

British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006)

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Introduction

This summary document is an update to the full British HIV Association (BHIVA) Treatment Guidelines published in *HIV Medicine* in July 2005 (Volume 6, Supplement 2). Only the 'What to start with' and 'Treatment-experienced patients' sections have been completely rewritten. The tables of recommendations (Tables 1–7) have also been updated to include new data. Please refer to the full guidelines for more information.

Adherence

Since the last version of these guidelines there have been few new data relating to adherence to medication in general, or to highly active antiretroviral therapy (HAART) in particular. Studies continue to support a role for brief interventions including treatment-related education and individualized adherence problem-solving in increasing adherence (at least over the following months) [1,2]. A study looking at using long-term partners to support adherence showed a marked beneficial effect on adherence in the short term, but this was not sustained at 6 months [3]. In the Gilead 934 study, although adherence (measured by pill count) was statistically significantly higher in the once-daily arm vs. twice-daily, the clinical difference was small (3%) and may have arisen because of the poorer tolerability of the twice-daily arm rather than because of any benefit of once-daily dosing [4].

Research in the USA examined the costs in real terms of delivering a variety of adherence interventions over the first year of patient support. The majority of interventions were delivered by nurses. Median direct annual cost was $420 (range $60–700) per patient; 66% of this was attributed to staffing but this also included $72 per annum for patient incentives, which are unlikely to be deployed in the UK. Although it is difficult to extrapolate these costs to NHS services in the UK, the absolute cost of adherence interventions appears to be relatively low, and slightly less than that of a genotype resistance test [5].

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When to start treatment

Primary HIV infection

No new data have emerged in the past year to change the view of the Committee that, if antiretroviral therapy is started in the context of primary HIV infection, it should normally only be in the setting of a clinical trial (e.g. the MRC SPARTAC study [6]).

Established HIV infection

Decisions on when to start treatment are based on an assessment of the risk of disease progression over the medium term if treatment is not started (e.g. using data from the CASCADE collaboration [7]), vs. the potential risks of starting treatment earlier (toxicity and resistance). The risk of disease progression is determined largely by the CD4 cell count, plasma viral load and the age of the patient. No new data have emerged since the previous guidelines to alter the Committee's view that treatment should start before the CD4 cell count has fallen to below 200 cells/μL. This is because of the higher risk of death or disease progression in patients who delay starting treatment until their CD4 cell count has fallen to this level, and the reduced efficacy of HAART when introduced at a count of <200 cells/μL in some studies. The implication of this is that earlier diagnosis of infection remains paramount; this is only likely to be achieved by much more widespread and normalized use of HIV antibody testing [8]. In patients with counts above this level, the risk of disease progression without therapy should be considered. Therapy should be started if the patient wishes to start, the medium-term risk

of disease progression is high (e.g. > 2–4% in 6 months) and the likelihood of harm as a result of drug toxicity or the selection of resistant virus is considered to be low. This is likely to mean that the majority of patients with CD4 counts > 350 cells/μL should continue to defer treatment. Although cohort studies [9–11] have consistently shown that the risk of disease progression in this group tends to be lower for up to several years if therapy is started earlier, this is at the cost of significant drug toxicity, necessitating drug switching or stopping therapy in a significant minority [9], and the absolute risk of disease progression in this group remains very low. Other cohort studies (albeit in patient groups using regimens that might not be recommended currently [12,13]) have demonstrated that selection of drug-resistant virus occurs in 25% of patients after 2–3 years, suggesting that deferral of initiation may preserve future treatment options.

Patients randomized to the drug conservation (DC) arm (i.e. intermittent therapy) of the SMART study [14] had a significantly increased risk of opportunistic infection or death after 16 months of follow up compared to those in the virological suppression (VS) arm (i.e. continuous therapy). Importantly, this benefit was seen across all CD4 cell count strata, not only in those with a nadir CD4 count of < 350 cells/μL. These data have been interpreted as evidence that drug treatment should be started at an earlier stage than is currently the case. However, analyses of the relative rates of disease progression in the two arms indicate that the absolute risk of disease progression remains relatively low in the DC arm of the study (approximately 2% per year compared to 1% in the VS arm). This is consistent with existing data from cohort studies, and as such does not provide convincing evidence to change the recommendations of the 2005 guidelines. Rather, this reinforces the evidence that there is a continuous increase in the risk of disease progression and death in untreated patients as the CD4 cell count falls, and that decisions on starting therapy need to be individualized, taking into account the specific circumstances and risks present in each patient. Patients in the DC arm were also found to have much higher rates of cardiovascular, renal and hepatic disease than were seen in the VS arm. If this phenomenon is attributable to the effect of untreated HIV infection, this would be a further argument for earlier therapy. As the tolerability and toxicity profiles of initial therapy improve and the risk of selecting resistant virus with initial therapy falls [15], it will increasingly become reasonable to consider starting therapy earlier than previously (i.e. earlier in the CD4 count range 200–350 cells/μL, and above counts of 350 cells/μL in selected patients, such as older patients, those with higher viral load, and those with other comorbidities such as hepatitis B or C virus infection).

What to start with

There is overwhelming evidence from cohort studies that the very dramatic fall in AIDS-related mortality and frequency of AIDS events seen in the developed world over the last 10 years coincides with the introduction of HAART. Further improvements in treatment have led to fewer naïve patients now failing first-line therapy. Measurement of the success of a regimen is achieving a viral load of < 50 HIV-1 RNA copies/mL within 3–6 months of starting therapy and then maintaining this thereafter. Regardless of the baseline viral load, a level of 1000 copies/mL has been found to be achievable in the majority of people by 4 weeks from start of therapy. Failure to achieve this is strongly associated with failure to reach viral load below 50 copies/mL within 24 weeks. A viral load above 1000 copies/mL measured 4 weeks after the initiation of therapy therefore should prompt questions over possible poor adherence or other reasons such as reduced drug levels or primary drug resistance.

HAART regimens should be individualized in order to achieve the best potency, adherence and tolerability; to minimize potential long-term toxicity and to avoid any likely drug–drug interactions. The cost of the regimen should also be considered.

Which HAART regimen is best?

Previous guidelines have been hampered by the paucity of published data to definitively inform whether HAART based around a non-nucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI) regimen is preferable. Moreover, there have been only limited data on comparative efficacy among boosted PIs.

Studies have shown the superiority of efavirenz (EFV)-containing regimens over nelfinavir (NFV)-, boosted saquinavir (SQV)- and boosted amprenavir-containing regimens [16–18]. A recently presented controlled trial comparing a currently recommended boosted PI [ritonavir-boosted lopinavir (LPV/r)] with EFV in naïve patients has demonstrated on intention-to-treat (ITT) analysis the superiority of an EFV-based HAART regimen over 96 weeks [19]. This resulted from a lower rate of virological failure in the EFV arm, with no significant difference between the arms in treatment-limiting toxicity. Less class-emergent resistance and improved immunological response was, however, seen in the boosted LPV arm. In addition, a 48-week study comparing LPV/r with ritonavir-boosted fosamprenavir (FOS/r) has demonstrated the noninferiority of twice-daily FOS/r at all CD4 cell count and viral load strata [20].

It is important to select the regimen best suited to the individual patient, and therefore to fully assess baseline

risk factors for resistance, hepatitis B/hepatitis C virus coinfection, cardiovascular disease, diabetes, and psychiatric disease. In addition, lifestyle issues including smoking, obesity, alcohol use, and recreational drug use should be taken into account, as well as gender and the potential for pregnancy. The advantages and disadvantages in terms of potency, convenience, toxicity, salvageability and potential drug–drug interactions are discussed below.

In view of these recently presented data, the Committee recommends that EFV-based HAART should ordinarily be the first-line choice for naïve patients. However, it must be emphasized that any drug combination must be tailored to the patient and, in many instances, including primary reverse transcriptase resistance, a boosted PI is preferable. This therefore remains a recommended alternative option.

With a second wave of drugs within the PI and NNRTI classes as well as novel target classes currently in Phase III/IV studies, we believe that patients should continue to be informed about and encouraged to participate in available clinical trials to further answer these questions.

Two nucleoside reverse transcriptase inhibitors (NRTIs) plus an NNRTI

NNRTI-based regimens have now been extensively studied with good durability data available for EFV beyond 3 years [21,22]. They have the advantages of convenience and lack of long-term toxicity and EFV is the preferred NNRTI for initial therapy. However, EFV is not a drug that is well tolerated by all patients and the side-effect profile needs to be carefully explained to each patient before starting therapy. Three per cent of patients may experience extreme disorientation including paranoia, nightmares and suicidal ideation, and discontinuation rates of 10–20% have been reported over time in clinical practice. Nevirapine (NVP) is the alternative NNRTI but is associated with a worse toxicity profile.

EFV (preferred regimen)

In many randomized controlled trials, EFV has demonstrated improved virological efficacy when compared to other treatment regimens including PI-, boosted PI-, NVP- and 3NRTI-based regimens.

In the 2NN study [23,24], data were obtained to compare EFV and NVP in a randomized manner and showed that they were comparable in potency. Equivalence was not formally proven, with a small chance that NVP was superior to EFV and a greater chance of the reverse. However, the principal reason for the recommendation of EFV as the preferred NNRTI is related to toxicity in the NVP arm.

The major limitation of EFV, as for all currently available NNRTIs, is the low genetic barrier to resistance. This is becoming a major concern because of the continuing and, in some countries/groups, increasing incidence of primary resistance. A single mutation is sufficient to confer resistance to EFV (leading to the loss of currently licensed drugs in this class in future regimens), although not to the second-generation NNRTIs currently under evaluation in Phase III/IV studies. NNRTI resistance is also almost always accompanied by the emergence of nucleoside mutations, limiting options for this class as well.

The major side effect of EFV is dysphoria, which needs to be discussed in detail with the patient prior to commencing the drug. Manifestations include vivid dreams and/or nightmares, sleep and mood disturbance, drowsiness and disorientation. Most are mild–moderate and self-limiting and can be managed with a short course of hypnotics: it is unusual for patients to discontinue the drug for this reason within trials. Nevertheless, in a small minority, symptoms persist and may be severe enough to warrant switching to an alternative agent. The evidence is conflicting as to whether or not side effects are more common in individuals with a previous psychiatric disturbance [25]. Rashes do occur, but severe rashes with EFV are unusual (the incidence of Stevens–Johnson syndrome is 0.1%). Similarly, hypersensitivity hepatitis occurs (3.4% in the 2NN study) but fulminant hepatitis is exceptionally rare. Lipid abnormalities, mainly rises above baseline values in total and low-density lipoprotein (LDL) cholesterol, are not infrequently observed in patients on EFV-containing combinations [23].

EFV may be teratogenic and there have been four retrospective reports of neural tube defects in mothers taking EFV in the first trimester. Such defects have not been described in prospectively collected data and the relative risk of its use in early pregnancy remains uncertain [26]. Nevertheless, women of childbearing age should be warned about becoming pregnant whilst on EFV and, wherever possible, it should be avoided in women who may contemplate pregnancy.

EFV has a long half-life when compared with nucleosides and it is important to maintain viral suppression for a period after discontinuation to prevent functional monotherapy and the emergence of resistance. This can be achieved by either continuing the nucleosides or substitution of a boosted PI. The optimal duration of staggered discontinuation is undetermined but is longer in certain ethnic groups and may range from 1 to 3 weeks.

NVP (alternative regimen)

As discussed above, NVP has been compared with EFV in the 2NN study and has been shown to be of comparable potency. In this study, however, there was more serious toxicity in the NVP arm, with two drug-related deaths, one from liver failure and one from methicillin-resistant *Staphylococcus aureus* septicaemia in a patient with Stevens–Johnson syndrome.

The major side effects are rash and hepatitis. The rash is usually mild and self-limiting but may occasionally manifest as Stevens–Johnson syndrome (incidence 0.3%) with rare fatalities. The rash is not reduced by the coadministration of steroids, which should be avoided [27]. Hepatitis is an infrequent side effect that occurs in the first 6 weeks of therapy but fulminant liver failure and deaths have been reported. Recent analyses have shown a 12-fold higher incidence of symptomatic hepatic events in women with CD4 counts >250 cells/μL (11% vs. 0.9%) and a 6-fold higher incidence in men with CD4 counts >400 cells/μL (8% vs. 1.2%) and this drug should be avoided in these patients, as well as those with active hepatitis B or C virus infection or patients with elevated liver function tests at baseline. NVP is currently used twice a day, but the pharmacokinetics and now clinical trial data indicate that once-daily dosing is possible, although this leads to more abnormalities of liver function [23].

Based on these data, NVP is not now recommended as a preferred regimen in patients starting HAART, but should be used in patients in whom other regimens would have disadvantages (e.g. women desiring to become pregnant and possibly those with a previous psychiatric history) and only within the CD4 cell count recommendations. It remains a well-tolerated drug with no adverse effect on lipids, and, when used within the restrictions above, the risk of hepatotoxicity is probably extremely low. There are also cost benefits of NVP over EFV. A 14-day lead-in period of 200 mg daily should be prescribed before increasing to twice-daily dosing unless switching directly from EFV. The same recommendations apply when discontinuing NVP as apply for EFV.

Delavirdine – not recommended

Delavirdine is currently unlicensed in the UK and is not recommended.

Two NRTIs plus a boosted PI

The dramatic decline in clinical progression and HIV-related deaths followed the introduction of the PI class of antiretrovirals. These agents have shown clinical and surrogate marker efficacy in clinical practice, with a possible enhanced rise in CD4 cell count over NNRTIs in naïve patients. Sustained suppression of plasma HIV-1 RNA levels has been observed with more than 7 years of continued immunological recovery in patients treated with a boosted PI. There is now enough data to recommend that if a PI is chosen as part of an initial HAART regimen then, with few exceptions, this should be a boosted agent. This is because ritonavir (RTV) boosting increases drug exposure and prolongs the drug half-life, thereby reducing pill burden and dosing frequency, and optimizing adherence. It also limits the development of resistance. The disadvantage of this approach is a possible risk of greater lipid abnormalities, particularly raised fasting triglycerides.

In randomized studies, the development of resistance in patients failing therapy has been shown to be higher in those starting with NNRTI or unboosted PI regimens compared with those starting with boosted PIs [28,29]. This was evident in the class comparison study between boosted LPV and EFV where, of those viruses sequenced in patients with virological failure, NNRTI and primary PI mutations were 48% and 4%, respectively, with NRTI mutations being twice as frequent in the NNRTI arm (33 vs. 15%) [19]. The Committee recommends LPV/r or FOS/r dosed twice daily as the preferred regimens, with alternatives to include boosted SQV (hard gel capsule or film-coated capsule) or boosted atazanavir (ATZ).

LPV/r (preferred regimen)

Data from the original licensing study [30] showed superior surrogate marker endpoint for patients using LPV/r when compared to NFV, with lower numbers of patients discontinuing for side effects. Additionally, patients randomized to LPV/r who developed virological failure had no evidence of PI resistance. The main side effects of this regimen are lipid abnormalities and gastrointestinal side effects, with diarrhoea being the predominant symptom. The new formulation of LPV/r tablet is now available with lower pill burden, no food requirement and less interpatient pharmacokinetic variability, and does not need refrigeration.

FOS/r (preferred regimen)

Boosted FOS has been compared as once-daily dosed 1400 mg/200 mg to NFV (SOLO) and as twice-daily dosed 700 mg/100 mg to boosted LPV (KLEAN) in clinical studies in naïve patients [20,31]. Against NFV, there was no overall difference in the surrogate marker endpoint of <400 copies/mL (69% in the FOS/r arm vs. 68% in the NFV arm) although significantly more patients with viral loads $\geq 100\,000$ copies/mL and randomized to RTV-boosted fosamprenavir achieved viral load suppression. Findings from the KLEAN study show FOS/r to be noninferior to LPV/r (66% of those randomized to FOS/r and 65% of those randomized to LPV/r had viral loads <50 copies/mL at 48 weeks on ITT analysis). Virological failure was low (3.7% in the FOS arm vs. 5.4% in the LPV arm) and no major PI mutations were identified. Data from the SOLO study have also demonstrated that boosted FOS shows durable responses to 120 weeks in naïve patients with only one case of emergent PI resistance reported to date.

This regimen has a low pill burden and flexible dosing, with the same tolerability and level of dyslipidaemia as boosted LPV. It is licensed in the UK to be dosed twice daily.

SQV-r (alternative regimen)

Boosted SQV has demonstrated potency in once- and twice-daily schedules. It has been compared as a twice-daily dose to RTV-boosted indinavir (IDV-r) [32] and LPV/r [33], where approximately one-third of patients were drug-naïve. By the protocol-defined primary endpoint of time to virological failure, LPV/r was superior to SQV/r and SQV/r was superior to IDV/r. With the advent of the 500 mg film-coated tablet, RTV-boosted SQV has a relatively low pill burden (three tablets twice daily), and represents a well-tolerated alternative to RTV-boosted LPV in naïve patients, with possibly less gastrointestinal toxicity. Again, lipid abnormalities may represent a potential long-term toxicity issue. The once-daily dose is not licensed in the UK and SQV/r should be used twice daily. This advice may change pending the results of clinical trials.

RTV-boosted or unboosted ATZ (specific groups)

Unboosted ATZ has been shown to have similar efficacy to NFV and EFV in three clinical studies [34–36]. A fourth study comparing boosted and unboosted ATZ demonstrated no difference on ITT analysis at 48 weeks, although there were more virological failures in the unboosted arm [37]. ATZ/r has also been shown to have similar efficacy to LPV/r in PI-experienced patients.

The main advantages of ATZ/r are that the drug is dosed once daily and has fewer adverse effects on lipids than other boosted PI regimens. Its main side effect is hyperbilirubinaemia with or without jaundice, but this is not associated with liver enzyme changes and seldom results in the need to discontinue treatment. It is not licensed in the UK for naïve patients. A disadvantage is the interaction of ATZ with acid-reducing agents, notably protein-pump inhibitors. This is not overcome by RTV boosting, and where alternative agents cannot be used, atazanavir should be avoided. The Committee feels that use of this drug should be boosted in naïve patients and restricted to those with established cardiovascular risk factors and where a PI is required. This advice may change pending the results of clinical trials.

Three NRTIs

There is now surrogate marker endpoint data suggesting that zidovudine/lamivudine/abacavir (ZDV/3TC/ABC, usually combined as Trizivir) is less potent than the combination of two NRTIs with either an NNRTI or a PI. In ACTG 5095, the Trizivir arm was less potent than the other two arms (Trizivir/EFV or Combivir/EFV). This finding was found both at high and low entry viral loads. The Committee now feels that Trizivir should only be considered as a starting regimen in very occasional circumstances, for example informed patient choice based on likely poor adherence if alternative options are used, or concomitant medication needed such as for tuberculosis. Nonthymidine-containing 3NRTI regimens [e.g. ABC/3TC/tenofovir (TDF) or didanosine (ddI)/3TC/TDF] should not be used because of unacceptably high rates of virological failure [38,39]. Currently, no triple-NRTI regimen can be recommended. However, data suggest that ZDV/3TC/TDF with or without ABC is a possible option when a PI- or NNRTI-based HAART cannot be administered.

Choice of 2NRTIs (include nucleoside and nucleotide RTI) (Table 4)

Two NRTIs remain an integral component of HAART with either an NNRTI or an RTV-boosted PI. There is no evidence that a third NRTI provides additional benefits and two-class NRTI-sparing combinations are associated with more discontinuations because of toxicity and resistance. There are now seven NRTI analogues (zalcitabine having been withdrawn), and four NRTI coformulations. The availability of two new fixed-dose combinations [Truvada (TDF/FTC) and Kivexa (ABC/3TC)] in addition to ZDV/3TC has led to the majority of patients who are naïve to medications being prescribed one of these as their 2NRTI backbone. With increasing emphasis on short-term tolerability, convenience, absence of long-term toxicity, and cost, there are merits and limitations of each coformulated 2NRTI backbone, which are discussed below. Pretreatment drug resistance will also influence the choice of NRTI backbone, although currently there is no discernible increase in the UK in the rate of NRTI mutations in recently infected patients.

Coformulated 2NRTIs

ZDV/3TC (coformulated as Combivir) is the most studied of the dual NRTI backbones and has, until recently, been the most popular 2NRTI combination in the UK [40]. When combined with EFV, it has similar virological efficacy to ABC/3TC at 48 weeks [41]. However, in the Gilead 934 study, coformulated ZDV/3TC was compared with individually dosed emtricitabine (FTC)/TDF with EFV as the third agent. Ninety-six-week results demonstrated a significantly higher frequency of patients with virological rebound greater than 400 copies/mL (5 vs. $<1\%$) and adverse events leading to discontinuation in the ZDV/3TC arm (12 vs. 5%) [42]. In this study and the Gilead 903 study [22], TDF with either 3TC or FTC both dosed with EFV showed high and durable virological activity with good tolerability and minimal long-term toxicity. ABC/3TC is the third coformulated compound (Kivexa) and has been shown to give effective lasting virological control. In

studies where the third drug was either EFV or a boosted PI, the proportion of patients who failed virologically was 4–10% at 48 weeks [20,41,43]. For both Truvada and Kivexa, the individual components have been shown to be bioequivalent with the fixed-dose combinations [44]. Higher CD4 cell counts at 48 weeks have been demonstrated with both TDF/FTC and ABC/3TC when compared to ZDV/3TC. All three NRTI combinations perform well virologically.

Most clinician experience is of twice-daily ZDV/3TC. However, because of the increasing evidence implicating longer term use with lipoatrophy, the Committee believes it is essential to carefully monitor for this complication in patients who receive ZDV, possibly with dual energy X-ray absorptiometry (DEXA) scanning, with a switch to an alternative NRTI as soon as there is any subjective or objective indication of its development.

TDF with either 3TC or FTC has a better tolerability/toxicity profile than ZDV, including less dyslipidaemia. Because of isolated reports of renal tubular damage and an association between related compounds and nephrotoxicity, concern has been raised about possible long-term renal toxicity with TDF. Numerous studies, including clinical trial, observational cohort, and expanded access data, have identified serious renal toxicity in approximately 0.5% of patients, a rate no different to that observed with comparator NRTIs [45–47]. However, other studies have demonstrated a small but significant reduction in renal function over time when compared to other nucleosides [48,49]. It is clear that TDF should be used cautiously in patients who have, or are at risk of developing, renal disease, including those coprescribed potentially nephrotoxic agents. Moreover, blood biochemistry and urinalysis should be performed prior to initiating TDF with regular monitoring throughout treatment. However, in this management context, the Committee feels that TDF is a safe and effective NRTI. When using TDF as first-line therapy, the K65R mutation has been observed in a minority of patients receiving EFV/TDF/3TC. In the Gilead 903 study, this mutation occurred in 2.4% at 48 weeks (overall virological failure rate 9.7%). This was mainly observed in those with CD4 counts of <50 cells/μL and viral loads $>100\,000$ copies/mL: K65R has not been observed in patients with pretreatment wild-type virus when receiving LPV/r/TDF/FTC to 48 weeks and EFV/FTC/TDF to 96 weeks [4,50]. The generation of this mutation and M184 V will also be influenced by the third drug choice (NNRTI or boosted PI).

ABC/3TC is generally well tolerated but a hypersensitivity reaction (HSR) may occur in the first 6 weeks (median 11 days from drug commencement) and all patients need counselling. It has been identified in approximately 8% of naïve-patient studies and is independent of dosing frequency. These studies used a case reporting form (where HSR was also reported in 3% of ZDV-treated patients in a double-blind study) and the summary of product characteristics (SPC) states an HSR rate of 5.4%. Pharmacogenetic analysis has identified a close association between HSR and carriage of the class 1 HLAB*5701 allele, which to a large extent explains the racially defined differences in susceptibility [51]. Absence of this allele has a high negative predictive value for HSR in predominantly Caucasian populations [52]. The prospective use of this test in clinical practice has been shown to significantly decrease the rate of HSR from approximately 5–8% to <1–2%, although its utility remains to be proven in a randomized clinical trial and in racially diverse populations. Consequently, many centres are now routinely screening and avoiding ABC in patients with the HLAB*5701 allele. Although undeniably of significant benefit in reducing the likelihood of HSR, the Committee feels that there are still only limited and nonrandomized data on its use in clinical practice and that the emphasis remains with patient counselling and physician vigilance. There is no evidence of longer term toxicity with ABC to date, although dyslipidaemia is greater than with ZDV. The L74 V mutation is seen in <1% at 48 weeks in patients on EFV/ABC/3TC or a boosted PI (overall virological failure rate 4.0–9.9%) [20,41]. Both K65R and L74 V mutations can lead to difficulties in choice of subsequent NRTI drugs if they develop.

In summary, these three NRTI backbones offer good antiviral efficacy and can all be recommended. When combined with EFV, TDF/FTC leads to fewer outcome failures than ZDV/3TC, a difference driven mainly by ZDV-related toxicity in the first 24 weeks. Complicating lipoatrophy with long-term ZDV is also an important factor in choice of backbone NRTIs. Use of ABC/3TC is likely to increase with prospective screening for HLAB*5701, but a negative test does not rule out the possibility of HSR, and the need for careful counselling and monitoring for ABC HSR remains. Ongoing monitoring for long-term toxicity and resistance development with all three fixed-dose combinations is important, particularly for TDF/FTC and ABC/3TC, where experience is still limited by comparison to ZDV/3TC. The relative costs of the individual NRTIs is becoming an increasingly important factor in defining treatment pathways in naïve patients; these are given in Table 1.

Other 2NRTI combinations

Stavudine (d4T)/3TC is a well-studied nucleoside combination with equal antiviral effectiveness to TDF/3TC and ABC/3TC but with significantly greater mitochondrial toxicity, including peripheral neuropathy and lipoatrophy [22,53]. Because of this, d4T is not recommended for initial therapy. TDF/ddI is a once-daily two-tablet combination. However, all studies where this 2NRTI backbone has been used with an NNRTI as the third agent have demonstrated an unacceptably high

Table 1 Cost of preferred regimens as per Table 4, showing the monthly (30-day) cost as set out in list price (May 2006) + VAT at 17.5% in £

Column A	Cost (£)
NNRTI	
EFV	245
NVP	188
PI/r	
LPV/r	361
ATZ/r[1]	411
FOS/r[2]	402
SQV/r[2]	393
IDV/r[2†]	256
TPV/r[4*]	734
PI	
ATZ 300 mg	371
NFV	321
NRTI	
ABC	261‡
Entry inhibitor	
T20*	1349

r[1], r[2] or r[4] indicates the number of ritonavir capsules per day.
*For experienced patients only.
†Not a preferred regimen but recognized potential cost savings.
‡Trizivir® £635.
ABC, abacavir; ATZ, atazanavir; IDV, indinavir; EFV, efavirenz; FOS, fosamprenavir; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, ritonavir; SQV, saquinavir; TPV, tipranovir; T20, enfurvitide.

Column B		Column C		
NRTI-1	Cost (£)	NRTI-2	Cost (£)	Total cost
ZDV 250 mg	196	3TC†/FTC		375/388
TDF	300			179/192
ABC	261			479/492
ddI 400 mg	192			440/453
D4T 40 mg*	201			371/384
Combivir®				380/393
Truvada®				374
Kivexa®				492
				439

*d4T/3TC is as effective as other regimens but more toxic and not a preferred regimen.
†150 mg tablets.
ABC, abacavir; ddI, didanosine; d4T, stavudine; FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitor; 3TC, lamivudine; TDF, tenofovir; ZDV, zidovudine.

failure rate, with the development of early resistance, which was more marked in patients with more advanced disease [54]. There is also potential for TDF to potentiate ddI-related toxicity. The combination is not recommended. ddI/3TC or ddI/FTC as a 2NRTI combination is well tolerated and effective [55]. However, ddI-related restrictions on food and the potential for long-term mitochondrial toxicity make this choice less popular. ZDV/ddI was a common 2NRTI combination prior to HAART. However, no data exist with ZDV/enteric-coated ddI in HAART. Similarly, TDF/ABC and ABC/ddI have not been evaluated in naïve patients: none of these 2NRTI combinations can be recommended.

Conclusions

Most clinicians in the UK favour an NNRTI-based regimen for initial therapy, reserving boosted PIs for later. This is based on the perceived low risk of toxicity, the ease of administration, and the genetic frailty of an NNRTI in patients failing a boosted-PI HAART. The recently presented controlled trial comparing boosted LPV with EFV, which demonstrated the superiority of an efavirenz-based HAART regimen, provides support for this practice. Moreover, there is cost benefit in selecting an NNRTI-based regimen rather than most boosted PIs, which needs to be taken into account. Therefore, the Committee recommends that EFV-based HAART should ordinarily be the first-line choice for naïve patients. However, for some a boosted PI will be preferable and therefore boosted LPV and FOS remain alternative recommended drugs. It is anticipated that clinicians will favour one of the three coformulated NRTI drugs. They offer excellent antiviral efficacy with a demonstrable benefit of TDF/FTC over Combivir. They differ in dosing schedule, tolerability, short- and long-term toxicity, and cost. Above all, choice should be tailored to the individual patient.

Treatment-experienced patients

Data from the Health Protection Agency indicate that, among treatment-experienced patients, NNRTI resistance has remained relatively stable in recent years, whereas NRTI and PI resistance has declined. The number of individuals infected with triple-class-resistant viruses has fallen from a peak of around 15% in 1999–2001 to around 8% in 2003–2004 [57].

When to switch

The goals of treatment for the majority of treatment-experienced patients have changed, and the new paradigm should be aiming for an undetectable and durable HIV plasma viral load supression, wherever possible, leading to immunological improvement with lack of clinical progression and improvement in quality of life. This may not be possible for a minority of heavily pretreated patients with virological failure and multiple mutations. In this setting, the goal should be maintaining quality of life by preserving if not improving immunological status. In so doing, we should still aim to optimize viral suppression and impaired viral fitness. If not previously examined, reasons for virological failure should be explored and managed accordingly.

The key considerations in the choice of HIV therapy include treatment history, comorbid conditions, tolerability,

adherence, drug–drug interactions, resistance testing, current and future available treatment options, and the clinical status of the patient.

In treatment-experienced patients with therapy options there are data suggesting that switching as soon as possible is more likely to be successful in terms of achieving an undetectable viral load when the CD4 cell count is higher and viral load lower. When there are few drug options, it may be better to maintain the patient on a failing regimen which maximizes the fitness effect and has minimal side effects.

What to switch to

The patient with therapy options

In treatment-experienced patients with therapy options, the physician should construct a new HIV treatment which includes at least two (or preferably three) active agents guided by HIV resistance testing and by the patient's previous antiretroviral (ARV) history. The use of an agent from a new drug class is likely to be more effective [56–58]. The available data for enfuvirtide (T20) show that it is most effective when used with other drugs to which the patient is susceptible, based on resistance testing and antiviral experience. When used as the only effective agent, resistance to it occurs within weeks and a future opportunity for constructing an effective regimen is lost. If tipranavir (TPV) or darunavir (TMC114) is used in a similar way, then the regimen is less effective than in combination with other effective drugs such as T20. In the Toro 1 and 2 combined analysis of LPV/r-naïve patients, the percentage reaching less than 400 copies/mL doubled from 30 to 60% at 24 weeks if T20 was used. In the combined analysis of TPV/r patients in the RESIST study, the percentage reaching less than 400 copies/mL went from 30 to 54% at 24 weeks if T20 was used, and in the combined analysis in the POWER1 and POWER2 studies of TMC114/r-naïve patients the percentage reaching less than 50 copies/mL increased from 46 to 64% at 24 weeks if T20 was used [59,60].

Although these studies had different designs and entry criteria they underline the principle that new regimens should contain two or more fully active drugs. However, this strategy may not be a realistic option when managing some highly treatment-experienced patients.

The patient with few or no therapy options: continue, interrupt or change therapy?

Continue? In treatment-experienced patients with few or no therapy options, especially if the CD4 cell count is well maintained, it may be better to wait to change treatment until an investigational agent is available that will increase the likelihood of constructing a virologically suppressive and durable regimen. Several drugs that have activity against currently resistant viruses are in a late phase of development and will be used to create an effective drug combination.

Even partial virological suppression of HIV RNA $>0.5\log_{10}$ copies/mL from baseline correlates with clinical benefits [61], although this must be balanced with the ongoing risk of accumulating additional resistance mutations. There is good evidence that continuing therapy, even in the presence of viraemia without CD4 cell count increases, reduces the risk of disease progression [62]. Other cohort studies suggest continued immunological and clinical benefits if the HIV RNA level is maintained at 10 000–20 000 copies/mL [63,64].

Virological failure on continuous antiretroviral therapy is associated with variable changes in CD4 cell counts which appear to correlate with the replicative capacity of the virus, its ability to induce apoptosis in both infected and uninfected CD4 cells, and its use of CXCR4 vs. CCR5 receptor for entry [65]. There is currently no test that can predict CD4 cell count responses in individual patients continuing a failing regimen. The replication capacity assay provides only a partial measure of the multiple factors that influence virus fitness and pathogenicity.

Once resistant virus has become established as the dominant species, the emergence of further resistance mutations detectable by routine genotypic testing is widely believed to occur slowly. In one study of patients with viral load >200 copies/mL, the average increase per year in the number of mutations was 0.5 for reverse transcriptase (RT) mutations, 0.2 for major PI mutations and 0.3 for minor PI mutations [66]. Within the SCOPE clinical cohort, however, among persons with viral load >1000 copies/mL while on stable therapy, as many as 44% accumulated at least one new mutation at year 1, and 30% lost at least one active drug [67]. The highest risk for the emergence of further mutations is in persons who initially have limited resistance. Conversely, in some patients with multiple mutations a genetic deadlock may be achieved that limits further evolution of resistance. However, the majority of patients keep accumulating new resistance mutations, including mutations present only as minority variants that escape detection by routine testing.

A 'V-shape' relationship exists between the number of mutations and viral load in the setting of treatment failure. Above a certain threshold, the number of mutations is associated with increases in viral load, reflecting compensatory changes that improve virus fitness and pathogenicity [68]. Variants with compensatory changes may carry mutations in several regions of the HIV genome and do not necessarily display further increases in drug resistance [69].

Table 2 Recommendations for starting treatment

Presentation	Surrogate markers	Recommendation
Primary HIV infection		Treatment only recommended in a clinical trial, or if severe illness (CIV)
Established infection	CD4 <200 cells/μL, any viral load	Treat (AI)
	CD4 201–350 cells/μL	Start treatment, taking into account viral load (BIII), rate of CD4 decline (BIII), patient's wishes, presence of hepatitis C (CIV)
	CD4 >350 cells/μL	Defer treatment (BIII)
Symptomatic disease or AIDS	Any CD4 count or viral load	Treat (AI)

Please refer to the full guidelines for further information (*HIV Med* 2005; 6 (Suppl. 2): 1–61).

Table 3 Comparison of boosted protease inhibitors (PIs)

	Lopinavir/ritonavir	Saquinavir/ritonavir	Fosamprenavir/ritonavir	Atazanavir/ritonavir
Potency naives	+ + + +	+ + +	+ + + +	+ + +[§]
Durability data	+ + + +	+ +	+ + +	+ +
Convenience	+ + +*	+ + +[†]	+ + +	+ + + +
Tolerability	+ +	+ + +	+ + +	+ + + +
Lipid profile	+	+	+	+ + + +
Fat changes profile[§]	+ +	+ +	+ +	+ + +
Resistance barrier	+ + + +	+ + + +[‡]	+ + + +	+ + + +[‡]
Interaction profile	+ + +	+ +	+ + +	+
Active against resistant virus	+ + + +	+ + +[§]	+ + +	+ + +

+ + + +, excellent; + + +, very good; + +, moderately good; +, not good.
*Tablet formulation.
[†]500 mg tablet.
[‡]Limited data in naïve patients. However, the Committee feels that there is sufficient evidence available for boosted PIs to allow careful extrapolation of data.
[§]Limited data available.

In addition, under prolonged drug-selective pressure, mutations initially present on separate virus variants can accumulate on the same viral genome. Such linkage cannot be detected by standard genotype analysis [70].

Taken together, these observations indicate that continuing a failing regimen can be deleterious and should be reserved only for those patients lacking effective treatment options and maintained for the shortest period possible pending the availability of new treatments.

Treatment interrupt? Until recently, treatment interruptions were used as one experimental strategy for these patients. Four studies confirm that interrupting treatment in an effort to revert to wild type prior to initiation of a salvage regimen is not associated with significant durable benefits [71–74]. Instead, it may be associated with a rapid increase in HIV RNA, loss of CD4 cells or clinical disease progression. The OPTIMA study, which addresses the issues of the optimal number of drugs and the benefits of treatment interruption, has now completed accrual. Pending these results, total treatment interruption cannot be recommended in the management of the treatment-experienced patient.

Change? Until investigational drugs that are effective against currently resistant virus are available, it might be possible to change the regimen and recycle drugs previously used or omit drugs from the treatment that are having little antiviral effect and/or contributing to side effects. Partially interrupting components of a treatment regimen may have a role to play in such heavily treatment-experienced patients and may reduce toxicity and potential for drug interactions.

Data from a small pilot study showed that interruption of PI treatment was associated with stable HIV RNA levels and waning of PI mutations. However, viral replicative capacity and HIV RNA levels eventually started to increase after long-term (more than 6 months) observation. In contrast, subjects interrupting their reverse transcriptase inhibitor treatment then experienced an immediate rise in HIV RNA. Interestingly, most subjects had a subsequent loss of the M184V mutation. These results suggest that NRTIs may retain direct antiviral activity against the resistant variant [75].

One controlled clinical trial including 3TC in a subsequent regimen after the development of an M184V mutation has shown no benefit, but was discontinued for futility [76]. However, 3TC retains antiviral activity even in the face of complete phenotypic resistance [77]. It was recently demonstrated that withdrawal of 3TC from a failing antiviral regimen led to an average increase of 0.5 $\log_{10}$ in viral load [78]. This adds further support to the notion that 3TC retains some of its activity even in the presence of genotypic resistance. If, on the basis of resistance testing, there are more potent NRTIs available, then these can be used with or instead of 3TC.

In those patients with no current active therapy options, 3TC may contribute to a salvage regimen even in the presence of high-level genotypic resistance. This situation has led to the possibility of treating patients with 3TC monotherapy. This strategy has only been used, however, in the setting of treatment failure in patients with the M184V mutation and CD4 counts of >500 cells/μL. Fifty-eight treatment-experienced patients harbouring 3TC-resistant virus were randomized in a trial comparing the immunological and clinical outcomes of 3TC monotherapy and complete therapy interruption. By week 48 in ITT analysis, immunological failure (CD4 count falling to <350 cells/μL) or clinical failure (grade B or C clinical event) occurred in 69% of persons (20/29) in the structured treatment interruption (TI) group and 41% of persons (12/29) in the 3TC monotherapy group. 3TC monotherapy significantly delayed CD4 cell count decline and reduced viral load rebound compared to TI, and only patients in the TI groups experienced clinical failure. Disappearance of resistant variants was reduced and replication capacity was significantly lower in the 3TC group, implying a beneficial effect of impaired viral fitness [79].

A judicious selection of maintenance therapy is required in these patients, guided by resistance testing as well as considerations of tolerability. Each case should be judged on its merits, but as general guidance: (a) it is preferable to select drugs to which the patient already shows extensive resistance; (b) attempts should be made at inducing or maintaining resistance patterns known to be associated with reduced viral fitness, including exploiting antagonisms between resistance pathways and potential hypersusceptibility effects; (c) the immunological efficacy of the regimen should be reviewed closely; (d) it should be understood that standard genotypic (and phenotypic) testing does not necessarily reflect virological changes that may impact on immunological success and the preservation of future treatment options.

It should be remembered that the strategy of using incompletely suppressive regimes will always be a short-term one. It is only relevant until a regimen likely to suppress viral replication completely can be found.

Resistance testing

Primary or transmitted resistance

There is extensive evidence for the transmission of drug-resistant variants among populations in Europe, with especially high rates of resistance to NRTIs and NNRTIs [80,81]. Current estimates from unselected cohorts in London indicate a prevalence of 7% overall and 16% among those born in the UK [82].

Table 4 Preferred regimens (choose one drug from columns A, B and C)

Regimen	A	B	C
Preferred	EFV LPV/r FOS/r	ZDV[§] ABC[¶] TDF[#]	3TC[§¶] FTC[#]
Alternative	SQV/r	ddI	
Specific groups	NVP* ATZ[†‡] ATZ/r[†‡]		

*Only when CD4 <250 cells/μL in female patients and <400 cells/μL in male patients.
[†]Where there are established cardiovascular disease risk factors and a protease inhibitor (PI) is required.
[‡]Currently unlicensed for naïve patients in the UK.
[§]Coformulated as Combivir®.
[¶]Coformulated as Kivexa®.
[#]Coformulated as Truvada®.
ABC, abacavir; ATZ, atazanavir; ddI, didanosine; EFV, efavirenz; FOS, fosamprenavir; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; r, ritonavir; SQV, saquinavir; 3TC, lamivudine; TDF, tenofovir; ZDV, zidovudine.

Testing for transmitted resistance continues to be recommended in all newly diagnosed patients. This includes patients with acute seroconversion, established infection or infection of unknown duration, regardless of demographic characteristics. The most appropriate sample is the one closest to the time of diagnosis.

The true risk of superinfection remains to be determined, but may be significant in persons with early infection who engage in high-risk behaviour. Following baseline resistance testing, repeat testing is not routinely recommended prior to starting therapy, although it may be considered in selected persons.

Resistance in treatment-experienced cohorts

Cohorts with detectable viral load while on HAART show a high prevalence of drug resistance [83]. A trend towards a declining rate of resistance has been observed in drug-experienced patients in the UK, as a result of improved management of antiretroviral therapy and treatment failure [84].

Resistance testing and interpretation

Current assays require a viral load of at least 500–1000 copies/mL to reliably provide a result. Although it is possible to obtain results at levels of only a few hundred copies/mL, the genotypes (and phenotypes) obtained are not necessarily representative of the dominant virus species and results can be misleading [85].

Routine resistance assays do not detect resistant viruses present at low levels (<20–30% of the total virus population), even if these resistant viruses were previously

Table 5 Changing therapy on first virological failure (BIII)

Presentation	Viral load pattern	Recommended action
Inadequate virological response to initial regimen	Failure to achieve viral load <50 copies/mL.	Consider factors affecting plasma drug levels.* If drug exposure optimal and likelihood of resistance low, consider augmenting treatment regimen. If likelihood of resistance high, consider changing all drugs.
Persistent viral load rebound where previously <50 copies/mL	Viral load >50 and <400 copies/mL. Sustained viral load rebound to >400 copies/mL.†	Consider factors affecting plasma drug levels.* Consider changing all drugs if effective option available likely to reduce viral load to undetectable levels. Continue regimen and monitor if no effective option currently available for reasons of drug potency, likely poor adherence or tolerability.‡

*Factors affecting plasma drug levels include poor adherence, intolerability, drug interactions and incorrect dosing.
†A viral load rebound to >1000 copies/mL will allow resistance testing to be performed. Resistance testing with expert interpretation has been shown to have a beneficial effect on short-term virological response to the subsequent regimen.
‡There is a risk of developing further mutations in allowing a patient to remain on a virologically failing regimen, which could limit further options for treatment.
Please refer to the full guidelines for further information (*HIV Med* 2005; 6 (Suppl. 2): 1–61).

dominant. Limited data indicate that minority resistant quasispecies including NNRTI resistance mutations and M184V may affect virological responses [86]. The prevalence of resistance mutations that impact on virological responses is not known and may vary for different mutations and antiretroviral regimens. Although assays to detect minority species have been developed, they are complex, not standardized and remain research tools only.

Current resistance assays target the reverse transcriptase, protease and gp41 regions of HIV. There is increasing evidence that other viral regions, including gag for the PIs and RNAseH for the NRTIs, play a role in drug resistance. In most cases these changes alone are not sufficient to confer resistance, but further evidence is awaited.

The interpretation of resistance test results is complex. Although informative interpretation systems based on clinical outcome measures have been introduced, none of the available interpretation systems is completely accurate and all are subject to change as more data become available. Interpretation of resistance tests is especially difficult with new drugs and this problem affects both genotypic and phenotypic resistance assays. Genotypic scores and 'clinical cut-offs' are being determined for a growing number of drugs, which correlate specific mutation patterns and viral phenotype with virological responses, respectively. Phenotypic cut-offs may vary depending on the phenotypic assay used. Most importantly, they reflect the treatment history and resistance patterns of the treatment-experienced cohort(s) from which they have been derived and rely heavily on complex statistical analysis.

There are subtype-specific treatment-associated mutations that have unknown effects on drug susceptibility. Overall, however, recognized mutations that confer resistance in subtype B also cause resistance in non-B subtypes and vice versa [87].

Therapeutic drug monitoring (TDM)

Large randomized prospective controlled trials remain a high priority to refine the population needing therapeutic drug monitoring (TDM) of NNRTIs/PIs and define the clinical benefit of this test. TDM has been shown to be beneficial in particular clinical scenarios where drug concentrations are difficult to predict, such as the management of drug interactions, the settings of pregnancy and paediatrics, salvage therapy settings when TDM and resistance test results can be integrated, cases of patients with renal or hepatic impairment and transplant patients, cases of toxicity, and the use of alternative dosing regimens whose safety and efficacy have not been established.

Clinical data supporting the use of inhibitory quotients are limited; however, these appear to be superior in predicting failure compared to drug concentrations or resistance testing alone in extensively pretreated patients commencing salvage regimens.

Metabolic complications

As the prognosis of HIV infection has markedly improved, so has our need to manage long-term morbidity associated with HIV and HAART.

Abnormalities of lipid homeostasis and fat distribution are likely to assume a central role in guiding choices for antiretroviral therapy. This is the result of the growing awareness of the increase of stigmatization and reduction of adherence associated with lipodystrophy, especially lipoatrophy, and of the increased cardiovascular risk associated with drug-induced metabolic abnormalities. Few prospective studies address the relative risk of different regimens causing the features of lipodystrophy, although ACTG384 suggests that the risks are greater with PIs than with NNRTIs and greater with d4T than with ZDV [88].

Table 6 What to change to after first virological failure: summary of recommendations (BII/IV)

Change all drugs if possible **Resistance test recommended**	
Initial regimen	**Options to consider**
2NRTIs + PI (with or without low-dose ritonavir)	2NRTIs*† + NNRTI or 2NRTIs* + boosted PI‡ or 2NRTIs* + NNRTI§ + boosted PI
2NRTIs + NNRTI	Boosted PI + 2NRTIs*
3NRTIs	2NRTIs*† + NNRTI or boosted PI + 2NRTIs* or boosted PI + 2NRTIs* + NNRTI§

*Change to two new and active NRTIs guided if possible by resistance testing.
†This could lead to rapid development of resistance to NNRTIs if the potential exists for NRTI cross-resistance.
‡Low-dose ritonavir-boosted PI should be considered if resistance to PIs is not found or limited.
§Studies with low-dose ritonavir-boosted PI + an NNRTI have shown good results.
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
Please refer to the full guidelines for further information (*HIV Med* 2005; 6 (Suppl. 2): 1–61).

Table 7 British HIV Association (BHIVA) Guidelines for the use of therapeutic drug monitoring (TDM)

Indication	**Recommendation**
Routine use	Not recommended. Insufficient data
Drug interaction	Recommended (BIII)
Liver impairment	Recommended (BIII)
Pregnancy	Recommended (BIII)
Minimizing toxicity	Recommended (BIII) for IDV, EFV and ATZ Consider (CIII) for other drugs
Monitoring adherence	Consider (CIII)
Virological failure	Consider (CIII)
Malabsorption	Recommended (BIII)
Unusual or unlicensed dosing regimens	Consider (CIII). Examples are once-daily boosted (LPV, SQV, APV, IDV) or unboosted (NFV) regimens
Children	Recommended (BIII)

APV, amprenavir; ATZ, atazanavir; EFV, efavirenz; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; SQV, saquinavir.
Please refer to the full guidelines for further information (*HIV Med* 2005; 6 (Suppl. 2): 1061).

Studies have shown a slow reversal of lipoatrophy when d4T and possibly ZDV are substituted by other drugs such as ABC and TDF. There are convincing data to suggest that avoiding PIs as first line, or switching from them, leads to a better lipid profile, a reduction in calculated risk of future cardiovascular events and possibly a reduction of insulin resistance. This class effect on lipids and insulin resistance does not apply to ATZ, and boosting with ritonavir does not appear to change this.

The application of current health promotion approaches to our patients should include assessments of cardiovascular risks and their appropriate management according to the most recent international guidelines, particularly as it has been suggested that HIV, because of its proinflammatory profile, might present a greater risk for the development of cardiovascular disease. Nonetheless, other considerations, such as toxicity and resistance, may outweigh potential cardiovascular risks, especially in therapy-experienced patients.

New drugs

This section is intended to cover only those drugs that are likely to be licensed before the next iteration of the guidelines.

Etravirine (TMC125)

This is a second-generation NNRTI which was developed because of its activity against viruses resistant to present members of the NNRTI class. Monotherapy studies have demonstrated a viral load drop of greater than 1 $\log_{10}$ over a 10-day period in naïve patients with a smaller fall in those with previous NNRTI experience. A Phase II study comparing TMC125 to a PI-based regimen in patients who had failed an initial regimen of two nucleoside analogues and an NNRTI and were PI-naive was discontinued at week 12 because of a higher virological failure rate in the TMC125 arm. Bioavailability has since been improved with a new formulation. In triple-class experienced patients, TMC125 was shown to produce an approximate 1 $\log_{10}$ drop in viral load at 48 weeks, with 30% of patients having a viral load less than 400 copies/mL compared with 8% treated with optimized backbone therapy alone. Antiviral response was inversely related to the number of NNRTI mutations, with no single mutation predicting high-level resistance. However, a range of double mutations in the NNRTI pocket was associated with reduced response, particularly when one of these was at codon 181. The side effects were few in these studies apart from an evanescent rash. At present this drug is given as two pills twice a day although it does have a long half-life and could be given as four pills once a day. TMC125 will be available on a compassionate release basis in the UK from October 2006.

Darunavir (TMC114)

This PI, which has a similar structure to amprenavir, was developed because of its *in vitro* activity against viral mutants resistant to many of the current members of the PI class. In Phase IIB studies (POWER 1 and 2) which have led to the licensure of this drug in the USA, TMC114 600 mg twice daily boosted by ritonavir was shown to be the optimum dose. In these studies of triple-class experienced

patients, many of whom had viruses resistant to all the presently available PIs, 46% of patients in the TMC114 arm had virological undetectability at 48 weeks (<50 copies/mL) compared to 10% in the comparator boosted-PI arm [88]. The rates of undetectability were related to the number of sensitive drugs (including T20) that the patients received concomitantly and the phenotypic sensitivity to TMC114 at the start of the study. Lipid abnormalities and other side effects were similar to those seen in the optimized background regimen. On virological failure of TMC114, the majority of isolates sensitive to TPV at baseline remained sensitive to this drug. Studies in naïve patients are examining a lower dose of TMC114 given once a day compared with a boosted LPV regimen. TMC114 is available on a compassionate release basis in the UK.

Integrase inhibitors

This novel class of drug interferes with the ability of HIV to integrate into the human genome, and three different companies (Gilead Sciences, GlaxoSmithKline and Merck) have drugs in development. The most advanced of these drugs is the Merck product and there are preliminary results from Phase IIb/III dose-ranging studies in both naïve and triple-class experienced patients. In the experienced patient group, approximately 80% of patients had a viral load of less than 400 copies/mL by 16 weeks compared with 20% in the optimized background-only group. In the naïve study, high rates of virological undetectability equal to those observed with EFV were seen with a TDF/3TC backbone (>85% in all arms by 24 weeks), with a more rapid decline in viral load in the integrase arms at weeks 4 and 8. Both studies are ongoing, but so far few side effects have been observed. Durability and long-term toxicity have yet to be defined, but importantly the drug is metabolized by glucuronidination and does not require RTV boosting. It is hoped that this drug will become an important new treatment option, and it will be available on a compassionate release basis in the UK from October 2006.

CCR5 inhibitors

One drug in this class (aplaviroc) has been discontinued for hepatotoxicity and, with another, suboptimal performance in a naïve population was observed because of inadequate dosing (vicriviroc). The most advanced drug in this class is maraviroc (UK-427857), which is in Phase IIb/III trials in both experienced and naïve patients. The naïve study compares once-daily (lower dose) UK-427857, twice-daily UK-427857, and EFV, with a backbone of Combivir in patients with CCR5 tropic virus. The study is ongoing, although the lower once-a-day dosing arm was discontinued at 16 weeks because of a higher virological failure rate. Studies in treatment-experienced patients with CCR5 tropic virus are ongoing but a study in those with dual/mixed tropic virus (R5 and X4) demonstrated no benefits over the optimized background arm, although the drug appeared safe and well tolerated. This is reassuring, as it does not suggest that emergence of potentially more virulent X4 tropic strains will be a significant problem with this class of drugs. Dose adjustment with RTV is required.

The above drugs are likely to find a role in triple-class experienced patients, where the available options are diminishing. In addition, if appropriate studies are carried out, these drugs may be used as a substitute for one of the nucleoside analogue backbone drugs, particularly after initial treatment failure when finding a second appropriate nucleoside analogue is often difficult.

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