

Investigating optimal treatment allocation strategies in resource limited settings



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Background

- In resource limited settings, many HIV-positive patients die before receiving appropriate treatment. In these settings it is therefore important to ensure that systems of queuing for treatment are optimised.
- Current WHO treatment guidelines state that patients become eligible to receive treatment either when their CD4 cell count drops below 200 cells/mm³ or when they have advanced disease (WHO disease stage IV OR stage III coupled with CD4<350 cells/mm³).
- Even given these constraints, there are not enough resources to treat all eligible patients. Simulation studies may be useful in examining how to optimize treatment allocation strategies.

Objectives

- Develop models of disease progression for patients on the waiting list for anti-retroviral treatment and for patients after starting treatment.
- Apply different strategies of treatment allocation to move patients from the first model to the second.
- Assess effectiveness of treatment allocation strategies in terms of mortality.

Methods

- This work is a pilot study based on a synthesis of data from South African sources.
- Patients are categorised into health states according to their CD4 count and AIDS status. Health states are labelled X_{i,j} where the i index represents their CD4 count category (i=1, 2, 3 represents CD4<200, between 200 and 350, and CD4>350 respectively) and the j index represents their AIDS status (j=0, 1 represents No AIDS and AIDS respectively).

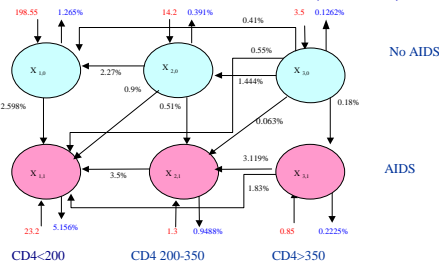
Modelling disease progression

- Markov models were used to model the monthly progression of HIV infection, defined in terms of CD4 category change, progression to AIDS and mortality, in both patients who are not on treatment (Model 1) and patients who have started treatment (Model 2). Transition probabilities to inform these models came from data published from the Cape Town AIDS Cohort (Badri, et al 2006, Antiviral Therapy).
- Average monthly arrivals to the queue for treatment and numbers receiving treatment were obtained from data on the Free State Province, South Africa. See Figure 1 for these numbers.

Treatment allocation strategies

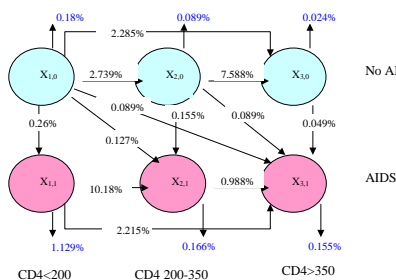
- Treatment allocation strategies took the form of an ordering of the health states. If a health state takes priority, then all patients in that health state are given treatment until the treatment runs out. If there is treatment left, move on to treating the next health state in the priority list. See Figure 3 for an example of treatment strategy 1.
- Eight different treatment allocation strategies were applied in order to move patients from Model 1 to Model 2.
 - Strategy 1: X₁₁ X₂₁ X₃₁ X₁₀ X₂₀ X₃₀.** Treat patients with AIDS and CD4<200 (X₁₁) first, followed by: AIDS and CD4 200-350 (X₂₁), AIDS and CD4>350 (X₃₁), No AIDS and CD4<200 (X₁₀), No AIDS and CD4 200-350 (X₂₀), No AIDS and CD4>350 (X₃₀). **PRIORITISING PATIENTS WITH AIDS.**
 - Strategy 2: X₁₁ X₁₀ X₂₁ X₂₀ X₃₁ X₃₀.** **PRIORITISING PATIENTS WITH LOW CD4 COUNTS.**
 - Strategy 3: X₃₀ X₃₁ X₂₀ X₂₁ X₁₀ X₁₁.** **PRIORITISING THE MOST HEALTHY PATIENTS.**
 - Strategy 4: X₁₁ X₁₀ X₂₁ X₃₁ X₂₀ X₃₀.** This strategy considers a "threshold" effect with CD4 cell count i.e. patients with CD4<200 are treated first, after this, the priority is to treat patients with AIDS, then moving on to look at those with CD4>200 and No AIDS.
 - Strategy 5: X₁₁ X₂₁ X₁₀ X₂₀ X₃₁ X₃₀.** This strategy also considers a "threshold" effect with CD4 cell count, but here the threshold is set to prioritize patients with CD4<350.
 - Strategy 6: X₁₀ X₂₀ X₃₀ X₁₁ X₂₁ X₃₁.** This strategy prioritizes patients with No AIDS and low CD4 cell counts, with the aim being to prevent patients developing AIDS.
 - Strategy 7: X₃₁ X₃₀ X₂₁ X₂₀ X₁₁ X₁₀.** This strategy prioritizes patients with high CD4 cell counts, with the aim being to prevent patients reaching low CD4 cell counts.
 - Strategy 8: X₃₀ X₂₀ X₁₀ X₃₁ X₂₁ X₁₁.** This strategy prioritizes patients with No AIDS and high CD4 cell counts, with the aim being to prevent patients developing AIDS.
- Based on data from the Free State Province in 2004-5, starting patients on treatment is limited to 134.2 patients each month on average.
- The models were run over 100 months and estimated mortality was recorded for each of the eight strategies.

Figure 1: Monthly Disease Progression Model for patients on the waiting list for anti-retroviral treatment (Model 1)



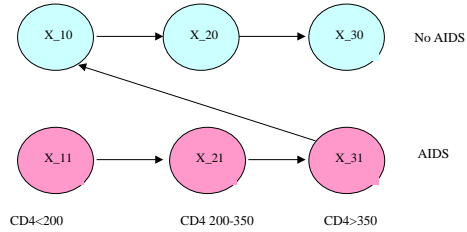
Numbers in red represent the monthly average number of enrolments to HIV clinics for that health state. Percentages in blue represent monthly mortality rates from each health state if patients receive no treatment. The remaining percentages represent monthly transition probabilities between health states.

Figure 2: Monthly Disease Progression Model for patients who have started treatment (Model 2)



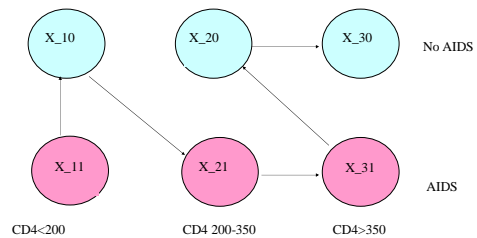
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Figure 3: Treatment allocation strategy 1



Patients in state X₁₁ (AIDS and CD4<200) are the first priority to receive treatment. Any treatment left over then goes to treat patients in state X₂₁, then any treatment left goes to treat patients in health state X₃₁, and so on with health states X₁₀, X₂₀ and X₃₀ until treatment runs out.

Figure 4: Treatment allocation strategy 4



Results

- An estimated 24,160 patients entered the system over 100 months (241.6 patients per month).
- Under these conditions, many of the strategies are similar or equivalent. Strategies 3 and 8 are almost indistinguishable and so, only strategy 3 has been displayed in Figure 5.
- Strategies 1, 2, 4 and 5 are all indistinguishable on the graph and it turns out that under these conditions strategies 2 and 4 are equivalent. Only strategy 2 has therefore been displayed in Figure 5.
- The strategy that resulted in the fewest deaths over 100 months was strategy 2 or strategy 4 (with the amount of treatment available in this scenario these strategies are equivalent).
- Strategy 2 prioritised treating patients with AIDS and CD4 <200. Any treatment left over should then be given to patients in the following order: (1) No AIDS and CD4 <200, (2) AIDS and CD4 200-350, (3) No AIDS and CD4 200-350, (4) AIDS and CD4>350 (5) No AIDS and CD4>350.
- This strategy resulted in 6219 deaths (25.7%) over 100 months. (See Figure 5)
- By comparison, the worst performing strategy was strategy 3. Strategy 3 prioritised giving treatment to the most 'healthy' patients first (i.e. those with No AIDS and CD4>350).
- This resulted in 7791 deaths (32.2%) over 100 months.
- Treating no-one leads to 15424 deaths (63.8%). Treating all patients resulted in 1263 deaths (5.2%).
- Figure 6 shows that when run for 100 months Strategies 2 and 4 result in the least mortality, however when run for 200 months Strategy 6 then results in the least mortality.

Figure 5

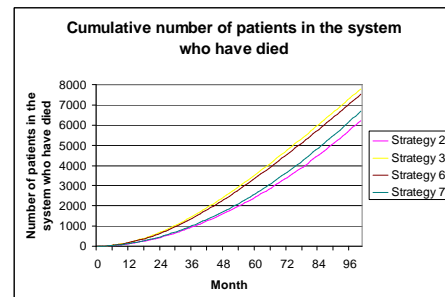


Figure 6

| | S1 | S2 | S3 | S4 | S5 | S6 | S7 | S8 |
|----------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Number of deaths over 50 months | 1764 | 1754 | 2620 | 1754 | 1759 | 2484 | 1866 | 2620 |
| Number of deaths over 100 months | 6232 | 6219 | 7791 | 6219 | 6226 | 7623 | 6673 | 7718 |
| Number of deaths over 200 months | 19794 | 19770 | 19570 | 19770 | 19789 | 19272 | 20136 | 19529 |

Discussion

- Operational research on appropriate strategies to allocate treatment in resource-constrained settings could help to minimise mortality or at least model the effect on mortality of different levels of access to treatment.
- There is also interest in looking at how strategies perform when they are run over different time periods. The treatment strategy which results in the least mortality in the short term may not be the best strategy over the long term. As access to treatment improves the long term outcome will become more important.
- It is of particular interest to consider models using health states based on a more refined categorisation of CD4 cell count. In resource poor settings, questions of how to deal with patients enrolling in HIV clinics with CD4 cell counts of <25, <50, <100 are particularly pertinent.
- Models such as these could be applied to different settings once better data has been collected as part of the International Epidemiologic Databases on Evaluating AIDS (IeDEA) initiative.

Further Work

- In this preliminary work models were run deterministically, i.e. the uncertainty in the input parameters (transition probabilities, numbers arriving to the queue and numbers receiving treatment each month) was not modelled. Future work will assess the sensitivity of these results to parameter uncertainty.
- Further work will also include grouping patients into more refined categories of CD4 cell count and also assessing how strategies perform when run over different periods of time.