

## PRACTICE



## THERAPEUTICS

# Drug treatment for adults with HIV infection

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at [practice@bmj.com](mailto:practice@bmj.com).

A 65 year old man who had been living with HIV for the past 20 years visited his general practitioner for continued management of chronic obstructive pulmonary disease. His HIV was well controlled on an antiretroviral therapy (ART) regimen comprising tenofovir, emtricitabine, darunavir, and ritonavir. His GP thought that he would benefit from a combination inhaler (long acting  $\beta_2$  agonist and inhaled corticosteroid) but decided first to ask the HIV clinic about potential drug-drug interactions with ART.

## What is antiretroviral therapy?

By suppressing HIV replication, ART limits further HIV associated pathology and enables immune recovery. The primary goal of ART is to reduce HIV morbidity and mortality in people with HIV. Guidelines also recommend its use to reduce the risks of onward transmission to sexual partners<sup>1</sup> and of mother to child transmission of HIV.<sup>2</sup>

This article focuses on the use of ART in HIV positive adults. Antiretroviral drugs can also be prescribed, off licence in the United Kingdom, to HIV negative people as post exposure prophylaxis, to reduce the risk of acquiring HIV after a high risk exposure. Ongoing studies are assessing the efficacy of pre-exposure prophylaxis for people who are often exposed to HIV.

Licensed antiretroviral agents belong to one of five drug classes, which are based on the stage in the HIV replication cycle that is targeted (figure 1): entry inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INIs) (see table 1 for examples).

Antiretroviral drugs suppress viral replication but do not cure HIV. ART must therefore be continued for life and high levels of adherence are essential to maintain viral suppression.

## How well does ART work?

With the introduction of effective ART in 1996, age adjusted excess mortality in people living with HIV participating in an international cohort fell from 31.4/1000 person years pre-1996 to 6.1/1000 person years in 2004-06.<sup>3</sup> Prospective cohort data from 21 388 people with HIV in the UK between 2000 and 2010 suggest that the stage of disease at which ART is started affects life expectancy. The expected age of death of a 35 year old man with HIV who started ART with a CD4<sup>+</sup> cell count  $\geq 350 \times 10^6$  cells/L (relatively early stage HIV) was 81 years compared with 71 years if ART was started when the CD4<sup>+</sup> cell count was  $< 200 \times 10^6$  cells/L.<sup>4</sup>

ART has also dramatically reduced the incidence of mother to child transmission. In the UK, universal testing in pregnancy together with effective ART and avoidance of breast feeding has reduced the risk of such transmission from 25.6% in 1993 to  $< 1\%$  in women who had received at least 14 days of ART before delivery.<sup>2</sup>

The risk of onward HIV transmission to sexual partners can also be reduced by ART. Among 1763 couples in which one partner was HIV positive and the other was HIV negative, the incidence rate of onward HIV transmission from HIV positive to HIV negative partners was 0.1 per 100 person years (95% confidence interval 0.0 to 0.4) in those randomised to receive early therapy (CD4<sup>+</sup> cell count 350-550  $\times 10^6$  cells/L); however, if therapy was delayed until the CD4<sup>+</sup> cell count approached 250  $\times 10^6$  cells/L, the transmission rate was 1.7 per 100 person years (1.1 to 2.5).<sup>5</sup>

## How safe is ART?

ART associated adverse events are common. In a prospective cohort of 1078 people living with HIV, 45% experienced a

**The bottom line**

- Antiretroviral therapy (ART) has dramatically reduced the mortality associated with HIV, which can now be considered a chronic treatable disease. ART does not, however, cure HIV so treatment is life long
- Effective ART reduces the risk of onward transmission of HIV to sexual partners and mother to child transmission
- Many antiretroviral drugs interact with commonly prescribed drugs such as steroid inhalers. Clinicians should always check for drug interactions when patients are taking ART and seek specialist advice when unsure.
- Antiretroviral therapy can only be initiated once a diagnosis of HIV is made. Delayed diagnosis of HIV and delayed initiation of ART can be associated with increased mortality

**How patients were involved in the creation of this article**

- We sought guidance from an HIV positive treatment advocate who works to encourage people living with HIV to take an active role in their own health, and who coordinates the i-Base treatment information services
- He reviewed a draft and advised us on both content and presentation
- He suggested important changes to the tips for patients section, and in particular improved the clarity and readability for patients

clinical ART associated adverse effects, although most effects were not severe.<sup>6</sup> Adverse effects may be common to the class used or drug specific. Some older drugs of the NRTI class, such as zalcitabine, stavudine, didanosine, and zidovudine, are no longer recommended, because they have been associated with serious complications (such as peripheral neuropathy, myopathy, hepatic steatosis, and lactic acidosis),<sup>1</sup> which may persist even after the drugs are discontinued.

Currently recommended antiretroviral drugs have fewer reported adverse effects, but all have potential short and long term toxicities.<sup>1</sup> Fatigue, nausea, and diarrhoea are commonly reported, with gastrointestinal intolerance being especially associated with PIs. These symptoms often subside, but persistent side effects may dictate a change in therapy.

Some common or serious adverse effects are outlined below.

**ART associated neuropsychiatric toxicity**

Central nervous system toxicity, such as vivid dreams, impaired concentration, and mood disturbances, is reported in 25-70% of people with HIV who receive the NNRTI efavirenz. Symptoms start immediately after initiation and usually subside to acceptable levels within one or two months.<sup>7</sup> Similar side effects are reported with other NNRTIs (such as etravirine<sup>8</sup> and rilpivirine<sup>9</sup>), although less often. Secondary analysis of data from four randomised controlled trials showed higher incidence of suicidal ideation, attempted suicide, and completed suicide in those taking efavirenz compared with those not taking it (8.08 v 3.66 per 1000 person years; hazard ratio 2.28, 1.27 to 4.10).<sup>10</sup>

**Acute hypersensitivity**

Many antiretroviral drugs can cause hypersensitivity reactions (probably through the major histocompatibility complex), although clinical manifestations and severity vary. Skin reactions, typically a maculopapular rash, are common and can often be managed conservatively. Severe skin reactions such as Stevens-Johnson syndrome occur in under 0.5% of patients. Constitutional symptoms (such as fevers, rigors, and malaise) and internal organ involvement (including hepatitis and nephrotoxicity) can occur with or without cutaneous manifestations and may indicate a more severe hypersensitivity reaction. Constitutional involvement may be associated with eosinophilia and mononucleosis, indicating the DRESS syndrome (drug reaction with eosinophilia and systemic symptoms). Because studies have shown that the presence of the HLA B5701 allele has very high sensitivity for predicting immunologically confirmed abacavir hypersensitivity, this allele

is routinely screened for in the UK before prescribing abacavir.<sup>1 11</sup>

**Hepatotoxicity**

Many antiretroviral drugs can cause hepatic injury—from asymptomatic hepatic transaminitis to liver failure. Mechanisms include hypersensitivity reactions, mitochondrial toxicity, immune reconstitution phenomena, and secondary metabolic effects. The incidence of viral hepatitis is high in people with HIV and its presence increases the risk of drug induced liver injury.<sup>12</sup> Drug induced hepatitis often occurs as part of a hypersensitivity syndrome, as described above, within the first few weeks of exposure. The risk of drug induced hepatitis is greater with certain antiretroviral drugs, such as the NNRTI nevirapine. In a randomised clinical trial, 2.6% of participants taking nevirapine and 0.5% of those taking efavirenz developed clinical hepatitis.<sup>1 13</sup>

**Renal toxicity**

Tenofovir, ritonavir boosted atazanavir, and to a lesser extent ritonavir boosted lopinavir are not recommended in patients with stage 3-5 chronic kidney disease,<sup>1</sup> because they are associated with a reduction in the estimated glomerular filtration rate,<sup>14</sup> although mechanisms vary. Some antiretroviral drugs, including rilpivirine, cobicistat, ritonavir, and dolutegravir are associated with increased serum creatinine, but this is not thought to be clinically relevant.

**Lipid metabolism and lipodystrophy**

Antiretroviral associated dyslipidaemia can occur with or without lipodystrophy, a recognised pattern of body shape changes, typically peripheral lipoatrophy or central lipohypertrophy (associated particularly with raised total and low density lipoprotein cholesterol and insulin resistance).<sup>15</sup> Although lipodystrophy is more common with older drugs that are no longer recommended, including zidovudine,<sup>15 16</sup> it is also reported with some drugs in current use. For example, lopinavir-ritonavir is associated with lipohypertrophy and raised triglycerides.<sup>16</sup>

As with any patient, abnormalities of lipid metabolism should not be viewed in isolation but considered along with other established risk factors for cardiovascular disease, such as smoking and hypertension.

## Other organ specific toxicities

Some cohort studies have shown an increased risk of cardiovascular disease in people with HIV. This is thought to be due to a combination of HIV infection itself, an increased prevalence of traditional risk factors, and the potential for some ART drugs to increase cardiovascular risk.<sup>17 18</sup> Observational data show that bone mineral density (BMD) is lower in people with HIV compared with the general population.<sup>19</sup> The first one or two years after ART initiation is associated with a decline in BMD (especially with tenofovir<sup>20</sup>), followed by BMD stabilisation and recovery.

## Immune reconstitution inflammatory syndrome (IRIS)

Restoration of the immune system can result in the paradoxical worsening of pre-existing infections or cancers through a pathogen specific immune response, known as IRIS, although this is not actually a form of drug toxicity. Factors associated with IRIS include a low baseline CD4<sup>+</sup> cell count, an inadequately treated opportunistic infection, and a rapid immunological and virological response to ART.<sup>21</sup>

## How cost effective is ART?

A review of cost effectiveness analyses across different countries concluded that the direct healthcare costs of HIV treatment are greatest in late stage disease (especially CD4<sup>+</sup> cell count <100×10<sup>6</sup> cells/L<sup>22</sup>), highlighting the need for early diagnosis. WHO suggests that starting ART in people with a CD4<sup>+</sup> cell count <500×10<sup>6</sup> cells/L would have substantial health benefits, and some of the costs of this strategy would be offset by a reduction in onward HIV transmission. The benefits, however, depend on a prevailing infrastructure to promote high testing uptake, high treatment coverage, sustained adherence, and high rates of retention in care.<sup>23</sup>

## How are antiretroviral drugs taken?

ART is usually prescribed as a combination of at least three active drugs. Two NRTIs are usually combined with a third agent from another class—an NNRTI, PI, or INI. If the choice is limited by factors such as drug resistance or drug-drug interactions, other combinations may be used.<sup>1</sup> Almost all currently licensed antiretroviral drugs are taken orally, except for enfuvirtide, which is given by subcutaneous injection. Most drugs are taken once daily, although some require twice daily administration.

## When should ART be started? The role of CD4<sup>+</sup> T cells

All guidelines recommend ART in patients presenting with an AIDS defining illness, specified comorbidities, or chronic systemic HIV related symptoms, including weight loss, regardless of CD4<sup>+</sup> cell count. They also support starting ART at any CD4<sup>+</sup> cell count in pregnant women, to reduce the risk of mother to child transmission,<sup>2</sup> and in people who wish to prevent onward transmission to HIV negative partners.<sup>1</sup>

For people with chronic HIV infection who are otherwise in good health, international guidelines differ regarding the optimal CD4<sup>+</sup> cell count at which to start ART, varying from 350×10<sup>6</sup> cells/L<sup>1</sup> to higher counts.<sup>24 25</sup> However, there is no clear evidence of additional clinical benefit from starting ART at >350×10<sup>6</sup> CD4<sup>+</sup> cells/L.<sup>26</sup>

In deciding when to start ART, the benefits of treatment must be balanced with the risks of toxicity, the need for high adherence to therapy, and the patient's informed choice.

## What are the precautions?

Tailor the optimal antiretroviral regimen to the individual, considering viral factors and patient factors, including those discussed above.<sup>1</sup> Patients should be fully engaged in their treatment decisions, including a clear discussion of the possible side effects, risks, and benefits of therapy.

**Pregnancy:** Prospective observational studies have found no evidence of teratogenicity for any of the currently recommended antiretrovirals, although data on newly licensed drugs are limited.<sup>27</sup>

**Breast feeding:** HIV can be transmitted from mother to child through breast milk. However, there is evidence that ART reduces the risk of transmission if continued for the duration of breast feeding. In view of the risks associated with formula feeding in countries with unsafe water sources, WHO recommends each country's national authority should decide whether to promote complete avoidance of breast feeding (as in the UK<sup>2</sup>) or breast feeding with ART.<sup>28</sup> The 2012 British HIV Association (BHIVA) guidelines acknowledge that despite counselling some women choose to breast feed and should be supported with continued antiretroviral therapy and regular HIV viral load checks.

**Renal disease:** Monitor renal function with estimated glomerular filtration rate and urinalysis, before and during ART initiation and at least annually thereafter. BHIVA guidelines recommend against the use of potentially nephrotoxic antiretroviral drugs, such as tenofovir and atazanavir, in patients with stage 3-5 kidney disease if other options are available. Renally cleared antiretroviral drugs, such as lamivudine, should be dose adjusted according to renal function in patients with chronic kidney disease or in those on dialysis.<sup>1</sup>

**Liver disease:** BHIVA guidelines recommend close monitoring of liver function tests soon after initiation of ART. Avoid drugs such as nevirapine, which have been associated with severe hepatotoxicity, in patients with pre-existing liver disease.<sup>1</sup> The final choice of ART needs to consider the degree and cause of hepatic dysfunction.

**Hepatitis B infection:** The presence of HIV infection must prompt screening for hepatitis B co-infection and vice versa, given the similar routes of transmission. Because agents such as tenofovir, lamivudine, and emtricitabine are active against both infections, in co-infected people select ART regimens that suppress both infections. Failure to do so could result in partial treatment of HIV or hepatitis B and lead to the development of antiretroviral resistance in either of the two viruses.

**Antiretroviral drug resistance:** Subtherapeutic antiretroviral concentrations can result in the development of mutations that reduce the susceptibility of the HIV virus to specific antiretroviral agents. Suboptimal antiretroviral concentrations are mostly due to inadequate drug adherence, but other factors, including drug-drug interactions and impaired drug absorption, may be responsible. Some antiretrovirals, such as PIs, have a "high genetic barrier" to resistance, whereby several mutations are needed before the drug becomes ineffective or resistance mutations accumulate slowly. By contrast, the commonly used NNRTIs have a low barrier to resistance, and even one or two missed doses greatly increase the risk of failure.<sup>1</sup> Resistance mutations can be identified through genotypic analysis of the HIV virus in the presence of a raised viral load. If antiretroviral

resistance is suspected or identified, ART regimens are adapted to ensure the presence of drugs active against the HIV virus.

**Drug-drug interactions:** These can occur during drug absorption, distribution, metabolism, and elimination. For example, antacids reduce the absorption of some antiretrovirals, such as atazanavir and rilpivirine. Such interactions can lead to toxicity from seemingly innocuous agents—for example, ritonavir inhibits fluticasone hepatic cytochrome P450 metabolism,<sup>1</sup> and use of the two drugs together can result in Cushing's syndrome.

Web based resources exist to guide doctors in safe prescribing ([www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)) but specialist centres should be contacted when doubt exists. This applies equally to the use of over-the-counter drugs.

## How is treatment with ART monitored?

Successful ART will achieve and maintain suppression of active viral replication, which in practice is taken to mean a plasma HIV viral load <50 copies/mL. Viraemia >50 copies/mL after 12-24 weeks on ART is a predictor of subsequent virological failure and should be investigated (box).<sup>1</sup>

BHIVA recommends monitoring immediately after the initiation of ART and then every three to six months if the patient is stable on therapy. Assessments include HIV viral load; recording of patient reported drug adherence; identification of potential drug-drug interactions; and assessment for ART related adverse effects through symptom review, physical examination, and laboratory investigation (box).<sup>12</sup> Because recovery of CD4<sup>+</sup> cells varies between individuals do not rely on CD4<sup>+</sup> counts to assess therapeutic efficacy.

## Case outcome

The HIV clinic advised the GP that ritonavir can increase plasma fluticasone concentrations, potentially causing Cushing's syndrome and adrenal axis suppression. He was advised to prescribe beclomethasone instead because there is no clinically significant drug interaction for this combination, and this is the preferred inhaled corticosteroid for people with HIV taking this antiretroviral regimen.

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Gilead Sciences, ViiV Healthcare, BMS, Merck, and Janssen. AW has been involved in the development of educational material for BMS. BP has received research grants or been a consultant or investigator in clinical trials supported by Abbott, GlaxoSmithKline, Merck, and Bionor Immuno. BP is on the advisory board of Bionor Immuno, which is researching into immunotherapeutic HIV vaccines.

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- Williams I, Churchill D, Anderson J, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). *HIV Med* 2014;15(suppl 1):1-85.
- Taylor GP, Clayden P, Dhar J, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012;13(suppl 2):87-157.
- Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* 2008;300:51-9.
- May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4<sup>+</sup> cell count and viral load response to antiretroviral therapy. *AIDS* 2014;28:1193-202.
- Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493-505.
- Keiser O, Fellay J, Opravil M, et al. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: effect on mortality and treatment modification. *Antiviral Ther* 2007;12:1157-64.
- Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. *J Antimicrob Chemother* 2009;64:910-28.
- Gazzard B, Duvivier C, Zagler C, et al. Phase 2 double-blind, randomized trial of etravirine versus efavirenz in treatment-naïve patients: 48-week results. *AIDS* 2011;25:2249-58.
- Mills AM, Antinori A, Clotet B, et al. Neurological and psychiatric tolerability of rilpivirine (TMC278) vs. efavirenz in treatment-naïve, HIV-1-infected patients at 48 weeks. *HIV Med* 2013;14:391-400.
- Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med* 2014;161:1-10.
- Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *Br J Clin Pharmacol* 2011;71:659-71.
- Asboe D, Aitken C, Boffito M, et al. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012;13:1-44.
- Van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004;363:1253-63.
- Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis* 2013;207:1359-69.
- Carr A, Emery S, Law M, et al. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. *Lancet* 2003;361:726-35.
- Guaraldi G, Stentarelli C, Zona S, et al. HIV-associated lipodystrophy: impact of antiretroviral therapy. *Drugs* 2013;73:1431-50.
- Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One* 2013;8:e59551.
- Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009;338:a3172.
- Peters BS, Perry M, Wierzbicki AS, et al. A cross-sectional randomised study of fracture risk in people with HIV infection in the probono 1 study. *PLoS One* 2013;8:e78048.
- Bolland MJ, Grey A, Reid IR. Skeletal health in adults with HIV infection. *Lancet Diabetes Endocrinol* 2015;3:63-74.
- Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs deferred ART during an opportunistic infection. *PLoS One* 2010;5:e11416.
- Levy A, Johnston K, Annemans L, et al. The impact of disease stage on direct medical costs of HIV management: a review of the international literature. *Pharmacoeconomics* 2010;28(suppl 1):35-47.
- WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013. [http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf).
- Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2014. [www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf).
- Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA* 2012;308:387-402.
- Sabin CA, Phillips AN. Should HIV therapy be started at a CD4 cell count above 350 cells/microl in asymptomatic HIV-1-infected patients? *Curr Opin Infect Dis* 2009;22:191-7.
- Mohanna K. Teaching made easy: a manual for health professionals. 3rd ed. Radcliffe Publishing, 2011.
- WHO. Guidelines on HIV and infant feeding. 2010. Principles and recommendation for infant feeding in the context of HIV and a summary of evidence. [www.who.int/maternal\\_child\\_adolescent/documents/9789241599535/en/](http://www.who.int/maternal_child_adolescent/documents/9789241599535/en/).

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**Box: Summary of monitoring for patients on antiretroviral therapy (ART)<sup>12</sup>**

This is currently organised through specialist HIV clinics in the UK, although some routine monitoring may be undertaken in the community in future.

*First few months after starting ART*

- Advise patients to self report any new, severe, or unexpected symptoms.
- Within two to four weeks of starting ART evaluate adherence and side effects and request the following laboratory tests: full blood count, liver function tests, serum creatinine, estimated glomerular filtration rate, glucose, bone profile (serum calcium, phosphate, and albumin concentrations), and fasting lipids.
- Whether monitoring occurs at two or four weeks depends on patient factors such as comorbidities and the chosen regimen—for example, patients starting a nevirapine containing regimen must have liver function tested after two weeks.
- Measure plasma HIV viral load four and 12 weeks after ART is started. After four weeks, plasma HIV RNA should fall by more than 1 log<sub>10</sub> copies/mL compared with pre-ART values. Suppression to <50 copies/mL should occur by 12-24 weeks of ART initiation. If this does not occur, assess drug adherence; look for the presence of drug-drug interactions, which may influence plasma ART concentrations; ask about comorbidities, which could influence drug absorption; and ask whether dietary advice related to dosing is being followed.

*Routine visits when established on therapy (after 3-6 months)*

- Review those who are stable on therapy every 3-6 months, more often if needed.
- Ask directly about tolerability and adherence to drugs, use of concomitant drugs, and features indicative of long term side effects, such as body shape changes.
- Routine investigations include urine analysis for evidence of proteinuria and glycosuria. Laboratory tests include full blood count, liver function tests, serum creatinine, estimated glomerular filtration rate, glucose, bone profile (serum calcium, phosphate, and albumin concentrations), and fasting lipids. Frequency of testing depends on the ART regimen and patient characteristics.
- Assess plasma HIV viral load every 3-6 months. A single test result of 50-400 copies/mL, may be a "blip" and is usually not a cause for concern. HIV viral load >400 copies/mL may indicate virological failure and requires assessment of drug adherence, drug-drug interactions, and comorbidities. Consider testing for resistance mutations, which may reduce the efficacy of ART.
- All patients should have a 12 monthly cardiovascular risk assessment.
- Assess fracture risk every three years in those over 50 years, and bone mineral density in all men over 70 years and women over 65 years.

**Tips for patients***What drugs to treat HIV infection can achieve*

HIV is treated with antiretroviral drugs, also known as antiretroviral therapy (ART). These drugs work by stopping HIV from reproducing. ART limits the damage HIV causes to the immune system.

Current treatment is very effective but is not a cure, so treatment is usually life long. ART should not be stopped unless there is a medical reason. Without treatment, HIV viral load will quickly rebound.

Life expectancy for many HIV positive people is now similar to that of HIV negative people, especially if treatment is started early—before the CD4<sup>+</sup> cell count falls below 350×10<sup>6</sup> cells/L. This depends on early diagnosis and on access to treatment.

*Why it is important to avoid missing any doses?*

Adherence is the term for taking ART on time and as prescribed. If doses are missed or late, drugs may fall to levels at which drug resistance can develop. This can lead to treatment failure.

Adherence to ART needs to be high, and more than 95% of doses may need to be taken on time. Some combinations allow greater flexibility once the virus is undetectable.

Good adherence can be hard, but with support most people do well. HIV clinics can help patients by asking about adherence at each visit. People should feel able to talk about problems in confidence.

Simple changes can sometimes make a big difference. Focus on things that can help. This includes using a pill box, linking doses to daily routines, and using pill alarms.

*Treatment to prevent transmission of HIV*

ART greatly reduces the risk of transmission. An undetectable viral load makes someone much less infectious. This is called treatment as prevention (TasP).

UK guidelines recommend talking about this aspect of treatment with every patient. This should be an option for reducing further transmission. Information on TasP should be accompanied by information on other ways to reduce the risk of HIV transmission, including the importance of condoms.

Treatment also greatly reduces the chance of HIV passing from mother to baby during pregnancy and at birth.

*Side effects of HIV treatment*

Different antiretroviral drugs have different side effects. It is therefore important to discuss side effects before choosing a treatment.

Although serious side effects are rare they can be life threatening and include allergy and liver damage.

All people starting or changing treatment need information about side effects. This includes information about both common and serious symptoms.

*Interactions between HIV drugs and other drugs*

Many antiretroviral drugs can interact with other drugs—prescribed and over-the-counter drugs and recreational drugs.

This resource (for healthcare workers and patients) on drug interactions related to HIV drugs includes an app for Apple and android mobile devices: [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org). If in any doubt, contact the specialist clinic for advice.

*Further resources to support people living with HIV*

High quality web based resources and support groups that can provide independent information include:

- National Aids Map ([www.aidsmap.com](http://www.aidsmap.com))—High quality information on many topics relating to HIV infection
- HIV i-Base (<http://i-base.info>)—High quality information on topics related to HIV treatment
- Terrence Higgins Trust ([www.tht.org.uk](http://www.tht.org.uk))—Information and services for people living with HIV
- British HIV Association ([www.bhiva.org/guidelines-summaries.aspx](http://www.bhiva.org/guidelines-summaries.aspx))—Patient friendly guideline summaries

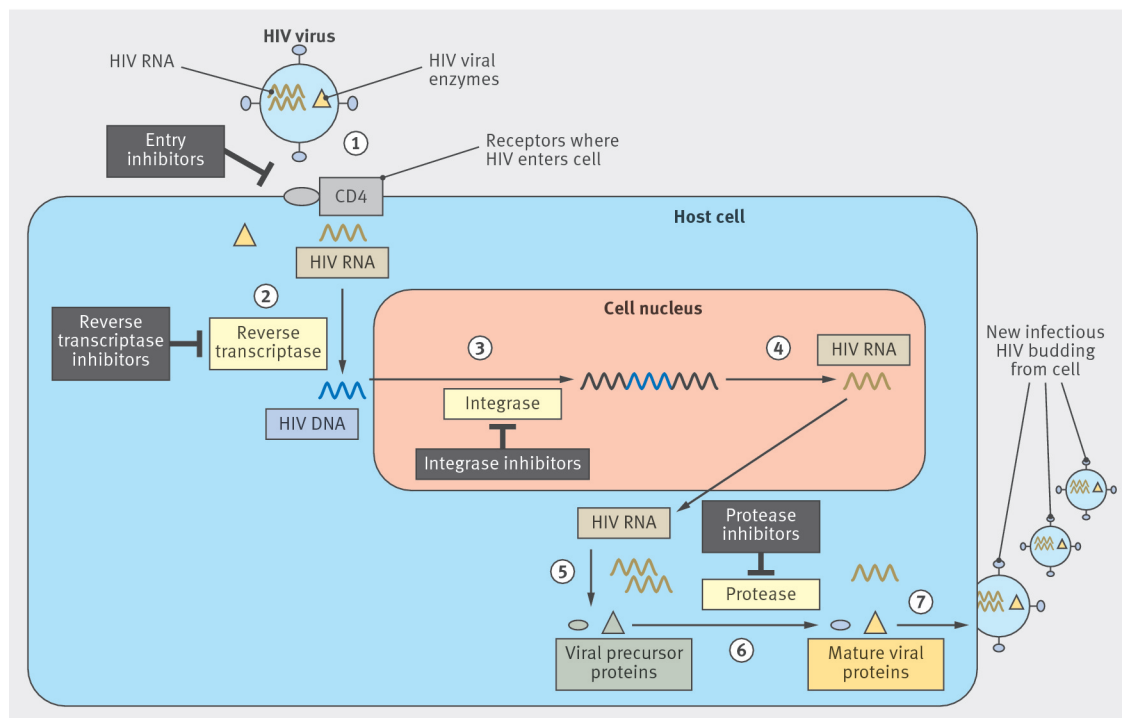
## Table

**Table 1 | Commonly used antiretroviral drugs and drug combinations**

Drug class	Examples
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Tenofovir disoproxil fumarate
	Abacavir
	Lamivudine
	Emtricitabine
	Zidovudine
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz
	Etravirine
	Rilpivirine
	Nevirapine
Protease inhibitors (PIs)	Darunavir
	Atazanavir
	Fosamprenavir
	Lopinavir
Integrase inhibitors (INIs)	Raltegravir
	Elvitegravir
	Dolutegravir
Entry inhibitors	Maraviroc
	Enfuvirtide
Fixed dose combinations	Truvada (tenofovir + emtricitabine)
	Kivexa (abacavir + lamivudine)
	Atripla (tenofovir + emtricitabine + efavirenz)
	Stribild (tenofovir + emtricitabine + elvitegravir + cobicistat)
	Triumeq (abacavir + lamivudine + dolutegravir)
Boosters*	Ritonavir
	Cobicistat

\*Boosters are prescribed in combination with certain antiretrovirals to increase the plasma concentrations of these drugs through inhibition of their metabolism. PIs are usually co-prescribed with a booster drug, most commonly ritonavir, to achieve therapeutic plasma concentrations. Elvitegravir is the only integrase inhibitor that must be co-prescribed with a boosting agent.

Figure



**Fig 1** HIV life cycle, illustrating sites of antiretroviral action. (1) The HIV viral particle (virion) binds CD4 receptors and coreceptors on the host cell membrane. The HIV RNA genome is released into the host cell along with viral enzymes reverse transcriptase, integrase, and protease. (2) Reverse transcriptase synthesises HIV DNA using the HIV RNA template. (3) HIV DNA is transported into the cell nucleus and integrated into the host cell genome by the viral enzyme integrase. (4) HIV DNA is synthesised into HIV RNA using the host cell's RNA polymerase. (5) HIV RNA is translated into viral precursor proteins using host cell ribosomes. (6) The viral enzyme protease cleaves the precursor proteins into mature viral proteins. (7) The viral proteins combine with HIV RNA to assemble new generations of virions, which bud from the host cell membrane