Antiretroviral therapy options for treatment-naive patients with HIV-1

Human immunodeficiency virus (HIV) is a chronic infection with no available cure or vaccine; management remains drug focussed. This article reviews options for initial treatment in adults: when and what to start, monitoring, drug–drug interactions and adherence. Stopping and switching therapy, subsequent lines of therapy, paediatric infection and HIV-2 will not be covered.

The virus

In 1981 acquired immune deficiency syndrome (AIDS) was first described after five gay men in California were treated for *Pneumocystis carinii* pneumonia (Centers for Disease Control, 1981); HIV was subsequently identified as the causative agent. HIV is a retrovirus transmitted through sexual contact, injecting drug use, unsafe medical practices or from mother to child; its natural history can be divided into three stages: primary infection, chronic infection and AIDS.

Primary HIV is the time from initial infection to development of HIV antibodies, characterized by high levels of viral replication and transient CD4 cell decline. Approximately 1 month after infection features of acute HIV syndrome/seroconversion illness may develop, including fever, rash, arthralgia, sore throat, night sweats and weight loss. During this stage patients may be highly infectious because they have a high HIV viral load (Alder et al, 2012).

Miss Lucy Hedley *is Senior Clinical Pharmacist – HIV and Infectious Diseases,* **Mrs June Minton** *is Lead Pharmacist – HIV and Infectious Diseases and* **Dr Gabriel Wallis** *is Core Medical Trainee in the Department of Infectious and Tropical Diseases, University College London Hospital, London NW1 2BU, and* **Dr Laura Waters** *is Consultant Physician in HIV and Genitourinary Medicine in the Department of GU/HIV Medicine, Central and North West London, London*

Correspondence to: Miss L Hedley (lucy.hedley@nhs.net)

Following primary HIV infection, relative equilibrium between viral replication and host immune response is reached. HIV antibodies remain detectable while the amount of virus in blood and lymphoid tissues falls as replication slows. Without antiretroviral therapy there is an inexorable CD4 decline over time, around 50–100 cells/mm^3 per year. Untreated this leads to AIDS, opportunistic infections and death (Alder et al, 2012). Median time from infection to developing AIDS is highly variable, ranging from 18 months to 25 years.

Two interesting subgroups of patients are elite controllers, controlling HIV viraemia without antiretroviral therapy, and long-term non-progressors, who maintain a steady elevated CD4 count without antiretroviral therapy. The desirable characteristics of these two groups provide models for a functional cure of HIV.

Treatment aims

The goal of antiretroviral therapy is to suppress viral replication to undetectable levels, enabling immune reconstitution. This markedly reduces the morbidity and mortality associated with chronic, untreated HIV infection with a low cost of drug toxicity. Untreated HIV remains a deadly disease with a worldwide estimate of 1.6 million people dying in 2012 of HIV-related causes (Ford et al, 2013).

Effectiveness and tolerability of antiretroviral therapy has improved dramatically over the last 15 years; most patients receiving antiretroviral therapy in the UK achieve long-term virological suppression and good treatment outcomes (Churchill et al, 2015). Consequently HIV infection can be described as a chronic disease with a good prognosis provided treatment is started appropriately and the patient is able to maintain lifelong adherence to antiretroviral therapy (May et al, 2011). May et al (2014) demonstrated that an individual in the UK on suppressive antiretroviral therapy with a CD4 count of 350 cells/mm^3 or greater has the same life expectancy as the general population.

When to start

Late diagnosis and late antiretroviral therapy initiation are risk factors for suboptimal treatment outcomes. Starting antiretroviral therapy with a CD4 count of less than 200 cells/mm^3 is estimated to result in a 10-year reduction in life expectancy compared with starting treatment when the CD4 count has fallen below 350 cells/mm^3 (May et al, 2011).

Although a number of cohort studies suggested a benefit to earlier antiretroviral therapy it was not until the results of the START study, a large trial recruiting treatment-naïve individuals with high CD4 (greater than 500 cells/mm^3) to immediate or deferred therapy initiation, that good quality randomized evidence was available to address the 'when to start' question. START showed significantly fewer clinical events (serious AIDS/non-AIDS/death) in those who started therapy immediately (average CD4 at start 652 cells/mm^3) compared with those randomized to the deferred arm (average CD4 at start 408 cells/mm^3) (INSIGHT START Study Group, 2015).

On the basis of START, the British HIV Association treatment guidelines have been updated to recommend that patients with chronic HIV infection should start antiretroviral therapy at any CD4 count when they are ready to do so (Churchill at al, 2015). The previous national guidance recommended commencing therapy at a CD4 of 350 cells/mm^3 but listed several conditions where earlier treatment was recommended including: hepatitis B or C co-infection, AIDS-related illnesses, HIV-related symptoms or morbidity (including HIV-associated nephropathy and neurocognitive impairment), malignancy and prevention of transmission (mother-to-child transmission and transmission to sexual partners) – these are now considered circumstances where antiretroviral therapy should be initiated promptly.

Deciding when to start antiretroviral therapy in patients presenting with low CD4 count and an AIDS-defining or seri-

ous bacterial infection is complicated by the risk of immune reconstitution disorder. The ACTG 5164 study demonstrated improved outcomes, and no increase in the incidence of immune reconstitution, when antiretroviral therapy was commenced within 14 days compared with after completion of treatment for acute infection (median 45 days) (Zolopa et al, 2009). However, the majority of patients in this study had *Pneumocystis* pneumonia and were well enough to take oral medications. Whether the findings can be generalized to include severely unwell patients and those requiring ventilator or other organ support is unclear.

In particular British HIV Association guidelines for opportunistic infection emphasize caution starting antiretroviral therapy in individuals with cryptococcal meningitis (Nelson et al, 2011). The COAT study demonstrated significant improvement in survival for individuals randomized to delayed antiretroviral therapy (5 weeks after cryptococcal meningitis diagnosis) *vs* early (1–2 weeks after cryptococcal meningitis diagnosis) (Boulware et al, 2014).

There is now compelling observational data from the PARTNER study (Rodger et al, 2014) and randomized trial data (Cohen et al, 2011) to support a dramatic reduction in risk of transmission from individuals on suppressive antiretroviral therapy. This evidence should be discussed with all patients and antiretroviral therapy offered promptly to any individual who wishes to start antiretroviral therapy for this reason (Churchill et al, 2015).

The final situation where prompt treatment initiation may be of particular benefit is in individuals with acute or primary HIV infection – very early therapy may limit immune destruction and the size of the HIV reservoir in chronic infection. These potential benefits, in combination with the fact that acute HIV is usually associated with very high viral loads and a high risk of onward transmission, make the recognition of primary HIV an important skill for all clinicians.

Baseline tests

Before initiation of antiretroviral therapy a series of baseline investigations should be carried out. These include full blood count, renal, liver and bone profiles, lipids, glucose, urinalysis, urine protein, CD4 count, HIV-1 plasma viral load, HLA B*5701 testing (if considering abacavir) and an HIV resistance test if not previously carried out (Asboe et al, 2012).

What to start

British HIV Association guidelines (Churchill et al, 2015) recommend starting antiretroviral therapy with two nucleoside reverse transcriptase inhibitors plus one from another class: non-nucleoside reverse transcriptase or ritonavir-boosted protease inhibitor or integrase inhibitor (*Table 1*). Comorbidities, resistance or drug interactions should be considered.

The preferred nucleoside reverse transcriptase inhibitor backbone is the fixed dose combination Truvada (tenofovir/emtricitabine) with Kivexa (fixed dose combination of abacavir/lamivudine) an alternative (and only if HLA B*5701 negative and viral load <100 000 copies/ml). The preferred third agents are rilpivirine (non-nucleoside reverse transcriptase), darunavir/ritonavir or atazanavir/ritonavir (ritonavir-boosted protease inhibitor), dolutegravir, raltegravir, or elvitegravir/cobicistat (integrase inhibitor). Where appropriate, aids to adherence such as combination preparations or once-daily dosing may be considered (Churchill et al, 2015).

It is important to note that all recommended protease inhibitors require pharmacokinetic boosting with ritonavir, an old antiretroviral no longer used as treatment but given in sub-therapeutic doses for its potent inhibition of the 3A4 isoenzyme of the cytochrome P450 system of hepatic enzymes (CYP3A4). As protease inhibitor are metabolized by CYP3A4, ritonavir significantly increases plasma concentrations of the concomitant protease inhibitor allowing lower and less frequent doses. The integrase inhibitor elvitegravir must also be boosted; currently it is only available in the UK as part of the fixed dose combination Stribild which contains the CYP3A4 inhibitor cobicistat. Both ritonavir and cobicitat, in addition to their potent inhibition of CYP3A4, interact with numerous other enzymes and transporters so are particularly associated with drug–drug interactions (see later section). *Table 2* gives the mechanisms of action of the antiretroviral drugs.

Special populations

Patients co-infected with tuberculosis should start antiretroviral therapy with tenofovir/emtricitabine/efavirenz if the tuberculosis treatment regimen includes rifampicin; the dose of efavirenz may require modification. If ritonavir-boosted protease inhibitor-based antiretroviral therapy is required rifabutin should be used instead of rifampicin.

Hepatitis co-infected patients should start antiretroviral therapy and those with hepatitis B should receive a tenofovir/emtricitabine containing regimen in order to treat both viruses. Hepatitis C co-infected patients should ideally start antiretroviral therapy before hepatitis C treatment; the choice of the third agent will depend on whether hepatitis C virus treatment is required.

HIV patients requiring immunosuppressive cancer treatment should ideally start antiretroviral therapy – a non-ritonavir/cobicistat-containing regimen may be optimal to minimize the drug–drug interaction potential. Consideration should be given to avoid overlapping drug toxicities.

Table 1. Summary recommendations for choice of combined antiretroviral therapy in treatment-naïve patients

	Preferred	Alternative
Nucleoside reverse transcriptase inhibitors backbone	Truvada	Kivexa*†
Third drug	Atazanavir/ritonavir	Efavirenz
	Darunavir/ritonavir	
	Dolutegravir	
	Elvitegravir/cobicistat	
	Raltegravir	
	Rilpivirine	

*Abacavir is contraindicated in HLA-B*57:01-positive individuals. † Use recommended only if baseline viral load <100 000 copies/ml: abacavir and lamivudine as nucleoside reverse transcriptase inhibitor backbone (no viral load restriction with dolutegravir), rilpivirine as a third agent.

Table 2. Mechanism of action of currently available antiretroviral drugs

Class	Target stage of HIV replication	Mechanism of action	Examples
Nucleoside/nucleotide reverse transcriptase inhibitor	Reverse transcription	Compete with natural nucleosides for binding to the active site of the reverse transcriptase. Nucleotide reverse transcriptase inhibitors are incorporated into DNA, resulting in chain termination and incomplete sections of DNA	Abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine
Non-nucleoside reverse transcriptase inhibitor	Reverse transcription	Structurally different from nucleotide reverse transcriptase inhibitors. Act before incorporation of HIV DNA into host cell DNA by binding directly to reverse transcriptase at regions away from the active site	Efavirenz, nevirapine, rilpivirine, etravirine
Protease inhibitor	Maturation	Inhibit the protease enzyme to prevent cleavage of viral proteins and maturation of HIV	Darunavir, atazanavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir, ritonavir*
Fusion/entry inhibitor	Fusion and entry	Bind to extracellular proteins, block the fusion or entry of HIV into a host cell	Enfuvirtide, maraviroc†
Integrase inhibitor	Integration	Inhibit the enzyme integrase, preventing integration of proviral DNA into host DNA	Raltegravir, elvitegravir, dolutegravir

* Only used for pharmacoenhancement. † CCR5 antagonist (cobicistat not listed as it has no antiretroviral properties)

All patients with evidence of HIV-related neurocognitive impairment should be started promptly on a standard first-line antiretroviral therapy regimen.

Patients with significant cardiovascular disease should potentially avoid abacavir, and some older protease inhibitors.

Patients with HIV-associated nephropathy should start antiretroviral therapy immediately, avoiding nephrotoxic drugs and with renal-adjusted doses where necessary. Patients with end stage kidney disease should also start antiretroviral therapy immediately, especially if they are candidates for transplantation.

Monitoring

Efficacy and safety of antiretroviral therapy should be monitored 2–4 weeks after initiation with creatinine, liver function tests, glucose, bone profile, assessment for proteinuria and viral load. Viral load should be checked every 1–2 months until it is fully suppressed (<20–50 copies/ml) then every 3–6 months when stable on treatment. A reduction in viral load of $1\log^{10}$ copies/ml at week 4 compared to baseline is a predictor of viral suppression at 6 months. The viral load should be fully suppressed in most patients by 3–4 months but may take longer if the starting viral load is higher (Asboe et al, 2012).

Side effects

Side effects may occur early in therapy or as longer-term toxicity. Common initial side effects include rash (rarely Stevens–Johnson syndrome), nausea, headache and diarrhoea; these may be associated with any antiretroviral classes but are usually mild and short-lived. Efavirenz can cause CNS side effects such as dizziness, vivid dreams and morning drowsiness, and protease inhibitors are known for gastrointestinal side effects; these are usually self-limiting and less common with modern agents. All antiretrovirals have potential to cause hepatotoxicity; atazanavir causes an unconjugated hyperbilirubinaemia – in isolation this is not of concern. Side effects often coincide with peak drug levels and are more intense until a steady state is achieved; changing the timing of the medication can help.

Longer term toxicities include declining renal function and bone mineral density, dyslipidaemia, possible increased risk of cardiovascular disease, peripheral neuropathy and lipodystrophy. Management strategies include antiretroviral therapy switch, lifestyle change and pharmaceutical intervention.

Adherence

High levels of adherence to combined antiretroviral therapy are essential to treatment success. Reasons why patients may struggle with adherence are manifold, including:

- Failure to accept their status and need for therapy
- Lack of understanding of therapy benefits
- Perceived impact upon lifestyle
- Fear of disclosing HIV status
- Fear of stigmatizing side effects
- Perceived harm from taking antiretrovirals
- Intolerance of side effects
- Misunderstanding how to take combined antiretroviral therapy
- Forgetting to take combined antiretroviral therapy – life getting in the way.

It is recommended that patients take at least 95% of their doses on time as drug resistance can develop rapidly when drugs are taken late, missed or stopped suddenly. Since combined antiretroviral therapy is a lifelong commitment, adherence support and counselling are fundamental for successful outcomes. Advice should be tailored to individuals and their particular barriers and concerns.

Drug interactions

Clinically significant drug interactions are prevalent among combined antiretroviral therapy-treated individuals. The HIV-positive population is ageing, increasingly with comorbidities requiring pharmaceutical intervention. As a general rule, protease inhibitors, non-nucleoside reverse transcriptases and cobicistat have the greatest interaction potential. Although many interactions involve induction/inhibition of CYP3A4, p-glycoproteins and transport proteins may also be involved. There are many potential interactions, some formally studied, most predicted, which may be complex and bi-directional.

Potential interactions also apply to non-prescribed medication, including over-the-counter medicines, herbal remedies and recreational drugs. Patients may receive medication from multiple sources, different doctors and pharmacies, so interactions may be missed. The University of Liverpool HIV drug interactions website (www.hiv-druginteractions.org) is an excellent resource for checking HIV drug inter-

actions; always check for interaction if a patient is taking any prescribed, non-prescribed or recreational drugs. A good example of an often unanticipated interaction is that between ritonavir/cobicistat and inhaled or intra-articular steroids such as fluticasone or triamcinolone respectively. Several reports have described steroid toxicity leading to Cushing's and Addisonian crisis as a result of boosting of steroid effects via CYP3A4 inhibition. Involve a specialist pharmacist in discussions about drug interactions and potential implications as they will have experience accessing and interpreting the data. Prescribers should be aware that:

- Acid-reducing agents are a common source of interactions – particular caution with rilpivirine and proton pump inhibitors
- Interactions can occur with non-oral medication, e.g. topical, inhaled, intranasal, intra-articular
- Medications within the same class can have different interaction profiles, e.g. statins
- Dose adjustment of antiretroviral therapy or co-administered medication may be required
- Therapeutic drug monitoring can be useful to ensure adequate levels of antiretroviral therapy but is seldom used in practice
- It may be necessary to change antiretroviral therapy components although only in conjunction with the patient's HIV team.

Conclusions

This article has summarized recommended first-line treatments, monitoring, drug interactions and common side effects. It is vital to emphasize that 25% of HIV in the UK remains undiagnosed; readers should refer to national testing guidelines. **BJHM**

Conflict of interest: Miss L Hedley has received sponsorship from ViiV, Boerhinger Ingelheim and Gilead to cover conferences fees, accommodation and travel to attend conferences, speaker fees from Janssen and Gilead, and is a member of the Gilead Speakers Bureau plus advisory board for Gilead; Mrs J Minton has received conference sponsorship or attended advisory boards for Gilead, Janssen, Merck Sharp and Dohme, Abbvie and Boehringer Ingelheim; Dr G Wallis: none; Dr L Waters has received speaker fees or conference support from Gilead Sciences, ViiV Healthcare, Janssen, Merck Sharp & Dohme, and AbbVie, and advisory board fees from ViiV, Gilead and AbbVie.

Alder MW, Edwards SG, Miller RF, Sethi G, Williams IG (2012) *ABC of HIV and AIDS.* 6th edn. Wiley-Blackwell, Oxford

Asboe D, Aitken C, Boffito M et al (2012) British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* **13**: 1–44 (doi: 10.1111/j.1468-1293.2011.00971.x)

Boulware DR, Meya DB, Muzoora C et al (2014) Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med* **370**(26): 2487–98 (doi: 10.1056/NEJMoa1312884)

Centers for Disease Control (1981) Pneumocystis Pneumonia - Los Angeles. *Morb Mortal Wkly Rep* **30**: 250–2

Churchill D, Waters L, Ahmed N et al (2015) BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. www.bhiva.org/documents/Guidelines/Treatment/consultation/150621-BHIVA-Treatment-GL-Final-draft-for-consultation.pdf (accessed 15 July 2015)

Cohen MS, Chen YQ, McCauley M et al (2011) Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **365**(6): 493–505

Ford N, Vitoria M, Hirnschall G, Doherty M (2013) Getting to zero HIV deaths: progress, challenges and ways forward. *J Int AIDS Soc* **16**: 18927

INSIGHT START Study Group (2015) Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* (doi: 10.1056/NEJMoa1506816)

May M, Gompels M, Delpech V, Dunn D, Palfreeman A (2011) Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *BMJ* **343**: d6016 (doi: 10.1136/bmj.d6016)

May MT, Gompels M, Delpech V et al (2014) Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy: UK cohort study. *AIDS* **28**(8): 1193–202 (doi: 10.1097/QAD.0000000000000243)

Nelson M, Dockrell DH, Edwards S et al (2011) British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Med* **12** (Suppl. 2): 1–5 (doi: 10.1111/j.1468-1293.2011.00944_1.x)

Rodger A, Cambiano V, Bruun T et al (2014) HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. 21st CROI, 3-6 March 2014, Boston. Oral late breaker abstract 153LB. www.croiwebcasts.org/console/player/22072 (accessed 4 April 2015)

Zolopa A, Andersen J, Powderly W et al (2009) Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One* **4**: e5575 (doi: 10.1371/journal.pone.0005575)

KEY POINTS

- Despite many attempts there remains no cure for HIV.
- HIV can be well controlled long term with combination therapy, although consistent and high levels of adherence are required.
- Individuals with access to antiretroviral therapy can expect near-normal or normal life expectancy.
- In the setting of viral suppression on antiretroviral therapy the risk of transmission to others is negligible.
- Managing drug interactions is a crucial aspect of HIV care and requires collaboration and education of patients and other health-care professionals.
- In the UK 1 in 4 individuals with HIV remain undiagnosed – all readers should be familiar with national testing guidance.

TOP TIPS

- Always think about testing acute admissions and outpatients with risks or indicator conditions for HIV.
- Patients will assume you have checked for drug interactions, as will GPs – please do! Always think twice with steroids and statins.
- Most people with HIV live normal lives but the risk of several age-related comorbidities is higher – have a lower threshold of suspicion.
- Stigma is still a big issue for many people living with HIV – don't assume friends or family know. Check before writing to GPs – some patients have yet to disclose although this proportion is small.

USEFUL RESOURCES

Patient information leaflets and HIV education, training and support: www.hivpa.org, www.aidsmap.com

Drug interactions: hiv-druginteractions.org, www.hivclinic.ca/main/drugs_interact.html

Guidelines: www.bhiva.org

Epidemiological data: www.hpa.org.uk