Modeling Aids control strategies

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Plasma HIV-1 RNA to guide patient selection for antiretroviral therapy in resource-poor settings: efficiency related to active case finding

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Chapter Six

Abstract

We determined whether patient selection for the initiation of HAART based on plasma HIV-1 RNA levels rather than or in addition to CD4 cell counts could result in a stronger reduction of the AIDS incidence in resource-poor settings. For this purpose, we estimated the one-year AIDS risk as a function of plasma HIV-1 RNA level and CD4 cell count, both in untreated HIV-1 infection and after the initiation of HAART, using data from the Amsterdam Cohort Studies on HIV infection and AIDS. We calculated the expected HAART administration rate and one-year AIDS incidence corresponding to different criteria for initiating HAART, in a community-based and in a hospital-based setting. Scenario analyses show that in a population presenting with HIV-1 in an intermediate stage of infection, the reduction in the one-year AIDS incidence would be higher for a given HAART administration rate if patients were selected on criteria for plasma HIV-1 RNA level rather than CD4 cell count. In a population presenting at a more advanced stage of HIV-1 infection, the reduction of the one-year AIDS incidence would be the same for a given HAART administration rate if patients were selected on a single CD4 cell count criterion as compared to selection on (additional) criteria for plasma HIV-1 RNA. In a hospital-based setting, decisions on the administration of HAART can be efficiently accomplished based solely on CD4 cell count. Additional criteria for plasma HIV-1 RNA level can ensure a more efficient allocation of therapy when patients are identified at less advanced stages of infection.
Introduction

According to Western guidelines for treatment of adults asymptptomatically infected with HIV-1, decisions for therapeutic intervention should be based on both the number of CD4 T lymphocytes in peripheral blood and the plasma concentration of HIV-1 RNA.\textsuperscript{13}

The WHO has adopted other criteria, to be used in resource-poor settings, for initiating HAART in asymptptomatically HIV-1–infected adults. If CD4 cell counts can be determined, those with less than 200 cells/mm\textsuperscript{3} are eligible for HAART, while for those with more than 200 cells/mm\textsuperscript{3} the presence of minor symptoms of immunodeficiency and the rate of CD4 cell count decline should be considered in making decisions about HAART initiation. If CD4 cell counting is not possible, total lymphocyte count may be used as a substitute marker. Assessment of viral load is not considered essential for the decision whether or not to start therapy.\textsuperscript{4}

Although the current laboratory procedures to accurately quantify CD4 cell count and plasma HIV-1 RNA level make wide-scale use in developing countries unaffordable, alternative technologies are being developed at low cost to guide better informed decisions than those based on total lymphocyte count or the presence of minor symptoms.\textsuperscript{5,7} The efficiency of such technology would be determined by the specific cutoffs of the diagnostic assays as well as by the algorithm that combines CD4 cell counts and viral load measurements. Different strategies for the selection of patients to start HAART might reflect distinct approaches for identifying patients at increased risk for near-term development of AIDS. Whether supplying HAART to patients at increased risk of AIDS represents a more efficient treatment allocation is a question of paramount importance in settings where resources are limited.

We evaluated different criteria for initiating HAART, based on CD4 cell count and plasma HIV-1 RNA level in two settings: a community-based and a hospital-based treatment programme. Populations are characterized by distributions for CD4 cell count and plasma HIV-1 RNA level as observed in sub-Saharan African populations. Strategies were evaluated and compared in terms of the expected one-year cumulative incidence of AIDS–defining events, at a range of HAART administration rates, using different HAART eligibility criteria. Our analysis relies on estimates for near-term disease progression, both in untreated HIV-1 infection and after the initiation of HAART, obtained through the Amsterdam Cohort Studies on HIV infection and AIDS (ACS).

Methods

Estimates for the one-year cumulative hazard of AIDS were derived from the ACS among homosexual men, which started in October 1984.\textsuperscript{8} We used follow-up information collected until May 2001, when 695 HIV-1–seropositive men had been identified; 494 were seropositive at enrolment and 201 seroconverted during follow-up. Onset of AIDS was considered according to the clinical part of the 1993 revised surveillance case definition for AIDS among adolescents and adults.\textsuperscript{9} A total of 300 participants have developed AIDS; 285 had died by May 2001. Only primary AIDS diagnoses were included in this analysis. In total, 260 patients started with HAART, defined as an antiretroviral regimen consisting of either three or more antiretroviral drugs, or two if either one is a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (nNRTI). The
median follow-up from first positive HIV-1 antibody testing to the last sampling time point before either start of antiretroviral therapy, AIDS diagnosis, or end of follow-up was 4.1 years. The median follow-up from start of HAART to either AIDS diagnosis or end of follow-up was 3.3 years.

**Laboratory techniques.** CD4 cell count and plasma HIV-1 RNA level were measured approximately every three months. Plasma HIV-1 RNA was measured with a nucleic acid sequence-based amplification (NASBA) assay (HIV-1 RNA QT or Nuclisens, Organon Teknika, Boxtel, The Netherlands) or with a reverse transcriptase-polymerase chain reaction (RT-PCR) assay (Amplicor HIV-1 Monitor, Roche Diagnostic Systems, Branchburg, NJ, USA). Undetectable plasma HIV-1 RNA was coded as the lower limit of detection of the assay used. Peripheral blood mononuclear cells were isolated from heparinized venous blood using density-gradient centrifugation on Ficoll-Paque (Pharmacia, Uppsala, Sweden) and absolute numbers of CD4 T lymphocytes were determined by cytofluorometry.

**Cox regression analysis**

In order to use the Cox regression model for the estimation of hazards based on irregularly observed time-dependent covariates, the data first were stratified for the AIDS diagnoses. The risk set within each stratum then consisted of those patients still at risk of progressing to AIDS at the time of the index event. Within each stratum, the last available CD4 cell count and plasma HIV-1 RNA level were used in the Cox regression model. Regression coefficients were estimated taking into account the time elapsed from the last available measurement to the index event.

The one-year AIDS risk after initiating HAART was estimated in the subgroup of 200 patients who had started HAART before April 2000 and had not been diagnosed with AIDS before. A Cox proportional hazards model was fitted, including the last available measurements on CD4 cell count and plasma HIV-1 RNA level before start of therapy, as well as the time elapsed since these measurements to the starting date of HAART. In this subgroup, 14 patients had progressed to AIDS after initiating HAART. Progression to AIDS after initiating HAART was studied on an intention-to-treat basis; modification of antiretroviral regimens was not taken into account.

To allow for a non-linear dependence of the AIDS log-hazard on CD4 cell count and log$_{10}$ plasma HIV-1 RNA level, we used polynomial functions of CD4 cell count and log$_{10}$ plasma HIV-1 RNA level in the Cox regression model, including interaction terms. Improvement of model fit upon addition of higher order polynomial or interaction terms was assessed using the likelihood ratio test statistic with significance level set at 0.05.

**Modeling population settings**

The effects of different HAART eligibility criteria on the population AIDS incidence were evaluated using joint distributions for CD4 cell count and plasma HIV-1 RNA level in the population at risk of AIDS. We wanted these distributions to reflect two different scenarios: (a) supply of HAART in a community-based setting with active case finding, where patients would present predominantly with intermediate-stage HIV-1 infection; and (b) supply of HAART in a hospital-based setting, where patients would present predominantly with late-stage HIV-1 infection. The joint distribution for CD4 cell count and plasma HIV-1 RNA level was modelled with a bivariate normal density function, following power transformations that provided best fit to marginal distributions as observed in two representative surveys performed in sub-Saharan African populations.
The first is a community-based survey on HIV-1 infection among adults in rural Uganda conducted in 1996. The second relates to a hospital-based study among HIV-1--infected adults who presented at infectious disease clinics in Senegal between 1994 and 1998. Contour plots of the two joint distributions are given in Figures 1a and 1b, respectively. Correlation between CD4 count and plasma RNA on the power-transformed scales was estimated from our own cohort data.

![Contour plots of the two joint distributions](image)

**Figure 1** In a sub-Saharan African community-based population setting, CD4~\( \sim \) Normal(12, 3.7) with \( \lambda=0.4, \) RNA~\( \sim \) Normal(7.6, 2.0) with \( \lambda=1.3 \) and \( r=-0.37. \) In a sub-Saharan African hospital-based population setting, CD4~\( \sim \) Normal(1.7, 0.19) with \( \lambda=0.1, \) RNA~\( \sim \) Normal(19, 6.7) with \( \lambda=1.8 \) and \( r=-0.38. \) Contour plots of the two joint distributions are given in figures A and B, respectively.

To evaluate the efficiency of HAART in both populations, we calculated the one-year cumulative AIDS incidence as

\[
1 - \int \int f(x_1, x_2) \exp \{-H(1 \mid x_1, x_2)\} \, dx_1 \, dx_2,
\]

where \( f(x_1, x_2) \) is the joint distribution for plasma HIV-1 RNA level and CD4 cell count in the population at risk of AIDS and \( H(1 \mid x_1, x_2) \) reflects the one-year cumulative AIDS hazard. For the part of the population that is supplied with HAART, according to one or more criteria, \( H(1 \mid x_1, x_2) \) is taken from the Cox model for the AIDS hazard after initiating HAART. For the rest of the population, \( H(1 \mid x_1, x_2) \) is taken from the Cox model for the AIDS hazard in the absence of HAART.
We plotted the expected one-year AIDS incidence against the administration rate of HAART that corresponded to the respective thresholds using different HAART eligibility criteria: (i) CD4 cell count below threshold; (ii) plasma HIV-1 RNA level above threshold; (iii) CD4 count below 200 cells/mm$^3$ or plasma RNA above threshold; and (iv) CD4 count below 350 cells/mm$^3$ and plasma RNA above threshold.

Data were analyzed using the SAS system, release 8.02 (SAS Inc., Cary, NC, USA) and S-Plus 2000, professional release 1 (Insightful Corp., Seattle, WA, USA).

**Results**

In the sub-Saharan African community-based study, half of the patients presented with HIV-1 infection at CD4 counts above 500 cells/mm$^3$ and less than 15% presented with HIV-1 infection at CD4 counts below 200 cells/mm$^3$. The HIV-1 RNA levels reported in this study were derived from serum and were, considering the distribution of CD4 cell counts, very high. Only 23% of the HIV-1-infected patients had HIV-1 RNA levels below 10,000 copies per millilitre (cp/mL), whereas 40% had HIV-1 RNA levels above 100,000 cp/mL (Figure 1a). In the hospital-based study performed in Western Africa, patients presented with HIV-1 infection at much lower CD4 cell counts: 16% above 500 cells/mm$^3$ and 53% below 200 cells/mm$^3$. HIV-1 RNA levels were even higher: 18% below 10,000 HIV-1 RNA cp/mL and 57% above 100,000 HIV-1 RNA cp/mL (Figure 1b).

The one-year cumulative AIDS hazard functions in untreated HIV-1 infection and after initiation of HAART, estimated from ACS data, are presented in Figures 2a and 2b. Both CD4 cell count and plasma HIV-1 RNA level are significant predictors of progression to AIDS in chronic, untreated HIV-1 infection, but they do not act independently. The one-year hazard of AIDS conditional on plasma HIV-1 RNA level remains fairly constant at CD4 counts above 350 cells/mm$^3$ and shows a sharp increase at CD4 counts below 200 cells/mm$^3$, especially for higher levels of plasma HIV-1 RNA (Figure 2a).

Similar trends apply to the one-year hazard of AIDS after initiation of HAART, but the AIDS hazard is substantially reduced compared to the AIDS hazard in untreated HIV-1 infection (Figure 2b; note the different scaling of the y-axis). If HAART is initiated at CD4 counts below 200 cells/mm$^3$, patients are at increased risk to develop AIDS compared with initiation at higher CD4 cell counts. For CD4 counts below 350 cells/mm$^3$, the AIDS risk increases gradually with higher plasma HIV-1 RNA levels at initiation of HAART.

In the absence of treatment, the one-year AIDS incidence is estimated at 14% in the community-based setting (Figure 3a), and at 30% in the hospital-based setting (Figure 3b). Selecting patients for initiating HAART based on CD4 cell counts or on plasma HIV-1 RNA levels would lead to HAART administration rates that increase with the respective thresholds (Figure 3). If either a plasma HIV-1 RNA level above threshold or a CD4 cell count below threshold is a criterion for initiating HAART, the number of patients eligible for HAART would further increase. On the other hand, if both plasma RNA above threshold and CD4 count below threshold are required to initiate HAART, the number of patients eligible for HAART will decrease, compared to eligibility criteria based on either plasma HIV-1 RNA level or CD4 cell count.
A. One-year cumulative AIDS hazard in untreated HIV-1 infection

![Graph](image)

B. One-year cumulative AIDS hazard after initiation of HAART

![Graph](image)

**Figure 2** The regression equation for the hazard of AIDS in untreated chronic HIV-1 infection as determined by a stratified Cox proportional hazards model was estimated as $-13 \text{CD}^4 + 23 \text{CD}^4 \times 22 \text{CD}^4 + 11 \text{CD}^4 - 2.1 \text{CD}^4 - 0.27 \text{RNA}^2 + 0.13 \text{RNA}^2 + 2.7 \text{RNA}^2 \times \text{CD}^4 + 0.34 \text{RNA}^2 \times \text{CD}^4$.

The regression equation for the hazard of AIDS after initiation of HAART as determined by a standard Cox proportional hazards model was estimated as $-9.6 \times \text{CD}^4 + 0.93 \times \text{RNA}^2$.

In these equations, $\text{CD}^4$ stands for CD4 cell count (in cells/mm$^3$) to the power $\lambda$ minus mean $\text{CD}^4$; $\text{RNA}^2$ stands for plasma HIV-1-RNA level (in log$_{10}$ copies/ml) to the power $\lambda$ minus mean $\text{RNA}^2$, and $\text{RNA}^2 \times \text{CD}^4$ stands for interaction between $\text{RNA}^2$ and $\text{CD}^4$.

All parameters where statistically significant at $p < 0.05$. Additional terms did not improve model fit.

Less stringent eligibility criteria for HAART allow a larger proportion of the population at risk of AIDS to initiate treatment. Higher HAART administration rates may reduce the one-year incidence of AIDS-defining events, but the extent to which this incidence is reduced depends on the set of patients selected for HAART. In a community-based setting, the selection of patients for HAART initiation on the basis of plasma HIV-1 RNA level rather than CD4 cell count would result in a higher reduction of the one-year AIDS incidence at a particular HAART administration rate, thereby increasing the efficiency of treatment (Figure 3a). In this situation, selection of patients to initiate HAART on the basis of a combined criterion would increase the efficiency of HAART even more. For instance, supplying HAART to all patients with CD4 counts below 350 cells/mm$^3$ is expected to
reduce the one-year AIDS incidence to 7.9% at an administration rate of 33%. In contrast, supplying HAART to patients with less than 200 CD4 cells/mm$^3$ or more than 300,000 HIV-1 RNA cp/mL would lead to a comparable administration rate of 32%, but would result in a one-year AIDS incidence of 6.7% (Figure 3a). To achieve a comparable reduction of the one-year AIDS incidence by relying on CD4 cell counts only, all patients with CD4 cell counts below 500 cells/mm$^3$ would have to initiate HAART. Such a strategy would result in an administration rate of almost 50% (Figure 3a).

**Figure 3** The markings at a zero HAART administration rate correspond to a scenario without supply of ART, and thus represent the background incidence of AIDS-defining events in absence of treatment. The different lines represent different strategies for the selection of patients for HAART initiation. Solid lines only consider CD4 cell count below threshold. The specific CD4 cell count threshold, below which HAART is to be initiated, is varied along the lines, from 100 cells/mm$^3$ (left) to 500 cells/mm$^3$ (right). Broken lines require plasma HIV-1 RNA level above threshold, either as a single eligibility criterion for HAART or in combination with a CD4 cell count criterion. The specific plasma HIV-1 RNA threshold, above which HAART is to be initiated, is varied along the lines, from 300,000 copies/ml (left) to 10,000 copies/ml (right).

In a hospital-based setting, the reduction of the one-year AIDS incidence at a particular HAART administration rate would be more or less the same if patients were selected on the basis of plasma HIV-1 RNA level, CD4 cell count or a combination of both (Figure...
3b). For example, if HAART is supplied to all patients with CD4 counts below 350 CD4 cells/mm³, the one-year AIDS incidence is reduced to 15% at an administration rate of 74%. Supplying HAART to patients with less than 200 CD4 cells/mm³ or more than 100,000 HIV-1 RNA cp/mL would yield almost similar figures: a one-year AIDS incidence of 14% at an administration rate of 73% (Figure 3b). Using plasma HIV-1 RNA level instead of, or in addition to, CD4 cell counts cannot further increase the efficiency of HAART in a hospital-based setting (Figure 3b).

Discussion

We evaluated the efficiency of HAART on the population level according to alternative criteria for the selection of patients to initiate treatment in resource-poor settings. Our analysis demonstrates a higher efficiency of HAART administration if patients are selected using criteria for both CD4 cell count and plasma HIV-1 RNA level in populations that tend to present with HIV-1 in intermediate stages of infection. If patients present with HIV-1 in more advanced stages of infection, the use of plasma HIV-1 RNA level does not increase the efficiency of treatment.

We have previously shown that restriction of HAART to those with CD4 cell counts below 200 cells/mm³ represents an efficient allocation of limited resources in populations where people at risk of AIDS tend to present with HIV-1 in advanced stages of infection. In this paper we show that relying on plasma HIV-1 RNA levels for initiating HAART will not improve the efficiency of treatment in these populations. This finding provides evidence to the current WHO recommendations, where viral load assessment is not considered an essential preliminary to therapy in resource-poor settings. Yet, the WHO recommendations do not distinguish a hospital-based setting from a community-based setting. In a hospital-based setting patients can be expected to present at more advanced stages of HIV-1 infection. Active case finding in community-based treatment programmes is likely to identify patients with HIV-1 in less advanced stages of infection, for which viral load assessment may improve the efficiency of HAART administration.

Our AIDS hazard estimates in untreated HIV-1 infection are in accordance with previous findings that plasma HIV-1 RNA level is associated with the risk of progression to AIDS at all levels of CD4 cell count, whereas the prognostic value of CD4 cell count increases with ongoing infection, i.e. at lower levels of CD4 cell count. Similarly, we confirm that patients are at increased risk for developing AIDS if HAART is initiated at CD4 cell counts below 200 cells/mm³, compared with initiation at higher CD4 cell counts.

In our analysis, we have defined HAART as triple-drug therapy, or dual-drug therapy if either drug was a PI or NNRTI. Moreover, we have included patients with a history of sub-optimal therapy before starting HAART, which might have increased the likelihood of HAART failure. Since the current recommended first-line regimen is triple-drug therapy, we may have underestimated the effectiveness of treatment prescription according to current guidelines.

Introduction of HAART in settings with a poor health infrastructure has evoked concerns about the potential development and spread of drug-resistant HIV-1. Whether these concerns are confounded due the specific history of sub-optimal antiretroviral drug use in Western countries and could be overcome if triple-drug HAART is concurrently introduced through HIV-1 treatment programmes that utilize the health infrastructure.
already available in resource-poor settings, e.g. embedded in existing tuberculosis control programs, remains open to debate.\textsuperscript{21,22} In any case, the prevalence of viral resistance in the HIV-1-infected population will be rare in the initial phases of an antiretroviral treatment programme. Effectiveness of HAART is then more likely to depend on the prevalence of adverse reactions to HAART and the compliance of patients to HAART. The efficiency of distinct HAART administration strategies might be differentially affected if drug-induced toxicity and poor adherence are related to the CD4 cell count or plasma HIV-1 RNA level at start of therapy, but there is no direct evidence to support this possibility.\textsuperscript{23,24} Close monitoring of patients is nonetheless essential in order to assess the efficiency of the treatment strategy followed and re-examine eligibility criteria when data on toxicity, adherence and resistance emerge from treatment programmes outside of the clinical trial setting.

In evaluating the efficiency of different eligibility criteria for HAART initiation in resource-poor settings, we used distributions for CD4 cell count and plasma HIV-1 RNA level as observed in studies performed in Uganda and Senegal.\textsuperscript{1,12} The levels of viremia that were reported in these studies are much higher than in the Amsterdam cohort, even after adjustment for CD4 cell count. In the Ugandan study HIV-1 RNA was derived from serum, whereas in our cohort study it was derived from plasma. Quantification of HIV-1 RNA derived from serum generally gives lower estimates of viremia as compared to quantification of plasma-derived HIV-1 RNA.\textsuperscript{25} This indicates a truly higher level of circulating virus in sub-Saharan African people. Few studies have reported associations between systemic infections, such as malaria, and high levels of viremia in HIV-1 infection, but whether this is a cause or consequence of the increased plasma HIV-1 RNA levels is unclear.\textsuperscript{26-28} Good reference values for the levels of viremia in HIV-1-infected populations in sub-Saharan Africa are indispensable for the development of sound and manageable eligibility criteria for HAART.

Progression to symptomatic disease is reported to occur more rapidly in HIV-1-infected populations in Uganda and Western Africa,\textsuperscript{29,30} but the time from seroconversion to AIDS and death in Uganda is similar to that in developed countries before the introduction of antiretroviral therapy.\textsuperscript{31} The community-based study that we have used for evaluation of a setting with active case finding showed a cumulative mortality of 12% within one year of follow-up.\textsuperscript{13} Based on our approximation of the joint distribution for CD4 cell count and plasma HIV-1 RNA level in this population, and using risk estimates derived from the ACS, we calculated a one-year AIDS incidence of 14%. Although it is not clear whether all deaths reported in the Ugandan cohort were related to HIV-1, it does not seem that extrapolation of our risk estimates is flawed due to the high HIV-1 RNA levels in sub-Saharan African populations.

Antiretroviral therapy provides a means to break the vicious circle in which many resource-poor countries find themselves, as the ongoing AIDS epidemic is expected to lead to increased mortality rates in young and economically productive age groups, leading to further impoverishment and social decline.\textsuperscript{32} Community-based treatment programmes can only be sustained if treatment is offered equitably and judiciously to ensure that patients with similar needs have an equal chance to receive treatment, within the bounds of capacity of a particular health care system.\textsuperscript{33} In a setting that relies on active case finding, selection of patients to initiate HAART by additional criteria regarding plasma HIV-1 RNA level could result in a more efficient supply of HAART as compared to selection on CD4 cell count criteria alone. Whether such a strategy is also cost-effective
will be determined by the total costs of the monitoring strategy put in place, including the costs of RNA testing and of the particular criteria for treatment eligibility.

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