An update on HAART: part 1

This year marks the 10th anniversary of the breakthrough in HIV and AIDS treatment known as “highly active antiretroviral therapy”. In the first of two articles, Rosy Weston, Simon Portsmouth and Andrew Benzie give an update on antiretroviral therapy for patients with HIV

Acquired immunodeficiency syndrome (AIDS) was first described in 1981. It is caused by the human immunodeficiency virus (HIV), which destroys and impairs the cells of the body’s immune system, notably CD4+ T-cells (“CD4”). Over time, the resulting immunosuppression permits the development of opportunistic infections. These are due to pathogens that cause asymptomatic infection or minor illness in the immunocompetent, but can cause potentially life-threatening infection or malignancy in those who are immunosuppressed.

The US Centers for Disease Control and Prevention define AIDS as the presence of one of 26 conditions indicating severe immunosuppression associated with HIV infection, such as Pneumocystis jiroveci pneumonia (“PCP”). A diagnosis of AIDS in the US is also given to HIV-infected individuals when their CD4 count falls below 200 cells/mm³. On average, an uninfected adult will have a CD4 count between 800 and 1,500 cells/mm³.

In December 2005, the Health Protection Agency released the latest statistics for people living with HIV in the UK. Nearly 60,000 people are living with the virus but, of those, more than one third remain unaware of their infection. This news, combined with the report of increasing baseline resistance to antiretroviral therapy, is cause for concern.

HIV drug resistance

The UK has one of the highest reported rates of primary resistance to HIV drugs worldwide. This is when a drug-resistant virus is transferred from one HIV-positive individual to a non-infected individual. This can limit treatment options for that newly infected individual.

The increasing prevalence of transmitted resistance has prompted the British HIV Association (BHIVA) guideline writing committee to recommend that all HIV-positive patients have a blood test to look for baseline resistance. The presence of specific virus mutations can identify patients who have been infected with a strain of HIV which is already resistant to certain drugs or classes. This can help the clinician choose initial therapy and maximise the chance of achieving viral suppression. The baseline resistance test should be performed as soon as possible after diagnosis. A resistance test is also recommended after treatment failure.

What is HAART?

It was previously thought that viral replication could be slowed or even halted with the use of one or two antiretroviral drugs but it is now accepted that this is not the case. Current prescribing of antiretroviral therapy should provide at least three drugs, acting at different stages of the HIV life cycle. “Combination therapy” and “highly active antiretroviral therapy” (HAART) are the terms used to describe

Panel 1: BHIVA recommendations for starting treatment

<table>
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<tr>
<th>Presentation</th>
<th>Surrogate markers</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Initial HIV infection (within six months of exposure to HIV)</td>
<td>CD4 &lt; 200, or any viral load</td>
<td>Treat</td>
</tr>
<tr>
<td>Established infection</td>
<td>CD4 201–350</td>
<td>Start treatment taking into account viral load, rate of CD4 decline, patient’s wishes or presence of hepatitis C</td>
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<tr>
<td>Symptomatics of disease or AIDS</td>
<td>CD4 &gt; 350</td>
<td>Defer treatment</td>
</tr>
<tr>
<td></td>
<td>Any CD4 or viral load</td>
<td>Treat</td>
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three or more antiretrovirals drugs used for the treatment of HIV.

HAART has dramatically improved the prognosis of people living with HIV. For those with access to it, HIV is now regarded as a chronic manageable disease.

In addition, the development of new antiretrovirals, new drug classes and co-formulations, together with a greater understanding of their pharmacokinetics, has noticeably improved the tolerability and clinical efficacy of treatment. Moreover, a greater understanding of factors that affect an individual's adherence to medication has led to a more individualised approach to treatment. However, despite success with antiretroviral treatment to date, we are still faced with many challenges.

The fact that HIV has the ability to persist in certain latently infected cells and cannot be eradicated is the main barrier to cure of HIV.

The aim of HAART is to prolong and improve the patient's quality of life by suppressing viral replication, ideally to below the current level of detection of the virus (<50 copies/ml) and to maintain this degree of viral suppression for as long as possible. In doing so this should restore the immunological response and prevent the development of opportunistic infections.

BHIVA treatment guidelines were updated in August 2005 and provide health care professionals with evidence-based recommendations on the use of antiretrovirals. Panel 1 (p631) describes the recommendations for whether or not treatment should be started.

Markers: An individual's CD4 count and plasma viral load (copies/ml) are used as surrogate markers to measure disease progression as well as to evaluate the impact of treatment. The CD4 count is a measure of the extent of damage to the immune system and the most reliable single indicator of the probability of developing an opportunistic infection. HIV viral load, on the other hand, is the best marker of response to antiretroviral therapy. Viral load is also measured routinely in patients who have not yet started drug therapy.

Once therapy is started, viral suppression should be achieved within 16 weeks. This is normally associated with an increase in the CD4 count. Viral suppression will not be achieved if a patient is not adhering to medication but poor absorption, drug interactions, drug resistance (which can occur as a result of poor adherence) and inadequate drug levels could also be responsible.

Patients are described as being on “stable” antiretroviral therapy when the viral load remains below the lower limit of detection of the available test (<50 copies/ml) and there is a sustained increase in the CD4 count. HIV clinics should perform routine monitoring of CD4 count, viral load, blood count, urea and electrolytes at three- to six-monthly intervals. Screening for sexually transmitted infections

Panel 3: Initial regimen choices

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Recommendation</th>
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<tr>
<td>2 NRTIs + 1 NNRTI (Efavirenz is the preferred first NNRTI option)</td>
<td>Recommended</td>
</tr>
<tr>
<td>2 NRTIs + boosted protease inhibitor (Lopinavir boosted with ritonavir is the preferred first option protease inhibitor)</td>
<td>Recommended</td>
</tr>
<tr>
<td>3 NRTIs</td>
<td>Not recommended unless the baseline viral load is low or there are concerns about the patient's ability to adhere to a regimen</td>
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Panel 2: Life cycle of HIV and drug target sites

Once in the body, the virus binds to a CD4 receptor and one of two co-receptors (chemokine receptors CCR5 and CXCR4) on the surface of a CD4 T-lymphocyte. After fusion with the host cell, the virus releases its genetic material, ribonucleic acid (RNA). Reverse transcriptase then converts single-stranded HIV RNA to double-stranded HIV DNA, which enters the host cell's nucleus and is integrated into the genetic material of the cell.

The integrated HIV DNA is called a provirus. The provirus uses host cell RNA polymerase to create copies (by transcription) of the HIV genomic material, as well as shorter strands of RNA called messenger RNA (mRNA). The mRNA is used as a blueprint to make long chains of viral proteins.

An HIV enzyme called protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new virus particle is assembled.

Following assembly at the cell surface, many copies of the virus then bud from the host cell and are released to infect other cells.
Panel 4: NRTIs — additional information*

**Abacavir (Ziagen)**
- Abacavir is associated with a hypersensitivity reaction in 6–8 per cent of patients, which is characterised by rash, fever, nausea, a general feeling of being unwell, diarrhoea, upper respiratory tract symptoms and musculoskeletal symptoms. The median time to onset is 11 days, with symptoms usually appearing within the first six to eight weeks of starting therapy. Co-formulated abacavir-containing products include Trizivir (abacavir, lamivudine and zidovudine) and Kivexa (abacavir and lamivudine). Patients should be advised to carry the alert card (found inside the product packaging) at all times. If they feel unwell or develop a rash they should contact their clinic doctor immediately for advice or attend a casualty department and show the alert card. Abacavir and its co-formulations should never be restarted if treatment was previously discontinued due to a hypersensitivity reaction — the effects can be fatal.
- A genetic test for the presence of a genetic marker called HLA B*5701 is now being used to detect patients who should not receive abacavir. Presence of this marker indicates that the patient will develop a hypersensitivity reaction but, until this test has been fully validated, all patients must be counselled about the signs and symptoms of the hypersensitivity reaction, even if the test is negative.

**Didanosine (Videx)**
- Because the dose of didanosine is calculated from the patient’s weight, pharmacists should check with the patient to confirm weight (and therefore dose) each time a prescription is dispensed.
- Didanosine is available as tablets or enteric coated capsules with different requirements for administration. The tablets are infrequently prescribed. They contain a buffer (calcium and magnesium antacids), which is important for drug absorption and the dose must not be split to ensure adequate proportion of buffer to drug for adequate absorption.
- The tablets are large and are intended to be chewed or dispersed in water. They can be taken with clear apple juice, as recommended in the summary of product characteristics. The capsules should be swallowed whole with a small glass of water or clear apple juice.

**Lamivudine (Epivir)**
- Lamivudine reduces serum phosphate levels and increases serum creatinine so close monitoring is required.

**Stavudine (Zerit)**
- Because the dose of stavudine is calculated from the patient’s weight, pharmacists should check with the patient to confirm weight (and dose) each time a prescription is dispensed.

**Tenofovir (Viread)**
- Tenofovir can reduce serum phosphate levels and increase serum creatinine so close monitoring is required.

* See British National Formulary for standard adult doses

**Classes of antiretroviral agents**

There are multiple points of intervention in the life cycle of HIV (see Panel 2). Currently, the European Medicines Evaluation Agency (EMEA) has approved 17 antiretroviral drugs and four combination products. The antiretroviral drugs can be divided into four main classes:

- **Nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs)**. Tenofovir is the only nucleotide analogue.
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**
- **Protease inhibitors**
- **Entry inhibitors**

The backbone of HAART remains two NRTIs and most clinicians choose an NNRTI as the third agent in first-line therapy. Panel 3 lists the initial regimen choices as recommended by the BHIVA. There are no conclusive data to support the choice of an NNRTI over a “boosted” protease inhibitor (see the second part of this CPD article) but there are some concerns regarding long-term metabolic toxicities associated with the use of protease inhibitors. If a patient is unable to tolerate a drug in any antiretroviral combination, another agent from the same class but with a different side-effect profile may be substituted.

**Initial therapy**

Patients being treated in large clinics are often asked if they wish to participate in a clinical trial for initial therapy. For those who do not wish to, or are ineligible to enter a particular study, the decision to offer one drug combination over another is made following discussion between the patient and health care provider.

Because antiretroviral therapy is a life-long commitment for the patient, a balance must be achieved between using a highly effective drug combination that fits the patient’s lifestyle while minimising the side effects of these highly potent drugs. Lifestyle factors that influence patient choice include work patterns or nature of work.

People who have not disclosed their HIV status to friends or colleagues at work may
Panel 5: NNRTIs — additional information*

Efavirenz (Sustiva)
- Efavirenz can cause initial dizziness so patients are often recommended to take it at night. Patients should be advised that they may still feel drowsy in the morning and, if affected, they should not drive or operate machinery. Vivid or disturbing dreams as well as altered sleep patterns often occur. Sometimes taking efavirenz earlier in the evening rather than at bedtime can help. Central nervous system effects usually wear off within six weeks but in some cases can persist for months or years.
- Efavirenz can be taken any time in relation to food but high fat meals should be avoided because they increase absorption, leading to a higher incidence of CNS side effects in some patients.
- Rash is a reported side effect but is thought to be less frequent than with nevirapine. Patients should seek advice from their clinic doctor or present at casualty if a rash develops.
- Higher doses of efavirenz may need to be prescribed if the patient is prescribed an enzyme inducer (eg, rifampicin for the treatment of tuberculosis in HIV-TB co-infection).
- Efavirenz is available in the form of tablets, capsules or an oral solution. The oral solution is not bioequivalent to the tablets or capsules.

Nevirapine (Viramune)
- Nevirapine is associated with hepatotoxicity and Stevens-Johnson syndrome. It should, therefore, be prescribed and monitored strictly according to recommendations in the SPC.
- Nevirapine should not be used in women with CD4 counts greater than 250cells/mm³ or men with a count of greater than 400cells/mm³ due to an increased incidence of liver toxicity and rash.
- Liver function test results (LFTs) may be elevated within the first six to eight weeks of therapy and should be monitored for up to 18 weeks following initiation.
- Patients starting nevirapine should be instructed to contact their clinic doctor or casualty department if they develop a rash or any irritation to mucous membranes (eg, sore mouth or itchy eyes).
- Occasionally nevirapine is prescribed as a daily dose of 400mg but this is not licensed in the UK and it is recommended that the patient should be stabilised on 200mg bd for several months before changing to zidovudine and to check the patient’s LFTs.

In general, while NNRTIs do not need to be taken with food, patients may wish, for example, to take a combination of drugs which can be taken once daily and choose a time when they will be able to take their medicines discreetly.

Patients' concerns about either the possibility of or having to manage a certain side effect can also influence decisions. For example, someone who works in the food industry may not want to risk taking a drug that might cause an increase in bilirubin because the associated yellow discoloration may be mistaken for hepatitis.

NRTIs The NRTIs (also known as “nukes”) target the enzyme reverse transcriptase, halting viral DNA synthesis. The NRTIs need to be phosphorylated within the cell to the active form. For this reason, measuring the amount of drug in the blood does not correlate with the clinical effect. It is not easy to measure levels within the cells.

There is now increasing evidence that NRTIs are associated with damage to the mitochondria. This can result in the development of lipoatrophy (subcutaneous fat loss from the face, arms and legs), pancreatitis, and increasing lactate levels which, in turn, can result in lactic acidosis, such as abdominal pain, nausea and vomiting. Zidovudine and stavudine are increasingly associated with the appearance of lipoatrophy and, for this reason, they are infrequently prescribed as initial therapy.

Further information about individual NRTIs is given in Panel 4 (p633).

There are now four NRTI co-formulations available that contain fixed dose combinations of two or more NRTI drugs. This has the advantage of reducing pill burden or dose frequency for patients, or both.

NNRTIs The non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind directly to reverse transcriptase causing disruption of the catalytic site. Unlike NRTIs they do not require intracellular phosphorylation to their active form.

All first generation NNRTIs have a low genetic barrier to the development of drug resistance, in that a single mutation in reverse transcriptase produces highly resistant variants of HIV and causes cross-class resistance. Because NNRTIs have long plasma half-lives, if all the drugs in an NNRTI-containing regimen are stopped for any reason, drug plasma levels of the NNRTIs are likely to fall more rapidly that that of the NNRTI.

Periods of NNRTI monotherapy increase the likelihood of an NNRTI-resistant virus developing (ie, selection). In these instances, the BHIVA guidelines suggest continuing NNRTIs for a further seven to 14 days, or switching the NNRTI to a protease inhibitor and using three drugs with similar (short) half-lives when stopping all drugs at the same time.

Further information about individual NNRTIs is given in Panel 5.

The second part of this article will be published on 10 June.

References

* See British National Formulary for standard adult doses

Patients taking NRTIs should be counselled about the early warning symptoms of lactic acidosis, such as abdominal pain, nausea and vomiting.

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