UNIVERSITÄT BERN

Division of International and Environmental Health

Institute of Social and Preventive Medicine, University of Berne, Switzerland

Progression and mortality of untreated HIV-positive individuals living in resource-limited settings:

Update of literature review and evidence synthesis

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Marcel Zwahlen and Matthias Egger

Correspondence to:

Professor Matthias Egger
Institute of Social and Preventive Medicine
University of Bern
Finkenhubelweg 12
CH-3012 Bern
Switzerland
Tel +41 31 631 35 01
Fax +41 31 631 35 20
egger@ispm.unibe.ch

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Introduction

The increasingly widespread use since 1996 of highly active antiretroviral therapy (HAART), a combination of at least three drugs that typically includes either a protease inhibitor (PI) or a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) and two nucleoside analogue reverse transcriptase inhibitors (NRTIs), has substantially improved the prognosis of HIV-infected patients who have access to these drugs in industrialised countries[1-3].

In resource-poor settings in Africa, Asia and South America, where 90% of people with HIV/AIDS live, access to HAART has been limited to a small minority of patients, due to the high cost of drugs and the lack of an infrastructure capable of delivering the therapy. With falling prices of proprietary drugs, the increasing availability of generic formulations and the launch of initiatives by international agencies, including WHO's '3 by 5' target (3 million patients treated by 2005), the Global Fund to fight AIDS, Tuberculosis and Malaria, and the United States President's Emergency Plan for AIDS Relief (PEPFAR), this situation is changing. For example, UNAIDS estimates that in Africa the number of people on antiretroviral therapy more than doubled in 2005 alone, with roughly one in six people who needed treatment receiving antiretrovirals by December 2005[4].

These developments clearly demonstrate that the debate on HAART in developing countries has irrevocably moved from the question whether the introduction of HAART is cost-effective in the light of competing priorities and fragile health systems[5;6] to questions of how effective potent antiretroviral therapy will be in these settings[7-9]. There is widespread agreement that research and evaluation efforts are needed, so that epidemiological and clinical data can be collected and the programmes can be modified and improved over time[10].

The Reference Group on Estimates, Modelling and Projections ("Epidemiology Reference Group") of UNAIDS (http://www.epidem.org) organized a workshop in Athens in December 2005. The group advises UNAIDS, the World Health Organization and other international organizations on the most appropriate methods and assumptions for their global estimates. The present document was prepared following this workshop. It aims to contribute to the evidence base required to update estimates of the number of HIV-positive persons who are in need of treatment.

Objectives

1) To estimate the time period between eligibility for antiretroviral treatment and death, in the absence of HAART, for adults from low- and middle income countries, based on a literature review and analyses of existing datasets. Eligibility for HAART was based on recent WHO recommendations[11]:

- WHO stage IV disease (clinical AIDS), regardless of CD4 count;
- WHO state III disease, with consideration of using CD4 cell counts $<350/mm^3$ to assist decision-making
- WHO stages I or II with a CD4 count $\leq 200/mm^3$;

2) To explore factors that are associated with progression rates, and to quantify the period between eligibility for HAART and death according to important modifying factors, including age, geographic area, gender, mode of transmission, HIV subtype, prophylaxis for opportunistic infections, and other non-ART treatments.

3) To examine differences in the time period between eligibility for antiretroviral treatment and death, between low- and middle income countries, and high-income countries in the pre-ART era.

Methods

A literature search was performed in Medline and Embase. The original search covered the period from 1990 to November 2003 and was updated in November 2005 for the time period 2003 to 2005. We used search terms 'AIDS', 'HIV infections', 'disease progression', and 'mortality'. The reference lists of relevant original papers and review articles were also scrutinized. Because of time constraints, conference abstracts were not considered.

We extracted information on time to death, measuring time from different levels of immune deficiency defined by CD4 cell counts, and from having developed an AIDS defining illness. In various reports, this information had to be estimated from published Kaplan-Meier curves or calculated from survival estimates at 1, 2 or 5 years reported in tables. We then estimated median survival time from these figures assuming a constant hazard function λ, as follows:

$$T_{med} = \ln(2) / \lambda$$

We used reported incidence rates (number of events per 100 person-years of observation) to estimate λ, which then allowed the calculation of median survival times, for example by CD4 cell strata.

For comparisons of the survival experience between low and middle income and industrialised countries we performed

- Analyses of the Swiss HIV Cohort study[1] for the calendar periods before antiretroviral therapy was introduced. Patients with presumed heterosexual or homosexual transmission were included in analyses.
- Bayesian evidence synthesis that incorporated three data sources:
    - Estimates of the causal effect of HAART on progression to AIDS or death from the Swiss HIV cohort study, which take into account confounding by indication[12],
    - Differences in short-term survival among patients receiving HAART between high-income and lower-income countries[9],
    - Survival estimates from various CD4 strata or from AIDS obtained from the ART Cohort Collaboration (ART-CC)[13-15].

All statistical analyses were done in Stata (version 9.1, College Station, Texas, USA) or WinBUGS (version 1.4, Cambridge, UK).[16;17] Results are presented as estimates of median survival time, probabilities of survival and hazard ratios, with 95% confidence intervals (95% CI) or 95% credibility intervals.

Results

1. Literature search

In 2003, we examined over 300 references of potentially relevant studies from resource-limited settings[18]. Two-hundred and forty studies were found not to be relevant based on the abstract; 65 papers were ordered and examined in detail. Forty-six were excluded because outcomes were not relevant or crucial information was missing. Twenty studies were finally included in the review.

For the 2003-2005 update we identified 199 articles (Table 1), retained 19 for detailed examination of which two[19;20] reported relevant information on mortality of untreated individuals in resource limited countries for CD4 strata of 200 to 350 cells/mm^3 (Table 2).

Table 1: Results of 2003-2005 update of literature search.

Type of articles	Number of articles	Comments
Abstracts found :	199	
Retained for full text[19-37]	19	
Of full text		
Reviews[24;32]		- HIV-2 vs. HIV-1 - Models of impact of HAART on HIV-incidence
Studies in developed countries[23;25-27;37]		Spain, Canada, Switzerland France (only HV-2), Italy
Studies in resource-limited countries[19-22;28-30;36]		See Table 2

Table 2: Studies done in resource-constrained settings with natural history information, published between November 2003 and November 2005.

Author and year	Country	Subjects and samples size	Endpoints	Can available natural history information be used for this review?
Badri, 2004[19]	Cape Town, South Africa	292 with HAART, 974 without HAART	AIDS Death	Yes
Costello, 2005[20]	Thailand	836 heterosexuals with HIV-subtype CRF01_AE	Death	Yes
Lawn, 2005[36]	Cape Town, South Africa	712 patients with median CD4 cells of 94 starting ART	Death	Yes, for natural history from low CD4 cell counts only (no high CD4 levels at entry)
Zhou, 2005[30]	Asia HIV Observational Database	1260 patients including 321 not on treatment	AIDS or death	No (no separate analysis of non-treated participants)
Bakari, 2004[21]	Tanzania, Dar es Salaam	196 sero-prevalent and 133 sero-incident persons	Death	No (no proper time to event analysis)
Rangsin, 2004[28]	Thailand	235 men known serconverters	Death	No (survival time from seroconversion)
Senkaali, 2004[29]	Uganda	142 HIV-1 patients according to V3 serotype	AIDS or death Death CD4 below 200	No (results only according V3 subtype)
Duncombe, 2005[22]	Thailand	417 patients enrolled in a series of randomized ART trials 1996-2001	AIDS or death	No (only treated patients)

2. Time from AIDS to death

Eight studies from resource-limited settings[38-45] provided data on the time between the occurrence of first AIDS-defining events and death. Median survival after diagnosis of AIDS ranged between 6 and 19 months. Study characteristics are summarised below in Table 3:

Table 3: Survival from AIDS to death.

Study, year of publication	N	Country	Years	Median survival (*T*med) and 95% CI [months]	Comments
Bégaud, 2003[38]	11	Central African Republic	1995-2000	6.5 (2.5 - 16)	
Hira, 2003[39]	54	Mumbai, India	1994-2000	19	25% with TB
Menesia, 2001[40]	1231	Riberão Preto, Brazil	1986-1997	10.3	10 months in 1991-1995; 28 months in 1996-1997
Post, 2001[41]	280	Cape Town, South Africa	1984-1997	11.5	Median CD4 count of 111
French, 1999[42]	56	Entebbe, Uganda	before 1998	6	
Fonseca, 1999[45]	48	São Paolo, Brazil	1987-1995	19	AIDS, some patients on ART
Morgan, 1997 & 2002[43;46]	44	Rural area, Uganda,	1990-2000	9.3 (3.4 - 16.6)	
Kitayaporn, 1996[44]	329	Hospital in Bangkok, Thailand	1987-1993	7	Median total lymphocyte count 904; 30% mortality in first month

For comparison, six studies of clinical progression[47-52] that were conducted in industrialised countries before the introduction of combination therapy found mean survival rates after onset of AIDS between 9.5 and 22 months[18].

3. Time from < 200 CD4 lymphocytes per mm^3 to death

A CD4 lymphocyte count below 200 cells/mm^3 is an important risk factor for clinical progression, indicating that antiretroviral treatment should be started without delay. Several reports provided information on the time between a CD4 cell count below 200 cells and death (Table 4). Unfortunately, the exact number of CD4 lymphocytes was rarely reported. Survival ranged between 7 and 38 months, and survival was longer for patients who received some antiretroviral therapy:

Table 4: Survival from < 200 CD4 lymphocytes per mm^3 to death.

Study, year of publication	N	Country	Years	Median survival (*T*med) and 95% CI [months]	Comments
Lawn, 2005[36]	134 (patients not receiving ART)	South Africa	2002 - 2005	20 (14 -28)	mean CD4 count was 94 cells/mm3
Costello, 2005[20]	207	Thailand	1993-1999	21.6 (19 – 24)	HIV subtype CRF01_AE
Badri, 2004[19]	447	South Africa	1992-2001	23.6 (21 -27)	
Pathipvanich, 2003[53]	422	Lampang province, Thailand	1995-1999	10.8 (na)	82% < 100 CD4 cells, partially treated
Pathipvanich, 2003[53]		Lampang province, Thailand	1995-1999	38 (28 - 62)	100-199 CD4 cells, partially treated
Kumarasamy, 2003[54]	71	Chennai, southern India	1996-2000	33	46 months with ART
Schim van der Loeff, 2002[55]	378	Fajara in The Gambia	1986-1997	7 (5 - 9)	
Kilmarx, 2000[56]	15	Northern Thailand	1991-1998	11 (7 - 15)	96% subtype E
French, 1999[42]	78	Semi-rural Entebbe, Uganda	before 1998	9 (7 - 15)	

4. Time from 200 - 350 CD4 lymphocytes per mm^3 to death

Five studies reported median survival times for patients with CD4 cell counts in the range of 200 to 500 cells per mm^3 (Table 5). Only one study[19] gave separate results for persons with a CD4 cell count between 200 and 350 cells per mm^3.

Table 5: Survival from 200 - 350 CD4 lymphocytes per mm^3 to death.

Study	Population, Country, Years	Median survival (Tmed) and 95% CI [months]	CD4 interval	Issues
Costello,2005[20]	Thailand	58 (47 – 72)*	200 – 500	HIV subtype CRF01_AE
Badri, 2004[19]	South Africa	34.2 (28 – 43)	200 – 350	
Kilmarx, 2000[56]	88 Northern Thailand, 1991-1998	91 (63 –131)	200 – 500	96% HIV-subtype E
French, 1999[42]	Uganda, before 1998	48 (35 – 75)*	200 – 499	
Schim van der Loeff, 2002[55]	Gambia, 1986-1997 (N=303)	40 (33 – 51)	200 – 499	

* 95% CI from our calculations

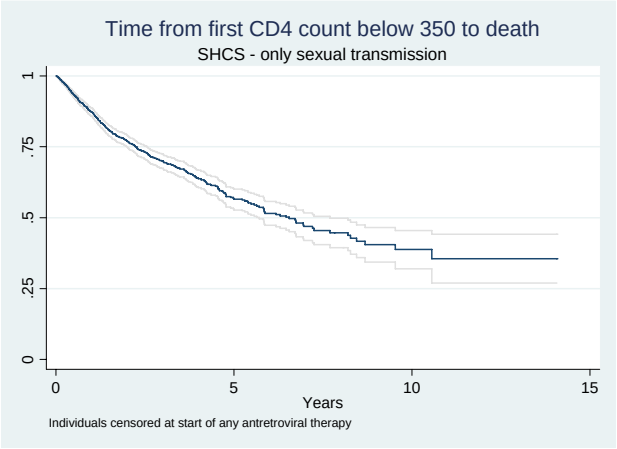
Based on these data and the assumption that persons with CD4 cell counts between 200 and 500

cells/mm^3 have on average 350 cells/mm^3 we can state that the median survival from 350 CD4 cell counts is about 4 to 5 years, but there is substantial uncertainty.

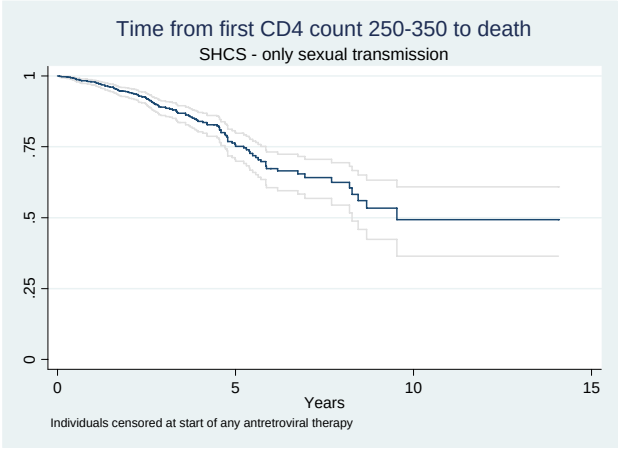
To put this estimate into perspective, we performed an analysis of the Swiss HIV Cohort Study, restricting observation time to the period before antiretroviral treatment became available. Individuals were censored at the time they started any type of antiretroviral treatment and only individuals with presumed heterosexual or homosexual transmission were included. We measured time from the first study visit with a documented CD4 cell count below 350 cells/mm^3 and also from the first visit with a CD4 cell count between 250 and 350 cells/mm^3.

The Kaplan-Meier plots shown in Figure 1 indicate that the median survival from first CD4 cell count below 350 cells/mm^3 is longer than 5 years, and therefore is longer than that observed in HIV-infected individuals in resource limited countries. The median CD4 count at time 0 in this group was 210 cells/mm^3 compared to 304 cells/mm^3 in the group starting from a CD4 count between 250 and 350 cells/mm^3. Median survival in the latter group was > 8 years.

Figure 1: Kaplan-Meier survival plots of participants of the Swiss HIV cohort study



Median CD4 count at time 0: **210** cells/mm^3.
Median survival of 6.5 years (95% CI 5.7 – 7.7)



Median CD4 count at time 0: **304** cells/mm^3.
Median survival cannot be estimated with precision, but is > 8 years

5. Bayesian evidence synthesis

We took advantage of the following relationship that generally holds true for the hazard ratio *hr* comparing the survival experience of two groups of individuals:

$$hr_{1vs2} = \frac{\log(p(\text{survival at T in group 1}))}{\log(p(\text{survival at T in group 2}))}$$

Of note, this holds for any shape of the hazard function and for any T as long as the proportional hazards assumption is met[57].

We used data from the ART Cohort Collaboration[13] and restricted our analysis to the 4,223 patients who started HAART with a CD4 cell count between 200 and 350 cells/mm^3. In this group 109 deaths were recorded during 12,271 years of follow-up. The estimated 5-year survival

was 95.2% (95% CI 94.0 % - 96.1%).

We then incorporated the estimated treatment effect of HAART on progression to AIDS or death (vs. no therapy) from a recent analysis of the Swiss HIV Cohort Study, which used marginal structural models to control for confounding by indication[12]. Note that for ethical reasons there have been no placebo-controlled trials of highly active combination ART, and the analysis of the Swiss cohort[12] may be the best available evidence on the causal effect of HAART. The overall hazard ratio for HAART compared with no treatment was 0.14 (95% CI 0.07 – 0.29).

For the present Bayesian evidence synthesis we used the treatment effect estimated for those patients who started HAART with 200 to 350 cells per mm^3, i.e.0.16 (95% CI 0.07 – 0.36). Additionally we included the following information on factors modifying prognosis:

- We assumed that mortality is increased in patients starting HAART in resource-limited settings compared to industrialized countries. For describing this geographical mortality differential we based the prior information on the unadjusted results comparing the mortality hazards between patients treated in the ART-LINC compared to those in the ART-CC collaboration[9]. We think that this estimate reflects more the existing differentials that also incorporates that type of treatment and distribution of clinical presentation at start of HAART are different between the two regions. For this comparison the prior information consisted of the estimate of the hazard ratio of 2.0 (1.0 –4.0) which is the estimate for the second half of the first year on HAART[9]. We think that this estimate more reasonably describes the likely medium to long term mortality differential between resource-limited and industrialized countries.
- In addition we derived estimates that accounted for the fact that mortality is increased in patients who start HAART when more advanced disease (WHO stage III or IV) is already present. Here we based our prior information on the results from the ART-LINC collaboration that reported in table 3 of their article a hazard ratio of 2.0 (95% CI 1.0 – 4.0) [9].

Finally, we used the formula given above to obtain estimates of the 5-year survival probability without HAART. The uncertainty of estimates were obtained from probabilistic sampling implemented in WinBUGS (http://www.mrc-bsu.cam.ac.uk/bugs) . The results are shown in Table 6.

Table 6: 5-year survival probabilities for patients without HAART with CD4 cell counts 200 to 350 cells per mm^3.

Population	Estimates from Bayesian evidence synthesis (95% credibility intervals)	Direct estimate from the Swiss HIV cohort study (95% confidence intervals)
Patients from industrialized countries	72.6% (48.6% - 86.7%)	73.0% (68.4% - 77.2%)
Patients from resource-limited countries	52.7% (15.7% – 80.2%)	
Patients from resource-limited countries with advanced disease (WHO stage III or IV)	27.7% (1.1% - 70.0%)	

The estimates for patients in resource-limited countries translate into a median time to death from CD4 counts 200 to 350 cells/mm^3 of 5.4 years (95% credibility intervals 1.9 – 15.7 years), and to 2.7 years (95% credibility intervals 0.76 – 9.6 years) for patients who present with WHO clinical stage III or IV.

6. Brief review of prognostic factors

Age
Various studies, both from developing[46] and from industrialized countries[58], have shown that younger age is associated with longer survival, independently of the mode of HIV transmission.

Sex
Sex does not seem to be associated with survival. Particularly in developing countries, women are infected at younger age; sex may thus act as a confounder[9]. Based on limited data, pregnancy does not appear to have a major effect on clinical progression[59].

Cohort effects
In industrialised countries, cohorts infected in the late 1980s have longer survival than those with earlier seroconversion, probably due to the gain in physicians' expertise and improvements overall in the care for these patients[49]. The wider use of prophylaxis against opportunistic infections will also have contributed to increasing survival.

Immunological and virological parameters
As in the industrialised world, low CD4 lymphocytes and high viral load are associated with faster disease progression in resource-poor countries[9].

Clinical stage
More advanced disease clearly increases the risk of death both in untreated[19] and in treated patients[9;13].

Type of virus
HIV-2 is less pathogenic than HIV-1 and patients infected with HIV-2 have slower progression of disease[24;60]. The role, if any, of HIV-1 subtypes is unclear[61].

Summary and conclusions

Survival after developing AIDS-defining illnesses or reaching low CD4 lymphocyte counts tends to be shorter in developing than in industrialised countries. In developing countries, estimates of median survival after AIDS scatter around 1 year. Similar results are obtained for survival after CD4 cell counts have dropped below 200 cells per mm^3, but estimates are more heterogeneous.

Results will be influenced by the exact distribution of CD4 cell counts among patients with less than 200 cells, as illustrated in our previous report[18]. Here we showed a similar effect for the survival of HIV-infected individuals with CD4 cell counts below 350 cells/mm^3, again using data from the Swiss HIV Cohort Study. The Kaplan-Meier plots show that the estimated median survival time differ substantially between patient groups defined by having a first CD4 cell measurement below 350 cells/mm^3, or patients who have a first CD4 cell count between 200 and 350 cells/mm^3. We acknowledge that these results may be biased due to the fact that follow-up was censored at the time of starting anti-retroviral treatment, which means that slow progressors will tend to be overrepresented. Furthermore, some patient will have received prophylactic treatment to prevent AIDS defining complications. The results nevertheless illustrate the crucial importance of the CD4 cell count at time 0.

Unfortunately, the information that is available from resource-constrained settings on the natural history of untreated patients who reached a CD4 count below 350 cells/mm^3 is limited. We summarized the available data and found that the median survival time for this group of HIV-infected persons is about 4 to 5 years, but there is substantial uncertainty . This estimate is in agreement with the results from the Bayesian evidence synthesis incorporating information of patients receiving HAART, 5.4 years (95% credibility intervals 1.9 – 15.7 years). The latter also allowed us to incorporate prior information on the progression of patients who present with WHO stage III or IV, which resulted in a median survival of 2.7 years (95% credibility intervals 0.76 – 9.6 years).

Our review has several limitations. The literature search was restricted to published studies and did not include conference abstracts, grey literature or unpublished material. It seems unlikely, however, that the inclusion of studies reported as abstracts only or unpublished studies would have materially changed our conclusions.

The type of data reported on survival was heterogeneous, confirming earlier observations on common difficulties with systematic reviews of prognostic studies[62]. Indeed, the studies reviewed here presented data in various ways, as median survival, Kaplan-Meier curves, estimates of survival at 1, 2 or 5 years or as incidence rates (events per person-years of observation). This meant that the required information sometimes had to be extracted from graphs or estimates of median survival time had to be calculated from rates, which may have introduced both systematic and random error. Furthermore, definitions of AIDS and CD4 lymphocyte categories varied. Studies sometimes included patients both prospectively and retrospectively, and a few studies included patients on antiretroviral monotherapy. A formal meta-analysis could not be performed. A collaborative individual-patient-data (IPD) analysis would be required to overcome these limitations. Such collaborations are under way but at present include patients receiving or starting ART only[9;63]. The Bayesian evidence synthesis approach allowed us to use data on the causal effect of HAART and survival in treated patients to obtain information on the natural history of HIV-infection in the absence of treatment.

We conclude that the data presented here may represent the best available information, which should be used in the spirit of sensitivity analysis when estimating the number of HIV-infected people in need of potent antiretroviral treatment in low income countries.

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