

HATiP

HIV & AIDS Treatment in Practice

Issue 69 | 20 June 2006



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Monitoring antiretroviral treatment with limited laboratory services

By Theo Smart

As part of the roll out of antiretroviral therapy, laboratory services are now being scaled up in many low- and middle-income countries but will the efforts be enough to provide high quality monitoring of people with HIV on ART?

In developed countries, CD4 cell count, viral load and resistance testing are a standard part of clinical management for patients with HIV. These lab tests help to guide the decisions of when to start or switch treatment. For example, the decision of when to treat is guided by CD4 cell counts (treatment is recommended before an individual's CD4 cell count falls below 200 CD4 cells, and people should begin preparing to start once the CD4 count falls below 350), with some guidelines advocating earlier treatment for patients with very high viral loads.

Treatment failure is usually recognised by rising viral load measurements, sometimes combined with the detection of drug resistance mutations or declining CD4 cell counts. Although opinions and guidance differs as to what viral load measurements make a change in treatment necessary, in general, the goal is to switch treatments *before* CD4 cells slip significantly and put the patient at risk of clinical progression, and also before ongoing viral replication on the failing treatment permits the accumulation of drug resistance mutations which could impair responses to subsequent regimens.

But in much of the world, access to these tests and laboratory capacity is severely limited, and even the most basic services are often unavailable or unreliable. According to the 2006 UN Global Report on HIV & AIDS "over the next few years, most patients in low- and medium-income countries will continue to be monitored clinically."

Although the absence of HIV monitoring tests should not delay the institution of HIV treatment programmes, and ART *can* be initiated on the basis of clinical staging (as the World Health Organisation set out when it launched the 3x5 Initiative in 2003), a study presented at the International AIDS Society conference in Rio de Janeiro last year, has since shown that the use of clinical staging alone (treating those with WHO Stage III and IV disease) misses many of the people who would qualify for treatment on the basis of CD4 cell counts.

Those results were confirmed by a study presented at the 2006 PEPFAR Implementers Meeting, held June 12-15, in Durban, South Africa which found that clinical staging would miss up to half of the patients who would qualify for treatment on the basis of low CD4 cell counts (below 200).

In response to such findings, WHO has updated its staging guidelines to encourage more widespread use of CD4 cell counts. In some cases, donors are assisting the scale-up of CD4 testing services and as access improves, the point at which people initiate ART should come more in line to what is considered best practice in industrialised countries.

However, introducing new lab services into low-income countries is fraught with challenges — although several presentations at the 2006 PEPFAR Implementers Meeting, held June 12-15, in Durban,

South Africa show that it is possible to scale up services for people with HIV *and* improve lab services available to everyone in the country.

Finally, in most low and middle income settings, the decision on when to switch patients from a failing regimen remains challenging because there is little consensus on when to act on decreasing CD4 cell counts (if available) and clinical events are often only very late signs of failure. Viral load testing is even less common than CD4 cell testing, and even when available, the test can greatly increase the cost of managing a person with HIV. So how can a clinician working with limited laboratory resources recognise treatment failure in these patients on ART before they become seriously ill or develop high level resistance?

One potential answer may be to use criteria for failure drawn from treatment history, adherence, early clinical and basic laboratory indicators of failure, which when used together, could screen for virological treatment failure in patients taking antiretroviral therapy (ART) in resource limited settings — without having to regularly use expensive lab tests or wait for the patient's disease to progress substantially (Colebunders 2006) (see below). Studies to validate the evidence base of the algorithm are now underway, though the precise formula may have to be adapted from setting to setting.

Nevertheless, studies at the PEPFAR meeting suggest that strategic use of viral load tests will still be necessary to confirm any suspicion of failure made on the basis of falling CD4 cell counts, clinical signs or algorithms — especially in children.

Laboratory capacity in resource-poor countries

Even the most basic laboratory services are often missing or unreliable in the most resource constrained settings. According to a recent review article by Petti et al in *Clinical Infectious Diseases*, the laboratory infrastructures in low income countries generally:

- Lack basic essential equipment.
- Have a limited number of skilled personnel.
- Lack laboratory consumables (such as sterile urine-specimen containers).
- Lack educators and training programmes.
- Have inadequate logistical support.
- Suffer from a de-emphasis of laboratory testing by clinical staff.
- Have insufficient monitoring of test quality.
- Have decentralised facilities that have been set up as parallel and competing infrastructures (where governmental, non-governmental organisations and commercial (for-profit) organisations operate independent laboratories).
- Have no governmental standards for laboratory testing.

"Laboratory services are one of the most neglected areas of health care provision... and are disproportionately affected by the staff shortages, poor communications, inadequate equipment, low morale, and lack of training that impinge on all those involved in delivering health care in poorer African countries," wrote Bates and Maitland in an accompanying editorial.

In one poster presentation at the PEPFAR meeting, a team from the Institute of Human Virology (University of Maryland) working to develop quality assurance programmes for the laboratory infrastructure in Nigeria described shocking findings after visits to twelve laboratories between September 2005 and March 2006:

"Over half of the laboratories had no record of the lab staff credentials; had limited inventory systems and had no programme for calibrating pipettes. A number had no policy on accidental exposure to infectious agents and did not disinfect their bench tops daily..." (Abimiku 2006).

Likewise, another poster reported similar findings in Uganda:

"In 2002... there was a scarcity of qualified staff that was poorly deployed... there was low uptake of laboratory services due to lack of trust of results by clinicians... supplies were not regular, some basic equipment was lacking but existing equipment was not well maintained..." (Haumba 2006).

Nevertheless, thanks in part to price reductions and international donor assistance from PEPFAR, the World Bank and others, access to CD4 cell count (especially) and viral load testing are being introduced into these settings anyway.

However, several studies have shown that this can be technically challenging. Also according to Petti et al, there is a danger that AIDS funding could lead to the development of new laboratory facilities that exist in parallel to, and compete with, basic but necessary government services:

Integrating CD4 cell testing into the laboratory infrastructure at the referral level in Kenya

The way to avoid developing parallel laboratory systems is to integrate HIV monitoring tests into the existing laboratory services – but in order to do this, the infrastructure usually must first be *totally* revamped.

At the recent PEPFAR meeting, Dr Jedida Wachira of Management Sciences for Health (MSH) from Nairobi, Kenya described how CD4 cell testing was integrated into the existing infrastructure at one public sector hospital in Mombasa, Kenya. The effort is part of a programme called Rational Pharmaceutical Management Plus (RPMP), developed by MSH and the Kenyan Ministry of Health to strengthen laboratory capacity at the national level, with the support of PEPFAR via USAID.

Dr Wachira presented RPMP's experience at the Coast Provincial General Hospital (CPGH), a 700-bed referral hospital where 60-80% of the patients in medical wards are estimated to be HIV-positive. The hospital began its HIV programme in June 2003 and by March 2006, 5000 patients were receiving HIV care through the hospital with 1500 on ART. And yet, according to Dr Wachira, "the role of the laboratory in the ART programme at CPGH was really not fully appreciated until it became a major constraint to good patient management and care."

In preparation for initiation of ART services, they conducted a rapid assessment of laboratory services at the hospital and found them to be in a sorry state. Day to day laboratory practices were very poor: "Samples were getting lost, they were clotted, the volumes were insufficient for the tests required, the results were getting misplaced and getting delayed," said Dr Wachira. Plus, "there were inadequate policy guidelines and no standard operating procedures in a number of areas." The support systems were weak, with inadequate and poorly trained staff, the information management system was in shambles, and they lacked important and essential equipment. Finally, commodity management practices were not adequate and the lab suffered frequent stock-outs.

SOPs:

First, they developed standard operating procedures (SOPs) for the laboratory in specimen management (including specimen collection, handling, shipment, and processing); equipment maintenance and servicing; inventory management; various testing procedures;

internal quality control (IQC). They also introduced a post-exposure prophylaxis (PEP) policy.

Equipment:

MSH renovated the laboratory and installed essential equipment including a CyFlow (a modified cytometer) CD4 system, a rotor/shaker and new multi-channel and precision pipettes. Before this, Dr. Wachira said, there had only been "one pipette, which was moving from serology, to clinical chemistry, to haematology and everybody had to wait for the other one to finish." They also set up a system to closely monitor breakdown of the equipment – which was initially frequent with the CD4 system due to the staff's unfamiliarity with computer-based systems (and misuse of the computer for other purposes).

Human resources/training:

RPMP introduced training programmes in several areas to improve human resource capacity development. This included training the laboratory staff on how patients on ART are managed with monitoring of adverse drug reactions (this was a multi-disciplinary training for the entire multidisciplinary patient management team). In addition to training the staff on CD4/CD8 testing, they familiarised the staff on the new SOPs, as well as good laboratory practices, specimen management, safety and even correct pipetting: "Basic things, that you'd think that people already had, needed refreshing and some of them needed entirely new training," said Dr Wachira.

They also introduced workload monitoring which revealed, as the laboratory services improved and were increasingly taken up, that the lab needed more staff. As a result, the staffing budget was increased by 50%.

Information management systems:

A lab test request and registry system was developed, which included lab request and report forms and registers for various lab service points to enhance specimen management. This improved sample sorting and distribution for processing, streamlined tracking of specimens and results and ultimately improved turnaround time for test results.

Such systems could be, in the worst case scenario be on paper or, preferably, computerised. Another poster presented at the meeting (Kakkar 2006), suggested that there could be a couple of routes to developing computerised laboratory information systems to support ART-laboratory services – each with its own strengths and weakness.

For example, in Vietnam, with guidance from the US Office of the Global AIDS Coordinator, local stake-holders have been tasked with software selection/development and implementation – which results in local ownership of the project but also takes more time and an ongoing commitment. Meanwhile, in Uganda, outside information specialists were hired to rapidly develop a system: "however, implementers were faced with the lack of computer skills among laboratory staff... [the need for...] data entry [to become part of] laboratory workflow which resulted in heavy reliance on informatics specialists from outside the country," the authors wrote.

Commodity management systems:

A system was developed to monitor reagent and supply use and to accurately forecast when more needed to be ordered. In addition, the laboratory storage spaces were renovated and reorganised.

Internal quality control (IQC):

Procedures for IQC were standardised, and daily IQC performance and recording was instituted. This included monitoring equipment calibration and servicing.

Outcomes:

As a result of all of these interventions, not only did CD4 cell monitoring become accessible, but the lab's capacity increased and the quality of the results (and clinician confidence in them), improved dramatically. "Testing for all tests, other than just for ART patients increased tremendously," said Dr Wachira. "And the image of the laboratory improved to the extent that private practitioners began sending requests to this public hospital."

Similar results were reported in the poster by Haumba et al after four years of comprehensive efforts to upgrade the laboratory infrastructure in Uganda: "Service utilisation statistics showed increased uptake of the laboratory services and number of tests for HIV, TB, malaria and syphilis increased from 288,269 tests in 2003 to 1,353,383 tests in 2005.

Both projects demonstrate that CD4 cell testing, if integrated into the existing (but improved) public sector laboratory infrastructure, can be made available and result in improving laboratory services and care for *all* patients.

Improving patient monitoring at the primary healthcare level

Several studies at the PEPFAR Implementers meeting demonstrated that patients on ART may best receive ongoing care at primary health care facilities closest to where they live — with lower losses to follow-up than seen among patients attending tertiary referral hospitals. However, if basic skills and equipment are often lacking at the referral hospital level, can primary healthcare level facilities offer equitable monitoring of their patients on ART?

At the PEPFAR Implementers meeting, a number of presentations suggested that this is indeed a challenge. However, Dr Kwasi Torpey, the Director of Technical Support for the Zambia Prevention Care and Treatment Partnership (ZPCT), reported on a successful effort to improve access at the primary health level to a range of quality ART services in five provinces of Zambia.

Zambia has a population of over ten million people, and an HIV prevalence of 16%. Around 20% of eligible patients, mostly in urban areas, have access to treatment, leaving the rural population heavily under-served. But with funding from PEPFAR, through USAID, ZPCT worked with the Zambian Ministry of Health, Family Health International and MSH to strengthen the capacity of rural and peri-urban health centres to provide care for people with HIV.

As in Kenya, the basic laboratory infrastructure was weak, so the primary health centres were provided with basic haematology and chemistry analysers (and the training and systems to use them). "We know from experience that HIV patients are not immune to the background diseases that every community faces, so it is important that there be access to basic haematology and clinical chemistry," said Dr Torpey. Again, this should improve the care received by all patients served by the facility.

Still, flow cytometry to measure CD4 cell counts is beyond the scope of what can be implemented at the primary health level. So in order to offer CD4 cell monitoring for people with HIV at the clinics, a sample referral system was set up, using motorcycles provided by USAID (and niftily branded with its logo) to transport samples from the outlying clinics to referral laboratories set up in strategic areas with CD4 cell monitoring equipment. Sample transport from the

clinics was coordinated on specific days in order to make the most efficient use of Zambia's limited laboratory equipment and staff.

"So within the health centre, we are able to provide a level of service that you see in a hospital. We don't have the CD4 cell on-site, but we have access to almost everything through simple systems such as this," said Dr Torpey.

Between May 2005 and March 2006, these outlying clinics have been able to start 1868 clients on ART on the basis of CD4 cell counts and clinical staging.

Of course, not every primary health care clinic in Africa has been outfitted with its own motorcycle courier service by USAID. In the meantime, according to Dr Wachira, many sites are transporting samples to the reference labs by putting couriers with cold storage boxes onto the same regular public mini-taxis (mini-vans) that many Africans use to get from place to place.

Monitoring for treatment failure in people on ART

While these efforts should improve the timely initiation of ART for people with HIV, as ART programmes mature, growing numbers of patients will inevitably fail treatment. How to recognise treatment failure — and the time to switch to a second-line regimen (if available) — with limited laboratory resources remains an open question.

Viral load testing, inarguably the best way to directly measure a regimen's ongoing antiretroviral activity, is commonly available only in the wealthier countries, or at reference laboratories. While it may be possible to transport the samples to the reference lab, the test is very expensive by developing world standards, ranging between \$15 and \$150 per viral load, depending upon the equipment and how efficiently it is used (and batch sizes, etc.).

Meanwhile, although studies have shown that effective antiretroviral therapy usually increases CD4 cell counts (in both resource-rich and constrained settings), CD4 cell counts are an indirect and imperfect measure of an ART regimen's antiretroviral activity — particularly in young children. For instance, after starting ART, some patients can have CD4 cell counts that remain elevated for months — long after the drugs have stopped having an effect against the virus (putting the patient in danger of developing high level drug resistance that could impair responses to the second-line regimen). In addition, CD4 cell counts can be *reduced* by infections such as TB, which can occur in people with undetectable viral loads. Other endemic infections, in particular parasitic infections such as schistosomiasis, or nutrient deficiencies could also blunt CD4 cell responses.

A team from Harvard working in Tanzania reported how just problematic the use of immunological (CD4 cell count) failure is in a poster presentation at the recent PEPFAR meeting (Cardiello 2006). Immunological failure in Tanzania is defined as a 30% drop in CD4 cell count from peak value or a return to the pre-ART baseline or lower. Of the seventy-nine patients in the Tanzanian programme who have had an immunological failure on treatment, viral load results are available for 43. According to the viral load results however, 21 (51%) of those with immunological failure have viral loads below 400 copies per ml, while 27 (63%) have viral loads below 5000 copies per ml. "We found that 51-63% of patients would likely have been switched to second line ART if the viral load result were unknown," the authors wrote.

Given the high cost of second-line (protease inhibitor) based therapy, this is an important finding. However, using a slightly different definition of immunological failure (a 50% reduction from

peak or simply a return to baseline CD4 cell count) may alter the results.

In the absence of laboratory support, many ART programmes and projects rely on clinical signs and symptoms of disease both to decide when to treat, and to monitor treatment. The World Health Organisation guidelines suggest that new or recurrent WHO stage III or IV conditions can be used as signs of treatment failure.

While this is true, in the first several months after starting ART, clinical events can occur that have nothing to do with treatment failure, either because infections set in before the immune system can respond to treatment, or, conversely, because of immune reactivation inflammatory syndrome (IRIS) which may cause previously sub-clinical infections to “flare up.” In addition, tuberculosis, malaria and malignancies may still strike people even when their viral loads are fully suppressed by on ART.

After three to six months, any stage III or IV clinical events may be more indicative of treatment failure. But again, having to wait for serious clinical progression clearly puts the patient at unacceptable risk.

The model at Makerere

A team of physicians and researchers working with the Makerere Medical School in Kampala, Uganda have developed a model, published in January's Lancet Infectious Diseases by Colebunders et al, which uses a checklist combining a number of factors that may be early indicators of treatment failure. These factors are drawn from the patients' own treatment and adherence history, clinical markers (such as HIV-related signs or symptoms or opportunistic infections), as well as laboratory tests such as CD4 cell counts or alternatively haemoglobin levels and total lymphocyte counts (TLCs). Those patients meeting enough failure criteria (one major or at least three minor criteria from different categories) can be identified as no longer responding to their ART regimen - often before severe clinical progression or immunological deterioration sets in.

Risk factors for clinical failure

System for assessing the risk of virological failure in the absence of viral load testing after at least six months of treatment.

Treatment failure is estimated as probable if one major or at least three minor criteria from different categories are present.

Adapted from Colebunders R et al. Lancet Inf Dis 2006.

Treatment history	
Previous monotherapy or bithersapy with NRTIs for more than 6 months	Minor
Previous exposure to nevirapine for prevention of mother to child transmission of HIV	Minor
Infected with HIV by a partner with a history of ARV exposure	Minor
Current 'weak' antiretroviral regimen (eg 3NRTIs, 2NRTIs and 1NRTI)	Minor
Long-term use of drugs that could reduce antiretroviral drug levels	Minor
Adherence history	
Day to day adherence score <95% >80%	Minor
Day to day adherence score <80% >60%	Major

History of stopping an NNRTI-containing regimen without continuing NRTIs for at least 5 days	Minor
Clinical history	
Appearance or worsening of unexplained prurigo	Minor
Reappearance of unexplained prurigo and at least one other HIV-related sign or symptom (not in the first six months of treatment and not related to IRIS)	Major
Reappearance of at least two HIV-related symptoms (not in the first six months of treatment and not related to IRIS)	Minor
Body weight equal or lower than the patient's weight before starting ART or more than 10% weight loss from peak values in the absence of lipodystrophy	Minor
Development of a WHO stage IV opportunistic infection (excluding extrapulmonary tuberculosis or IRIS) or malignancy (not in the first six months of treatment and not related to IRIS)	Major
A recurrent WHO stage III opportunistic infection	Minor
Tuberculosis and no evidence of TB IRIS (abscess/cavity formation)	Minor
Worsening Kaposi's sarcoma	Minor
Worsening after initial improvement of Kaposi's sarcoma	Major
Laboratory history	
Unexplained decline of 10% or more in haemoglobin on two occasions and a reduction in total lymphocyte count* of 50% from peak values on consecutive testing, OR haemoglobin and TLC* falling below baseline on two consecutive tests	Minor
A reduction in CD4 count of 50% from peak values since starting treatment on two consecutive tests*	Minor
CD4 count below baseline on two consecutive tests*	Minor

* These tests should be ideally carried out in the absence of acute intercurrent illness

A patient's treatment history may reveal some risk factors with a minor predictive value for ART failure, such as previous exposure to antiretrovirals, being infected by a partner with treatment experience, current use of a weak regimen (such as triple nucleoside analogues) or long-term use of drugs that lower antiretroviral drug levels (such as methadone).

For adherence history, very poor adherence to treatment (with a day-to-day adherence below 80% but above 60%) is a major predictor of failure. Better, though less than 95% day-to-day adherence, may put the patient at more modest risk of failure.

A good clinical history could also provide important clues to whether a patient is failing treatment because after the first six months on ART, reoccurrence of earlier HIV-related signs and symptoms could indicate treatment failure. These signs include prurigo, unexplained persistent diarrhoea, unexplained persistent

fever, unexplained weight loss, unexplained polyneuritis (excluding drug induced neuropathies), unexplained cognitive impairment, loss of developmental milestones or growth retardation in children.

In particular, the reappearance of prurigo (combined with at least one other HIV-related sign) may have major predictive value for failure (at least in Uganda and much of Africa) as does the development of any major WHO stage IV opportunistic infection (aside from TB or IRIS) or the worsening - after initial improvement - of Kaposi's sarcoma (KS). Worsening of KS or the development of other new or recurrent infections or symptoms of HIV or significant weight loss are postulated to be risk factors with minor predictive value.

Finally, falling CD4 cell counts (to 50% of peak values or below baseline) have a minor predictive value for failure. When CD4 cell counts are not available, an unexplained drop in haemoglobin levels (by 10% or more on two occasions) and a fall in TLCs counts to 50% of peak values on consecutive tests, or haemoglobin or TLCs below baseline (on two consecutive tests) could have a similar predictive value to falling CD4 cell counts.

While this particular model may require some simplification before it can be used at the primary care level using and needs to be evaluated in different settings to see how well it works in practice, using such a strategy could reduce patient monitoring costs by conserving viral load testing for those in whom there is a high suspicion of failure. It could also reduce costs by preventing patients from being prematurely switched to expensive second line regimens or conversely improve patients' outcomes by switching them to the second-line ART regimen while they still have a chance of benefiting from them.

Researchers in Uganda are presently conducting a study to compare the use of clinical, immunological, and virological indicators (and combinations thereof) as criteria for switching treatment in resource limited settings.

However, the decision to switch treatment regimens ultimately depends upon whether there are second-line treatment regimens available to switch to. Switching too early could leave patients in resource-limited settings with no other treatment options - and this single concern could make many clinicians hesitant to use anything other than serious clinical or immunological deterioration (to below 200 CD4 cells) as the basis for switching treatment.

Reserving viral loads for failure

Nevertheless, viral load is being used in some resource-constrained settings — especially in PEPFAR programme countries. For instance, in South Africa, viral loads are offered only once a patient initiates treatment, and at regular intervals thereafter in order to monitor for treatment failure.

But even in lower income countries, samples are increasingly being transported by courier to the reference lab to confirm the suspicion of failure in patients. But according to Dr Wachira, in Kenya, no baseline measurement is assessed. Rather the test is only used after the patient seems to be failing based upon other

criteria — a high viral load (for example above 5000 copies per ml) serves as confirmation that the drugs are indeed not working (or that the patient is not taking them).

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