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Monitoring Patients on Antiretroviral Therapy

Introduction

Close monitoring of patients who have started antiretroviral therapy (ART) is important for several reasons: the evaluation and reinforcement of adherence can be done on an ongoing basis; clinical problems such as toxicities or

decisions regarding switching to second-line ART regimens.

Immunological and Clinical Monitoring

Immunological monitoring (CD4 count) is an important element in the continuing care of all patients on ART. While CD4 count is neither a highly sensitive nor specific marker of virological failure,³⁻⁶ it provides useful information on response to ART and risk for clinical complications.^{7,8} Similarly, several studies demonstrate the limitations of utilizing clinical failure as a surrogate for virological failure.⁹⁻¹¹ However, clinical monitoring is important to detect adverse side effects, as well as opportunistic infections unmasked by ART particularly during the first 12 months after ART initiation when mortality is highest. Routine clinical and

development of virological failure and drug resistance on first-line ART. The new WHO guideline recommends using immunological criteria for deciding when to switch ART if virological testing is unavailable.²

Adherence Monitoring

Non-adherence is closely associated with virological failure, clinical progression, and death.¹³⁻¹⁵ One recent population-based cohort study in Vancouver, for example, found that ART-naïve patients with incomplete adherence (<95% adherence) were 3 times more likely to die than highly adherent patients (≥95% adherence) (HR 3.13, 95% CI 1.95-5.05).¹⁶ Adherence in this study was defined as the number of days of ART dispensed divided by the number of days of follow up (expressed as a percent). Further research in this cohort also found that poor adherence was associated with increased drug resistance.¹⁷

Recent Studies

Two international presentations were

Clinical failure	New or recurrent WHO stage 4 condition (some stage 3 conditions should be considered e.g. pulmonary tuberculosis) occurring after 6 or more months of antiretroviral therapy
Immunologic failure	Fall of CD4 count to pre-therapy baseline or below, or fall of 50% from on treatment peak value, or persistence of CD4 count below 100 cells/ μ l after at least 6 months of therapy
Virologic failure	Plasma viral load above 5,000 copies/ml after at least 6 months of therapy

immune reconstitution inflammatory syndrome (IRIS) can be identified early; and evidence of treatment failure can be detected in a timely fashion, enabling a prompt work-up and ART regimen switch if indicated.

Identification of ART Treatment Failure

The World Health Organization (WHO) criteria for "treatment failure" are listed above in Table 1. Where viral load measurement is routinely available, WHO recommends that it be used every 6 months, as an early indicator of treatment failure and as a guide in determining when to switch regimens.² However, in ICAP-supported settings, it is unlikely that reliable routine viral load testing is available. Here we review the evidence for using careful clinical and immunological (CD4 count) monitoring as well as adherence assessment to follow patients and guide

immunological monitoring together, in the absence of viral load testing, have been studied by Pujades et. al., who reviewed data from 48,000 patients across 62 clinical sites in Africa. They found that patients (n=370) who were started on second-line ART based on immunological and/or clinical criteria had good early outcomes.¹² The probability of being alive and in care was 0.86 (95% CI: 0.81-0.90) and 0.77 (95% CI: 0.69-0.83) at 12 and 24 months respectively, despite the presumed

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Regular adherence assessment is vital in patients on ART.

recently made regarding the relative roles of clinical and immunological monitoring in managing patients on ART in Africa. While neither analysis is published at this time, the results have generated a great deal of discussion, interest and controversy regarding the optimal way to monitor patients on ART in the absence of routine viral load testing.

The Home-Based Care project (HBAC)⁹: This study was conducted in rural Uganda and evaluated three strategies for monitoring patients who initiated ART. Patients were randomized to one of three arms: weekly clinical monitoring alone, weekly clinical monitoring and quarterly CD4 counts, or weekly clinical monitoring and quarterly CD4 counts and viral load testing. Over 3 years, those randomized to clinical monitoring alone were at significantly greater risk of developing a new AIDS-defining illness or death, compared to those randomized to clinical monitoring and CD4 count testing (adjusted hazard ratio [HR_{adj}] 1.5, p=0.047). There was no significant mortality or morbidity difference between those who were monitored with clinical monitoring plus CD4 and viral load testing, and those randomized to clinical monitoring and CD4 testing alone (HR_{adj} 1.3, p=0.26).

The Development of Antiretroviral Treatment in Africa (DART) trial¹⁰: This study was conducted in Uganda and Zimbabwe and evaluated two strategies for monitoring patients on ART. It involved randomization of ART-naïve patients to either monthly clinical monitoring alone, or monthly clinical monitoring plus quarterly

laboratory monitoring (FBC, chemistry and CD4 count). Patients randomized to clinical monitoring alone had a greater risk of new WHO stage 4 events or death compared to those randomized to clinical plus laboratory monitoring (HR 1.31, 95% CI 1.14-1.51, p=0.0001), although survival over the 5 years of the study was excellent in both groups (87% and 90%, respectively). It is important to note that patients randomized to clinical monitoring alone could also have lab monitoring (FBC and chemistry tests) as needed, but not CD4 counts.

A Recommended Approach

Existing evidence supports the importance of assessing patients for improvement and adherence once placed on ART, as well as for the need to change regimens in a timely fashion if improvement does not occur. The new WHO guideline for ART monitoring has just been released,² and supports the following recommendations.

Regular CD4 monitoring: CD4 counts should be obtained **at least every six months**. Results should be promptly reviewed, and patients who demonstrate evidence of immunological failure should have repeat CD4 counts (with early return appointment, e.g., 1-2 weeks) to confirm immunological failure. Once immunological failure is confirmed, adherence must be carefully assessed and concerns addressed, and a timely regimen switch should be considered.

Clinical monitoring: this should be done **monthly in the first three months of ART, and every three months thereafter**, and should include assessment for symptoms and signs of HIV-related illnesses, as well as weight

measurement. Frequent evaluation is especially important in the first 12 months of therapy as patients are most vulnerable to drug toxicity and IRIS during this period. If lack of clinical improvement exists, or if clinical deterioration is detected, a timely regimen switch should be considered.

Adherence assessment: Measuring adherence quantitatively at every visit, through 3- or 7-day recall, or using pharmacy refill data, is critical to further assess situations in which there is evidence of clinical, immunological or virological failure. If there is evidence of non-adherence, a qualitative assessment of barriers to adherence should be done, and support efforts should be intensified to achieve high rates of adherence. Patients who report high rates of adherence in the presence of evidence of ART failure should be candidates for a switch in therapy. (NB: The next issue of Topics will be devoted exclusively to Adherence Assessment.)

Multidisciplinary Approach: A multidisciplinary approach involving clinicians, laboratorians, pharmacy staff, counselors and peer support workers is necessary to appropriately monitor patients who have initiated ART, and to identify the appropriate point at which to consider a regimen switch. Discussion of patients who may have evidence of treatment failure at a multidisciplinary team meeting attended by providers (e.g. clinicians, counselors, peer workers) may help identify those patients with immunological and/or clinical failure who are either (i) non-adherent and require intensive adherence support before considering a switch to second-line ART, or (ii) adherent and need ART regimen change promptly.¹¹

Viral load monitoring: In settings where viral load testing is available for routine monitoring of patients on ART, it should be ordered and interpreted **every six months**. In other settings, where there is only limited access to viral load testing, **targeted use** of viral load testing should be considered. For example, in adherent patients who demonstrate new or persistent Stage 3 or 4 illnesses, and/or persistent immunological failure, viral load testing should be done after any concurrent illness is treated, the CD4 count is rechecked, and the patient is discussed by the multidisciplinary team. If the patient demonstrates elevated viral load (>5,000 copies/ml), this is evidence of

Table 2: Recommended Approach to Monitoring Patients on ART

Component	Frequency
Clinical monitoring	Monthly for first 3 months of ART, then every 3 months
CD4 testing	Every 6 months
Quantitative adherence assessment	Every visit
Viral load testing	Every 6 months (if routinely available), or targeted (if access is limited)

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treatment failure and a switch to a second-line regimen should be made as soon as possible.

Summary

As ART scale-up in developing countries continues, there is an increasing need to closely monitor patients on ART in order to identify emerging clinical and psychosocial issues. Patients switched from first- to second-line ART regimens can have good clinical outcomes. Decisions about regimen switching must be made on a timely basis and as accurately as possible; changing patients to second-line regimens prematurely may compromise the benefits of first-line ART, while changing them too late may

compromise the effectiveness of second-line drugs. Regular and ongoing monitoring of all patients on ART is especially crucial in the first 12 months after ART initiation, when mortality is highest.

Identification of the time to switch regimens can be made by several means. CD4 testing, viral load assays and routine clinical evaluations can all be used effectively to identify those patients at risk for HIV progression who would benefit from a switch. Evidence of immunological failure, a rising viral load, or a new Stage 3 or 4 clinical event are all markers of HIV disease progression and, in patients on ART, are all signs that an individual is not responding to the ART regimen they are receiving. Adherence assessment and intervention become key

factors in determining management strategy.

As a consequence, an integrated, patient-focused approach is vital. This should include strong links across clinical services, involving clinicians, counselors, expert clients, laboratorians and pharmacists. Thorough clinical monitoring and adherence support by this multidisciplinary team, in concert with routine CD4 count monitoring, is essential in the management of all patients on ART. Viral load testing can be of value in such monitoring; however, due to constraints in access to such testing, viral load measurement may be more feasible as a tool for the management of complex patients.

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