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Lowering the threshold — Is there a case for re-evaluating eligibility criteria for ART?

Modelling the cost-effectiveness of WHO versus US DHHS guidelines in South Africa

One key study was presented at the World AIDS Conference in Toronto by Dr Peter Mazonson, founder of Mosaic, a health care consulting firm specialising in health economics and outcomes research. Developed in collaboration with leading international and South African HIV clinical and economic experts (including Dr Osman Ebrahim of Brenthurst Clinic in Johannesburg, Dr Ian Sanne of the University of Witwatersrand, Dr Nick Hellman of the Gates Foundation and Dr Gillian Sanders of Duke Clinical Research Institute), the Mosaic study's main objective was to model the cost effectiveness of using the WHO guidelines for starting ART versus the cost-effectiveness of composite guidelines with three major modifications to bring them closer in line with clinical practice in the US:

- 1) Initiating ART at a CD4 count of 350 instead of 200
- 2) Initiating ART if the viral load was above 100,000 copies per ml (viral load is not included in the WHO guidelines)
- 3) Testing viral load and CD4 counts every three months as opposed to every six months for CD4 count alone as per the WHO guidelines

This study used a Markov model which incorporated HIV transmission; in other words, it looked not only at the cost effectiveness for the index patient, but also for anyone to whom the index patient might transmit the virus. The researchers chose a starting population of treatment-naïve HIV-positive heterosexual adults between the ages of 15 and 49 living in South Africa. The model used South African cost data expressed in 2005 US dollars.

The study evaluated a number of potential outcomes, including quality-adjusted life-years (QALYs), direct medical costs of providing ART, indirect costs, the incremental cost per QALY, clinical outcomes for both the index patient and other persons to whom he or she might transmit HIV. Finally, the researchers performed a 'budget impact analysis' evaluating the economic impact for South Africa if it were to move from the WHO guidelines to the composite guidelines, both over five years and over a lifetime.

In the model, treatment-naïve people with HIV can start at or transition to different HIV disease states over time (from having over 350 CD4 cells, onto more advanced stages of disease or death). Once on therapy, people also can move between a number of response states, from virological suppression, failure due to toxicity, or virological failure either initially or at any point over time, and, after treatment options are exhausted, back to disease progression and death.

The baseline natural history data used in the model were derived from a paper (and unpublished data) from Dr. Bertran Auvert of the French ANRS, who a few years ago performed a cross-sectional study assessing sexual behaviour, HIV status, CD4 cell counts and viral loads among a random sample of approximately 1000 men and women from a township near Johannesburg. That study had concluded that, WHO guidelines were used, only about 9.5% of the HIV-infected people in the sample would qualify for treatment and

the effect on reducing the sexual transmission of HIV would be minor. However, if DHHS guidelines were used, roughly 56% of the infected cohort would qualify for treatment — and sexual transmission would be reduced by as much as 72%.

The treatments in the Mosaic model are the same as those recommended in the current WHO guidelines (first line: nevirapine or efavirenz in combination with d4T/3TC with AZT substitution for d4T toxicity; second line: *Kaletra* plus tenofovir/ddl etc...). The model also assumed that the likelihood of achieving virological suppression decreases after failing the first-line regimen, unless that failure was due to toxicity. Treatment failure under the WHO guidelines is defined as a drop in CD4 cells count of 50% below the peak value, or a CD4 count of less than 200 cells, while the composite guidelines considered treatment failure as a viral load over 400 copies/ml (note that this may be a rather severe definition for failure when, at best, there are only two treatment regimens available).

The model assumed that the rate of HIV transmission depends on the infected patient's sex, their number of sexual partners and their viral load. As several studies have shown, reductions in viral load reduce the risk of HIV transmission. However, this model did not factor in any behaviour modification that could occur as a result of testing and counselling — or from being on treatment (recent data suggest that being on ART is actually associated with lower sexual risk taking among Ugandans, see

<http://www.aidsmap.com/en/news/6F55C5E7-4896-4C74-BBDC-D412BE9064E.asp>).

Key results

When looking at the index patient only, over a lifetime, the cost of treatment would be significantly higher using the composite guidelines than with the current WHO 3 by 5 guidelines — but the advantage would be that people would live longer, with a 2.09 increase in quality adjusted life years (QALY) in the model (see Table A).

TABLE A

Strategy	Lifetime costs (\$)	Incremental costs (\$)	QALY (years)	Incremental QALY
For the index patient alone				
Current WHO guidelines	12,354		10.98	
Composite guidelines	22,677	10,323	13.07	2.09
For the index patient and sexual partners				
Current WHO guidelines	13,630		9.14	
Composite guidelines	25,856	12,226	12.3	3.16

When the incremental cost is expressed as a ratio of QALY, the cost per quality adjusted life year would be \$4,939, which in South Africa is a cost effective result. (According to a report in 2001, the WHO defined any intervention where the cost per QALY is less than the GDP per capita as highly cost effective; and in 2005, the GDP per capita was \$4900 for South Africa.)

When the analysis included transmission effects (when both the index patient and the persons to whom they might transmit the virus are included), the costs of treatment would go up further, but the effectiveness would also increase. The incremental cost effective ratio (ICER) or cost per QALY would then drop to \$3,869.

The researchers then teased out the relative costs and contributions of each of the three modifications in the composite guidelines (see Table B).

TABLE B

Which factors are driving these results?

Base case (with transmission)

	ICER (/QALY)	%contribution for effectiveness	% contribution for cost
Impact of starting treatment at CD4 cells <350	\$1,254	51%	27%
Impact of viral load testing only	\$3,700	41%	65%
Impact of CD4 testing every 3 months	\$2,576	8%	8%

“About half of the benefit that we derived from the model is from just bumping the CD4 threshold from 200 to 350 and the other half is from viral load and more frequent testing,” said Dr Mazonson.

“But... the incremental cost effectiveness ratios... [are] all below \$4000 and that's again considered a highly cost effective result.”

There would however be a significant economic impact for South Africa if it were to move from the WHO guidelines to the composite guidelines. In the five year analysis, treating patients with the composite guidelines would increase direct costs by \$13 billion but it would result in 400,000 fewer deaths, one million fewer AIDS cases and 320,000 fewer incident HIV cases.

However, the model also incorporated an indirect cost analysis of AIDS-related death for both the index patients. The indirect cost was calculated per patient by taking the GDP per capita in South Africa multiplied by the difference in potential years of life lost by those who were treated as per the WHO guidelines versus the composite guidelines.

“Now, some people would argue that indirect cost analysis in the developing world settings doesn't make sense because so many people are unemployed,” said Dr Mazonson, “but by looking at average GDP per capita, we're basically looking at the average productivity of an employee in that economy, taking into account those who are employed and those who are unemployed.”

Over the 38 year lifetime of the model using the composite guidelines would cost \$62 billion more in direct medical costs, but the indirect cost savings would amount to around \$123 billion, for a total cost savings of about \$61 billion. The model indicates that much of the financial pain would be felt in the first five to ten years.

“I guess you would say, on net, there would be a 62 billion dollar short term pain for long term gain which is really what's happened in the developed world where we've managed to turn this into a chronic illness,” said Dr Mazonson.

“But even without including indirect cost, the results that we got for use of the composite guidelines were highly cost effective.

Furthermore when we looked at each of those three components separately, they were all cost effective by themselves. And, in fact, if you were to initiate this over the lifetime of the model of 38 years throughout South Africa, you would actually save quite a bit of money when you include indirect cost. So we think this is also important for - not only South Africa. - but also could be extrapolated to other upper middle income countries,” Dr Mazonson concluded.

Supporting studies

A couple of other recent papers that have looked specifically at the use of higher CD4 cell thresholds or the potential role for viral load measurements in the sub-Saharan African setting support some of the Mosaic study findings.

For example, a recent paper by Badri et al also used a Markov model to determine the cost effectiveness of no treatment or using different CD4 count thresholds (<200, 200-350 and >350) using primary treatment outcomes, healthcare utilisation and cost data (January 2004 local prices; US dollars 1=7.6 Rands) taken from the Cape Town AIDS Cohort. The study was much less conservative than the Mosaic study in calculating the effectiveness of ART).

In this model, ART more than tripled the mean projected life-expectancy (from around 6 years up to a peak of around 23 years if treatment was begun early). The much longer life-expectancy projected in this study did significantly increase the estimated lifetime cost of treatment, however the researchers concluded that “deferring treatment to <200 might reduce the aggregate cost of treatment, but this should be balanced against the significant clinical benefits associated with early therapy.” Commenting on this study, Dr Mazonson pointed out that it also did not consider indirect costs, or the benefits associated with reduced transmission.

Meanwhile, a recent study by Bogaards et al concluded that viral load measurements could achieve a more efficient allocation of antiretroviral therapy in patients with “intermediate” CD4 cell counts (above 200) in a sub-Saharan African community-based setting — though not in a hospital based setting where people present with more advanced disease. In this study, in the community-based setting, less than 15% of patients presenting with HIV infection had CD4 cell counts below 200 cells (compared to 53% of patients presenting with HIV in a hospital setting in West Africa). However, only 23% of the HIV-infected patients in the community-based setting had viral load levels below 10,000 copies/mL, and 40% had viral load levels above 100,000 copies/mL.

The study then calculated the patient's 1-year cumulative hazard of AIDS based upon data derived from an Amsterdam cohort study in people with HIV before ART. People with CD4 cell counts below 200 were, of course, at higher risk of developing AIDS-defining symptoms in both settings, and viral load didn't add much to the predictive value in the hospital setting.

However, in the community setting, where most people with HIV presented with higher CD4 cells, the researchers determined that using high viral loads level rather than CD4 cell counts to select who should receive ART would result in a greater reduction of the 1-year AIDS incidence — even though essentially the same number of people would receive treatment — thereby increasing the efficiency of treatment. Using a combined criterion for initiating treatment, based on CD4 cells below 200 and a viral load of over 300,000 copies per ml, further increased the efficiency of ART. “To achieve a comparable reduction of the 1-year AIDS incidence by relying on CD4 cell counts only, all patients with CD4 counts below 500 cells would have to start HAART. Such a strategy would result in a HAART

administration rate of almost 50%” [as compared to 32% if the combined criterion were used], Bogaard and colleagues wrote.

However, they also added: “whether viral load-driven strategies may become attractive from an economic point of view requires thoughtful cost-effectiveness analysis.”

Caveats, critics and crowded clinics

To some extent, the Mosaic study may have provided some of this analysis. However, the study could not possibly account for all of the costs of scaling up screening and treatment to the level of universal treatment.

For example, the cost of providing treatment through existing infrastructure may be relatively inexpensive, but once that infrastructure is fully utilised, the cost of scaling up could increase the cost of care substantially. New laboratory and treatment facilities would need to be built, often in remote settings. The healthcare workers to staff these facilities would have to come from somewhere — and be trained. Millions of asymptomatic people with HIV would have to be identified and screened. Logistics, supply chain and quality control costs could grow dramatically.

An advantage of the more simplified WHO guidance is that it is scaleable to the primary health level — while introducing the composite approach to the primary care level could be significantly more difficult. After his talk, Dr Mazonson was asked about this.

“They [the WHO guidelines] might be 'scaleable' but one of our key take home points is that you really don't get at the transmission component through the CD4 count. Because the people that are really the sickest, aren't really transmitting the disease that much because they're not that sexually active. It's the people with high viral loads who you're completely missing. So, basically the 3 by 5 programme makes sense from an equity point of view on treating the sickest patients first. But in terms of getting an economic [handle] on the disease, you never do that because you are kind of 'bottom feeding'. At the top you keep cycling the disease and keep creating more and more transmission which you don't pick up unless you're monitoring the viral load.”

And yet, at least one other study by Baggalety et al has concluded that ART will only have a limited impact upon transmission. Some of the paper's conclusions are partly the result of some rather bleak assumptions about the efficacy of treatment, the likelihood of resistance developing and/or being transmitted, and the ability of African countries to scale up. “In reality, scaling up programmes is likely to compromise quality, meaning higher dropout rates and mortality and treatment failure, negating the beneficial impacts of ART and increasing the rate of drug resistance emergence,” Baggalety wrote.

So far, there are few data on ART programmes in Africa to support the paper's more pessimistic predictions. However, the paper raises at least one interesting point: that the coverage of the ART programme may need to be quite high in order to have a significant impact upon HIV transmission at the population level.

And to approach anything near universal treatment won't only take more money up front, it requires political will that has thus far been lacking in the country examined in the Mosaic paper. In the discussion session after Dr Mazonson's talk, one audience member asked whether he had presented his results to the South African Government, and what their response had been.

“The answer is no,” said Dr Mazonson, “but we'd love to do so.”

The irony is of course that while Dr Mazonson was presenting this study, South Africa's exhibition booth at the World AIDS Conference featured baskets of lemons, beetroot, African potatoes

and clumps of garlic which the Minister of Health proposed as a being an equally valid choice for treatment of HIV (see <http://www.health-e.org.za/news/article.php?uid=20031487>).

Even were South Africa to adopt something like the composite guidelines or any of its aspects, such as a higher CD4 threshold for starting treating, there would have to be a major change in the leadership to reach anywhere near the coverage required for the Mosaic model. As for viral load, at present South Africa's programme only pays for the test after someone's CD4 cell count has fallen below 200.

Botswana, on the other hand, has the progressive leadership in abundance — and perhaps, eventually, the capacity to demonstrate the accuracy of the Mosaic's study's predictions. After all, data have recently shown that the government's ARV programme has led to a reduction in the national adult mortality (see <http://www.aidsmap.com/en/news/FA96D301-87C5-43E5-BB63-6F6921A12F7A.asp>)

“In the end analysis, they'll say it [changing the CD4 threshold to 350] is expensive, but by the same token, all these will eventually end up on treatment,” said Dr Gaolathe at the Botswana conference.

Furthermore, they may be in more immediate need of treatment than previously thought. Data now suggest that people with 200-350 CD4 cells are much more likely to die or progress to serious illness than people with over 200 CD4 cells in the UK, Europe or America (<http://www.aidsmap.com/en/news/37AEC801-171D-4C0F-B95F-413F922CE4CD.asp>).

In that South African study, 52% of people followed after HIV diagnosis in the Cape Town HIV Cohort died before they reached WHO stage 4 (AIDS), and the study found that South African patients with a CD4 count between 200 and 350 with WHO stage 3 disease were 1.9 times more likely to die during a median 16 months of follow-up than their counterparts in high-income country cohort studies, presumably due to higher rates of TB.

However, not every expert in attendance at the Botswana meeting believes the step is advisable.

“You should stop any talk as far as giving antiretroviral care at 350. I think it's not going to happen in the U.K. It shouldn't happen here,” said Dr Brian Gazzard of Chelsea Westminster.

Indeed, the BHIVA guidelines in the UK do not make a blanket recommendation for treatment of people with less than 350 CD4 cells. However, they do recommend something somewhat closer to what was investigated by Bogaards et al. Within the range 200 to 350 cells, individuals with a viral load above 100,000 copies/ml or a CD4 cell count falling by more than 80 cells per year may be considered for earlier intervention. In fact, a marked decline in CD4 cell counts within this range could serve as an alternative to viral load measurements where that capacity is not yet available, or too expensive to use routinely.

However, any step that Botswana or any other country takes in the direction of expanding the number of people eligible for ART must not come at the expense of people currently on treatment. There is some truth to the concern that too rapid a scale up could result in a decline in the quality of service. Most countries may first need to focus on streamlining patient management and decentralising care in order to prevent overcrowded clinics and preserve the quality of care.

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about HATiP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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