British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2005)

B Gazzard on behalf of the BHIVA Writing Committee*

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1.0 Summary

1.1 HIV testing

The Committee believes that a potentially important mechanism for limiting the HIV epidemic is the widespread use of HIV testing in a variety of clinical settings. The availability of effective antiretroviral treatment improves outcome and potentially reduces onward transmission.

1.2 Methodology

The section on methodology has been extensively updated since the last version. Additional information includes new discussion of the definition of viral load endpoints, including an explanation of the 'time to loss of virologic response' (TLOVR) algorithm, and a section on issues surrounding non-inferiority trials.

1.3 Adherence

Current evidence does not support adherence interventions that include intensive, frequent or prolonged contact with specialist staff or structured group interventions. There is more likely to be some benefit from brief individualized interventions. Treatment simplification should not be at the price of reduced clinical efficacy. Medication alarms may impede adherence.

It is important that adherence support should be part of the routine clinical care provided by all health professionals in HIV medicine rather than being the exclusive role of specialist staff members. Every prescribing unit should adopt a standardized approach to assessing adherence and have a written policy on provision of adherence support. Staff must be appropriately trained to make delivery of such support possible. Treatment adherence data should be recorded routinely alongside other clinical parameters in order to detect patients in greatest need of additional treatment support.

1.4 Gender and ethnicity

Increasing numbers of women and people of diverse ethnic backgrounds are being diagnosed with HIV in the UK. Much of the evidence underpinning therapy has been gained from observations in men from resource-rich settings. Although some gender differences in surrogate markers have been observed, clinical outcomes to highly active antiretroviral therapy (HAART) are at least as good in women as they are in men. Adverse events may show some differences between men and women and the selection of medications needs to be mindful of women's child bearing capacity. The increasing ethnic diversity of the UK HIV-positive population has particular implications for access to and uptake of care. In addition, a wider range of HIV viral subtypes is being seen in clinical practice. When equal access to care is available, clinical outcomes on HAART are equivalent, although some ethnic differences in adverse event profiles have been observed.

1.5 When to start treatment

1.5.1 Primary HIV infection (PHI)

Longer-term follow-up of small numbers of patients treated during PHI, with subsequent treatment interruption, have not supported initial hopes that early treatment would alter the natural history of HIV infection. It is, therefore, the view of the panel that we should not change the recommendation that patients diagnosed during PHI should be offered recruitment into a clinical trial that will address the issue of whether treatment is beneficial in this setting [1].

1.5.2 Symptomatic HIV Infection

There is no change to the recommendation in the 2003 guidelines – i.e. that initiation of treatment is recommended in individuals with symptomatic disease and/or an AIDS diagnosis (with the possible exception of pulmonary tuberculosis).

1.5.3 Asymptomatic HIV Infection

1.5.3.1 Individuals with CD4 counts < 200 cells/μL. There is no change to the previous recommendations – i.e. that initiation of therapy is recommended before the CD4 count falls below 200 and in any individual with a confirmed CD4 count < 200 cells/μL at diagnosis.

1.5.3.2 Individuals with CD4 counts > 350 cells/μL. Although some recent studies have added to the data suggesting a benefit, in the short to medium term, on mortality and morbidity with initiation of HAART at a CD4 of > 350 cells/μL, these need to be interpreted with consideration to the likelihood that patients with HIV may live for decades after treatment with HAART. In this group of patients, where the short-term risk of disease progression is low, it is still considered that initiation of HAART may result in greater morbidity, and possibly mortality, in the longer term as a result of drug toxicity and earlier exhaustion of treatment options.

1.5.3.3 Individuals with CD4 counts 201–350 cells/μL. It is recommended that the majority of people should initiate therapy with CD4 counts between 200 and 350 cells/μL. Within this range, the time of initiation in a particular individual may be based upon patient preference, the rapidity of CD4 decline, symptoms, viral load, and co-morbidity such as hepatitis C infection.

1.6 What to start with

Treatment should be given with a dual nucleoside analogue and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI). The choice between an NNRTI and boosted PI remains largely a matter of opinion, but more data exist for NNRTI-based regimens in terms of efficacy. The fact that the current NNRTIs are generally more susceptible than PIs to marked loss of activity due to resistance can be used as an argument for using them in first-line therapy rather than in patients who have virologically failed previous regimens. This is on the basis that little benefit is likely to be gained from the NNRTIs if they are used with drugs to which some resistance has developed. However, the incidence of transmitted NNRTI resistance in the treatment-naive population is increasing, which may compromise their activity as first-line agents. NNRTIs have long half-lives that allow once-daily dosing and latitude around dose timing (forgiveness) and produced fewer disturbances in lipid metabolism. In favour of a boosted PI is a higher genetic barrier to resistance, which leads to the rarity of both transmitted resistance and development of PI resistance with treatment failure. The Committee believes that efavirenz (EFV) is the NNRTI of choice, except for women who may wish to become pregnant. Nevirapine (NVP) is an alternative in women with a CD4 count of less than 250 cells/μL and men with a CD4 count below 400 cells/μL, in whom the risks of hepatotoxicity are minimized. Lopinavir (LPV) boosted with ritonavir (RTV) is the PI for which the data on long-term vilorogical outcome is strongest in a PI-naive population. Alternatives are saquinavir (SQV) boosted with RTV and fosamprenavir boosted with RTV, but substantive direct comparisons between RTV-boosted PIs in such populations are not available. The Committee believes that there is insufficient data to recommend RTV-boosted atazanavir. However, if in trials that are currently in progress, the efficacy and durability of this regimen can be confirmed, the once-daily dosing and freedom from serum lipid abnormalities would be an advantage of this regimen.

Nucleoside analogues that should be considered when constructing a 2-nucleoside reverse transcriptase inhibitor (NRTI) backbone for initial regimens include: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), didanosine (ddI) and emtricitabine (FTC). Three 2NRTI combinations are available as co-formulated pills: Kivexa (ABC and 3TC), Truvada (FTC and TDF) and Combivir (ZDV and 3TC). While this adds to the convenience of the regimen, the Committee did not feel that this was sufficient to pay a large premium for a combination pill rather than using the components individually. Data suggests that ZDV/3TC is less well tolerated than TDF/FTC and produces a lower CD4 count rise than ABC/3TC, although the clinical significance of this is unknown. ZDV/3TC is likely to become considerably cheaper in the next 2 years as generic ZDV becomes available. The extent of the continuing use of ZDV/3TC combinations in the future is likely to depend upon the propensity of ZDV to produce lipodystrophy, which is in itself costly to treat and will be associated with poor adherence [2].

The choice between ABC/3TC and TDF/FTC requires a discussion with the patient about the short-term toxicity of ABC and its management vs. the lack of long-term toxicity data for TDF in clinic populations as opposed to selected patients in randomized controlled trials: in this uncertain situation with no clear data, the relative costs of the two combinations will legitimately be an important consideration.

1.7 When to switch therapy in the absence of virological failure

When an individual drug, as part of a regimen, is causing toxicity, the choice of agents to switch to is often self-evident and is usually within class. Regimen simplification, e.g. to a triple NRTI pill of ZDV, 3TC and ABC appears to be safe in those whose previous antiretroviral treatment has not failed, and may im-

prove adherence. Switching because of the development of abnormal lipids or the fat redistribution syndrome is more complex and of less certain benefit. It is dealt with in detail in the guidelines. Improvements in fat redistribution that occur as a result of such switching are slow.

1.8 Changing or stopping therapy for virological failure

- In patients experiencing viral load rebound, a clinical assessment of factors potentially contributing to reduced plasma drug levels such as adherence and drug–drug interactions should be undertaken and managed appropriately.
- The addition of a single new agent in individuals experiencing low-level viral load rebound is not recommended as the disadvantages of added toxicity and development of resistance to the new drug are probably greater than the likelihood of achieving a sustained undetectable viral load.
- Patients should be considered for a change of therapy if they show sustained rebound in viral load levels (as defined by two values at least 1 month apart >400 copies/mL), having previously been undetectable, or have never achieved undetectable levels on their current regimen.
- A resistance test should be undertaken once sustained viral load rebound occurs and while the patient is still on therapy.
- The decision to change therapy should be guided by the availability of a treatment option that is likely to have the potency to suppress viral load levels to undetectable levels (<50 copies/mL) and which the patient is likely to be able to adhere to and tolerate.
- The choice of a new regimen should be guided by the results of current and previous resistance testing, antiretroviral treatment history and the ability and likelihood of the patient to tolerate and adhere to individual drugs.
- The new regimen should contain at least three active drugs, including one from a new drug class. Active is defined as 'where a drug is likely to have significant antiviral activity *in vivo* based on the antiretroviral treatment history and the results of all current and previous genotypic resistance testing'.

1.9 Treatment for patients with evidence of resistance to NNRTIs, nucleoside analogues and PIs

In this setting, where it is unlikely that durable undetectable levels of HIV RNA are achievable, the aim of treatment should shift to maintaining or preserving immunological function and preventing clinical progression. Therefore, when treating patients with evidence of resistance to NNRTIs, nucleoside analogues and PIs, it is very important to maintain CD4 cell count rather than attempt to assess the HIV viral load undetectable with single agents.

Structured treatment interruption (STI) is NOT recommended in this setting and needs further evaluation.

For patients who are not at risk of rapid clinical progression (stable CD4 cell count 50–100 cells/μL and not falling rapidly), it would be sensible to wait for enough new active drugs to be available in order to have a realistic chance of durable viral suppression to <50 copies/mL. In particular, enfuvirtide (T20) should be used judiciously and, where possible, only when there is another fully active drug in the background regimen.

However, patients with multidrug-resistant HIV should be referred to or discussed with larger HIV centres where new investigational drugs are likely to be more accessible; this could be done as part of a managed clinical network or on a shared care basis.

1.10 Resistance testing

- Testing for transmitted resistance is recommended in all newly diagnosed patients. This includes patients with either acute seroconversion or established infection. The most appropriate sample is the one closest to the time of diagnosis and this should preferably be tested at the time of initial presentation.
- For existing patients, testing for transmitted resistance is recommended at the time of starting therapy.
- Minority species of resistant virus may be missed by conventional resistance testing. In patients without evidence of transmitted resistance using such tests, a suboptimal virological response to first-line therapy (<1 $\log_{10}$ copies/mL reduction in viral load by 4–8 weeks) should prompt resistance testing at that time.
- The reader should refer to the extended guidelines for additional recommendations.

(1) **Primary resistance.** There is now extensive evidence for the transmission of drug-resistant variants [3,4], and some evidence that transmitted resistance may compromise response to first-line therapy [5–7]. In some cases, the presence of resistance in an apparently drug-naive patient may in fact reflect previous undisclosed therapy.

(2) **Epidemiology of drug resistance in treatment-experienced cohorts.** Antiretroviral treatment failure continues to occur among patients on HAART and is frequently accompanied by the selection of drug

resistance. In a study of UK patients who started HAART (without previous mono or dual nucleoside therapy) between 1996 and 2003, there was a 38% risk of failure and a 27% or higher risk of developing resistance over 6 years of follow-up [8].

(3) **Benefit of resistance testing in treatment-experienced patients.** The routine use of genotypic resistance testing after treatment failure has been shown to be cost effective [9]. TORO-1 and TORO-2 [10,11] and RESIST-1 and RESIST-2 [12,13] trials provided indirect evidence of the clinical benefit of resistance testing in highly drug-experienced patients.

(4) **Interpretation of resistance test results**

a. Routine resistance assays do not detect resistant viruses present at low levels (<20% of the total virus population), even if these resistant viruses were previously dominant. Although assays to detect minority species have been developed, they are not routinely available and remain research tools only. Limited data indicate that minority resistant quasispecies may affect virological responses [14,15].
b. In the absence of drug pressure, the dominant virus population will revert to wild type [16]. Reversion is slower in transmitted resistance than in resistance selected by therapy [17–22]. Reversion of mutations may occur through intermediates or revertants (e.g. T215D/N/S from T215Y/F). Detection of revertants should be interpreted as evidence that fully resistant mutants are present as either minority quasispecies or archived resistance.
c. The interpretation of resistance test results is complex. The most informative interpretation systems are based on 'clinical cut-off' values, which are being determined for a growing number of drugs.
d. Antiretroviral resistance should be interpreted as a continuum. For the NRTIs and PIs (but not for the NNRTIs) [23], residual virological suppression can be observed with intermediate levels of resistance, which may reflect direct antiviral activity as well as the beneficial effects of reduced viral fitness [24].
e. Virus fitness is defined as the overall capacity of a virus to infect, replicate and produce mature infectious progeny in a defined host environment. The Replicative Capacity Assay is a clinically available test that provides one measure of viral fitness. The clinical utility of the test has not been demonstrated.
f. Hypersusceptibility effects can be demonstrated *in vitro*. Certain drug-resistance mutations confer resistance to some drugs but increase susceptibility to others. The clinical relevance of this is not clear.
g. Certain resistance pathways have been associated with the HIV-1 subtypes. HIV genetic diversity also impacts on phenotypic resistance assays, which use a B subtype virus backbone.

(5) Patients should be encouraged to have knowledge of their results and the i-Base treatment passport is an ideal vehicle for keeping an ongoing record of the CD4 count, viral load and resistance test results.

1.11 Therapeutic drug monitoring (TDM)

Randomized, prospective, controlled trials remain a high priority to evaluate the usefulness of TDM of NNRTIs and PIs. TDM has been shown to be beneficial in particular clinical scenarios where drug concentrations are difficult to predict. These include the management of drug interactions, pregnancy and paediatrics, and in highly treatment-experienced patients when TDM and resistance test results can be integrated, in patients with renal or hepatic impairment, transplant patients, potential toxicity, and in the use of alternative dosing regimens whose safety and efficacy have not been established.

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

1.12 Metabolic complications

As the prognosis of HIV infection has markedly improved, so has our need to recognize and 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 (ART). This is the result of the growing awareness of the increase of stigmatization and reduction of adherence associated with lipodystrophy, especially lipoatrophy, and for 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 the risks are greater with PIs than with NNRTIs and greater with stavudine (d4T) than with ZDV. 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 and possibly a reduction of insulin resistance. This class effect on lipids and insulin resistance does not apply to atazanavir, and boosting with RTV does not appear to change this.

The application of current health promotion approaches to our patients should include assessments of cardiovascular risk 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.

1.13 Co-infection with chronic hepatitis B or C and HIV

- Anti-hepatitis B virus (HBV) therapy should be included in antiretroviral therapy for all hepatitis B surface antigen (HBsAg)-patients who are hepatitis B 'e' antigen (HBeAg) positive, or who have a blood HBV-DNA level $>10^4$ genome equivalents/mL, or who have cirrhosis and any detectable HBV-DNA. In patients commencing ART with detectable HBV-DNA levels but $<10^4$ genome equivalents/mL, 3TC/FTC should be used either with TDF or not at all.
- If treating HIV and HBV, TDF alone or in combination with 3TC or FTC is recommended as part of HAART. 3TC or FTC should not be used alone or in combination with each other.
- Anti-HBV drugs should be continued in the context of controlled HBV replication when a switch of ART is contemplated.
- Consider all hepatitis C virus (HCV)-positive patients for therapy with pegylated interferon and ribavirin, to commence ideally before the CD4 count has fallen to levels where ART is required.
- If ART is required in HCV-positive patients, they should ideally be established on a stable regimen with a CD4 count >200 cells/μL before anti-HCV therapy is considered. Where possible ZDV, ddI and d4T should be avoided because of their interactions with ribavirin.
- If possible, avoid nevirapine (NVP) and high-dose (>1000 mg/day) RTV in all patients with chronic liver disease due to their potential hepatotoxicity. Low-dose RTV can be used safely.

1.14 Co-infection with tuberculosis (TB) and HIV

The guidelines for managing HIV-infected patients co-infected with TB can be found on http://www.bhiva.org

The management of such patients is complex and requires a multidisciplinary approach. It is important that physicians treating such patients are not only aware of the issues around the epidemiology, prevention control and treatment of TB in HIV but also the use of HAART.

When to start HIV treatment, which treatments to use, drug interactions, side effects and their management and other complications, including the Immune Reconstitution Inflammatory Syndrome (IRIS), are specifically addressed in these comprehensive guidelines.

2.0 New issues in these guidelines

2.1 HIV testing and diagnosis

The issues surrounding HIV testing are covered in detail in a number of publications [25–27]. Since the outlook for an HIV-seropositive patient has been transformed following the introduction of HAART, previous protocols for testing that include detailed pre-test counselling are less relevant in most situations. Thus, an important means to improve patient outcome and reduce transmission of HIV is the more widespread offer of HIV testing. It is important that clinical health-care professionals are alert to the symptoms, signs and histories that denote possible risk, and are then in a position to offer testing. We believe that an offer to undertake an HIV test should be within the competence of all doctors and is both possible and desirable within the context of a general medical clinic or general practice surgery. There is no need for special counselling skills outside those which all clinicians (nurses and doctors) require for their daily practice.

It is recognized that there might be exceptional circumstances, particularly when the risk of HIV infection is high. In these cases, an individual might require additional counselling before and following a positive test result, but certainly afterwards. Clinicians should familiarize themselves with the most recent guidelines from the ABI [28] on life insurance and have available telephone numbers of support organizations to help with the minority of patients who have a major reaction when a positive result is disclosed.

Unfortunately, there is still a widespread stigma attached to an HIV-positive diagnosis and therefore, patients need to be informed of the strict rules of confidentiality that medical practitioners abide by. Clinics performing HIV tests need to ensure that their staff observe this confidentiality.

If the test is positive, patients are likely to need specialized advice and support. Individuals should be advised to think through carefully the implications of disclosure of an HIV-positive diagnosis to relatives and friends. Increasingly, point-of-care testing using assays from which the diagnosis can be obtained in 15 min is being used to provide a 'one stop' service. This may prove difficult in a general practice setting, and the booking of a separate time to discuss a potentially positive HIV result may be more satisfactory. The most important outcome for those individuals with an HIV-positive result is the prompt

referral to someone with experience in the treatment of HIV and related infections.

2.2 New drugs

It is intended that this short summary of updated recommendations for antiretroviral treatments should be read in conjunction with the more extensive review of the existing data about such therapy present in the previous BHIVA guidelines [29]. The intention of this section is to update readers on drugs which are likely to be licensed in the near future or are already available on compassionate release.

2.2.1 Tipranavir

This PI, which is likely to be licensed shortly, has been developed because of its ability to inhibit viruses that are resistant to all presently available PIs *in vitro*. This ability has been confirmed *in vivo* in recently completed Phase 2 and 3 studies. In the combined RESIST 1 and 2 studies [12,13], 1483 patients previously exposed to all three classes of drugs and at least two PIs were randomized to optimized background plus or minus tipranavir. At 24 weeks, by intent to treat analysis, a viral load fall of at least 1 log was seen in 42% of tipranavir-treated patients (19% in the comparator arm) and 23% of patients (9.4% in the comparator arm) achieved a viral load of less than 50 copies/mL at this time point. A higher proportion of patients, who were naive to enfuvirtide (T20) and were given this as part of the optimized background, achieved undetectability. The entry criteria for these two studies were narrow. Patients were required to harbour a virus with one or more primary PI mutations present but with two or less mutations at specific sites in the genome (33, 82, 84 or 90). A further study, which was conducted in patients who had three or more PI mutations at these specific sites, also showed that tipranavir was able to reduce the short-term viral load (over 2 weeks) compared with other boosted PIs. This study also showed unexpected interactions between tipranavir and other PIs, making it difficult to use as part of a double-boosted PI regimen without dose adjustment or therapeutic drug monitoring.

The pharmacokinetics of tipranavir require it to be administered with ritonavir (RTV) 200 mg twice daily. The likelihood of the response to tipranavir can be gauged by the resistance profile of the virus and expert advice is helpful in deciding which boosted PI is most likely to be effective in a particular patient. Abnormalities of lipid, particularly triglyceride and liver function tests, are the main laboratory side effects, although the incidence of gastrointestinal side effects is not greater than with other boosted PIs.

Like other drugs essentially used as single, effective agents in advanced disease, the virological responses are often short-lived and the drug is much more likely to find a role in the early stages of disease when it is possible to construct a regimen capable of suppressing viral replication completely.

2.2.2 TMC114

TMC114 is an investigational twice-daily PI with activity against PI-resistant HIV-1. It is administered with RTV, 100 mg twice a day.

At the Conference on Retroviruses and Opportunistic Infections in 2005 [30], a planned 24-week interim analysis of two 96-week, dose-finding phase two trials in highly treatment-experienced patients was presented. Patients were experienced in three or more classes with a median viral load over 100 000 copies/mL at baseline (baseline median values were HIV RNA 4.6 $\log_{10}$ copies/mL). They all had one or more primary PI mutations. A total of 497 subjects were randomized to either optimized background (OB) with or without T20 or to OB plus TMC114. The primary endpoint was the decrease in viral load at 24 weeks. The 600/100 mg TMC114/r twice-daily dosing appeared to have the best antiviral effect with a change in viral load from a baseline of 1.85 $\log_{10}$ compared with that of the control group, of -0.27 $\log_{10}$. Overall, 47% of patients had a viral load of less than 50 copies at 24 weeks (9% in the OB arm) and this figure rose to 67% for those patients who also received T20, not having been exposed to this drug previously. The CD4 count in the TMC114 arm rose by 75 cells/μL. There was no difference in toxicity or adverse events between the arms.

2.2.3 TMC125

TMC125 is made by Tibotec/Janssen-Cilag and is a potent NNRTI active against NNRTI-resistant HIV-1. It has been tested against single and multiple mutants as well as clinical isolates with NNRTI-resistance associated mutations. It appears that a high number of mutations are required for a significant increase in the EC_{50}. The TMC125-C207 [31] study was performed over an 8-day period in patients who were failing in NNRTI therapy. Median and viral load was 4 to 4.25 log at baseline and after 7 days of TMC125-C207, the viral load had dropped 1 log. TMC125 is currently in phase IIB dose-finding studies.

2.3 Cost–benefit analysis

The prognosis of HIV infection has been revolutionized by antiretroviral treatment. The requirement for life-long treatment, however, has meant that the total cost of

antiretrovirals place a burden on third party payers. Antiretrovirals remain among the most cost-effective treatments to save a year of life for a chronic disease, with the high cost of drugs being partially offset by the reduction in expensive hospital in-patient care and the avoidance of opportunistic infections.

While the BHIVA Writing Committee continues to believe that the primary purpose of the guidelines is to produce a consensus view of optimal treatment based upon potency, durability and freedom from side effects, we are cognisant that it would not be right in the framework of medical ethics to ignore the issues of costs. These issues become more important as more expensive drugs are developed, which have no clear advantages in terms of antiviral efficacy, but may add to the convenience for patients.

2.3.1 Cost of antiretroviral drugs

Table 1 displays the current prices as set out in the BNF, plus VAT at 17.5% for the 2NRTI backbone, and the third drug according to the recommendations for preferred regimens in antiretroviral (ARV)-naive patients. While formulating this list, the Committee is aware that parallel importing, individual unit or regional discounting, and home delivery of drugs (which is zero-rated for VAT) may affect overall price to a significant level. Moreover, total drug costs may be misleading without considering the implications of reduced adherence to more complex regimens and the high cost of managing side effects such as lipid abnormalities. However, throughout the guidelines, for the first time, when the Committee believes that little distinguishes various drugs apart from cost, this will be mentioned.

Table 1 Cost of preferred regimens as per Table 5: monthly (30-day) cost as set out in list price (April 2005) + VAT at 17.5% in £

Column A NNRTI		Cost
	EFV	245
	NVP	188
PI/r		
	LOP/r	361
	ATAZ/r[1]	411
	FOS/r[2]	403
	SAQ/r[2]	397
	IND/r[2†]	222
PI		
	ATAZ 400 mg	371
	NFV	321
NRTI		
	ABC	261[‡]
Entry inhibitor		
	T-20*	1350

Column B		Column C		B + C
NRTI-1	Cost	NRTI-2	Cost	Total cost
ZDV 250 mg	196	3TC[¶]/FTC	179/192	375/388
TDF	300			479/492
ABC	261			440/453
ddI 400 mg	192			371/384
d4T 40 mg[§]	201			380/393
Combivir®				374
Truvada®				492
Kivexa®				439

r^1 or r^2 indicate number of ritonavir capsules per day.
*For experienced patients only.
†Not a preferred regimen but recognized potential cost-savings.
‡Trizivir® £683.
§d4T/3TC is as effective as other regimens but more toxic and not a preferred regimen.
¶150 mg tablets.
Costs do not reflect changes resulting from the pharmaceutical price regulation scheme (PPRS) 2005.

2.4 Structured treatment interruption (STI)

Supervised interruption of drug therapy may reduce drug costs and overall toxicity. Enthusiasm for this approach was initially increased by the biological plausibility that the reappearance of viral antigens in the circulation might stimulate the immune system to produce more effective control of viral replication. See the following sections:

(1) Seroconversion, see Section 5.0
(2) Chronic disease, see Section 7.3
(3) STI in three-class experienced patients, see Section 9.2.3

STIs of varying length, with re-starting of therapy as indicated by CD4 cells, have been shown to be a safe strategy in pilot studies, with potential cost benefits but less clear reductions in toxicity. This strategy is being examined in a large, international, randomized controlled trial with clinical endpoints (SMART) [32] over the next several years.

The chief short-term risks of STI are the development of a resistant virus because of virtual monotherapy with the component of the regimen with the longest half-life (usually the NNRTI). Particularly long half-lives have been found with some genetic polymorphisms of the Cytochrome P450 system, which may be more common in people of African origin. It is unclear how often resistance to NNRTIs develops but it would seem a reasonable precaution to either cover the withdrawal of the NNRTI with a shorter-acting PI that can subsequently stopped concomitantly with the two nucleoside analogues e.g. Kaletra or to stop the NNRTI 14 days prior to the NAs. The disadvantage of this approach is the variability in the terminal half-life of the NNRTI.

The Committee would only recommend a treatment interruption outside the clinical controlled trials in those patients who started ART with high CD4 counts e.g. above 400 cells/μL, in accordance with earlier guidelines. Such patients may be able to withdraw treatment for several years before they require treatment according to newer guidelines.

2.5 Gender and ethnicity – implications for therapy

The HIV epidemic in the UK is increasingly diverse. Although the majority of people with HIV in Britain are men, the number of women is rapidly increasing. In 2003, 45% of new diagnoses were in women, of whom almost 70% were from African backgrounds [33]. Much of the data available on both natural history and therapy of HIV have been generated from observations of men, leading to a relative lack of information about women. Ethnic diversity within the UK HIV-infected population is also rapidly changing. Since 1999, new diagnoses in Africans have overtaken those in other groups. Gender and ethnicity are bound up with social, psychological and environmental factors, which impact on both access to and uptake of, care [34–36]. Increasing data exist on the responses and resistance patterns of non-subtype B viral strains to antiretrovirals, as described in the section on Resistance. The management of HIV in women who are pregnant is given in the BHIVA pregnancy guidelines [37].

Factors that influence access to care may be implicated in the observations that late presenters are more likely to be female [38] and of African background [39]. In the UK, African men are diagnosed at an older age and have lower CD4 counts at diagnosis than African women [40]. A number of studies have shown that women are less likely to be prescribed antiretroviral drugs [41] and initiate therapy later in disease progression than men [42,43].

In HIV-seronegative populations, women have been observed to have higher CD4 counts than men [44]. At seroconversion, higher CD4 cell counts have been described in women than in men [45], which have been shown to persist with time [46]. Such gender differences in CD4 counts may lead to a delay of initiation of therapy in women compared with men, which has been estimated to be of the order of 12 months [47]. However, despite the later initiation of HAART, at a population level, women show at least the same HAART-related improvement in survival as men [48].

Viral load values have been noted to be lower in women, for the same stage of disease progression and CD4 count, than in men. A meta-analysis [49] confirms this finding to be consistent and of the order of 41%. This is of importance in situations when plasma HIV RNA thresholds are used to inform treatment recommendations for initiating ART. A lower threshold is indicated for women than for men.

The childbearing potential of women with HIV will influence therapeutic decision making. EFV is associated with teratogenicity and is contraindicated in pregnancy. It should not be used in women planning to conceive.

Once established on treatment, women fare at least as well as men [50–53], and on starting therapy, women may achieve virological suppression at a faster rate than men and have a more durable response [54]. In the UK, white ethnicity has been associated with greater increases in CD4 cell counts during the first 3 months of HAART [55] and in the USA with a more rapid and durable fall in viral load [56]. Large studies from the UK, Switzerland and Denmark [57–59] have all confirmed the prognosis of sub-Saharan African patients on triple therapy to be equivalent to that of northern European patients and that race and ethnic origin play no major role in the outcome associated with HAART if access to health-care is free.

Differences in tolerability of antiretroviral medications are marked, with higher rates of side effects in women [60,61]. This difference has been observed across all drug classes. Adverse reactions to NVP are more common in women [62,63]. This is particularly marked at CD4 counts greater than 250 cells/μL [64] in whom NVP should not be used. A relationship between NVP toxicity and low body mass index (BMI) in African women has been suggested [65]. High rates of neurological side effects and an associated reduced clearance of EFV have been closely linked with ethnicity but not gender [66,67]. Clearance has been shown to be 32% slower in African American and Hispanic patients than in Caucasians. ABC hypersensitivity has been described more commonly in white patients [68,69].

Drug interactions exist between PIs and oral contraceptives. Of particular note, some PIs (including NFV, LPV and RTV) reduce the effectiveness of the contraceptive pill and women must be advised to use additional methods of contraception [70].

The impact of HAART on lipid and insulin metabolism appears to be more pronounced in women than in men [71,72], which may cancel out the protective cardiovascular profile usually conferred on women. HAART-associated body shape changes have been noted more commonly in women [73]. The pattern of fat accumulation and loss differs between the sexes, with a greater accumulation in women and loss in men [74]. In an Australian study, black patients preserved both total body fat and limb fat when compared to other ethnic groups [75,76].

3.0 Methodology

3.1 Basing recommendations on evidence

The Committee used an evidence-based medicine approach to produce these guidelines. In reality, if only the most reliable form of clinical evidence was taken into account (i.e. results of one or more randomized controlled trials

with clinical endpoints), it would be impossible to formulate these guidelines. Many important aspects of clinical practice remain to be formally evaluated and very few trials with clinical endpoints are ongoing or planned. Many trials have been performed in order to obtain licensing approval for a drug. In many cases, they are the only source of evidence for comparing two drug regimens. However, the designs are not ideally suited to addressing questions concerning clinical use. The most significant drawbacks of such trials are their short duration and the lack of follow-up data on patients who switch therapy. In most cases, the only available data on long-term outcomes are from routine clinical cohorts. While such cohorts are representative of routine clinical populations, the lack of randomization to different regimens means that comparisons between the outcomes of different regimens are highly susceptible to bias [77,78]. Expert opinion forms an important part of all consensus guidelines; however, this is the least valuable and robust form of evidence.

3.2 Implications for research

Unless guidelines are interpreted and applied cautiously and sensibly, valuable research initiatives that might improve standards of care will be stifled. It would be wrong to suggest that certain clinical controlled trials would be unethical if they did not conform to the guidelines, especially when these guidelines are based mainly upon expert opinion rather than more reliable evidence [79].

3.3 Use of surrogate marker data

CD4 cell counts and plasma viral load are used as markers of the effect of ART. Reduction in viral load leads to a rise in peripheral blood CD4 count, with greater rises being seen in those with greater and more sustained viral suppression [80]. Changes in these markers in response to therapy are strongly associated with clinical response [81–85]. CD4 counts measured in people on ART have been associated with a risk of AIDS-defining diseases no higher than that expected in untreated individuals with similar CD4 counts [86–89]. The CD4 count is a better indicator of the immediate risk of AIDS-defining diseases than the viral load in those on ART [90,91]. However, it should be remembered that CD4 count and viral load responses do not precisely reflect the expected clinical outcome and are not perfect surrogates of the clinical response [84,92,93]. This is because the drugs have other effects with clinical consequences besides those reflected in viral load and CD4 count changes. Even so, for patients with a given CD4 count and viral load, the risk of AIDS disease appears to be similar, regardless of the specific antiretroviral drugs being used [94]. The relatively short length of trials designed to obtain drug approval means that, at the time of licensing, little is known about the drugs' long-term consequences.

3.4 Issues concerning design and analysis of clinical trials

3.4.1 Issues concerning design and analysis of clinical trials: trial designs

As stated above, most antiretroviral drug trials are performed by pharmaceutical companies as part of their efforts to obtain licensing approval and the designs are often not ideally suited to deriving information on using the drugs in clinical practice. Besides the short duration of follow-up, their key limitation is the lack of data on outcomes in people who change from the original randomized regimen, and also a description of what those new regimens are. The results are, therefore, only clearly interpretable as long as a high proportion of participants remain on the original, allocated regimens. Clinical questions about which drugs to start with or switch to require longer-term trials that continue despite changes to the original treatment. From a clinical perspective, it makes little sense to ignore what happens to patients after a specific regimen has been discontinued. The use of a given drug can affect outcomes long after it has been stopped. For example, it may select for virus resistant to drugs not yet encountered or cause toxicities that overlap with those caused by other drugs. However, interpretation of such trials is not straightforward, and account must be taken of which drugs were used subsequent to the original regimen in each arm.

The Committee generally favours entry into well-constructed trials for patients whose clinical circumstances are complex, with a number of specific instances being mentioned in these guidelines. NAM maintains a list of trials currently recruiting in the UK at www.aidsmap.com, and treatment units should work to ensure arrangements are in place to enable eligible patients to enter trials at centres within or indeed outside their clinical networks.

3.4.2 Issues concerning design and analysis of clinical trials: viral load outcome measures

In most efficacy trials, treatments are compared in terms of viral load as defined by plasma HIV RNA. Depending on the target population, the primary outcome measure may be defined to include the achievement of viral suppression below a certain limit (usually 50 HIV RNA copies/mL) at a pre-specified time (e.g. 24 or 48 weeks after randomizations), time to viral rebound or time-weighted average change from baseline. To avoid selection bias, all enrolled patients must be included in an analysis comparing the treatments as randomized (the intent to treat principle).

However, the inability to assess outcomes for some patients, leading to missing data, e.g. due to patient dropout before completion of the trial, is a potential source of bias. The frequency and reasons for missing outcomes may be affected by many factors including the efficacy of treatments, toxicity and length of follow-up. Interpretation of the results of the trial is particularly problematic if a substantial number of patients drop out for reasons related to the outcome whether by design, as in many pharmaceutical industry trials where patients are withdrawn when they change their randomized treatment, or otherwise. This problem can be addressed at three levels: in the design, conduct and analysis stages of the trial. Changes in treatment during the trial must be anticipated and it is necessary to continue collecting data on all patients, even if they have switched from the original regimen, and to pre-specify the statistical methods to be used for handling missing outcomes. In general, these methods impute values for those patients who have dropped out of the trial. When the outcome is the proportion of people with viral load <50 copies/mL at a given time point, the approach almost universally adopted is to assign >50 copies/mL to all patients with missing outcome (and those who have switched from the randomized treatment, regardless of whether they remain under follow-up), known as the missing = failure (MEF) approach [90–97]. This approach to missing outcome is used in trials for drug licensing because it assigns anyone who has to stop the drug of interest as having failed and thus prevents any tendency for drugs used in a patient after the drug of interest has failed to influence the trial results. Such an approach implicitly equates failure of a regimen due to inadequate potency and/or viral drug resistance not only with the inability to tolerate a regimen due to pill burden, inconvenience and/or adverse effects but also with missing assessments due to other reasons, including randomly missing visits, even though the implications of these outcomes are likely to be substantially different. This approach is often labelled conservative because it gives a minimum proportion of <50 copies/mL for any given treatment group over all possible approaches. However, the primary purpose of an endpoint is to compare treatment arms and the reasons for missing outcomes may well differ between treatments. In this context, this approach is not conservative in any general sense and its indiscriminate use without consideration of its inherent limitations involves a degree of risk of bias, which could be greater than simply ignoring missing values. For these reasons, trials that are conducted for purposes of licensing a particular drug, and which treat stopping of the drug as treatment failure and ignore outcomes occurring after the drug has stopped, do not always provide the type of information that is most useful for clinical practice.

In the past, trials have generally considered whether the viral load is below 50 copies/mL or not at a given time point (e.g. 48 weeks). In recent years, the tendency has been to consider whether virological failure (or 'loss of virologic response', usually defined as two consecutive values >50 copies/mL) has occurred *by* a certain time point, rather than whether the viral load *at* the time point is <50 copies/mL or not. In the (common) case where missing viral viral load values and switches in therapy are treated the same as values >50 copies/mL, this approach uses a 'time to loss of virologic response' (TLOVR) algorithm [97]. The two approaches will give similar but not identical results; e.g. patients can fulfil the definition of loss of virological response before 48 weeks but then have a viral load value <50 copies/mL at 48 weeks itself, without any change in regimen.

Randomization in a trial ensures balance in prognosis between the treatment arms at baseline. Inability to assess outcomes for some patients can disturb this balance and create bias in the comparison between the treatment arms. In order to avoid risk of such bias, analysis by intent to treat includes outcomes for all randomized patients. So called 'on treatment' analyses consider outcomes only in those still receiving the original allocated treatment. Here, the difference between assessing the proportion with viral load <50 copies/mL *at* a given time point, or the proportion with viral load >50 copies/mL *by* a given time point, becomes greater. In the context of an assessment of the proportion of people with viral load <50 copies/mL at a given time point, on treatment analyses makes little sense because therapy has been switched in patients who experience viral load rebound during a trial. Hence, all regimens that lead to a viral load <50 copies/mL in at least one person should lead to a value of 100%, unless there are patients who have viral load >50 copies/mL at the time point but are yet to have their regimen switched. In contrast, an assessment of whether the viral load was >50 copies/mL by a given time point (i.e. time to virological failure or loss of virologic response), which censors observation on patients once they have switched from the original randomized regimen may be more revealing, but is still subject to potential bias.

3.4.3 Issues concerning design and analysis of clinical trials: non-inferiority

In contrast to superiority trials where the primary objective is to demonstrate that a new treatment regimen, or strategy, is more efficacious than a well-established treatment, the aim of a non-inferiority trial is to show that there is no important

loss of efficacy if the new treatment is used instead of the established reference [98]. This is particularly relevant in evaluating simplification strategies where the new treatment strategy is better than the reference treatment in aspects other than efficacy, e.g. toxicity, tolerability or cost. To demonstrate non-inferiority, large numbers of patients are usually required because of the need to exclude moderate loss of efficacy with the new treatment. The trial protocol must prespecify a non-inferiority margin (e.g. the proportion with viral load <50 copies/mL at 48 weeks, in people receiving the new treatment, is not smaller than the same proportion in the reference treatment by more than 5%). The choice of the non-inferiority margin depends on what is considered to be a clinically unimportant difference in efficacy taking into account other potential advantages of the new treatment. Stating that the response to the new treatment was not significantly different from that of the reference treatment is not evidence for non-inferiority. Graphical representations that show overlapping increased CD4 cell counts or decreased viral loads in response to therapy may hide differences in efficacy between drugs. Non-inferiority is indicated when the (95%) confidence interval for the difference between the two treatments excludes loss of efficacy greater than the prespecified non-inferiority margin.

It is important to note that a very high standard of trial conduct (e.g. minimizing violations of entry criteria, non-adherence to allocated regimens and loss to follow-up) is more critical in non-inferiority than in superiority trials. Such deviations from the protocol would tend to bias the difference between the two treatments towards zero and thus increase the chance of erroneously concluding non-inferiority.

3.4.4 Issues concerning design and analysis of clinical trials: cross-study comparisons: presentation of data

It is tempting to compare results of individual drug combinations assessed in different trials. Such comparisons are, however, difficult to interpret because of differences in entry criteria (particularly with respect to viral load and CD4 cell counts), methods of analysis (e.g. intent to treat versus on treatment), degrees of adherence and sensitivities of viral load assays [99].

3.5 Adverse event reporting

Many previously unsuspected side effects of ART have been reported only after drug licensing. It is vital that prescribers report any adverse events as soon as possible so that these events are swiftly recognized. A blue-card scheme, organized by the Medicines Control Agency, the Committee for Safety of Medicines (CSM) and the Medical Research Council (MRC), operates in the UK for reporting adverse events relating to the treatment of HIV [100].

4.0 Adherence

The leading determinant of successful and durable virological and immunological responses to HAART is adherence, sustained without lapse at extraordinarily high levels for many years. Therefore, a core component of the clinical care of HIV-positive patients must be adherence support. This should commence before HAART is introduced and continue at varying intensity throughout the treatment course.

High adherence to therapy is the sum of many daily decisions to take therapy under the influence of diverse factors internal and external to the patient which change over time. While clinical trials for adherence support can only explore single or structure interventions, it is implausible that any single intervention will be effective in a sustained manner for all patients. A systematic review of all published studies of adherence interventions across medical specialties found that only 33 were adequately powered to detect clinically important effects. Effective interventions were usually complex and included combinations of information, counselling, reminders, self-monitoring, reinforcement and more convenient care; large improvements in adherence were not observed [101]. Therefore, the approach to supporting adherence in the clinic should be to deploy a range of techniques (based on evidence as it emerges from clinical trails) individualized to the need of each patient at any given time in their treatment career. Increased support may be required not only when starting and changing therapy or when side effects occur, but also when other non-treatment related factors intervene (e.g. mental illness, social upheaval).

Readers are referred to comprehensive guidelines produced in 2003 by BHIVA and the Medical Society for the Study of Venereal Diseases (MSSVD) for a full exploration of these issues. These are available from the BHIVA website (http://www.bhiva.org/guidelines.htm) and have recently been published [102]. Developments in the field since this document was produced are summarized below.

4.1 Adherence and resistance

In conceptual terms, the most significant development has been the emergence of evidence that different patterns of non-adherence may promote resistance by drug class, while for unboosted PIs, the risk of viral resistance has been found to be greatest in those with high adherence [103–106]; for NNRTIs, the risk may be greatest for those with the lowest adherence [107] or those who take unplanned drug holidays of >2 days [108]. Whether level of adherence has an effect on emergence of resistance to RTV-boosted PIs is unknown, but it is possible that it is

most likely to occur within a narrow range of moderate adherence, which is sufficient to permit replication of a less fit resistant virus [109].

4.2 Treatment simplification strategies

Unexpectedly poor results from recently reported trials of combinations, which might have had a role in constructing simplified regimens, serve as a caution against the use of untested combinations [110–113] in this context. Where there is a desire to offer a simpler regimen in the hope of optimizing adherence, the chosen combination should have demonstrated clinical efficacy and safety. Once-daily HAART has yet to show a clear advantage over twice-daily treatment; in the field of hypertension, a 6-month study showed that in a highly adherent population once-daily therapy did not significantly reduce the number of doses missed, but it did reduce the number of late doses [114]. A recent systematic review of all published studies of adherence interventions found only one study with adequate follow up in which adherence was shown to be higher on once-daily vs. twice-daily therapy [101,115].

4.3 Interventions to improve knowledge and skills

These are the most common forms of adherence support in current clinical practice. Several randomized trials have now been published; however, many have significant methodological problems, principally the lack of a predefined primary endpoint. Rather than describing virological outcome, the effect on patient self-reported adherence was most frequently measured in these studies, which in this context may be particularly vulnerable to self-presentational bias.

Two studies reported positive effects from educational interventions: a large study of four individual educational sessions compared with standard care reported increases in self-reported adherence sustained for 18 months [116]. A smaller study using electronic means to measure adherence more objectively appeared to support these findings, but the study was limited by inadequate follow-up (12 weeks) and high rates of attrition of participants [117].

The only study powered to detect a protective effect against virological rebound showed no benefit from frequent contact with a trained staff member delivering an individually tailored programme of adherence support [118]; however, a secondary endpoint comparing prevalence of plasma HIV RNA ≤ 400 copies/mL did find a significantly lower rate in the intervention arm [118]. A large unpowered trial found no effect on either adherence (measured electronically) or virological response of a structured programme of 4 weekly small group training sessions compared with standard care [119]. A small pilot study showed no significant effect on adherence over standard care of motivational interviewing techniques in adherence support [120].

4.4 Cognitive-behavioural interventions

A large randomized controlled trial (RCT) of 3 sessions of a cognitive-behavioural intervention reported increases in self-reported adherence compared with standard care sustained for 6 months and also a small effect on virological outcome [121]. A study of a similar brief intervention using an electronic measure of adherence was underpowered but showed superior adherence results on some but not all adherence measures at 4 weeks. By 24 weeks, the rate of loss to follow-up was too high to allow conclusions to be drawn [122]. Two trials comparing prolonged cognitive-behavioural interventions with either a video including similar content [123] or standard care [124] showed no overall beneficial effect on adherence or virological treatment outcome [124].

4.5 Pagers/alarms etc.

A very large RCT, powered to detect an effect on virological rebound, showed a significantly higher rate of virological treatment failure in patients randomized to a dose time alarm than those with no alarm (relative risk 1.25; $P = 0.02$) [118]. Whether the same applies to watch or mobile phone alarms, which may be more acceptable to patients, is unknown.

4.6 Pre-HAART practice placebo dosing

A large RCT showed no benefit, in terms of objectively measured adherence of a 2-week pre-treatment practice period, in taking placebo pills before commencing HAART [122].

4.7 Directly observed therapy (DOT)

In an institutional setting, DOT may be associated with improved adherence and virological outcome to standard care [125]. While lessons may be drawn from the treatment of tuberculosis, DOT for HIV presents unique difficulties including the need for indefinite treatment and the highly stigmatized nature of the condition. Modified DOT is being explored in randomized trials in marginalized populations in the USA; the results are awaited. A small non-randomized study among methadone users starting a new HAART regimen showed significantly better virological responses at 6 months for those receiving modified DOT

with their methadone dose than for those receiving standard care (58% vs. 22%; $P = 0.002$); adherence data were not reported [126]. Given the inherent difficulties of ensuring patient follow-up with DOT, modelling has suggested that large increases in adherence may reduce deaths and AIDS events but may increase the prevalence of drug resistance [127].

4.8 Injectable therapy

In a clinical trial setting, self-reported adherence to injectable therapy with enfuvirtide was high: 84% patients reported adherence of at least 95%; adherence to enfuvirtide did not differ from that reported for concomitant oral antiretrovirals [128].

4.9 Recommendations

Current evidence does not support specific adherence interventions that include intensive, frequent or prolonged contact with specialist staff or structured group interventions. However, brief individualized interventions have shown some benefits. Treatment simplification should not be at the price of reduced clinical efficacy. Medication alarms may impede adherence.

Adherence support should be part of the routine clinical care provided by all health professionals in HIV medicine rather than being the exclusive role of specialist staff members. Every prescribing unit should adopt a standardized approach to assessing adherence and have a written policy on provision of adherence support. Staff must be appropriately trained to make delivery of such support possible. Treatment adherence data should be recorded routinely alongside other clinical parameters in order to detect patients in greatest need of additional treatment support.

5.0 When to start treatment

With currently available antiretroviral agents, eradication of HIV infection is not likely to be possible [129]. The main aim of treatment is thus to prolong life and improve quality of life by maintaining suppression of virus replication for as long as possible.

The three groups of treatment-naive patients for whom treatment guidelines are required are patients with symptomatic HIV disease or AIDS, patients with asymptomatic HIV infection and patients with primary HIV infection. The recommendations are summarized in Table 2.

5.1 Primary HIV infection

5.1.1 Treatment of primary HIV infection to alter the natural history

There is one placebo-controlled study of ZDV monotherapy in primary HIV infection (PHI) [130] and it showed short-term benefit only. As yet, there is no evidence of long-term clinical benefit from any study of treatment of PHI compared with deferring treatment until later. However, if it is recognized clinically, the diagnosis of PHI may represent a unique opportunity for therapeutic intervention. It is likely that, at the time of PHI: (1) there is a narrowing of the genetic diversity of the infecting virus compared with the virus in the index case [131,132]; (2) viral ability to infect different cell types may be limited; and (3) the capacity to mount an immune response is usually greater than it is later on. Therefore, the treatment of PHI may preserve HIV-specific immune responses and it has been hypothesized that long-term benefit may ensue. A variety of triple-drug therapy regimens appear able to suppress viral replication in the plasma, lymph nodes and gut for the majority of patients treated within a few months of PHI [132,133]. Recent studies have demonstrated that shortly after PHI there is a specific and strong CD4 helper HIV response [134–137]. This is in contrast to chronic infection where, with the exception of long-term non-progressors [136], the HIV-specific CD4 helper response is generally reduced [138]. These CD4 helper responses may be important in maintaining an adequate CD8 response. Such immune responses appear to be maintained in people treated with potent ART shortly after PHI and perhaps represent the best biological evidence that treatment at this time might be beneficial. Recent data suggest that there is more rapid and complete immune reconstitution in patients

Table 2 Recommendations for starting treatment

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

starting therapy during PHI than in those starting later [139]. There is still no answer to the question of whether treatment at such an early stage will influence the longer-term natural history.

Control of viral replication with no return of viraemia after withdrawal of ART has apparently occurred in a few patients treated very soon after PHI [140]. However, longer-term follow-up of patients treated during PHI with subsequent treatment interruption have not supported these initial hopes that early treatment would alter the natural history of HIV infection [141]. The role of drugs that are known to inhibit CD4 activation, such as hydroxyurea [142] and cyclosporin A [143,144], in the suppression of viral replication and boosting of CD4 lymphocyte responses in this setting is unclear and requires further evaluation. Given the present lack of clarity, it remains reasonable to consider treating PHI, ideally within a clinical trial. These putative benefits of treatment during PHI should be tempered by the known risks of toxicity, including lipodystrophy [145,146] and the potential for developing drug resistance at an early stage. The potential difficulties of long-term adherence to available regimens cannot be overstated. It is possible that short-term ART in PHI may be of some immunological benefit [147], but it is not known if this is associated with improved clinical outcome.

5.1.2 Treatment during PHI for immediate clinical benefit
Individuals who present with severe or prolonged symptoms (such as meningoencephalitis) due to PHI may improve, if treated with antiretrovirals. However, the duration of therapy needed is unknown, and the possibility of further acute retroviral syndrome on withdrawal of therapy must be considered.

5.1.3 Treatment during PHI to reduce onward transmission
One study has suggested that many recently infected patients have acquired the infection from others who were themselves recently infected with HIV. Identification and treatment of PHI might thus have some effect on reducing HIV incidence [4]. Even if treatment is not started during PHI, there are many benefits of recognizing early HIV infection. These include recognition and monitoring of primary drug resistance, partner notification and contact tracing, and the possibility of preventing HIV transmission. Particular effort should thus be directed to identifying patients with PHI who may present to a wide range of health-care providers.

5.1.4 Recommendations for starting treatment in PHI [CIV]
At the time of PHI, patients and physicians should make the most appropriate decision based on the limited data available.

The biological plausibility that early treatment may be beneficial for the immune system should be balanced against considerations of adherence to long-term therapy, potential toxicity and development of resistance. The Committee's first choice would be for patients to enter a clinical controlled trial, where available. The Spartac study is currently recruiting at many centres across the UK [1].

For those, who are treated at this time, there are no currently available data as to the best therapeutic regimen. Thus, a regimen appropriate for treatment of chronic HIV infection should be used.

If treatment is started, the decision to stop or continue may be reviewed in the light of evolving data or poor adherence.

Patients who are currently being treated with ART started during PHI and who may wish to stop treatment should be encouraged to do so in the context of a clinical study.

5.2 Symptomatic HIV infection

All patients with late disease and/or symptomatic HIV infection with a CD4 lymphocyte count consistently <200 cells/μL, or who have been diagnosed with AIDS or severe/recurrent HIV related illnesses* or tumour at any CD4 count, should start therapy. This is because of the high risk of further opportunistic infections which, although often treatable, may cause irreversible damage or be life threatening.

5.3 Asymptomatic HIV infection

There are no ongoing controlled studies that address the optimum time to start therapy [148]. Current guidelines are, therefore, based upon previous studies of monotherapy and data from large clinical cohorts. Since the quality of evidence is relatively poor, opinion is divided on this question. The absolute CD4 count forms the basis of these guidelines, but treatment may also be considered for patients with a CD4 percentage below 12%.

In the UK, patients are often diagnosed with HIV infection at a late stage. Over 30% present with a CD4 count of <200 cells/μL [149] and, consequently, the 'early vs. late' debate is irrelevant to many. The decision on when to start treatment will be influenced principally by two considerations: the short-term risk of developing AIDS prior to treatment and the potential efficacy of starting treatment at various CD4 counts. Although it may be biologically plausible to start treatment early, this has to be tempered by the known potential for significant drug

*With the possible exception of pulmonary tuberculosis.

toxicity, difficulties with long-term adherence, and the selection of drug-resistant virus.

5.3.1 Individuals with CD4 counts < 200 cells/μL

Patients with CD4 counts < 200 cells/μL have a high short-term risk of disease progression and death [150]. Several cohort studies have suggested that patients who initiate therapy when the CD4 count is < 200 cells/μL have an increased mortality [151–153] compared with those starting with CD4 counts above this level. Some prospective studies have suggested that for some antiretroviral regimens, patients with a low baseline CD4 count have a poorer virological response [154,155]. All of these strands of data suggest that it is better to start therapy before the CD4 count has fallen to < 200 cells/μL.

5.3.2 Individuals with CD4 counts > 350 cells/μL

If the CD4 count is > 350 cells/μL, the risk of clinical progression in the short term is generally low [150] although individuals with a high viral load have a greater (but still small) short-term risk of disease progression. Although some recent studies have added to the data suggesting a benefit in the short to medium term, on mortality and morbidity, with initiation of HAART at a CD4 of > 350 cells/μL [156–159], these need to be interpreted in the light of the likelihood that patients with HIV may live for decades after treatment with HAART [160]. In this group of patients, where the short-term risk of disease progression is low, it is still considered that initiation of HAART may result in greater morbidity and possibly mortality in the longer term as a result of drug toxicity and earlier exhaustion of treatment options. Furthermore, a large cohort study [161] has suggested no difference in disease progression in individuals commencing therapy with CD4 counts > 350 vs. 201–350 cells/μL. For the majority of patients with CD4 counts > 350 cells/μL it is reasonable to defer therapy until the CD4 count is below 350 but above 200 cells/μL.

Previous studies have suggested that delaying therapy until the CD4 lymphocyte count has fallen to < 350 cells/μL might be associated with a greater subsequent risk of non-Hodgkin's lymphoma [162]. Recent data [163,164] have suggested that the association between CD4 count and risk of NHL is most strongly associated with current and not nadir CD4 count, and that the risk of NHL rises steeply only when counts are < 100 cells/μL.

These data support the view that HAART should not be started in the majority of patients with CD4 counts > 350 cells/μL.

5.3.3 Individuals with CD4 counts 201–350 cells/μL

Ideally, most individuals with established HIV infection should start therapy when the CD4 count is in the range 201–350 cells/μL. It is important not to let the CD4 count fall below this level before starting treatment for the reasons outlined above. While it may be safe to monitor the CD4 count in some individuals with counts in this range, in others there will be the unacceptable risk of disease progression or of CD4 count falling to < 200 cells/μL. These individuals may include those with a high viral load (e.g. > 60 000 copies/mL [165], > 100 000 copies/mL [150]. Patients with a rapidly falling CD4 count (e.g. falling to > 80 cells/μL per year on repeated testing) [166] have an increased risk of CD4 cell count decline to < 200 cells/μL in the next 6 months. People in these groups may thus be considered for initiation of therapy relatively earlier within the CD4 count range 200–350 cells/μL. A further group in whom earlier initiation of therapy may be considered is those with hepatitis C co-infection, since progression of liver disease occurs more rapidly with lower CD4 counts [167,168] and antiretroviral treatment is associated with a reduced rate of progression of liver disease [169]. An alternative strategy may be to treat the hepatitis C before it becomes necessary to treat the HIV.

5.3.4 Recommendations regarding asymptomatic chronic HIV infection

- Currently, our recommendation is that patients start therapy before the CD4 count falls to < 200 cells/μL (AIII).
- Given the available data and the limitations of currently available treatment, treatment is not recommended in asymptomatic individuals with a CD4 count of > 350 cells/μL (BII).
- Within the range 200–350 cells/μL, individuals with a rapidly falling CD4 count (BIII), a high viral load (BIII) or hepatitis C co-infection (CIV) may be considered for earlier intervention.

If patients to whom these recommendations apply choose not to go on treatment, it is suggested that their CD4 count and viral load be monitored intensively (e.g. every 2 months) and the decision to start treatment be reviewed at regular intervals (AIV).

6.0 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 8 years coincides with the introduction of HAART [88,170]. Any HAART regimen 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

(http://www.hiv-druginteractions.org/). The cost of the regimen should also be considered.

A measurement of a regimen's success 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. Therefore, if the viral load measured 4 weeks after the initiation of therapy remains above 1000 copies/mL, this should prompt questions over possible poor adherence or other reasons such as reduced drug levels or primary drug resistance.

6.1 Which HAART regimen is best?

There have been no definitive controlled trials in naive patients to demonstrate the clinical superiority of a HAART regimen containing a currently recommended boosted PI when compared with a regimen containing an NNRTI. Studies have, however, shown the superiority of EFV over NFV, boosted SQV, and boosted amprenavir-containing regimens [171]. There is, however, no data comparing RTV-boosted LPV or RTV-boosted fosamprenavir. We, therefore, believe that patients should continue to be informed about and encouraged to participate in available clinical trials to further answer this clinical question.

It is important to select a regimen best suited to the individual patient, and therefore to fully assess baseline risk factors for resistance, hepatitis B/hepatitis C co-infection, cardiovascular disease, diabetes and psychiatric disease. In addition, lifestyle issues including smoking, obesity and recreational drug use and alcohol use should be taken into account. The advantages and disadvantages in terms of potency, adherence, toxicity, salvageability and potential drug–drug interactions are summarized in (Table 3).

Previous guidelines suggested that patients with high viral loads may need more than three active drugs to achieve a rapid decline in viral load. Evidence from clinical trials, however, does not support this approach and we do not recommend this strategy.

6.1.1 Two NRTIs plus an NNRTI

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 every 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.

NVP is the alternative NNRTI. The potential of serious rash and fatal hepatoxicity that can occur within the first 6 weeks are well described and are discussed below, and have also been reported with EFV.

6.1.1.1 EFV – preferred regimen. EFV, in many randomized controlled trials, has demonstrated efficacy when compared to other treatment regimens including PIs, boosted PIs, NVP and 3NRTI-based regimens. In the 2NN study [172], data compared both drugs in a randomized manner and showed that EFV and NVP were comparable in potency. However, equivalence was not formally proven, with a small chance that NVP was superior to EFV and a greater chance of the reverse. In an important *post hoc* sensitivity analysis stratified by CD4 count and viral load, the risk of virological failure was greatest for those with

Table 3 Initial HAART regimens

Regimen	Recommendation	Advantages	Disadvantages
Choices of initial therapy: summary of recommendations			
2NRTIs + NNRTI*	Recommended	1. Equivalent or superior in surrogate marker trials compared with PI-based regimens at 104 weeks of follow-up 2. Easier adherence	1. No RCT clinical endpoint data 2. Shorter follow-up 3. Single mutations may lead to cross-class resistance
2NRTIs + boosted PI†	Recommended	3. Evidence of improved surrogate endpoint efficacy for lopinavir/ritonavir compared with a single PI 4. Better PK 5. Easier adherence 6. Less resistance at virological failure	4. No RCT clinical endpoint data 5. Possible increased toxicity and drug interactions
3 NRTIs	Not ordinarily recommended except for patients with low VL and major adherence concerns, but see Section 4.2.3.	7. Spares PI and NNRTI classes 8. Fewer drug interactions 9. Low pill burden	6. No RCT clinical endpoint data 7. Short-term surrogate marker data suggests less potent than NNRTIs or PIs 8. Is less effective at high viral loads

*The recommended NNRTI is EFV with nevirapine being an alternative. NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RCT, randomized controlled trial; PI, protease inhibitor; VL, viral load; EFV, efavirenz.

CD4 counts of <25 cells/μL for both drugs, although EFV did perform better numerically [173]. However, the principal reason for the recommendation of EFV as the preferred NNRTI is related to toxicity in the NVP arm, which will be discussed in the next section.

EFV appears to be potent when used in patients with high viral loads and low CD4 counts. Data also has demonstrated long-term durability of EFV-based regimens.

The major limitation of EFV as for all currently available NNRTIs, is the low genetic barrier to resistance. This is becoming a major concern due to the rising incidence of primary resistance. A single mutation is sufficient to confer resistance to EFV and the loss of this class in future regimens (at least until next generation inhibitors of this class are available). It 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 to 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 [174]. Nevertheless, in a small minority, symptoms persist and may be severe enough to warrant switch to an alternative agent. The evidence is conflicting as to whether or not side effects are common in individuals with a previous psychiatric disturbance [175,176]. Rashes do occur, but severe rashes with EFV are unusual (the incidence of Stevens–Johnson syndrome is 0.1%). Lipid abnormalities, mainly rises in cholesterol above baseline values, have been observed in patients on EFV-containing combinations [177].

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 [178]. Women of childbearing potential should be warned about becoming pregnant while on EFV and, wherever possible, EFV should be avoided in women who may contemplate pregnancy.

EFV has a long half-life when compared with nucleosides and caution is needed when stopping this regimen.

6.1.1.2 NVP – alternative regimen. As discussed above, NVP has been compared with EFV in the 2NN Study [179] and was 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 co-administration of steroids, which should be avoided [180–182]. 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 anlyses have shown a 12-fold higher incidence of serious hepatic events in women with CD4 counts >250 cells/μL and this drug should be avoided in these patients, as well as those with active hepatitis B or C infection. NVP is currently used twice a day, but the pharmacokinetics, and now clinical trial data, indicate that once-daily dosing is possible, although there are more abnormalities of liver function [172].

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 a previous psychiatric history). 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.

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

6.1.2 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. Sustained suppression of plasma HIV-1 RNA levels has been observed with more than 7 years of continued immunological recovery.

Most clinicians now use a PI in combination with low-dose RTV to provide a pharmacokinetic boosting effect when they start antiretroviral-naive patients on a PI-based regimen. The Committee feels that there is now enough data to suggest that if a PI is chosen as part of an initial HAART regimen, that this should be a boosted agent. This is because RTV boosting increases drug exposure, prolongs the drug half-life and reduces the pill burden and dosing frequency, improves adherence, and limits the development of resistance. The disadvantage of this approach is a possible risk of greater lipid abnormalities, particularly raised fasting triglycerides. The Committee recommends RTV-boosted LPV as the preferred regimen with an alternative regimen to include RTV-boosted fosamprenavir and RTV-boosted SQV (hard gel capsule or film-coated capsule).

In two randomized studies, the development of resistance in patients failing therapy has been shown to be higher in those starting with NNRTI than in those starting with boosted PI [8,183].

6.1.2.1 RTV-boosted lopinavir – preferred regimen. Data from the 863 study [172] showed superior surrogate marker endpoint for patients using LPV/ritonavir (r) when compared to those using 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, only 3TC mutations, while most of the patients in the NFV arm had PI mutations in addition to 3TC resistance. The main side effects of this regimen are lipid abnormalities and gastrointestinal side effects with diarrhoea being the predominant symptom.

6.1.2.2 RTV-boosted fosamprenavir – alternative regimen. Fosamprenavir boosted by RTV has been compared to NFV in clinical studies in naive patients. More patients randomized to RTV-boosted fosamprenavir with viral loads $>100\,000$ achieved viral load suppression than those receiving NFV. Data has also shown that RTV-boosted fosamprenavir shows durable responses of up 96 weeks in naive patients, with no emergent PI resistance reported to date.

This regimen has a low pill burden (2 bid). Flexible dosing is generally well tolerated although the development of lipid abnormalities is a potential long-term toxicity issue. It is licensed dosed twice daily in the UK.

6.1.2.3 RTV-boosted saquinavir – alternative regimen. RTV-boosted SQV has demonstrated potency in once- and twice-daily schedules. It has been compared (twice daily) to RTV-boosted indinavir (IDV) and LPV (MaxCMin1 and MaxCMin2, respectively) [184,185], where approximately one-third of patients were drug-naive. 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 [184,185]. With the advent of the 500 mg film-coated capsule, RTV-boosted SQV represents a relatively low pill burden (3 bid), well-tolerated alternative to RTV-boosted LPV in naive patients, with possibly less gastrointestinal (GI) 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.

6.1.2.4 RTV-boosted or unboosted atazanavir. Unboosted atazanavir has been shown to have similar efficacy to NFV and EFV in three clinical studies [186–188]. RTV-boosted atazanavir has also been shown to have similar efficacy to LPV/r in PI-experienced patients.

The main advantages of atazanavir/r are that the drug is dosed once daily and has less 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 in naive patients. The Committee feel that use of this drug, boosted or unboosted, in naive patients should be restricted to those with established cardiovascular risk factors and where a PI is required. This advice may change pending the results of clinical trials (Table 4).

6.1.3 Three NRTIs

There is now surrogate marker endpoint data suggesting that ZDV/3TC/ABC (usually combined as Trizivir) is less potent than combining two NRTIs with either an NNRTI or a PI [189]. In ACTG 5095, the 3 NRTI arm was stopped by the DSMB [191], as Trizivir was less potent than the other two arms (Trizivir/EFV or Combivir/EFV). Fewer patients had suppressed their viral load to <50 copies/mL by 48 weeks in the Trizivir arm than those in the other two arms (61% vs. 81%). This finding was observed at both high and low entry viral loads. Adherence was unlikely to have been a factor in these results as the pill burden was low in all groups. The Committee now feels that Trizivir should only be considered as a starting regimen in very occasional circumstances, e.g. in informed patient choice based on likely poor adherence if alternative options are used, or when concomitant medication is needed such as for TB. Non-thymidine-containing 3NRTI regimens (e.g. ABC/3TC/TDF or DDI/3TC/TDF) should not be used because of unacceptably high rates of virological failure [113, 191,192]. Currently, no triple NRTI regimen can be recommended. However, 48-week data suggests that ZDV/

Table 4 Comparison of boosted PIs

	Lopinavir/ ritonavir	Saquinavir/ ritonavir	Fosamprenavir/ 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.
*500 mg capsule.
†Limited data for ritonavir-boosted saquinavir in naive patients. However, the Committee feel there is sufficient evidence available for boosted-PIs to allow careful extrapolation of data.
‡Limited data available.

3TC/ABC with TDF is a possible option when a PI or NNRTI-based HAART cannot be administered.

6.2 Choice of 2NRTIs (includes nucleoside and nucleotide RTI) [Table 5]

Two NRTIs remain an integral component of HAART with either an NNRTI or a RTV-boosted PI. As yet, there is no evidence that a third NRTI provides additional benefits or that NRTI-sparing combinations are as effective. There are now eight NRTI analogues, three 2NRTI co-formulations, and one triple NRTI combination to choose from. The availability of two new co-formulations (TDF/FTC and ABC/3TC) in addition to ZDV/3TC has the potential to have a significant impact on prescribing patterns with clinicians likely to be choosing the 2NRTI backbone from one of these three. Considerations in the choice include tolerability, convenience, fit with other components of the combination, long-term toxicity, and the expected resistance pattern and therefore future options on virological failure. Pre-existing primary drug resistance will also influence choice of initial NRTIs. Major difference in costs between these combination pills also exists in some countries including the UK.

6.2.1 Co-formulated 2NRTIs

ZDV/3TC (co-formulated as Combivir) is the most studied of the dual NRTI backbones with both NNRTIs [110,111,190,193–195] and PIs [187,188,190,193] and has been the most popular 2NRTI combination in the UK [196]. It has similar virological efficacy to ABC/3TC and TDF/FTC at 48 weeks [194,197]. Limitations include twice-daily dosing and ZDV-related side effects of nausea/vomiting, anaemia, and after a variable period of time, fat wasting. In a randomized trial comparing co-formulated ZDV/3TC with individually dosed FTC/TDF, both dosed with EFV, 48-week results demonstrated a significantly higher frequency of adverse events leading to discontinuation in the ZDV/3TC arm (9% vs. 4%) [197]. Evaluation of a TDF/FTC backbone is restricted to Kaletra [198] (no comparator 2NRTI) and EFV [197] (compared to ZDV/3TC). However, given the comparability of FTC and 3TC, extrapolating the data from the Gilead 903 seems justifiable. This demonstrated TDF/3TC with EFV to be highly and durably active, with good tolerability and minimal long-term toxicity [199]. Data out to 144 weeks demonstrates viral load of <50 copies/mL in 73%, with only 16% suffering virological failure (>400 copies/mL).

ABC/3TC is the third co-formulated compound. 2NRTI combination has been studied with EFV [194,200–202] and with fosamprenavir/r [203]. At 48 weeks, 8–10% suffered virological failure. Hypersensitivity reactions (HSR) from ABC were identified in approximately 8% in these studies. These studies used a case reporting form (where HSR was also reported in 3% of zidovudine-treated patients in a double-blind study) and the SPC states a rate of HSR of 5.4%. Higher CD4 counts at 48 weeks have been demonstrated with both TDF/FTC and ABC/3TC than with ZDV/3TC [197].

All three NRTI combinations perform well. Most clinician experience exists for ZDV/3TC with EFV. However, there are genuine concerns about lipoatrophy with ZDV in the long term. TDF with either 3TC or FTC is durably potent with few virological failures: when combined with EFV, it is better tolerated than ZDV/3TC with significantly fewer discontinuations in the first 48 weeks [197]. Some cohort studies indicate that TDF may be associated with a reduction in glomular filtration rate although this was not seen in randomized studies. The 903 study showed a small reduction in bone mineral density in individuals taking TDF compared with those on d4T. There is a general perception that the K65R mutation is common with TDF/3TC, although this was only seen in 2.4% at 48 weeks in those patients on EFV/TDF/3TC (overall virological failure rate 9.7%). This was mainly observed in those with CD4 counts of <50 copies/μL and viral loads of $>100\,000$ copies/mL: K65R has not been observed in patients with pre-treatment wild-type virus when they were receiving TDF/FTC and either EFV or LPV/r arm out to 48 weeks [197].

Table 5 Preferred regimens

Regimen	A	B	C
Choose one drug from columns A, B and C			
Preferred			
	EFV	ZDV[¶]	3TC[¶#]
	LPV/r	ABC[#]	FTC[††]
		TDF[††]	
		ddi	
Alternative			
	FOS/r[§]		
	SQV/r[§]		
Specific groups			
	NVP*		
	ATAZ[†‡]		
	ATAZ/r[†‡]		

EFV, efavirenz; LPV, lopinavir; FOS, fosamprenavir; NVP, nevirapine; ATAZ, atazanavir; ZDV, zidovidine; ABC, abacavir; TDF, tenofovir; ddi, didanosine; 3TC, lamivudine; FTC, emtricitabine; r, ritonavir; PI, protease inhibitor; SQV, saguinavir.
*Only when CD4 is <250 cells/μL in females, <400 cells/μL in males.
[†]Where established cardiovascular disease risk factors and PI required.
[‡]Currently unlicensed for naive patients in the UK.
[§]Circumstances where preferable over LPV/r (see text).
[¶]Co-formulated as Combivir®.
[#]Co-formulated as Kivexa®.
[††]Co-formulated as Truvada®.

ABC/3TC is also potent and well tolerated: hypersensitivity reactions may occur early and patients need counselling. Where HLA genotyping is available, the absence of the HLA B*5701 allele has a negative predictive value of >99% and the risk of drug hypersensitivity is reduced to <1–2% [204]. The L74V mutation is seen in <1% at 48 weeks in patients on EFV/ABC/3TC (overall virological failure rate 6.2–9.9%). Both K65R and L74V mutations can lead to difficulties in choice of subsequent NRTI drugs if they develop.

These three NRTI backbones probably offer comparable antiviral efficacy and can all be recommended. When combined with EFV, TDF/FTC gives rise to significantly less outcome failures at 48 weeks when compared to ZDV/3TC [197]. This difference is driven by ZDV-related toxicity in the first 24 weeks. Ongoing monitoring for long-term toxicity and resistance development with TDF/FTC and ABC/3TC co-formulations will be important. The relative costs of the individual NRTIs are given in Table 1.

6.2.2 Other 2NRTI/NtRTI combinations

d4T/3TC is a well-studied nucleoside combination [199,201,205,206] with equal antiviral effectiveness to TDF/3TC [199] and ABC/3TC [201] but with significantly greater d4T-related mitochondrial toxicity, including lipoatrophy. Because of this, d4T is not recommended for initial therapy. A small study comparing ddI with either TDF or 3TC and EFV showed, an unacceptably high rate of failure from early resistance with TDF/ddI, which was most marked in patients with more advanced disease [113]. There is also potential for TDF to potentiate ddI-related toxicity. This combination is therefore not recommended. ddI/3TC [113,207] or ddI/FTC [208] as a 2NRTI combination is well tolerated and effective. 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 for ZDV/enteric-coated ddI in HAART. Similarly, TDF/ABC and ABC/ddI have not been evaluated in naive patients: none of these 2NRTI combinations can be recommended.

6.3 Conclusions

Most clinicians in the UK favour an NNRTI-based regimen for initial therapy, reserving boosted PIs for later use based on the lower perceived risk of toxicity and the ease of administration of NNRTIs. There is no conclusive comparative evidence to support this stance. However, there are cost benefits for selecting an NNRTI-based regimen in contrast to most boosted PIs and this needs to be taken into account. With the reported increasing levels of primary resistance in newly acquired HIV infections, clinical practice may change with lower pill burden PI-containing regimens becoming available, which do not produce lipid abnormalities. It is anticipated that clinicians will favour one of the three co-formulated NRTI drugs. They offer comparable antiviral efficacy but differ in dosing schedule, tolerability, short and long-term toxicity and cost. The Committee feel that there is insufficient evidence as yet to make recommendations between them.

7.0 Changing or stopping therapy in the absence of virological failure

7.1 Patients started on regimens that are not currently recommended for initial therapy

Many patients are currently established on regimens that are no longer recommended for initial therapy. Such patients should be advised of recent study results and should have explained to them where changes in therapy may reduce the risk of virological rebound and improve their quality of life. Those who are stable with evidence of sustained virological suppression (viral load of <50 copies/mL for 6 months or more) and who are not experiencing side effects (including lipoatrophy), may prefer to remain on their current therapy, as the longer the period of complete suppression, the lower the risk of subsequent virological rebound is likely to be.

7.1.1 2NRTI plus unboosted PI regimens

Patients who are on PIs suitable for boosting (i.e. IDV or SQV) may find a boosted regimen simpler to take, with fewer daily doses and food restrictions. Although switching to a boosted regimen may improve quality of life [209], some studies have shown evidence of a significant increase in toxicity [210]. NFV is not suitable for boosting and can be continued if the patient is stable with undetectable viral load.

7.1.2 3NRTIs

Patients taking triple NRTI regimens should be advised of recent trial results indicating a higher risk of virological rebound than with currently recommended regimens. A change in therapy should be considered for those who have not achieved sustained virological suppression (<50 copies/mL for more than 6 months) or who have achieved viral suppression but have previously received mono or dual nucleoside therapy.

7.1.3 Regimens containing stavudine (d4T)

d4T is no longer recommended for initial therapy largely because of data from several studies suggesting that it is

associated with an increased risk of lipoatrophy [211]. Patients who are on a d4T-containing regimen should consider switching if treatment history and resistance data suggest that an alternative drug is likely to be active. A switch to ZDV may delay but is not likely to prevent the development of lipodystrophy. However, a switch to either ABC or TFV is associated with an increase in subcutaneous fat [212–214]. Alternatively, reducing the dose of d4T from 40 to 30 mg bid in those over 50 kg may be associated with reduced risk of lipoatrophy [215].

7.1.4 Regimens containing ZDV

In view of the increasing recognition that long-term treatment with ZDV may lead to lipoatrophy, physicians may wish to discuss the option of switching to either ABC or TFV. Since lipoatrophy may not be fully reversible by switching after it has developed, patients may prefer to make such a switch pre-emptively.

7.1.5 Non-HAART regimens

A small number of patients may still remain on non-HAART regimens (e.g. 2 NRTIs). Even if plasma viral load is undetectable or low, there is likely to be significant ongoing viral replication [216] and thus evolution of drug resistance, which will limit future options. Consideration should thus be given to switching all remaining patients to HAART regimens. Patients currently on a non-HAART regimen who started therapy with a high nadir CD4 count (e.g. above 300) should be considered for treatment interruption (see Sections 2.4 and 7.3.3).

7.1.6 NNRTI regimens with TDF and ddI

When given with EFV, the 2NRTI combination of TDF/ddI has been shown to be inferior to ddI/3TC and, by justifiable extrapolation and comparative data with other trials, to other recommended 2NRTI combinations. This data should be discussed with patients currently receiving this combination and the possibility of switching one or both of the NRTIs considered.

7.2 Patients on recommended regimens

Patients who have difficulty with adherence should be assessed individually in accordance with the adherence guidelines. Where appropriate, they may be switched to simpler regimens such as once-daily therapy. This appears to be safe, except in those who have had either sub-optimal therapy or therapy that may have produced viruses with reduced sensitivity (resistance) to drugs involved in the simplification regimen.

When switching because of life-threatening toxicity, e.g. fulminant hepatic failure, all drug therapy should be stopped until the patient has recovered.

7.2.1 Switching from PI-based regimens

A number of studies have evaluated the approach of switching the PI in a HAART regimen to an NNRTI [217] or to ABC in patients who have a persistently suppressed viral load. There are several potential advantages of such an approach, including the reduction of central adiposity and hyperlipidaemia. A variable proportion of patients in such studies have experienced early virological failure, often because of pre-existing NRTI resistance before switching [218]. It is very important to consider the possibility of NRTI resistance, particularly in patients who have previously experienced virological failure, by reviewing treatment history and the results of resistance tests (carried out on stored samples, if available), as switching one or more NRTIs may also be necessary at the same time to ensure continued virological suppression.

7.2.2 Switching between NNRTIs

For a serious skin rash in individuals taking an NNRTI-containing regimen, the drug needs to be stopped immediately. It may be safe to switch to an alternative NNRTI, although patients who develop a severe rash after starting NVP and switch to EFV may have an increased risk of developing a rash due to EFV.

The optimum policy for switching from EFV to NVP remains to be determined in large studies. One small study has indicated that switching to full dose NVP immediately produces drug levels of a therapeutic range [219]. This is because EFV also induces cytochrome P450, enhancing the metabolism of NVP. However, the manufacturers still recommend a 14-day lead-in period with 200 mg daily.

The manufacturer of NVP has recently issued a warning regarding the increased risk of life-threatening hepatic and cutaneous reactions to the drug in women with CD4 counts over 250 cells/μL and men with CD4 counts over 400 cells/μL. The Committee recommends that the relevant CD4 count is the one at the point of switching.

7.2.3 Stopping NNRTI-based regimens in non-emergency situations

EFV and NVP have long plasma half-lives; although variable, this has been found to be as long as 3 weeks in some patients. If all the drugs in a regimen containing 2 NRTIs and one of these drugs are stopped at the same time, levels of the NRTIs are likely to fall more rapidly that the NNRTI, leaving a period of functional NNRTI monotherapy. This may be sufficient to select NNRTI-resistant virus [220,221] although this functional monotherapy occurs

when viral replication is either completely suppressed or very low. Ways to limit this risk are to switch the NNRTI to a short-acting PI before stopping the whole regimen or to continue with the two NRTI drugs for a period after stopping the NNRTI of 7–14 days. The optimum time period for either policy in unclear and likely to be based on the individual pharmacokinetics of the patient.

7.3 Stopping therapy in individuals with complete viral suppression (STI)

STI has been investigated in chronic therapy both to enhance immune responses and as a means of decreasing drug exposure, with the potential of limiting toxicity and perhaps reducing costs. Results have varied depending on the pattern of treatment interruption used.

7.3.1 Intermittent on–off therapy cycles of 1 month or longer

The largest study of longer intermittent therapy cycles is the Swiss–Spanish Intermittent Treatment (SSIT) trial of patients who had had <50 copies/mL for longer than 6 months [222]. The patients stop therapy for 2 months, followed by 8 weeks back on therapy. After four such cycles, therapy is stopped until the patient's HIV RNA load increases to >5000 copies/mL. There was no significant difference between the continuous and intermittent therapy groups on the primary outcome of the study, which was the change in viral load pre- and post-treatment.

Another controlled trial of 70 patients being treated with cycles of 1 month on followed by 1 month off therapy [223] was abandoned after the virus rebounded with each interruption in the first 15 subjects, leading to the development of drug resistance in several patients.

7.3.2 Intermittent on–off therapy cycles of 1 week

Another approach involved a cohort of 11 subjects given cycles of intermittent therapy, consisting of 1 week on followed by 1 week off therapy [224]. Although short-term results looked promising, this study was also discontinued due to the later development of viral rebound and drug resistance. In addition, data from a sub-group of the SSIT Trial showed that even after 1 week of treatment interruption, significant viral replication can be induced [225]. The HIVNAT 014 study was also unsuccessful in respect of a group of treatment-experienced patients using 1-week on–off therapy cycles, 20–30% of whom showed viral breakthrough, with development of resistance in some cases. In conclusion, the Committee feels there are insufficient data to recommend intermittent cycling of treatment outside rigorously controlled clinical trials.

7.3.3 Discontinuation of therapy with re-start based on CD4 count (CII)

In individuals with complete virological suppression, treatment interruption tends to lead to viral load rebound in a few days and CD4 count decline. In individuals whose CD4 count never fell to low levels, interruption is unlikely to rapidly result in CD4 count decline to levels associated with substantial risk of clinical disease. Interruption of therapy is, therefore, an option in such patients, if there is a strong desire to do so, due to toxicity or other reasons. The HIVNAT 014 study used this approach [226] and a larger study with similar CD4 count guidance is being undertaken by the CPCRA. It should be understood that it may require years of therapy after the interruption to re-attain the CD4 count level prior to the interruption.

We would recommend that any structured treatment interruption should be planned, that particular care should be taken with withdrawal of drugs with extremely long half-life such as EFV, and that treatment should be re-started based on the CD4 count. Patients should be counselled and understand these issues. The issues associated with treatment interruption should all be discussed in detail, including the need for relatively frequent CD4 monitoring during an interruption, the small risk of developing an acute retroviral syndrome similar to PHI, and the risk of onward transmission, which will probably increase as the viral load rises.

8.0 Changing or stopping therapy for virological failure

The viral load nadir achieved within the first few months on treatment is predictive of the subsequent risk of virological failure [227]. To limit the risk of virological treatment failure, an objective of initial therapy (and subsequent treatment regimens, if achievable) is to suppress viral load to <50 copies/mL. Once suppressed, patients may subsequently experience transient rises in viral load to just above detectable (blips) or sustained viral load rebound.

Recommendations on action to be taken on first virological failure are shown in Table 6.

At all stages of virological rebound, patients should be clinically assessed to determine factors which may have reduced plasma drug levels to below optimal levels such as drug–drug interactions, poor adherence, incorrect dosing or factors which may have increased viral replication such as inter-current infections and vaccinations.

Table 6 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 is optimal and likelihood of resistance low, consider augmenting treatment regimen. If likelihood of resistance is 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[2]	Consider factors affecting plasma drug levels.* Consider: 1. Changing all drugs if effective option available is likely to reduce viral load to undetectable levels. 2. Continue regimen and monitor if no effective option is 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 benefit on short-term virological response to the subsequent regimen.
‡There is a risk of developing further mutations by allowing a patient to remain on a virologically failing regimen, which could limit further options for treatment.

8.1 Viral load blips

Transient rises in viral load to levels to just above detectable (viral blip) are reported to occur in a significant proportion of patients on treatment over time [228,229]. Patients who are developing sustained virological rebound (failure) would show further increases in viral load, whereas those whose viral load is transiently detectable because of assay-related problems or other factors will show no further rise or revert to undetectable, usually within 4–6 weeks. It is controversial whether viral blips are associated with an increased future risk of virological failure in those who have already achieved viral suppression. Most studies have failed to detect an association with virological failure or the development of antiretroviral resistance [229,230]. One study [228] suggested that although a low level viral blip was not a predictor of failure, those with repeated episodes or sustained low level viral rebound were more likely to experience virological failure in the future. Patients with frequent blips related to possible inadequate drug potency in the absence of genotypic resistance to their current regimen may be candidates for intensification or change of therapy.

8.2 Sustained viral load rebound

Falls in CD4 count and clinical disease progression are not usually seen in patients experiencing low-level viral-load rebound but are the usual eventual outcome in patients whose viral load continues to rise towards pre-treatment levels [231]. Although resistance to all drugs in a treatment regimen may not be detected in patients experiencing virological failure, it is likely that the higher the copy number, the more probable the development of resistance. For some drugs (e.g. 3TC, NNRTIs) mutations at one position in the reverse transcriptase gene can cause high-level phenotypic resistance and usually emerge at low levels of viral load rebound. Reduced susceptibility to other drugs requires the accumulation of two or more mutations in the viral genome and occurs with ongoing viral replication in the presence of drugs. Thus, if significant levels of viral replication develop and persist on therapy and other options are available, which can completely suppress it, then therapy should be changed. The lower limit for a definition of significant levels of viral replication is somewhat arbitrary. For practical reasons, many clinicians would accept a persistent (two values at least 1 month apart) viral load level of >400 copies/mL for consideration of a treatment switch. This may change as further information is gained on the frequency and the emergence of genotypic mutations at low level viraemia on different drug combinations and how this may influence the treatment response to subsequent regimens, together with improvement in the sensitivity of assays to detect drug resistance, which is presently only reliable with viral loads of >1000 copies/mL.

8.3 Changing therapy [BII]

Patients should be considered for a change of therapy if they show sustained rebound in viral load levels, previously undetectable, or have not achieved undetectable levels on their current treatment regimen after 24–36 weeks. The likelihood of achieving an undetectable viral load on changing therapy is predicted by the number of active drugs in the new regimen [10,11] plus factors influencing tolerability and adherence. The decision to change therapy should be guided by the availability of a

treatment option that is likely to have the potency to suppress viral load to undetectable levels (< 50 copies/mL) and which the patient is likely to be able to adhere to and tolerate.

Although the addition of a single new agent in individuals experiencing low level viral load rebound may result in a proportion becoming undetectable [232], this strategy is not recommended as the disadvantages in terms of added toxicity and development of resistance to the new drug are probably greater than the likelihood of achieving a sustained undetectable viral load.

The choice of a new regimen should be guided by the results of current and previous resistance testing, treatment history and the ability of the patient to adhere to and tolerate individual drugs. Resistance testing is important to identify which drugs will possibly be of most benefit i.e. active. Active is defined as 'where a drug is likely to have significant antiviral activity *in vivo* based on the antiretroviral treatment history and the results of all current and previous resistance testing'.

8.3.1 Virological failure with no resistance

Patients may experience virological failure but have no resistance mutations detected on genotypic resistance testing. Failure here is probably due to poor treatment adherence with drug levels that are both insufficient to maintain viral load suppression and inadequate to select out viral mutations associated with drug resistance. However, the absence of detectable resistant mutations does not exclude the presence of mutations in minor virus populations [14,15,233,234].

In this situation, factors affecting adherence and drug exposure should be fully evaluated and the choice of the next regimen guided by previous treatment experience and the likelihood of the patient to adhere to and tolerate individual drugs.

8.3.2 Virological failure with PI mutations [BII]

There is no clear randomized control trial evidence to guide the optimal treatment strategy in patients with PI mutations with or without NRTI mutations, which may follow treatment failure with 2 nucleoside analogues and a PI.

One option is to change both NRTIs and introduce a new class by switching the PI to an NNRTI. If there is cross-resistance among the NRTIs, limiting the benefit of new NRTIs, there is likely to be a high risk of more rapid virological failure and development of resistance to the NNRTI with this strategy. In this situation, a more effective option would be a new PI plus 1 or 2 active NRTIs with or without an NNRTI. In a number of cohort studies, RTV-boosted LPV in combination with either EFV or NVP, reduced viral loads to below detectable limits in NNRTI naive, PI-experienced patients [235,236]. The decision to include a NNRTI or not may depend on the extent of cross-resistance among the NRTIs and thus the availability of active NRTIs.

There are comparative data assessing which RTV-boosted PI regimen is more effective in PI-experienced patients with detectable PI mutations at baseline, and further data will be available from ongoing trials. Similar virological efficacy at 48 weeks has been demonstrated between LPV/r and atazanavir/r in patients who have previously failed at least 2 regimens including at least 1 containing a PI [237]. Gastrointestinal side effects and hyperlipidaemia were more common with LPV/r. Hyperbilirubinaemia and, in a small number of patients, clinical jaundice were the most common side effect with atazanavir/r.

In patients who had previously experienced treatment failure to 1 or 2 PIs, non-inferiority of fosamprenavir/r compared to LPV/r using the primary endpoint of time-averaged change in viral load from baseline could not be established [238]. However, similar proportions of patients achieved VL < 50 copies/mL at 48 weeks with LPV/r and twice-daily fosamprenavir/r, but not with once daily. Once-daily fosamprenavir/r is not recommended in patients with previous PI failure.

Although SQV/r was inferior to LPV/r in one study, this was due mainly to tolerability problems of the SQV formulation [239]. The choice of which boosted PI to use is likely to be determined by the pattern and number of PI mutations detected, the side effect profile and factors affecting adherence and tolerability.

8.3.3 Virological failure with NNRTI mutations [BIII]

No randomized comparative study has addressed the optimal treatment strategy in patients who have NNRTI mutations plus or minus NRTI mutations, following failure of two nucleoside analogues plus a NNRTI. Unlike PIs, the presence of one or more NNRTI-associated mutations usually indicates cross-resistance to both NVP and EFV.

As a PI-based regimen improves the clinical outcome after NRTI therapy [240], it is likely to do so after 2NRTIs and an NNRTI. Thus, most physicians would treat virological failure with the presence of NNRTI mutations by discontinuing the NNRTI, and guided by resistance testing change to two active NRTIs and add a boosted PI [184,185]. There is only limited data from studies in patients who are ART-experienced but PI-naive to guide choice of the boosted PI. Data from trials in PI-experienced patients (see Section 7.2.2) and ART-naive patients may help to inform choice. In ART-naive patients, LPV/r [205] has greater virological efficacy than NFV (thrice daily). In another study of once-daily fosamprenavir/r [204] com-

pared with NFV (twice daily), similar virological efficacy by ITT analysis at 48 weeks was demonstrated although protocol-defined virological failure was less in the fosamprenavir group. Studies comparing different boosted PIs in patients who are PI-naive are ongoing.

8.3.4 Virological failure with NRTI mutations alone [BIV]
Virological failure with NRTI mutations alone may follow treatment with triple NRTI regimens or 2NRTIs and a PI. It is unusual to fail with NRTI mutations alone in patients experiencing treatment failure on 2NRTIs and an NNRTI. In patients who have failed an NNRTI-containing regimen, minor populations of NNRTI mutations may be present, which are not detectable on routine resistance testing, but are likely to affect response to future NNRTI-containing regimens [15,234].

The number and pattern of genotypic mutations in the reverse transcriptase gene will determine the extent of cross-resistance among the NRTIs and whether two active and potent NRTIs could be included in the new regimen. If there is no or limited cross-resistance detected, then an option is to switch to a regimen comprising two active and potent NRTIs plus either a boosted PI or an NNRTI. Although the latter may not be as effective as a boosted PI, because of the low genetic resistance barrier of an NNRTI or the presence of NNRTI mutations in minor virus populations from previous NNRTI exposure, and the possible presence of greater cross-resistance among the NRTIs than detected by current genotypic assays. If the likelihood of cross-resistance among the NRTIs is high (i.e. there are not two fully active drugs), then switching to a regimen comprising a boosted PI with two, at least partially active NRTIs is recommended. In NNRTI-naive patients, a regimen containing a boosted PI and an NNRTI and one or two active NRTIs is an alternative. In patients who are PI-experienced, but do not have detectable PI mutations, it is not known whether their virological response to a new regimen containing a PI is different from those who are PI-treatment naive.

8.3.5 Use of enfuvirtide (T20)
Enfuvirtide (T20) has recently been licensed for use in treatment-experienced patients. Optimally, it should be used with one or more active drugs in the regimen. Predictive factors for response to enfuvirtide have been identified and may be helpful to identify patients suitable for treatment with enfuvirtide [241].

T20 is a 36 amino acid peptide derived from HIV GP41. It inhibits GP41-mediated fusion and is active in nanomolar ranges in T-cell lines. It is active against NSI and SI viruses and is synergistic with reverse transcriptase inhibitors, PIs and other entry inhibitors. It is self-administered by subcutaneous injection, the usual dose being 90 mg twice a day. It shows no cross-resistance with other antiretroviral classes. Because it works extra-cellularly, it has a low potential for both drug–drug interaction and for any interaction with cellular metabolic processes. Its activity is independent of co-receptor usage.

Although clinical efficacy has been demonstrated in individuals with triple-class experience [10,11], it is more effective to use this drug where it can be combined with other active agents, rather than as an add-on to a failing regimen or where it is the sole active agent in a new combination, as resistance can occur rapidly. A higher virological response rate was seen in patients who had lower plasma viral load and higher CD4 count at baseline, a history of exposure to fewer antiretroviral agents and 2 or more other active drugs in the regimen [10,11].

Enfuvirtide has to be reconstituted and injected subcutaneously twice a day. The majority of patients develop injection site reactions but these are only rarely a cause of discontinuation. It is substantially more expensive than any other licensed antiretroviral drug (Tables 6 and 7).

9.0 Treatment for patients with evidence of resistance to NNRTIs, nucleoside analogues and PIs

9.1 Patients whose therapy fails after having used at least three classes of drugs ('salvage therapy')

The term salvage therapy is used commonly by both physicians and patients, but is not always clearly defined. One possible definition is treatment following exposure to multiple drugs from all available classes of antiretroviral agents, yet many so-called salvage studies have been carried out in patients who are naive with respect to one class of drugs. Moreover, this definition of salvage becomes a moving target as more classes of drugs (e.g. chemokine or fusion inhibitors) become available. Based on the UK CHIC cohort study, it is estimated that nearly 40% of HIV-infected patients in the UK have experienced all main classes of antiretroviral drugs and of these 15% are known to have virologically failed all three classes [242].

The reasons for drug failure are complex. To date, most studies of therapy after more than one treatment failure have not distinguished between virological failure due to poor adherence and failure due to other causes, such as poor pharmacokinetics. Individuals who have been poorly adherent to therapy but have not developed a resistant virus may be effectively treated if adherence is improved. Low blood levels of PIs, because of either poor absorption or unforeseen pharmacokinetic interactions, may also lead to failure with or without the development of resistance to PIs.

Table 7 What to do after first virological failure: a 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.

9.2 Criteria for success in patients exposed to multiple drug classes

Suppressing viral load to below detectability (i.e. to below 50 copies/mL) at 24–48 weeks has become an accepted measure of success in antiviral therapy. This criterion may not be useful in determining success in highly antiretroviral-experienced patients in whom the potency of subsequent regimens is attenuated because of the presence of a resistant virus. The goals of therapy in treatment-experienced patients may also need to be reconsidered, and it must be recognized that complete suppression of viral replication is not always an achievable goal. As options for new regimens decrease, increasing importance should be attached to preserving immune function and maximizing suppression of viral replication, while minimizing toxicity as much as possible. Data from a number of large clinical endpoint studies, mainly in treatment-naive patients, show that more modest declines in viral load correlate with improvements in clinical outcome. Viral load reductions of greater than 0.5 log 10 copies/mL may be responsible for clinical improvement and may imply that such a regimen is worth pursuing [85,241,244].

Many salvage studies have been of short duration with little follow-up data, making it difficult to judge whether or not any viral suppression will be maintained over the long term. In late disease, the immediate risk of death is much more closely associated with the CD4 count than with the viral load and thus, perhaps, a more important criterion in salvage studies is the degree to which the CD4 count rises.

In late stage disease, where it is unlikely that durable undetectable levels of HIV RNA are achievable, the aim of treatment should shift to maintaining or preserving immunological function and preventing clinical progression. In this setting, it is therefore important to maintain the CD4 cell count rather than to attempt to get the HIV viral load undetectable with single agents.

In many patients, the CD4 cell count is stable despite a stable or rising viral load. In one study of 380 HIV-infected adults receiving long-term PI-based therapy, patients with HIV RNA levels persistently above 1500 copies/mL generally had CD4 cell counts that remained greater than pretherapy baseline levels through 96 weeks of follow-up [231].

A subsequent study showed that maintenance of stable CD4 cell counts depended on continuing ART, even in the face of virological failure of their antiretroviral regimen [245]. In that study, discontinuation of therapy for 12 weeks was associated with a median decrease in CD4 cell count of nearly 130 cells/μL and an increase in plasma HIV-1 RNA of more than 0.8 $\log_{10}$ copies/mL.

The benefits of continued administration of ART in this setting must be balanced against potential drug toxicity and the accumulation of additional drug resistance mutations leading to broader cross-resistance limiting future drug options [246].

It is important to remember that continuing a failing regimen is merely a temporizing measure until new drugs are available. Over time, patients' viruses become increasingly resistant, with slowly increasing viral load and declining immune competence [247].

The immediate increase in viral load following treatment interruption suggests that residual activity of the antiretroviral regimen contributes to the maintenance of partial viral suppression, despite high-level drug resistance. More recent studies have suggested that it is the nucleoside RT inhibitors, rather than the PIs, that retain partial activity [248]. These findings have been corroborated in two separate studies in which interruption of d4T or 3TC was associated with a significant increase in plasma HIV-1 RNA levels and decline in CD4 cell count, despite the presence of a d4T- or 3TC-resistant virus, respectively [249,250].

9.2.1 Principles of optimizing success in highly treatment-experienced patients

Both cohort and clinical controlled studies identify a number of general principles to consider when deciding upon a 'salvage' regimen. First, prevention would be the best policy and success is most likely if individuals are naive to one class of drugs. It seems to be particularly important to give these agents whenever possible as part of

a fully suppressive regimen to avoid the rapid emergence of resistance.

Second, improved outcome is more likely with the use of drugs *within classes* to which the patient has not been exposed and to which resistance is unlikely or proven to be absent.

Third, therapy is more successful at reducing the viral load to undetectable levels in those who commence at a lower viral load (e.g. <5000–$10\,000$ copies/mL). This has been attributed to an accumulation of additional mutations within the viral population in those who continue on failing therapy with a high viral load, which increases the likelihood of cross-resistance to new agents tried subsequently. Additionally, the potency of new regimens may be sub-optimal but enough to suppress low viral loads.

Fourth, resistance testing is strongly recommended in all cases where there are difficult choices to make concerning the most beneficial treatment. A number of retrospective and prospective studies demonstrate that responses to drugs in failing regimens can be predicted by genotype or phenotype.

Finally, plasma drug concentrates may influence therapy outcome. The Viradapt study [251] demonstrated the best virological response in patients who had optimal drug concentration as well as genotyping to guide future choices. See TDM section 11.0. for further information.

9.2.3 Patient assessment

Where there is any doubt about management, we recommend that advice be sought from or the patient be referred to a larger HIV centre where there is more clinical expertise with multidrug-resistant HIV and where new investigational drugs would be more readily available. At present a number of new promising investigational drugs are available on a trial basis (see section on new investigational drugs). We recommend that the care of such patients be delivered on a shared care basis or as part of a clinical network.

9.3 Management of patients with multiple class resistance

A number of approaches have been tried in this situation.

9.3.1 Stopping therapy long term

Stopping therapy long term is not recommended as data indicates that this produces a large fall in CD4 count and rise in viral load. However, stopping certain components of therapy may be associated with reduced toxicity and less resistance development, while maintaining CD4 count.

9.3.2 MEGA HAART

Although responses in viral load are likely to be small when using a drug to which the virus is resistant, it is possible that using a number of such drugs together might have a cumulative benefit that outweighs the potential toxicity [252]. Varying success has been reported by combining five or more drugs [253], so-called MEGA HAART or GIGA HAART [254], despite resistance to many of the individual components. A number of small cohort studies have reported successful maintenance of the viral load below 400 copies/mL for up to 2 years in individuals exposed to all three classes of drugs [255] using a mega HAART approach. Such studies are difficult to analyse and, in the long term, toxicity is likely to outweigh benefit. Although the regimens contain multiple drugs, drug adherence was often relatively good, partly because the drugs were taken only twice a day. However, in the French GIGA HAART, just under half of the patients remained on the same treatment at 1 year.

While we are waiting for new drugs to be made available, it appears best for patients to be maintained on some form of ART rather than have a prolonged treatment interruption with its associated rise in viral load, drop in CD4 count and potential for disease progression [256,257]. This type of strategy probably relies on the poor fitness of a virus with multiple mutations to maintain the status quo.

9.3.3 STI

One postulated strategy for managing patients who have failed treatment with HIV resistance to multiple drugs is the use of STI to allow drug-sensitive virus to outgrow and replace the resistant virus, with the hope of enhancing responses to subsequent therapy. Unfortunately, resistant virus that had previously evolved is likely to re-emerge during subsequent therapy despite STI. There can be an immunological price to pay for STI. In 22 heavily experienced patients, after a median STI of 20 weeks, there was a mean CD4 decrease of 88 cells/μL and three patients developed opportunistic infections. After restarting a new salvage regimen, most patients eventually increased their CD4 counts to the pre-STI level [258]. In another study, patients infected with multidrug-resistant HIV, a 4-month structured interruption, followed by a change in antiretroviral, regimen was associated with greater progression of disease and did not confer immunological or virological benefits or improve the overall quality of life [259]. On the other hand, the French GIGA HAART study of an 8-week treatment interruption followed by multidrug therapy (minimum of seven drugs) in patients with multidrug failures and CD4 cell count <200 cells/μL (median CD4 count was only 25 cells/μL) found that treatment interruption was beneficial in terms of viral load outcome for

treatment-experienced HIV-infected patients with advanced HIV disease and multidrug-resistant virus [260]. Each trial enrolled a distinctive patient population, studied different treatment regimens and different durations of treatment interruption. The strategy of STI in the setting of the drug-resistant virus may only be beneficial in patients similar to, and treated in a like manner to those in the GIGA HAART trial and not those in CPCRA 064 [261]. Patients in the CPCRA study had higher CD4 cell counts and more treatment options, while those in the GIGA HAART study had no options and were treated much more intensively. Further studies will hopefully clarify this situation (e.g. Optima Study [262]).

In those patients who have other antiretroviral options, we would not recommend a structured treatment interruption. In these patients, STI may lead to an increase in the rate of progression to AIDS and large falls in CD4 counts, which may not be regained for up to 48 weeks after restarting treatment [259].

In those patients who have no obvious treatment options, an 8-week interruption followed by GIGA HAART using a minimum of seven drugs appears to give an advantage at 48 weeks in terms of surrogate marker responses [261].

9.3.4 New agents

In multidrug-class-resistant patients, the long-term outcome is crucially dependent upon the development of new drugs, which, when used in combination, may be successful in suppressing viral replication completely. The addition of single new agents in individuals with a stable CD4 count above 50–100 cells/μL needs to be reviewed with caution outside of a controlled trial setting as resistance is likely to develop rapidly unless the addition of a new drug is capable of reducing the viral load to undetectable limits. The long-term outcome of patients may be improved by delaying the introduction of new drugs until several can be combined together to achieve virological undetectabililty.

RESIST-1 and 2 studies provide data that the PI tipranavir is an active agent for the management of drug-resistant HIV in highly treatment-experienced patients. Around one third of patients in the tipranavir arm had viral loads of <400 copies at week 24, compared with 14–17% in the comparator arm without tipranavir. A favourable resistance pattern and another active drug available, as well as tipranavir (in this case T20), increase substantially the rate of virological response. A limitation of the use of tipranavir is its wide range of interactions with other drugs, particularly with other PIs, but also with fluconazole, atorvostatin, antacids and rifampin, and the requirement for a higher dose ritonavir [12,13,263].

9.3.4.1 Use of T20 (enfuvirtide). See Section 8.3.5. TORO stands for 'T20 versus Optimise Regimen Only'. There were two 48-week open label randomized multicentre international phase 2 safety and efficacy studies. TORO-1 in the US and TORO-2 in Europe and Australia. Although there were differences in the study design of TORO-1 and -2, these were only slight and did not impact the combine analysis.

Triple-class experience in HIV-infected patients with HIV RNA greater than 5000 but no CD4 count limit were randomized to either optimized background alone or optimized background plus enfuvirtide (T20) 90 mg, subcutaneously, twice a day for 48 weeks. The selection of the optimized background of 3–5 agents was guided by the results of genotypic and phenotypic resistance tests.

In those on the optimized background alone arm, changes of drugs were allowed and enfurvirtide was permitted at virological failure or at week 48. At baseline, the median baseline HIV RNA was 5.2 logs, with a CD4 of 88 in the enfurvirtide group and 97 in the optimized background alone. These were very heavily experienced patients with a median duration of prior protease use of almost 4 years, and the median number of prior antiviral drugs ever taken was 12.

The main findings showed a greater than twofold higher virological response in the enfurvirtide arm at week 48 compared with the optimized background arm $P<0.001$, whether a 1 $\log_{10}$ decrease from baseline or HIV-1 RNA reduction to less than 400 copies was analysed.

A total of 18.3% of the enfurvirtide arm became undetectable at <50 copies at week 48. There was a significantly longer time to virological failure in the enfurvirtide arm than the OB arm, 32 vs. 11 weeks. There were significantly greater increases in the CD4 count and a greater improvement in constitutional symptoms in those given enfurvirtide.

The most common adverse event was injection site reactions seen in nearly all the patients but resulting in discontinuation of enfurvirtide in only 4.4%. Interestingly, there was an increase rate of bacterial pneumonia in the enfurvirtide arm at 6.6 vs. 0.6 per 100 patient years. Enfurvirtide Toro studies, 48-week results confirm the 24-week findings [264]. The suggested optimal use of this drug has been described above and in brief a better virological response was seen in patients who had plasma viral load of less than 100 000 copies/μL and CD4-cell count at baseline of >100 cells/μL, a history of exposure to fewer than 10 antiretroviral agents and two or more other active drugs in the regimen [10,11]. It is important that this drug is not used, if at all possible, in a regimen where it is the only effective antiretroviral agent.

9.4 Recommendations for subsequent virological failure (third or more regimen)

Reasons for virological failure should be assessed.

- Test for genotypic resistance: a phenotypic assay or virtual phenotype may be necessary if the genotype assay is difficult to interpret.
- If a new regimen that contains at least two or three active drugs is available, then the advice would be to strongly consider changing treatment. In this situation, change as many drugs as possible only if a number of active drugs are available.
- A new class of drugs should be introduced, preferably combined with one or more active drugs.
- If such a regimen cannot be constructed, it would be better to defer any change in treatment until such options are available, especially in patients maintaining a CD4 count of 50–100 cells/μL. Some patients may benefit in terms of reducing pill burden and side effects if part of the regimen was stopped and close monitoring showed a stable CD4 count and viral load subsequently.
- Treatment intensification is generally not recommended as it is a strategy used in less treatment-experienced patients with viral loads of <2000 copies/mL.
- Referral to centres running clinical trials of new agents and/or with expertise in the management of such complex patients should be considered.

10.0 Resistance testing

10.1 Drug-naive patients

There is now extensive evidence for the transmission of drug-resistant variants [3,4]. In some cases, the presence of resistance in an apparently drug-naive patient may in fact reflect previous undisclosed therapy. The reported prevalence of primary resistance varies from 5% to 26% in different cohorts [5,6,8,265–267], reflecting the heterogeneity of the methodologies and definitions used for resistance.

In newly diagnosed patients with established infection, the overall prevalence of primary resistance appears to be lower than in acute seroconverters. This may be explained by the fact that the time of infection for these individuals could have occurred some years previously, prior to the upsurge in transmission of resistance. Alternatively, the transmitted resistant virus may subsequently evolve, with reversion to wild-type. Recent data indicate that transmitted resistant strains often persist for years [17–19,21,22], indicating that it is of value to test any available sample prior to initiating therapy. However, variations in the rate of reversion of transmitted drug-resistant mutants indicate that the optimal sample for resistance testing remains the earliest available following diagnosis [20]. Transmitted resistance appears to compromise the speed of response to first-line therapy when initiated soon after primary infection [5,6] and, when including T215 variants in reverse transcriptase, responses to thymidine analogue-containing therapy [7]. Although the long-term impact on disease progression and response to treatment remains to be determined, knowledge of such resistance prior to initiating HAART will allow optimization of first-line therapy. Cost effectiveness analyses have shown that when prevalence rates for primary resistance reach between 4% and 10% there is an advantage to test for resistance in antiretroviral-naive patients [268,269].

10.2 Drug-experienced patients

Antiretroviral treatment failure continues to occur among patients on HAART and is frequently accompanied by the selection of drug resistance. In a study of UK patients who started HAART (without previous mono- or dual-nucleoside therapy) between 1996 and 2003, there was a 38% risk of failure and a 27% or higher risk of developing resistance over 6 years of follow-up [8]. In a Canadian cohort of 1191 drug-naive adults initiating HAART, drug-resistance mutations were detected in 25% of subjects during 30 months of follow-up. Factors significantly associated with the detection of drug-resistance mutations included high baseline viral load and adherence [270].

Antiretroviral drug resistance has been described retrospectively, *in vitro* and *in vivo*, to be associated with poor virological and clinical outcomes. Short-term prospective, randomized controlled trials have, in some studies, demonstrated the short-term benefits of resistance testing over standard of care [271–281]. It is likely that the relatively modest benefits demonstrated are due in part to inadequate interpretation of results at the time of the study. Other factors leading to differences between studies include the proportion of patients who are NNRTI naive at the time of therapy switch, the availability of expert advice (EA), and the overall therapy experience of participants. A meta-analysis of the VIRADAPT, GART, HAVANA, ARGENTA, NARVAL and VIRA301 [282] showed that a higher proportion of patients had undetectable viral loads at 3 and 6 months in the genotype testing groups. This particular analysis supports the use of genotypic but not phenotypic resistance tests and shows that EA can increase the virological response. Further, the MRC ERA Study, which randomized drug-experienced patients to genotypic or genotypic plus phenotypic testing, found no clear evidence that phenotypic resistance testing provided added value relative to genotypic resistance testing [283].

Genotypic assays are cheaper than phenotypic assays, and can normally be undertaken within specialist clinical virology laboratories. By contrast, real time phenotypic assays are generally provided by a few commercial laboratories and currently require dedicated category 3 facilities. It is unlikely that randomized, controlled studies of resistance assays will be undertaken in the future, and further insight into the best use of resistance tests may come from large cohort studies and clinical database analysis.

The TORO-1 [10] and TORO-2 [11] and RESIST-1 [12] and RESIST-2 [13] trials provided indirect evidence of the clinical benefit of resistance testing in highly drug-experienced patients. In these studies, the selection of active drugs in the background regimens guided by resistance testing improved responses to enfuvirtide [10,11] or RTV-boosted PIs [12,13].

Routine use of genotypic resistance testing after treatment failures has been shown to be cost effective [9]. In drug-experienced patients who stop therapy, pre-existing wild-type virus, archived from prior therapy, can rapidly emerge within 1 month [284], and resistance testing subsequent to this time will only yield this non-resistant strain. It is, therefore, uninformative. If possible, testing should always be undertaken on virus from a patient while he or she is receiving therapy.

10.3 Interpretation of resistance

Resistance interpretation is continually updated. Readers are referred to the latest IAS-USA algorithm [285].

Resistance testing has technical limitations. Both genotypic and phenotypic testing depend on polymerase chain reaction (PCR) amplification of virus from plasma, and therefore do not address the properties of different virus components (i.e. whole virus vs. reverse transcriptase/protease genes alone). The likelihood of generating sufficient genome product to undertake the further analysis depends on the starting concentration of the virus. Thus, most current assays require at least 1000 copies/mL to reliably provide a result, although it may be possible to obtain results at lower viral load levels using nested PCR techniques and a larger starting quantity of blood.

Routine resistance assays do not detect resistant viruses present at low levels ($<20\%$ of the total virus population), even if these resistant viruses were previously dominant. Although assays to detect minority species have been developed, they are not routinely available and remain research tools only. Limited data indicate that minority resistant quasispecies may affect virological responses [14,15]. Thus, in NNRTI-experienced patients, suboptimal virological responses to NNRTI-based therapy have been observed in patients with NNRTI resistance demonstrable only by ultrasensitive methods [16].

In the absence of drug pressure, the dominant virus population will revert to wild-type [16]. Reversion is slower in transmitted resistance than in resistance selected by therapy [17–22]. Reversion of mutations may occur through intermediates or revertants (e.g. T215D/N/S from T215Y/F). Detection of revertants should be interpreted as evidence that fully-resistant mutants are present as either minority quasispecies or archived resistance, and may contribute to treatment failure [7].

The interpretation of resistance test results is complex. The most informative interpretation systems are based on 'clinical cut-off' values, which are being determined for a growing number of drugs. Clinical cut-offs correlate specific mutation patterns with viral phenotype and the phenotype with subsequent *in vivo* virological response. However, they may vary depending on the phenotypic assay used. For many drugs, both an upper and a lower cut-off are being proposed, the first indicating a threshold for diminished responses and the second indicating the level of resistance at which responses are essentially lost.

Antiretroviral resistance should be interpreted as a continuum. For the NRTIs and PIs (but not for the NNRTIs) [23], residual virological suppression can be observed with intermediate levels of resistance, which may reflect direct antiviral activity as well as the beneficial effects of reduced viral fitness [24].

Virus fitness is defined as the overall capacity of a virus to infect, replicate and produce mature infectious progeny in a defined host environment. The Replicative Capacity Assay is a clinically available test that provides one measure of viral fitness, by testing the growth of a recombinant resistant virus in the absence of drug pressure, relative to the growth of a recombinant wild-type virus. The clinical utility of the test has not been demonstrated.

Hypersusceptibility effects can be demonstrated *in vitro*. Certain drug-resistant mutations confer resistance to some drugs but increase susceptibility to others. Overall, the clinical relevance of this is not clear, but hypersusceptibility to amprenavir in viruses with N88S [286] and to the NNRTIs in viruses with NRTI mutations [287–289] have been associated with improved virological responses. Such findings may not yet be represented within interpretation algorithms.

HIV-1 genetic diversity within the UK is widening. In 2002, heterosexual infection from sub-Saharan Africa represented the majority of new diagnoses. These individuals are infected with viruses with significant genetic difference from the subtype B virus common within the gay epidemic. The impact on resistance testing is two-fold. Firstly, PCR-based assays require optimization of

efficiently produced results from such viruses, and secondly, the presence of 'secondary' resistance mutations as normal variants in such viruses may require the modification of resistance interpretation systems. Certain resistance pathways have been associated with the HIV-1 subtypes. For example, EFV failure in patients infected with subtype C occurs frequently in association with the V106M mutations, which is uncommonly seen in patients infected with the B subtype [290]. HIV genetic diversity also has an impact on phenotypic resistance assays, which use a B subtype virus backbone.

10.4 Recommendations

- Testing for transmitted resistance is recommended in all newly diagnosed patients who present with either acute seroconversion or established infection. The most appropriate sample is the one closest to the time of diagnosis. This should preferably be tested at the time of initial presentation, as facilities for long-term sample storage may be limited and sample deterioration is likely to occur over several years of storage. In addition, knowledge of baseline resistance impacts patient management by informing decisions on when to start therapy and what drugs to use. Once testing of the baseline sample has been performed, repeat testing prior to starting therapy is not considered cost effective and is not currently recommended.
- For existing patients, testing for transmitted resistance is recommended at the time of starting therapy. The most appropriate sample is the one closest to the time of diagnosis, provided it is available and suitable for testing.
- Although superinfection has been described, there is currently insufficient evidence to undertake testing of multiple samples prior to initiation of therapy.
- Minority species of resistant virus may be missed by conventional resistance testing. In patients without evidence of transmitted resistance using such tests, a suboptimal virological response to first-line therapy ($< 1 \log_{10}$ copies/mL reduction in viral load by 4–8 weeks) should prompt resistance testing at that time, having excluded problems with adherence and, where indicated, drug levels.
- For patients on therapy, resistance testing should be undertaken at each point of viral rebound (although, as stated above, a viral load of at least 1000 copies/mL is required for a reliable assay), unless a patient is on a treatment interruption.
- There is little evidence for an advantage of phenotypic over genotypic testing. Both require interpretation of complex data, and the interpretation systems for fold resistance (phenotype, and phenotypic interpretation of genotype – virtual phenotype) and mutations (genotype) are subject to change as more clinical outcome data becomes available. Genotypic assays are currently cheaper, more rapid and more widely available than phenotypic assays.
- It is essential that interpretation of resistance testing and choice of new therapy is taken in the light of all clinical information, including prior therapies and toxicities. Previous resistance test results must be considered, and resistance apparent at that previous time must be assumed to be permanently represented within the virus population. Samples taken for viral load should be stored frozen within the laboratory, in order that retrospective resistance testing can be undertaken.
- In drug-experienced patients, resistance testing should be undertaken while the patient is receiving therapy, to avoid misleading results.
- Resistance tests are technically demanding, and external quality control is essential. This is addressed by national and international pathology laboratory accreditation programmes. Laboratories undertaking resistance testing should be equipped to provide clinical support to HIV clinics, and demonstrate participation in external quality control programmes and accreditation by national/international agencies (Clinical Pathology Accreditation in the UK). They should store samples and assay data according to guidelines of the Royal College of Pathologists.
- Patients should be encouraged to have knowledge of their results and the i-Base treatment passport is an ideal vehicle for keeping an ongoing record of the CD4 count, viral load and resistance test results. This treatment history can help to develop an active understanding of their own health-care and may help doctors explain the importance of these results to their patients. A free booklet is available to order in bulk online at http://www.i-Base.info.

11.0 Therapeutic drug monitoring (TDM)

This section discusses the role of TDM for PIs and NNRTIs. TDM is likely to be of little value for NRTIs as these agents require intracellular activation and levels of intracellular drug-triphosphate bear little relationship to plasma levels of the parent compound. The abbreviations C_{min}, C_{max} and area under curve (AUC) refer to the plasma trough (usually at the end of the dosing interval), peak plasma levels and area under the concentration–time curve, respectively.

Europe has seen an increasing uptake of TDM and incorporation of TDM into national HIV treatment

guidelines in several countries. This is despite a surprising lack of data to confirm the benefit of TDM in routine clinical use, and the opportunity to conduct these trials has largely passed. Nevertheless, prospective surveys suggest $\sim$ 20% patients in clinic have sub-therapeutic (below target for wild-type HIV) plasma concentrations of PIs and NNRTIs [291–293]. Moreover, the inter-individual variability in plasma concentrations is immense ($\geq$ 50-fold difference) despite standard dosing [291], and may vary according to ethnicity [294], gender [295] and body weight [236].

11.1 Evidence of a concentration–effect relationship

11.1.1 Efficacy

A large number of observational studies have confirmed that drug exposure (C_{min} or AUC) of PIs correlate with virological suppression in patients prospectively followed up in Phase II studies (SQV, IDV, amprenavir (APV), treatment-naive patients (including phase III studies) commencing therapy (SQV, NFV, IDV, RTV), dual PI regimens (SQV, NFV, RTV), salvage ART (SQV, IDV, RTV) or else a broader population of clinic patients on ART (SQV, NFV, IDV, RTV) [296]. In general, the association between drug concentrations and virological response varies according to patient group, and is less apparent in heavily pre-treated patients, in whom resistance is likely.

Data for NNRTIs are less convincing. NVP concentrations were associated with treatment response in treatment-naive patients in the INCAS trial, but not in unselected clinic patients who may have been treatment-experienced [297,298]. A relationship between EFV concentrations and both efficacy and central nervous system (CNS) toxicity has been reported [294,299]. In a subset of adherent patients from the 2NN study, patients with predicted EFV $C_{min} > 1.1$ μg/mL were less likely to experience virological failure, whereas NVP C_{min} was a poor predictor of virological failure [300]; associations with toxicity were not analysed.

11.1.2 Toxicity

High-plasma PI concentrations have been associated with some toxicities, e.g. renal or urological toxicity (IDV) [301,302], gastrointestinal (RTV, NFV, LPV, SQV) [198,303,304], elevated lipids (RTV, and possibly LPV) [305–307], hyperbilirubinaemia [308] and possibly lipodystrophy (NFV, LPV) [309,310].

An association between CNS toxicity and EFV concentrations has been reported [299] in a cross-sectional study of 130 patients who received the drug for an average of 8 months, and in patients with genetic polymorphism of cytochrome 2B6 (G516T) in whom both higher EFV exposure and CNS toxicity at 1 week were more common [294]. Data relating NVP exposure to hepatotoxicity are conflicting; however, the higher rate of hepatotoxicity with once-daily than with twice-daily NVP in the 2NN study suggests that liver injury may be related to exposure (C_{max}) of NVP [300].

11.2 Controlled trials of TDM

Randomized, controlled trials of TDM have been few, difficult to interpret and may not reflect commonly used regimens today. An intensive study [311] of 49 adults commencing ZDV, 3TC and IDV randomized patients to receive conventional therapy versus TDM, where full plasma profiles for all three drugs plus subsequent multiple sampling was performed. Patients in the TDM arm had significantly more rapid and durable virological responses to therapy. In the ATHENA study [312], a subset of treatment-naive patients randomized to receive TDM had improved efficacy (NFV) or reduced toxicity (IDV). However, these analyses were *post hoc*, and in the overall study cohort, analysis was complicated by 'unblinding' of controls as well as low compliance to TDM recommendations by attending clinicians. Two French studies (Genophar and Pharmadapt) have failed to observe any benefit of TDM [313,314] in a group of pre-treated patients. Assessment of TDM was limited by only a short window in which to observe any effect, since any dose modification was only instituted at 8 weeks for the TDM arm, while all patients in the non-TDM arm received TDM from week 12 onwards. A US study (CCTG 578) seeks to evaluate TDM and adherence in a randomized, factorial design. The results are awaited.

11.3 Other potential problems with TDM

Many of the potential problems with TDM have been overcome. A consensus of what efficacy targets should be for each drug has emerged (www.hivpharmacology.com), although toxicity targets are more problematic. An international quality assurance programme is now in place. For most centres, a trough measurement ($\pm$ post-dose concentration) is preferred. The important question of whether dose modification successfully achieves the desired change in plasma drug concentrations has not been properly evaluated. One recent study [315] reported that this was readily achieved with LPV and IDV-containing regimens, but not with NFV (in contrast to the ATHENA Study [313]). Moreover, PIs (and to a lesser degree, NNRTIs) appear to have significant intra-individual variability [316] suggesting that clinical decisions should not be made solely on the basis of a single TDM result, where possible.

11.4 Utility of TDM

It needs to be assessed how TDM should be used in clinical practice. The utility of TDM as an investigation goes beyond the identification of patients with sub-therapeutic or excessive drug concentrations, since a 'normal' result can be clinically useful in discounting a significant interaction, or provide reassurance that a chosen dose is correct, or caution against dose reduction for toxicity or pill burden, where little scope for doing so exists. Where clinical options are limited, TDM may also allow use of drug combinations that are relatively contra-indicated, such as LPV with fosamprenavir, or PIs with anti-tuberculous therapy, or proton pump inhibitors with certain PIs. Formal studies assessing the utility of TDM are difficult to design, but urgently required.

11.5 Inhibitory quotients

Inhibitory quotients (IQs) comprise the C_{min} of drug divided by some measure of resistance (phenotype, 'virtual' phenotype or genotype). Lack of standardization means that even within the major forms of (phenotypic) IQ, (genotypic) gIQ, ('virtual') vIQ and ('normalized') nIQ, there are important variations in practice, e.g. correction for protein binding, which mutations 'count' for gIQs and how population denominators are calculated for nIQ and gIQ 'units'. Nevertheless, inhibitory quotients appear to be superior in predicting failure compared to drug concentrations or resistance testing alone, in patients undergoing salvage therapy with LPV, amprenavir/fosamprenavir, SQV, IDV and atazanavir [317–327]. An attempt to establish a target inhibitory quotient has been made for LPV (IQ, gIQ, vIQ, nIQ) [317–319], amprenavir/fosamprenavir (IQ, gIQ, nIQ) [320–323], SQV (IQ, gIQ, nIQ) [324–326], IDV (IQ, vIQ) [325–327] and NFV (IQ) [325]. Preliminary data are also available for atazanavir (gIQ) [308] and tipranavir (IQ) [328]. However, there is no convincing evidence that inhibitory quotients are of value with NNRTIs, perhaps because of their low genetic barrier to resistance. It is important to recognize that the target IQ for optimal response is likely to be different for different drugs; thus, cross comparisons between different agents are not valid. The key question as to whether inhibitory quotients can be sufficiently improved by dose escalation to positively influence virological suppression remains unanswered.

11.6 TDM recommendations

BHIVA recommendations for TDM in adults are shown in Table 8.

Routine, unselected patients. Despite the large inter-individual variability and significant minority of clinic patients who may have sub-optimal drug exposure, there are insufficient data to recommend the routine use of TDM in unselected clinic patients.

Table 8 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 ATV. 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).

IDV, indinavir; EFV, efavirenz; LPV, lopanavir, SQV, saquinavir; APV, amprenavir.

TDM should therefore be considered a niche investigation, and is recommended for particular scenarios such as the following:

(i) **Drug interactions (BIII).** PIs and NNRTIs are extensively metabolized by cytochrome P450 isoenzymes. They may affect the metabolism of other drugs that share the same metabolic pathway, and, in addition, may themselves be affected by those drugs. Individual drug interactions are beyond the scope of this discussion and may be found elsewhere (e.g. http://www.hiv-druginteractions.org). TDM could be considered in situations where multiple drugs are given that have direct or indirect interactions with each other, e.g. dual PIs, PI + NNRTI or other inducers/inhibitors of CYP3A4. This would include patients undergoing chemotherapy or organ transplantation.

Recent data have highlighted difficulties in predicting interactions with widely prescribed co-medications. Examples include the adverse interactions observed with the use of proton pump inhibitors, H2 receptor antagonists (and to a lesser extent antacids) and PIs (atazanavir [329], fosamprenavir [330], IDV [331] and possibly tipranavir [332]); as well as the remarkable inter-individual variability observed for EFV clearance (especially in black African women) [333] as a result of genetic variability in drug metabolism [294]. This is especially true when cytochrome P450 inducers (rifampicin and EFV) are co-administered: EFV concentrations at standard doses (600 mg once daily) ranged from sub-therapeutic to excessively high in studies from Thailand [334] and South Africa [335], making dose optimization in any single individual difficult without TDM.

(ii) **Liver impairment (BIII).** The risk of marked elevation of PI/NNRTI concentrations progressively increases with increasing liver damage (rather than with hepatitis B or C status *per se* [308]). This has most clearly been demonstrated with NFV, IDV, APV and NVP [305,336–339].

The optimal dose for any patient cannot easily be predicted and TDM offers a means of tailoring the dose to fit the patient.

(iii) **Pregnancy (BIII).** With PIs increasingly preferred over NVP for prevention of perinatal infection, data show that drug exposure is substantially reduced during pregnancy (typically third trimester) for NFV, LPV, SQV, RTV and IDV [340]. Despite the lack of data, similar effects are also likely with atazanavir and fosamprenavir. To allow sufficient time for dose optimization, TDM should be undertaken as soon as steady state is reached ($\sim$2 weeks after commencing a PI) in previously untreated mothers.

(iv) **Minimizing concentration-related toxicities (BIII for EFV, IDV and atazanavir; CIII for other drugs).** Some toxicities e.g. rash/hypersensitivity are idiosyncratic and probably not related to plasma drug concentrations. TDM may be useful for concentration-related toxicities such as those listed in 5.5.1 above. Most importantly, TDM may be utilized to allow dosage reduction in patients who are most at risk of drug toxicity because of previous intolerance, concurrent medication with overlapping toxicities or other pre-existing disease.

(v) **Adherence (CIII).** The short half-life of most PIs (even with RTV) only gives an indicator of recent adherence, in contrast to the longer half-lives of NNRTIs. An adequate or high plasma PI concentration only provides information about adherence to the preceding few doses rather than over the long term. Near/complete absence of detectable drug in plasma is a good indicator of poor adherence. Subtherapeutic levels are a less useful indicator of adherence except on a background of repeatedly optimal concentrations, or when concentrations are adequate following the observed ingestion of medication.

A comparison against MEMS and unannounced pill counts [341,342] suggests that TDM may contribute to the assessment of adherence over and above taking an adherence history, with limited sensitivity of 44% but reasonable specificity of 88% for IDV, NFV, NVP and EFV [342].

(vi) **Virological failure (CIII).** TDM is of little value once high-level antiviral resistance has developed. TDM may be considered when treatment intensification is an option (e.g. suboptimal viral load response early in a new regimen), when viral resistance testing suggests that resistance is unlikely or to overcome a low level virological rebound.

(vii) **Malabsorption (BIII).** TDM should be considered in patients with chronic gastrointestinal disease, e.g. cryptosporidiosis or other evidence of malabsorption.

(viii) **'Unusual' or unlicensed dosing regimens (CIII).** Once-daily PI regimens containing SQV, NFV, IDV, LPV and APV are associated with large variability towards the end of the dosing interval, and may not be sufficiently robust for some patients. TDM should be considered for these, and other regimens using unlicensed doses, in order to individualize dosing.

In addition, PENTA guidelines recommend TDM for very young children (http://www.ctu.mrc.ac.uk/penta/guidelin.pdf).

12.0 Metabolic complications

12.1 Lipodystrophy

Lipodystrophy has a twofold clinical significance. There are the stigmata of body shape changes, which may not cause physical morbidity, but can be psychologically and socially debilitating [343]. This may lead patients to delay initiation of therapy or stop therapy, or may promote poor adherence. Also, there are the metabolic changes, which do not usually affect the patient in the short term, but add to the long-term risks of morbidity and mortality.

Because we are dealing with a set of conditions with multifactorial and uncertain aetiologies, there is little robust trial evidence to direct our management. Furthermore, it may be that the underlying pro-inflammatory nature of HIV infection means that HIV in itself might multiply any existing inherent cardiovascular risk. These issues should be regularly assessed, at least to the extent recommended for the general population.

Arguments continue as to the linkage of the main components of the syndrome and as to whether several

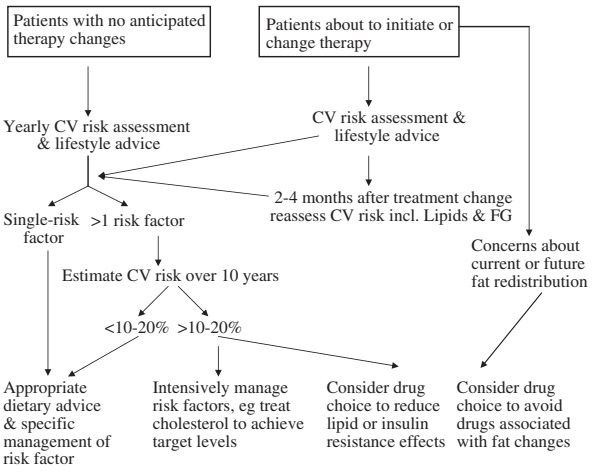

Fig. 1 Management algorithm for HIV-associated coronary heart disease risk.

different, overlapping syndromes exist. The main components, which may be observed individually or in combination include the following:

- dyslipidaemia with raised total cholesterol, low HDL cholesterol and raised triglycerides, with increased lipid cycling or turnover;
- insulin resistance with hyperglycaemia, particularly in susceptible individuals;
- visceral, breast and/or local fat accumulation;
- generalized diminution of subcutaneous fat mass, possibly with fat cell loss.

In addition, other metabolic and physical changes may be present in individuals on long-term antiretroviral therapy including raised serum lactate, low bone mineral density, hypogonadism (and possibly other endocrine abnormalities) and hypertension.

A clinical case definition, based on physician and patient agreement regarding significant and characteristic morphological changes, potentially enabling more homogeneous populations to be studied and comparisons to be made across intervention studies, has been developed [344].

This case definition is of limited value for individual patient assessment and management, because of its lack of specificity, and we do not recommend its routine use in this context.

The estimated prevalence of HIV-associated lipodystrophy depends on both the extent of investigation and examination, and the patient population concerned, particularly in relation to age and antiretroviral use. This is reflected by reported prevalences between 11 and 83% in cross-sectional studies [345,346].

12.1.1 Aetiology

Understanding the aetiology of lipodystrophy is important but remains speculative. Evidence from cross-sectional surveys points to an interaction between HIV disease and/or immune recovery and antiretroviral medication [347], with PIs and nucleoside analogues being implicated [348–350]. Evidence to date suggests these hypotheses to be, at best, incomplete [351,352]. Patients with the syndrome who have never received PIs [353,354] or have never received (or have developed the syndrome while not receiving) nucleoside analogues [355–357] have been reported, indicating that these agents alone are probably not the sole cause [211]. The highest cumulative prevalence of morphologic abnormalities in these studies appears to be in persons receiving both PIs and nucleoside analogues together, relative to dual or triple nucleoside or nucleoside plus non-nucleoside regimens. As d4T appears to have the highest relative risk of lipoatrophy [358,359], particularly in combination with ddI, its use should generally be restricted to individuals not suitable for alternative agents such as ABC, ddI and ZDV. The co-administration of d4T and ddI should be especially avoided. Although ZDV compares favourably with d4T in terms of the extent of fat atrophy [360–362], it is nonetheless closely associated with lipoatrophy [363–366]. Hence, until the situation becomes clearer, the increased likelihood of lipoatrophy underlines the need to use ZDV judiciously as initial therapy (either alone or in Combivir) and the importance of close monitoring for early features of fat loss. Furthermore, for those already on ZDV, consideration should be given to the issue of lipoatrophy, and whether a switch might be indicated. Clearly for many patients, the current efficacy and tolerability of their ZDV-containing combination will weigh towards its continued use. There will be patients, however, for whom the possibility of lipoatrophy causes sufficient anxiety such that they will elect to switch after the issues are discussed with them.

12.1.2 Lipid abnormalities

A large cross-sectional study, the DAD study, noted an increase in cholesterol (>6.2 mmol/L) in 27% on regimens that included a PI, compared to 23% and 10%, respectively, for NNRTI and NRTI regimens, and 8% for those naive to treatment [367]. The respective values for triglycerides raised above 2.3 mmol/L were 40, 32, 23 and 15%. These results must be interpreted with caution. For example, d4T-containing regimens are more closely associated with dyslipidaemia than other NRTIs [199]. Most PIs are associated with dyslipidaemia, but there are distinct variations [368,369]; Kaletra primarily raises triglycerides, whereas atazanavir does not significantly perturb any lipid fraction. Switching from a PI-associated regimen tends to improve lipid parameters. Insulin resistance is an important, and under-recognized, consequence of HIV therapy. Diabetes mellitus occurred in 7% of patients with fat atrophy or accumulation in one study, which was 14 times commoner than healthy, matched controls [370]. The mechanisms whereby ART leads to glucose intolerance have been suggested by a number of studies [371–378]. Interference with the transport of glucose through the cell by inhibition of the GLUT 4 enzyme is strongly implicated in insulin resistance, as are several other associated mechanisms [379]. The main drug class that is implicated is the PIs but the NRTIs might also have an indirect effect by promoting changes in fat distribution. Although most PIs are associated with significant glucose intolerance, SQV has relatively little effect, and atazanavir appears to have no discernable effect [380,381].

12.1.3 Management of lipodystrophy

Treatment for many of the aspects of LPD leads to disappointing outcomes; therefore, prevention is an important goal. Issues for prevention include the following:

- increased awareness among patient and physician and regular assessment;
- choice of regimens that avoid combining PIs and certain NRTIs;
- choice of regimens that favour agents that are less associated with lipoatrophy such as TDF, 3TC, FTC and ABC rather than those with a stronger association such as the thymidine analogues (especially d4T but also ZDV);
- consideration of early intervention for metabolic changes as these may be harbingers of lipodystrophy;
- dietary advice, possibly dietary supplementation (fibre, omega-3 fatty acids) and exercise.

Possibly also the initiation of therapy before 200 CD4 cells/μL and before AIDS is diagnosed.

Benefits for these suggestions are not fully established from randomized clinical trials but are extrapolated from cross-sectional and limited prospective data with their incumbent limitations.

A structured approach needs to be adopted by those looking after patients with HIV, and a summary of our recommendations is given in the algorithm. It is important that all patients are made aware of the potential manifestations of lipodystrophy, especially in terms of body shape changes. In the algorithm, when we refer to CV risk assessment, we include a full lipid profile, including HDL, LDL, fasting glucose and also where possible, insulin levels and OGTTs.

Once established, the management of lipodystrophy or individual metabolic problems falls into five categories:

- Adequate assessment and follow-up (see management algorithm);
- Lifestyle such as smoking, diet, possibly dietary supplementation and exercise;
- Additional therapies, generally focusing on managing individual manifestations;
- Modifying the treatment regimen away from d4T (and possibly ZDV) to ABC or TDF;
- Corrective procedures.

The risk versus benefit of these approaches has not been comprehensively tested, although the risk of diet and exercise can be considered minimal. Broadly, dietary advice should include a Mediterranean diet rich in omega-3 fatty acids, fresh fruit and vegetables. Fibre is known to improve insulin sensitivity. Evidence of benefit for specific food supplements is not established. Regular exercise, a mixture of cardio and weight training, may also improve some metabolic parameters and abdominal shape [382].

Individuals switching therapy must consider that they may risk their long-term HIV management in exchange for an uncertain outcome with regard to their lipodystrophy. Specifically, benefits in terms of clinically evident lipoatrophy have not been consistently observed in trials and, anecdotally, do not appear evident with even prolonged (>6 months) treatment interruption. The majority of early switch studies that have reported data focusing on switching away from PIs [383]. As mentioned, while metabolic benefits are achieved by switching away from PIs to NNRTIs or ABC in many patients, morphological benefits are more limited or absent. Switching away from d4T and possibly ZDV to ABC, TDF or to a PI NNRTI regimen is associated with some gain in fat, detectable by DEXA scanning over 24–48 weeks [365]. It is not known if this recovery of fat is complete or durable. Improvements in metabolic parameters with this switch are not impressive and, for a PI/NNRTI regimen, may worsen.

Switching away from a PI-NRTI-based regimen to a PI-sparing regimen does, however, currently represent the first step in management of metabolic abnormalities whenever feasible. NVP, EFV and ABC perform similarly virologically in treatment-naive persons but ABC should be avoided in those with prior NRTI resistance or mono/dual therapy exposure. Additionally, consideration should be given to whether ABC should be used as an alternative to an NNRTI or PI or to another NRTI. Lipids and insulin sensitivity generally improve with all these approaches; cholesterol improvement may be greatest with ABC although HDL may rise most with NVP [384].

Switching from PI-based regimens may be most beneficial with regard to metabolic parameters but is not effective at managing peripheral lipoatrophy. Switching from thymidine analogues, especially d4T but probably also ZDV, to ABC or TDF appears the only successful approach in this regard.

12.1.4 Other therapies

Metformin may benefit fat accumulations and insulin resistance, and may improve some lipid and coaguability factors [385]. Benefits on peripheral lipoatrophy have not been reported. Studies with glitazones are now underway in the US, Australia and the UK. Evidence of their efficacy, increasing fat mass in familial lipodystrophy [386], provides no guarantee of benefit in HIV-associated lipodystrophy. In HIV-associated lipodystrophy, a small randomized trial of rosiglitazone showed no benefit during short-term follow-up, although larger studies are now in progress. Additionally, the safety and potential for pharmacokinetic interactions with these drugs in people

with HIV requires clarification before their use can be considered or recommended in persons with HIV, especially those with a hepatitis co-infection [387,388].

Growth hormone may improve fat management [389] and lead to improvements in appearance of both fat accumulation and lipoatrophy, including facial changes. However, its use is likely to be limited by expense. Adverse effects, including the risk of hyperglycaemia, were common at high doses (6 mg/day) and the use of lower doses is now recommended and is the subject of further research.

Anabolic steroids may best be avoided, due to concerns regarding worsening lipid profiles, fat loss and potential for liver function disturbances, although testosterone replacement for repeatedly hypogonadal and symptomatic men, who are not hypogonadal due to previous treatment with anabolic steroids, may be considered.

The use of statins and fibrates is appropriate for the management of dyslipidaemia but no benefits have been described with regard to morphologic changes. The benefits of these agents appear similar to improvements in cholesterol or triglycerides described in endogenous dyslipidaemia [390,391] although relatively few individuals are reported to have achieved response goals as outlined in the NCEP guidelines [392]. Pravastatin is the most well-studied agent due to the low likelihood of drug interactions with PIs. Simvastatin is contraindicated due to substantial risk of drug interactions with PIs, and atorvastatin levels may be increased about twofold suggesting caution should be used when using this agent. Interactions between statins and NNRTIs have not been described. Interactions with fibrates and PIs or NNRTIs are not expected to be clinically important. Advice from a lipidologist should be sought before combining fibrates and statins, and in patients with persistent severe hyperlipidaemia, where further ARV changes threaten persistent virological control.

12.1.5 Corrective procedures for HAART-associated lipoatrophy

Despite switching away from thymidine drugs when possible, restoration of fat in patients with HAART-associated lipoatrophy is likely to be incomplete and, if severe, often clinically undetectable. There is currently no treatment to reverse fat loss or to generate new fat cells to grow after significant loss caused by HIV treatment. Rates of new onset lipoatrophy are now lower because physicians proactively choose newer drugs that are less likely to cause fat loss and follow guidelines that urge avoidance rather than treatment. Nevertheless, this leaves a significant minority of patients with a significantly reduced quality of life, often leading to complicated social problems and withdrawal. Consequently, a range of bioabsorbable and permanent injectable skin fillers and fat/dermal transplants that are used to correct lost tissue mass have been assessed. Bioabsorbable products include hyaluronic acid, collagen and polylactic acid (PLA) (New-Fill), with polymethylacrylate, silicon and polyalkylamide (Bio-Alcamid) being examples of permanent fillers. Bioabsorbable products have only been evaluated in facial lipoatrophy. Each filler/implant has its limitations and limited scientific data exists to support their use. However, polylactic acid has been approved in most industrialized nations in recognition of the importance of this complication and the striking benefits of treatment. This is despite the absence of large comparative trials with long-term follow-up. Whichever technique is used, the training of operators is crucial to safety and success. For permanent fillers and implants, the procedure should only be performed by an accredited plastic surgeon or dermatologist.

In the UK, most experience has been gained with PLA (Sculptra, New-Fill), which is offered by several larger HIV centres. PLA is immunologically inert, causing only limited inflammatory response. It stimulates dermal fibroblasts to produce collagen leading to thicker skin, which persists despite resorption of PLA. Sunken facial areas are built up with multiple small-volume injections spaced fortnightly. There is an immediate mechanical improvement relating to volume of injection but this disappears and is followed by more durable tissue replacement. Following a course of three to four injections, the majority of patients have a satisfactory result with thickening of the buccal and temporal tissues, which may continue for several months following the final injection [393–401]. The number of treatments required to obtain a successful correction is largely related to the severity of fat loss. Patients with severe wasting can require six or more rounds of injections to achieve reasonable results. There are few data on the long-term use of New-Fill or specifically on its use in women or dark-skinned men. However, after 18–24 months, approximately half the patients need a further injection [399]. Side effects include mild to moderate pain, post-inflammatory nodules and occasional bruising. Massage of the injected tissues in the first few days is vital to prevent palpable tissue nodules. Other biodegradable products such as hyaluronic acid and collagen produce similar effects but are less durable and repeated injections are often needed after 3–6 months. The low relative cost of this procedure, the recognition that it is a reparative procedure to reverse treatment-related toxicity and the high impact on quality of life has lead to PLA being provided by some health trusts. However, availability and funding for polylactic acid remain major issues for many other patients and physicians.

Transplanting autologous harvested fat cells is more invasive and requires general anaesthesia and hospitalization, as well as a longer recovery period. Other problems include the absence of suitable fat to transfer, the likelihood that transplanted fat will undergo the same atrophic process as the original cells, and the higher associated costs. However, in suitable patients, results can be very effective [401–403] and, at 24 weeks, comparable to New-Fill [401]. Nevertheless, it is likely to be suitable for only a minority of patients.

Polyalkylamide (Bio-Alcamid) is a permanent filler that has been demonstrated to correct HAART-associated LA without significant side-effects [404,405]. Its major advantages are that fewer injections are required (1–4), higher volumes can be used, non-facial lipoatrophy can be potentially corrected, and it may be able to be removed in case of over-filling. Insufficient scientific information exists on Bio-Alcamid to base any guidance on. However, as first occurred with PLA, many patients are accessing private clinics for treatment and patient satisfaction is high. Costs to achieve successful results in severe cases are comparable to, or less than, using PLA. As severe lipoatrophy is likely to be lifelong, a permanent solution for these patients would provide longer-term cost and quality of life advantages. There is limited data on other permanent fillers such as polymethylmethacrylate [Artecoll (PMMA)] [406,407]. However, in experienced hands, these techniques have demonstrated effective and durable results. Silicone readily migrates and cannot be removed and, therefore, should not be used.

There is a general concern with permanent fillers that if lipoatrophy continues to worsen, the edges of the filler may become visible and if fat mass increases (after switching nucleosides), the permanent filler may over-correct the original defect and become obvious. Non-surgical removal may also not be straightforward. These concerns are greatest for those with mild to moderate fat loss. In the majority of cases of mild facial lipoatrophy associated with a thymidine-containing combination, a switch to a non-thymidine HAART should be tried before recourse to using any facial filler. Where moderate facial lipoatrophy exists or in milder disease when ZDV or d4T cannot be switched, PLA is recommended as the facial filler of choice. For patients with severe lipoatrophy, it is unlikely that PLA will correct the defect durably or completely, and Bio-Alcamid may be preferable. Long-term safety data are important, but this should not be used as an obstacle to treatment for patients requiring treatment now. A comparative study between these two agents is needed.

Lipohypertrophy of the head and neck can be equally distressing and when severe can lead to neck pain, restriction of movement and sleep apnoea. The anatomical sites of fat deposits are dorsocervical, submandibular, trapezio-occipital and mastoid. Treatment options include standard surgical removal and liposuction (ultrasound-assisted or tumescent). Using liposuction, reduction of posterior lipohypertrophy is markedly more successful than with submandibular fat. However, up to half of those with dorsocervical disease develop a recurrence after 1–2 years. Where significant fat has accumulated around the breast, surgery is an option. Breast reduction surgery is invasive and needs to be discussed carefully between the patient, her partner and a specialist surgeon. Again, there is the possibility of fat return, especially if the patient cannot be established on a PI-sparing regimen. Surgery is not an option for patients with abdominal lipohypertrophy.

12.1.6 Conclusions

Lipoatrophy is best avoided as it is difficult to treat. Its appearance may be delayed by avoiding d4T and judicious use of ZDV in the initial regimen.

- Insulin resistance should be treated with metformin.
- Abnormal lipid profiles should be treated by switching drugs wherever possible and by the use of both statins and fibrates.
- Exercise and diet may have a modest effect on both body habitus and lipid abnormalities.
- Lipoatrophy should be managed by a switch away from thymidines, with or without polylactic acid injections, when mild to moderate. When severe, advice should be sought as to the benefit of a permanent filler.

12.2 Mitochondrial toxicity and lactic acidosis

The link between NRTIs and mitochondrial damage was first suggested in 1989 in relation to myopathy in patients on ZDV. Subsequently, mitochondrial toxicity has been implicated in a wide range of other NRTI-associated toxicities, including neurological disease in infants, peripheral neuropathy, hepatic steatosis and lactic acidosis. The role of mitochondrial toxicity in causing these NRTI-associated toxicities has yet to be established in most cases. However, the link for which evidence appears strongest – lactic acidosis – is one with a potentially fatal outcome.

12.2.1 Aetiology of NRTI-induced mitochondrial toxicity

NRTIs inhibit gamma DNA polymerase, the enzyme responsible for copying mitochondrial DNA [408]. Inhibitory effects of NRTIs on other enzymes key to normal mitochondrial function have also been described. Evidence to support DNA polymerase inhibition has been shown by studies that demonstrate reduced mitochondrial respiratory chain enzyme complex activity, reduced mitochondrial DNA concentrations, as well as electromyographic changes

seen previously with mitochondrial muscle damage [409–411]. Different NRTIs preferentially affect different cell lineages leading to a variety of clinical syndromes. Hence, there appears to be a hierarchy for which NRTIs cause DNA polymerase gamma inhibition, with d4T, DDC and ddI causing more inhibition of mitochondrial DNA replication [408,412], whereas ZDV may inhibit other mitochondrial enzymes [413] and cause more cytotoxicity in some cell lines [414]. Some evidence for this was suggested by the improvement in laboratory findings and clinical features when d4T was switched to ZDV or ABC in patients with symptomatic hyperlactataemia [415]. Mitochondrial toxicity may, however, represent only one mechanism by which NRTIs cause adverse effects [412]. For example, recent data in volunteers have suggested that within 2 weeks of administering thymidine analogue, mRNA and PPAR-γ are significantly lowered and this is not reversed by rosiglitazone [416].

12.2.2 Lactic acidosis and hyperlactataemia

These two terms are not interchangeable. Hyperlactataemia may occur in physiological as well as pathological circumstances and is not necessarily accompanied by changes in blood pH or anion gap. The clinical significance of hyperlactataemia is not established and routine screening of asymptomatic individuals is not currently recommended. Lactic acidosis is always a serious condition requiring immediate withdrawal of ART and other supportive therapy. Definitions are as follows:

Hyperlactataemia: venous lactate >2.5–5 mmol/L.
Lactic acidosis: arterial pH <7.35, venous lactate >5 mmol/L.

12.2.2.1 Incidence. Fatal lactic acidosis associated with NRTI use was first reported in 1993 [417]. A review of a heterogeneous group of patients receiving ART in the 5-year period beginning 1989 showed that the risk of developing lactic acidosis with hepatomegaly and hepatic steatosis was approximately 0.1% per patient per year [418]. More recent estimates are higher, at 1% to 2% per year, particularly if 'symptomatic hyperlactataemia' is included [419–421]. The risk increases with increased weight, and the risk is greater in females [422,423]. The definition of symptomatic hyperlactataemia is unclear and in general has included a range of symptoms also present in persons with consistently normal lactates (e.g. fatigue). Asymptomatic hyperlactataemia may present in up to 16% or more of individuals on therapy and may be intermittent in nature [424,425]. This compares to a reported incidence of 2% of those not on ART [425]. The duration of the ART is important in some studies, and certainly an exposure of at least several months appears to be the norm for most reported cases [426].

12.2.2.2 Clinical and laboratory features. Hyperlactataemia, defined as between 2 or 2.5 and 5 mmol/L, is often asymptomatic. Intervention is not required but the individual should be carefully monitored with repeat lactate samples taken uncuffed and at rest. If accompanied by symptoms such as nausea, malaise, weight loss, abdominal pain, tender hepatomegaly, worsening of hepatic enzyme abnormalities and/or biochemical changes, therapy should be interrupted.

Clinical features commonly accompany lactate levels of >5 mmol/L. Features of lactic acidosis include weight loss, fatigue, abdominal pain, tender hepatomegaly, respiratory distress and failure. As well as a raised lactate and acidosis and an anion gap that is usually widened (>18 mmol/L), other laboratory features that might be present include raised hepatic aminotransferases, raised creatine kinase, lactate dehydrogenase and amylase [383]. The anion gap is calculated as $[Na^+ + K^+] - [Cl^- + HCO3^-]$ and should be <12 mmol/L.

Lactic acidosis has been reported in infants of mothers receiving ZDV or ZDV + 3TC during pregnancy. Additionally, d4T + ddI has been associated with several reports of lactic acidosis in women who became pregnant while taking these medications. Consideration should be given to monitoring lactate in women receiving ART during pregnancy.

12.2.3 Management of hyperlactataemia and lactic acidosis

There is currently no rationale for performing routine serum lactate measurements or evidence for the routine use of anion gap or lactate: pyruvate ratios. Instead, it is important to maintain a high index of suspicion for lactic acidosis on the basis of associated symptoms and signs that could justify the measurement of serum lactate.

A clinician's decision to reintroduce NRTIs in patients who have had previous acidosis would justify monitoring serum lactate in those patients. However, there is insufficient evidence to establish whether NRTIs can be safely re-introduced following hyperlactataemia and, if so, in which group of patients.

The management of lactic acidosis is cessation of antiretrovirals (and any other possible contributory agents) and exclusion of other causes. Supportive measures such as ensuring adequate perfusion, providing oxygen or if necessary assisted ventilation, haemodialysis or dichloracetate may also be useful [427]. Components required by the mitochondrial respiratory pathway, such as thiamine [428], riboflavin [429] and co-enzyme Q and carnitine,

have been administered without apparent toxicity, but the evidence for their use is anecdotal.

12.2.4 Recommendations for managing lactic acidosis

The recommended minimum requirements for managing lactic acidosis are as follows:

- All patients should be informed of possible signs and symptoms and encouraged to attend an available clinic.
- All clinicians should be fully conversant with the clinical presentations of lactic acidosis and symptomatic hyperlactataemia and have immediate access to means of measuring lactate levels in specified patients.
- All clinicians should be familiar with means of managing lactic acidosis. Identifying symptomatic patients whose current antiretroviral medication should be immediately stopped is of particular importance.

13.0 Treating patients with chronic hepatitis B or C

This section should be read in conjunction with the BHIVA hepatitis B or hepatitis C management guidelines [430,431].

Someone with chronic hepatitis B or C is at risk of progression to cirrhosis and liver cancer and this risk is increased when there is HIV co-infection, with a 25–30% lifetime risk for either complication [432–434]. The mortality rate of dual HIV/HBV or HIV/HCV infected patients is approximately 10 times higher than those infected with either infection alone [434,435]. Therefore, the treatment of HBV and HCV is assuming increasing significance as the prognosis of HIV has so dramatically improved.

13.1 Hepatitis B

There are three licensed antiretrovirals that also have significant anti-HBV activity: 3TC, FTC and TDF. All are very effective at suppressing HBV-DNA and normalizing the aminotransferase levels when used in the long term but HBeAg to anti-HBe seroconversion is less likely than in HIV-negative patients. The main problem with 3TC and FTC is acquired resistance in the HBV [436,437]. Tenofovir resistance seems to be less common, although experience in treating HBV with this drug is more limited [438]. Early experience of combining TDF with 3TC shows that this is effective in the short term (up to 2 years) at reducing HBV-DNA, normalizing aminotransferase levels and inducing HBeAg seroconversion [439,440]. Current evidence also suggests that 3TC resistance is reduced when given in combination with TDF, with no TDF resistance in the small number of patients reported [439,440].

13.2 Hepatitis C

Three large multicentre trials have shown that cure is possible for chronic hepatitis C in HIV-positive patients when treated with pegylated interferon and ribavirin for up to 12 months. Sustained response rates were 11–29% for genotype 1 and 43–73% for non-type 1 genotypes (usually 2 or 3) [441–443]. Other factors influencing response include the CD4 count, HCV viral load and presence/absence of cirrhosis. The decision to treat is based largely on the degree of liver damage (based on the Ishak score of histology), especially for those with genotype 1. There is an argument for treating those with genotypes 2/3 irrespective of the liver histology (except cirrhosis) as the response is moderately good. Treatment is best given at a high CD4 count, preferably before ART has commenced. If the patient meets the criteria for ART, this treatment should be given and the patient stabilized on this before anti-HCV therapy is considered. Ideally, the CD4 count should have risen to >200 cells/μL before anti-HCV therapy is commenced. Because of significant interactions with ribavirin, the following antiretrovirals should be avoided: ZDV (anaemia); ddI or d4T/ddI (lactic acidosis) [444–446].

13.3 Avoiding antiretroviral hepatotoxicity

All antiretrovirals have the potential to cause acute and long-term hepatotoxicity and this risk is increased two- to threefold in the presence of chronic liver disease such as that due to hepatitis B or C. Patients should be carefully monitored for hepatotoxicity when HAART is commenced or changed. There is some evidence that NVP and high-dose RTV (1000 mg/day) increase the incidence of severe acute hepatotoxicity [305,447] and NVP may also be linked to increased liver fibrosis [448]. High-dose RTV is no longer recommended in HAART and low-dose RTV (in doses used to boost other PIs) is not associated with significant liver problems. Until further information is available, it is recommended that NVP is only used where necessary in HIV/hepatitis co-infected individuals.

13.4 Recommendations

- All patients who are HBeAg positive or HBV-DNA positive $>10^4$ genome equivalents/mL should be treated, as should those with cirrhosis positive for HBV-DNA at any level.
- All patients who require antiretroviral and anti-HBV therapy should receive TDF or TDF plus 3TC or FTC as part of the regimen. 3TC or FTC should not be used alone or in combination with each other. If showing continuing anti-HBV activity, TDF and 3TC/FTC should

not be stopped when changing the antiretroviral regimen because of HIV-resistance. This, therefore, may mean adding three further antiretroviral agents.
- Consideration should be given to treating (as above) other HBsAg-positive patients who do not meet the treatment criteria, as a means of preventing future disease relapse or progression.
- All patients with chronic hepatitis C should be assessed for treatment with pegylated interferon and ribavirin. Ideally, anti-HCV therapy should be given before ART is commenced and when there is a high CD4 count.
- If ART needs to be started then ZDV, ddI and d4T/ddI combination should be avoided in any patient who is going to be commenced on anti-HCV therapy.
- NVP and high-dose ritonovir (> 1000 mg/day) should be avoided if possible in all patients with liver disease including chronic HBV and HCV.

Conflict of interest

The Writing Committee is conscious of the importance that should be attached to the guidelines being written by individuals with no financial ties to the pharmaceutical industry. However, in the context of HIV, most active researchers and major prescribers of antiretrovirals do have such connections and we believe that for the present full disclosure of such financial relationships guards against the possibility of bias.

Dr Jane Anderson has received unrestricted educational support, honoraria for lectures and consultancy advice and conference sponsorship from GlaxoSmithKline, Bristol-Myers Squibb, Roche, Gilead Sciences and Abbott. She has received research funding from Gilead Sciences and has acted as a consultant for the Embrace Project (GlaxoSmithKline).

Professor Abdel Babiker is the Head of the HIV Group at the MRC Clinical Trials Unit. The Group has received research support in terms of funds, drug supplies, assay kits or educational grants from various pharmaceutical companies including Bristol-Myers Squibb, GlaxoSmithKline, Roche, Gilead Sciences, Roche Molecular Systems, Boehringer Ingelheim, Merck Sharp and Dohme, Virco and Chiron-Bayer Diagnostics.

Dr Marta Boffito has received travel grants or has been on the speakers' bureau or on the medical advisory boards of the following pharmaceutical companies: Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Roche and Vertex.

Dr Gary Brook has participated as an investigator for a clinical trial and has lectured at a meeting sponsored by Gilead Sciences.

Dr Duncan Churchill has sat on advisory panels for, received sponsorship to attend scientific meetings from, or acted as a paid speaker for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme, Gilead Sciences, Boehringer Ingelheim, DuPont, Abbott Laboratories and Roche.

Dr Martin Fisher has received honoraria and travelling scholarships and has acted as an advisor to, or has received research funding from the following companies: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline and Roche.

Dr Andrew Freedman has sat on advisory panels for, and received sponsorship to attend scientific meetings from various companies, including Roche, Gilead Sciences, GlaxoSmithKline, Bristol-Myers Squibb and Boehringer Ingelheim.

Dr Anna Maria Geretti has received consultancy and speaker honoraria from Abbott, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Roche and Virco.

Professor Brian Gazzard has received financial support for speaking and research and has been on the advisory boards for the following companies: Bristol-Myers Squibb, Gilead Sciences, Bayer Pharmaceuticals, Boehringer Ingelheim, Abbott and GlaxoSmithKline.

Professor Margaret Johnson has received honoraria and traveling scholarships and has acted as an advisor to, or has received research funding from the following companies: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline and Roche.

Dr Saye H Khoo has received research grants, travel grants and speaking honoraria from GlaxoSmithKline, Gilead Sciences, Roche and Bristol-Myers Squibb, and consulting agreements with Vertex, Gilead Sciences, Bristol-Myers Squibb and Roche. Therapeutic Drug Monitoring (TDM) for HIV drugs in the UK is supported by GlaxoSmithKline, Roche, Abbott Laboratories and Merck Sharp & Dohme. The University of Liverpool has an agreement with Delphic Europe Ltd to market TDM.

Dr Clifford Leen has received travel grants or has been on the speakers' bureau or on the medical advisory boards of the following pharmaceuticals companies: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Johnson & Johnson and Roche. He has received research grants from the following companies: ARK, Abbott, Bayer, Boehringer Ingelhiem, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche, Pfizer and Tibotec.

Dr Devaki Nair has been on advisory boards for Merck Sharp & Dohme and Astra Zeneca. She has received sponsorship for attending meetings and honoraria for lectures from Bristol-Myers Squibb, Abbott, Pfizer, Merck Sharpe & Dohme and Merck Pharmaceuticals.

In the past 12 months, Dr Barry Petters has given lectures or chaired lectures that were sponsored by Roche and Bristol-Myers Squibb and has also attended advisory boards for Abbott, Gilead Sciences and Bristol-Myers Squibb.

Professor Andrew Phillips has received reimbursement for either/or attending a symposium; a fee for speaking; a fee for organizing education; funds for research; funds for a member of staff and fees for consulting from various pharmaceutical companies including Roche, Bristol-Myers Squibb, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Gilead Sciences, Tibotec and Oxxon Therapeutic.

Dr Deenan Pillay has received honoraria/research grants from Gilead, GlaxoSmithKline, Roche, Bristol-Myers Squibb and Boehringer Ingelheim.

Dr Anton Pozniak has been an advisor on HIV therapy and has received travel and educational grants from Roche, GlaxoSmithKline, Bristol-Myers Squibb, Abbott, Boehringer Ingelheim, Gilead and Tibotec.

Dr John Walsh has sat on the advisory board for Roche, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline and Gilead Sciences. He has also received consulting fees for advice on study design from Bristol-Myers Squibb.

Dr Ed Wilkins has received educational grants from, and participated in an advisory capacity for GlaxoSmithKline, Bristol-Myers Squibb, Gilead Sciences, Roche, Abbott and Boehringer Ingelheim.

Dr Ian Williams, within the last 2 years, has received research grants from Agouron and Gilead Sciences and unrestricted educational and travel grants for conference attendance from Bristol-Myers Squibb, Gilead Sciences, Abbott Laboratories, Boehringer Ingelheim and Roche; been a member of medical advisory boards for Bristol-Myers Squibb, Abbott Laboratories, Roche, Gilead Sciences, Boehringer Ingelheim and GSK and participated in industry-sponsored symposia and educational events for which both he and his employers, University College London, have received honoraria.

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