The treatment of HIV is currently focused on drug intervention with antiretrovirals (ARVs). There is no known cure for HIV or a preventive vaccine. Combination ARV therapy (CART) is the use of at least three ARVs in combination to treat individuals infected with HIV, with the aim of prolonging life and improving its quality. According to the Health Protection Agency, 70% of diagnosed HIV-positive people in the UK are currently receiving CART.

Treatment objectives are to suppress viral replication to a viral load (VL) below the level of detection (currently <50 copies/ml); increase the number of CD4 cells; and preserve the function of the immune system. A patient's CD4 count is used as a surrogate marker of immune system functioning, and CART aims to improve or preserve this count and maintain viral suppression for as long as possible.

Treatment of HIV is lifelong and adherence to CART is essential. Recent developments in CART have centred on improving tolerability, reducing long-term side effects and providing convenience in administration. Early detection of HIV and drug treatment with effective ARVs is crucial to successful management of the patient. This article will focus on CART, treatment monitoring and future strategies in adults.

**When to start**

Historically the question of when to start anti-HIV treatment has been dictated by the toxicity and tolerability of ARVs and the ability of individual patients to adhere to regimens. Early CART regimens involved multiple daily doses and high pill burden.

The development of less toxic medicines and new ways of using older treatments has helped reduce both dosing frequency and pill burden with improved patient tolerability. With CART now being better tolerated and more convenient to take, the debate concerning the best time to start therapy has begun. Data from several large cohort studies suggest that treating patients earlier in the course of their infection (CD4 cell counts >350 cells/µl) can delay the development of AIDS-related infections and reduce morbidity and mortality from conditions that have not traditionally been associated with HIV. A large multinational randomised controlled trial aims to address the important question of when to start CART.

The British HIV Association (BHIVA) adult treatment guidelines recommend when to start treatment (see Box 1).

**SUMMARY**

The diagnosed HIV population in the UK is living longer, developing significant comorbidities and accessing more healthcare services. Combination antiretroviral therapy (CART) is the cornerstone of HIV treatment and is essential to prevent disease progression and the development of opportunistic infections.

Surrogate markers are used to monitor response to CART, along with clinical symptoms and side effects. CART changes are often needed to avoid toxicity and to overcome virological and immunological failure. Treatment-experienced patients have complex treatment needs and should be managed with expert advice. Management of drug interactions is critical to ensure adequate drug levels and avoidance of drug toxicity.

Future strategies are focusing on reducing treatment toxicity, HIV prevention and other immune therapies.

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**Box 1: BHIVA guidance on when to start CART**

<table>
<thead>
<tr>
<th><strong>PRESENTATION</strong></th>
<th><strong>RECOMMENDATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infection on neurological involvement</td>
<td>Treat in clinical trial</td>
</tr>
<tr>
<td>on CD4 count &lt;200 cells/µl for more than three months on AIDS-defining illness</td>
<td></td>
</tr>
<tr>
<td>Established infection</td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200 cells/µl</td>
<td>Treat</td>
</tr>
<tr>
<td>CD4 201–350 cells/µl</td>
<td>Treat as soon as possible when patient ready</td>
</tr>
<tr>
<td>CD4 351–500 cells/µl</td>
<td>Treat in specific situations*</td>
</tr>
<tr>
<td>CD4 &gt;500 cells/µl</td>
<td>Consider enrolment in “when to start trial”</td>
</tr>
<tr>
<td>AIDS diagnosis</td>
<td>Treat</td>
</tr>
</tbody>
</table>

* HIV-related comorbidities; consider treatment where treatment is indicated for hepatitis B also; patients with established cardiovascular disease or a very high risk of cardiovascular events may consider treatment

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This guidance is based on current evidence and expert opinion.

**What to start with**

Currently there are 22 ARVs licensed for the treatment of HIV (see Box 2, p394).

Treatment selection is dependent on patient-specific factors, such as presence of hepatitis, tuberculosis, cardiovascular risk factors, neurocognitive impairment and other comorbidities. It is also important to consider patient preference for individual medicines or formulations and concerns around potential toxicities.

Some patients may have transmitted or primary resistance, which means that the virus has genetic mutations since the advent of combination antiretroviral therapy in the mid-1990s HIV-infected individuals are now living longer with improved quality of life. Medication adherence is vital for successful treatment of HIV.
associated with ARV resistance despite the patient not having being exposed to any ARVs. The prevalence of drug resistance in treatment-naive patients in the UK is around 8%. BHIVA guidelines recommend that a resistance test should be undertaken for all newly diagnosed patients, because the presence of mutations associated with drug resistance can have an impact on CART selection.

BHIVA guidelines also recommend which ARVs to consider first line for treatment-naive patients (Box 3).

**Mechanisms of action** ARVs can be divided into five main classes depending on where they act in the replication cycle (see Box 4 and p388 of accompanying article).

**Monitoring response to treatment** Effective CART in treatment-naive patients should achieve viral suppression with an undetectable VL within 12 to 24 weeks of starting therapy. If the VL decline is slow, then the individual’s adherence should be checked along with other potential reasons for poor response, such as drug-drug interactions or presence of resistance. Patients are described as being on stable antiretroviral therapy when the VL remains below 50 copies/ml with a sustained CD4+ cell response.

**Adherence and treatment support** High levels of adherence to antiretroviral therapy are critical to achieving treatment success. The reasons why patients find taking anti-HIV medicines difficult are many and some examples include:

- Failure to acknowledge that they need treatment
- Not understanding the benefits of treatment
- Perceived harm from taking antiretrovirals
- Fear of developing stigmatising side effects
- Intolerance to side effects
- Misunderstanding how to take CART
- Forgetting to take CART
- Fear of disclosure of HIV status

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**Box 2: ARVs available in the UK (by class)**

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PROTEASE INHIBITOR</th>
<th>ENTRY/FUSION INHIBITOR</th>
<th>INTEGRASE INHIBITOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir*</td>
<td>Efavirenz*</td>
<td>Atazanavir</td>
<td>Enfuvirtide</td>
<td>Raltegravir*</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Nevirapine (Efavirenz)*</td>
<td>Darunavir</td>
<td>Maraviroc</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Lamivudine**</td>
<td>Indinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>Nelfinavir</td>
<td>Lopinavir/ritonavir*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Ritonavir</td>
<td>Saquinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Tipranavir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Co-formulated as Kivex  
† Co-formulated as Tizovir  
§ Co-formulated as Atripla  
¶ Co-formulated as Kaletra  
* Unlicensed medicines undergoing late-stage clinical investigation (shown in brackets)

**Box 3: BHIVA guidance on what CART to start**

<table>
<thead>
<tr>
<th>GUIDELINE</th>
<th>SUMMARY</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PROTEASE INHIBITOR (PI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHIVA 2008</td>
<td>Preferred</td>
<td>Two NRTIs + efavirenz</td>
<td>Lamivudine or Didanosine + emtricitabine</td>
<td>Lopinavir/ritonavir* or Fosamprenavir/ritonavir*</td>
</tr>
<tr>
<td>BHIVA 2008</td>
<td>Alternative</td>
<td>Two NRTIs + ritonavir-boosted PI</td>
<td>Lamivudine or Didanosine + emtricitabine</td>
<td>Atazanavir/ritonavir* or Saquinavir/ritonavir*</td>
</tr>
</tbody>
</table>

* Boosting dose of ritonavir  
† Only when CD4 cell count <250 cells/μl (women) or <400 cells/μl (men)  
‡ When cardiovascular disease established and a PI is required

**Box 4: Mechanisms of action**

| Entry inhibitors | Bind to chemokine receptors (X4/R5) on host cells, blocking their use as a co-receptor for HIV cell entry  
|                  | A proprietary assay (Trofile) is used to determine the viral tropism, which is the type of chemokine receptor the virus uses — either X4, R5 or both  
|                  | Trofile guides use of X4 or R5 entry inhibitor — currently only an R5 inhibitor is licensed (maraviroc) |
| Fusion inhibitors | Block the viral surface protein gp41 preventing the conformational change necessary to allow fusion of viral and cell membranes |
| Reverse transcriptase inhibitors | Three types — nucleosides, nucleotides and non-nucleosides  
|                  | Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) act on the viral reverse transcriptase enzyme, which converts viral RNA into DNA. They work by terminating the DNA chain  
|                  | Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind tightly to and block reverse transcriptase |
| Integrase inhibitors | Block the integrase enzyme, which incorporates viral DNA into the host cell DNA |
| Protease inhibitors | Bind to the viral protease enzyme blocking cleavage of the viral amino acid chain to its constituent proteins  
|                  | Almost always used in conjunction with a small dose of ritonavir which inhibits the metabolism of PIs. This results in higher PI levels, improving potency and permitting more flexible dosing. This practice is known as “boosting” |
HIV drug resistance can develop rapidly if drugs are taken late, missed or stopped suddenly. The latter is especially important for drug combinations containing medicines with both long and short half-lives. Levels of ARVs with longer half-lives can remain within the body, whereas those with short half-lives decline rapidly after stopping treatment. In some situations this can result in monotherapy — which can lead to the development of resistance.

Since drug therapy is a life-long commitment, adherence support and medication counselling are fundamental to ensure successful patient outcomes.

**Toxicity**

Patients may experience toxicity to CART either early in treatment or longer-term.

These toxicities can range from barely noticeable to distressing with considerable impact on the patient’s quality of life. Common side effects are listed in Box 5.

A metabolic syndrome — involving dyslipidaemia, body shape changes and diabetes — is often described as a long-term toxicity. Pharmaceutical intervention with lipid-lowering drugs and antidiabetic medicines, along with lifestyle changes (cessation of smoking and suitable diet and exercise) are important to improve patient outcomes.

**Box 5: Examples of ARV side effects**

<table>
<thead>
<tr>
<th>Side effects associated with initial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Abdominal bloating and flatulence</td>
</tr>
<tr>
<td>Mild-to-moderate rash, rarely Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Abnormal liver function tests and hepatotoxicity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side effects associated with long-term therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in renal function</td>
</tr>
<tr>
<td>Changes in bone mineral density</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td>Diabetes and changes in glucose control</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Lipodystrophy and changes in body shape</td>
</tr>
</tbody>
</table>

**Box 6: CART change after first virological failure**

<table>
<thead>
<tr>
<th>INITIAL REGIMEN</th>
<th>OPTIONS TO CONSIDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 × NRTI + 1 × PI</td>
<td>2 × NRTI 1 + 1 × NNRTI</td>
</tr>
<tr>
<td>OR</td>
<td>2 × NRTI 1 + 1 × boosted PI</td>
</tr>
<tr>
<td>OR</td>
<td>1 × NNRTI + 1 × boosted PI 1 + 1–2 × NRTI</td>
</tr>
<tr>
<td>2 × NRTI + 1 × NNRTI</td>
<td>2 × NRTI 1 + 1 × boosted PI</td>
</tr>
<tr>
<td>3 × NRTI</td>
<td>2 × NRTI 1 + 1 × NNRTI</td>
</tr>
<tr>
<td>OR</td>
<td>2 × NRTI 1 + 1 × boosted PI</td>
</tr>
<tr>
<td>OR</td>
<td>1 × NNRTI + 1 × boosted PI 1 + 1–2 × NRTI</td>
</tr>
</tbody>
</table>

Change all medicines if possible and a resistance test is recommended

* Change to new and active NRTIs guided by resistance testing

† This could lead to rapid development of resistance to NNRTIs. If potential exists for NRTI cross-resistance

‡ Studies with a low-dose ritonavir-boosted PI + an NNRTI have shown good results

NRTI = Nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI = Non-nucleoside reverse transcriptase inhibitor
PI = Protease inhibitor

**Treatment changes and failure**

Individuals on treatment may need to change therapy due to the development or persistence of side effects, or because of virological or immunological failure (see below).

Patients who experience initial side effects that are unable to be alleviated by medicines for symptom control may be forced to change one or more of the ARVs. As discussed previously some patients who have been on treatment for many years will develop long-term toxicity to medicines and also need treatment modification.

**Virological failure**

Virological failure is when the VL is not suppressed by CART to <50 copies/ml or when there is a sustained VL rebound. Each of these can be associated with poor adherence, baseline resistance to ARV, inadequate drug levels, or lack of CART potency. BHIVA recommends that patients who fail virologically for the first time should have a resistance test performed and their ARVs switched (see Box 6).

**Immunological failure**

Immunological failure is when the patient’s immune system fails to respond to treatment; CD4 cell counts may not improve despite the VL being undetectable. Such patients can be difficult to treat, but some ARV switches may increase the individual’s CD4 count. Because the CD4 count is only a surrogate marker, it is important to monitor these patients closely for any symptoms of disease progression.

**Treatment-experienced patients**

A small proportion of individuals in the UK are heavily treatment-experienced. In such patients the virus has developed resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). ARV resistance evolves differently in each class, with NNRTIs having a lower barrier to resistance than PIs.

Management of treatment-experienced patients is complex and there are often limited treatment options. The choice of viable CART should be made by reviewing resistance reports, ARV history and the ability of patients...
to tolerate ARVs. Expert advice should be sought from virologists and experienced HIV pharmacists and medical staff. Some patients will have long-term toxicities and require adjunct therapies or ARV switches — and may be suitable for entry into clinical trials for new ARVs.

**Drug-drug interactions**

Clinically significant drug interactions are highly prevalent among HIV-infected patients receiving CART. The HIV-positive population is ageing and developing significant comorbidities that require pharmaceutical intervention. Interactions can occur between commonly prescribed medicines and ARVs (Box 7).

Patients may receive medicines from multiple prescribers and pharmacies, which increases the risk of drug interactions not being identified and dealt with. Many drug interactions are avoidable by selecting alternative medicines to allow continuation of CART. Some interactions require dose-adjustment of the co-administered medicine or components of CART.

Therapeutic drug monitoring (TDM) can be a useful tool to ensure adequate levels of ARV. TDM is commercially available for PIs, NNRTIs and integrase inhibitors.

**Clinical practice points**

Pharmacists should take the following steps to ensure patients with HIV are not affected by interactions with ARVs:

- Check medication histories — identify patients at risk of clinically significant drug interactions regardless of clinical setting.
- Check for other medicines — this should include over-the-counter, herbal and recreational drugs, as well as medicines purchased through the internet.
- Check for interactions — the British National Formulary provides basic information on important drug interactions; a Liverpool University website expands on this and is a useful internet reference source (Box 8, p399).
- Provide advice or refer — all clinically significant interactions identified should be acted upon by contacting the prescriber or the pharmacy at the patient's HIV centre.

**Pregnancy**

Perhaps the most effective intervention to prevent HIV transmission has been the implementation of antenatal HIV screening. HIV-infected women are identified, and receive ARV therapy and other measures to prevent mother-to-child transmission.

Pregnant women already receiving CART before conception can continue on their current regimens. In some situations CART may be modified to avoid ARVs with limited evidence for use in pregnancy.

For women who have not required CART for their own health, treatment is initiated after the first trimester. The newborn also receives ARVs — this can range from mono- or dual therapy to CART depending on the risk of transmission related to the maternal VL, labour and birth. With effective treatment transmissions are rare. (BHIVA pregnancy guidelines are available at www.bhiva.org.)
Hepatitis co-infection

Treating HIV-positive patients co-infected with hepatitis B or hepatitis C can be complex.

Treatment of both HIV and hepatitis can be difficult because of overlapping toxicities of antiviral medicines. Tenofovir, lamivudine and entecavir are active against both HIV and hepatitis B. These medicines should not be administered to any hepatitis B-infected patient without first checking HIV status. HIV patients requiring active treatment for hepatitis B are recommended to start CART containing medicines active against both HIV and hepatitis B. When switching treatment it is important to confirm the patient’s hepatitis status, since removing anti-hepatitis B medicines can cause reactivation of the hepatitis infection.

Historically many patients with hepatitis C have undergone hepatitis C treatment before commencing CART. This is mainly due to the overlapping toxicity of anti-hepatitis C medicines and ARVs. Many patients will also have been above the threshold for initiation of CART. In the future if HIV treatment is initiated earlier patients may undergo hepatitis C treatment also. Future studies aim to investigate the safety and efficacy of co-administration of ARVs and anti-hepatitis C medicines.

The BHIVA hepatitis guidelines should be consulted when treating co-infected patients.

Future strategies

Earlier initiation of treatment is currently being studied and may lead to starting treatment much closer to HIV diagnosis. Studies have looked at treatment during seroconversion and this continues to be an area for future research.

Treatment of HIV in the future will focus on minimising long-term toxicity to ARVs and managing patient comorbidities. Novel strategies currently being studied include protease inhibitor monotherapy and reverse transcriptase inhibitor-sparing regimens. These strategies aim to avoid long-term reverse transcriptase inhibitor toxicity.

Pre-exposure prophylaxis (PrEP) has been studied (see p391 of accompanying article), with success in animal models. Further human studies are ongoing in populations with high HIV prevalence, with individuals at high risk of exposure to HIV taking ARVs to prevent infection.

Studies involving the use of vaccines as both prophylaxis and therapeutic strategies are ongoing. Unpublished preliminary data from immunotherapy studies looking at boosting the immune system or surrogate markers such as the CD4 counts have had poor results in terms of treatment outcomes. Nonetheless, this area of research is important because it could delay the use of ARVs.

References


Box 8: Further reading and resources

British HIV Association www.bhiva.org

- UK guidelines for the management of sexual and reproductive health of people living with HIV infection
- Immunisation
- Management of HIV infection in pregnant women
- HIV associated with malignancies
- An online drug-drug interaction resource
- Immunodeficiency clinic (Toronto) www.hivclinic.ca/main/drugs_interact.html
- An online drug-drug interaction resource
- Health Protection Agency www.hpa.org.uk
- Epidemiology

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