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Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings

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Abstract

Purpose of review—We review recently published literature concerning early morbidity and mortality during antiretroviral therapy (ART) among patients in resource-limited settings. We focus on articles providing insights into this burden of disease and strategies to address it.

Recent findings—In sub-Saharan Africa mortality rates during the first year of ART are very high (8%-26%), with most deaths occurring in the first few months. This compares to 3%-13% in programmes in Latin America and the Caribbean and 11%-13% in South-East Asia. Risk factors generally reflect late presentation with advanced symptomatic disease. Key causes of morbidity and mortality include tuberculosis, acute sepsis, cryptococcal meningitis, malignancy, wasting syndrome/chronic diarrhoea. Current literature shows the fundamental need is for much earlier HIV diagnosis and initiation of ART. In addition, further studies provide data on the role of screening and prophylaxis against opportunistic diseases (particularly TB, bacterial sepsis and cryptococcal disease) and the management of specific opportunistic diseases and complications of ART. Effective and sustainable delivery of these interventions requires strengthening of programmes.

Summary—Strategies to address this disease burden should include earlier HIV diagnosis and ART initiation, screening and prophylaxis for opportunistic infections, optimised management of specific diseases and treatment complications, and programme strengthening.

Keywords

HIV; antiretroviral; mortality; death; morbidity; resource-limited; low-income

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Introduction

In 2007 an estimated 33 million people worldwide were living with HIV and 2.0 million died [1]. Over 90% of infected people were in resource-limited settings, with sub-Saharan Africa accounting for 22.0 million of these and South & South-East Asia, Latin America and East & Central Europe accounting for a further 4.2 million, 1.7 million and 1.5 million people, respectively [1]. Following the commitment of United Nations member states to provide universal access to prevention, treatment, care and support by 2010, substantial progress has been made in scaling up antiretroviral treatment (ART) [2]. By the end of 2008, between 3.8 and 4.3 million people in resource-limited settings were estimated to have started ART, with sub-Saharan Africa accounting for approximately 3.0 million of these [3].

One of the key clinical and programmatic challenges to scale-up of ART in resource-limited settings is the very high rates of mortality and morbidity within the first year of treatment [4,5**,6**]. In this article, we review recent literature concerning this issue in adult patients. A large proportion of the literature arises from studies conducted in sub-Saharan Africa which has borne the brunt of the epidemic. However, we acknowledge that there is likely to be considerable geographical variation in the magnitude, causes and potential solutions to this problem.

Mortality

Considerable literature has now accumulated concerning the rates, risk factors and temporal distribution of mortality in ART programmes, but data on causes of death are comparatively scarce.

Mortality risk—A study published in 2006 by the Antiretroviral Therapy in Low Income Countries (ART-LINC) Collaboration was one of the first studies to highlight the disproportionately high mortality of patients treated in resource-limited settings compared to those treated in high-income settings [4]. Despite similar immunological and virological responses to ART, patients treated in low-income settings had a several-fold greater risk of death in the initial months of treatment, even after adjustment for baseline characteristics [4].

A subsequent review of data from sub-Saharan Africa included 18 ART cohort studies published between 2002 and 2008 [5**]. These cohorts had median baseline CD4 cell counts ranging between 43 and 147 cells/μL and represented almost 40,000 patients. Substantial mortality accrued in each of these cohorts; Kaplan-Meier estimates ranged between 8% and 26% during the first year of ART and only two cohorts reported estimates of <10%. These high rates may even be underestimates as a recent meta-analysis confirms earlier reports that in some cohorts in sub-Saharan Africa a substantial proportion of patients initially classified as ‘lost to follow-up’ have actually died [7].

Tuboi and colleagues reported on mortality in 7 ART sites in Latin America and the Caribbean [6**]. Median baseline CD4 cell counts in these cohorts ranged from 79 cells/μL to 163 cells/μL. Overall mortality at one year was 8.3% (95%CI, 7.6-9.1%), but ranged from 2.6% to 13.0% [6**]. In South-East Asia, the national ART programme in Thailand treated over 58,000 patients in 839 health care facilities between 2002 and 2007 and reported a one year mortality of 11% [8**]. This is similar to a rate of 13% in a single cohort in neighbouring Cambodia [9]. Thus, mortality rates in ART programmes in resource-limited settings are higher than in industrialised countries, but are heterogeneouswith generally much higher rates in sub-Saharan Africa compared to other regions [5**].

Temporal distribution of mortality—In most cohorts mortality risk is substantially higher in the first few months of ART and especially in those with the greatest overall cumulative mortality [5**, 6**, 8**]. This is illustrated by comparison of mortality risk in cohorts in South Africa and Switzerland (Figure 1) [10]. Compared to the Swiss cohort, those treated in South Africa had more advanced immunodeficiency at baseline and yet similar virological and immunological responses to ART. It is clearly seen that the great disparity in mortality risk was particularly marked within the first 3-6 months of treatment (Figure 1).

The immunological response to ART is the key modifiable variable that is likely to explain temporal changes in mortality risk [11**]. In a study from South Africa, changes in CD4 cell counts measured every 4 months during ART were directly related to changes in mortality risk (Figure 2a). Mortality rates decreased rapidly as CD4 cell counts increased during early ART. However, once CD4 cell counts exceeded a threshold of 200 cells/μL, no further significant reductions in mortality were observed during ongoing CD4 count recovery [11**]. Those with poor CD4 cell recovery, however, remained at high mortality risk.

Mortality risk factors—Baseline risk factors for death are generally indicative of advanced immunodeficiency – low blood CD4 cell counts, advanced WHO clinical stage of disease, low body mass index and anaemia [4,5**,6**, 8**, 13]. Patients enrolling in a South African ART programme with CD4 cell counts <100 cells/μL had approximately twice the cumulative mortality risk of patients enrolling with CD4 counts >100 cells/ μL (Figure 3). A key overall conclusion of these studies is the need to provide ART to patients earlier in the disease course. Confirming the findings of previous publications [5**], recent studies have also specifically highlighted men as having higher risk of early mortality compared to women, which is only in part explained by late presentation [8**, 14, 15].

The need to pay for treatment is another strong predictor of poor treatment outcomes and it is clear that provision of free treatment is essential [4, 16, 17]. Macro-economic factors may also be important, with lower national gross domestic product (GDP) per capita being broadly associated with poorer treatment outcomes (Figure 4). During the initial months of ART in patients with advanced immunodeficiency, medical management can be complex and resource-intensive. Thus, mortality rates may in part be higher in resource-constrained environments as a result of limitations in healthcare provision.

Causes of death—Very few data are available concerning the key causes of death during early ART and these data are largely based on clinical assessments rather than post-mortem examinations. Comprehensive studies of the causes of death in different geographical regions are needed. In cohort studies from sub-Saharan Africa, the most commonly identified causes of death were tuberculosis (TB), cryptococcal meningitis, acute sepsis, Kaposi's sarcoma (KS) and wasting syndrome / chronic diarrheoa [5**,19*]. In Haiti wasting syndrome was by far the commonest cause [20, 21]. In India, most deaths were reported as being due to TB, *Pneumocystis jirovecii* pneumonia, cerebral toxoplasmosis and cerebrovascular disease [22].

Patients with prevalent TB at ART initiation have high mortality risk [23-26]. However, a study from South Africa suggested that prevalent TB was not an independent risk factor for death but might simply reflect an association with advanced immunodeficiency in that setting [27*]. While this is consistent with data from other African cohorts [28, 29], these analyses may fail to account for deaths occurring very early during TB treatment prior to ART initiation and also for the high burden of TB in this patient group that remains unascertained [30].

Consistent with previous data from Africa [23, 24], a study from Haiti found that patients who develop TB during the first 3 months of ART have high (27%) mortality risk during the first year of ART [25]. This study also reported that the mortality risk of such patients greatly exceeded that of a comparator group consisting of pooled data from patients with either prevalent TB at baseline or incident TB presenting after 3 months of ART. Selection and survival biases, however, may in part account for this apparent difference [31].

It has been speculated that immune reconstitution disease might be associated with increased mortality risk although it should be borne in mind that this complication develops in those with the most advanced immunodeficiency who have high pre-existing risk. Overall mortality associated with TB immune reconstitution disease, however, appears to be low [19*,32]. Even among patients with involvement of the central nervous system, just 3 of 23 (13%) of patients died during 6 months follow-up in a recent study from South Africa, although some were lost to follow-up [33]. In Uganda where KS-associated immune reconstitution disease is relatively frequent, it is rarely life-threatening [34]. Cryptococcal meningitis and cryptococcal immune reconstitution disease have been highlighted as important causes of mortality [19*,35-38]. Cryptococcal antigenaemia present at baseline has been found to be an independent risk factor for mortality in a study from South Africa [39*], potentially providing a means to direct pre-emptive treatment.

Morbidity

Key causes of serious morbidity are likely to largely reflect the causes of death described above and are likely to vary substantially between geographical regions. Detailed studies of morbidity during ART, however, are relatively few with the exception of TB.

Bacterial sepsis—In a West African study cohort with a median baseline CD4 cell count of 252 cells/μL, the two key causes of severe morbidity were identified as TB and invasive bacterial infections [40]. Bacterial diseases were predominantly episodes of pneumonia, bacteraemia, enteritis and pyelonephritis and the most commonly isolated pathogens were *Streptococcus pneumoniae*, non-typhoidal *Salmonella* and *Escherichia coli* [40]. Gastrointestinal mucosal dysfunction, which has emerged as an important component of HIV pathogenesis [41], might serve as an important factor underlying systemic gram-negative sepsis as well as wasting syndrome.

Tuberculosis—TB incidence rates are very high during the initial months of ART and decrease with increasing duration of treatment [23, 24, 42-44] (Figure 5). Although overall rates are much higher in resource-limited settings, the proportionate reduction in rates during ART is similar in high- and low-income settings [44]. In a South African study, TB risk was strongly associated with changes in CD4 cell counts measured serially during ART [12**]. The risk was almost 10-fold higher when patients had CD4 counts <100 cells/μL compared to when counts exceeded >500 cells/μL (Figure 2b) [12**]. In contrast to mortality (Figure 2a), substantial rates of TB persisted at CD4 counts of 200-500 cells/μL (Fig 2b).

This South African study also found that during long-term ART, there was a substantial excess TB incidence rate (1.7-fold) during the first 4 months of ART that was not explained by CD4 cell counts and other covariates. From these data, the authors reasoned that approximately 40% of the TB cases presenting in the first 4 months of ART were likely to be attributable to immune-mediated ‘unmasking’ of sub-clinical TB that was not recognised at baseline [12**, 45]. This is supported by subsequent findings in the same cohort that systematic culture-based screening detected a very high prevalence (25%) of sputum culture-positive disease at baseline [46*]. Much of this disease was sub-clinical or pauci-symptomatic.

Immune reconstitution disease—In addition to TB, a range of other opportunistic infections is associated with development of immune reconstitution disease. In a prospective South African cohort with a median baseline CD4 cell count of 115 cells/μL, 10% (n=44) of patients developed immune reconstitution disease during the first 6 months of ART [47*]. Almost half were associated with TB and a majority of the remainder were associated with cutaneous abscesses and folliculitis, varicella zoster, herpes simplex, cryptococcal meningitis, molluscum contagiosum and Kaposi's sarcoma. Although most cases were mild, one quarter of cases required hospital admission and two (4.5%) resulted in death (one case of TB and one case of cryptococcal disease) [47*]. The overlap between paradoxical immune reconstitution disease in patients with MDR-TB has been highlighted in South Africa [48]; this complicates both diagnosis and management.

Higher rates of morbidity and mortality in low-resource settings

Much higher rates of early morbidity and mortality among patients receiving ART in resource-limited settings compared to high-income settings are only partially explained by the presentation of patients with more advanced immunodeficiency [4-6, 8]. This may reflect much higher event frequencies during the natural history of HIV in resource-limited settings [49]. For example, in a South African natural history cohort, patients with CD4 cell counts in the range 50-200 cells/μL who either have WHO stage 1&2, stage 3 or stage 4 disease had very high 6-month mortality risks of 3-5%, 6-12% and 14-22%, respectively [49]. This has important implications for the appropriate CD4 count thresholds at which to start ART as discussed below.

Strategies to reduce early morbidity and mortality

A number of strategies are likely to be needed to reduce early morbidity and mortality during ART:

1. Earlier HIV diagnosis—A critical stumbling block is that most infected people do not know their HIV status and most HIV diagnoses are only made once patients present to the health services with WHO stage 3 or stage 4 (ie advanced symptomatic) disease. Such patients by definition have a high burden of morbidity and high mortality risk [49].

Revised WHO guidelines now recommend that all individuals accessing health care services in high HIV prevalence settings (antenatal prevalence >1%) should be tested for HIV unless they specifically opt out [50]. In a community-based study in South Africa in which testing increased from 4% to 20% between 2001 and 2006, however, median CD4 counts and WHO stage of disease among newly diagnosed patients remained stable rather than improving [51]. Rates of HIV testing may need to be even more radically improved to promote earlier diagnosis and should also be provided within communities outside the context of health care facilities.

2. Availability of CD4 count testing—CD4 count testing needs to be scaled up at the district and health centre level to assess ART eligibility. With the current impetus to decentralise HIV care and treatment services to more peripheral sites, this will require much simpler technology such as a point-of-care CD4 count tests, which are currently under development and evaluation.

3. Pre-ART care—The majority of health services in sub-Saharan Africa fail the HIV-infected people who are not yet eligible for ART and the concept of "pre-ART" care needs to be championed. A package of regular care and support that includes clinical assessment, CD4 count measurement and co-trimoxazole and isoniazid preventive therapy would go a long way to decreasing subsequent late presentation and high early mortality on ART. The

mortality risk of patients just prior to starting ART is extremely high [37, 52] and delays within the health system need to be minimised.

4. Guidelines recommending earlier ART—Current international [53] and national guidelines in resource-limited settings recommend starting treatment at CD4 cell counts of either up to 200 cells/μL or up to 200-350 cells/μL. Observational data from South Africa, however, show that the 12-month mortality for untreated patients with CD4 counts of 200-350 cells/μL is 22% [54] compared to 4% in industrialised settings [55]. These data strongly suggest the need for earlier ART initiation as has been clearly demonstrated in the CIPRA HT001 trial from Haiti. This relatively small randomised controlled study (n=816) compared initiation of ART at CD4 counts between 200-350 cells/μL versus deferral of ART until the CD4 count had decreased to <200 cells/μL [56**]. The mortality rate was 4-fold higher and the TB rate two-fold higher in the deferred treatment arm, providing the first data from a randomised study to provide compelling evidence to support earlier ART initiation in resource-limited settings.

5. Co-trimoxazole prophylaxis—WHO/UNAIDS published provisional and updated recommendations in 2000 and 2006 for prophylaxis with trimethoprim-sulphamethoxazole (co-trimoxazle) in all patients with symptomatic HIV infection in resource-limited settings [57]. However, many countries have not widely implemented this important intervention for a variety of reasons, including concerns over efficacy in the context of high rates of resistant bacteria. Thus, a further randomized controlled trial was completed in one such country (Zambia) in 2008 and this confirmed that this is a safe intervention that reduces mortality among HIV-infected patients with TB [58]. In an ART programme in Cambodia, co-trimoxazole use was associated with an 85% reduction in adjusted hazards of death with benefit observed among those with baseline CD4 cell counts <200 cells/μL [18].

6. TB screening and prophylaxis—In 2008, the WHO launched the 3I's policy - a new initiative to reduce the burden of TB in HIV-infected people [59]. This comprises the use of intensified case finding, isoniazid prophylaxis and infection control to be scaled up in tandem with ART.

The tools available for intensified case finding in patients with advanced HIV infection are blunt, however [60]. Recent studies from South Africa found a prevalence of sputum culture-positive TB of 20%-25% in patients just prior to ART initiation [46*, 61] but culture-based diagnosis was slow, the sensitivity of fluorescence smear microscopy was < 20% and chest radiology performed poorly [62]. These data suggest the potential need for routine culture-based screening in this setting and the need for new rapid and point of care diagnostics.

Following the fatal outbreak of multidrug- and extensively drug-resistant TB (MDR-TB and XDR-TB) among ART patients attending a facility in Kwazulu Natal, South Africa, in 2005-2006 [63], the WHO has recommended the implementation of molecular line-probe assays in resource-limited settings [64]. This should greatly expedite the diagnosis of MDR-TB.

Isoniazid prophylaxis substantially reduces TB risk and shows a trend towards a reduction in mortality in patients not receiving ART and who have a positive tuberculin skin test [65]. Using observational data from Brazil and South Africa, it has been suggested that there may also be an additive effect of isoniazid preventive therapy when administered prior to or during ART [66, 67]. A number of considerations, however, suggest that initiation of IPT at the same time as ART initiation might be inadvisable in patients with low CD4 cell counts since there may be a high prevalence of active undiagnosed TB [46, 61], the negative

predictive value of TB screening algorithms is limited [60] and combined use of isoniazid during the initial weeks of stavudine-containing ART is associated with a high incidence of peripheral neuropathy [68]. Initiation of isoniazid after completion of the initial months of ART has therefore been suggested as an alternative strategy [12**].

7. Screening and prophylaxis for cryptococcal disease—Two retrospective studies from Africa have found that detectable cryptococcal antigenaemia in patients starting ART is an independent predictor of mortality [37*, 69]. In the more recent study, the prevalence of antigenaemia was 13% among patients with CD4 cell counts <100 cells/μL and an antigen titre of ≥1:8 was 100% sensitive and 96% specific for predicting development of cryptococcal meningitis during the first year of ART [39*]. Use of this as a screening test pre-ART might permit implementation of a targeted pre-emptive treatment strategy.

Importantly, a study from Cambodia found that use of fluconazole prophylaxis during ART was associated with a 50% reduction in adjusted hazards of death, with benefit being observed among those with baseline CD4 cell counts of <100 cells/μL [18]. No comment was made on whether this was due to prevention of cryptococcosis, oesophageal candidiasis or other locally prevalent fungal pathogens such as *Penicillium marneffei*.

8. Optimised management of opportunistic diseases—Management strategies need to be optimised to address serious and life-threatening morbidity. Expertise in the treatment TB and HIV concurrently is gradually evolving through observational studies [70*]. Use of efavirenz rather than nevirapine-containing ART appears to be preferable when combined with rifampicin-containing TB treatment, both with regard to ART efficacy and toxicity [71]. Results of randomised controlled trials informing the optimum time to initiate ART during TB treatment are awaited, but interim results from the South African SAPIT trial found a very high mortality among patients deferring ART initiation to the end of TB the 6-month treatment phase compared to initiation during or at the end of the 2-month intensive phase [72]. MDR-TB and HIV co-infection carries a poor prognosis and much remains to be learned about MDR-TB management during ART.

A randomised placebo-controlled trial of corticosteroids has been evaluated in the management of moderate (non-life-threatening) TB immune reconstitution disease in South Africa [73*]. Although no mortality benefit was observed, there was a significant reduction in the need for hospitalisation and interventions in the treatment arm.

Optimum regimens are needed for treatment of cryptococcal meningitis. Although high dose intravenous amphotericin and flucytosine evaluated in South Africa may be the ideal [74], this is neither logistically feasible nor affordable in many low-income settings. Data from Uganda suggest dose oral fluconazole at a high dose (1200 mg per day) may be more rapidly fungicidal than currently used lower doses [75*].

9. Improving treatment access and retention in care—Recognition of and pragmatic solutions to address the factors that hinder treatment access and retention in care are essential. These include the need for free treatment [4, 16, 17], the critical issue of high transport costs to and from clinics [76], the importance of uninterrupted drug supplies in health facility pharmacies and decentralisation of services so that they are nearer to patients' homes. Every attempt must be made by ART clinics to link their services with the community and particularly with associations of people living with HIV/AIDS. Care packages such as home treatment of opportunistic infections, support to family carers, referral of patients with possible adverse drug reactions, continuing adherence counselling and defaulter tracing are, not surprisingly, associated with better ART treatment outcomes [77]. The community is an unrecognised and largely unexploited resource that could play an

important contributory role in improving ART retention provided there are well defined structured links to the health services.

Conclusions

Rates of early morbidity and mortality are much higher among patients treated in resource-limited settings compared to those in high-income settings. However, these are very heterogeneous across resource-limited settings and a range of biomedical, economic and social factors may underlie this. The high burden of disease needs to be addressed by strategies that broadly enhance earlier HIV diagnosis and access to ART, screening and prophylaxis for opportunistic infections, optimised opportunistic disease management and strengthening of ART services. Managing patients with advanced immunodeficiency and high rates of morbidity and mortality is a major challenge using the simplified public health approach to ART delivery. Nevertheless, this has been very successful indeed in enabling rapid expansion to treatment to permit millions of people to gain the benefits of ART.

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Abbreviations

AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
HIV	human immunodeficiency virus
KS	Kaposi’s sarcoma
MDR-TB	multi-drug resistant tuberculosis
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively resistant tuberculosis

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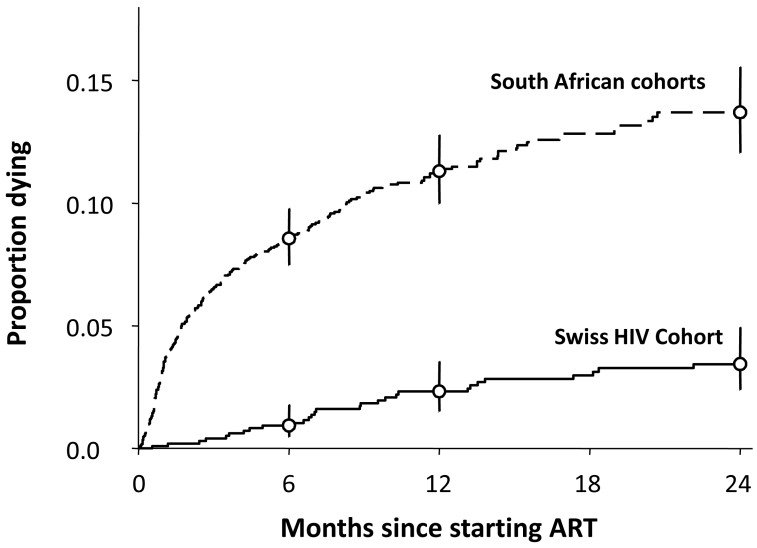

Figure 1.

Kaplan Meier plots comparing the cumulative mortality during ART in South African (Gugulethu and Khayelitsha) cohorts and the Swiss HIV Cohort Study. Baseline CD4 cell counts were 80 cells/μL and 204 cells/ μL, respectively. Graph reproduced from [10].

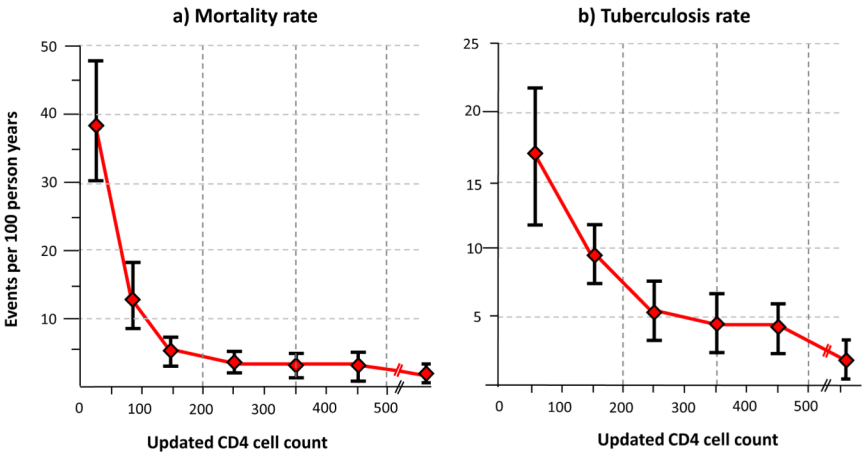

Figure 2.

Graphs showing (a) mortality rates and (b) tuberculosis (TB) incidence rates (95% confidence intervals, deaths per 100 person-years) plotted against CD4 counts measured at baseline and updated every 4-months during ART (updated CD4 counts). As CD4 cell counts increased, the mortality rate is seen to fall very steeply. Above a CD4 count threshold of 200 cells/μL, however, no further significant reductions occurred with further CD4 cell count recovery. TB rates similarly decreased with increasing CD4 cell counts, but substantial rates persisted at CD4 counts of 200-500 cells/ μL but significantly decreased above a threshold of 500 cells/μL. Data adapted from [11**] and [12**].

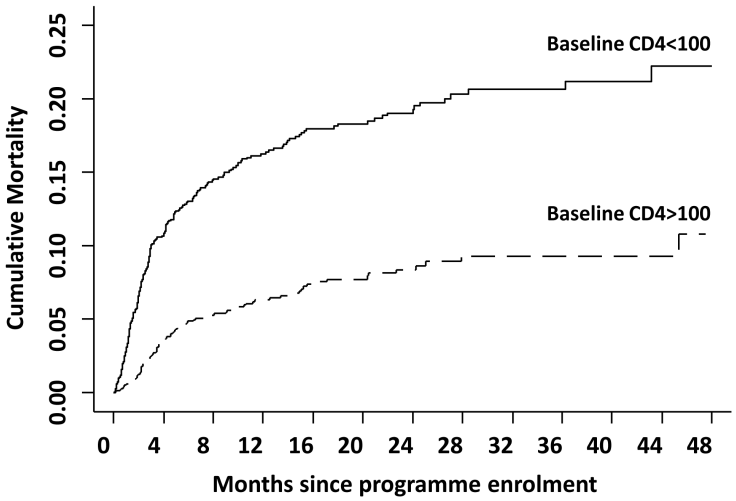

Figure 3.

Kaplan Meier plot showing the cumulative mortality in the Gugulethu cohort in groups of patients with baseline CD4 cell counts <100 cells/μL or >100 cells/μL from the time of enrolment into the programme (includes mortality accruing in one month pre-ART period plus mortality on ART). Data adapted from [11**].

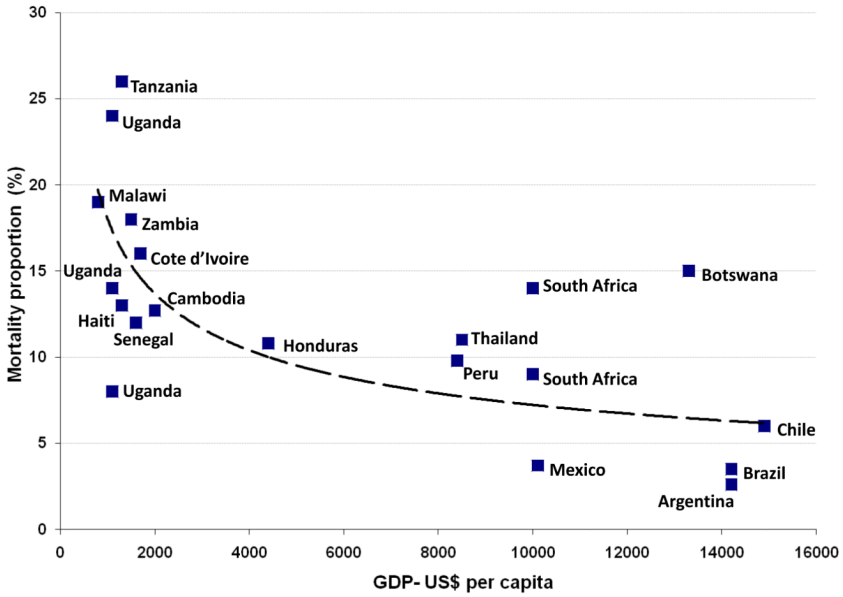

Figure 4.

Graph showing mortality after one year of ART for 21 cohorts plotted against the Gross Domestic Product (GDP) per capita (in US dollars) for the countries represented. Cohorts included are from countries in sub-Saharan Africa, Latin America and the Caribbean and South East Asia from references [5**, 6**, 8**, 18]. The countries from which the data are derived are indicated and some are represented by more than one cohort. Mortality risk is very heterogeneous, but cohorts in countries with lower GDP tend to be associated with higher mortality risk.

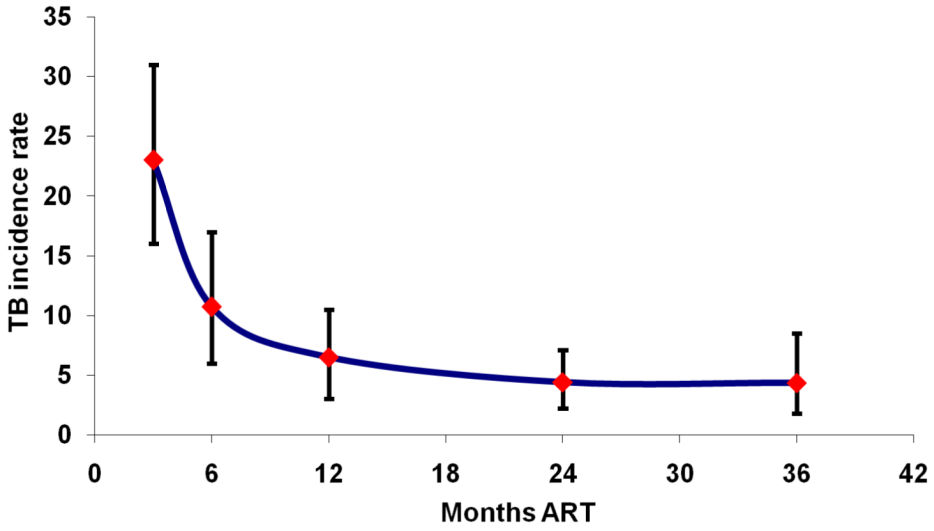

Figure 5.

Graph showing changing tuberculosis (TB) incidence rate (95% confidence intervals, cases per 100 person-years) with increasing duration of antiretroviral therapy (ART) in a South African cohort. The incidence rate is extremely high in the first 3 months but rapidly decreases thereafter. Data adapted from [23, 12].