The art of HAART: a practical approach to antiretroviral therapy

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The development of effective treatment for HIV infection is the major medical success story of the late 20th century. HIV infection can now be regarded as a chronic, manageable disease.

Antiretroviral therapy (ART) is intended to maintain durable HIV viral load suppression, allowing immunological recovery. This results in a greatly reduced risk of HIV-related illness. These benefits can only be obtained by combining at least three antiretroviral drugs, known as highly active antiretroviral therapy (HAART).

Successful therapy is critically dependent on the HIV clinician and the patient establishing a robust therapeutic relationship. The prescribing doctor must take responsibility for advising the patient on the choice of ART and for supporting the patient on therapy. Incorrect combinations or dosing can lead to failure of therapy and subsequent development of viral resistance. The patient must accept the need for long-term adherence to medication and should understand both the risks and benefits offered by ART.

Poor management can deprive a patient of the chance to derive long-term benefit from HAART.

WHEN TO START HAART – GETTING IT IN PERSPECTIVE

Clinical criteria for commencing therapy, that is HIV stage and CD4 count, should follow the latest South African HIV Clinicians Society Guidelines, as should the drug regimen chosen (Tables I and II). Clinicians and patients frequently either find it difficult to accept that therapy can be safely postponed for many years or worry unduly about the risks and side-effects associated with HAART.

Timing, benefits and risks can be put into perspective by telling a story:

Imagine you are hiking through the bushveld and enjoying the bird life and the game. But, in the distance, you see a lion stalking you. You aren't too worried because you have a gun. But there are only two bullets in the gun, so you need to be quite sure about the best time to shoot. If you shoot too soon there is a good chance that you will miss the lion, and that the explosion will chase away all the wildlife. If you leave it too late the lion may be on top of you before you can take aim.

The lion represents AIDS and the distance between you and the lion shows how strong your immune system is — the closer the lion the weaker your immune system. The gun with two bullets is your antiretroviral therapy, which you need to learn how to use properly so that you don't hurt yourself. The sound of the gun being fired represents the potential side-effects from the antiretroviral therapy — a real nuisance if the lion is far away, but the last thing you'd worry about when the lion is getting close!

Antiretroviral therapy needs to be used responsibly.

Some patients, despite fitting the clinical criteria exactly, do not do well on therapy. Picking these people out in advance is

Table I. Clinical reasons to commence ART

Symptomatic patient (excluding TB)	**Treatment**
Presence of HIV-related symptoms, current or previous HIV-associated disease (includes AIDS-defining illnesses, unexplained weight loss >10%, unexplained diarrhoea >1 month, oral candidiasis or oral hairy leukoplakia)	Treatment recommended
Patient with tuberculosis	
CD4 count <200 cells/µl	Delay treatment until after 2-month intensive phase of TB treatment unless the patient has other serious HIV-related illness or a CD4 count <50 cells/µl, when ART should be introduced as soon as the patient is stabilised
CD4 count >200 cells/µl	Commence therapy after completing 6 months of TB therapy. Consider CD4 guidelines below if asymptomatic once TB treatment completed.
Asymptomatic patient	
CD4 count <200 cells/µl	Treatment recommended
CD4 count 200 - 350 cells/µl	Monitor CD4 count: if count decreases in excess of the expected 20 - 80 cells per year or count approaches 200, commence therapy
CD4 count >350 cells/µl	Defer treatment

Table II. Options for ART*

Category I (NRTIs)	**Category II (NRTIs)**	**Category III (NRTI)**	**Category IV (NNRTIs)**	**Category V (PIs)**
Stavudine (d4T)	Didanosine (ddI)	Abacavir (ABC)	Nevirapine (NVP)	Nelfinavir (NFV)
Zidovudine (AZT)	Lamivudine (3TC)		Efavirenz† (EFV)	Indinavir/RTV (IDV)
	Zalcitabine (ddC)			Saquinavir/RTV (soft gel) (SQV)
				Lopinavir/RTV combination
				Ritonavir (RTV)‡

NRTI = nucleoside reverse transcriptase inhibitor; N NRTI = non- nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
*For initiation of therapy in an ART-naïve patient use 2 N RTIs (one from category I and one from category II) together with one NNRTI (category IV).
† EFV is teratogenic. Avoid in women of childbearing potential. Only use if no other ART available and patient can guarantee hormonal contraception is used as well as barrier methods.
‡ RTV is most often used in combination with another protease inhibitor at a low dose of 100 mg twice daily. Here it is being used as a p450 inhibitor to boost the levels of the combined PI. It is not a useful antiretroviral agent at this low dose. In adults it is rarely used as an antiretroviral in its own right (600 mg twice daily) due to increased adverse events (e.g. diarrhoea).

close to impossible. There are, however, certain patient-related factors which make adherence less likely and which should be addressed before starting HAART:

- The patient must have come to terms with being infected with HIV — *do not start therapy in someone with a recent diagnosis*. Patients who have adjusted to their HIV status should be comfortable enough to disclose to chosen friends or family members. *Non-disclosure predicts treatment failure*.
- Patients should have good understanding of HIV disease and progression to immune system failure and AIDS.
- Similarly they should have a basic understanding of the action of antiretrovirals, and be willing to learn about the medication they are planning to take.
- Significant depression makes adherence to ART difficult. Psychotherapy and an antidepressant may be necessary before embarking on HAART.
- The personal and social disruption associated with drug and alcohol abuse makes long-term adherence to a HAART regimen problematic.

PRE-THERAPY INPUT

HAART never needs to be started as a matter of urgency. Educating the patient about HAART before beginning therapy is worth the time. Key points for the patient are:

- HAART is for life. There are no breaks or holidays — in fact treatment interruptions can be detrimental to long-term success. Viral suppression hinges on maintaining adequate drug levels in the blood.
- Dual nucleoside combinations are best avoided, as they are unable to deliver long-term benefit.
- The first HAART regimen is the one most likely to have success. Once exposed to ART, subsequent regimens have a poorer outcome. Make your first regimen work for you.
- Missing even one dose a week can result in treatment failure and viral resistance over time. *Do not start therapy if you are not ready to make a full commitment to daily therapy for life.*
- Do not stop any of your medications without consulting your doctor. If stopping is unavoidable (e.g. due to a side-effect), stop *all three* medications together. (Note that non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a very long half-life, and should ideally be stopped 4 days before the nucleoside reverse transcriptase inhibitors (NRTIs)). Ask your doctor what side-effects may be expected.
- When a dose is twice a day it means 12 hours apart (e.g. 8 am and 8 pm). Once a day means 24 hours apart. Sticking as close as possible to these dosing intervals is important for viral suppression.
- Get food restrictions right: if a tablet, e.g. ddI (Videx), needs to be taken on an empty stomach, an hour before eating, do that. If you don't the drug may not be absorbed.
- Check that any other medication you are prescribed does not interact with your ART.

WHICH DRUGS TO USE

Ideally triple antiretroviral regimens should be tailored to individual patients:

- Keep it simple — avoid three times daily dosing as people frequently don't take the midday dose. Most medications can be taken once or twice daily (for example 800 mg of indinavir can be 'boosted' with 100 mg of ritonavir, which extends the dosing interval from 8 to 12 hourly). Note potential side-effects — do not choose drugs that might exacerbate existing clinical problems e.g. liver disease, peripheral neuropathy or hyperlipidaemia.
- Watch the practicalities of dosing — complex food restrictions should be kept to a minimum. Be careful about drug interactions (e.g. is the patient on antiepileptics, rifampicin, fluconazole, erythromycin or peptic ulcer therapy?)
- Keep the daily number of tablets low — remember supplements add up too.
- The patient's budget is a crucial factor in the decision-making process. ART is expensive so don't push the patient into an unaffordable regimen. Many initiatives are underway to broaden access to HAART.

GETTING GOING

- Initially offer increased visits, at least once a month. People starting nevirapine need liver functions monitored at 2, 4 and 6 weeks. Make the most of the visit — discuss how many doses have been missed over the past three days and why, and resolve any issues which can negatively affect adherence.
- Watch out for side-effects. Encourage your patient to come to you before stopping the medication. Minor adverse events, such as ongoing nausea, can prevent adherence. Pay attention to these seemingly 'unimportant' issues.
- Support groups are beneficial. Encourage your patient to see a

counsellor regularly or join a support group. Discussion provides emotional and practical support.
- Ask the patient to select a treatment partner from among the people to whom he/she has disclosed.This partner can assist by reminding the patient to take his/her medication, and by providing emotional support. He/she may also be able to add insight into the home circumstances of the patient.

The following case histories highlight some of the important problems associated with HAART.

CASE 1: INTRODUCING HAART IN ANTIRETROVIRAL-NAÏVE PATIENTS

A 31-year-old woman presents to the surgery, having been diagnosed with HIV 18 months previously following recurrent bouts of vaginal candidiasis. Her CD4 count at diagnosis was 310 cells/mm^3.

At the time of diagnosis, she declared herself not yet ready to begin antiretrovirals, and she has been managed by you with ongoing counselling, intercurrent disease management, and 6-monthly CD4 counts.

At this visit, her CD4 count is 204 cells/mm^3, and she requests that she begin antiretroviral therapy. An HIV viral load reveals a level of 110 000 copies/ml. A baseline ALT reveals a level of 42 U/l.

Following adherence counselling, she is started on:
- D4T 40 mg po bd (weight 68 kg)
- 3TC 150 mg po bd
- nevirapine 200 mg po/day to increase to 200 mg po bd at 2 weeks.

On day eight of therapy she contacts the surgery complaining of diffuse pruritus and a rash. She is asked to come in, and examination reveals her to have a diffuse maculopapular rash, with no evidence of systemic symptoms, mucosal lesions, or fever. In consultation with the patient, it is decided to continue the treatment, but to add oral chlorpeniramine (4 mg orally tds) for symptomatic relief. An ALT is sent to check for possible hepatitis. This comes back within the normal range at 38 U/l. On day 13, the rash has resolved, and the symptomatic treatment is stopped. For safety reasons, the dose step-up of nevirapine is delayed for 1 week, and on day 21 of therapy she increases her nevirapine to 200 mg bd.

Watch out for side-effects. Encourage your patient to come to you before stopping the med - ication. Minor adverse events, such as ongoing nausea, can prevent adherence.

At three months her CD4 count is 270 cells/mm^3, and her viral load is less than 400 copies/ml. She is booked for further 6-monthly assessments.

This case demonstrates several important facts about commencing antiretroviral therapy in antiretroviral-naïve patients:
- The most important factor is patient acceptance, and counselling regarding high-level regimen compliance. No regimen should be started without attention to this aspect.
- The sequence of drugs used follows a fairly typical pattern. A backbone of NRTI agents (one thymidine analogue — D4T; one non-thymidine analogue — 3TC) is utilised, and a third highly active agent (NNRTI class — nevirapine) is added to complete the regimen.
- Early side-effects tend to occur in the first 2 - 6 weeks of therapy, and are generally mild to moderate. Most can be managed without stopping the regimen.

CASE 2: CHANGING THERAPY AFTER FIRST-LINE THERAPY FAILURE

A 29-year-old man, well known to the practice, presents for his regular 6-monthly assessment. He is HIV-positive, and has been on antiretrovirals for over 3 years. In 1999, he was started on:
- AZT 300 mg po bd
- 3TC 150 mg po bd
- Nevirapine 200 mg po bd.

His initial CD4 count was 118 cells/mm^3, and his viral load pre-

therapy was 240 000 copies/ml. He responded well to antiretroviral therapy, and has had an undetectable viral load (less than 400 copies/ml) since week 24 of therapy. His last CD4 count (6 months previously) was 385 cells/mm^3. He has been clinically well. His CD4 count is now 320 cells/mm^3, and his viral load is measured at 18 000 copies/ml.A repeat viral load in 2 weeks is 20 000 copies/ml, and he is assessed as failing initial therapy. Excluding intercurrent illness, recent vaccination, malabsorption and compliance problems, the most likely cause of failure is development of viral resistance to the current regimen. He is therefore changed to:

- D4T 40 mg po bd (weight 76 kg)
- DDI 200 mg po bd
- lopinavir/ritonavir 400/100 mg po bd.

A 6-week viral load is undetectable (less than 400 copies/ml), and the minor nausea of the first week of therapy (probably induced by the ritonavir) is treated with cyclizine 50 mg bd.

He continues to have an undetectable viral load and increasing CD4 count at his next 6-month assessment.

Changing antiretroviral regimens, particularly when moving from a first- to a second-line regimen, generally follows a predictable pattern. Once failure has been determined, all drugs are altered in order to get as many 'clean' agents in the new regimen as possible. The new regimen is constructed according to the template in case one above. Backbone: one thymidine analogue NRTI: AZT changed to D4T; one non-thymidine analogue NRTI: 3TC changed to DDI; NNRTI class (nevirapine) changed to PI class (lopinavir/ritonavir).

RECOMMENDED READING

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IN A NUTSHELL

HAART is very effective treatment for advanced (CD4 count < 200 cells/µl) or symptomatic HIV infection.

Once initiated, HAART must be continued for life.

Dual therapy should never be prescribed as the benefits are transient and resistance develops quickly.

Before committing to HAART patients should have come to terms with their HIV infection and should have the support of family or friends.

Psychological issues and depression should be addressed before HAART is commenced.

In advanced HIV infection the risk of side-effects from HAART is outweighed by the benefits of viral suppression.

The importance of strict adherence to a HAART regimen should be emphasised, and problems that may compromise adherence should be managed proactively.

Clinicians should have a high index of suspicion for ART-induced drug side-effects, especially for lactic acidosis/acidaemia, which has very nonspecific symptoms including fatigue, weight loss, nausea, dyspnoea and abdominal pain.

SINGLE SUTURE

Graduate v. undergraduate training

Several Australian medical schools have moved to graduate-entry, problem-based programmes and others are considering changes to their curricula and entry criteria.Who is best prepared for hospital practice — the graduate-entry students, or the more traditional undergraduate students who also receive problem-based education? A recent study in the *Medical Journal of Australia* (2003: **178:** 163-166) found that graduates from the newer approach were less well prepared for their intern year than graduates from the traditional and undergraduate problem-based programmes.