

# Current use of antiretroviral treatment

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**Introduction:** Antiretroviral therapy for HIV infection has transformed it from a terminal illness to a chronic manageable condition. This review summarizes the history of the treatment and explains the current practice in the field, including uses in prevention strategies.

**Sources of data:** National and international guidelines, important publications in peer reviewed literature and recent important conference abstracts.

**Areas of agreement:** There is a broad agreement on the choice of drug regimens and on the need to treat patients with symptomatic HIV infection and with CD4 cell counts less than 350 cells/mm<sup>3</sup>. The need to adapt therapy to individual circumstances is also well accepted, e.g. hepatitis co-infection and pregnancy.

**Areas of controversy:** Treatment of acute HIV infection and the optimum time to commence therapy in asymptomatic chronic infection remain controversial. Use of antiretrovirals for prevention, e.g. pre-exposure and post-exposure prophylaxis, is still developing.

**Growing points:** This article summarizes the current use of anti-HIV medication and the evidence behind it for the non-specialist.

**Areas timely for developing research:** New strategies for using current drugs, the best use of newly available drugs and new uses of antiretroviral drugs, such as in prevention of HIV transmission, are key areas for research. Further research addressing the question of when to start antiretrovirals and assessing their long-term effects is also needed.

**Keywords:** HIV/antiretroviral therapy/prevention/hepatitis co-infection/opportunistic infections

## Introduction

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HIV is a retrovirus, discovered in 1983 to be the cause of AIDS,<sup>1</sup> a clinical syndrome of immunodeficiency first described in gay men in the USA in 1981, with the first UK cases described shortly afterwards.<sup>2</sup> The current epidemiology, with 40 million people infected worldwide has been well documented.<sup>3</sup> There are two types of HIV, with HIV-1 causing the overwhelming majority of infections and the focus of this article.

From the beginning of the epidemic, treatment was urgently sought with the simple aims of prolonging life and preventing opportunistic infections. The first drug, AZT (zidovudine), became available in 1987 but effective treatment was achieved in 1996/7 with the advent of highly active antiretroviral therapy (HAART), initially based on two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI).<sup>4</sup> The first successful regimens were relatively toxic, with a high pill burden and complexity but the impact on morbidity and mortality was dramatic, as shown in Figure 1.

Since then, therapeutic developments have improved potency and tolerability and, with more than 20 drugs licensed for HIV treatment, there are now regimens which can potentially keep infected individuals well for decades. The current issues in HIV are therefore access to treatment, especially in developing countries which bear the brunt of the epidemic, and avoiding or managing long-term toxicities and drug resistance. This article aims to discuss the current use of HAART, with an emphasis on practice in the UK/developed world and potential future developments in the field.

## Antiretroviral agents—mechanisms of action

There are now six classes (including two classes of entry inhibitor) of antiretroviral active against HIV (Table 1). The mechanisms of action are best understood with reference to the viral life cycle shown below (Fig. 2).

1. Entry inhibitors—currently available drugs bind to CCR5 receptors on immune cells, blocking their use as a co-receptor for cell entry by HIV.

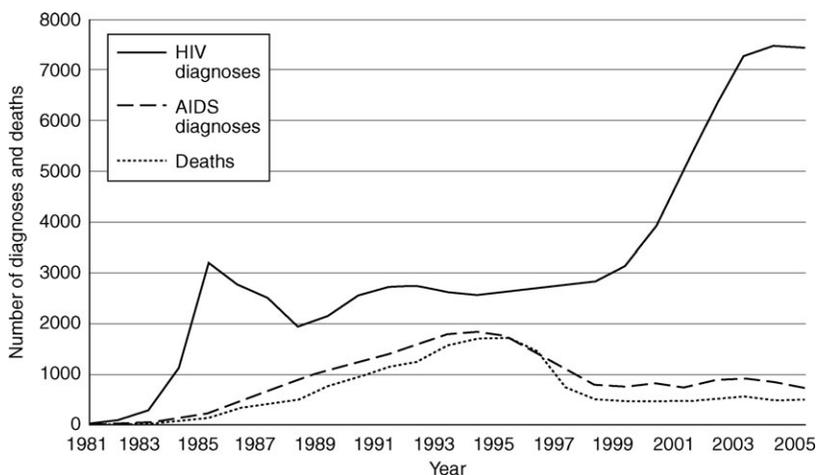


Fig. 1 HIV diagnoses, AIDS diagnoses and deaths in UK to end 2004 (Source: HPA<sup>5</sup>).

**Table 1** Currently available antiretroviral drugs by class.

NRTI	NNRTI	PIs	Entry inhibitors	Integrase inhibitors
Abacavir*	Efavirenz <sup>†</sup>	Atazanavir	Enfuvirtide	Raltegravir
Didanosine	Etravirine	Darunavir	Maraviroc	(Elvitegravir)
Emtricitabine <sup>†‡</sup>	Nevirapine	Fosamprenavir	(Vicriviroc)	
Lamivudine* <sup>§</sup>	(Ralpivirine)	Indinavir		
Stavudine		Lopinavir <sup>¶</sup>		
Tenofovir <sup>†‡</sup>		Nelfinavir		
Zidovudine <sup>§</sup>		Ritonavir <sup>¶</sup>		
		Saquinavir		
		Tipranavir		

This table refers to the UK. In the developing world, generic versions of some drugs, mainly stavudine, zidovudine, lamivudine, nevirapine, efavirenz and various fixed-dose combinations of these, are available at much lower prices than the proprietary brands, and are the mainstay of the World Health Organisation push to roll out antiretroviral treatment globally. Unlicensed medications shown in brackets.

\*Co-formulated as Kivexa<sup>®</sup>.

<sup>†</sup>Co-formulated as Atripla<sup>®</sup>.

<sup>‡</sup>Co-formulated as Truvada<sup>®</sup>.

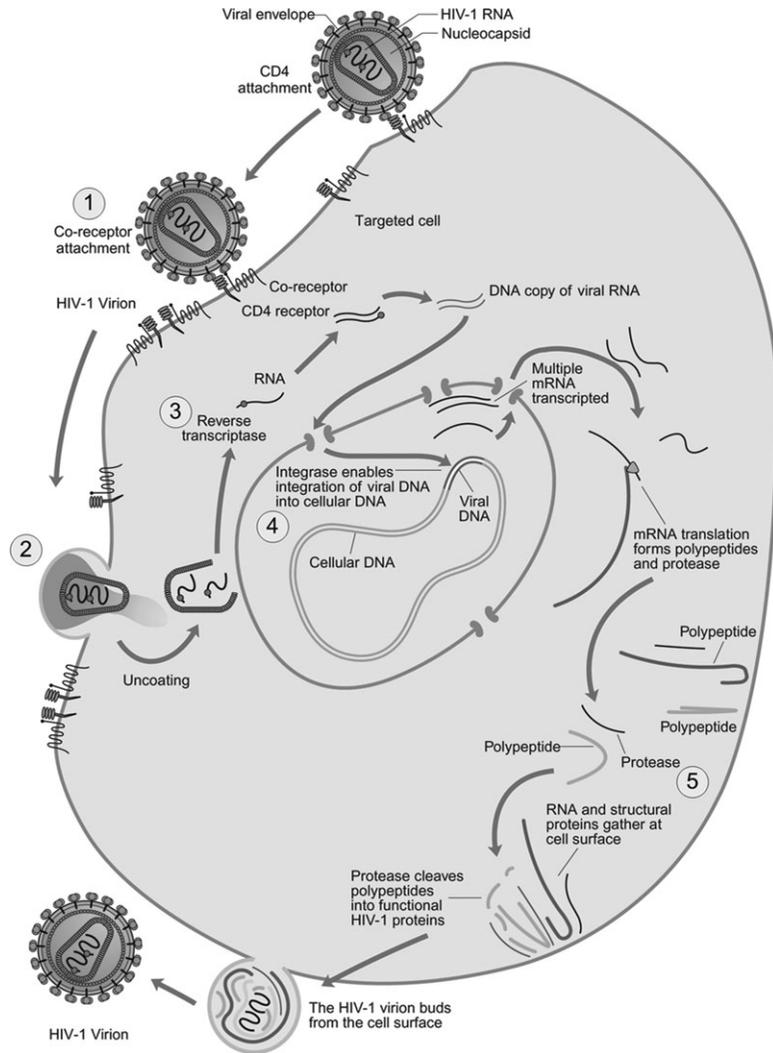
<sup>§</sup>Co-formulated as Combivir<sup>®</sup>.

<sup>¶</sup>Co-formulated as Kaletra<sup>®</sup>.

2. Fusion inhibitors block gp41, a viral surface protein, preventing the conformational change necessary to allow fusion of viral and cell membranes, thereby preventing entry of viral nuclear material into the cell.
3. Two classes of drug act on the viral reverse transcriptase enzyme: NRTIs and closely related nucleotide reverse transcriptase inhibitors (NtRTIs) are nucleic acid analogues and work by terminating the DNA chain as reverse transcriptase copies viral RNA into DNA. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) block the enzyme by binding it tightly.
4. Integrase inhibitors block the integrase enzyme which incorporates viral copy DNA into the cellular DNA.
5. PIs bind to the viral protease blocking cleavage of the viral amino acid chain to its constituent proteins.

## When to start treatment for HIV

To treat HIV infection, we must first diagnose it. One-third of UK patients are still diagnosed late, i.e. with significant immunosuppression or opportunistic infections (OIs) at diagnosis. Late diagnosis leads to increased morbidity and mortality from the disease and increased chances of failing therapy. Many of those who are diagnosed late with HIV infection have presented to medical services in the years preceding diagnosis and opportunities to diagnose their HIV were missed.<sup>6</sup> The education of all medical practitioners, to make HIV a routine



**Fig. 2** The life cycle of HIV and mechanism of action of antiretroviral drugs (Source: Adapted from Whittlesea C. (eds). Leake-Date H, Fisher M, HIV Infection. In: Walker R. Clinical Pharmacy and Therapeutics. 4th edn. Oxford: Churchill Livingstone (Elsevier), 2007; 572–572.).

part of differential diagnosis in all specialities, is now key to optimizing outcomes in the UK.

### Primary HIV infection

The current guidelines do not recommend treatment outside clinical trials,<sup>7</sup> as evidence of benefit is lacking, unless symptoms of sero-conversion are severe, e.g. meningoencephalitis.

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## Chronic HIV infection

### Symptomatic patients

For symptomatic patients, with OIs or other AIDS-defining conditions, HAART should be commenced regardless of CD4 cell count or HIV viral load. One possible exception to this is individuals with pulmonary tuberculosis alone, where CD4 cell count may be considered.<sup>7-9</sup>

Timing the initiation of antiretrovirals relative to treatment of the OI can be difficult for three reasons.

1. Toxicity may be increased when HAART is co-administered with treatments for opportunistic infections.<sup>10</sup>
2. Significant interactions exist between antiretrovirals and OI drugs.<sup>10</sup>
3. There is a risk of immune reconstitution syndrome (IRS), a paradoxical worsening of clinical condition associated with immune recovery. IRS is particularly important in mycobacterial infections but has been described in most OIs.<sup>11</sup>

For short courses of OI treatment, e.g. PCP, HAART is often deferred until after completion, although a recently presented study suggests a benefit from starting earlier.<sup>12</sup> For longer treatment periods, the risk of disease progression from delaying HAART is too great and co-administration cannot be avoided. Careful monitoring for toxicity and IRS is then required.

### Asymptomatic patients

Initial data indicated that the time from infection with HIV to clinical disease progression is, on average, 10 years. When HAART first became available, there was a move to treat early infection, the so-called 'hit early, hit hard' approach, aiming to influence long-term prognosis. As drug toxicities and the difficulties of taking a complex regimen accurately for many years became apparent, this approach was replaced by a more conservative one, based on data from cohort studies assessing risk of disease progression at different levels of CD4 cell count and HIV viral load in the medium term (3 years).<sup>13</sup>

However, the pendulum may be swinging back towards earlier treatment, in part due to improvements in therapy, such that toxicity is reduced and success and durability of first-line regimens are increased. There are a number of arguments in favour of earlier treatment. First, there are data to suggest that individuals in higher CD4 strata (200–350 and >350) gain morbidity and mortality benefits from HAART compared to those with similar counts off therapy.<sup>14</sup> There is also a suggestion that the definitions of clinical progression, previously limited to AIDS diagnoses, need to be broadened to include, for example, liver disease, cardiovascular disease and non-AIDS cancers because treatment with HAART reduces the risk of these morbidities

**Table 2** Summary of guidance on starting HAART.

CD4 cell count	Previous recommendation (2006)	Current recommendation (2008)
<200	Start HAART without delay	Start HAART without delay
201–350	Consider HAART	Start HAART when patient ready
>350	Defer HAART	Defer HAART

significantly, even at higher CD4 cell counts.<sup>13</sup> Furthermore, cohort data suggest that those who commence therapy with a CD4 cell count below 350 are unlikely to achieve a normal CD4 cell count within 7 years of virological suppression,<sup>15</sup> although data from another cohort suggest that if suppression is maintained, CD4 increases will continue until normal levels are reached.<sup>16</sup> The clinical significance of achieving a normal CD4 count is unknown. Finally, it has been postulated that using HAART earlier could affect transmission of HIV and reduce incidence of new infections but the ethics of treating for public health rather than individual benefit are unclear.<sup>17</sup> The current guidance is summarized in Table 2.

A randomized controlled trial to address the issue of the optimum time to start HAART, taking into account all these issues, is needed to inform guidelines and decision-making and may start in late 2008.

## What treatment to start

### *First-line treatment choice*

The aim of treatment is to suppress viral replication to a level where drug resistance cannot develop. This has required the use of three drugs, and the current treatment paradigm for those who are naive to antiretrovirals is a triple drug regimen, usually two NRTIs and either a boosted PI or an NNRTI. In cohort studies and more recently in a randomized trial, NNRTIs have consistently performed slightly better than PI-based regimens.<sup>18</sup> NNRTIs have possible advantages in terms of pill burden and once daily dosing (although nevirapine is licensed twice daily, once therapy is established, it is often used once daily) and have a lesser effect on lipid metabolism than PIs. Boosted PIs, however, have a higher barrier to resistance (multiple mutations in the viral genome are required to impact on potency, therefore resistance increases gradually in a stepwise fashion c.f. a single mutation conferring complete resistance with first generation NNRTIs).

Within each class, certain drugs may be preferred, for example, efavirenz is often preferred to nevirapine because it has less severe early

toxicities (nevirapine can cause Stevens–Johnson syndrome and fulminant hepatic failure), except in women of childbearing potential (given subsequently).

Among PIs, it is clear that boosted PIs are more potent than unboosted PIs (giving a small ‘boosting’ dose of ritonavir with other PIs improves pharmacokinetic parameters and increases efficacy), but there is less evidence to suggest a clear preference for a particular drug. Lopinavir/ritonavir has the greatest duration of follow-up and is co-formulated as a heat-stable tablet. All other boosted PIs require ritonavir capsules, which need refrigeration. Fosamprenavir/ritonavir has been shown to be non-inferior to lopinavir/ritonavir in naive patients and is a first-line choice in the British HIV association (BHIVA) guidelines.<sup>7,19</sup> A comparative study of saquinavir/ritonavir versus lopinavir/ritonavir is underway and 48-week data presented in October 2007 showed no difference in the proportion of patients virologically suppressed in the two arms.<sup>20</sup> Atazanavir/ritonavir is recently licensed in treatment-naive patients in the UK following the presentation of a study which demonstrates non-inferiority of this combination to lopinavir/ritonavir in this population, with a lower incidence of gastrointestinal and lipid side effects.<sup>21</sup> The renal toxicity of indinavir has led to it falling out of use in many centres.

The choice of nucleoside backbone is between two preferred combinations: tenofovir + emtricitabine or abacavir + lamivudine. These are both available as once daily co-formulated tablets and have performed well when compared with Combivir<sup>®</sup> (AZT + 3TC), the previous gold standard.<sup>7</sup> In the HEAT study,<sup>7</sup> abacavir + lamivudine demonstrated non-inferiority to tenofovir + emtricitabine. However, a recent ACTG trial comparing the two backbones has been partially unblinded after more patients failed virologically in the abacavir arm.<sup>22</sup> Publication of this study and further studies comparing the efficacy of these two regimens are awaited. In terms of toxicity, neither combination is currently implicated as a cause of lipoatrophy, a distressing side effect where fat loss occurs, causing a characteristic facial and body appearance, and both are well tolerated. In the past, abacavir had a significant disadvantage because it causes a hypersensitivity reaction in 5–8% of (Caucasian) patients. In these individuals, the drug must be stopped and re-exposure can be fatal. However, the susceptibility to this reaction is linked to a specific HLA type, HLA B\*5701, and testing for this in advance in order to exclude carriers from abacavir therapy eliminated the risk of hypersensitivity in a recent study.<sup>23</sup> Further data are required for non-Caucasians. Recent cohort data have suggested that there is an excess incidence of myocardial infarction in patients on abacavir.<sup>24</sup>

The mechanism is as yet unexplained and the effect is most marked in those with a high cardiovascular risk. Thus far, insufficient data exist to perform similar analyses in patients on tenofovir, but this information will be available soon. There have been case reports of renal toxicity and Fanconi's syndrome with tenofovir, but in clinical trials and post-marketing surveillance, the incidence is low.<sup>2,5</sup> The choice between these NRTI backbones remains controversial and further data to inform choice are anticipated. Lamivudine and emtricitabine are similar drugs with similar mechanisms of action and the same resistance pathway. The possible advantage of emtricitabine is that it has a longer half-life and could therefore be more 'forgiving' of late doses. However, it also has a unique toxicity, rarely causing pigmentation of palms and soles, and some patients report central nervous system (CNS) side effects such as dizziness with this drug. Ultimately, most clinicians select the third agent on the basis that it is co-formulated with their choice of abacavir or tenofovir rather than any particular feature of the drug itself.

A triple drug combination tablet containing tenofovir/emtricitabine/efavirenz is now available in the UK, producing a single daily tablet regimen for the first time. Licensing issues in Europe delayed the launch because the summary of product characteristics for efavirenz states that it should be taken without food, whereas that for Truvada (tenofovir + emtricitabine) requires it to be taken with food. The tablet is consequently licensed only for patients already virologically suppressed (Table 3).

**Table 3** Summary of recommendations for antiretroviral agents in treatment-naïve patients.

Regimen	A	B	C
Preferred	Efavirenz*	Tenofovir* <sup>†</sup> Abacavir <sup>‡</sup>	Lamivudine <sup>§</sup> <sup>5</sup> Emtricitabine* <sup>†</sup>
Alternative	Lopinavir/ritonavir* Fosamprenavir/ritonavir Atazanavir/ritonavir	Didanosine Zidovudine <sup>§</sup>	
Specific groups	Nevirapine <sup>  </sup> Atazanavir <sup>#</sup>		

Source: Taken from Gazzard BG on behalf of the BHIVA Treatment Guidelines Writing Group.<sup>7</sup>

Use one drug from each column.

\*Co-formulated as Atripla<sup>®</sup>. (licensed for virologically suppressed patients only).

<sup>†</sup>Co-formulated as Truvada<sup>®</sup>.

<sup>‡</sup>Co-formulated as Kivexa<sup>®</sup>.

<sup>§</sup>Co-formulated as Combivir<sup>®</sup>.

<sup>¶</sup>Co-formulated as Kaletra<sup>®</sup>.

<sup>||</sup>Only in men with CD4 <400 cells/mm<sup>3</sup> and women with CD4 <250 cells/mm<sup>3</sup>.

<sup>#</sup>Unlicensed in the UK, recommended where established cardiovascular risk factors and a PI required.

### Non standard combinations

Other combinations of drugs have also been tried, in particular the NRTI-sparing combination of lopinavir/ritonavir plus efavirenz.<sup>18</sup> This is as effective as the standard combinations and may be less likely to cause mitochondrial toxicities but does lead to marked increases in lipid parameters. The low toxicity and convenience of current NRTIs ensure this strategy is an uncommon choice.

Another investigational strategy is boosted PI monotherapy, which has been tried with lopinavir/ritonavir in a number of studies and with some other PIs including atazanavir/ritonavir. This may be useful in selected patients but is not a preferred option.<sup>26</sup>

### What not to start

Some combinations of drugs are absolutely contraindicated.

1. Zidovudine with stavudine, which share a metabolic pathway and are mutually antagonistic.
2. Didanosine with stavudine in pregnant women, who have a high incidence of lactic acidosis when treated with this combination.
3. Lamivudine with emtricitabine, as they share a mechanism of action and do not add benefit to each other.

Other combinations are no longer recommended as they lack potency when compared with current gold standards:

- (i) triple NRTI combinations;
- (ii) unboosted PIs;
- (iii) tenofovir + didanosine + efavirenz has been associated with high rates of virological failure in clinical trials and is therefore avoided.

There are other drugs and combinations that are generally not used now for treatment-naïve patients as the risks usually outweigh the benefits:

- (i) stavudine or zidovudine cause lipodystrophy;
- (ii) tenofovir with didanosine cause an increased incidence of pancreatitis due to an intracellular interaction and may also cause a fall in CD4 cell count;
- (iii) nevirapine in women with CD4 cell counts over 250 cells/mm<sup>3</sup> and men with CD4 cell counts over 400 cells/mm<sup>3</sup> when the risk of hepatotoxicity increases markedly.

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## Special groups

### *Pregnant (or potential to become pregnant) women*

HAART may be started early for prevention of mother to child transmission (PMTCT), i.e. at higher CD4 counts, than it would be commenced in non-pregnant women. Regimens which are proved to work for PMTCT and which are not thought to be teratogenic are required. AZT is therefore preferred, as there is proven efficacy in this setting. Efavirenz is avoided because it was teratogenic in animal studies, although prospective surveillance in humans so far has not shown an effect (numbers are still too small to be certain and there have been four cases of malformations reported post-occurrence).<sup>27</sup> The pharmacokinetic changes in pregnancy affect drug levels and may lead to potentially sub-therapeutic levels, a particular concern with PIs. Therapeutic drug monitoring is recommended.

### *Hepatitis co-infection*

This is a common problem because hepatitis B and C share transmission modes with HIV. In patients with hepatitis B, tenofovir and lamivudine or emtricitabine are the preferred nucleosides because they are effective against hepatitis B as well as HIV.<sup>28</sup> In patients requiring or likely to require hepatitis C treatment, zidovudine and didanosine are avoided to prevent increased toxicity with ribavirin and abacavir is avoided as it interacts with ribavirin and may reduce efficacy.<sup>29</sup> In patients with liver disease, it may be preferable to avoid nevirapine and high doses of ritonavir because there is an increased risk of liver toxicity in this group.

### *Tuberculosis co-infection*

Quadruple TB therapy and HAART have overlapping toxicities and major interactions.<sup>10</sup> In particular, co-administration with rifampicin reduces levels of boosted PIs significantly and leads to a high incidence of liver toxicity. Nevirapine levels are also reduced by rifampicin and co-administration is not generally recommended where alternatives are available, although treatment outcomes have been satisfactory in developing world studies where this strategy has been used. Efavirenz can be used with rifampicin, but dose adjustment may be necessary.

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## Problems associated with HAART

### *Side effects*

Short-term side effects may be general, such as nausea and fatigue, or specific to certain drugs, such as the dizziness and sleep disturbance caused by efavirenz. Most of these effects settle within weeks and, if warned in advance to expect them, most patients cope with support. If symptoms persist into the longer term, they can have a significant impact on adherence and clinicians must be prepared to switch drugs if patients are unable to tolerate them.

Drug-specific side effects and long-term concerns are discussed earlier in this article.

### *Drug–drug interactions*

PIs and NNRTIs interact with the cytochrome P450 system and hence with many commonly prescribed, over-the-counter and recreational drugs, e.g. simvastatin, Methyl Diethyl MetAmphetamine ('Ecstasy').<sup>10</sup> Absorption may be affected by antacid agents such as proton pump inhibitors, which reduce the levels of atazanavir significantly and can affect potency. It is therefore imperative that patients are educated about their medications and that communication with other health professionals prescribing to patients on HAART is effective. Information about drug interactions with HAART is available at [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org).

### *Resistance*

Resistance in HIV can be measured phenotypically, by culturing virus and testing different drug concentrations, or genotypically, by sequencing the viral genome and looking for signature mutations known to be associated with resistance. Resistance can be acquired or primary/transmitted, both having a detrimental effect on response to treatment and consequently mortality. Up to half of treated patients have some degree of drug resistance, with 9% of treatment-naïve patients in the UK in 2005 having some transmitted resistance.<sup>30</sup> To maximize the efficacy and durability of a regimen, it is, therefore, crucial to check for transmitted resistance before commencing therapy with a proven HAART regimen. Acquired resistance can progress rapidly when a regimen fails, often reducing susceptibility to whole classes of drugs. Regular monitoring and early switching of failing regimens will help preserve future options.

Of note, HIV-2 (and subtype O HIV-1, a very rare variant) are naturally resistant to NNRTIs, and patients with these subtypes are therefore treated with PI-based regimens.<sup>31</sup>

## *Adherence*

The success of HAART is heavily dependant on the ability of the patient to maintain adherence to the regimen in the long term. It has been shown that it may be necessary to take at least 95% of doses at the correct time to achieve long-term virological suppression<sup>7</sup>(although as newer agents have improved pharmacokinetics, this may be less crucial), and continuing to do this over many years is a significant challenge. Simplification of regimens, patient education, individualized multidisciplinary support and prompt palliation of side effects are all important to ensure patients remain committed to taking their regimen.

## **When to switch treatment**

### *Switching for toxicity*

If a patient experiences a significant toxicity or side effect, it will be necessary to switch that drug, with the degree of urgency depending on severity. It is usually safe to switch the likely drug within the same class if treatment is otherwise effective.

### *Switching for failure*

Failure of treatment can be clinical (progression of disease, e.g. development of a new opportunistic infection or AIDS condition), immunological (a fall in the CD4 cell count or a failure to achieve an increase in the CD4 count from baseline level) or virological (an increase in HIV viral load to >400 copies per ml on two consecutive measurements at least 1 month apart). Virological failure is the primary definition used in the UK.<sup>7</sup>

The important factors in successful switching are determining and addressing the reason for failure, e.g. adherence, baseline resistance and switching all the drugs at once to a regimen which, guided by treatment history and resistance testing, contains at least two active drugs. Addition of a single drug to a failing regimen is not advisable.

The aim of treatment for patients with previous HAART failure is now virological suppression as new drugs become available with

activity against resistant viruses. It may be preferable, when extensive resistance is present, to await new agents allowing the construction of a potent suppressive regimen rather than 'wasting' drugs by giving a single new agent. However, this must be balanced against the risks of disease progression and acquiring further resistance by continuing a failing regimen.

## Newer agents and classes

The '2nd' generation PIs, tipranavir and darunavir, have shown activity against PI-resistant virus and made virological suppression an achievable aim for former 'salvage' patients.<sup>7</sup> The second generation NNRTIs, which have activity against viruses with resistance to efavirenz and nevirapine and a higher genetic barrier to resistance than the first generation drugs, are also coming through, with etravirine available on a named patient basis and rilpivirine in development.<sup>9,32</sup>

There are also new classes of drug with new targets. The first of these, enfuvirtide, a fusion inhibitor, was licensed in 2003 but is administered by subcutaneous injection. The CCR5 inhibitors have also shown benefit in experienced patients in clinical trials and the first, maraviroc, has just been licensed. Integrase inhibitors, of which the first, raltegravir, is now licensed, have also demonstrated benefit for patients with highly resistant virus. All of these drugs have shown effect individually with optimized background therapy but the key to success remains constructing a regimen with at least two active drugs.<sup>9</sup>

The potential for use of new agents in naive patients, particularly where there are significant benefits in terms of robustness or high genetic barrier to resistance or in terms of toxicity when compared with current first-line agents, has yet to be fully elucidated. Maraviroc has been shown to be less potent than efavirenz in naive patients but was less toxic. Raltegravir has also been tested versus efavirenz in treatment-naive patients, with results showing similar rates of virological suppression at 48 weeks.<sup>9</sup> Tipranavir appears more toxic than current first-line regimens<sup>33</sup> and etravirine has been less potent in that population,<sup>9</sup> but rilpivirine, which lacks CNS side effects, may in time be preferred to efavirenz in naive patients, with good potency so far.<sup>32</sup> Data on darunavir in naive patients are also promising.<sup>9</sup>

## New strategies

The current treatment paradigm, start HAART with three drugs and continue for ever, has been challenged as new drugs become available.

One alternative strategy, which has been tested in a randomized controlled trial (the SMART study) is that of structured treatment interruptions. SMART randomized patients to a virological suppression arm (with the aim of using HAART to maintain virological suppression throughout) or a drug conservation arm (where treatment was interrupted when CD4 count was greater than 350 and restarted again when the count fell below 250). This trial was stopped early after a significantly increased mortality and morbidity in the drug conservation arm due to both opportunistic infections and, unexpectedly, non-AIDS events such as cardiovascular disease and liver disease which it was previously thought were more related to HAART than to HIV itself. The strategy of treatment interruptions has currently been abandoned.<sup>34</sup>

Another possible strategy for using HAART is the idea of induction and maintenance phases of therapy, using multiple drugs early to bring down viral load and then maintaining suppression with fewer drugs, perhaps even just a boosted PI. The Forte study showed a benefit in terms of virological suppression from an initial four drug strategy, reducing to three drugs after a maximum time of 32 weeks.<sup>35</sup> Further investigation of this strategy, which may have advantages over the current gold standard in terms of cost and toxicity, is needed.

## **Use of HAART drugs in prevention of HIV**

### *PMTCT and breastfeeding*

The use of antiretroviral drugs to prevent vertical transmission of HIV was established in the mid-1990s with the ACTG 076 trial using AZT. Since then, it has become a routine indication for HAART in many developed countries, with simplified regimens being developed for application in developing countries. The risk of transmission from mother to child can be reduced from 30 to <1% using triple drug regimens and avoiding breastfeeding.<sup>27</sup> A further potential use is preventing transmission during exclusive breastfeeding in settings where formula feeding is unsafe, with early data extremely encouraging in two African studies.<sup>36</sup>

### *Post-exposure prophylaxis*

A short (28 day) course of anti-HIV medications to prevent infection in an exposed individual has been used in healthcare settings since AZT became available. More recently, use has been expanded to

include individuals with sexual exposure to HIV and this has been shown to be cost effective. There are no randomized controlled trials of post-exposure prophylaxis (PEP), but a case-control study demonstrated an 80% reduction in the risk of acquiring HIV with AZT alone.<sup>37</sup>

After risk assessment and baseline HIV testing, the individual is prescribed (usually) three HAART drugs and supported to take them for 28 days. Follow-up HIV testing at 3 months is recommended. Concerns that availability of PEP will increase risk-taking have not been confirmed thus far in studies in gay men.<sup>37</sup>

### *Pre-exposure prophylaxis*

Pre-exposure prophylaxis (PrEP) is currently undergoing efficacy trials in humans in a variety of settings, having shown promise in animal studies.<sup>38</sup> The use of tenofovir or tenofovir/emtricitabine in this way is potentially a very effective strategy, but will need to be carefully studied to identify adverse effects, resistance patterns in those who seroconvert despite PrEP and effects on risk behaviour.

### *Microbicides*

Animal studies have suggested that a tenofovir containing rectal microbicide was effective against an SIV challenge.<sup>39</sup> Human studies are awaited and use of novel antiretroviral agents such as entry inhibitors in microbicide products remains to be investigated.

## **Conclusion**

HAART is an effective treatment for HIV infection and has transformed the outlook for infected individuals. The optimum time to start therapy and the best strategy for use of antiretrovirals, new and old, to maintain health for multiple decades are yet to be determined. The field is rapidly evolving and best practice changes over time, requiring those treating HIV infection to consider expert opinion and guidelines in the context of the needs and beliefs of individual patients to tailor therapy and achieve best results.

It is clear that early diagnosis of HIV improves outcome and there is a need to increase the proportion of HIV infections diagnosed before the disease is symptomatic.

Use of antiretroviral drugs to prevent HIV infections is increasing worldwide, and strategies such as PrEP and PEP may play an important role in controlling the epidemic.

## Conflict of interest

AB has received educational grants from the following companies: Boehringer Ingelheim, Bristol Myers Squibb, Glaxo Smith Kline. MF has worked as an advisor for or received educational grants or research funding from the following companies: Abbott, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Glaxo Smith Kline, Merck, Pfizer, Roche, Schering Plough, Tibotec.

## References

- 1 Barré-Sinoussi F, Chermann JC, Rey F *et al.* (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*, **220**, 868–871.
- 2 Dubois RM, Branthwaite MA, Mikhail JR *et al.* (1981) Primary Pneumocystis Carinii and cytomegalovirus infections. *Lancet*, **318**, 1339.
- 3 Simon V, Ho DD, Abdool Karim Q (2006) HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet*, **368**, 489–504.
- 4 Weller IV, Williams IG (2001) ABC of AIDS. Antiretroviral drugs. *BMJ*, **322**, 1410–1412.
- 5 The UK Collaborative Group for HIV and STI Surveillance. A Complex Picture. HIV and other Sexually Transmitted Infections in the United Kingdom: 2006. London: Health Protection Agency, Centre for Infections. November 2006.
- 6 Fisher M (2008) Late diagnosis of HIV infection: major consequences and missed opportunities. *Curr Opin Infect Dis*, **21**, 1–3.
- 7 Gazzard BG on behalf of the BHIVA Treatment Guidelines Writing Group (2008) British HIV Association Guidelines for the treatment of HIV-infected adults with antiretroviral therapy, *HIV Med*, in press. Available at <http://www.bhiva.org/cms122226.asp>.
- 8 Clumeck N, Pozniak A, Raffi F (2008) European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. *HIV Med*, **9**, 65–71.
- 9 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 29, 2008; 1–128. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
- 10 Piscitelli SC, Gallicano KD (2001) Interactions among drugs for HIV and opportunistic infections. *N Engl J Med*, **344**, 984–996.
- 11 Lipman M, Breen R (2006) Immune reconstitution inflammatory syndrome in HIV. *Curr Opin Infect Dis*, **19**, 20–25.
- 12 Zolopa A, Anderson J, Komarow L *et al.* (2008) ACTG 5164 study team. Immediate vs Deferred ART in the Setting of Acute AIDS-related Opportunistic Infection: Final Results of a Randomized Strategy Trial, ACTG A5164. Fifteenth conference on retroviruses and opportunistic infections, Boston.
- 13 Phillips AN, Gazzard BG, Clumeck N, Losso MH, Lundgren JD (2007) When should antiretroviral therapy for HIV be started? *BMJ*, **334**, 76–78.
- 14 Emery S, Neuhaus JA, Phillips AN *et al.* (2008) Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis*, **197**, 1133–1144.

- 15 Gras L, Kesselring AM, Griffin JT *et al.* (2007) CD4 cell counts of 800 cells/mm<sup>3</sup> or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm<sup>3</sup> or greater. *J Acquir Immune Defic Syndr*, **45**, 183–192.
- 16 Mocroft A, Phillips AN, Gatell J *et al.* (2007) Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet*, **370**, 407–413.
- 17 Wood E, Montaner JS (2007) When to initiate HIV antiretroviral therapy: do benefits other than survival deserve greater attention? *J Acquir Immune Defic Syndr*, **45**, 131–132.
- 18 Riddler SA, Haubrich R, DiRienzo AG *et al.* (2008) Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*, **358**, 2095–106.
- 19 Eron J Jr, Yeni P, Gathe J Jr *et al.* (2006) The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*, **368**, 476–482.
- 20 Walmsley S, Ruxrungtham K, Slim J *et al.* (2007) Saquinavir/r (SQV/r) BiD versus lopinavir/r (LPV/r) BiD, plus emtricitabine/tenofovir (FTC/TDF) QD as initial therapy in HIV-1 infected patients: the GEMINI study. Eleventh European AIDS Conference, Madrid.
- 21 Molina J-M, Andrade-Villanueva J, Echevarria J *et al.* (2008) Efficacy and safety of once-daily atazanavir/ritonavir compared to twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine in ARV-naïve HIV-1-infected subjects: the CASTLE study, 48-week results. Fifteenth Conference on Retroviruses and Opportunistic Infections, Boston.
- 22 Sax P, Tierney C, Collier A *et al.* (2008) ACTG 5202: shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination therapy in treatment-naïve subjects with screening HIV RNA  $\geq$  100,000 c/mL. Program and abstracts of the 17th International AIDS Conference; August 3–8; Mexico City, Mexico. Abstract THAB0303.
- 23 Mallal S, Phillips E, Carosi G *et al.* (2008) HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med*, **358**, 568–579.
- 24 D:A:D Study Group (2008) Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *The Lancet*, **371**:1417–1426
- 25 Nelson MR, Katlama C, Montaner JS *et al.* (2007) The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS*, **21**, 1273–1281.
- 26 Delfraissy JF, Flandre P, Delaugerre C *et al.* (2008) Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naïve HIV-infected patients. *AIDS*, **22**, 385–393.
- 27 Hawkins D, Blott M, Clayden P *et al.* (2005) Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV. *HIV Med*, **2** (Suppl 6), 107–148.
- 28 Levy V, Grant RM (2006) Antiretroviral therapy for hepatitis B virus-HIV-coinfected patients: promises and pitfalls. *Clin Infect Dis*, **43**, 904–910.
- 29 Soriano V, Barreiro P, Martin-Carbonero L *et al.* (2007) Update on the treatment of chronic hepatitis C in HIV-infected patients. *AIDS Rev*, **9**, 99–113.
- 30 The UK Collaborative Group for HIV and STI Surveillance. Testing Times. HIV and other Sexually Transmitted Infections in the United Kingdom: 2007. London: Health Protection Agency, Centre for Infections. November 2007.
- 31 Parkin NT, Schapiro JM (2004) Antiretroviral drug resistance in non-subtype B HIV-1, HIV-2 and SIV. *Antivir Ther*, **9**, 3–12.
- 32 Pozniak A, Morales-Ramirez J, Mohapi L *et al.* (2007) 48-Week primary analysis of trial TMC278-C204: TMC278 demonstrates potent and sustained efficacy in ART-naïve patients. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles.
- 33 Youle M (2007) Overview of boosted protease inhibitors in treatment-experienced HIV-infected patients. *J Antimicrob Chemother*, **60**:1195–1205.
- 34 El-Sadr WM, Lundgren JD, Neaton JD *et al.* (2006) CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*, **355**, 2283–2296.
- 35 Asboe D, Williams IG, Goodall RL, Darbyshire JH, Hooker MH, Babiker AG (2007) A virological benefit from an induction/maintenance strategy: the Forte trial. *Antivir Ther*, **12**, 47–54.

- 36 Coovadia H, Kindra G (2008) Breastfeeding to prevent HIV transmission in infants: balancing pros and cons. *Curr Opin Infect Dis*, **21**, 11–15.
- 37 Fisher M, Benn P, Evans B *et al.* (2006) UK Guideline for the use of post-exposure prophylaxis for HIV following sexual exposure. *Int J STD AIDS*, **17**, 81–92.
- 38 Paxton LA, Hope T, Jaffe HW (2007) Pre-exposure prophylaxis for HIV infection: what if it works? *Lancet*, **370**, 89–93.
- 39 Cranage M, Sharpe S, Cope A *et al.* (2007) Pre-exposure prophylaxis in macaques against rectal SIV challenge by mucosally applied PMPA: potential for complementation of microbicide and vaccination strategies. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles.