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Editorial Review

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Word Count. Abstract=238; Text = 4,404; Tables = 3; Figures = 2; References = 96

Key Words: HIV, AIDS, HAART, antiretroviral treatment, mortality, death, Africa

Abstract

Two-thirds of the world's HIV-infected people live in sub-Saharan Africa and more than 1.5 million of them die annually. As access to antiretroviral treatment (ART) has expanded within the region, early pessimism concerning the delivery of ART using a large-scale public health approach has, at least in the short term, proved to be broadly unfounded. Immunological and virological responses to ART are similar to responses in patients treated in high-income countries. Despite this, however, early mortality rates in sub-Saharan Africa are very high; between 8% and 26% of patients die in the first year of ART, with most deaths occurring in the first few months. Patients typically access ART with advanced symptomatic disease, and mortality is strongly associated with baseline CD4 cell count <50 cells/μL and WHO stage 4 disease (AIDS). Although data are limited, leading causes of death appear to be tuberculosis, acute sepsis, cryptococcal meningitis, malignancy and wasting syndrome. Mortality rates are likely to depend not only on the care delivered by ART programmes, but more fundamentally on how advanced disease is at programme enrolment and the quality of preceding health-care. In addition to improving delivery of ART and providing this free of charge to the patient, strategies to reduce mortality must include earlier diagnosis of HIV infection, strengthening of longitudinal HIV care and timely initiation of ART. Health systems delays in ART initiation must be minimised, especially in patients who present with advanced immunodeficiency.

Keywords

HIV; AIDS; antiretroviral treatment; HAART; ART; mortality; death; Africa

Introduction

Development of highly active antiretroviral treatment (ART) in the mid-1990s revolutionised the care of HIV-infected patients and led to marked reductions in HIV-associated morbidity and mortality in many industrialised countries [1-3]. Over 10 years later, access to ART remains limited in sub-Saharan Africa and other resource-constrained settings where the need is greatest. Although only 10% of the world's population live in sub-Saharan Africa, the region is nevertheless home to around two-thirds of the world's HIV-infected people [4]. In 2007 an estimated 22.5 million adults and children in the region were living with HIV/AIDS and 1.6 million died, representing 76% of global AIDS deaths [4]. Great progress has been made in providing access to ART in sub-Saharan Africa; by April 2007 approximately 1.3 million people were receiving ART - some 28% of the 4.8 million people estimated to be in need [5]. However, in addition to much needed HIV prevention measures, ongoing expansion of capacity to effectively deliver ART long-term to large numbers of people is urgently required.

Early pessimism concerning effective delivery of ART on a large scale using a simplified public health approach has largely proven unfounded, at least in the short term. For example, ART access has been rapidly expanded on a massive scale in Lusaka, Zambia, in Abidjan, Cote D'Ivoire, and on a country-wide scale in Malawi with good early clinical outcomes [6-8]. High levels of treatment compliance and virological suppression have been achieved in both hospital-based and community-based programmes [9-11]. Meta-analyses of data from treatment cohorts have found that the efficacy of ART, as reflected by rates of viral load suppression and CD4 cell count recovery, is similar among patients treated in high-income and resource-limited settings [12, 13]. ART has been demonstrated to be a cost-effective intervention in

resource-poor settings [14-16]. Furthermore, ART was estimated to have averted 250,000-350,000 deaths in low and middle income countries in 2005 alone [17].

Despite these positive findings, data from the region suggest that early mortality rates among adults in ART programmes are high [12], contributing to substantial losses in overall patient retention [18]. The ART-LINC collaboration compared outcomes from 18 ART programmes in lower-income settings (predominantly in Africa) with those in 12 HIV cohort studies from Europe and North America [12]. This analysis found that early mortality following initiation of ART was several-fold higher among patients in resource-limited settings compared to that of patients treated in high-income settings, even after adjusting for baseline immunodeficiency [12]. High mortality rates have also been reported by individual cohorts in sub-Saharan Africa. To gain a greater understanding of this problem, we review the mortality rates, temporal distribution, risk factors and causes of death among adult patients accessing ART programmes in sub-Saharan Africa and consider possible strategies to address this.

Search strategy and selection criteria

We searched English-language publications in MEDLINE, using the terms "antiretroviral*", "HAART", "ART", "Africa", "mortality", "death". Searches were completed up to December 2007 to identify published reports from observational ART cohorts in sub-Saharan Africa; those reporting on survival proportions over time and those describing the spectrum of causes of death were selected. Additional articles were identified from references in published papers and abstracts from major international AIDS conferences in the preceding 12 months. For cohorts with multiple presentations of mortality data from different time periods, the most recent report was

used. Data from controlled clinical trials were not included in the assessment of mortality rates as these data are unlikely to be generalizable to the scale-up of ART services in the general population. Summary estimates of the hazard ratios for the association of early mortality with CD4 count and with advanced WHO stage was conducted using a random-effects model [19].

Rates and temporal distribution of mortality

Data from 18 published cohort studies containing 39,536 patients treated in countries in west, east and southern African are summarised in Table 1. Patients were mainly receiving public sector treatment. Twelve of the cohorts were based in urban settings and 6 were rural. The median baseline CD4 cell count in these studies ranged between 43 and 147 cells/μL and the median duration of follow-up ranged between 3 and 46 months. The vast majority of these patients were ART-naive and most initiated triple-drug therapy that incorporated two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor.

Using product-limit methods, the 12-month survival proportion in patients who were not lost to follow-up ranged between 0.74 and 0.92, with the greatest burden of mortality occurring during the initial months of ART (Table 1). Heterogeneity in outcomes between programmes may reflect differences in both baseline patient characteristics and programme characteristics [20]. Survival proportions were reported at both 12 and 24 months of follow-up in 9 studies and these showed that mortality accruing in the second year of ART was much less than that in the first.

Longitudinal changes in mortality rates were calculated in some studies [21-23]. In a South African cohort, the rate in the first 4 months of ART was 19.1 deaths/100 person-years (100PYs), decreasing to 2.9 deaths/100PYs beyond 4 months and 1.3

deaths/100PYs beyond one year [22]. A similar pattern of mortality was observed in another South African cohort [10] and in both studies rates of viral load suppression <400 copies/ml were high (>93% and >89%) [10, 22]. In other studies, however, substantial mortality accrued between 12 and 24 months of follow-up [23, 24]. Mortality rates in a cohort in Senegal, for example, were 12.5, 6.6 and 4.5 deaths/100PYs in the first, second and third years of treatment respectively [23]. The higher mortality rates beyond the first year of ART in these studies might be explained by lower rates of virological suppression and associated poor immunological recovery, for example [23, 25].

In all 20 cohorts (Table 1), the mortality proportions at 12 months of follow-up (range 8% - 26%) exceeded ART-LINC summary mortality estimate of 6.4% (95% CI 5.1-7.7) [12]. The ART-LINC estimate was derived from 4,810 patients receiving ART between 2001 and 2004 in resource-limited settings and included 3,449 patients in sub-Saharan Africa. Since then, there has been a more than 10-fold increase in the number patients receiving ART in the region whose outcomes have been published. The current literature included in this review suggests that further updated collaborative analyses might show a substantially higher early mortality rate than initially derived from the original ART-LINC cohorts.

Reliability of mortality data

There may be a tendency for mortality rates in the published literature to be lower than those observed in most large-scale ART programmes that haven't published their data because of selective reporting from well-run ART programmes in urban settings with more intensive service delivery and fewer resource constraints. The quality of mortality data is unclear in some reports; mortality is likely to be underestimated to a

degree by most cohorts due to misclassification of unascertained patient deaths as 'losses to follow-up'. The greater the loss to follow-up rate the greater the potential for misclassifications. Rates of loss to follow-up differed greatly between studies, ranging between 2% and 24% (Table 1) and unrecorded mortality among these patients may only be detected by intensive active follow-up [12, 26-28]. The efficacy of active follow-up may vary considerably between cohorts and details concerning the intensity of patient tracing are infrequently reported.

Analysis of the characteristics of losses to follow-up may provide insights into the reliability of programme mortality data. ART cohorts in South African and Cote-D'Ivoire ART with good ascertainment of outcomes found that whereas most deaths occurred in the first months of ART in patients with the lowest baseline CD4 cell counts, losses to follow-up were evenly distributed over time and were not associated with CD4 cell counts [8, 22]. Thus, if a programme reports a high loss to follow-up rate in the first months of ART among patients with the lowest baseline CD4 cell counts, this may be suggestive of high rates of unascertained deaths in this period.

In-programme mortality prior to ART initiation

Very high mortality rates recorded during the initial months of ART may reflect a high mortality rate among individuals who are eligible for ART but have yet to start treatment. This includes individuals enrolled in care who are awaiting treatment as well as those elsewhere in the health care system awaiting referral to HIV treatment services.

Two cohorts in South Africa have reported on deaths occurring in the interval between enrolment of patients into the ART programme and initiation of treatment [21, 22, 29]. In the Cape Town study, this interval of approximately 30 days permitted

thorough investigation and treatment of coinfections and preparation of patients for ART, the mortality rate in this interval was very high (approximately 30 deaths/100PYs). Deaths occurring in this short period accounted for 67% of deaths within the first three months from programme enrolment [21]. Similarly, in the Free State cohort, 87% of deaths occurred among patients prior to ART initiation [29]. Thus, it is likely that even short delays in ART initiation are associated with considerable pre-treatment mortality risk. Thus, delays in patient referral, waiting lists for ART initiation and the time taken to prepare patients to start life-long treatment are likely to contribute to overall mortality risk.

Such delays and associated mortality are not typically reported by cohorts and so the optimum period for preparation for ART is therefore unclear. How to balance the need for thorough preparation of patients for life-long therapy with the high risk of death among individuals waiting to start therapy requires urgent research attention. Clearly flexibility in the timing is needed as many patients with advanced immunodeficiency need therapy urgently.

Risk factors for mortality

In the cohorts summarised in Table 1, low baseline CD4 cell count was a strong risk factor for early mortality in all 17 of the 20 cohorts with available data. The summary hazard ratio for the association between CD4 count <50 cells/μL (versus CD4 >50 cells/μL) was 2.5 (95% CI, 1.9-3.2) in studies with appropriate data [10, 11, 21, 24, 25, 30, 31]. A graded association with CD4 cell count was reported in some studies [6, 12, 22] (Figure 2a) but baseline viral load was not found to be an independent risk factor in any of the studies.

Symptomatic disease (WHO stages 3 and 4) was associated with mortality in some [6, 8, 12, 21, 32] but not all [11, 23] studies (Figure 2b), possibly reflecting differences in the accuracy of clinical staging or homogeneity of cohorts with respect to this variable. WHO stage 4 disease, however, was found to be a strong predictor of mortality in all studies reporting on this [6, 21, 22, 24, 30, 33-37]. In three studies comparing patients with WHO stage 4 disease at baseline with those with WHO stages 1-3, WHO stage 4 was associated with more than a doubling in the hazard of death (summary hazard ratio, 2.2; 95% CI, 1.5-3.2) [10, 22, 30].

Low body mass index [6, 8, 23, 24, 35, 36, 38, 39] and anaemia [6, 8, 23, 36, 39, 40] were independently associated with mortality in some studies. Anaemia may be associated with a variety of conditions such as extrapulmonary TB, gastrointestinal Kaposi's sarcoma and severe malnutrition or may reflect the direct effects of advanced HIV on haematopoiesis. Male sex was associated with poorer survival in 6 studies [6, 8, 10, 22, 24, 37]; the reasons for this are unknown, but could relate to differences in health seeking behaviour or poorer treatment adherence among men [41].

In contrast to data from high-income settings [2], increasing age was associated with higher mortality risk in only one cohort [8]. The lack of an association may reflect the younger age and narrower age distribution of patients receiving ART in Africa. Alternatively, this may simply reflect the relatively short duration of follow-up in these studies since immunological recovery during the first 4 months of treatment is not age-dependent [42-44].

Patients with TB at enrolment to ART programmes have a high mortality risk [45, 46] and yet paradoxically TB and TB disease activity have not been found to be independent risk factors for mortality during ART [6, 35, 47]. Many deaths, however,

may occur before ART is initiated [47, 48] and also much of the true burden of disease may remain unascertained [49]. In contrast, detectable cryptococcal antigen in serum was an independent predictor of early mortality in a rural cohort in Uganda [50].

Although the type of ART regimen and the type of healthcare facility (primary versus secondary) have not been found to be associated with mortality [8, 12, 23-25], programmes in which patients were required to pay for medication were associated with a 4-fold greater mortality risk [12]. This concurs with the findings of a meta-analysis of treatment outcomes in resource-poor settings; due to limitations in finances, patients who had to pay part or all the cost of therapy had an approximately 30% lower probability of having an undetectable viral load at 6 and 12 months compared to patients whose medication was supplied free of charge [13]. In keeping with this, ART adherence has been found to be predictive of mortality [39, 41].

Risk factors for mortality may alter during the course ART. While mortality during the first 4 months of ART in one cohort was associated with patient characteristics at baseline, mortality beyond this time-point was only associated with the updated absolute CD4 cell count at 4 months and with failure of viral load suppression [22]. These data suggest that the key long-term determinant of mortality is the response to ART as also suggested by more recent findings from Abidjan [38].

Causes of death

Five observational cohort studies from a range of countries in sub-Saharan Africa report on the spectrum of causes of early deaths [21, 23, 35, 39, 51]. The most important causes of death reported include tuberculosis, acute sepsis, cryptococcal

meningitis, malignancies (especially Kaposi's sarcoma) and chronic diarrhoea or wasting syndrome.

Diagnostic facilities are limited in many settings, especially for rural cohorts, and no identifiable cause could be identified in a proportion of deaths. No systematic post-mortem studies of deaths during ART have been reported and the overall data are therefore limited. Deaths in the first weeks of ART are likely to be caused by conditions that are either pre-existing at programme enrolment or new conditions arising in the context of persisting immunodeficiency. In one study causes of death during the first 4 months of ART were found to reflect those occurring just prior to ART with the addition of deaths due to immune reconstitution disease associated with cryptococcal meningitis and tuberculosis [21].

TB was among the two leading causes of death in 4 of the 5 cohorts, accounting for up to 21% of deaths [21, 23, 39, 51]. However, TB is likely to be an under-reported cause of death. Post-mortem studies have found in the pre-ART era that up to 54% of untreated patients dying from AIDS in Africa have evidence of occult disseminated TB [52, 53] and that this may be a common underlying cause of 'slim disease' [54]. Although wasting syndrome (defined as wasting with unexplained fever and / or chronic diarrhoea) was specifically reported as an important cause of death among in only one cohort [21], this may have been more common as 'chronic diarrhoea' was also reported as a common cause [35] and wasting was a common risk factor for mortality in many cohorts as described earlier.

The contribution of TB immune reconstitution disease to mortality has yet to fully emerge [55]. While most cases appear to be self-limiting, some are severe and deaths have been reported from cohorts in South Africa and Thailand [56, 57]. However, background mortality rates were also very high among TB patients who did not

develop this complication and neither study found immune reconstitution disease to be associated with a significant excess mortality risk. Larger prospective studies are needed to clarify this issue.

Cryptococcal meningitis was among the two leading causes of mortality in 4 of the 5 cohorts [21, 23, 39, 51], accounting for up to 20% of deaths. Many of the deaths from cryptococcal disease in a South African cohort were attributed to immune reconstitution disease [58] and this was a more common cause of death than TB immune reconstitution disease [21]. Many patients developing this complication have previously been treated for cryptococcal meningitis with fluconazole monotherapy [21, 58, 59]. Although this is the standard of care throughout much of Africa, fluconazole is a fungistatic drug with far less efficacy than amphotericin in clearing the organism from cerebrospinal fluid (CSF) and especially so in the context of fluconazole resistance [60]. Persistence of cryptococci or cryptococcal antigen in the CSF is likely to predispose patients to immune reconstitution disease, which has a high mortality risk [58, 59, 61, 62].

Kaposi's sarcoma and other malignancies were among the three leading causes of death in 3 of the 5 cohorts [21, 35, 51], accounting for up to 14% of deaths. Acute sepsis was another important cause of mortality identified in some cohorts despite widespread use of trimethoprim-sulphamethoxazole (co-trimoxazole), [21, 39]. Respiratory disease, acute gastroenteritis or systemic sepsis with no identifiable focus were the most common forms of sepsis and collectively sepsis accounted for up to 19% of deaths. *Pneumocystis jiroveci* pneumonia was reported in up to 9% of deaths in two Ugandan studies [39, 51] but the basis for these diagnoses is not clear.

Microbiological causes of death from acute bacterial infections have not been reported. In studies of acute sepsis during co-trimoxazole prophylaxis in Abidjan,

Cote D'Ivoire [31, 63-65], the predominant pathogens were non-typhoidal salmonella, *Escherichia coli*, *Shigella* spp and *Streptococcus pneumoniae*. Although high rates of co-trimoxazole resistance among non-typhoidal salmonellae and pneumococcal isolates have been reported in Uganda and Malawi [66, 67], prophylaxis with this drug is still effective in reducing mortality in both countries [67, 68].

The most widely used regimens in Africa include stavudine (d4T) and nevirapine, which have the potential for serious toxicity including hepatotoxicity, Stevens-Johnson syndrome and lactic acidosis [69, 70]. However, drug toxicity does not appear to be a major cause of early mortality. Among 226 deaths reported by 4 cohorts, 7 (3.1%) were attributed to ART toxicity [10, 21, 23, 51]. These were comparatively well-resourced programmes with access to biochemical laboratory monitoring; mortality rates may be higher where monitoring is not possible. Analysis of the temporal distribution of drug substitutions due to toxicity shows that nevirapine and zidovudine (AZT) toxicity occur during the first few months of ART whereas stavudine (d4T)-associated toxicity such as lactic acidosis occurs cumulatively from around 6 months onwards [71, 72]. Thus, the contribution of drug toxicity to overall mortality may change over time and may proportionately increase as the risk of opportunistic infections diminishes after the first 6 months of ART.

Deaths associated with nevirapine-induced hepatotoxicity have been reported from South Africa when used concurrently with rifampicin [69] but more data from large cohorts are needed to quantify the risk of concurrent TB treatment. In contrast, efavirenz is very well tolerated [64] and concurrent use of rifampicin and efavirenz in cohorts in South Africa did not result in mortality [47, 73].

Strategies to reduce mortality

Early mortality rates are strongly associated with the degree of immunodeficiency in patients at the time they enrol into ART programmes. Strategies to reduce mortality must therefore focus not only on delivery of care within ART programmes but more fundamentally they must promote early HIV diagnosis and improved pre-ART HIV care (Table 2).

Early HIV diagnosis and longitudinal HIV care (Table 2). Patients entering ART programmes in sub-Saharan Africa have typically had their HIV infection diagnosed following presentation to the health services with advanced symptomatic disease. Such patients have high mortality risk in the period leading up to ART as well as during early ART (Figure 2). Provision of accessible and user-friendly services for serial voluntary counselling and testing (VCT) and CD4 cell count estimation is vital to promote early HIV diagnosis and assessment of ART eligibility. Early diagnosis and initiation of appropriate longitudinal care would probably be associated with much lower mortality risk in the period leading up to ART as well as during the initial months of ART (Figure 2).

Similar to the management of many chronic diseases in Africa, longitudinal care from the time of HIV diagnosis until requirement for ART is often poor. Thus, even those patients who are diagnosed with relatively early HIV infection are often lost to medical care only to later re-enter medical services with advanced disease. Longitudinal care must be strengthened and should include screening for and treatment of opportunistic infections, initiation of co-trimoxazole prophylaxis, isoniazid preventive therapy (IPT), reproductive health care, and serial CD4 cell count

assessment until eligibility for ART is reached. This will require strengthening of HIV care services and more widespread availability of CD4 cell count measurement.

Prevention, screening and management of opportunistic infections are needed throughout the HIV care pathway. Co-trimoxazole prophylaxis should be initiated after HIV diagnosis and continued during ART [74] as this is associated with additional gains in life expectancy [16, 75]. Isoniazid preventive therapy (IPT) is an underused intervention in Africa [76]. Key obstacles include the difficulty of excluding active TB in patients with moderate or advanced immunodeficiency. IPT would therefore be more easily used among patients with less advanced disease and yet adherence to treatment among such patients and the infrastructure to efficiently deliver and monitor IPT remain a challenge.

Delivery of ART (Table 2). National ART programme criteria for ART eligibility require ongoing re-evaluation. Initial WHO guidelines (2002) for resource-poor settings recommended treatment only for those with stage 4 disease or a CD4 cell count <200 cells/μL [77]. These were modified in 2003 [78] and in 2006 [79], bringing them closer to guidelines for high-income settings. However, some national programmes have retained earlier more restrictive eligibility criteria. For example South Africa's national programme has retained the 2002 WHO recommendations despite the fact that under these guidelines much HIV-associated morbidity and mortality occurs prior to eligibility for ART [80, 81]. Studies of when to initiate ART in resource-limited settings are needed. There are currently two trials which aim to address this issue in Cote D'Ivoire and Haiti [82, 83].

As soon as patients are identified as being eligible for ART, prompt referral for ART should be made. Where possible, waiting lists for ART should be minimised and

those with highest risk might be prioritised [21, 22]. Supply of medication free of charge to the patient is key [12, 13]. While some international agencies advocate the privatisation of health services and private financing of health services through user fees, this is very unrealistic for most patients living in resource-limited settings who require life-long ART.

The use of regimens in Africa with higher toxicity than those used in the west is due to their low cost and the availability of fixed dose combination formulations. While provision of treatment to the millions of people living with HIV/AIDS who do not yet have treatment access should be the priority, implementation of less toxic regimens is nevertheless desirable.

Although laboratory monitoring and use of point-of-care lactic acid meters may help detect and manage drug adverse effects, no data yet exist to indicate that provision of such monitoring reduces mortality risk. This issue is being studied in the DART (Development of AntiRetroviral Therapy in Africa) trial [84]. Braitstein et al. found no impact of viral load monitoring on mortality in the first year of ART [12]. However, any benefits are only likely to occur during longer term treatment rather than during the first year.

Effective strategies to screen for active TB at entry to ART programmes need to be developed, including detection of the high prevalence of both clinical and sub-clinical disease [45, 46, 85, 86]. Prompt initiation of TB treatment may reduce patient mortality and reduce risks of nosocomial TB transmission. The optimal timing for initiation of ART among TB patients remains unknown and randomised controlled trials of early versus delayed initiation of ART are currently underway [87]. Similar to data from the UK [88, 89] observational data from South Africa strongly suggest that expedited initiation of treatment is needed among those with baseline CD4 cell counts

<100 cells/μl in this setting in view of their exceptionally high mortality rate while awaiting ART [90, 91].

Randomised controlled trials are needed to define both the optimal management of moderate and severe TB immune reconstitution disease [55] and to assess the efficacy of concurrent isoniazid prophylaxis in reducing the high rates of TB that persist during ART [45, 92]. In addition, the utility of pre-ART screening for and management of asymptomatic cryptococcal antigenaemia has yet to be defined [50]. Provision of a better standard of care for cryptococcal meningitis using amphotericin might be considered in settings with adequate facilities to administer this drug safely. Guidelines for the prevention, diagnosis and management of cryptococcal immune reconstitution disease are also needed.

Despite early reports that treatment adherence does not pose a major barrier to treatment success in sub-Saharan Africa [93], more recent research suggests that overall adherence rates and retention on ART in sub-Saharan Africa are quite variable and often poor [18, 94]. Adherence is predictive of mortality [41] and development of locally appropriate strategies to promote adherence are central to the success of ART programmes. Research is also needed to determine what cadre of health-care professional is needed to deliver ART effectively with good outcomes.

Conclusions

High early mortality within ART programmes in sub-Saharan Africa has emerged as a key challenge. Between 8% and 26% of patients die in the first year of ART and key issues surrounding this problem are summarised in Table 3. Early death rates threaten the credibility of ART delivery among communities accessing such therapy and among health workers who are responsible for providing this care. While many

factors are likely to contribute to this mortality, an over-riding issue is that patients typically present for ART once they have developed advanced symptomatic disease. Much may be done within ART services to potentially reduce this mortality by providing medication free of charge, implementing effective screening, treatment and prevention of opportunistic infections, reinforcing treatment adherence and using regimens with low toxicity. However, despite optimising ART delivery, a proportion of early deaths among patients with very advanced disease is not likely to be preventable. Thus, a more fundamental issue and the greater challenge is the need for early HIV diagnosis and provision of appropriate longitudinal HIV care prior to ART eligibility.

Acknowledgements

SDL is funded by the Wellcome Trust, London, UK with grant 074641/Z/04/Z. RW is funded in part by the National Institutes of Health, USA, RO1 grant (A1058736-01A1) and a CIPRA grant 1U19AI53217-01. XA is funded in part by the ANRS (Agence nationale de recherches sur le SIDA et les hépatites virales, Paris, France (grant ANRS 1269).

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Table 1. Mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa

Study[a]	Year	Country	n	Setting	Median(IQR) CD4 count (cells/µL)	Median follow-up (months)	On-treatment survival proportion		Survival proportion at 12 months of ART		Temporal distribution of deaths	Losses to follow-up
							12m	24m	CD4<50[a]	CD4>50[a]		
Weidle [25]	2002	Uganda	476	Urban	73 (15-187)	3	0.74	-	0.67	0.82	57% deaths in first 3 m	24%
Djomand [30]	2003	Cote D'Ivoire	480	Urban	[37% <50]	6	0.84	-	-	-	-	Not reported
Seyler [31]	2003	Cote D'Ivoire	101	Urban	135 (55-221)	17	-	-	0.80	0.96	50% deaths in first 3.3 m	Not reported
Coetzee[10]	2004	S. Africa	287	Urban	43 (13-94)	13.9	0.86	0.86	0.82	0.91	71% deaths in first 3 m	2%
Laurent [40]	2005	Senegal	176	Urban	144 (58-224)	30	-	0.84	-	-	Median time to death 9 m	Not reported
Wester [11]	2005	Botswana	153	Urban	96 (33-165)	12	0.85	-	0.76	0.90	Majority of deaths in first 6 m	8% at 12 m[c]
Lawn[22]	2006	S. Africa	927	Urban	100 (47-160)	7	0.91	0.90	0.85	0.94	87% between enrolment and first 4 m ART	2%
Ferradini [24]	2006	Malawi	1308	Rural	112 (59-176)	8.3	0.81	0.72	-	-	77% deaths in first 6 m	5% at 12 m[c]
Etard [23]	2006	Senegal	404	Urban	128 (54-127)	46	0.88	0.83	0.80	0.90	50% deaths in first 12 m	2% at 12 m
Stringer [6]	2006	Zambia	16,198	Urban	147 (69-268)	7	0.82	-	0.80	-	71% within first 3 m	Not reported
Zachariah [35]	2006	Malawi	1507	Rural	123 (58-206)	10[b]	0.87	-	0.77	0.92	61% in first 3 m; 79% in first 6m	3%
Makombe [95]	2007	Malawi	4580	Rural	-	12	0.87	-	-	-	>90% in first 6 m	11% at 12 m
Bajunirwe [37]	2007	Uganda	398	Rural	-	-	0.76	0.71	-	-	-	Not reported
De Iaco [32]	2007	Burkina Faso	315	Urban	97	18	0.69	0.83	-	-	Mortality rate 2.3-fold higher in first 6 m ART	Not reported
Johannessen [36]	2007	Tanzania	336	Rural	-	12	0.74	0.68	-	-	60% deaths in first 3 m	11%
Kambugu [51]	2007	Uganda	559	Urban	104	12	0.86	-	-	-	73% in first 6 m	Not reported
Moore [39]	2007	Uganda	1120	Rural	127	24	0.92	0.91	-	-	68% in first 6 m	Not reported
Toure [8]	2008	Cote D'Ivoire	10,211	Urban	123 (47-207)	7.7	-	-	0.76	>0.86	75% in first 4.6 m	19% total losses at 12 m[c]

[a]CD4 cell counts in cells/µL. [b]Mean (SD). [c] Kaplan-Meier estimate. m = months.

Table 2. Potential strategies to reduce mortality during antiretroviral treatment (ART)

A. Early HIV diagnosis and longitudinal HIV care pre-ART

1. Promote HIV testing and early diagnosis
2. Strengthen long-term HIV care services prior to ART eligibility
3. Optimise prevention, screening and treatment of opportunistic infections
4. Provide longitudinal clinical and CD4 cell count monitoring to facilitate timely initiation of ART
5. Minimise health system delays in ART initiation

B. Delivery of ART

1. Provide ART without charge to the patient
2. Use updated WHO guidelines for ART eligibility
3. Develop locally effective ART adherence strategies
4. Use ART regimens with lower toxicity
5. Opportunistic infections
    a. Co-trimoxazole prophylaxis during ART
    b. Optimise screening for TB at ART programme entry
    c. Optimise diagnosis and management of TB immune reconstitution disease
    d. Prevent nosocomial transmission of TB
    e. Consider concurrent isoniazid preventive therapy (IPT) during ART to reduce long term TB incidence (trial data awaited)
    f. Optimise prevention, diagnosis and treatment of cryptococcal meningitis and immune reconstitution disease
6. Use of laboratory monitoring
    a. Laboratory monitoring for drug toxicity
    b. Define appropriate strategies for monitoring response to ART

Table 3 Summary of key issues

Summary points

- Although virological and immunological responses to ART are similar in patients living in high-income and resource-limited countries, early mortality rates are much higher
- 9-26% of patients die during the first year of ART in sub-Saharan Africa.
- Most deaths occur in the first few months of ART
- A high loss to follow-up rate may conceal true mortality rates
- High mortality rates during early ART also reflect high mortality rates in the period preceding ART.
- Key risk factors for early mortality include low CD4 cell count, advanced clinical stage of disease, and the need for patients to pay for treatment.
- Early deaths largely reflect the spectrum of causes of death prior to ART initiation plus immune reconstitution disease.
- Common causes of death are tuberculosis, acute sepsis, cryptococcal meningitis malignancies and wasting syndrome.
- Drug adverse effects are a relatively minor cause of early mortality.
- Strategies to reduce early mortality include promotion of early HIV diagnosis, strengthening of the patient care pathway pre-ART, timely initiation of ART, provision of ART free of charge to the patient, adherence support, and optimal prevention, screening and management of opportunistic infections.

Figure Legends

Figure 1. Kaplan Meier plot showing survival proportion over 21 months among patients (n=1235) from the time of entering a community-based antiretroviral treatment (ART) programme in South Africa. The period covered includes the interval between programme enrolment and ART initiation – a median of 33 days. The survival proportions are shown according to (a) baseline CD4 cell count and (b) baseline WHO clinical stage. The graphs show the strong unadjusted association between CD4 cell count, WHO clinical stage and mortality risk in the first year of ART and the low mortality risk in the second year. Data adapted from reference [22].

Figure 2. Hypothetical graph showing relative mortality risk (95% CI) among patients accessing ART with late HIV diagnoses and advanced symptomatic disease (diamonds) versus mortality rates among patients whose HIV was diagnosed early and who received appropriate longitudinal HIV care and timely referral for ART (squares). Mortality risk is shown broken down by period: pre-ART (the interval between enrolment in the ART programme and the time ART is started), early ART (first 4 months of ART) and late ART (beyond 4 months of ART). Data on patients with late diagnoses are based on reference [22] and data from patients with early diagnoses and care are hypothetical, being based approximately on data from references [22, 81, 96].