the era of combination antiretroviral therapy. *Am J Med* 2002;113:91-8.

12. Bonnet F, Morlat P, Chêne G, Mercié P, Neau D, Chossat I, *et al.* Causes of death among HIV-infected patients in the era of highly active

antiretroviral therapy, Bordeaux, France, 1998-1999. *HIV Med* 2002;3:195-9.

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