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Prioritising increasing access to ART, or improving monitoring of patients already on ART?

Challenges of implementing the 2013 WHO ART guidelines

The Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, issued by WHO in July 2013, include a number of important changes to previous guidelines. These include:

- ART should be initiated for all HIV-infected adults and children over the age of 5 with CD4 counts 500 cells/mm^3 regardless of WHO clinical stage (up from 350 cells/mm^3 in the 2010 guidelines)
- Children aged less than 5 years should start ART at diagnosis
- In order to simplify treatment delivery and to improve prevention of mother to child transmission, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment
- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure

The first two of these recommendations mean that, according to the EPP/Spectrum models used by WHO, the number of people eligible for ART rises from 16.7 million to 25.9 million. Even under the 2010 eligibility criteria, 32% of people in need of treatment in sub-Saharan Africa were not receiving it by the end of 2012. The number of people in need of treatment who are not on treatment has jumped from 7 million to 16.2 million globally. Getting these people on to treatment will require substantial additional resources.

The viral load recommendation will also add considerably to the costs of HIV treatment programmes, as the laboratory tests are expensive and inaccessible in most locations. In order to increase treatment coverage, it is being rolled out to lower level health facilities where laboratory facilities and transport for patients and samples

Key Points

- The 2013 WHO Guidelines include 3 notable recommendations:
  - Encouraging use of viral load monitoring for people on ART
  - Increasing the threshold for ART initiation from <350 cells/mm3 to <500 cells/mm3 in adults and children aged >5 years, and start all children aged <5years on ART at diagnosis
  - Starting all HIV-infected pregnant women on ART for life (Option B+)
- In most settings budget constraints mean that not all the recommendations can be adopted at once without threatening the roll-out of ART to those most in need, meaning policymakers have to prioritise the recommendations that will bring the most overall health gains with the available resources
- Where large coverage gaps remain and clinical monitoring is used, more lives will be saved if increasing access to ART is prioritised over moving to viral load monitoring
- Moving to routine viral load monitoring is important for improving health care and limiting drug resistance, but should only be a priority once ART coverage for those eligible for treatment is close to full
- In the meantime, strategies such as clinical monitoring, targeted 'tiebreaker' CD4 tests, or CD4 monitoring will allow more people to access ART than routine viral load testing
- Reducing the costs of second line regimens and viral load tests may improve the cost-effectiveness of viral load monitoring, but this ranking of priorities is unlikely to change in the near future

are least likely to be available, making viral load testing hard to implement.

Although the new guidelines have been widely welcomed, they have not been accompanied by announcements of large increases in funding for HIV treatment programmes. Full coverage of ART based upon these recommendations appears a distant hope. This means that national policymakers will have to make difficult decisions on which recommendations from the guidelines to prioritise. Doing everything at once is not an option for those countries most affected by HIV.

This brief considers evidence on the effectiveness, cost-effectiveness and opportunity costs of the WHO recommendations for monitoring people on ART. It draws on modelling and cost-effectiveness work carried out by the HIV Modelling Consortium, commissioned by WHO for the guidelines, as well as randomised controlled trials looking into this question.

The effectiveness of different monitoring strategies

Several randomised controlled trials have been carried out, comparing the effectiveness of different monitoring strategies.

Clinically-driven monitoring

Clinically driven monitoring approaches rely on routine appointments with doctors, clinical officers or nurses to monitor patients on ART. This can be supported by use of a check-list to help the health-worker identify any signs or symptoms that indicate that laboratory tests (to diagnose illness or drug side-effects) or changes to treatment are needed.

Clinically driven monitoring has been shown to lead to good outcomes: 87% of people in the clinically driven monitoring arm of the DART trial (carried out in Uganda and Zimbabwe) were alive five years after starting ART, which is a major achievement as their median CD4 count at initiation was 86 cells/mm^3. In the ARROW trial (carried out in Uganda and Zimbabwe), which compared clinically-driven with routine CD4 monitoring for children, 96% of children were alive five years after starting ART, irrespective of monitoring strategy.

The DART trial also found that targeted CD4 tests with a threshold of <250 cells/mm^3, used to confirm clinically-suspected treatment failure, can be used to efficiently identify patients failing first-line treatment, and exclude those who are likely to be virally suppressed.

Routine CD4 monitoring

Routine CD4 monitoring has been shown to have some small survival benefits over clinically driven monitoring. The DART trial found that adult patients monitored by CD4 count switched earlier to second-line therapy than those monitored clinically. For the first two years there was no difference in survival, but after 5 years 90% (with CD4 monitoring) versus 87% (with clinically driven monitoring) were alive. The HBAC trial (carried out in Uganda) found, after three years, that patients monitored using routine CD4 tests had significantly better outcomes than those monitored only clinically, with 6.0 episodes of severe illness or death per 100 person years, compared to 7.6 in those monitored clinically. Most of these were illness rather than death. The ARROW trial found a small difference (2.0 vs 1.7 per 100 child-years) in WHO stage 4 events and deaths. Unlike the adults in the DART trial, children in clinically driven monitoring arm of ARROW did not switch at lower CD4 counts than those in the laboratory monitoring arm. Monitoring children's weight gain seemed to be an effective way of identifying treatment failure.

Viral load monitoring

A systematic review carried out to inform the new guidelines identified three randomized clinical trials on viral load versus CD4 and clinical monitoring. Compared with CD4 and/or clinical monitoring, adding viral load monitoring has not been associated with reduced mortality in any of the trials. The ESTHER trial (carried out in Cameroon) found that clinically driven monitoring was inferior to laboratory monitoring (viral load and CD4 testing) in terms of CD4 count recovery. Patients in the clinical monitoring arm had a CD4 count an average of 31 cells per µl lower than those in the laboratory monitoring arm after 2 years on treatment. They found no difference between the arms in terms of viral suppression, resistance, disease progression or mortality. The HBAC trial found that viral load with CD4 monitoring had better outcomes than clinical monitoring alone, but there was no significant difference in outcomes between those who were monitored by CD4 alone versus viral load and CD4 after 3 years. The PHPT-3 trial (carried out in Thailand) found that routine monitoring with CD4 counts was non-inferior to viral load testing in terms of risk of clinical failure. There was also no difference in CD4 count or viral suppression between the two monitoring approaches at the end of 3 years follow-up. It has been suggested that greater benefits may have been seen if the trials had followed-up patients for longer.

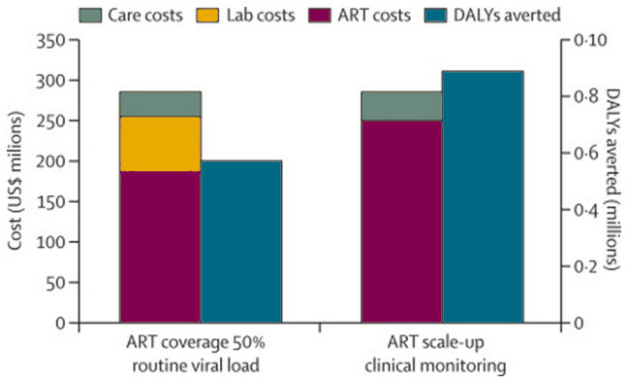
Viral load does offer the advantage that it may allow clinicians to identify cases of poor adherence, which provides the opportunity to intervene with adherence support before switching to second-line treatment.

As CD4 tests remain necessary for assessing treatment eligibility for most patients (except pregnant women under Option B+, or those with WHO stage 3 or 4 disease), countries will still need to have the laboratory infrastructure to carry these out. Using these machines at low volume (if routine CD4 monitoring is replaced with routine viral load monitoring) is likely to increase the cost per test.

The effectiveness of different monitoring strategies

The HIV Modelling Consortium used three independently developed models to examine the implications of different monitoring strategies. They examined

Figure 1: Costs and benefits (DALYS averted) of alternative uses of resources per 1 million HIV-infected people (Braithwaite model, Keebler et al. 2013)



DALY=disability-adjusted life-year

Results are per 100 000 HIV-infected individuals with both benefits and costs estimated over a 20 year budgeting horizon and discounted at 3% per annum.

country-specific costs, using Malawi, Zambia and South Africa to represent lower, middle and higher resource settings in sub-Saharan Africa.

All three models found that a theoretical strategy of no monitoring and no switching is the least costly and least effective strategy (see Keebler et al., 2013). Clinical monitoring offers significant benefits for low incremental costs compared to no monitoring and no switching. The addition of CD4 monitoring provides more benefits than clinical monitoring, and is likely to be affordable in more settings than regular viral load testing. Viral load monitoring every 6 months is the most costly and most effective. Viral load monitoring every 12 months is the next-most-effective strategy, and slightly less costly. One of the models suggested that regular CD4 monitoring, with targeted viral load tests to confirm suspected failure, may provide a stepping stone towards routine viral load monitoring, although if viral load machines are used at low volume this is less likely to be cost-effective.

It is not enough for policymakers to know that a certain strategy provides more benefits at greater costs. To understand whether that strategy should be adopted, we need to know whether that money could buy greater health gains if it was spent in a different way.

Prioritising between improving monitoring and increasing access to ART

In order to help prioritise between the viral load monitoring recommendation and improving access to treatment, the HIV Modelling Consortium calculated which approach would save the most disability-adjusted life years (DALYs). In a scenario with low coverage (based on the 350 cells/mm^3 threshold) and clinically-driven monitoring, investing additional resources in increasing ART coverage would lead to much greater health benefits than moving to 6-monthly viral load monitoring. This scenario is fairly typical of the situation in many eastern and southern African countries.

The modelling study also found that, in a setting like Zambia, where there is high coverage of ART in adults (based on the 350 cells/mm^3 threshold) using CD4 monitoring, extending ART coverage to those with CD4 counts of <500 cells/mm^3 would provide greater public health gains from available resources than moving to routine viral load monitoring. It should be noted, however, that evidence on the individual health benefits to initiating treatment at CD4 >350 is still very limited. The START trial will provide further insights into this.

Results from the modelling study suggest that expanding treatment to more patients, while using clinical or immunological monitoring, would be a more effective use of resources than investing in more extensive patient monitoring using viral load tests.

Other considerations

Effectiveness and cost-effectiveness are not the only factors that need to be taken into account when deciding how to respond to the new WHO guidelines. Feasibility is an important consideration. The move towards starting all HIV-infected pregnant women on lifelong ART (Option B+) has led to more primary care facilities providing ART in Malawi. This is important to ensure that pregnant women can access treatment, and also to relieve the pressure on secondary and tertiary facilities. However, a survey of health facilities in Malawi, Uganda and Zimbabwe carried out in 2012 found that only 6 of the 58 facilities surveyed had regular access to viral load testing and all testing was in selected patients (rather than routinely). Until cheap point-of-care tests are available that do not rely on the availability of machines that are likely to break down, or scarce laboratory technicians, moving to viral load testing while trying to decentralise ART provision is going to be challenging. Equity also needs to be considered, as resource constraints mean there is a trade-off between providing ART to everyone who needs it, and providing the best possible monitoring for those already on ART. This is particularly important where specific groups (such as children, people in rural areas, or high-risk populations) have poorer access to treatment.

Looking forwards

While the scenarios discussed are relevant now, priorities will need to be re-examined when the situation changes. Reductions in the cost of second line drugs and/or viral load tests may shift the balance. A cheap point-of-care viral load test that can be used in primary health facilities is still some way off, but could make a difference to feasibility and costs once available. Cheap point-of-care CD4 tests are closer to being ready, and may also change the feasibility of expanded CD4 testing.

CONCLUSIONS

The new WHO guidelines are aspirational. Until resources are available to implement them in full to all in need of ART, national policymakers will need to make tough decisions as to how to tailor them for their own setting. While viral load monitoring was found in modelling studies to provide some benefits over CD4 and clinically-driven monitoring, those benefits are small in relation to the extra cost.

In many settings in sub-Saharan Africa, more lives could be saved by expanding treatment to more patients, while using clinical or CD4 monitoring, than using routine viral load monitoring.

With the current costs, routine viral load monitoring may only be appropriate in wealthier countries that have scaled-up to close-to-full ART coverage, or if the cost of viral load testing were to fall considerably.

RECOMMENDATIONS

- National policymakers need to prioritise between the new WHO recommendations, based on current coverage, monitoring approaches and the resources available, to maximise the health gains in the population
- Increasing access to ART with clinical or CD4 monitoring should be a higher priority than moving to routine viral load testing
- Lack of access to viral load testing should not be a barrier to ART roll out
- Using a single 'tiebreaker' CD4 test with 250 cells/mm^3 threshold, when a patient is clinically failing, may be a good interim strategy
- At current costs, viral load monitoring should only be considered after close to full ART coverage at CD4<350 cells/mm^3 has been achieved
- International funders should continue to provide incentives to encourage the development of cheap, feasible point-of-care viral load tests that could be used in lower-level health facilities

Recommended reading

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Credits

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