The Impact of Delaying Uptake of Second Line Therapy on the Cost-Effectiveness of Antiretroviral Treatment in South Africa

Running Head: Cost-Effectiveness of Adherence to HAART in South Africa

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Abstract

Background: Maximizing the benefit of antiretroviral therapy (ART) requires limiting treatment failure. Interventions, such as adherence counseling, that ensure consistently high adherence to therapy may play an important role in this process. There is little evidence on the efficiency of such interventions.

Methods: A cost-effectiveness analysis was conducted from a public healthcare perspective to compare non-provision of ART (No-ART) with the incremental provision of ART (ART-AC) and an adherence counselor intervention (ART+AC). The analysis was based on primary treatment outcome, healthcare utilization, cost and quality-adjusted life year (QALY) data from a single South African cohort of ART patients. A Markov state-transition model was constructed with states defined by CD4 cell count stratum, WHO clinical stage, time since ART commencement and ART regimen.

Results: Mean life-expectancy was 3.4, 14.3 and 16.3 years, discounted (3%) QALYs were 2.2, 8.3 and 9.1 and discounted lifetime costs were $14,490, $17,474 and $17,567 in the No-ART, ART-AC and ART+AC arms respectively. The incremental cost-effectiveness ratio (ICER) of providing ART alone was $488 per QALY, while adding AC to ART had an ICER of $444 per QALY versus No-ART and $116 per QALY compared to ART-AC. The intervention was not very sensitive to varying AC efficacy; at an 8% discount rate all interventions were cost-saving.

Conclusions: The use of adherence counseling in the provision of ART in Africa adds little to the lifetime cost of treating HIV-positive persons and may well be cost-effective in a South African setting.

Background:

The widespread provision of highly-active antiretroviral therapy (ART) in low- and middle-income countries is now a reality, with an estimated 1.3 million persons receiving such treatment by the end of 2005.[1] This, however, represents only 20% of the total need in these nations. International funding commitments for ART programs are already falling short of expected need,[2] while a shortage of healthcare providers has been seen in several settings.[3,4] In response to these constraints programs have limited the range of antiretrovirals available through the public-sector, often to an initial non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen plus a second protease-inhibitor (PI)-based regimen.[5,6]

With a maximum of two ART regimens being available, conservation of treatment options through limitation of treatment failure is crucial to long-term patient survival. Studies suggest that very high levels of adherence to therapy are needed to avoid the emergence of resistant strains of HIV, and hence treatment failure.[7,8] Trials of individualized adherence-improvement interventions in richer nations have shown them to be linked to a consistent rise in adherence levels, and in several cases a significant difference in HIV RNA viral load change, rates of viral suppression or rates of viral breakthrough.[9-14]

Evaluating the cost-effectiveness of adherence interventions is, however, complicated by the lack of data directly linking interventions to improved long-term outcomes (15). Two existing studies have assessed through modelling the cost-effectiveness of adherence interventions with varying hypothetical costs and benefits in the United States.[16,17] A third study conducted a limited evaluation of an existing program in Brazil.[18]

This study evaluates the potential impact of an existing peer-based adherence counsellor program on the cost-effectiveness of reduced failure on first-line therapy (FLT), and hence progression to second-line therapy (SLT).

Methods:

Study Population

This analysis was based on a cohort of patients at the Hannan Crusaid Treatment Centre (HCTC), a clinic in a peri-urban settlement near Cape Town, South Africa. The site began recruitment in September 2002, and is now part of the national public-sector antiretroviral roll-out. Its work has been previously described.[19] The HCTC acts as primary healthcare facility to all patients enrolled in it, referring them to other health services as needed. Clinical enrolment criteria are a CD4 lymphocyte count < 200 cells/μl or an AIDS-defining illness, in line with national public-sector treatment guidelines.[5,6]

The adherence counsellor (AC) intervention consists of both pre- and on-treatment elements. At their screening visit, each patient is allocated a therapeutic adherence counsellor, a person from the same community who is openly living with HIV, who provides ongoing treatment support. A counsellor is responsible for up to 50 patients. Pre-treatment support involves patient attendance of three group education sessions conducted by the counsellors, and a home-visit from the counsellor. On-treatment support includes further home-visits and group discussions at scheduled clinic visits. CD4 count and viral load are monitored at scheduled visits every 16 weeks; home-visits and support are intensified if a viral load >1000 copies/ml is observed. A second

consecutive viral load >1000 copies/ml is considered treatment failure and the patient is moved to SLT. Patients need not have ever been virally suppressed in order to fail.

Cost-effectiveness Model

Cost-effectiveness analysis was conducted as a Monte-Carlo simulation of a Markov state-transition model using TreeAge Pro 2005 (TreeAge Software: Williamsontown, MA). The model used four-month (112 day) cycles. The model compared the non-provision of ART (No-ART) to the hypothetical provision of ART only (ART-AC) and the actual provision of ART and adherence counselling (ART+AC).

The states in each arm of the model were defined by CD4 cell count stratum (<100/μl; 100-199/μl; 200-349/μl; >350/μl), by clinical stage (Non-AIDS: WHO stage 1,2,3; AIDS: WHO stage 4) and in the ART arms by time since commencement of ART (1-4 months; 5-12 months; >12 months). A single state was created for second-line therapy (SLT). Based on evidence that risk of treatment failure is less more strongly correlated with initial WHO stage after six months on treatment,[20] and from tests of proportion for differences in transition probabilities using Stata version 9.1 (StataCorp: College Station, TX), many of the states were merged.

The No-ART arm constrained individuals to progressing to lower CD4 cell counts (Figure 1). For the first 12 months on treatment the ART arms used non-recursive states from which an individual had to progress at the end of each period; after 12 months they reverted to a standard Markov model. Progression to death was possible from all states; progression to SLT or loss to follow-up (LTFU) was possible from all FLT states (Figure 2). As a conservative assumption, due to limited data, persons LTFU were assumed to progress immediately to the highest-risk state of 'Off-ART,

AIDS, CD4 <100/µl'. The model was run for 163 cycles (50 years). All costs and QALYs were discounted at 3% in line with international guidelines.[21]

Transition Probabilities

Transition probabilities for HIV-positive persons not receiving antiretrovirals were derived from the Cape Town AIDS Cohort (CTAC), consisting of patients seen at a dedicated HIV clinic in Cape Town between 1994 and 2000.[22] For the purposes of this study patients joined the cohort at first CD4 count <200 cells/µl or at AIDS diagnosis, and were followed up until death, LTFU or the end of observation at 31 December 2000.

Transition probabilities for HIV-positive persons receiving antiretrovirals were calculated from all patients who had commenced antiretrovirals at the HCTC prior to 11 August 2005. Each patient was followed up from commencement to death, LTFU, transfer to another clinic, commencement of SLT or their first scheduled visit after 11 August 2005. In the ART-AC arm FLT failure, and hence SLT commencement, was modelled to occur on the date at which a first viral load >1000 copies/ml was recorded.

Given limited data on lopinavir/ritonavir (the PI used in the South African public-sector) in Africa, risks of failure or death on SLT were derived from published, four-year efficacy data for lopinavir-based regimens in Italy and the United States.[23,24] As a conservative assumption, the lowest efficacy figure from these data was used as the base case.

Initial state probabilities for patients in all arms were based on the distribution in the HCTC cohort at enrolment. Transition probabilities were calculated as the number of transition events seen divided by the number of four-month periods at risk in each state

with an exact Binomial distribution. Non-HIV mortality risk was derived from South African life tables for the relevant income group, under the assumption that individuals entered at the HCTC cohort's median age.[25]

Utilization and Cost data

Utilization and cost of healthcare services for each Markov state were calculated from all eligible patients enrolled at the HCTC prior to 2004 using a public healthcare provider perspective. These patients and their utilization of care have been described previously.[26] Data on utilization, both at the HCTC and at higher levels of care, were collected from paper and electronic files, and mean annual visits at each level calculated with an exact Binomial distribution.

The cost of each visit was calculated from a combination of bottom-up and top-down methods. Mean use of medical tests, procedures and non- antiretroviral medicines were calculated from the utilization data. Costs were based on provincial hospital tender prices (Varnee Niecker, personal communication, July 2005) for medicines, medical tests from public-sector tariffs (Nanette Spencer, personal communication, August 2004) and medical procedure costs from cost-recovery charges made to private patients.[27]

Personnel and overhead costs for hospital care were calculated from 2004-05 expenditure data on a per patient-day equivalent using step-down accounting methods, with an inpatient day being weighted as 3.77 outpatient visits. [28,29] Personnel and overhead costs for the HCTC care were calculated per patient-visit based on data from the 2005-06 financial year.

Antiretroviral costs were those of the public-sector tender (Liezl Channing, personal communication, May 2005). The primary regimen was NNRTI-based and modelled as consisting of stavudine, lamivudine and efavirenz (over 90% of the HCTC cohort began on this combination). In the case of virological failure, or adverse reaction, a second, PI-based regimen of zidovudine, didanosine and lopinavir/ritonavir was provided.

The AC intervention was costed from the bottom up for the 2005-06 financial year to arrive at a cost per patient-day enrolled at the HCTC. Treatment costs for tuberculosis directly-observed treatment (DOTS), which was not provided by the HCTC, were taken from a cost study of the local tuberculosis clinic conducted in 2000.[30] Given the limited available data on utilization on SLT, the SLT state used mean utilization from all patient-time >12 months on treatment. All costs were adjusted to 2004 prices using the South African Consumer Price Index excluding mortgage payments, [31] and converted to US dollars at the average 2004 exchange rate of US1=SAR6.4347.[32]

Exploratory regressions using a gamma distribution with a log link found a baseline AIDS diagnosis to be most strongly predictive of total costs prior to, and from 1-4 on, treatment, while CD4 count <100 cells/μl was more strongly predictive after 4 months on treatment. Utilization rates were determined in four categories: 'AIDS' and 'No-AIDS' prior to 4 months on treatment, and 'CD4<100' and 'CD4>100' thereafter. These rates were then multiplied by unit costs to reach total costs for these categories.

Quality of Life

Quality of life values were derived from questionnaire data from the HCTC site. The Medical Outcomes Survey Short Form (SF-36) was administered at patients' screening visit, their treatment commencement visit and every sixteen weeks thereafter between September 2002 and November 2004 to a subsample of patients from the ART cohort.[33]

The raw scores were converted into the SF-6D form and then into Quality Adjusted Life Years (QALY) using British general population standard gamble valuations.[34]

Each score was matched to the relevant Markov state based on baseline WHO stage and CD4 cell count at the start of each period. Given the smaller sample sizes for visits after the first four-month period on treatment, and the relative homogeneity of the QALY scores for each Markov state, all week 16 and week 32 scores, and all week 48 and above scores, were merged to form values for 5-12 and >12 months on-treatment. The latter value was also used for the SLT state. Bias-corrected and accelerated 95% confidence intervals were calculated by conducting 10,000 bootstrap repetitions for each state.

Sensitivity Analyses

Probabilistic sensitivity analysis was used to provide an indication of the uncertainty arising from the parameter estimates in the model .[35] Triangular distributions were constructed non-parametric around all costs, QALYs and transition probabilities using the 95% confidence intervals derived above. A second-order Monte-Carlo simulation was then run, randomly selected values from the triangular distributions 10,000 times, to create a probability distribution.

A one-way sensitivity analysis was performed on the benefit provided by the AC intervention by varying the rate at which patients failed FLT. As a low estimate of its benefit, the ART-AC progression rates to SLT were reduced to half the difference between the ART+AC and ART-AC baseline figures; as a high estimate of its benefit, the ART-AC progression rates were doubled.

A second sensitivity analysis considered the effect of faster or slower progression from second line to death or LTFU using the highest rates from the HCTC cohort (all patient-time >12 months on treatment) and the lowest rates from the literature. A third sensitivity analysis was conducted using 0 and 8% discount rates, the latter reflecting the return on long-term government bonds in South Africa (36).

Results:

Study Population

The baseline characteristics of the three samples drawn from the HCTC cohort and that drawn from CTAC are described in Table 1. Median age, CD4 count distribution and mean viral load (not available for CTAC) were similar across all groups. A larger proportion of the HCTC cohorts were female than the CTAC sample. Variation in baseline WHO stage was seen, but in all cases more than a quarter of patients had had an AIDS-defining illness and over two-thirds were symptomatic. Markov state transition probabilities for all arms are shown in Table 2.

Healthcare utilization and cost

The annual cost of ART was US$104 and US$253 for FLT and SLT respectively. Monitoring tests cost US$119 from baseline visit to four months and US$82 in each four-month period thereafter. The Adherence Counsellor program cost US$8.40 per period. These non-visit-specific costs were added to the visit-specific costs in Table 3 to generate total Markov state costs (Table 4). Quality of life values are also shown in this table.

Cost-effectiveness analysis

The undiscounted mean life-expectancy in the No-ART arm was 3.4 years, compared with 14.3 years for the ART-AC arm and 16.3 years for the ART+AC arm. A similar pattern was seen for QALYs (Table 5). The mean lifetime cost of treatment, discounted at 3%, was $14,490 for the No-ART arm, $17,474 for the ART-AC arm and $17,567 for the ART+AC arm.

ART+AC had an incremental cost-effectiveness ratio (ICER) of $444 per QALY compared to No-ART. ART-AC had an ICER of $488 compared to No-ART. The ICER of AC provision was $116 per QALY.

Sensitivity analysis

Confidence intervals for this analysis, calculated from probabilistic sensitivity analysis, are provided in parentheses in Table 5. They suggested that the point estimates for costs and QALYs in the ART+AC and ART-AC arms were towards the upper end of their respective distributions. This was reflected particularly in the ICERs for these arms compared to the No-ART arm.

One-way sensitivity analyses suggested that the results were sensitive to the discount rate used: at 8% all incremental interventions were cost-saving. The results were not sensitive to variation in the rates of progression to failure or LTFU on SLT within the range of values tested. One-way variation of the rate at which patients progressed to SLT indicated that the ICER was somewhat sensitive to the level of benefit provided by the AC intervention.

Discussion:

This is the first study of which the authors are aware that has considered the cost-effectiveness of an adherence intervention outside of the Americas and the first worldwide to use cost data from an existing program. The analysis finds the AC program at the intervention site to be of low absolute annual ($27) and incremental lifetime ($93) cost, and within plausible estimates of its benefit to be highly cost-effective ($116/QALY). It should, however, be noted that parameter uncertainty in the model makes this result very uncertain.

A secondary result is to confirm earlier research in similar settings, which found the cost-effectiveness of providing ART compared to not providing ART to be low.[36,37] In this study, including both inpatient and outpatient care at several levels of service and using the locally-relevant discount rate, the overall package of ART, including AC, is cost-saving compared to not providing ART. Even at the international standard of 3% the intervention was extremely cost-effective by commonly accepted standards,[38,39] costing less than 15% of per capita gross domestic income per QALY (South African 2004 GDP was $3,630).[40]

The key strength of this analysis is the data used. All data come from a single city, and the great majority from a single setting. Furthermore, healthcare utilization was recorded at all healthcare facilities visited, rather than a single clinic or hospital. Consequently the results are very likely to reflect reality in this setting. The limitation of this is that they may not be applicable in other settings, even within South Africa, since patients' access to healthcare services in the Cape Town area is likely be better than in less urban areas. This bias is likely to be non-differential between model arms, however, and should thus not significantly affect the results.

A second concern is uncertainty as to the efficacy of the AC intervention. In the baseline model the intervention was modelled to be the sole cause of 71% of all viral loads measured >1000 cells/μl not being confirmed as treatment failures at a second test, six to eight weeks later. This may be an overestimate if some of these recoveries were due to random fluctuation in viral load or improved adherence for some other reason. Alternatively, this may be an underestimate if the AC intervention had played a role in keeping the number of patients presenting with a first viral load >1000 cell/μl to the extremely low levels seen in this cohort. Reassuringly, one-way sensitivity analysis does not suggest that the results are highly sensitive to the benefit provided by the intervention.

A third limitation is that the lack of lifetime survival data for patients on ART. This remains a shortcoming of any cost-effectiveness study of ART, but once again sensitivity analysis did not suggest that the results were highly sensitive to progression rates from SLT to death and LTFU.

The specific type of intervention used at this site – a peer-based, ongoing adherence counsellor service providing both pre- and on-treatment patient support – has three additional benefits over alternative adherence interventions in African settings. First, it meets a number of the criteria that previous reviews of successful adherence interventions for chronic illnesses, both ART and other, have identified as being important for maintenance of therapy.[41,42] In particular, it is multi-faceted, involves regular reinforcement, reminders and counselling and is a long-term intervention.

Second, it is complementary to, rather than consumptive of, health service personnel. Given existing concerns as to the shortage of qualified health professionals, such a program has the potential to relieve some pressure on this key resource.

Third, it provides economic support to the community in which patients live. Although this study does not attempt to quantify the indirect benefits of ART, including productivity not lost to illness and the burden of supporting orphaned children,[43] the high level of poverty and unemployment in many highly-HIV-affected communities means that this source of employment is not an insignificant benefit.[44]

It is important to note, however, that successful adherence interventions are often difficult to disentangle from the settings in which they are designed.[42] It is therefore advisable that interventions be designed *in situ*, rather than trying to precisely replicating this program elsewhere.

This study found that the additional lifetime cost of providing a peer-based adherence counsellor service is small relative to the overall cost of healthcare services for those living with HIV (0.5% of the total lifetime cost in the baseline model). It also found the intervention to have an ICER such that it would be considered cost-effective in most African settings, even if its impact on virological outcomes was limited. As a result, interventions of this type should be seriously considered as part of a core ART-provision package across the less developed world.

References:

1. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond (March 2006). Geneva: World Health Organisation/UNAIDS. 2006.

2. Mozynski P. Global Fund calls for increased AIDS funding. Br Med J 2005; 331 (7516): 533.

3. Kober K, Van Damme W. Scaling up access to antiretroviral treatment in southern Africa: who will do the job? Lancet 2004; 364: 103-7.

4. Marchal B, De Brouwere V, Kegels G. Viewpoint: HIV/AIDS and the health workforce crisis: what are the next steps? Trop Med Int Health 2005 Apr; 10(4): 300-4.

5. South African National Antiretroviral Treatment Guidelines, National Department of Health, South Africa. First edition, 2004. Available from URL: http://www.doh.gov.za/docs/factsheets/guidelines/artguidelines04/intro.pdf [Accessed 27 July 2006]

6. World Health Organisation. Scaling up antiretroviral therapy in resource limited settings - guidelines for a public health approach. Geneva: WHO 2002.

7. Bangsberg D, Hecht F, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load and development of drug resistance in an indigent population. AIDS 2000; 14: 357-366.

8. Paterson D, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes inpatients with HIV infection. Ann Intern Med 2000; 133: 21-30.

9. Tuldrà A, Fumaz CR, Ferrer MJ, Bayés RM, Arnó A, Balagué M et al. Prospective Randomized Two-Arm Controlled Study to Determine the Efficacy of a Specific Intervention to Improve Long-Term Adherence to Highly Active Antiretroviral Therapy. J Acquir Immune Defic Syndr 2000; 25: 221-8.

10. Pradier C, Bentz L, Spire B, Tourette-Tugis C, Morin M, Souville M et al. Efficacy of an Educational and Counseling Intervention on Adherence to Highly Active Antiretroviral Therapy: French Prospective Controlled Study. HIV Clin Trials 2003; 4(2): 121-31.

11. Goujard C, Bernard N, Sohier N, Peyramond D, Lançon F, Chwalow J et al. Impact of a Patient Education Program on Adherence to HIV Medication: A Randomized Clinical Trial. J Acquir Immune Defic Syndr 2003; 34: 191-4.

12. Weber R, Christen L, Christen S, Tschopp S, Znoj H, Schneider C et al. Effect of Individual Cognitive Behaviour Intervention on Adherence to Antiretroviral Therapy: Prospective Randomized Trial. Antivir Ther 2004; 9: 85-95.

13. Rathbun RC, Farmer KC, Stephens JR, Lockhart SM. Impact of an Adherence Clinic on Behavioral Outcomes and Virological Response in the Treatment of HIV Infection: A Prospective, Randomized, Controlled Pilot Study. Clin Ther 2005; 27(2): 199-209.

14. Doxanakis A, Read T, Levy R, Mijch A, Fairly CK. Cohort Analysis of Two Multidisciplined Adherence Intervention Programmes for Patients on Antiretroviral Therapy. Int J STD AIDS 2006; 17:257-9.

15. Bozzette SA, Gifford AL. The Economic Viability of Antiretroviral Interventions. Am J Med 2003; 115 (8): 672-3.

16. Goldie SJ, Paltiel AD, Weinstein MC, Losina E, Seage GR, Kimmel AD et al. Projecting the Cost-effectiveness of Adherence Interventions in Persons with Human Immunodeficiency Virus Infection. Am J Med 2003; 115 (8): 632-41.

17. Zaric GS, Bayoumi A, Brandeau ML, Owens DK. Cost-Effectiveness of Improved Adherence to Antiretroviral Therapy. Value Health 2003; 6(3): 266.

18. Acurcio Fde A, Puig-Junoy J, Bonolo Pde F, Braga Ceccato MG, Guimaraes MD. [Cost-effectiveness of initial adherence to antiretroviral therapy among HIV infected patients in Belo Horizonte, Brazil]. Rev Esp Salud Publica 2006; 80(1): 41-54.

19. Bekker LG, Myer L, Orrell C, Lawn S, Wood R. Rapid scale-up of a community-based HIV treatment service: programme performance over 3 consecutive years in Guguletu, South Africa. S Afr Med J 2006; 96(4): 315-20.

20. Van Sighem AI, van de Wiel MA, Ghani AC, Jambroes M, Reiss P, Gyssens IC, Brinkman K, Lange JM, de Wolf F. Mortality and Progression to AIDS After Starting Highly Active Antiretroviral Therapy. AIDS 2003; 17: 2227-2236.

21. Gold MR, Siegel JE, Russell LB, Weinstein MC (eds). Cost-effectiveness in Health and Medicine. New York: Oxford University Press. 1996.

22. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. Lancet. 2002; 359(9323): 2059-64.

23. Bongiovanni M, Bini T, Capetti A, Trovati S, Di Biagio A, Tordato F, Monforte A. Long-term antiretroviral efficacy and safety of lopinavir/ritonavir in HAART-experienced subjects: 4 year follow-up study. AIDS 2005; 19(16): 1934-6.

24. Hicks C, King MS, Gulick RM, White AC Jr, Eron JJ Jr, Kessler HA, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients: 4 year follow-up study. AIDS 2004; 18(5): 775-9.

25. Koch RJ. Quantum Yearbook. 12th Edition. Port Elizabeth: Van Zyl, Rudd & Associates. 2003.

26. Harling G, Orrell C, Wood R. Healthcare utilization by a cohort of late-stage HIV-positive patients commencing antiretroviral medication in South Africa. Abstract No WEPE0085. XVI International AIDS Conference, Toronto, Canada. August 2006.

27. User Guide – UPFS (with revised 2004 tariffs): Uniform Patient Fee Schedule for Patients Attending Public Hospitals. Pretoria: Department of Health, Republic of South Africa. October 2004.

28. Department of Health Budget Review 2004/2005. Cape Town: Provincial Administration of the Western Cape. 2006.

29. Cleary S, Boulle A, McIntyre D, Coetzee D. Cost-Effectiveness of Antiretroviral Treatment for HIV-Positive Adults in a South African Township. Durban: Health Systems Trust. 2004. Available from URL: ftp://ftp.hst.org.za/pubs/research/arvcost/arv_cost.pdf [Accessed 27 July 2006].

30. Sinanovic E, Floyd K, Dudley L, Azevedo V, Grant R, Maher D. Cost and cost-effectiveness of community-based care for tuberculosis in Cape Town, South Africa. Int J Tuberc Lung Dis 2003; 7 (Suppl. 1): S56-S62.

31. Statistics South Africa. CPIX History: Metropolitan and Other Urban Areas. 2006. Available from URL: http://www.statssa.gov.za/keyindicators/CPI/CPIX.pdf [Accessed 27 July 2006].

32. Year Average of Exchange Rates 2004. Bank of Canada: Financial Markets Department. Available from URL: http://www.bankofcanada.ca/pdf/nraa04.pdf [Accessed 27 July 2006].

33. Pitt J, Badri M, Wood R. Changes in Quality of Life in a South African Antiretroviral Programme. Abstract No MoPeD3782. XIV International AIDS Conference, Bangkok, Thailand July 12-16, 2004.

34. Brazier J, Roberts J, Deverill M. The Estimation of a Preference-Based Measure for Health from the SF-36. Journal of Health Economics 2002; 21: 271-92.

35. Briggs AH. Handling Uncertainty in Cost-Effectiveness Models. Pharmacoeconomics 2000; 17(5): 479-500.

36. Badri M, Maartens G, Mandalia S et al. Cost-Effectiveness of Highly Active Antiretroviral Therapy in South Africa. PLoS Med 2006; 3(1): e4

37. Badri M, Cleary S, Maartens G, Pitt J, Bekker LG, Orrell C, Wood R. When to initiate highly active antiretroviral therapy in sub-Saharan Africa? A South African cost-effectiveness study. Antivir Ther 2006; 11(1): 63-72.

38. Report of the Commission on Macroeconomics and Health. Geneva: World Health Organisation. 2002.

39. Moatti JP, N'Doye I, Hammer SM, Hale P, Kazatchkine M. Antiretroviral Treatment for HIV Infection in Developing Countries: An Attainable New Paradigm. Nature Med 2003; 9(12): 1449-52.

40. World Development Indicators 2004. World Bank. Available from URL: http://devdata.worldbank.org/data-query [Accessed 27 July 2006].

41. Lucas GM, Wu AW, Cheever LW. Adherence to Antiretroviral Therapy: An Update of Current Concepts. Curr HIV/AIDS Rep 2004; 1: 172-80.

42. McDonald HP, Garg AX, Haynes RB. Interventions to Enhance Patient Adherence to Medication Prescriptions. JAMA 2002; 288(22): 2868-79.

43. Skordis J, Nattrass N. Paying to waste lives: the affordability of reducing mother-to-child transmission of HIV in South Africa. J Health Econ 2002; 21: 405-21.

44. Bachmann MO, Booysen FLR. Health and Economic Impact of HIV/AIDS on South African Households: A Cohort Study. BMC Public Health 2003; 3:14.

Figures/Tables:

Figure 1: Markov States in the No-ART arm: progression is strictly down or to the right.

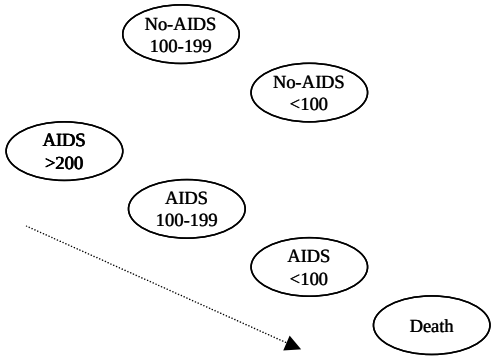

Figure 2: Markov model structure in ART arms. The line represents end of first-line therapy: above the line progression is strictly to the right until >12 months on treatment but may be up or down; below the line progression is strictly down.

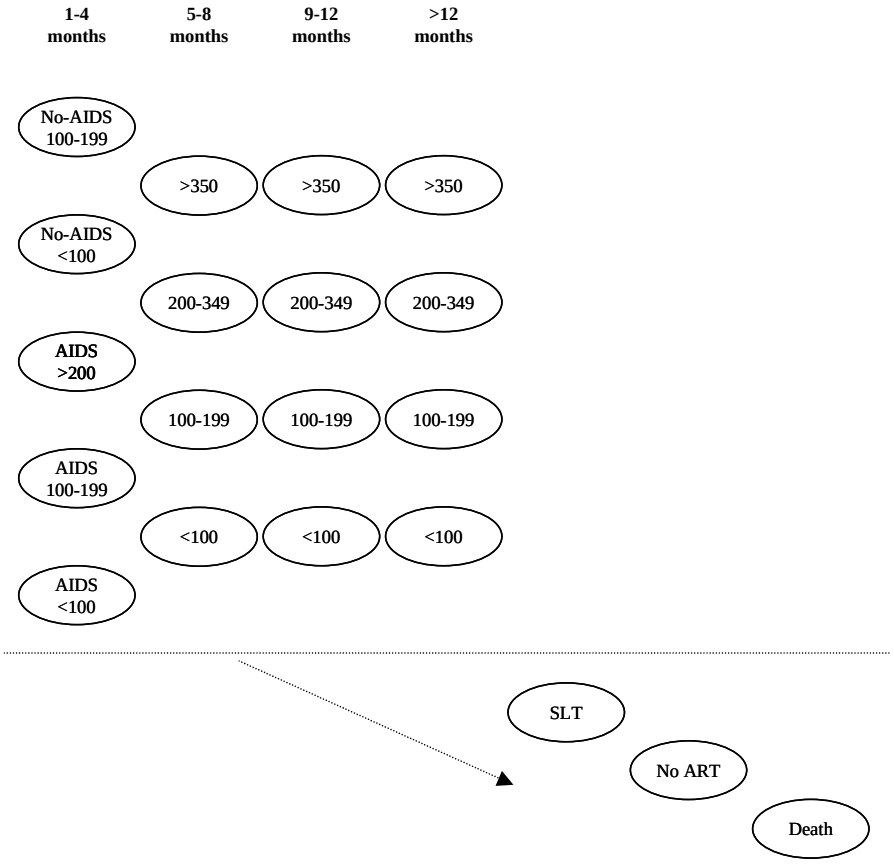

Table 1: Baseline patient characteristics for samples used: number (percent) unless otherwise stated

	Transition Probabilities			
	ART	**No-ART (CTAC)**	**Quality of Life**	**Cost**
Sample size	868	733	380	212
Age [Median (IQR)]	33 (28-38)	32 (27-39)	33 (28-38)	33 (28-38)
Female	634 (73.0)	358 (49.9)*	285 (75.0)	153 (72.5)
WHO stage				
Stage 1&2	158 (18.2)	183 (27.6)	53 (13.9)	22 (10.4)
Stage 3	470 (54.1)	348 (47.5)	191 (50.3)	97 (45.8)
Stage 4	240 (27.6)	202 (27.6)	136 (35.8)	93 (43.8)
CD4 cell count				
<100	454 (52.3)	345 (47.1)	219 (57.6)	124 (58.8)
100-199	338 (38.9)	335 (45.7)	137 (36.1)	71 (33.6)
>200	76 (8.8)	53 (7.2)	24 (6.3)	16 (7.6)
Viral load [mean]	4.78	-	4.86	4.89

* The sex of 15 patients in this cohort was not recorded.

Table 2: Markov state transition probabilities (%) per 4 months (112 days)

	From state:		To state:								
	WHO Stage				No-AIDS	No-AIDS	AIDS	AIDS	AIDS		
Treatment period		**CD4 Count**	**Death**		**< 100**	**100-199**	**< 100**	**100-199**	**200-349**		
No ART	AIDS	< 100	16.23								
	AIDS	100-199	4.90				10.22				
	AIDS	200-349	2.22				1.11	7.76			
	No-AIDS	< 100	5.40				14.85				
	No-AIDS	100-199	1.89		5.10		0.57	3.59			
			Death	**LFTU**	**< 100**	**100-199**	**200-349**	**> 349**		**SLT (ART+AC)**	**SLT (ART-AC)**
FLT 1-4 months	AIDS	< 100	16.67	1.28		33.97	17.31	3.85		1.92	0.00
	AIDS	100-199	3.13	4.69	0.00		46.88	10.94		0.00	0.00
	AIDS	200-349	0.00	0.00	0.00	22.22		27.78		5.56	5.56
	No-AIDS	< 100	4.03	1.34		45.64	20.13	2.01		0.34	0.00
	No-AIDS	100-199	2.55	1.82	2.19		47.45	13.87		1.82	0.00
FLT 5-12 months		< 100	8.00	0.80		40.80	8.80	0.80		0.00	4.00
		100-199	1.69	2.54	3.67		37.57	2.54		0.56	3.67
		200-349	0.27	0.53	0.27	16.71		19.89		1.06	5.04
		> 349	0.77	0.77	0.00	3.85	23.08			0.00	7.69
FLT >12 months		< 100	9.09	0.00		31.82	13.64	0.00		13.64	27.27
		100-199	1.82	0.61	1.21		43.64	4.85		1.21	10.9
		200-349	0.00	1.07	0.00	11.26		26.54		0.54	1.61
		> 349	0.00	0.62	0.00	1.23	13.85			0.62	0.62
SLT			0.37	2.34						-	-

ART: Antiretroviral therapy; FLT: First-line therapy; SLT: Second line therapy. Default progression is to the same CD4 cell count state at the next time period.

Table 3: Mean cost (US$) and number per patient-year of hospital outpatient visits, inpatient stays and days on a TB DOTS program

Treatment Period	CD4 Count / WHO Stage	Inpatient			Outpatient			TB DOTS[a]
		Tuberculosis	Secondary	Tertiary	Primary	Secondary	Tertiary	
Unit cost		55.09	154.39	393.92	76.35	57.00	178.72	2.57
No ART	AIDS	33.17 (29.98 - 36.58)	2.74 (1.85 - 3.91)	3.29 (2.31 - 4.55)	21.84 (19.23 - 24.69)	1.92 (1.19 - 2.93)	2.28 (1.48 - 3.37)	68.45 (64.07 - 72.99)
	No-AIDS	10.77 (9.15 - 12.58)	2.39 (1.66 - 3.34)	1.76 (1.14 - 2.59)	19.35 (17.18 - 21.7)	0.28 (0.08 - 0.72)	0.28 (0.08 - 0.72)	63.89 (60.15 - 67.77)
FLT 1-4 months	AIDS	3.14 (2.47 - 3.93)	7.99 (6.91 - 9.19)	4.64 (3.82 - 5.58)	13.64 (12.22 - 15.17)	0.63 (0.35 - 1.03)	1.38 (0.95 - 1.94)	60.33 (57.5 - 63.23)
	No-AIDS	- (0 - 0.11)	2.50 (2 - 3.09)	1.73 (1.32 - 2.24)	12.70 (11.54 - 13.93)	0.12 (0.03 - 0.30)	0.50 (0.29 - 0.80)	39.67 (37.69 - 41.72)
FLT >4 months	< 100	- (0 - 0.33)	4.72 (3.53 - 6.17)	10.70 (8.88 - 12.78)	7.16 (5.68 - 8.91)	0.36 (0.1 - 0.93)	2.18 (1.4 - 3.23)	70.46 (66.05 - 75.04)
	> 100	0.04 (0.02 - 0.09)	0.51 (0.41 - 0.63)	0.31 (0.24 - 0.4)	5.02 (4.7 - 5.35)	0.29 (0.22 - 0.38)	0.42 (0.33 - 0.53)	15.12 (14.58 - 15.68)
SLT		0.04 (0.02 - 0.08)	0.75 (0.63 - 0.88)	0.90 (0.77 - 1.04)	5.14 (4.83 - 5.46)	0.30 (0.22 - 0.38)	0.52 (0.42 - 0.63)	18.23 (17.65 - 18.82)

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Table 4: Cost per day (US$) excluding Adherence Counsellor program and Quality of Life for each Markov health state

Treatment Period	CD4 Count	WHO Stage	Cost		Quality of Life	
No ART	< 100	AIDS	16.17	(13.17 - 19.85)	0.67398	(0.64747 - 0.70049)
	100-199	AIDS			0.67619	(0.62237 - 0.73001)
	200-349	AIDS			0.66742	(0.60242 - 0.73241)
	< 100	No-AIDS	9.21	(7.37 - 11.58)	0.73665	(0.70981 - 0.76349)
	100-199	No-AIDS			0.73212	(0.70063 - 0.76362)
FLT 1-4 months	< 100	AIDS	14.25	(12.24 - 16.57)	0.74518	(0.71990 - 0.77046)
	100-199	AIDS			0.78284	(0.73895 - 0.82673)
	200-349	AIDS			0.82006	(0.76985 - 0.87026)
	< 100	No-AIDS	7.46	(6.44 - 8.72)	0.79850	(0.78058 - 0.81643)
	100-199	No-AIDS			0.79377	(0.77381 - 0.81373)
FLT 5-12 months	< 100		17.67	(14.44 - 21.57)	0.82628	(0.81245 - 0.8401)
	100-199					
	200-349		2.99	(2.74 - 3.28)		
	> 349					
FLT >12 months	< 100		17.67	(14.44 - 21.57)	0.80173	(0.77435 - 0.82912)
	100-199					
	200-349		2.99	(2.74 - 3.28)		
	> 349					
SLT			4.22	(3.90 - 4.58)	0.80173	(0.77435 - 0.82912)

ART: Antiretroviral therapy; FLT: First-line therapy; SLT: Second line therapy

Table 5: Cost-effectiveness of antiretroviral treatment for HIV-infected patients

	Total Lifetime Costs		Effectiveness		Incremental Cost-Effectiveness Ratio			
					vs. No ART		vs. No Adherence	
	SA Rand	US $	LYs	QALYs	R/QALY	$/QALY	R/QALY	$/QALY
Baseline model								
No ART	93,240	14,490	3.1	2.2				
	(79,664 - 108,479)	(12,380 - 16,858)	(2.8 - 3.3)	(2.0 - 2.3)				
ART-AC	112,439	17,474	10.5	8.3	3,138	488		
	(95,533 - 119,199)	(14,847 - 18,524)	(8.7 - 11.2)	(6.9 - 9.0)	(-314 - 4,539)	(-49 - 705)		
ART+AC	113,038	17,567	11.4	9.1	2,859	444	743	116
	(91,873 - 115,100)	(14,278 - 17,887)	(8.4 - 11.2)	(6.7 - 8.9)	(-991 - 4,003)	(-154 - 622)	(-187,207 - 222,273)	(-29,093 - 34,543)
Undiscounted								
No ART	101,912	15,838	3.4	2.4				
ART-AC	155,748	24,204	14.3	11.3	6,002	933		
ART+AC	161,034	25,026	16.3	12.9	5.601	871	3,334	518
Discounted 8%								
No ART	81,878	12,724	2.7	1.9				
ART-AC	75,745	11.171	7.1	5.7	-1,642	-255		
ART+AC	74,431	11,567	7.5	6.0	-1.836	-285	-4,081	-634
SLT Failure	**(ART+AC and ART-AC arms vary; ART+AC arm shown)**							
As FLT >12m	115,745	17,988	12.0	9.6	3,043	473	**ART-AC arm dominated**	
Literature best-case	118,453	18,470	12.2	9.7	3,400	528		
FLT Failure	**(ART-AC arm varies & shown)**							
Half the difference	112,357	17,461	10.9	8.7			1,542	240
Double failure rate	113,099	17,576	9.7	7.7			-43	-7

FLT: First-Line Therapy; SLT: Second-Line Therapy; LY: Life-Year; QALY: Quality-Adjusted Life Year.