Objective: To evaluate CD4 cell count-driven strategies for the initiation of highly active antiretroviral therapy (HAART) in terms of the reduction of the incidence of AIDS-defining events in resource-poor settings.

Methods: Data from the Amsterdam Cohort Study on HIV infection and AIDS were used to estimate the hazard of AIDS in untreated HIV-1 infection and after initiation of HAART, respectively, conditional on CD4 cell count. Different strategies for initiating therapy were compared by calculating the expected HAART administration rate and 1-year cumulative AIDS incidence in three different population settings, varying in the stage of HIV-1 infection at the time of presentation.

Results: Among 695 HIV-1-infected cohort participants, the 1-year AIDS incidence density (ID) ranged from 3.2 per 100 person-years for CD4 cell counts 600–700 cells/mm³, to 31.9 per 100 person-years for CD4 cell counts 100–200 cells/mm³ and 77.9 per 100 person-years for CD4 cell counts below 100 cells/mm³. Upon initiation of HAART, the ID in the lowest CD4 strata declined to 13.3 and 16.3 per 100 person-years, respectively. Extrapolated to developing countries, supply of HAART to patients presenting with HIV-1 infection below 200 CD4 cells/mm³ is expected to give an administration rate of 67%, while the AIDS incidence will drop from over 30% to almost 10%.

Conclusions: Introduction of HAART in populations with advanced HIV-1 infection can accomplish a threefold reduction of the AIDS incidence when HAART is administered to patients with CD4 cell counts below 200 cells/mm³. In a hospital-based setting in resource-poor environments this ensures an efficient treatment allocation.

Introduction

Since 1996 the Western world has seen a remarkable decline in AIDS-related death and morbidity, coinciding with the introduction of highly active antiretroviral therapy (HAART) as the preferred initial treatment regimen in human immunodeficiency virus type 1 (HIV-1) infection [1]. If the global donor community adequately supplied antiretroviral medication to countries where prevalence and incidence rates of HIV-1 infection are highest [2], millions of HIV-1-infected patients could be treated and the global AIDS incidence might be curbed [3,4]. To direct a rational allocation of limited resources, decision strategies for initiating HAART in resource-limited settings are required. Ideally, sound laboratory criteria for starting HAART could be used to develop semiquantitative diagnostic assays to support implementation of HIV-1 treatment programmes in developing countries.

The decision to start HAART in HIV-1 infection in the developed world is guided by a complicated set of considerations [5]. If the initial treatment regimen is inadequately adhered to or not potent enough, early therapy may severely compromise future treatment options. Outweighing arguments in favour of very early treatment [6–8] are growing concerns regarding long-term adverse effects of therapy [9], and the potential development and transmission of drug-resistant virus [10]. In a setting with limited diagnostic and therapeutic resources, HAART should be restricted to those patients at highest risk for developing AIDS [11,12].
Following the World Health Organization (WHO) recommendation for the selection of patients for initiating antiretroviral therapy [13], this concerns HIV-1-infected patients who present with WHO stage IV disease or patients with a CD4 cell count below 200 cells/mm³ if CD4 testing is available. According to current published international guidelines, decisions for therapeutic intervention should consider both CD4 cell count and the plasma concentration of HIV-1 RNA [14,15]. The CD4 cell count is the more easily adopted laboratory marker of HIV-1 infection from a technical viewpoint, due to the evolutionary conserved appearance of the CD4 cell surface marker among various primates, including human populations [16]. In contrast, HIV-1 has evolved into a wide array of subtypes in a few decades time and is likely to continue its evolutionary diversification in the near future, making the measurement of HIV-1 RNA prone to inaccuracy [17].

The aim of the present study is to compare different strategies of providing HAART in resource-limited settings, based on the determination of CD4 cell count. Different CD4 cell count thresholds for the initiation of HAART are compared in terms of the expected HAART administration rate and the reduction of the incidence of AIDS-defining events in three different population settings, based on the stage of HIV-1 infection at the time of presentation.

Methods

For the purpose of this analysis, HAART is defined as an antiretroviral regimen consisting of either at least three antiretroviral drugs, or two if either one is a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). To evaluate CD4 cell count-driven strategies for initiation of HAART in a given population at risk for AIDS, we sought to identify and quantify (i) the proportion of patients in need of treatment at time of seroconversion and (ii) the average risk of progression to AIDS as the expected 1-year cumulative incidence of AIDS-defining events. These measures were evaluated for different CD4 cell count thresholds at which HAART can be initiated and were illustrated using three imaginary countries with different HIV/AIDS healthcare systems.

Estimates for the 1-year cumulative hazard of AIDS were derived from the Amsterdam Cohort Study on HIV infection and AIDS among homosexual men. This cohort study started in October 1984 [18]. Participants were HIV-1-seropositive at entry or seroconverted during follow-up. They were seen every 3–6 months, at which time blood samples were taken. Peripheral blood mononuclear cells were isolated from heparinized venous blood using density-gradient centrifugation on Ficoll-Pacque (Pharmacia, Uppsala, Sweden). Absolute numbers of CD4 T lymphocytes were determined by cytofluorometry. Only primary CDC-C events were included in the present analysis. Diagnoses were made by confirming each condition according to the Centers for Disease Control (CDC) recommendation [19]. We used follow-up information collected until May 2001.

A person-years analysis was performed to estimate the 1-year cumulative hazard of AIDS conditional on CD4 cell count. Estimates were obtained by categorizing CD4 cell count into intervals of 50 cells/mm³. Incidence density (ID) was calculated for a single year of follow-up after attaining a specific CD4 cell count stratum while still at risk for AIDS and before the start of any antiretroviral treatment (ART) regimen. The ID is the ratio of observed events to total observation time.

Since patients were likely to have started ART if they were at high risk for AIDS, censoring the observation time at start of ART would lead to an underestimation of the 1-year cumulative hazard of AIDS in untreated HIV-1 infection. Therefore, we also calculated uncensored estimates. If a patient started ART at a CD4 cell count of 100–150 cells/mm³ and developed AIDS within a year, this was considered an event in the uncensored person-years analysis but not in the censored analysis. We compared the censored estimates to uncensored estimates. Finally, death without prior AIDS diagnosis was also considered an event. No adjustment was made for the use of prophylactic treatment against AIDS-defining opportunistic diseases, most notably prophylaxis against Pneumocystis carinii pneumonia or cytomegalovirus (CMV) disease.

The 1-year cumulative hazard of AIDS after initiating HAART was stratified by the CD4 cell count at the start of therapy, defined as the last available measurement in the half-year preceding HAART. The 1-year cumulative hazard after initiation of HAART was calculated as the ID in the first year of follow-up for those patients who started HAART. Progression to clinical events after initiating HAART was studied on an intention-to-treat basis; modification of antiretroviral regimens was not taken into account.

The CD4 cell count in the population presenting with HIV-1 infection was modeled such as to mimic three countries with different HIV/AIDS healthcare systems. In a developed country, we assume CD4 cell count in a population presenting with HIV-1 infection follows a distribution similar to the CD4 cell count in our cohort study in 1995, prior to the introduction of HAART (Table 1). Data for less developed countries were obtained from hospital-based cross-sectional studies. In a developing country, patients presenting with HIV-1...
infection already have profound immunosuppression \cite{20,21}, while intermediate countries are in between the developed and the developing countries \cite{22}.

For each population the 1-year cumulative AIDS incidence is calculated, based on CD4 cell count distributions (Figure 1) with similar proportions as in Table 1. The 1-year cumulative AIDS incidence is calculated as \(1 - \sum p_i \exp\{-h_i\}\), where \(p_i\) is the proportion of patients with baseline CD4 cell count in stratum \(i\). For a specific CD4 cell count stratum, \(h_i\) reflects the 1-year cumulative hazard of AIDS, either after initiation of HAART if treatment is supplied, or otherwise from untreated HIV-1 infection.

As potential thresholds for initiating HAART we choose CD4 cell counts in the range 100–500 cells/mm\(^3\), with increments of 50 cells/mm\(^3\). The difference between the expected 1-year incidence in presence and absence of HAART is proportional to the number of AIDS events prevented due to HAART. The number needed to treat to prevent one AIDS event was calculated by dividing the proportion of patients receiving treatment by this number.

Data were analysed using the SAS system, version 6.12 (SAS Inc., Cary, NC, USA) and S-Plus 2000, professional release 1 (Insightful Corp., Seattle, Wash., USA).

**Results**

Between 1984 and 2001 a total of 695 homosexual men with HIV-1 infection participated in the Amsterdam Cohort Study. Of them, 494 were seropositive at enrolment and 201 seroconverted during follow-up. A total of 300 participants (43\%) developed AIDS, while a total of 285 (41\%) died by May 2001. Forty-one people died without a prior AIDS diagnosis, leaving 244 patients who died after AIDS was diagnosed. The onset of AIDS occurred over a wide range of CD4 cell counts. The CD4 cell count at diagnosis of AIDS was calculated based on the measurement that was nearest to the date of diagnosis, using a window from 185 days before to 90 days after diagnosis. The median CD4 cell count at an AIDS diagnosis was 150 cells/mm\(^3\) (IQR: 70–310) and 95\% of AIDS diagnoses were made at CD4 cell counts below 500 cells/mm\(^3\).

In Table 2, uncensored estimates are shown for the 1-year cumulative hazard of AIDS in untreated HIV-1 infection per 100 person-years conditional on CD4 cell count as categorized per 100 cells/mm\(^3\). The hazard of AIDS increases with declining CD4 cell counts. For CD4 cell counts below 300 cells/mm\(^3\) the 1-year cumulative hazard more than doubles with each CD4 cell count decline of 100 cells/mm\(^3\). If CD4 cell count is observed between 300 and 400 cells/mm\(^3\) the ID is 8.6 cases per 100 person-years, while below 100 cells/mm\(^3\) the ID is 77.9 cases per 100 person-years.

Similar trends apply to the hazard if either observation time is censored at start of ART or death is included as an end-point (Table 2). The 1-year cumulative hazard of AIDS is substantially underestimated if censored estimates are used, while the inclusion of death only marginally affects the uncensored estimates. Therefore, for the remainder of the analysis we used the uncensored incidence densities as estimates for the 1-year cumulative hazard of AIDS in untreated HIV-1 infection.

In total, 260 patients had started HAART before April 2000, 50\% of them before March 1997. Only patients with CD4 cell counts measured at most 6 months before

**Table 1.** Three settings for the CD4 cell count distribution in a population at risk for AIDS, representing countries with different HIV/AIDS healthcare systems

<table>
<thead>
<tr>
<th>CD4 stratum (cells/mm³)</th>
<th>Developed country (%)</th>
<th>Intermediate country (%)</th>
<th>Developing country (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥500</td>
<td>33</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>200–500</td>
<td>57</td>
<td>42</td>
<td>25</td>
</tr>
<tr>
<td>&lt;200</td>
<td>10</td>
<td>26</td>
<td>65</td>
</tr>
</tbody>
</table>

Data for The Netherlands represent a cross-sectional sample taken from the Amsterdam Cohort Study on HIV infection and AIDS in 1995, prior to the introduction of HAART. Data for Côte d’Ivoire \cite{20,21} and South Africa \cite{22} are obtained from hospital-based cross-sectional studies.


We derived aggregated values from the literature and constructed Weibull functions to obtain similar values as observed in the referenced populations. To represent a population presenting with HIV-1 infection in a developed country, we used a Weibull function with scale 2.5 and rate 0.002, which corresponds roughly to the distribution of CD4 cell count in our own cohort study in 1995, prior to the large-scale introduction of HAART. We set the scale at 0.75 and the rate at 0.006 to represent a population from developing countries with late presentation of HIV-1 infection. Intermediate populations were modelled with scale 1.5 and rate 0.0025.
HAART and no previous AIDS diagnosis were considered for this analysis. We observed no AIDS-defining events in the first year from initiation of HAART if therapy was started at CD4 cell counts above 200 cells/mm³. Patients who started HAART at a more advanced stage of immunosuppression still had a considerable risk of developing AIDS in the first year after initiating HAART (Table 3). The ID was 16.6 cases per 100 person-years if HAART was initiated at a CD4 cell count below 100 cells/mm³. For those who started HAART at a CD4 cell count between 100 and 200 cells/mm³ the ID was 13.3 cases per 100 person-years. It must be noted that three patients, including one with baseline CD4 cell count between 250–300 cells/mm³, developed AIDS in the second year since start of HAART. These events have not been included in the present analysis. The incidence densities have wide confidence intervals due to the small number of patients that started HAART within each CD4 cell count stratum. However, if CD4 cell count strata above 200 cells/mm³ were pooled, the 95% upper confidence bound would be 3.4 events per 100 person-years, which is in agreement with the literature.

Figure 2A shows the expected HAART administration rate among HIV-1-infected persons according to various CD4 cell count-driven strategies in three countries with different HIV/AIDS healthcare systems. In a developing country with late-stage presentation of HIV-1 infection, two out of three patients present with HIV-1 infection at CD4 cell counts below 200 cells/mm³. Supply of HAART to people with CD4 cell counts below this level would thus concern 67%, while in a developed country this would concern only 10%. If every patient presenting with HIV-1 infection at CD4 cell counts below 500 cells/mm³ were to initiate HAART, the administration rate would be 90% in developing countries and 63% in developed countries.

In Figure 2B the expected 1-year cumulative incidence of AIDS-defining events is depicted as a function of the CD4 cell count threshold for HAART, where a 0 threshold stands for a scenario in which no antiretroviral drugs would be administered. In developing countries, the 1-year incidence of AIDS would already be substantially reduced from 35 to 16% if HAART were only supplied to those patients presenting with HIV-1 infection at CD4 cell counts below 100 cells/mm³. The AIDS incidence is further reduced to 12% if HAART was only supplied to those patients with CD4 cell counts below 200 cells/mm³, a treatment coverage of two-thirds of the population at risk for AIDS. Initiating HAART at higher CD4 cell counts might prove beneficial for the individual patient but has a negligible effect on the AIDS incidence in a hospital-based setting in developing countries, since the 1-year AIDS incidence would still be 10% if all patients presenting with HIV-1 infection were given HAART. In contrast, in a setting with relatively early presentation of HIV-1 infection, the expected 1-year incidence is much lower.

### Table 2. Three alternative estimates of the 1-year cumulative hazard of AIDS according to CD4 cell count observed in untreated HIV-1 infection

<table>
<thead>
<tr>
<th>CD4 stratum (cells/mm³)</th>
<th>n</th>
<th>Events</th>
<th>Obs. time (py)</th>
<th>Uncensored ID (events/100 py)</th>
<th>Censored ID (events/100 py)</th>
<th>Incl. death ID (events/100 py)</th>
</tr>
</thead>
<tbody>
<tr>
<td>600–700</td>
<td>353</td>
<td>11</td>
<td>347</td>
<td>3.2</td>
<td>2.1</td>
<td>3.7</td>
</tr>
<tr>
<td>500–600</td>
<td>424</td>
<td>26</td>
<td>409</td>
<td>6.4</td>
<td>4.2</td>
<td>6.8</td>
</tr>
<tr>
<td>400–500</td>
<td>450</td>
<td>31</td>
<td>432</td>
<td>7.2</td>
<td>4.2</td>
<td>7.6</td>
</tr>
<tr>
<td>300–400</td>
<td>453</td>
<td>37</td>
<td>428</td>
<td>8.6</td>
<td>7.5</td>
<td>8.9</td>
</tr>
<tr>
<td>200–300</td>
<td>368</td>
<td>44</td>
<td>341</td>
<td>12.9</td>
<td>9.3</td>
<td>13.8</td>
</tr>
<tr>
<td>100–200</td>
<td>230</td>
<td>61</td>
<td>191</td>
<td>31.9</td>
<td>27.9</td>
<td>33.3</td>
</tr>
<tr>
<td>&lt;100</td>
<td>96</td>
<td>48</td>
<td>62</td>
<td>77.9</td>
<td>58.6</td>
<td>82.4</td>
</tr>
</tbody>
</table>

The number of events and the corresponding observation time after attaining a specific CD4 cell count stratum in untreated HIV-1 infection, correspond to the uncensored estimates for which the observation time was not censored at start of antiretroviral treatment. Estimates censored at start of any antiretroviral regimen, as well as uncensored estimates including death as an event are presented for comparison.

### Table 3. Estimate of the 1-year cumulative hazard of AIDS after initiation of HAART according to CD4 cell count at start of therapy

<table>
<thead>
<tr>
<th>CD4 stratum (cells/mm³)</th>
<th>n</th>
<th>Events</th>
<th>Obs. time (py)</th>
<th>ID (events/100 py) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400–500</td>
<td>36</td>
<td>0</td>
<td>35</td>
<td>0 (0–10.5)</td>
</tr>
<tr>
<td>300–400</td>
<td>31</td>
<td>0</td>
<td>30</td>
<td>0 (0–12.3)</td>
</tr>
<tr>
<td>200–300</td>
<td>46</td>
<td>0</td>
<td>45</td>
<td>0 (0–8.2)</td>
</tr>
<tr>
<td>100–200</td>
<td>32</td>
<td>4</td>
<td>30</td>
<td>13.3 (3.6–34.1)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>26</td>
<td>4</td>
<td>24</td>
<td>16.6 (4.5–42.7)</td>
</tr>
</tbody>
</table>

Occurrence of AIDS following HAART is only considered in the first year after initiation of therapy. Modification of antiretroviral regimens was not taken into account. Confidence intervals reflect the 95% limits from a Poisson distribution for the number of observed events.

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cumulative incidence of AIDS could be reduced to almost 0 if all patients immediately started HAART at the time of seropositive testing (Figure 2B).

**Discussion**

The aim of the present study was to estimate the reduction in AIDS incidence when HAART is initiated based on a single CD4 cell count in HIV-1-infected people in resource-poor settings. The supply of antiretroviral medication can affect a maximum threefold reduction of the AIDS incidence in populations with HIV-1-infected patients presenting in an advanced stage of immunosuppression. Supply of HAART to people who present with HIV-1 infection at CD4 cell counts below 200 cells/mm³ is expected to give an administration rate of 67%, while preventing one AIDS-defining event for every three patients treated in countries characterized by late, often symptomatic, presentation of HIV-1 infection.

We sought to assess the benefit from initiating HAART with a 12-month horizon. The choice for an assessment on a 1-year base was motivated by considerations on the frequency with which patients would be monitored after being tested HIV-1-positive. An annual assessment constitutes a realistic monitoring frequency in resource-poor settings, while a lower frequency of monitoring is not desirable, considering the rate of CD4 cell count decline in untreated HIV-1 infection [23,24].

Several aspects of our approach might jeopardize the generalization of our findings to resource-limited environments. First, the spectrum of opportunistic diseases in resource-limited environments differs from that in our reference population. We have restricted the analysis to primary CDC-C events in our cohort study. Together, they represent a range of immunosuppression levels characteristic for the development of AIDS [25]. The overall hazard of AIDS conditional on CD4 cell count might be reasonably well approximated by our uncensored estimates if we can assume a similar pathogenesis in resource-poor environments.

Three studies performed in Western [26], Central [26,27] and Eastern [28] Africa provide estimates for the rate of CD4 cell count decline in sub-Saharan HIV-1-infected populations, which are lower when compared to estimates obtained from our cohort and cohort studies in the UK [23] and USA [24]. This suggests a different natural history of HIV-1 infection in sub-Saharan African populations. In the study in Eastern Africa, a faster progression was found from first positive HIV-1 test to symptomatic disease [29]. A study on disease progression among HIV-1-infected Africans of black ethnicity living in London but born in sub-Saharan Africa showed a significant lower CD4 cell count at first positive HIV-1 test and a faster progression to AIDS as compared to non-Africans. However, after adjustment for initial CD4 cell count, presence of CDC-B symptoms at presentation, year of first positive HIV-1 test, age and gender, the difference in rate of progression was no longer significant [30]. The lower CD4 cell count at first positive HIV-1 test might indicate a later presentation. The CD4 cell count at AIDS diagnosis in this London-based cohort was not significantly different between the Africans and the non-Africans [31]. The median CD4 cell count in
patients with AIDS in an Ethiopian study (78 cells/mm$^3$) [32] was lower as observed in our cohort study (150 cells/mm$^3$). This might be due to methodological biases, such as later presentation with, or later diagnosis of, clinical AIDS. Moreover, if pulmonary tuberculosis in HIV-1-infected Africans would be an AIDS-defining condition, which is not the case according to the current WHO classification system, the CD4 cell count at AIDS diagnosis would be more like the value observed in our cohort study.

In resource-limited countries most patients are currently naive to prophylactic and antiretroviral therapy [13]. In the developed world, prophylaxis is generally prescribed if the CD4 cell count drops below 200 cells/mm$^3$, while prophylaxis can be safely discontinued if the CD4 cell count rises above 200 cells/mm$^3$ during HAART [33,34]. We have made no correction for the use of prophylactic treatment against opportunistic disease, such as P. carinii pneumonia and CMV disease, nor have we considered the effect of mono- or combination antiretroviral regimens prior to HAART. In developing countries, both the expected AIDS incidence in untreated HIV-1 infection and the reduction due to HAART might then be underestimated. The best way to validate our analysis would be to use the very estimates of disease occurrence from resource-poor countries and develop strategies specifically targeted at those countries. Unfortunately, no data are available from cohort studies in resource-poor countries to provide the necessary information, most certainly not for the estimation of the AIDS risk following initiation of HAART.

A large proportion of HIV-1-infected patients in resource-poor countries is economically productive. Supply of HAART to those with low CD4 cell counts achieves a substantial reduction in the population level AIDS incidence, and might maintain the social and economic structure in these countries. As a side effect, transmission of HIV-1 may also be reduced due to HAART by lowering the level of circulating HIV-1 RNA [35], since low CD4 cell count is correlated with high-level viral replication. However, to reduce transmission of HIV-1, HIV-1 RNA levels should be lowered in all HIV-1-infected subjects, which is not the case when CD4 cell count is used for the initiation of HAART.

The flow cytometric procedure for the enumeration of CD4 cells is expensive as well as complex and might be unaffordable for wide-scale use in developing countries. Simple quantitative determination of CD4 cells may provide a feasible alternative, but still requires sophisticated instrumentation [36]. Semi-quantitative CD4 cell count assays could be developed at low cost and conveniently guide informed decision-making in the allocation of antiretroviral medication.

HAART has proven very successful in reducing AIDS-related morbidity and mortality, even in patients with advanced immunodeficiency [37]. Nevertheless, if HAART is started at a CD4 cell count below 200 cells/mm$^3$, patients are still at substantial risk for near-term development of AIDS or death, which has been demonstrated recently by Hogg and colleagues [38]. The current WHO recommendation for initiating HAART in resource-limited settings is a CD4 cell count below 200 cells/mm$^3$ [13]. Such a strategy could give a threefold reduction of the incidence of AIDS-defining disease and safeguard treatment efficiency in populations presenting at hospital in advanced stages of HIV-1 infection.

In order to present a scenario for the introduction of HAART in a developing country, we choose a hospital-based setting where patients presenting with HIV-1 already are in an advanced stage of immunosuppression. In resource-poor environments, HIV-1-infected patients do not come into contact with the healthcare system easily, comparable to subgroups in developed countries that are hard to reach for the purpose of surveillance, prevention and treatment [39]. Also, the scarcity of medical equipment and therapeutic options make active case finding and counselling about HIV-1 infection difficult. Availability of antiretroviral medication may increase the awareness of HIV-1 infection and make voluntary testing desirable, and could as such contribute to a further reduction of the AIDS incidence [40]. Whether this will happen in the near future is an important qualification for the long-term success of HIV-1 treatment programmes. Therefore, any protocol for the selection of patients for initiating HAART should be evaluated and adjusted upon introduction.

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