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British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012

(Updated November 2013. All changed text is cast in yellow highlight.)

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For citation purposes readers should refer to the original text published at
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NHS Evidence has accredited the process used by the British HIV Association (BHIVA) to produce guidelines. Accreditation is valid for five years from July 2012 and is applicable to guidance produced using the processes described in the British HIV Association (BHIVA) Guideline Development Manual. More information on accreditation can be viewed at www.nice.org.uk/accreditation

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1.0 Introduction

1.1 Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of adults with HIV infection with antiretroviral therapy (ART). The scope includes: (i) guidance on the initiation of ART in those previously naïve to therapy; (ii) support of patients on treatment; (iii) management of patients experiencing virological failure; and (iv) recommendations in specific patient populations where other factors need to be taken into consideration. The guidelines are aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection and at community advocates responsible for promoting the best interests and care of HIV-positive adults. They should be read in conjunction with other published BHIVA guidelines.

1.2 Methodology

1.2.1 Guideline development process

BHIVA revised and updated the association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and development of recommendations [2,3]. Full details of the guideline development process, including conflict of interest policy, are outlined in the manual.

The scope, purpose and guideline topics were agreed by the Writing Group. Questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist. Details of the search questions and strategy (including the definition of populations, interventions and outcomes) are outlined in Appendix 2. BHIVA adult ART guidelines were last published in 2008 [4]. For the 2012 guidelines the literature search dates were 1 January 2008 to 16 September 2011 and included MEDLINE, EMBASE and the Cochrane library. Abstracts from selected conferences (see Appendix 2) were searched between 1 January 2009 and 16 September 2011. For each topic and healthcare question, evidence was identified and evaluated by Writing Group members with expertise in the field. Using the modified GRADE system (Appendix 1), panel members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. An important aspect of evaluating evidence is an understanding of the design and analysis of clinical trials, including the use of surrogate marker data.

Limited further searches concerning specific third agents (rilpivirine [RPV] and elvitegravir [ELV]/cobicistat [COBI]) covering the period from September 2011 were carried out in 2013.

For a number of questions, GRADE evidence profile and summary of findings tables were constructed, using predefined and rated treatment outcomes (Appendix 3), to help achieve consensus for key recommendations and aid transparency of the process. Before final approval by the Writing Group, the guidelines were published online for public consultation and an external peer review was commissioned.

1.2.2 Patient involvement

BHIVA views the involvement of patient and community representatives in the guideline development process as essential. The Writing Group included two patient representatives appointed through the UK HIV Community Advisory Board (UK CAB) who were involved in all aspects of the guideline development process. In addition, two meetings with patients and community representatives were held to discuss and receive feedback and comment on the proposed guideline recommendations. The first was held before the Writing Group's consensus meeting and the second as part of the public consultation process.

1.2.3 GRADE

The GRADE Working Group [3] has developed an approach to grading evidence that moves away from initial reliance on study design to consider the overall quality of evidence across outcomes. BHIVA has adopted the modified GRADE system for its guideline development.

The advantages of the modified GRADE system are (i) the grading system provides an informative, transparent summary for clinicians, patients and policy makers by combining an explicit evaluation of the strength of the recommendation with a judgement of the quality of the evidence for each recommendation, and (ii) the two-level grading system of recommendations has the merit of simplicity and provides clear direction to patients, clinicians and policy makers.

A *Grade 1 recommendation* is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all

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patients. Most clinicians and patients should and would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'we recommend'.

A *Grade 2 recommendation* is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Most clinicians and patients would want to follow a weak or conditional recommendation but many would not. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'we suggest'.

The *strength of a recommendation* is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences and, where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

The *quality of evidence* is graded from A to D and for the purpose of these guidelines is defined as the following.

Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomized controlled trials (RCTs), or overwhelming evidence of some other sort (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.

Grade B evidence means moderate-quality evidence from randomized trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strengths such as observational studies with consistent effects and exclusion of most potential sources of bias.

Grade C evidence means low-quality evidence from controlled trials with several very serious limitations or observational studies with limited evidence on effects and exclusion of most potential sources of bias.

Grade D evidence on the other hand is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there is likely to be little confidence in the effect estimate.

1.2.4 Good practice points

In addition to graded recommendations, the BHIVA Writing Group has also included good practice points (GPP), which are recommendations based on the clinical judgement and experience of the working group. GPPs emphasize an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment and care that is regarded as such sound clinical practice that healthcare professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable. It must be emphasized that GPPs are not an alternative to evidence-based recommendations.

1.2.5 Dissemination and implementation

The following measures have/will be undertaken to disseminate and aid implementation of the guidelines:

- E-publication on the BHIVA website and the journal *HIV Medicine*.
- Publication in *HIV Medicine*.
- Shortened version detailing concise summary of recommendations.
- E-learning module accredited for CME.
- Educational slide set to support local and regional educational meetings.
- National BHIVA audit programme.

1.2.6 Guideline updates and date of next review

The guidelines will be next fully updated and revised in 2014. However, the Writing Group will continue to meet regularly to consider new information from high-quality studies and publish amendments and addendums to the current recommendations before the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

1.3 Treatment aims

The primary aim of ART is the prevention of the mortality and morbidity associated with chronic HIV infection at low cost of drug toxicity. Treatment should improve the physical and psychological well-being of people living with HIV infection. The effectiveness and tolerability of ART has improved significantly over the last 15 years. The overwhelming majority of patients attending HIV services in the UK and receiving ART experience long-term virological suppression and good treatment outcomes [5], which compare very favourably with other developed countries.

Recent data have shown that life expectancy in the UK of someone living with HIV infection has improved significantly over recent years but is still about 13 years less than that of the UK population as a whole [6]. For someone aged 20 years starting ART, life expectancy increased from 30.0

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to 45.8 years from 1996–1999 to 2006–2008. The impact of starting ART late is large, with up to 15 years of reduced life expectancy if ART is started later than the current BHIVA guidelines recommend. Other data have shown that for HIV-positive men who have sex with men living in a developed country with extensive access to HIV care and assuming a high rate of HIV diagnosis, the projected life expectancy was 75 years [7]. The authors concluded that the greatest risk of excess mortality is due to delays in HIV diagnosis. Decreasing late diagnosis, starting ART earlier at recommended CD4 cell count levels, maintaining patients in care and reducing long-term drug toxicity and non-AIDS co-morbidities are crucial to further improving life expectancy and the well-being of people living with HIV infection.

A further aim of treatment is the reduction in sexual transmission of HIV and for some patients may be the primary aim. The use of ART to prevent mother-to-child transmission is universally accepted and best practice is addressed in the *BHIVA guidelines for the management of HIV infection in pregnant women* [8]. Recently, the size of the effect of ART on reducing the risk of sexual transmission of HIV has been estimated at >95% [9,10]. At a population level, ART may be potentially important in reducing the incidence of HIV infection. ART is usually started for the health benefit of the individual, but in certain circumstances, it may be beneficial to start ART to primarily reduce the risk of onward sexual transmission of HIV.

1.4 Resource use

ART is extremely cost-effective and compares favourably with the cost of management of many other chronic diseases. Estimates of the cost-effectiveness of ART have been assessed in studies in North America and Europe [11–13]. Their findings have been consistent with an estimated incremental cost-effectiveness ratio of about US$20 000 per quality adjusted life year for combination ART compared with no therapy based on drug costs and treatment patterns in the USA and Europe [14].

The number of people living with HIV in the UK continues to increase and by the end of 2010 was estimated to be 91 500 of whom 24% were undiagnosed. Of those diagnosed, 69 400 accessed HIV services in 2010 of whom 82% were on ART [5]. With ongoing HIV transmission, increased HIV testing and a reduction in the undiagnosed fraction, the number of people diagnosed with HIV and accessing HIV services will continue to increase. It has been estimated that the annual population treatment and care costs rose from £104 million in 1997 to £483 million in 2006, rising to a projected annual cost of £721 million in 2013 [15]. It is likely this estimated projected cost is an overestimate due to various factors, including earlier diagnosis and a lower proportion of patients with symptoms. However, in the current economic climate containing and reducing annual costs without affecting the current high standards of care and treatment outcomes will be an immense challenge to commissioners, healthcare professionals and patients alike. A collaborative approach is required.

In the UK, higher annual treatment and care costs have been associated with late diagnosis and initiation of ART at lower CD4 cell counts than the BHIVA guidelines recommend [16,17]. In addition to earlier diagnosis and initiation of ART, reducing inpatient episodes, decreasing drug toxicity, preventing HIV-associated co-morbidities and innovations in models of care are likely to have a beneficial effect on annual costs. However, the cost of antiretroviral (ARV) drugs remains the major factor contributing to treatment and care costs. With the future availability of generic drugs and the introduction of a standard tariff for HIV services (in England), clinicians and patients will be faced with difficult choices about the value and benefit of different ARV drugs.

The BHIVA Writing Group recognizes that cost of drugs is an important issue in the choice of ART regimens There are limited cost-effectiveness data in the UK comparing different ARV drugs and for this reason the Writing Group did not include cost-effectiveness as an outcome in ART comparisons. However, the Writing Group believes that decreasing the risk of virological failure, drug resistance and drug-associated toxicity are likely to have a beneficial impact on long-term cost-effectiveness and resource use. In the setting of equivalent virological efficacy, determining the acceptable threshold at which differences in the risk of toxicity, tolerability and convenience outweigh differences in resource use and cost will be important. These thresholds may differ among clinicians and patients alike.

In developing the recommendations in these guidelines, the Writing Group has taken into account differences in critical treatment outcomes between different drug regimens in determining preferred and alternative treatment regimens. The Writing Group recognizes and supports that commissioning arrangements and local drug costs will and should influence ART choice where outcomes, across a range of clinical measures, are equivalent between individual drugs in the treatment of defined patient populations. The Writing Group, however, believes that reducing treatment costs should not be at the cost of an increased risk of poorer treatment outcomes and quality of care, not least as these are likely to have a detrimental impact on long-term cost.

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1.5 Implications for research

In reviewing quality of evidence, guidelines will identify areas of treatment and care where there is either an absence of evidence or limited confidence in the size of effect to influence choice of treatments or determine treatment and management strategies. For this reason, it is not the intention of these guidelines to stifle clinical research but help promote continued research with the aim to further improve clinical care and treatment outcomes. The Writing Group supports the development and provision of HIV clinical trials within the UK and participation in a clinical trial should be open and offered to patients where appropriate.

1.6 References

1 BHIVA. Guideline development manual, 13 September 2011. http://www.bhiva.org

2 Guyatt GH, Oxman AD, Kunz R *et al*. Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051.

3 Development and Evaluation (Short GRADE) Working Group. The grading of recommendations assessment. Available at http://www.gradeworkinggroup.org (accessed April 2012).

4 Gazzard B, on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med* 2008; **9**: 563–608.

5 Health Protection Agency. HIV in the United Kingdom: 2011 report. Available at http://www.hpa.org.uk/HIV (accessed April 2012).

6 May M, Gompels M, Delpech V *et al*. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *BMJ* 2011; **343**: d61016.

7 Nakagawa F, Lodwick RK, Smith CJ *et al*. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS* 2012; **26**: 335–343.

8 Taylor GT, Clayden P, Dhar J *et al*. BHIVA guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012; **13** (Suppl. 2): 87–157.

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

10 Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009; **23**: 1397–1404.

11 Sendi P, Butcher H, Harr T *et al*. Cost effectiveness of highly active antiretroviral therapy in HIV infected patients: Swiss HIV Cohort study. *AIDS* 1999; **13**: 1115–1122.

12 Miners AH, Sabin CA, Trueman P *et al*. Assessing cost effectiveness of highly active antiretroviral therapy for adults with HIV in England. *HIV Med* 2001; **2**: 52–58.

13 Freedberg KA, Losina E, Weinstein MC *et al*. The cost effectiveness of combination antiretroviral therapy in HIV disease. *N Engl J Med* 2001; **344**: 824–831.

14 Yazdanpanah Y. Costs associated with combination antiretroviral therapy in HIV infected persons. *J Antimicrob Chemother* 2004; **53**: 558–561.

15 Mandalia S, Mandalia R, Lo G *et al*. Rising population cost for treating people living with HIV in the UK, 1997–2013. *PLoS ONE* 2010; **5**: e15677. doi:10.1371/journal.pone.0015677.

16 Beck EJ, Mandalia S, Sangha R *et al*. The cost effectiveness of early access to HIV services and starting cART in the UK 1996–2008. *PLoS ONE* 2011; **6**: e27830.

17 Beck EJ, Mandalia S, Lo G *et al*. Cost-effectiveness of early treatment with first-line NNRTI-based HAART regimens in the UK, 1996–2006. *PLoS ONE* 2011; **6**: e20200.

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2.0 Recommendations and auditable outcomes

2.1 Recommendations (GRADE)

2.1.1 Patient involvement in decision making (Section 3)

3.1	We recommend patients are given the opportunity to be involved in making decisions about their treatment.	GPP

2.1.2 When to start (Section 4)

2.1.2.1 Chronic infection

4.1	We recommend patients with chronic infection start ART if the CD4 cell count is ≤350 cells/μL: it is important not to delay treatment initiation if the CD4 cell count is close to this threshold.	1A
	We recommend patients with the following conditions start ART:	
	• AIDS diagnosis [e.g. Kaposi sarcoma (KS)] irrespective of CD4 cell count.	1A
	• HIV-related co-morbidity, including HIV-associated nephropathy (HIVAN), idiopathic thrombocytopenic purpura, symptomatic HIV-associated neurocognitive (NC) disorders irrespective of CD4 cell count.	1C
	• Coinfection with hepatitis B virus (HBV) if the CD4 cell count is ≤500 cells/μL (see Section 8.2.2 Hepatitis B).	1B
	• Coinfection with hepatitis C virus (HCV) if the CD4 cell count is ≤500 cells/μL (Section 8.2.3 Hepatitis C).	1C
	• Non-AIDS-defining malignancies requiring immunosuppressive radiotherapy or chemotherapy (Section 8.3.2 When to start ART: non-AIDS-defining malignancies).	1C
	We suggest patients with the following conditions start ART:	
	• Coinfection with HBV if the CD4 cell count is >500 cells/μL and treatment of hepatitis B is indicated (see Section 8.2.2 Hepatitis B).	2B

2.1.2.2 Patients presenting with AIDS or a major infection

4.2	We recommend patients presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 cell count <200 cells/μL, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy.	1B

2.1.2.3 Treatment of primary HIV infection

4.3	We recommend patients presenting with primary HIV infection (PHI) and meeting any one of the following criteria start ART:	
	• Neurological involvement.	1D
	• Any AIDS-defining illness.	1A
	• Confirmed CD4 cell count <350 cells/μL.	1C

2.1.2.4 Treatment to reduce transmission

4.4	We recommend the evidence that treatment with ART lowers the risk of transmission is discussed with all patients, and an assessment of the current risk of transmission to others is made at the time of this discussion.	GPP
	We recommend following discussion, if a patient with a CD4 cell count >350 cells/μL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started.	GPP

2.1.3 What to start (Section 5)

5.1	We recommend therapy-naïve patients start ART containing two nucleos(t)ide reverse transcriptase inhibitor (NRTIs) plus one of the following: a ritonavir-boosted protease inhibitor (PI/r), an NNRTI or an integrase inhibitor (INI).	1A

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Summary recommendations for choice of ART:

	Preferred	Alternative
NRTI backbone	Tenofovir and emtricitabine	Rilpivirine‡
Third agent	Atazanavir/ritonavir	Abacavir and lamivudine*‡
	Darunavir/ritonavir	Lopinavir/ritonavir
	Efavirenz	Fosamprenavir/ritonavir
	Raltegravir	Nevirapine†
	Elvitegravir/cobicistat	

*Abacavir is contraindicated if HLA-B*57:01 positive.
†Nevirapine is contraindicated if baseline CD4 cell count is greater than 250/400 cells/μL in women/men.
‡Use recommended only if baseline VL <100 000 copies/mL: rilpivirine as a third agent, abacavir and lamivudine as NRTI backbone.

The presence or future risk of co-morbidities and potential adverse effects need to be considered in the choice of ARV drugs in individual patients.

2.1.3.1 Which nucleoside reverse transcriptase inhibitor backbone

5.3 We recommend therapy-naïve patients start combination ART containing tenofovir (TDF) and emtricitabine (FTC) as the NRTI backbone. 1A

We suggest abacavir (ABC) and lamivudine (3TC) is an acceptable alternative NRTI backbone in therapy-naïve patients who, before starting ART, have baseline viral load (VL) of ≤100 000 copies/mL. 2A

ABC must not be used in patients who are HLA-B*57:01 positive. 1A

2.1.3.2 Which third agent

5.4 We recommend therapy-naïve patients start combination ART containing one of the following as the third agent: atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), efavirenz (EFV), raltegravir (RAL) or elvitegravir (ELV)/cobicistat (COBI). 1A

We suggest that in therapy-naïve patients lopinavir/ritonavir (LPV/r) and fosamprenavir/ritonavir (FPV/r) are acceptable alternative PIs, and nevirapine (NVP) is an acceptable alternative NNRTI. 2A

2.1.3.3 Novel antiretroviral therapy strategies

5.5 We recommend against the use of PI monotherapy as initial therapy for treatment-naïve patients. 1C

We recommend against the use of PI-based dual ART with a single NRTI, NNRTI, C–C chemokine receptor type 5 (CCR5) receptor antagonist or INI as initial therapy for treatment-naïve patients. 1C

2.1.4 Supporting patients on therapy (Section 6)

2.1.4.1 Adherence

Interventions to increase adherence to treatment

6.1.1 We recommend adherence and potential barriers to it are assessed and discussed with the patient whenever ART is prescribed or dispensed. GPP

We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/or practical barriers (e.g. limitations in capacity and resources) to adherence. GPP

2.1.4.2 Pharmacology

Drug interactions

6.2.1 We recommend that potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications are checked before administration (with tools such as http://www.hiv-druginteractions.org). GPP

Therapeutic drug monitoring

6.2.2 We recommend against the unselected use of therapeutic drug monitoring (TDM). GPP

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Stopping therapy: pharmacological considerations

6.2.3 We recommend patients stopping ART containing an NNRTI in combination with an NRTI backbone replace all drugs with a PI (LPV/r) for 4 weeks. 1C

We recommend patients stopping a PI-containing regimen stop all drugs simultaneously and no replacement is required. 1C

2.1.4.3 Switching antiretroviral therapies in virological suppression

Switching antiretrovirals in combination antiretroviral therapy

6.3.2 We recommend in patients on suppressive ART regimens, consideration is given to differences in side effect profile, drug–drug interaction (DDIs) and drug resistance patterns before switching any ARV component. GPP

We recommend, in patients with previous NRTI resistance mutations, against switching a PI/r to either an NNRTI or an INI as the third agent. 1B

Protease inhibitor monotherapy

6.3.3 We recommend continuing standard combination ART as the maintenance strategy in virologically suppressed patients. There are insufficient data to recommend PI/r monotherapy in this clinical situation. 1C

2.1.4.4 Stopping therapy

6.4 We recommend against treatment interruption or intermittent therapy in patients stable on a virally suppressive ART regimen. 1A

2.1.5 Managing virological failure (Section 7)

2.1.5.1 Blips, low-level viraemia and virological failure

7.2 In patients on ART:

A single VL 50–400 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern. GPP

We recommend a single VL >400 copies/mL is investigated further, as it is indicative of virological failure. 1C

We recommend in the context of repeated viral blips, resistance testing is attempted. 1D

2.1.5.2 Patients with no or limited drug resistance

7.3 We recommend patients experiencing virological failure on first-line ART with wild-type (WT) virus at baseline and without emergent resistance mutations at failure switch to a PI/r-based combination ART regimen. 1C

We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure switch to a new PI/r-based regimen with the addition of at least one, preferably two, active drugs. 1C

We recommend patients experiencing virological failure on first-line PI/r plus two-NRTI-based regimen, with major protease mutations, switch to a new active PI/r with the addition of at least one, preferably two, active agents of which one has a novel mechanism of action. 1C

We recommend against switching a PI/r to an INI or an NNRTI as the third agent in patients with historical or existing reverse transcriptase (RT) mutations associated with NRTI resistance or past virological failure on NRTIs. 1B

2.1.5.3 Patients with triple-class (non-nucleoside reverse transcriptase inhibitor, nucleoside reverse transcriptase inhibitor, protease inhibitor) virological failure with or without triple-class resistance

7.4 We recommend patients with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed/referred for expert advice (or through virtual clinic referral). GPP

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We recommend patients with triple-class resistance switch to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as DRV/r or tipranavir/ritonavir (TPV/r) and one agent with a novel mechanism (CCR5 receptor antagonist or integrase/fusion inhibitor) with etravirine (ETV) an option based on viral susceptibility. 1C

2.1.5.4 Patients with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

7.5 We recommend accessing newer agents through research trials, expanded access and named patient programmes. GPP

We suggest continuing/commencing NRTIs as this may contribute partial ARV activity to a regimen, despite drug resistance. 2C

We recommend the use of 3TC or FTC to maintain a mutation at codon position 184 of the RT gene. 1B

We recommend against discontinuing or interrupting ART. 1D

We recommend against adding a single, fully active ARV because of the risk of further resistance. 1D

We recommend against the use of maraviroc (MVC) to increase the CD4 cell count in the absence of CCR5 tropic virus. 1C

2.1.6 Antiretroviral therapy in specific populations (Section 8)

2.1.6.1 HIV with tuberculosis coinfection: when to start

8.1.1 Timing of initiation of ART during tuberculosis (TB) therapy 1B

CD4 cell count (cells/μL)	When to start highly active anti-retroviral therapy (HAART)
<100	As soon as practical within 2 weeks after starting TB therapy
100–350	As soon as practical, but can wait until after completing 2 months' TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities
>350	At physician's discretion

2.1.6.2 HIV with tuberculosis: what to start

8.1.2 We recommend EFV in combination with TDF and FTC as first-line ART in TB/HIV coinfection. 1C

We recommend that when rifampicin is used with EFV in patients over 60 kg, the EFV dose is increased to 800 mg daily. Standard doses of EFV are recommended if the patient weighs <60 kg. 1C

We recommend that rifampicin is not used with either NVP or a PI/r. 1C

We recommend that where effective ART necessitates the use of PI/r that rifabutin is used instead of rifampicin. 1C

2.1.6.3 HIV and viral hepatitis coinfection: summary of when to start recommendations

CD4 cell count (cells/μL)	HBV requiring treatment*	HBV not requiring treatment	HCV with immediate plan to start HCV treatment*	HCV with no immediate plan to start HCV treatment
>500	Start ART in some patients (2C) (Include TDF and FTC)	Defer ART	Defer ART	Defer ART
≤500	Start ART (1B) (Include TDF and FTC)	Start ART (1B) (Include TDF and FTC)	350–500 Start ART after HCV treatment commenced (1C) <350 Start ART before HCV treatment (1B) Discuss with HIV and viral hepatitis specialist	Start ART (1C)

*See *BHIVA Guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus* [1] for indications to treat hepatitis B and C.

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2.1.6.4 Hepatitis B: when to start

8.2.2.1	• We recommend patients with HIV and hepatitis B virus coinfection who have a CD4 cell count <500 cells/μL are treated with fully suppressive ART inclusive of anti-HBV active antivirals.	1B
	• We recommend patients with HIV and HBV coinfection who have a CD4 cell count ≥500 cells/μL and who have an HBV-DNA ≥2000 IU/mL and/or evidence of more than minimal fibrosis (Metavir ≥F2) are treated with fully suppressive ART inclusive of anti-HBV active antivirals.	1C

2.1.6.5 Hepatitis B: what to start

8.2.2.2	• We recommend TDF/FTC as part of a fully suppressive ART combination should be given to all patients where HBV treatment is deemed necessary.	1C
	• We recommend neither 3TC nor FTC be used as the sole active drug against HBV in ART due to the rapid emergence of HBV resistant to these agents.	1B
	• We recommend 3TC/FTC may be omitted from the ART regimen and tenofovir be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of 3TC/FTC-resistant HBV or HIV.	1D

2.1.6.6 Hepatitis C: when to start antiretroviral therapy

8.2.3.1	• We recommend all patients with HIV and hepatitis C virus coinfection be assessed for HCV treatment.	GPP
	• We suggest commencing ART when the CD4 cell count is greater than 500 cells/μL in all patients who are not to commence HCV treatment immediately.	2D
	• We recommend commencing ART when the CD4 cell count is less than 500 cells/μL in all patients who are not to commence anti-HCV treatment immediately.	1B
	• We recommend commencing ART to optimize immune status before anti-HCV therapy is initiated when the CD4 cell count is between 350 and 500 cells/μL unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilized on HCV therapy.	GPP
	• We recommend commencing ART to allow immune recovery before anti-HCV therapy is initiated when the CD4 cell count is less than 350 cells/μL.	GPP

2.1.6.7 Hepatitis C: what to start

8.2.3.2	• We recommend if patients are commencing ART, and DAAs are not being considered, standard first-line ART should be commenced.	GPP
	• We recommend when DAAs are to be used there is careful consideration of possible DDIs (1C) and current or archived HIV resistance. All drug interactions should be checked with an expert source (e.g., www.hiv-druginteractions.org).	
	• We recommend if boceprevir is to be used, RAL with TDF plus FTC should be the treatment of choice for those with wild-type HIV (1C): pharmacokinetic data would support ETV, RPV and MVC as alternatives.	
	• We recommend if telaprevir is to be used either RAL or standard-dose ATV/r should be used (1C): pharmacokinetic data would support ETV, RPV and MVC as alternatives. EFV may be used but the telaprevir dose needs to be increased to 1125 mg tds.	
	• We suggest that if ABC is to be used with ribavirin, the ribavirin should be weight-based dose-adjusted.	2C

2.1.6.8 HIV-related cancers: when to start

8.3.1	We recommend starting ART in HIV-positive patients with KS.	1A
	We recommend starting ART in HIV-positive patients with non-Hodgkin lymphoma (NHL).	1B
	We suggest starting ART in HIV-positive patients with cervical cancer.	1C
	We recommend starting ART in HIV-positive patients who are commencing radiotherapy or chemotherapy for cervical cancer.	1D
8.3.2	We suggest starting ART in HIV-positive patients with non-AIDS-defining malignancies (NADMs).	2C
	We recommend starting ART in HIV-positive patients who are commencing immunosuppressive radiotherapy or chemotherapy for NADMs.	1C

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2.1.6.9 HIV-related cancers: what to start

8.3.3 We recommend that potential pharmacokinetic interactions between ARVs and systemic anticancer therapy be checked before administration (with tools such as: http://www.hiv-druginteractions.org). GPP

We suggest avoiding ritonavir-boosted ART in HIV-positive patients who are to receive cytotoxic chemotherapy agents that are metabolized by the cytochrome P450 (CYP450) enzyme system. 2C

We recommend against the use of ATV in HIV-positive patients who are to receive irinotecan. 1C

We suggest avoiding ARV agents in HIV-positive patients who are to receive cytotoxic chemotherapy agents that have overlapping toxicities. 2C

2.1.6.10 HIV-associated neurocognitive impairment: when to start

8.4.2 We recommend patients with symptomatic HIV-associated NC disorders start ART irrespective of CD4 lymphocyte count. 1C

2.1.6.11 HIV-associated neurocognitive impairment: what to start

8.4.3 We recommend patients with HIV-associated NC disorders start standard combination ART regimens. 1C

2.1.6.12 HIV-associated neurocognitive impairment: modification of antiretroviral therapy

8.4.4 In patients with ongoing or worsening NC impairment despite ART we recommend the following best practice management: GPP

- Reassessment for confounding conditions.
- Assessment of cerebrospinal fluid (CSF) HIV RNA, CSF HIV genotropism and genotyping of CSF HIV RNA.
- In subjects with detectable CSF HIV RNA, modifications to ART should be based on plasma and CSF genotypic and genotropism results.

2.1.6.13 Chronic kidney disease: when to start

8.5.1 We recommend patients with HIVAN start ART immediately irrespective of CD4 cell count. 1C

We recommend patients with end-stage kidney disease who are suitable candidates for renal transplantation start ART irrespective of CD4 cell count. 1C

2.1.6.14 Chronic kidney disease: what to start

8.5.2 We recommend against the use of ARV drugs that are potentially nephrotoxic, in patients with stages 3–5 chronic kidney disease (CKD) if acceptable alternative ARV agents are available. GPP

We recommend dose adjustment of renally cleared ARV drugs in patients with reduced renal function. GPP

2.1.6.15 Cardiovascular disease: what to start

8.6.4 We suggest avoiding: ABC, FPV/r and LPV/r in patients with a high cardiovascular disease (CVD) risk, if acceptable alternative ARV drugs are available. 2C

2.1.6.16 Women: when to start

8.7.2 We recommend therapy-naïve HIV-positive women who are not pregnant start ART according to the same indicators as in men (see Section 4: When to Start) 1A

2.1.6.17 Women: what to start

8.7.3 We recommend therapy-naïve HIV-positive women start ART containing two NRTIs and one of the following: PI/r, NNRTI or INI, as per therapy-naïve HIV-positive men. 1A

We recommend therapy-naïve HIV-positive women start ART with preferred or alternative NRTI backbone and third agent as per therapy-naïve HIV-positive men (see Section 5.1: What to start: summary recommendations). 1A

Factors such as potential side effects, co-morbidities, drug interactions, patient preference and dosing convenience need to be considered in selecting ART in individual women.

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We recommend both HIV-positive women of childbearing potential and healthcare professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of HIV-positive women and for that of an unborn child. GPP

We recommend that potential pharmacokinetic interactions between ARVs, hormonal contraceptive agents and hormone replacement therapy be checked before administration (with tools such as: http://www.hiv-druginteractions.org). GPP

2.1.7 Reference

1 Brook G, Main J, Nelson M *et al*. BHIVA Viral Hepatitis Working Group. British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. *HIV Med* 2010; **11**: 1–30.

2.2 Summary of auditable measures

Percentage of patients who confirm they have been given the opportunity to be involved in making decisions about their treatment.
Proportion of patients with CD4 cell count <350 cells/μL not on ART.
Proportion of patients with CD4 cell count >350 cells/μL and an indication to start ART on ART.
Proportion of patients presenting with an AIDS-defining infection or with a serious bacterial infection and a CD4 cell count <200 cells/μL started on ART within 2 weeks of initiation of specific antimicrobial chemotherapy.
Proportion of patients presenting with PHI and neurological involvement, or an AIDS-defining illness or confirmed CD4 cell count <350 cells/μL started on ART.
Record in patient's notes of discussion, treatment with ART lowers risk of HIV transmission and an assessment of current risk of transmission.
Proportion of therapy-naïve patients not starting ART containing two NRTIs and one of the following: PI/r, NNRTI or INI (preferred or alternative agents).
Proportion of patients starting ART with TDF/FTC or ABC/3TC as the NRTI backbone.
Proportion of patients starting ART with ATV/r, DRV/r, EFV or RAL as the third agent.
Proportion of patients with undetectable VL <50 copies/mL at 6 and 12 months after starting ART.
Proportion of patients who switch therapy in the first 6 and 12 months.
Record in patient's notes of HLA-B*57:01 status before starting ABC.
Record in patient's notes of discussion and assessment of adherence and potential barriers to, before starting a new ART regimen and while on ART.
Record in patient's notes of provision or offer of adherence support.
Record in patient's notes of potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications.
Proportion of patients with undetectable VL on ART who, on stopping a regimen containing NNRTI in combination with an NRTI backbone, are switched to PI/r for 4 weeks.
Number of patients with an undetectable VL on current regimen and documented previous NRTI resistance who have switched a PI/r to either an NNRTI or INI as the third agent.
Number of patients on PI/r monotherapy as ART maintenance strategy in virologically suppressed patients and record of rationale.
Record in patient's notes of resistance result at ART initiation (if available) and at first VL >400 copies/mL and/or before switch.
Record in patient's notes of adherence assessment and tolerability/toxicity to ART, in patients experiencing virological failure or repeated viral blips.
Number of patients experiencing virological failure on current ART regimen.
Proportion of patients experiencing virological failure switched to a new suppressive regimen within 6 months.
Proportion of patients on ART with previous documented HIV drug resistance with VL <50 copies/mL.
Record of patients with three-class virological failure with or without three-class resistance referred/discussed in multidisciplinary team with expert advice.
Proportion of patients with TB and CD4 cell count <100 cells/μL started on ART within 2 weeks of starting TB therapy.
Proportion of patients with active TB on anti-TB therapy started on ART containing EFV, TDF and FTC.

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Proportion of patients with a CD4 cell count ≥500 cells/μL and an HBV DNA ≥2000 IU/mL and/or evidence of more than minimal fibrosis commencing ART inclusive of anti-HBV antivirals.
Proportion of patients with a CD4 cell count <500 cells/μL receiving TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen.
Proportion of patients receiving 3TC or FTC as the sole active drug against HBV in ART.
Proportion of patients with a CD4 cell count <500 cells/μL commencing ART.
Among patients receiving DAAs for HCV genotype 1 with ART for wild type HIV, the percentage on a recommended regimen, i.e. RAL with TDF plus FTC with boceprevir; or RAL or boosted ATV with standard dose telaprevir; or EFV with increased dose 1125 mg tds telaprevir.
Proportion of patients with an AIDS-defining malignancy on ART.
Proportion of patients with a non-AIDS-defining malignancy on ART.
Record in patient's notes of potential pharmacokinetic drug interactions between ARVs and systemic anticancer therapy.
Proportion of patients with symptomatic HIV-associated NC disorders on ART.
Proportion of patients with HIV-associated NC disorders on ART containing two NRTIs and one of the following: NNRTI, or PI/r or INI.
Proportion of patients with HIVAN started on ART within 2 weeks of diagnosis of CKD.
Number of patients with CKD stages 3–5 on ARVs that are potentially nephrotoxic and record of rationale.
Record in patient's notes of the calculated dose of renally cleared ARVs in patients with CKD stage 3 or greater.
Number of patients with high CVD risk on either ABC or FPV/r or LPV/r and record of rationale.
Proportion of HIV-positive women with CD4 cell count <350 cells/μL not on ART.

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3.0 Patient involvement in decision-making

3.1 Recommendations

- We recommend patients are given the opportunity to be involved in making decisions about their treatment (GPP).
- Provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources.

3.1.1 Auditable measure

Percentage of patients who confirm they have been given the opportunity to be involved in making decisions about their treatment.

3.2 Rationale

Patients should be given the opportunity to be involved in making decisions about their treatment [1]. Studies show that trust, a good-quality relationship and good communication skills between doctor and patient are associated with better adherence and treatment outcomes in HIV and in other disease areas [2–6].

Studies have shown that patient beliefs about the necessity, efficacy and side effects of ART, the practicability of taking it, and beliefs about their ability to adhere to therapy, all affect adherence [7–9].

Before prescribing ART (treatment initiation or switching), clinicians should assess:

- Patients' readiness to take therapy.
- Their knowledge of its mode of action and efficacy, and perceptions of their personal need for ART.
- Concerns about taking ART or specific ARV drugs, including potential adverse effects.
- Concerns with possible adverse social consequences, such as disclosure or interference with lifestyle.
- Their confidence that they will be able to adhere to the medication (self-efficacy);
- Psychological or NC issues that could impact on adherence;
- Socio-economic factors that could impact on adherence, including, but not limited to, poverty, housing, immigration status or domestic violence.

Community advocacy and peer support are helpful in supporting a patient's understanding and confidence around treatments and help the patient's readiness and decision to start therapy. Community organizations in the UK have been instrumental in providing a range of patient-information resources and peer-support services, including published and web-based information materials, telephone advice lines, treatment advocates and peer-support groups, working in collaboration with healthcare professionals. They are an important and essential adjunct to clinic-based services and are helpful in addressing the issues discussed below.

A number of patient factors may affect adherence, adverse effects and treatment outcomes. Depression is significantly associated with low adherence [10,11] and some studies report an independent association between depression and mortality in people with HIV [12]. Adherence can be improved by treating depression [13], so all patients should be screened for depression before starting therapy, using simple screening tools such as the Arroll two-question quick screen [14]. Patients should also be screened for anxiety and for cognitive impairment.

Current problematic alcohol and recreational drug use are also associated with low adherence [15–17], although a history of injecting drug use, or even active use, is not necessarily so [18]. Patients should be asked about alcohol and recreational drug use and offered support to moderate or manage it if desired.

Conversely, adherence has been associated with positive experiences of quality of life such as having a meaningful life, feeling comfortable and well cared for, using time wisely, and taking time for important things [19]. Patient self-management skills and courses that teach them have been associated with both improved adherence and better clinical outcomes in a number of studies [20–22] and it may be helpful to patients to inform them of these and other psychological support options locally available, in line with the BPS/BHIVA *Standards for Psychological Support for Adults Living with HIV* [23].

A patient's socio-economic status has a more direct effect on adherence and other healthcare behaviours, than clinicians realize. For instance, a US study found that poverty had a direct effect on adherence, largely due to food insufficiency [24]. A 2010 report on poverty in people with HIV in the UK found that 1-in-6 people with HIV was living in extreme poverty, in many cases due to unsettled immigration status [25]. Clinicians should be aware of patients' socio-economic status and refer to social support where necessary.

Clinicians should establish what level of involvement the patient would like and tailor their consultation style

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appropriately. Clinicians should also consider how to make information accessible and understandable to patients (e.g. with pictures, symbols, large print and different languages) [1], including linguistic and cultural issues. Youth is consistently associated with lower adherence to ART, loss to follow-up and other negative healthcare behaviours [26] and some studies have found an independent association between poorer adherence and attendance and female gender [27], so information and consultation style should be age and gender appropriate for the patient.

If there is a question about the patient's capacity to make an informed decision, this should be assessed using the principles in the Mental Capacity Act 2005 [28].

Patients presenting at the clinic may be at different stages of readiness to take therapy [29] and clinicians' first task is to assess their readiness, by means of open questions rather than closed, before supporting and furthering patients' decisions on therapy. However, if a patient presents in circumstances that necessitate starting ART immediately, for example with certain AIDS diagnoses or very low CD4 cell counts, then doctors should prescribe ART and provide support for the patient's adherence, especially through the first few weeks. Recognizing symptoms that patients attribute to ART side effects might avoid loss of adherence and deterioration of trust in the patient–provider relationship [30,31].

A 'perceptions and practicalities' approach should be used to tailor support to meet the needs of the individual, to identify both the perceptual factors (such as beliefs about ART) and practical factors (such as capacity and resources) influencing adherence [8,32].

Supporting patients requires good communication not just between clinician and patient but also between all healthcare staff involved with their care, including those in their HIV services, their GP and any clinicians involved in management of co-morbid conditions. Patients should be offered copies of letters about them sent to their GP and other physicians. The advantages of HIV status disclosure to the patient's GP should be discussed and considered best practice, as several situations require consensual clinical decision-making. A patient's decision not to disclose their status to their GP should, however, always be respected, subject to the clinician's duty to protect vulnerable individuals.

3.3 References

1 National Collaborating Centre for Primary Care. Medicines concordance and adherence: involving adults and carers in decisions about prescribed medicines. National Clinical Practice Guideline Number 76. 2009. Available at http://guidance.nice.org.uk/CG76 (accessed April 2012).

2 Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med* 2004; **19**: 1096–1103.

3 Kremer H, Ironson G. To tell or not to tell: why people with HIV share or don't share with their physicians whether they are taking their medications as prescribed. *AIDS Care* 2006; **18**: 520–528.

4 Roberts KJ. Physician-patient relationships, patient satisfaction, and antiretroviral medication adherence among HIV-infected adults attending a public health clinic. *AIDS Patient Care STDS* 2002; **16**: 43–50.

5 Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician–patient interaction. *Ann Intern Med* 1995; **122**: 107–112.

6 Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001; **26**: 331–342.

7 Horne R, Buick D, Fisher M *et al.* Doubts about necessity and concerns about adverse effects: identifying the types of beliefs that are associated with non-adherence to HAART. *Int J STD AIDS* 2004; **15**: 38–44.

8 Horne R, Cooper V, Gellaitry G, Date HL, Fisher M. Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and adherence: the utility of the necessity-concerns framework. *J Acquir Immune Defic Syndr* 2007; **45**: 334–341.

9 Gonzalez JS, Penedo FJ, Llabre MM *et al.* Physical symptoms, beliefs about medications, negative mood, and long-term HIV medication adherence. *Ann Behav Med* 2007; **34**: 46–55.

10 Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV treatment non-adherence: a review and meta-analysis. *J Acquir Immune Defic Syndr* 2011; **58**: 181–187.

11 Kacanek D, Jacobson DL, Spiegelman D *et al.* Incident depression symptoms are associated with poorer HAART adherence: a longitudinal analysis from the Nutrition for Healthy Living study. *J Acquir Immune Defic Syndr* 2009; **53**: 266–272.

12 Lima VD, Geller J, Bangsberg DR *et al.* The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 2007; **21**: 1175–1183.

13 Yun LW, Maravi M, Kobayashi JS *et al.* Antidepressant treatment improves adherence to antiretroviral therapy

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among depressed HIV-infected patients. *J Acquir Immune Defic Syndr* 2005; **38**: 432–438.
14 Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. *BMJ* 2003; **327**: 1144–1146.
15 Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. *J Acquir Immune Defic Syndr* 2009; **52**: 180–202.
16 Reback CJ, Larkins S, Shoptaw S. Methamphetamine abuse as a barrier to HIV medication adherence among gay and bisexual men. *AIDS Care* 2003; **15**: 775–785.
17 Halkitis PN, Kutnick AH, Borkowski T, Parsons JT. Adherence to HIV medications and club drug use among gay and bisexual men. *XIV International AIDS Conference*. Barcelona, Spain. July 2002 [Abstract ThPeE7856].
18 Wood E, Hogg RS, Lima VD *et al*. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. *JAMA* 2008; **300**: 550–554.
19 Holzemer WL, Corless IB, Nokes KM *et al*. Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care STDS* 1999; **13**: 185–197.
20 Smith SR, Rublein JC, Marcus C, Brock TP, Chesney MA. A medication self-management program to improve adherence to HIV therapy regimens. *Patient Educ Couns* 2003; **50**: 187–199.
21 Gifford AL, Laurent DD, Gonzales VM, Chesney MA, Lorig KR. Pilot randomized trial of education to improve self-management skills of men with symptomatic HIV/AIDS. *J Acquir Immune Defic Syndr* 1998; **18**: 136–144.
22 Lorig KR, Sobel DS, Stewart AL, Brown BW Jr *et al*. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. *Med Care* 1999; **37**: 5–14.
23 British Psychological Society, British HIV Association, Medical Foundation for AIDS and Sexual Health. Standards for psychological support for adults living with HIV. MedFASH, 2011. Available at http://www.bhiva.org/StandardsForPsychologicalSupport.aspx (accessed April 2012).
24 Kalichman SC, Grebler T. Stress and poverty predictors of treatment adherence among people with low-literacy living with HIV/AIDS. *Psychosom Med* 2010; **72**: 810–816.
25 National AIDS Trust, Terrence Higgins Trust. Hardship Fund. Report: poverty and HIV 2006–2009. NAT, THT, 2010. Available at http://www.tht.org.uk/binarylibrary/policy/povertyandhiv.pdf (accessed April 2012).
26 Fogarty L, Roter D, Larson S *et al*. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Educ Couns* 2002; **46**: 93–108.
27 Tapp C, Milloy MJ, Kerr T *et al*. Female gender predicts lower access and adherence to antiretroviral therapy in a setting of free healthcare. *BMC Infect Dis* 2011; **11**: 86.
28 General Medical Council. Guidance on good practice: consent guidance: capacity issues. 2010. Available at http://www.gmc-uk.org/guidance/ethical_guidance/consent_guidance_part3_capacity_issues.asp (accessed April 2012).
29 Prochaska JO, DiClemente CC, Norcross JC. In search of how people change: applications to addictive behaviors. *Am Psychol* 1992; **47**: 1102–1114.
30 Duran S, Spire B, Raffi F *et al*.; APROCO Cohort Study Group. Self-reported symptoms after initiation of a protease inhibitor in HIV-infected patients and their impact on adherence to HAART. *HIV Clin Trials* 2001; **2**: 38–45.
31 Préau M, Leport C, Villes V *et al*.; ANRS CO-8 APROCO Study Group. Prevalence and predictors of deterioration of a trustful patient-provider relationship among HIV-infected persons treated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2008; **47**: 467–471.
32 National Collaborating Centre for Primary Care (UK). Medicines Adherence: Involving Patients in Decisions About Prescribed Medicines and Supporting Adherence [Internet]. London: Royal College of General Practitioners (UK); 2009 Jan. (NICE Clinical Guidelines, No. 76). Available from: http://www.ncbi.nlm.nih.gov/books/NBK55440 (accessed October 2013).

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4.0 When to start

4.1 Chronic infection

4.1.1 Recommendations

- We recommend patients with chronic infection start ART if the CD4 cell count is ≤350 cells/μL (1A): it is important not to delay treatment initiation if the CD4 cell count is close to this threshold.

The absolute risk of disease progression is significantly higher for a given CD4 cell count in older people (see Table 4.1), so consideration should be given to starting at higher CD4 cell counts in older persons. Evidence from cohort studies suggest that the risk of disease progression is significantly higher once the CD4 cell count falls below 350 cells/μL. Therefore, it is important not to delay unnecessarily the initiation of ART if the CD4 cell count is close to this threshold.

We recommend patients with the following conditions start ART:

- AIDS diagnosis (e.g. KS) irrespective of CD4 cell count (1A).
- HIV-related co-morbidity, including HIVAN (1C), idiopathic thrombocytopenic purpura (1C), symptomatic HIV-associated NC disorders irrespective of CD4 cell count (1C).
- Coinfection with HBV if the CD4 cell count is ≤500 cells/μL (1B) (see Section 8.2.2 Hepatitis B).
- Coinfection with HCV if the CD4 cell count is ≤500 cells/μL (1C) (Section 8.2.3 Hepatitis C).
- NADMs requiring immunosuppressive radiotherapy or chemotherapy (1C) (Section 8.3.2 When to start ART: non-AIDS-defining malignancies).

We suggest patients with the following conditions start ART:

- Coinfection with HBV if the CD4 cell count is >500 cells/μL and treatment of hepatitis B is indicated (2B) (see Section 8.2.2 Hepatitis B).

4.1.1.1 Auditable measures

Proportion of patients with CD4 cell count <350 cells/μL not on ART.

Proportion of patients with CD4 cell count >350 cells/μL and an indication to start ART not on ART.

4.1.2 Rationale

To date there have been no published randomized trials that directly assess whether treatment-naïve people with higher CD4 cell counts should initiate ART immediately rather than defer until the CD4 cell count falls to ≤350 cells/μL; while the START trial is addressing this question, results are not expected until 2016. Only one trial [1] has randomized people with a CD4 cell count >350 cells/μL, but this used a comparator arm of delay of initiation of ARVs until the CD4 cell count has fallen below 250 cells/μL, and thus is likely to overestimate the apparent benefits of immediate treatment compared with starting at <350 cells/μL. There have been a number of observational studies that have attempted to address this issue [2–9], which have produced conflicting findings. Some of these studies have failed to take into account the lead time between an individual's CD4 cell count falling below the threshold for treatment and the date of starting treatment [8]; as this may introduce serious bias into treatment comparisons, these results do not resolve the question whether it is better to start ART at higher CD4 cell counts.

Where studies have used methods that take lead time into account, the statistical methods used are novel and different approaches have been used. The analyses reached substantially different conclusions on the mortality benefits of early ART initiation in people with a CD4 cell count >350 cells/μL, and particularly in those with CD4 cell count >500 cells/μL. Critically, none of these methods is able fully to adjust for potential confounding, which might well be large in this scenario and could create a bias that is in the same direction in all studies. Thus, we do not believe that the evidence is currently sufficiently strong to recommend a change in guidelines.

The current guidelines were produced via a rigorous process following a thorough review of the medical literature. The recommendation in the 2012 guidelines on when to start ART was that in chronic HIV infection, patients should start ART if their CD4 count is below 350 cells/μL, because the evidence suggests that the risk of disease progression increases below this level – thus, in this group, the benefits of ART clearly outweigh any possible disadvantages (i.e., side effects and the selection of drug-resistant virus). Clinicians should not delay starting ART if

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Table 4.1 Predicted 6-month risk of AIDS in antiretroviral therapy-naive patients according to current age [(a) 25 years, (b) 35 years, (c) 45 years and (d) 55 years], CD4 cell count, viral load and whether antiretroviral therapy is initiated immediately or deferred

		Risk (%)									
		CD4 count (cells/μL)									
Treatment	Viral load (copies/mL)	50	100	150	200	250	300	350	400	450	500
(a)											
Deferred	3000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
Initiated		2.3	1.2	0.8	0.5	0.4	0.3	0.2	0.2	0.1	0.1
Deferred	10 000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
Initiated		3.2	1.8	1.1	0.8	0.5	0.4	0.3	0.2	0.2	0.1
Deferred	30 000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
Initiated		4.4	2.5	1.6	1.1	0.7	0.5	0.4	0.3	0.2	0.2
Deferred	100 000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
Initiated		6.2	3.5	2.2	1.5	1.1	0.8	0.6	0.5	0.4	0.3
Deferred	300 000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Initiated		8.4	4.8	3.1	2.1	1.5	1.1	0.8	0.6	0.5	0.4
(b)											
Deferred	3000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
Initiated		2.8	1.6	1.0	0.7	0.5	0.3	0.3	0.2	0.2	0.1
Deferred	10 000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
Initiated		4.0	2.2	1.4	1.0	0.7	0.5	0.4	0.3	0.2	0.2
Deferred	30 000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
Initiated		5.5	3.1	2.0	1.3	0.9	0.7	0.5	0.4	0.3	0.2
Deferred	100 000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
Initiated		8.0	4.5	2.8	1.9	1.4	1.0	0.8	0.6	0.4	0.4
Deferred	300 000	30.8	18.0	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Initiated		10.3	6.0	3.9	2.7	1.9	1.4	1.0	0.8	0.6	0.5
(c)											
Deferred	3000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
Initiated		3.6	2.0	1.2	0.8	0.6	0.4	0.3	0.2	0.2	0.2
Deferred	10 000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
Initiated		5.0	2.8	1.8	1.2	0.9	0.6	0.5	0.4	0.3	0.2
Deferred	30 000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
Initiated		6.9	3.9	2.5	1.7	1.2	0.9	0.7	0.5	0.4	0.3
Deferred	100 000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
Initiated		9.5	5.5	3.5	2.4	1.7	1.3	1.0	0.7	0.6	0.4
Deferred	300 000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Initiated		12.5	7.5	4.9	3.4	2.4	1.8	1.3	1.0	0.8	0.6
(d)											
Deferred	3000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
Initiated		4.5	2.5	1.6	1.1	0.8	0.6	0.4	0.3	0.2	0.2
Deferred	10 000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
Initiated		6.3	3.6	2.3	1.5	1.1	0.8	0.6	0.5	0.4	0.3
Deferred	30 000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
Initiated		8.5	4.9	3.1	2.1	1.5	1.1	0.8	0.6	0.5	0.4
Deferred	100 000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
Initiated		11.5	6.8	4.4	3.1	2.2	1.6	1.2	0.9	0.7	0.6
Deferred	300 000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4
Initiated		14.9	9.2	6.1	4.2	3.0	2.2	1.7	1.3	1.0	0.8

Predicted risk of AIDS if antiretroviral therapy (ART) is deferred is taken from [10]. The predicted 6-month risk if ART is initiated is based on the assumption that the rate with immediate therapy initiation is one-third the rate without therapy initiation. This (probably conservative) value is based on considering evidence from multiple sources, including references [11–16].

the CD4 count is close to (but above) 350 cells/μL. In addition, some patients should start ART if their CD4 count is above 350 cells/μL, including pregnant women, some patients with hepatitis B and C, some patients with acute HIV infection, patients needing immunosuppressive treatments for cancer, and also patients with some HIV-related problems including symptomatic neurocognitive disorders, severe thrombocytopenia and HIV-associated nephropathy. Finally, patients wishing to start ART primarily to reduce the risk of transmission to others should be allowed to do so, at any CD4 cell count. This guidance has not changed in this current revision.

The 2012 guidelines did not recommend that all patients with CD4 counts below 500 cells/μL should start ART,

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because there are no data from any randomised clinical trial with a suitable comparator arm that provide unequivocal evidence that individual benefits outweigh the risks. Currently available data derive from cohort studies which have been analysed in different ways, and which cannot fully adjust for confounders, the effect of which may be large. Specifically, the balance between any small benefits of ART in this group and the risk of any side effects is unclear. The current revision of the guidelines will not alter this recommendation. The START trial (which is continuing to recruit in many countries around the world) is designed to specifically address exactly this issue for people with CD4 counts > 500 cells/μL such that future guidelines will have a sufficient evidence base to make an informed decision when considering earlier initiation of therapy for an individual patient.

The BHIVA treatment guidelines were developed primarily with patients from the UK in mind. In other settings, where there are particularly high TB rates, constraints on delivery of care, and high losses through the care and treatment cascade, earlier ART initiation may be more important to increase retention of patients in care after diagnosis.

4.1.3 References

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

2 Braithwaite RS, Roberts MS, Chang CC *et al.* Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy: a decision model. *Ann Intern Med* 2008; **148**: 178–185.

3 Braithwaite RS, Roberts MS, Goetz MB *et al.* Do benefits of earlier antiretroviral treatment initiation outweigh harms for individuals at risk for poor adherence? *Clin Infect Dis* 2009; **48**: 822–826.

4 HIV-CAUSAL Collaboration, Cain LE, Logan R, Robins JM *et al.* When to initiate combined antiretroviral therapy to reduce mortality and aids-defining illness in HIV-infected persons in developed countries. *Ann Intern Med* 2011; **154**: 509–515.

5 When To Start Consortium, Sterne JA, May M, Costagliola D *et al.* Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; **373**: 1352–1363.

6 Jaén A, Esteve A, Miró JM *et al.* Determinants of HIV progression and assessment of the optimal time to initiate highly active antiretroviral therapy: PISCIS Cohort (Spain). *J Acquir Immune Defic Syndr* 2008; **47**: 212–220.

7 Kitahata MM, Gange SJ, Abraham AG *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009; **360**: 1815–1826.

8 Plettenberg A, Brockmeyer NH, Haastert B *et al.* Impact of earlier ART initiation on the immune status and clinical course of treated patients on the basis of cohort data of the German Competence Network for HIV/AIDS. *Infection* 2011; **39**: 3–12.

9 Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med* 2011; **171**: 1560–1569.

10 Phillips A, Pezzotti P, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS* 2004; **18**: 51–58.

11 Emery S, Neuhaus JA, Phillips AN *et al.* Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART Study. *J Infect Dis* 2008; **197**: 1133–1144.

12 Katzenstein DA, Hammer SM, Hughes MD *et al.* The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. *N Engl J Med* 1996; **335**: 1091–1098.

13 Marschner IC, Collier AC, Coombs RW *et al.* Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis* 1998; **177**: 40–47.

14 Hammer SM, Squires KE, Hughes MD *et al.* A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; **337**: 725–733.

15 Antiretroviral Therapy Cohort Collaboration. Importance of baseline prognostic factors with increasing time since initiation of highly active antiretroviral therapy: collaboration analysis of cohorts of HIV-1-infected patients. *J Acquir Immune Defic* 2007; **46**: 607–615.

16 Sterne JA, Hernàn MA, Ledergerber B *et al.* Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005; **366**: 378–384.

4.2 Patients presenting with AIDS or a major infection

4.2.1 Recommendation

- We recommend patients presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 cell count <200 cells/μL, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy (1B).

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4.2.1.1 *Auditable measure*

Proportion of patients presenting with an AIDS-defining infection or with a serious bacterial infection and a CD4 cell count <200 cells/μL started on ART within 2 weeks of initiation of specific antimicrobial chemotherapy.

4.2.2 *Rationale*

This recommendation is largely based on the ACTG 5164 study that demonstrated fewer AIDS progressions/deaths and improved cost-effectiveness when ART was commenced within 14 days (median 12 days; IQR 9–13 days) compared with after completion of treatment for the acute infection (median 45 days; IQR 41–55 days) [1,2]. Those with TB as the primary infection were excluded from this study, and the majority of patients enrolled had *Pneumocystis* pneumonia, followed by lower proportions with cryptococcal meningitis and bacterial infections. The patients were well enough to give informed consent and to take oral medications, and therefore the findings may not be generalizable to those who are severely unwell or requiring intensive care. Previous observational data suggest a survival benefit for HIV-positive patients who are started on ART while in the intensive care unit [3,4], but the data are insufficient to make a recommendation in this group [3,4].

There was no increase in the incidence of immune reconstitution disorders (IRD) or adverse events generally with early ART initiation in ACTG 5164 [1,5]. However, those with intracranial opportunistic infections may be more prone to severe IRDs with early ART initiation. Some data suggest that caution should be particularly exercised with cryptococcal meningitis: two studies from sub-Saharan Africa have demonstrated an increased mortality with early ART initiation; however, both were in very different healthcare settings from the UK and one utilized antifungal regimens that would not be preferred [6,7]. The COAT study highlighted those with an acellular CSF and those with a decreased Glasgow Coma Scale as being particularly prone to increased mortality with early ART initiation [7].

Those presenting with TB and malignancies are discussed in Section 8.

4.2.3 *References*

1 Zolopa A, Andersen J, Powderly W *et al.* Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE* 2009; **4**: e5575.

2 Sax PE, Sloan CE, Schackman BR *et al.* Early antiretroviral therapy for patients with acute aids-related opportunistic infections: a cost-effectiveness analysis of ACTG A5164. *HIV Clin Trials* 2010; **11**: 248–259.

3 Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS* 2003; **17**: 73–80.

4 Croda J, Croda MG, Neves A, De Sousa dos Santos S. Benefit of antiretroviral therapy on survival of human immunodeficiency virus-infected patients admitted to an intensive care unit. *Crit Care Med* 2009; **37**: 1605–1611.

5 Grant PM, Komarow L, Andersen J *et al.* Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. *PLoS ONE* 2010; **5**: e11416.

6 Makadzange AT, Ndhlovu CE, Takarinda K *et al.* Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. *Clin Infect Dis* 2010; **50**: 1532–1538.

7 Boulware D, Meya D, Muzoora C *et al.* ART initiation within the first 2 weeks of cryptococcal meningitis is associated with higher mortality: a multisite randomized trial. *20th Conference on Retroviruses and Opportunistic Infections.* Atlanta, GA. March 2013. [Abstract OA144].

4.3 Treatment of primary HIV infection

4.3.1 *Recommendations*

We recommend patients presenting with PHI and meeting any one of the following criteria start ART:

- Neurological involvement (1D).
- Any AIDS-defining illness (1A).
- Confirmed CD4 cell count <350 cells/μL (1C).

4.3.1.1 *Auditable measure*

Proportion of patients presenting with PHI and neurological involvement, or an AIDS-defining illness or confirmed CD4 cell count <350 cells/μL started on ART.

4.3.2 *Rationale*

The scientific rationale for treating with ART in PHI is as follows.

(i) Preservation of specific anti-HIV CD4 T lymphocytes that would otherwise be destroyed by uncontrolled viral replication, the presence of which is associated with survival in untreated individuals [1].
(ii) Reduction in morbidity associated with high viraemia and profound CD4 cell depletion during acute infection [2–4].
(iii) Reduction in the enhanced risk of onward transmission of HIV associated with PHI [5–10].

Treatment of patients with PHI who present with AIDS-defining illnesses, neurological disease or a CD4 cell count

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of <350 cells/μL is consistent with the recommendations for patients with chronic infection. The rationale for treating patients with neurological disease is that ART may lead to regression of otherwise irreversible neurological disease (although there is no high-quality evidence for this effect of treatment in primary infection). Data from the CASCADE collaboration [11] showed that patients with primary infection, who had at least one CD4 cell count of <350 cells/μL in the first 6 months of infection, had a significantly greater mortality than those whose CD4 cell counts remained above this threshold, which supports early treatment in patients with lower CD4 cell counts.

Multiple observational studies have shown encouraging but inconclusive results following short-course ART initiated in PHI for individuals in whom ART would not otherwise be indicated [12,13]. There have been three RCTs comparing the role of interrupted ART initiated in PHI on time to reach CD4 <350 cells/μL or the need for initiation of lifelong ART [14–16]. Overall there was a modest benefit in terms of delaying the decline in CD4 cell count, or time from seroconversion, to requiring initiation of lifelong ART following a 48- [16] or 60- [15] week course of ART. A *post hoc* analysis from the SPARTAC trial [16] showed a non-significant trend towards benefit in time to CD4 cell count <350 cells/μL when ART was initiated closer to the time of infection (HR 0.48; $P = 0.09$). This randomized study supported cohort studies in which a more rapid rate of CD4 cell loss was seen in individuals presenting within 12 weeks of a negative HIV antibody test [17,18].

For this reason, we suggest that the following are discussed with those presenting with a very short test interval (≤12 weeks), in particular, those with severe symptoms of seroconversion such as rash, fever, weight loss, persistent lymphadenopathy, diarrhoea >4 days, malaise, headaches or laboratory evidence of acute HIV infection (e.g. as defined in SPARTAC [16]).

- A 48-week course of ART showed a benefit in surrogate markers of HIV-disease progression: delaying CD4 decline and lowering viral set point up to 60 weeks after stopping therapy. There was no such benefit from 12 weeks of ART. In those individuals presenting within 12 weeks of infection, this effect was more marked; however, there is no clear evidence of long-term clinical benefit of ART in this setting.
- No study has examined whether ART started during, or soon after, PHI should be continued long term, but most clinicians would recommend that irrespective of indication to start ART, once initiated, it should be continued indefinitely. Discontinuation of ART in the context of treatment of PHI was not commonly associated with morbidity, however [15,16].
- Initiation of a PI-based regimen is recommended if therapy is started before the availability of a genotype result, based on the prevalence of transmitted rates of drug resistance in the UK [19].
- There is no specific evidence to support the role of ART in PHI to prevent onward transmission of virus but there is little reason to consider that ART is any less effective in reducing infectivity at this time, so long as viral suppression has been achieved [20].
- Patients with recently diagnosed PHI may be in a particularly vulnerable psychological state, and thus ill-prepared to commit to starting long-term treatment.

4.3.3 References

1 Rosenberg ES, Altfeld M, Poon SH *et al.* Immune control of HIV-1 after early treatment of acute infection. *Nature* 2000; **407**: 523–526.

2 Socías ME, Sued O, Laufer N *et al.*; Grupo Argentino de Seroconversión Study Group. Acute retroviral syndrome and high baseline viral load are predictors of rapid HIV progression among untreated Argentinean seroconverters. *J Int AIDS Soc* 2011; **14**: 40.

3 Lodi S, Phillips A, Touloumi G *et al.*; CASCADE Collaboration in EuroCoord. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 cells/mm^3: assessment of need following changes in treatment guidelines. *Clin Infect Dis* 2011; **53**: 817–825.

4 Goujard C, Bonarek M, Meyer L *et al.*; Agence Nationale de Recherche sur le Sida PRIMO Study Group. CD4 cell count and HIV DNA level are independent predictors of disease progression after primary HIV type 1 infection in untreated patients. *Clin Infect Dis* 2006; **42**: 709–715.

5 Powers KA, Ghani AC, Miller WC *et al.* The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. *Lancet* 2011; **378**: 256–268.

6 Miller WC, Rosenberg NE, Rutstein SE, Powers KA. Role of acute and early HIV infection in the sexual transmission of HIV. *Curr Opin HIV AIDS* 2010; **5**: 277–282.

7 Pinkerton SD. Probability of HIV transmission during acute infection in Rakai, Uganda. *AIDS Behav* 2008; **12**: 677–684.

8 Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. *J Infect Dis* 2008; **198**: 687–693.

9 Pao D, Fisher M, Hué S *et al.* Transmission of HIV-1 during primary infection: relationship to sexual risk and sexually transmitted infections. *AIDS* 2005; **19**: 85–90.

10 Sabin C, Pillay D. Determinants of HIV-1 transmission in men who have sex with men: a combined clinical,

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epidemiological and phylogenetic approach. *AIDS* 2010; **24**: 1739–1747.
11 Lodi S, Fisher M, Phillips A *et al.*; CASCADE Collaboration. Identification of severe primary HIV infection through clinical, immunological and virological definitions. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA. February 2012 [Abstract 550].
12 Bell SK, Little SJ, Rosenberg ES. Clinical management of acute HIV infection: best practice remains unknown. *J Infect Dis* 2010; **202** (Suppl 2): S278–S288.
13 Fidler S, Fox J, Porter K, Weber J. Primary HIV infection: to treat or not to treat? *Curr Opin Infect Dis* 2008; **21**: 4–10.
14 Hogan C, DeGruttola V, Sun X *et al.* The SETPOINT study (ACTG A5127): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. *J Infect Dis* 2012; **205**: 87–96.
15 Grijsen ML, Steingrover R, Wit FW *et al.* No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: The randomised Primo SHM trial. *PLoS Med* 2012; **9**: e1001196.
16 SPARTAC, Fidler S, on behalf of the SPARTAC trial investigators. The effect of a short course of ART in primary HIV infection. Final results from an international randomised controlled study. *6th IAS on HIV Pathogenesis, Treatment and Prevention*. Rome, Italy. July 2011 [Abstract WELBX06].
17 The CASCADE Collaboration. The relationships between the HIV test interval, demographic factors and HIV disease progression. *Epidemiol Infect* 2001; **127**: 91–100.
18 Tyrer F, Walker AS, Gillett J, Porter K, UK Register of HIV Seroconverters. The relationship between HIV seroconversion illness, HIV test interval and time to AIDS in a seroconverter cohort. *Epidemiol Infect* 2003; **131**: 1117–1123.
19 Cane P, Chrystie I, Dunn D *et al.*; UK Group on Transmitted HIV Drug Resistance. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ* 2005; **331**: 1368.
20 Cohen MS, Chen YQ, McCauley M *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.

4.4 Treatment to reduce transmission

4.4.1 Recommendations

- We recommend the evidence that treatment with ART lowers the risk of transmission is discussed with all patients, and an assessment of the current risk of transmission to others is made at the time of this discussion (GPP).
- We recommend following discussion, if a patient with a CD4 cell count >350 cells/μL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started (GPP).

4.4.1.1 Auditable measures

Record in patient's notes of discussion that treatment with ART lowers risk of HIV transmission and an assessment of current risk of transmission.

The discussion should include the following:

- The decision to start ART is the patient's choice and must not be due to pressure from partners or others.
- ART lowers, rather than eliminates, the risk of transmission; other prevention strategies, including male and female condoms continue to be recommended to address concerns of any residual risk of transmission.
- For a patient with a CD4 cell count >350 cells/μL, it is uncertain whether any benefits of immediate treatment to their own health will be outweighed by any harm.
- Condoms, both male and female, continue to be recommended as protection from other sexually transmitted infections and unplanned pregnancy.
- There are risks associated with interrupting ART, and once started, it should generally be continued indefinitely.
- The evidence that ART lowers the risk of transmission mainly relates to vaginal sex. Although ART is highly likely to reduce the risk of transmission for anal sex, the residual risk could be higher than that seen in studies for vaginal sex. There are currently few data to inform this.
- High and consistent adherence to ART is required to maintain viral suppression and minimize transmission risk.
- Taking ART does not result in immediate complete viral suppression; it usually takes several months to achieve an undetectable VL in blood.
- The use of ART to reduce transmission risk is a particularly important consideration in serodiscordant heterosexual couples wishing to conceive and it is recommended that the HIV-positive partner be on fully suppressive ART.

4.4.2 Rationale

The potential effect of HIV treatment to reduce the risk of onward sexual transmission should be discussed with all patients as a part of safer sex messages in general. The discussion should include the HIV status of their partner(s) and whether ART is indicated for their own health.

This discussion should make clear that there is good evidence from one RCT (HPTN 052) [1] that ART treatment can markedly reduce (by 96%) the risk of transmission to HIV-negative partners. This is supported by the secondary outcomes of another trial [2] that also found a marked

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reduction in transmission from partners taking ART (by 92%). It is important to note that only 3% of the couples in HPTN 052 were men who have sex with men and the Partners in Prevention study was conducted entirely in heterosexual couples. The evidence base thus relates mainly to the risk of transmission for vaginal sex in heterosexual couples. It seems likely that a reduction in risk will also be seen for anal sex, but this is the subject of ongoing studies.

Before these randomized controlled studies, the evidence base for treatment to reduce transmission was based on a number of cohort studies that found that transmission between heterosexual couples where the HIV-positive partner had an undetectable VL on treatment was very rare or did not occur [3–7].

Viral suppression due to ART is usually as effective in reducing VL in semen [8] and in the rectum [9] as in plasma. This suggests that in the absence of other facilitators of transmission such as sexually transmitted infections, ART would be expected to be as effective in reducing infectiousness in men who have sex with men and other populations as it is in heterosexuals. Indirect evidence comes from a study of men who have sex with men attending HIV treatment services where ART was associated with a 96% reduction in HIV transmission [10].

Condoms should still be recommended to protect from other sexually transmitted infections, and to lower further any residual risk of transmission.

Patients should be informed that taking ART does not result in immediate viral suppression. Studies have shown that the mean time to suppression of VL to <50 copies/mL in patients taking ART is about 90 days, and that a proportion may take 9 months or more [11]. Patients should also be informed about the possibility of virological failure leading to transmission of HIV. Decisions on condom use and safer sex should always be based on a recent VL test result and not on an assumption that taking ART implies non-infectiousness.

For serodiscordant heterosexual couples wishing to conceive, irrespective of the method used for conception, the HIV-positive partner will need to be on ART with an undetectable plasma VL, regardless of his/her CD4 cell count or clinical status. This is likely to reduce the risk of transmission sufficiently to be the only risk-reduction method some couples will want, but additional measures such as sperm washing, artificial insemination and potentially pre-exposure prophylaxis (PrEP) to the HIV-negative partner have either been recommended in previous guidance [12] or are currently being assessed for couples wishing to address concerns of any residual risk of transmission.

Details of the use of ART to prevent mother-to-child transmission are covered in the *BHIVA guidelines for the management of HIV infection in pregnant women 2012* [13].

4.4.3 References

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

2 Donnell D, Baeten JM, Kiarie J *et al*. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; **375**: 2092–2098.

3 Castilla J, del Romero J, Hernando V *et al*. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr* 2005; **40**: 96–101.

4 Del Romero J, Castilla J, Hernando V, Rodriguez C, Garcia S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ* 2010; **340**: c2205.

5 Melo M, Varella I, Nielsen K, Turella L, Santos B. Demographic characteristics, sexual transmission and CD4 progression among heterosexual HIV-serodiscordant couples followed in Porto Alegre, Brazil. *16th International AIDS Conference*. Toronto. August 2006 [Abstract TUPE0430].

6 Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009; **23**: 1397–1404.

7 Barreiro P, del Romero J, Leal M *et al*. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. *J Acquir Immune Defic Syndr* 2006; **43**: 324–326.

8 Kalichman SC, Di Berto G, Eaton L. Human immunodeficiency virus viral load in blood plasma and semen: review and implications of empirical findings. *Sex Transm Dis* 2008; **35**: 55–60.

9 Kelley CF, Haaland RE, Patel P *et al*. HIV-1 RNA rectal shedding is reduced in men with low plasma HIV-1 RNA viral loads and is not enhanced by sexually transmitted infections in the rectum. *J Infect Dis* 2011; **204**: 761–767.

10 Fisher M, Pao D, Brown AE *et al*. Determinants of HIV-1 transmission in men who have sex with men: a combined clinical, epidemiological and a phylogenetic approach. *AIDS* 2010; **24**: 1739–1747.

11 Perez-Hoyos S, Rodríguez-Arenas MA, García de la Hera M *et al*. Progression to AIDS and death and response to HAART in men and women from a multicentre hospital-based cohort. *J Womens Health* 2007; **16**: 1052–1061.

12 Fakoya A, Lamba H, Mackie N *et al*. BHIVA, BASHH and FSRH guidelines for the management of sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.

13 Taylor GP, Clayden P, Dhar J *et al*. BHIVA guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012; **13** (Suppl. 2): 87–157.

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5.0 What to start

5.1 Summary recommendations

- We recommend therapy-naïve patients start ART containing two NRTIs plus one of the following: PI/r, NNRTI or INI (1A).

Summary recommendations for choice of ART:

	Preferred	Alternative
NRTI backbone	TDF and FTC	RPV‡
Third agent	ATV/r	ABC and 3TC*‡
	DRV/r	LPV/r
	EFV	FPV/r
	RAL	NVP†
	ELV/COBI	

*ABC is contraindicated if patient is HLA-B*57:01 positive.
†NVP is contraindicated if baseline CD4 cell count is >250/400 cells/μL in women/men.
‡Use recommended only if baseline VL is <100 000 copies/mL: RPV as a third agent; abacavir and 3TC as the NRTI backbone.

The presence or future risk of co-morbidities and potential adverse effects need to be considered in the choice of ARV drugs in individual patients.

5.1.1 Summary of auditable measures

Proportion of therapy-naïve patients not starting ART containing two NRTIs and one of the following: a PI/r, or an NNRTI or an INI (preferred or alternative agents).

Proportion of patients starting ART with either TDF/FTC or ABC/3TC as the NRTI backbone.

Proportion of patients starting ART with ATV/r, or DRV/r, or EFV or RAL as the third agent.

Proportion of patients with undetectable VL <50 copies/mL at 6 months and at 12 months after starting ART.

Proportion of patients who switch therapy in the first 6 and 12 months.

Record in patient's notes of HLA-B*57:01 status before starting ABC.

5.2 Introduction

For the 'which NRTI backbone' and 'which third agent' questions, evidence profiles and summary of findings tables were constructed to assess quality of evidence across predefined treatment outcomes (Appendices 3 and 4). Evidence from RCTs and systematic reviews was identified from a systematic literature review (Appendix 2). Outcomes were scored and ranked (critical, important, not important) by members of the Writing Group. The following were ranked as critical outcomes: viral suppression at 48/96 weeks, protocol-defined virological failure, drug resistance, quality of life, discontinuation for adverse events and grade 3/4 adverse events (overall), rash and alanine transaminase/aspartate transaminase elevation.

Treatments were compared and differences in critical outcomes assessed. Where there were differences, consensus opinion was sought to determine whether the difference in size of effect was above the threshold for clinical decision-making. If conflicting differences were detected, the balance of outcomes was based on consensus opinion of the Writing Group.

A treatment was defined as preferred or alternative to indicate strong or conditional recommendations and the decision based on the assessment of critical outcomes and the balance of desirable and undesirable effects in a general ART-naïve patient population. 'Preferred' indicates a strong recommendation that most clinicians and patients would want to follow unless there is a clear rationale not to do so. 'Alternative' indicates a conditional recommendation and is an acceptable treatment option for some patients and might be, in selected patients, the preferred option.

Factors including potential side effects, co-morbidities, patient preference and drug interactions need to be taken into account when selecting an ART regimen in individual patients, and may include both preferred and alternative treatment options.

For guidance on assessment of patients before initiation of ART and monitoring of patients on ART the reader should consult the *BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011* [1].

5.3 Which nucleoside reverse transcriptase inhibitor backbone

5.3.1 Recommendations

- We recommend therapy-naïve patients start combination ART containing TDF and FTC as the NRTI backbone (1A).
- We suggest ABC and 3TC is an acceptable alternative NRTI backbone in therapy-naïve patients who, before starting ART, have a baseline VL≤100 000 copies/mL (2A).
- ABC must not be used in patients who are HLA-B*57:01 positive (1A).

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5.3.2 Rationale

Three RCTs have compared TDF-FTC with ABC-3TC as the NRTI backbone in combination with different third agents: ATV/r or EFV [2–6], EFV [7–9] and LPV/r [10].

Assessment of virological efficacy as a critical outcome was complicated by different definitions across the three studies. In our analysis for GRADE (see Appendix 3.1), there was no difference in rates of virological suppression at 48 weeks or 96 weeks but the analysis excluded the largest of the three trials (ACTG 5202) and the quality of evidence for this outcome was assessed as low or very low. Assessment of the risk of protocol-defined virological failure at 48 weeks favoured TDF-FTC (RR 0.76, 95% CI 0.53–1.07), although the effect was not statistically significant and heterogeneity in the analysis was relatively high (I^2 46%). Assessment of protocol-defined virological failure at 96 weeks showed a significant difference favouring TDF-FTC (RR 0.73, 95% CI 0.59–0.92). Data were only available from one study [4] for this analysis; however, this was by far the largest of the three trials and the quality of evidence assessment for this outcome was rated as high. The difference in virological failure was assessed by the Writing Group to be large enough to be above the clinical threshold for decision-making. The difference equates to a number needed to treat to prevent one case of virological failure of approximately 20 patients treated for 1 year.

The results of ACTG 5202 [2–4] are complicated by early termination of those individuals with a baseline VL >100 000 copies/mL at the recommendation of the data and safety monitoring board due to significantly inferior performance in those subjects receiving ABC-3TC. No difference in virological efficacy between the TDF-FTC and ABC-3TC arms was seen in those in the lower VL stratum (baseline VL <100 000 copies/mL). The subsequent 96-week analysis, after discontinuation of those subjects in the higher VL stratum, may therefore underestimate the difference between the two backbones. HLA-B*57:01 screening was not routine in ACTG 5202 and this potentially may have influenced some of the safety endpoints, but appears not to have influenced the primary virological outcome. In the higher VL strata the number of patients with suspected hypersensitivity reactions was equal between both arms and virological failure in these patients was infrequent.

With regard to the assessment of the other critical and important outcomes, including drug resistance, discontinuation for adverse events and lipodystrophy, no difference was shown between TDF-FTC and ABC-3TC. No data were available to assess quality of life outcomes. For grade 3/4, adverse events (all) and grade 3/4 alanine transaminase/aspartate transaminase elevation there were trends that favoured TDF-FTC (see Appendix 3.1).

Although the rate of drug resistance was not different between the NRTI backbones, the number developing drug resistance was higher numerically in those receiving ABC-3TC, given the higher rate of virological failure.

The only outcome that significantly favoured ABC-3TC was bone mineral density but no difference in bone fractures was identified.

It is the view of the Writing Group that, given the favourable virological outcomes of TDF-FTC compared with ABC-3TC and the lack of other significant differences in critical and important adverse event outcomes, TDF-FTC is recommended as the preferred NRTI backbone of choice. ABC-3TC is an acceptable alternative option in patients with a baseline VL <100 000 copies/mL, but must only be used after ensuring a patient is HLA-B*57:01 negative.

When selecting an NRTI backbone, factors such as potential side effects, co-morbidities, patient preference and cost should also be considered. Observational studies have variably reported associations between ABC and CVD [11–13], and TDF may cause renal disease [14]. These aspects will be discussed in more detail in Section 8. However, based on the balance of current evidence we suggest ABC is not used in individuals at high risk of CVD (see Section 8.6 Cardiovascular disease) and TDF is not used in patients with stage 3–5 CKD or at high risk of progression of CKD (see Section 8.5 Chronic kidney disease) if acceptable alternative ARVs are available.

5.3.3 Not recommended

The Writing Group believes there is no routine role for other NRTI backbones in the treatment of ART-naïve patients. Zidovudine (ZDV)-3TC may be considered in certain specific circumstances (e.g. pregnancy; see *BHIVA Guidelines for the Management of HIV Infection in Pregnant Women 2012* [15]) but should not be given routinely due to the proven association with mitochondrial toxicity, particularly lipoatrophy, with ZDV. There is no place for the use of stavudine- or didanosine-containing regimens as initial therapy, due to the associations with significant mitochondrial and hepatic toxicities.

5.3.4 References

1 Asboe D, Aitken C, Boffito M *et al.* BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012; **13**: 1–44. Available at http://www.bhiva.org/PublishedandApproved.aspx (accessed April 2012).

2 Sax PE, Tierney C, Collier AC *et al.* Abacavir–lamivudine versus tenofovir–emtricitabine for initial HIV-1 therapy. *N Engl J Med* 2009; **361**: 2230–2240.

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3 Sax PE, Tierney C, Collier AC *et al.* Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis* 2011; **204**: 1191–1201.
4 Daar ES, Tierney C, Fischl MA *et al.* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med* 2011; **154**: 445–456.
5 McComsey GA, Kitch D, Daar ES *et al.* Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. *J Infect Dis* 2011; **203**: 1791–1801.
6 McComsey GA, Kitch D, Sax PE *et al.* Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis* 2011; **53**: 185–196.
7 Post FA, Moyle GJ, Stellbrink HJ, Domingo P, Podzamczer D. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT Study. *J Acquir Immune Defic Syndr* 2010; **55**: 49–57.
8 Stellbrink HJ, Orkin C, Arribas JR *et al.* Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT Study. *Clin Infect Dis* 2010; **51**: 963–972.
9 Moyle GJ, Stellbrink HJ, Compston J *et al.* Comparison of bone and renal toxicities in the ASSERT study: final 96 week results from a prospective randomized safety trial. *Antivir Ther* 2010; **15** (Suppl 4): A19.
10 Smith KY, Patel P, Fine D *et al.* Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS* 2009; **23**: 1547–1556.
11 Obel N, Farkas DK, Kronborg G *et al.* Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med* 2010; **11**: 130–136.
12 Worm SW, Sabin C, Weber R *et al.* Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* 2010; **201**: 318–330.
13 Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the HAART era. *Clin Infect Dis* 2011; **53**: 84–91.
14 Mocroft A, Kirk O, Reiss P *et al.* Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 2010; **24**: 1667–1678.
15 Taylor GP, Clayden P, Dhar J *et al.* BHIVA guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012; **13** (Suppl. 2): 87–157.

5.4 Which third agent

5.4.1 Recommendations

- We recommend therapy-naïve patients start combination ART containing ATV/r, DRV/r, EFV, RAL or ELV/COBI as the third agent (1A).
- We suggest that for therapy-naïve patients LPV/r and FPV/r are acceptable alternative PIs, and NVP and RPV are acceptable alternative NNRTIs (2A).
- NVP must only be used according to CD4 criteria and RPV should only be used in patients with baseline VL <100 000 copies/mL.

5.4.2 Rationale

The *BHIVA Guidelines for the Treatment of HIV-1-infected Adults with Antiretroviral Therapy 2008* [1] recommended EFV as the preferred third agent in view of significantly better virological outcomes compared with LPV/r [2]. A similar outcome was subsequently reported in a smaller randomized study of patients commencing ART with advanced disease, as defined by a CD4 cell count of <200 cells/μL [3].

Since the 2008 guidelines, a number of comparative studies against either EFV, LPV/r or ATV/r have been reported, investigating alternative third agents.

- Comparison with EFV: ATV/r [4–10]; RAL [11–14]; RPV [15–17]; ELV/COBI [18].
- Comparison with LPV/r: ATV/r [17]; DRV/r [20–22].
- Comparison with r/ATV; ELV/COBI [19].

For the current guidelines, evidence for agreed treatment outcomes for each potential third agent was compared with EFV, either directly or indirectly depending on the available evidence (Appendix 3).

ATV/r and RAL have been compared directly with EFV in RCTs. For critical virological efficacy and safety outcomes, no differences were identified between EFV and either ATV/r or RAL. For these outcomes the quality of evidence was rated as high or moderate.

There was a difference in the rate of drug resistance favouring ATV/r (RR 3.94, 95% CI 2.37–6.56; $P < 0.00001$) but the overall rate of emergent drug resistance was low for

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both treatments. This difference is a class effect and has previously been reported for other NNRTIs and PI/r.

Differences were also identified in the rate of grade 3/4 central nervous system (CNS) events and the rate of lipid abnormalities favouring both ATV/r and RAL. These differences may well influence the choice between preferred third agents for individual patients.

There are no RCTs comparing DRV/r *vs*. EFV directly. Thus an indirect comparison was undertaken using data from studies comparing DVR/r *vs*. LPV/r [20–22] and LPV/r *vs*. EFV [2,3] to assess outcomes between the two treatment options. Some differences between these studies were identified in terms of comparability and are outlined in Appendix 3. Overall, these differences were judged insufficient to invalidate an indirect comparison between EFV and DRV/r.

Comparing DRV/r and LPV/r there were clinically significant differences in the critical outcomes virological suppression, discontinuation due to adverse events and serious adverse events in favour of DRV/r but no differences in the critical outcomes virological failure and drug resistance. Comparing EFV and LPV/r there were clinically significant differences in the critical outcomes virological failure and suppression at 96 weeks in favour of EFV but no differences in the critical outcomes drug resistance and discontinuation due to adverse events. In addition, there were significant differences in some adverse events favouring EFV over LPV/r.

RPV has been compared directly with EFV in RCTs [15–17]. With respect to critical virological outcomes there was no difference in virological suppression but there were differences in drug resistance (RR 0.38, 95% CI 0.20–0.72; $P = 0.003$) and virological failure (RR 0.55, 95% CI 0.29–1.02; $P = 0.06$), both in favour of EFV. Pooled analyses by the investigators of the two RCTs showed the risk of virological failure with RPV was highest in patients with a baseline VL >100 000 copies/mL [17]. For critical safety outcomes there was a difference in the proportion discontinuing for adverse events in favour of RPV (RR 2.29, 95% CI 1.15–4.57; $P = 0.02$) but no difference in serious adverse events. RPV also had better lipid profile outcomes.

The StAR study showed overall noninferiority of the fixed-dose combination of TDF/FTC/RPV to fixed-dose TDF/FTC/EFV at 48 weeks. In a subgroup analysis in patients with baseline viral load less than 100 000 copies/mL, superiority of the RPV-based regimen was demonstrated. Similarly to ECHO and THRIVE, StAR confirmed higher rates of virological failure on RPV at high viral loads (greater than 100 000 copies/mL) but not at lower baseline viral load (less than 100 000 copies/mL). Because rilpivirine is currently licensed for use only in patients with baseline viral loads of <100 000 copies/mL, we believe that at present it should remain as an alternative third-line agent. However, in all three studies there was a lower incidence of neuropsychiatric adverse events with RPV than with EFV. RPV may be useful for individuals with viral loads below 100 000 copies/mL, where concerns about neuropsychiatric side effects are paramount, but it is important that patients given this drug can both comply with the dietary requirements and avoid acid-reducing agents. It is important to note that there are very few data regarding the administration of RPV with an ABC/3TC NRTI backbone.

Since the 2012 guidelines were published, the fixed dose combination of TDF/FTC/ELV/COBI (Stribild) has received licensing approval. The two pivotal studies have compared this regimen to fixed-dose TDF/FTC/EFV (GS-102) and TDF/FTC with ATV/r (GS-103) [18,19] (see Appendix 4). Virological failure rates have not been reported for these studies but discontinuations for 'lack of efficacy' were similar in both arms of each study. Since these studies demonstrate non-inferiority of Stribild to both EFV and ATV/r, both of which are currently preferred third agents, it the view of the Writing Committee that Stribild should also be a preferred option for first-line therapy. In addition Stribild may confer some advantages in terms of its toxicity profile, although there are multiple potential drug–drug interactions.

In summary, it is the view of the Writing Group that EFV, given its performance across multiple well-controlled randomized trials and the wealth of clinical experience, should remain a preferred third agent. In addition, because of similar critical treatment outcomes, it is the view of the Writing Group that ATV/r, DRV/r, RAL and ELV/COBI are also recommended as preferred third agents.

RPV remains an alternative agent and should only be used in patients with baseline VL < 100 000 copies/mL.

As in the 2008 BHIVA treatment guidelines [1], NVP remains an alternative third agent, based on the associated CD4 cell count restrictions that limit its use plus the higher risk of moderate-to-severe rash/hepatitis and discontinuation for adverse events compared with other agents [23,24].

LPV/r is listed as an alternative third agent based on comparison of virological outcomes with EFV [2,3] and DRV/r [20,21], which have been previously discussed. FPV/r is also listed as an alternative third agent as it has been shown to be non-inferior to LPV/r in terms of virological efficacy [25].

When selecting a third agent from either the preferred or alternative options, factors such as potential side effects, dosing requirements, dosing convenience, patient preference, co-morbidities, drug interactions and cost should be considered.

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Neuropsychiatric side effects have commonly been reported in patients treated with EFV and patients with a history of psychiatric disorders appear to be at a greater risk of serious psychiatric adverse events [26]. In patients with a current or a history of psychiatric disorders, including depression, anxiety and suicidal ideation, caution should be exercised in prescribing EFV and strong consideration given to using an acceptable alternative third agent.

EFV may be used in pregnancy and the reader is directed to the *BHIVA guidelines for the management of HIV infection in pregnant women 2012* [27], for full discussion on this issue. Further discussion of the choice of ART in selected populations is outlined in Section 8 (ART in specific populations).

5.4.3 Not recommended

Saquinavir/ritonavir (SQV/r) is not listed as a preferred or alternative option in the treatment of ART-naïve patients with chronic infection. This is because of a higher pill burden, the availability of alternative PI/rs and a recent update to the summary of product characteristics requiring dose escalation and careful ECG monitoring due to its association with QT interval prolongation. SQV/r has been reported as non-inferior to LPV/r in terms of virological and safety outcomes [28].

The CCR5 antagonist MVC and unboosted ATV are not licensed in Europe for initial ART and as such are not recommended.

5.4.4 References

1 Gazzard BG, on behalf of the BHIVA Treatment Guidelines Writing Group. BHIVA guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med* 2008; **9**: 563–608.

2 Riddler SA, Haubrich R, DiRienzo AG *et al.* for the AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358**: 2095–2106.

3 Sierra-Madero J, Villasis-Keever A, Mendez P *et al.* Prospective randomised open label trial of efavirenz vs lopinavir/rit HIV+ treatment naïve subjects with CD4+ <200 cell/mm^3. *J Acquir Immune Defic Syndr* 2010; **53**: 582–588.

4 Puls RL, Srasuebkul P, Petoumenos K *et al.* Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study. *Clin Infect Dis* 2010; **51**: 855–864.

5 Winston A, Duncombe C, Li PC *et al.* Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. *Clin Infect Dis* 2010; **50**: 920–929.

6 Sax PE, Tierney C, Collier AC *et al.* Abacavir–lamivudine versus tenofovir–emtricitabine for initial HIV-1 therapy. *N Engl J Med* 2009; **361**: 2230–2240.

7 Sax PE, Tierney C, Collier AC *et al.* Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis* 2011; **204**: 1191–1201.

8 Daar ES, Tierney C, Fischl MA *et al.* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med* 2011; **154**: 445–456.

9 McComsey GA, Kitch D, Daar ES *et al.* Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. *J Infect Dis* 2011; **203**: 1791–1801.

10 McComsey GA, Kitch D, Sax PE *et al.* Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis* 2011; **53**: 185–196.

11 Lennox JL, DeJesus E, Lazzarin A *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374**: 796–806.

12 Lennox JL, Dejesus E, Berger DS *et al.* Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *J Acquir Immune Defic Syndr* 2010; **55**: 39–48.

13 Markowitz M, Nguyen BY, Gotuzzo E *et al.* Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naive patients with HIV-1 infection. *J Acquir Immune Defic Syndr* 2009; **52**: 350–356.

14 Gotuzzo E, Nguyen B-Y, Markowitz M *et al.* Sustained efficacy and tolerability of raltegravir after 240 weeks of combination ART in treatment-naïve HIV-1 infected patients: final analysis of Protocol 004. *6th IAS on HIV Pathogenesis, Treatment and Prevention*. Rome, Italy. July 2011 [Abstract WEPDB0102].

15 Molina JM, Cahn P, Grinsztejn B *et al.* Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; **378**: 238–246.

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16 Cohen CJ, Andrade-Villanueva J, Clotet B *et al.* Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; **378**: 229–237.

17 Cohen C, Molina JM, Cahn P *et al.* Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised phase III trials comparing TMC278 versus efavirenz in treatment-naïve HIV-1-infected patients. *18th International AIDS Conference*. Vienna, Austria. July 2010 [Abstract THLBB206].

18 Zolopa A, Sax PE, DeJesus E *et al.* for the GS-US-236-0102 Study Team. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr* 2013; **63**: 96–100.

19 Rockstroh JK, DeJesus E, Henry K *et al.* for the GS-236-0103 Study Team. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr* 2013; **62**: 483–486.

20 Ortiz R, Dejesus E, Khanlou H *et al.* Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS* 2008; **22**: 1389–1397.

21 Mills AM, Nelson M, Jayaweera D *et al.* Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS* 2009; **23**: 1679–1688.

22 Nelson M, Girard PM, Demasi R *et al.* Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data. *J Antimicrob Chemother* 2010; **65**: 1505–1509.

23 van Leth F, Phanuphak P, Ruxrungtham K *et al.* Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; **363**: 1253–1263.

24 Soriano V, Arastéh K, Migrone H *et al.* Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther* 2011; **16**: 339–348.

25 Eron J Jr, Yeni P, Gathe J Jr *et al.* The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet* 2006; **368**: 476–482.

26 Efavirenz Summary of Product Characteristics (27 July 2011). Electronic Medicines Compendium. Available at http://www.medicines.org.uk/emc/medicine/11284 (accessed April 2012).

27 Taylor GP, Clayden P, Dhar J *et al.* BHIVA guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012; **13** (Suppl. 2): 87–157.

28 Walmsley S, Avihingsanon A, Slim J *et al.* Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr* 2009; **50**: 367–374.

5.5 Novel antiretroviral therapy strategies

5.5.1 Recommendation

- We recommend against the use of PI monotherapy as initial therapy for treatment-naïve patients (1C).

5.5.2 Rationale

Data on use of PI monotherapy as initial ART are limited. In one RCT comparing LPV/r *vs*. LPV/r plus ZDV and 3TC, the use of PI monotherapy as initial ART was associated with lower rates of virological suppression at 48 weeks and with the emergence of PI mutations [1]. There were no significant differences in tolerability. For this reason, PI monotherapy is not recommended as initial ART. However, as with other novel strategies there may be specific circumstances where a rationale for its use may be made.

5.5.3 Reference

1 Delfraissy JF, Flandre P, Delaugerre C *et al.* Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naïve HIV-infected patients. *AIDS* 2008; **22**: 385–393.

5.5.4 Recommendation

- We recommend against the use of PI-based dual ART with a single NRTI, NNRTI, CCR5 receptor antagonist or INI as an initial therapy for treatment-naïve patients (1C).

5.5.5 Rationale

A number of studies have assessed the use of PI-based dual ART as initial therapy in treatment-naïve patients. Many of these are either open label (not powered to demonstrate

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non-inferiority compared with triple therapy), single-arm studies or have only been reported as conference abstracts.

The combination of an NNRTI with a PI/r has been shown to have similar virological efficacy compared with triple-combination regimens in one study [1]. There were no significant differences in time to either virological or regimen failure with a combination of LPV/r and EFV compared with either two NRTIs and EFV or two NRTIs and LPV/r. There was, however, an increased rate of drug resistance in the NRTI-sparing arm, with the emergence of more NNRTI-associated resistance mutations than the comparator arms. An increased rate of grade 3/4 toxicities was observed, predominantly low-density lipoprotein cholesterol and triglyceride elevations.

Comparison of a dual-therapy regimen containing one NRTI with a PI/r (TDF and LPV/r *vs*. two NRTIs and LPV/r) failed to demonstrate non-inferiority of the dual-therapy arm compared with a standard triple-therapy combination [2].

The use of dual therapy with the CCR5-receptor antagonist MVC in combination with a PI/r has been assessed in one RCT but was not designed to show non-inferiority [3]. The comparative efficacy of the INI RAL plus a PI/r is being compared with standard triple therapy in several ongoing and/or unpublished studies [4–8]. Reports from one study [4,5] suggest similar rates of virological suppression at 48 and 96 weeks. However, in a single-arm study investigating RAL in combination with DRV/r, a significantly increased risk of virological failure with emergent INI resistance was seen in patients with baseline VL >100 000 copies/mL compared with those with a baseline VL < 100 000 copies/mL [9]. Further data are required and there is a need to await the results of ongoing randomized trials.

5.5.6 References

1 Riddler SA, Haubrich R, DiRienzo AG *et al.* for the AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 Infection. *N Engl J Med* 2008; **358**: 2095–2106.

2 Lazzarin PM, Antinori A, Carosi G *et al.* Lopinavir/ritonavir + tenofovir dual therapy versus lopinavir/ritonavir-based triple therapy in HIV-infected antiretroviral naïve subjects: the Kalead Study. *J Antivir Antiretrovir* 2010; **2**: 056–062. doi:10.4172/jaa.1000024.

3 Portsmouth S, Craig C, Mills A *et al.* 48-week results of once-daily maraviroc (MVC) 150 mg in combination with ritonavir-boosted atazanavir (ATV/r) compared to emtricitabine/tenofovir (FTC/TDF) + ATV/r in treatment-naïve patients infected with R5 HIV-1 (Study A4001078). *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention.* Rome, Italy. July 2011 [Abstract TUAB0103].

4 Reynes J, Adebayo L, Pulido F *et al.* Examination of noninferiority, safety, and tolerability of lopinavir/ritonavir and raltegravir compared with lopinavir/ritonavir and tenofovir/emtricitabine in antiretroviral naive subjects: the PROGRESS study, 48 week results. *HIV Clin Trials* 2011; **12**: 255–267.

5 Soto-Malave R, Lawal A, Reynes J *et al.* Lopinavir/ritonavir (LPV/r) combined with raltegravir (RAL) or tenofovir/emtricitabine (TDF/FTC) in antiretroviral-naïve subjects: 96-week efficacy and safety results of the PROGRESS Study. *XV Congreso Panamericano de Infectología*. Punta del Este, Uruguay. April 2011.

6 Bowman V, Rieg G, Jain S *et al.* 48 week results of a pilot randomized study of a nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen of raltegravir (RAL) + lopinavir/ritonavir (LPV/r) versus efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) in antiretroviral-naïve patients: CCTG 589. *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Rome, Italy. July 2011 [Abstract CDB336].

7 Bedimo R, Drechsler H, Cutrell J *et al.* RADAR study: raltegravir combined with boosted darunavir has similar safety and antiviral efficacy as tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naïve patients. *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Rome, Italy. July 2011 [Abstract MOPE214].

8 French National Agency for Research on AIDS and Viral Hepatitis, NEAT–European AIDS Treatment Network. An open-label randomised two-year trial comparing two first-line regimens in HIV-infected antiretroviral naïve subjects: darunavir/r + tenofovir/emtricitabine vs. darunavir/r + raltegravir (ANRS 143/NEAT 001). Available at http://clinicaltrials.gov/ct2/show/NCT01066962 (accessed April 2012).

9 Taiwo B, Zheng L, Gallien S *et al.*; ACTG A5262 Team. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). *AIDS* 2011; **25**: 2113–2122.

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6.0 Supporting patients on therapy

6.1 Adherence

6.1.1 Interventions to increase adherence to treatment

6.1.1.1 Recommendations

- We recommend adherence and potential barriers to it are assessed and discussed with the patient whenever ART is prescribed or dispensed (GPP).
- We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/or practical barriers (e.g. limitations in capacity and resources) to adherence (GPP).

Auditable measures

- Record in patient's notes of discussion and assessment of adherence and potential barriers to, before starting a new ART regimen and while on ART.
- Record in patient's notes of provision or offer of adherence support.

6.1.1.2 Rationale

Low adherence to ART is associated with drug resistance, progression to AIDS [1] and death [2–4]. Given the multiple adverse consequences of treatment failure (risk of disease progression, increase in complexity and costs of treatment, and risk of HIV transmission) engaging patients in treatment decisions and the monitoring and support of adherence are of paramount importance [5] (see Section 3: Patient involvement in decision-making).

Non-adherence is best understood as a variable behaviour with intentional and unintentional causes. Most people taking medication are non-adherent some of the time. Unintentional non-adherence is linked to limitations in capacity or resources that reduce the ability to adhere to the treatment as intended. Intentional non-adherence is the product of a decision informed by beliefs, emotions and preferences [6].

BHIVA recommendations on the monitoring of adherence to ART are available [7]. NICE has published detailed guidance on the assessment and support of adherence to medication in chronic diseases; key recommendations for adherence support are shown in Box 6.1 [8].

6.1.2 Should the choice of first-line antiretroviral therapy combination be affected by risk of non-adherence?

6.1.2.1 Recommendation

- In patients where there is clinical concern that doses may be missed intermittently, there is insufficient evidence to recommend a PI/r over EFV-based regimens. However, where there is a risk of frequent prolonged treatment interruptions, EFV-based regimens may be associated with more frequent selection for drug resistance compared with PI/r.

6.1.2.2 Rationale

Clinicians are poor at both predicting future adherence to ART in naïve subjects [11] and at detecting non-adherence during ART [12,13]. However, in a case where a clinician or patient has concerns about a patient's future adherence, should this influence the choice of first-line therapy?

The consequences of low adherence depend on drug pharmacokinetics, potency, fitness of resistant strains and genetic barrier to resistance [14]. Hence, both the level and pattern of non-adherence must be considered.

Large RCTs of first-line therapy may not be able to inform this choice as subjects likely to be non-adherent are often excluded from such trials. On the other hand, observational studies often select patients already established on ART [15,16] where the observed effects of non-adherence on treatment outcome are likely to differ from those in patients starting ART *de novo*. This selection bias may exclude those who have either experienced early virological failure, disease progression (or even death) or have defaulted from care. In addition, most studies either predate the use of boosted-PI regimens in first-line therapy [15,17] or include large numbers of patients on unboosted PI regimens.

Three different outcomes may be considered: virological suppression, selection of drug resistance, and effect of pattern of non-adherence.

Effect of adherence on viral suppression. There are no data from RCTs that directly address this question. Among subjects reporting <95% adherence in a RCT comparing LPV/r with once-daily DRV/r, virological failure was more likely in the LPV/r arm [18].

Among patients who were virologically suppressed initially, adherence <95% was associated with an increased

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Box 6.1 Summary of NICE guidance on adherence support [8]

- A 'no-blame' approach is important to facilitate open and honest discussion.
- A patient's motivation to start and continue with prescribed medication is influenced by the way in which they judge their personal need for medication (necessity beliefs), relative to their concerns about potential adverse effects. Delayed uptake and non-adherence are associated with doubts about personal need for ART and concerns about taking it [9,10].
- Interventions to support adherence should be individualized to address specific relevant perceptual and practical barriers. A three-step 'Perceptions and Practicalities Approach' [9] may be helpful:
  1. Identify and address any doubts about personal need for ART.
  2. Identify and address specific concerns about taking ART.
  3. Identify and address practical barriers to adherence.
- Because evidence is inconclusive, only use interventions to overcome practical problems if there is a specific need. Interventions might include:
  - suggesting patients record their medicine-taking;
  - encouraging patients to monitor their results;
  - simplifying the dosing regimen;
  - using a multicompartment medicines system;
  - If side effects are a problem:
    - discuss benefits and long-term effects and options for dealing with side effects;
    - consider adjusting the dosage, switching to another combination or other strategies such as changing the dose timing or formulation.
- Patients' experience of taking ART and their needs for adherence support may change over time.
  - patients' knowledge, understanding and concerns about medicines and the benefits they perceive should be reviewed regularly at agreed intervals.

risk of failure [16], and very low adherence (<50%) results in virological rebound irrespective of regimen [5,16,19]. However, virological suppression has been observed with only moderate adherence (50–75%) among patients on NNRTIs [5,16,19] and virological failure has been reported to be significantly more likely among all patients on unboosted PI-based regimens where adherence was <95% [16]. However, this finding may have been confounded by the once-daily dosing in the EFV group. A further study [20] examined only patients with undetectable viraemia and found no difference in rates of virological rebound for patients on PI/r *vs.* NNRTIs.

Effect of adherence on selection of drug resistance. The effect of level of non-adherence on selection of drug resistance varies by class. This was first described for unboosted PI regimens where moderate-to-high adherence was associated with increased risk of resistance [21]. The incidence of resistance in studies of boosted-PI regimens is low [18,22–26] but is observed with adherence just below 80–95% [15,27]. In contrast, for first-generation NNRTIs the selection for resistance has been associated with very low average adherence (<50%) [14,28].

Effect of pattern of non-adherence. The pattern of non-adherence may also be important. A number of small observational studies have examined short intermittent treatment interruptions (2–7 days) in patients with prolonged virological suppression. For EFV, cycles of 2 days off per week appeared no more likely to result in treatment failure than continuous therapy, as long as the treatment interruption was not prolonged [29,30]. However, cycles of 7- or 28-day treatment interruption resulted in failure of EFV and selection of resistance [31,32]. For PI/r, one study found that average adherence, rather than duration of treatment interruption, was associated with virological response [33].

6.1.3 Dosing frequency

A recent overview of systematic reviews of consumer-oriented medication interventions found that simplified dosing regimens improved adherence in the majority of studies in several reviews [34]. Another review of adherence interventions found that reducing dosing to once daily had some effect on adherence but no effect on treatment outcome was observed [35]. NICE [8] reviewed several RCTs of interventions to reduce dose frequency

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and found that adherence may increase with once-daily dosing. For ART regimens, a meta-analysis of once- *vs.* twice-daily ART regimens found that in the subgroup of treatment-naïve trials, once-daily ART was associated with a significantly improved adherence and virological outcome [36].

Therefore, once-daily dosing is a reasonable intervention to reduce unintentional non-adherence to ART.

6.1.4 Fixed-dose combinations

In examining whether fixed-dose combination formulations (FDCs) of drugs improve adherence or treatment outcome, only studies comparing the same drugs with the same dose frequency given as combination or separate pills were considered. No meta-analyses have been published on this subject for ART. A meta-analysis of nine RCTs and cohort studies in a range of diseases found the use of FDCs was associated with a significant reduction in the risk of non-adherence [36]. Gupta *et al.* [37] reported a meta-analysis of cohort studies and found that use of FDCs for antihypertensives was associated with increased adherence but with no improvement on the control of blood pressure.

There are no published studies in HIV therapy directly comparing outcomes with FDCs versus separate agents. A retrospective study of a pharmacy database found no benefit in persistence on first-line ART for any FDC over separate agents [38]. In the ECHO/ THRIVE studies a lower virological response rate in patients with baseline VL >100 000 copies was observed for RPV- versus EFV-based regimens when dosed as separate agents [39]; this was not repeated when formulated as FDCs in the preliminary 48-week results from the STaR study [40]. Although the use of FDCs may have driven this apparent improvement in performance of RPV, it may also have arisen due to the simpler once-daily regimens in STaR, other methodological differences or by chance.

A further advantage of FDCs is that they prevent patients from preferentially adhering less closely to one component of a regimen than others. A minority of patients in one study did report such 'differential' adherence, but this was not associated with outcome for currently used first-line strategies [41].

An observational study of outcomes following a switch from Atripla to multi-tablet regimens provides very low quality evidence that this may not result in an increase in virological failures [42]. However, the data are available in abstract only and raise methodological questions. In view of the higher quality evidence in support of FDCs and the implications and costs of treatment failure, there is insufficient evidence to support this strategy at present.

In summary FDCs support adherence to treatment, and this may well reduce the risk of virological failure. However, the size of this effect is yet to be defined.

6.1.5 References

1 Bangsberg DR, Perry S, Charlebois ED *et al.* Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* 2001; **15**: 1181–1183.

2 Garcia de OP, Knobel H, Carmona A *et al.* Impact of adherence and highly active antiretroviral therapy on survival in HIV- infected patients. *J Acquir Immune Defic Syndr* 2002; **30**: 105–110.

3 Hogg RS, Heath K, Bangsberg D *et al.* Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* 2002; **16**: 1051–1058.

4 Lima VD, Geller J, Bangsberg DR *et al.* The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 2007; **21**: 1175–1183.

5 Bangsberg DR. A paradigm shift to prevent HIV drug resistance. *PLoS Med* 2008; **5**: e111.

6 Horne R, Weinman J, Barber N, Elliott RA, Morgan M. *Concordance, Adherence and Compliance in Medicine Taking: A Conceptual Map and Research Priorities*. London, National Institute for Health Research (NIHR) Service Delivery and Organisation (SDO) Programme, 2005. Available at http://www.netscc.ac.uk/hsdr/files/project/SDO_FR_08-1412-076_V01.pdf (accessed May 2012).

7 Asboe D, Aitken C, Boffito M *et al.* BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012; **13**: 1–44. Available at http://www.bhiva.org/PublishedandApproved.aspx (accessed April 2012).

8 Nunes V, Neilson J, O'Flynn N *et al. Clinical Guidelines and Evidence Review for Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and Supporting Adherence*. London, National Collaborating Centre for Primary Care and Royal College of General Practitioners, 2009.

9 Horne R, Cooper V, Gellaitry G, Date HL, Fisher M. Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and adherence: the utility of the necessity-concerns framework. *J Acquir Immune Defic Syndr* 2007; **45**: 334–341.

10 Gonzalez JS, Penedo FJ, Llabre MM *et al.* Physical symptoms, beliefs about medications, negative mood, and long-term HIV medication adherence. *Ann Behav Med* 2007; **34**: 46–55.

11 Gross R, Bilker WB, Friedman HM, Coyne JC, Strom BL. Provider inaccuracy in assessing adherence and outcomes

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with newly initiated antiretroviral therapy. *AIDS* 2002; **16**: 1835–1837.
12 Bangsberg D, Hecht F, Clague H *et al.* Provider assessment of adherence to HIV antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001; **26**: 435–442.
13 Miller LG, Liu H, Hays RD *et al.* How well do clinicians estimate patients' adherence to combination antiretroviral therapy? *J Gen Intern Med* 2002; **17**: 1–11.
14 Gardner EM, Burman WJ, Steiner JF *et al.* Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS* 2009; **23**: 1035–1046.
15 Bangsberg DR, Acosta EP, Gupta R *et al.* Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS* 2006; **20**: 223–231.
16 Maggiolo F, Airoldi M, Kleinloog HD *et al.* Effect of adherence to HAART on virologic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-treated patients. *HIV Clin Trials* 2007; **8**: 282–292.
17 Trotta MP, Ammassari A, Cozzi-Lepri A *et al.* Adherence to highly active antiretroviral therapy is better in patients receiving non-nucleoside reverse transcriptase inhibitor-containing regimens than in those receiving protease inhibitor-containing regimens. *AIDS* 2003; **17**: 1099–1102.
18 Nelson M, Girard PM, DeMasi R *et al.* Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naïve HIV-infected patients: 96 week ARTEMIS data. *J Antimicrob Chemother* 2010; **65**: 1505–1509.
19 Cambiano V, Lampe FC, Rodger AJ *et al.* Use of a prescription-based measure of antiretroviral therapy adherence to predict viral rebound in HIV-infected individuals with viral suppression. *HIV Med* 2010; **11**: 216–224.
20 Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis* 2006; **43**: 939–941.
21 Martin M, Del Cacho E, Codina C *et al.* Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: a prospective cohort study. *AIDS Res Hum Retroviruses* 2008; **24**: 1263–1268.
22 Bangsberg DR, Hecht FM, Charlebois ED *et al.* Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000; **14**: 357–366.
23 Kempf DJ, King MS, Bernstein B *et al.* Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. *J Infect Dis* 2004; **189**: 51–60.
24 Walmsley S, Avihingsanon A, Slim J *et al.* Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr* 2009; **50**: 367–374.
25 Riddler SA, Haubrich R, DiRienzo AG *et al.* Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358**: 2095–2106.
26 Molina JM, Andrade-Villanueva J, Echevarria J *et al.*; CASTLE Study Team. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008; **372**: 646–655.
27 Daar ES, Tierney C, Fischl MA *et al.* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1: a randomized trial. *Ann Intern Med* 2011; **154**: 445–456.
28 King MS, Brun SC, Kempf DJ. Relationship between adherence and the development of resistance in antiretroviral-naive, HIV-1-infected patients receiving lopinavir/ritonavir or nelfinavir. *J Infect Dis* 2005; **191**: 2046–2052.
29 Cohen CJ, Colson AE, Sheble-Hall AG, McLaughlin KA, Morse GD. Pilot study of a novel short-cycle antiretroviral treatment interruption strategy: 48-week results of the five-days-on, two-days-off (FOTO) study. *HIV Clin Trials* 2007; **8**: 19–23.
30 Reynolds SJ, Kityo C, Hallahan CW *et al.* A randomized, controlled, trial of short cycle intermittent compared to continuous antiretroviral therapy for the treatment of HIV infection in Uganda. *PLoS ONE* 2010; **5**: e10307.
31 Dybul M, Nies-Kraske E, Daucher M *et al.* Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters. *J Infect Dis* 2003; **188**: 388–396.
32 Parienti JJ, Ragland K, Lucht F *et al.* Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication. *Clin Infect Dis* 2010; **50**: 1192–1197.
33 Ryan R, Santesso N, Hill S *et al.* Consumer-oriented interventions for evidence-based prescribing and medicines use: an overview of systematic reviews. *Cochrane Database Syst Rev* 2011; (5): CD007768.
34 Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; (2): CD000011.
35 Parienti JJ, Bangsberg D, Verdon R *et al.* Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis* 2009; **48**: 484–488.

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36 Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007; **120**: 713–719.
37 Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; **55**: 399–407.
38 Juday T, Grimm K, Zoe-Powers A *et al.* A retrospective study of HIV antiretroviral treatment persistence in a commercially insured population in the United States. *AIDS Care* 2011; **23**: 1154–1162.
39 Cohen CJ, Molina JM, Cassetti I *et al.* Week 96 efficacy and safety of rilpivirine in treatment-naïve, HIV-1 patients in two Phase III randomised trials. *AIDS* 2012 Dec 3 [Epub ahead of print].
40 Cohen C, Wohl D, Arribas J *et al.* STaR Study: Single-Tablet Regimen Emtricitabine/Rilpivirine/Tenofovir DF is Non-Inferior to Efavirenz/Emtricitabine/Tenofovir DF in ART-Naïve Adults Week 48 Results. *11th International Congress on Drug Therapy in HIV Infection.* Glasgow, Scotland. November 2012 [Abstract Oral 425].
41 Gardner EM, Sharma S, Peng G *et al.* Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. *AIDS* 2008; **22**: 75–82.
42 Engsig F, Gerstoft J, Helleberg M *et al.* Virological Response in Patients, Who for Economic Reasons Were Changed from Atripla to a Multi-tablet cART Regimen. *20th Conference on Retroviruses and Opportunistic Infections.* Atlanta, GA. March 2013 [Abstract Poster 579].

6.2 Pharmacology

More than for any other infection, patients receiving ART require their doctor to have a clear understanding of the basic principles of pharmacology to ensure effective and appropriate prescribing. This is especially the case in four therapeutic areas.

6.2.1 Drug interactions

6.2.1.1 Recommendations

- We recommend that potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications are checked before administration (with tools such as http://www.hiv-druginteractions.org) (GPP).

Auditable measure. Record in patient's notes of potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications.

6.2.1.2 Rationale

The importance of considering the potential for drug interactions in patients receiving ART cannot be overemphasized. DDIs may involve positive or negative interactions between ARV agents or between these and drugs used to treat other coexistent conditions. A detailed list is beyond the remit of these guidelines but clinically important interactions to consider when co-administering with ARV drugs include interactions with the following drugs: methadone, oral contraceptives, anti-epileptics, antidepressants, lipid-lowering agents, acid-reducing agents, certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole), some anti-arrhythmics, TB therapy, anticancer drugs, immunosuppressants, phosphodiesterase inhibitors and anti-HCV therapies. Most of these interactions can be managed safely (i.e. with/without dosage modification, together with enhanced clinical vigilance) but in some cases (e.g. rifampicin and PIs, proton pump inhibitors and ATV, and didanosine and HCV therapy) the nature of the interaction is such that co-administration must be avoided.

Importantly, patient education on the risks of drug interactions, including over-the-counter or recreational drugs, should be undertaken and patients should be encouraged to check with pharmacies or their healthcare professionals before commencing any new drugs, including those prescribed in primary care.

Large surveys report that about one-in-three-to-four patients receiving ART is at risk of a clinically significant drug interaction [1–6]. This suggests that safe management of HIV drug interactions is only possible if medication recording is complete, and if physicians are aware of the possibility that an interaction might exist. Incomplete or inaccurate medication recording has resulted from patient self-medication, between hospital and community health services [7] and within hospital settings particularly when multiple teams are involved, or when medical records are fragmented (e.g. with separate HIV case notes) [8].

More worryingly, one survey in the UK reported that even when medication recording is complete, physicians were only able to identify correctly one-third of clinically significant interactions involving HIV drugs [4]. In addition to HIV specialist and local drug information pharmacists, the University of Liverpool's comprehensive drug interaction website (http://www.hiv-druginteractions.org) is an excellent and highly recommended resource for information relating to potential drug interactions. Additional information resources also include the electronic medicines compendium (http://www.medicines.org.uk/emc) and medical information departments of pharmaceutical companies.

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Communication with GPs and other medical specialties involved in patient care is fundamental in minimizing the risk of adverse DDIs. All clinic letters should carry as a standard header or footer advice to check for interactions, and links to resources, such as http://www.hiv-druginteractions.org, to address the potential for drug interactions.

6.2.2 Therapeutic drug monitoring

6.2.2.1 Recommendation

- We recommend against the unselected use of TDM (GPP).
- TDM may be of clinical value in specific populations (e.g. children, pregnant women) or selected clinical scenarios (e.g. malabsorption, drug interactions, suspected non-adherence to therapy).

6.2.2.2 Rationale

TDM has been shown to be valuable in optimizing the management of certain patients; however, the general utility of this test in patients receiving ART has been poorly assessed. With the marked improvement in efficacy and tolerability of modern ARV regimens, the role of TDM in clinical management has also evolved. A Cochrane review of RCTs [9] suggested little value when used unselectively. However, TDM may aid the management of vulnerable populations or complex clinical situations.

(i) *Monitoring adherence*. While detection of drug at therapeutic or even high plasma concentrations does not exclude low adherence, absence of measurable drug, or else very low levels of drug, strongly suggest lack of medication intake, particularly in the absence of evidence of significant malabsorption. Here, TDM should rarely be interpreted in isolation, but rather integrated with virological rebound, particularly in the absence of any resistance mutations and other features in the history that suggest risk for low treatment adherence.

(ii) *Optimizing treatment in vulnerable patients* (e.g. children, pregnant women and patients with extremes of body mass index) *or in specific clinical situations* (e.g. liver and renal impairment, treatment failure, drug interactions both foreseen and unanticipated, malabsorption, suspected non-adherence and unlicensed once-daily dosing regimens). In these scenarios, the aim is to optimize dosing based either on known efficacy or toxicity cut-offs, or else to achieve the range of plasma concentrations encountered in patients without these factors, who have been recruited to pharmacokinetic studies at licensed treatment doses that are known to be both safe and efficacious.

(iii) *Managing drug interactions (see above)*. Where the HIV drug has the potential to be adversely affected by another drug, and the combination is unavoidable, TDM may be used either to manage that interaction, or else discount a significant interaction in a particular patient.

(iv) *Other situations*. Knowledge of plasma–drug concentrations may be clinically useful when evaluating whether there is scope for treatment simplification, or else confirming or refuting impaired drug absorption as a reason for virological failure.

More detailed recommendations for the use of TDM are available in the *BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011* [10]. As for all other investigations, it is essential that TDM is undertaken correctly, especially with regard to timing (undertaken when steady state has been achieved). A consensus has been achieved for defining targets [11] for many ARVs. With many newer agents, evidence for a defined minimum target for efficacy is either weak or lacking, and evidence for an upper toxicity cut-off for most ARVs is lacking.

6.2.3 Stopping therapy: pharmacological considerations

6.2.3.1 Recommendations

- We recommend patients stopping ART containing an NNRTI in combination with an NRTI backbone replace all drugs with a PI (LPV/r) for 4 weeks (1C).
- We recommend patients stopping a PI-containing regimen stop all drugs simultaneously and no replacement is required (1C).

Auditable measure. Proportion of patients with an undetectable VL on ART who, on stopping a regimen containing an NNRTI in combination with a NRTI backbone, are switched to PI/r for 4 weeks.

6.2.3.2 Rationale

In general, treatment interruptions are not recommended for most patients. Whatever the reason for stopping ART (e.g. drug toxicity, intercurrent illness, after pregnancy or patient choice), pharmacological issues must be considered for a clinician to give guidance. The half-life of each drug included in the regimen is critical. There is the potential for monotherapy or dual therapy if ARV drugs with different half-lives are stopped simultaneously.

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NNRTI and NRTI resistance mutations have been detected following discontinuation of previously suppressive regimens [12] and may have the potential to affect the likelihood of viral re-suppression on restarting an NNRTI-based ART regimen.

There are limited data on which to base recommendations for how to protect against development of resistance in the period immediately following treatment cessation. Several discontinuation strategies have been proposed [13], and choice is influenced by clinical considerations, patient wishes and pharmacological principles. Options include: (i) simultaneously stopping all drugs in a regimen containing drugs with similar half-lives; (ii) a staggered stop, discontinuing the drug with the longest half-life first in a regimen containing drugs with short and long half-lives; or (iii) replacing all drugs with a drug with a short half-life and high genetic barrier to resistance (i.e. a PI). There is no randomized comparison of these three strategies. However, in one study a lower number of emergent resistance mutations were seen in patients switching to a PI compared with those undertaking a simultaneous or staggered stop [12]. Therapeutic plasma concentrations of EFV can also be detected up to 3 weeks after stopping the drug in some patients and thus a staggered stop of 1 week may potentially be inadequate to prevent emergence of NNRTI mutations [14]. The optimal duration of replacement with a PI is not known, but 4 weeks is probably advisable.

6.2.4 Switching therapy: pharmacological considerations

6.2.4.1 Recommendations

Data on how to switch away from EFV to an alternative 'third' agent are either non-existent, or of low or very low quality. Based on pharmacological principles, there is little rationale for any strategy other than straightforward substitution when switching to a PI/r or RAL. Pharmacokinetic studies show that straightforward substitution with ETV and RPV may result in slightly lower concentrations of either drug for a short period following switching, but limited virological data suggest that risk of virological failure with this strategy is low. Different strategies for switching to NVP have been proposed, but no comparative data are available to guide the choice of strategy. Limited data suggest that the dose of MVC should be doubled in the week following switching (unless given together with a PI/r).

If switching away from EFV is undertaken when VL is likely to still to be detectable (e.g. because of CNS intolerance within the first few weeks of starting EFV), substitution with a PI/r in preference to a within-class switch is advised.

6.2.4.2 Rationale

Switching a component of an ART regimen is frequently considered in patients to manage drug side effects or address adherence issues. ARVs that either induce or inhibit drug-metabolizing enzymes have the potential to affect the plasma concentrations of the new agent. This applies in particular to switching away from NNRTIs. Induction of drug metabolizing enzymes by EFV is likely to persist for a period beyond drug cessation. Consideration should also be taken of whether or not VL is maximally suppressed when planning how to switch away from EFV to an alternative agent. Broadly, strategies for switching from EFV to an alternative 'third' agent may be summarized as follows.

Efavirenz to nevirapine. A pharmacokinetic study performed in HIV-positive individuals suggested that patients changing from EFV to NVP should commence on 200 mg twice a day to ensure therapeutic plasma concentrations and potentially avoid selection of resistance to NVP [15]. However, no patient in the NVP lead-in group experienced virological failure in the 3-month follow-up period. Switching without dose escalation is in direct contrast with the information in the Viramune summary of product characteristics, which advises administration of a NVP lead-in dose (200 mg once daily for 2 weeks) when starting NVP [16], as this has been shown to decrease the frequency of rash.

In ART-experienced patients who are virologically suppressed with an undetectable plasma HIV RNA level (<50 copies/mL), the risk of hypersensitivity and/or hepatotoxicity on switching to NVP is not increased in patients with higher CD4 cell counts (above the gender-specific CD4 cell count thresholds) [17]. In ART-experienced patients with detectable plasma HIV RNA levels, a switch to NVP is not advised.

Furthermore, the need to minimize any window for developing resistance is greatest in patients who discontinue EFV early on when virological suppression has not yet been achieved. The latter scenario is made more complex when enzyme induction has not yet been fully achieved, and if doubt exists, alternatives to switch to should be considered.

Efavirenz to etravirine. Steady-state (14 days following the switch) ETV pharmacokinetic parameters are lowered by previous EFV intake in the case of both once-daily (C_{min} was lowered by 33%) and twice-daily (C_{min} was lowered by 37%) administration. However, ETV concentrations have been shown to increase over time following the switch and in patients with undetectable VLs switching from EFV to ETV, standard doses of ETV can be commenced [18].

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To date, no data are available on what strategy to adopt in patients with active viral replication.

Efavirenz to rilpivirine. Concentrations of RPV are lowered by previous EFV administration. However, 28 days after the switch, they returned to levels comparable with those when RPV was administered without previous EFV treatment, except for a 25% lower C_{min}. Therefore, in patients with undetectable VLs switching from EFV to RPV, standard doses of RPV can be commenced [19]. To date, no data are available on what strategy to adopt in patients with active viral replication.

Efavirenz to a ritonavir-boosted protease inhibitor. Because of the strong inhibitory effect of ritonavir on CYP450 3A4, it is unlikely to require a modification of the PI/r dose when switching from EFV to PI/r. Formal pharmacokinetic data are unavailable. TDM data were presented on ATV/r and showed that after stopping EFV, ATV concentrations were above the suggested minimum effective concentration in all studied subjects [20].

Efavirenz to raltegravir. Although formal pharmacokinetic data are not available, switching EFV to RAL should not lead to clinically significant consequences, as co-administration of EFV with RAL led to a moderate-to-weak reduction in RAL C_{min} (21%) [21], which may persist for 2–4 weeks, after the switch but the degree of this reduction is unlikely to be clinically meaningful.

Efavirenz to maraviroc. A formal pharmacokinetic study in HIV-positive individuals showed that the induction effect of EFV necessitated an increase in MVC dose to 600 mg twice daily for 1 week following the switch [22]. MVC 300 mg twice daily (standard dose) seems to be safe after this period. Although there is an absence of data, when switching from EFV to MVC plus a PI/r, it is likely that a dose of 150 mg twice daily is safe from the first day after the switch. Whether it is advisable to use MVC 150 mg once daily in this context or for how long a twice-daily dose should be used after the switch remains unknown.

6.2.5 References

1 Miller CD, El-Kholi R, Faragon JJ, Lodise TP. Prevalence and risk factors for clinically significant drug interactions with antiretroviral therapy. *Pharmacotherapy* 2007; **27**: 1379–1386.

2 Shah S, Shah S, McGowan J *et al.* Identification of drug interactions involving ART in New York City HIV specialty clinics. *14th Conference on Retroviruses and Opportunistic Infections*. Los Angeles, CA. February 2007 [Abstract 573].

3 Marzolini C, Elzi L, Gibbons S *et al.*; Swiss HIV Cohort Study. Prevalence of co-medications and impact of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010; **15**: 413–423.

4 Evans-Jones JG, Cottle LE, Back DJ *et al.* Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis* 2010; **50**: 1419–1421.

5 Kigen G, Kimaiyo S, Nyandiko W *et al.*; USAID-Academic Model for Prevention Treatment of HIV/AIDS. Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large Kenyan cohort. *PLoS ONE* 2011; **6**: e16800.

6 Patel N, Abdelsayed S, Veve M, Miller CD. Predictors of clinically significant drug-drug interactions among patients treated with nonnucleoside reverse transcriptase inhibitor-, protease inhibitor-, and raltegravir-based antiretroviral regimens. *Ann Pharmacother* 2011; **45**: 317–324.

7 de Maat MM, Frankfort SV, Mathôt RA *et al.* Discrepancies between medical and pharmacy records for patients on anti-HIV drugs. *Ann Pharmacother* 2002; **36**: 410–415.

8 Seden K, Mathew T, Bradley M *et al.* Patients accessing HIV treatment via sexual health services: what are the risks of the dual case-note system? *Int J STD AIDS* 2012; **23**: 99–104.

9 Kredo T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. *Cochrane Database Syst Rev* 2009; (3): CD007268.

10 Asboe D, Aitken C, Boffito M *et al.* BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012; **13**: 1–44. Available at http://www.bhiva.org/PublishedandApproved.aspx (accessed April 2012).

11 la Porte C, Back D, Blaschke T *et al.* Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. *Rev Antivir Ther* 2006; **3**: 4–14.

12 Fox Z, Phillips A, Cohen C *et al.* Viral suppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor based regimen. *AIDS* 2008; **22**: 2279–2289.

13 Taylor S, Boffito M, Khoo S *et al.* Stopping antiretroviral therapy. *AIDS* 2007; **21**: 1673–1682.

14 Taylor S, Jayasuriya A, Fisher M *et al.* Lopinavir/ritonavir single agent therapy as a universal combination antiretroviral stopping strategy: results from the STOP 1 and STOP 2 studies. *J Antimicrob Chemother* 2012; **67**: 675–680.

15 Winston A, Pozniak A, Smith N *et al.* Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1-infected individuals? *AIDS* 2004; **18**: 572–574.

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16 *Viramune Summary of Product Characteristics*. UK, Boehringher Ingelheim Ltd, 2011.
17 Kesselring AM, Wit FW, Sabin CA *et al*. Risk factors for treatment limiting toxicities in patients starting nevirapine containing antiretroviral therapy. *AIDS* 2009; **23**: 1689–1699.
18 Waters L, Fisher M, Winston A *et al*. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS* 2011; **25**: 65–71.
19 Crauwels H, Vingerhoets J, Ryan R *et al*. Pharmacokinetic parameters of once-daily TMC278 following administration of EFV in healthy volunteers. *18th Conference on Retroviruses and Opportunistic Infections*. Boston MA. February 2011 [Abstract 630].
20 Maitland D, Boffito M, Back D *et al*. Therapeutic drug monitoring (TDM) of atazanavir (ATV) during the first 4 weeks of therapy after switching from efavirenz (EFV) containing regimen. *7th International Congress on Drug Therapy in HIV Infection*. Glasgow, UK. November 2004 [Abstract 293].
21 Iwamoto M, Wenning LA, Petry AS *et al*. Minimal effects of ritonavir and efavirenz on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother* 2008; **52**: 4338–4343.
22 Waters L, Newell S, Else L *et al*. Pharmacokinetics (PK), efficacy and safety of switching from efavirenz (EFV) to maraviroc (MVC) twice-daily (BID) in patients suppressed on an EFV-containing regimen as initial therapy. *13th European AIDS Conferenc*e. Belgrade, Serbia. October 2011.

6.3 Switching antiretroviral therapy in virological suppression

6.3.1 Introduction

In patients on fully virally suppressive regimens, switching individual components of the ART combination regimen is frequently considered for several reasons, including: management of ARV drug toxicity or intolerance, desire for once-daily dosing and reduced pill burden, management of potential DDIs, patient preference and cost [1]. Guidance on the management of drug toxicity of individual ARVs is not within the scope of these guidelines. Guidance on interventions to support adherence, including once-daily dosing and FDCs is addressed in Section 6.1 (Adherence) and pharmacological considerations on switching ARVs is discussed in Section 6.2.4 (Switching therapy: pharmacological considerations).

Switching individual components of an ART regimen may well improve adherence and tolerability, but should not be at the cost of virological efficacy. The following guidance concerns the impact on virological efficacy of either switching the third agent or the NRTI backbone in a combination ART regimen or simplifying to boosted PI monotherapy. Evidence from a systematic literature review (Appendix 2) was evaluated as well as the impact on critical treatment outcomes of the different switching strategies assessed. Critical outcomes included virological suppression at 48 weeks, virological failure and discontinuation from grade 3/4 events.

6.3.2 Switching antiretrovirals in combination antiretroviral therapy

6.3.2.1 Recommendations

- We recommend, in patients on suppressive ART regimens, consideration is given to differences in side effect profile, DDIs and drug resistance patterns before switching any ARV component (GPP).
- We recommend in patients with previous NRTI resistance mutations, against switching a PI/r to either an NNRTI or an INI as the third agent (1B).

Auditable measure. Number of patients with an undetectable VL on current regimen and documented previous NRTI resistance who have switched a PI/r to either an NNRTI or INI as the third agent.

6.3.2.2 Rationale

Within-class switches are usually undertaken to improve ARV tolerability. The available evidence for current recommended third agents is limited but switching PI/r or NNRTIs in virologically suppressed patients has, in a small number of studies, not been associated with loss of virological efficacy [2–4]. Consideration should, however, be given to differences in side effect profiles, DDIs and food effect and for switching between different PIs to the previous history of major PI mutations, as this may potentially have an adverse effect on the virological efficacy of the new PI/r.

For NRTIs, recent studies have mainly evaluated switching from a thymidine analogue to either TDF or ABC to manage patients with lipoatrophy or have investigated switching to one of two available NRTI FDCs (TDF and FTC or ABC and 3TC). If screening for HLA-B*57:01 positivity is undertaken before the switch to ABC, then similar virological efficacy is seen in patients switched to ABC-3TC FDC compared with a switch to TDF-FTC FDC [5]. In general, in the absence of previous resistance mutations, switching within class should result in maintaining virological suppression.

Several RCTs have assessed switching between classes (PI to NNRTI and PI to INI) in patients who are virologically suppressed. A meta-analysis of six trials showed non-inferiority in maintenance of virological suppression when

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switching from a PI (both ritonavir boosted and unboosted) to NVP compared with continuing the PI but was associated with more discontinuations due to liver toxicity [6]. Previous treatment failure on an NRTI-containing regimen has been associated with an increased risk of virological failure when switching from a PI to an NNRTI-based regimen [7]. A recent cohort analysis showed similar rates of virological failure at 12 months in patients switching from a first-line PI/r to either EFV or NVP compared with continuing on the PI/r [8]. If switching to NVP, consideration should be given to the risk of hypersensitivity reactions and hepatotoxicity. Similar rates have been reported in virologically suppressed compared with ART-naïve patients stratified for CD4 cell count and gender [9,10]. For patients without previous NRTI or NNRTI resistance mutations switching from a PI/r to any of the current licensed NNRTIs is likely to maintain virological efficacy and choice of NNRTI will depend on side effect profile, tolerability and patient preference.

Switching from a PI/r to the INI, RAL, in virologically suppressed patients has been evaluated in three RCTs. Two studies have shown that previous history of NRTI resistance mutations increases the risk of subsequent virological failure on switching compared with continuing on a PI/r [11,12]. This association was not seen in a third trial [13]. However, it is not surprising that switching from an ARV with a high genetic barrier to one with a low genetic barrier to resistance may potentially increase the risk of virological failure if the activity of the NRTI backbone has been compromised by previous NRTI resistance.

There are limited data on switching from an NNRTI to an alternative third agent in virologically suppressed patients; however, consideration must be given to previous treatment history and potential pharmacokinetic interactions. The latter is discussed in more detail in Section 6.2.4 (Switching therapy: pharmacological considerations).

6.3.2.3 References

1 Vo TT, Ledergerber B, Keiser O *et al.*; Swiss HIV Cohort Study. Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. *J Infect Dis* 2008; **197**: 1685–1694.

2 Mallolas J, Podzamczer D, Milinkovic A *et al.* Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. *J Acquir Immune Defic Syndr* 2009; **51**: 29–36.

3 Soriano V, García-Gasco P, Vispo E *et al.* Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. *J Antimicrob Chemother* 2008; **61**: 200–205.

4 Waters L, Fisher M, Winston A *et al.* A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS* 2011; **25**: 65–71.

5 Martin A, Bloch M, Amin J *et al.* Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clin Infect Dis* 2009; **49**: 1591–1601.

6 Ena J, Leach A, Nguyen P. Switching from suppressive protease inhibitor-based regimens to nevirapine-based regimens: a meta-analysis of randomized controlled trials. *HIV Med* 2008; **9**: 747–756.

7 Martinez E, Arnaiz JA, Podzamczer D *et al.* Substitution of nevirapine, efavirenz or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med* 2003; **349**: 1036–1046.

8 Bommenel T, Launay O, Meynard JL *et al.* Comparative effectiveness of continuing a virologically effective first-line boosted protease inhibitor combination or of switching to a three-drug regimen containing either efavirenz, nevirapine or abacavir. *J Antimicrob Chemother* 2011; **66**: 1869–1877.

9 Kesselring AM, Wit FW, Sabin CA *et al.* Risk factors for treatment limiting toxicities in patients starting nevirapine containing antiretroviral therapy. *AIDS* 2009; **23**: 1689–1699.

10 Wit FW, Kesselring AM, Gras L *et al.* Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis* 2008; **46**: 933–940.

11 Eron JJ, Young B, Cooper DA *et al.* Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 2010; **375**: 396–407.

12 Vispo E, Barreiro P, Maida I *et al.* Simplification from protease inhibitors to once- or twice-daily raltegravir: the ODIS trial. *HIV Clin Trials* 2010; **11**: 197–204.

13 Martínez E, Larrousse M, Llibre JM *et al.* Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS* 2010; **24**: 1697–1707.

6.3.3 Protease inhibitor monotherapy

6.3.3.1 Recommendation

- We recommend continuing standard combination ART as the maintenance strategy in virologically suppressed patients (1C). (There are insufficient data to recommend PI/r monotherapy in this clinical situation.)

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Auditable measure. Number of patients on PI/r monotherapy as ART maintenance strategy in virologically suppressed patients and record of rationale.

6.3.3.2 Rationale

For the assessment and evaluation of evidence, GRADE tables were constructed (Appendix 3). Virological suppression, drug resistance and serious adverse events were defined as critical outcomes. From the systematic literature review (Appendix 2) 10 RCTs were identified, investigating the use of either LPV/r or DRV/r in stable, virologically suppressed patients without active hepatitis B coinfection [1–13].

Assessment of virological suppression showed significantly fewer patients on PI monotherapy maintaining virological suppression compared with those continuing on standard combination ART (RR 0.95, 95% CI 0.9, 0.99), although the difference was small. A similar result has previously been reported in a meta-analysis [14]. VL rebound is usually at low level, and is easily reversed by reintroduction of NRTIs. The long-term consequences of this viral rebound and re-suppression are unknown. There were no differences in the frequency of emergence of viral resistance, or of serious adverse events, although few patients developed drug resistance and thus confidence in the estimate of this effect is low. One potential concern is the development of CNS disease in patients on PI monotherapy [6,11]; however, we did not identify a difference in this outcome although the quality of the evidence is low. Further data are required.

Overall, there is no significant clinical benefit of PI monotherapy compared with standard combination ART, which might offset the disadvantage of a lower rate of viral suppression with PI monotherapy. For this reason PI monotherapy should not be used in unselected patient populations for maintaining virological suppression where standard ART is an acceptable alternative. There may be potential benefits of PI monotherapy, in terms of drug resistance, long-term drug toxicity and cost [15] but further data are required. The ongoing 'Protease Inhibitor monotherapy *vs*. Ongoing Triple therapy in the long-term management of HIV infection' (PIVOT) trial has been designed to address these issues [16]. The primary endpoint is drug resistance.

We recognize that PI monotherapy may well be an acceptable option in some specific patient populations but there are few data to provide recommendations. Clinicians might consider PI monotherapy in patients who are unable to tolerate NRTIs due to toxicities or as a short-term measure to manage or bridge complex clinical scenarios (e.g. stopping certain NNRTI-containing regimens or managing toxicity overdose or acute illness). Where PI monotherapy is considered, DRV/r (dosed once or twice daily) or LPV/r (dosed twice daily) should be used. ATV/r monotherapy is not recommended as it has been associated with higher rates of virological failure [17,18]. PI monotherapy is not recommended in patients with active hepatitis B coinfection.

6.3.3.3 References

1 Arribas JR, Pulido F, Delgado R *et al*. Lopinavir/r as single drug therapy for maintenance of HIV-1 viral suppression. 48-week results of a randomised controlled open label proof of concept pilot clinical trial (OK study). *J Acquir Immune Defic Syndr* 2005; **40**: 280–287.

2 Pulido F, Arribas JR, Delgado R *et al*. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. *AIDS* 2008; **22**: F1–F9.

3 Arribas JR, Delgado R, Arranz A *et al*. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. *J Acquir Immune Defic Syndr* 2009; **51**: 147–152.

4 Arribas JR, Horban A, Gerstoft J *et al*. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS* 2010; **24**: 223–230.

5 Clumeck N, Rieger A, Banhegyi D *et al*. 96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline. *J Antimicrob Chemother* 2011; **66**: 1878–1885.

6 Winston A, Fätkenheuer G, Arribas J *et al*. Neuropsychiatric adverse events with ritonavir-boosted darunavir monotherapy in HIV-infected individuals: a randomised prospective study. *HIV Clin Trials* 2010; **11**: 163–169.

7 Cahn P, Montaner J, Junod P *et al*. Pilot, randomized study assessing safety, tolerability and efficacy of simplified LPV/r maintenance therapy in HIV patients on the 1 PI-based regimen. *PLoS ONE* 2011; **6**: e23726.

8 Katlama C, Valantin MA, Algarte-Genin M *et al*. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS* 2010; **24**: 2365–2374.

9 Meynard JL, Bouteloup V, Landman R *et al*. Lopinavir/ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the KALESOLO trial. *J Antimicrob Chemother* 2010; **65**: 2436–2444.

10 Nunes EP, Santini de Oliveira M, Merçon M *et al*. Monotherapy with lopinavir/ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (KalMo study). *HIV Clin Trials* 2009; **10**: 368–374.

11 Gutmann C, Cusini A, Günthard HF *et al*. Randomized controlled study demonstrating failure of LPV/r

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monotherapy in HIV: the role of compartment and CD4-nadir. *AIDS* 2010; **24**: 2347–2354.
12 Hasson H, Galli L, Gallotta G *et al.* HAART simplification with lopinavir/ritonavir monotherapy in HIV/HCV coinfected patients starting anti-HCV treatment: final results of a randomised, proof-of-principle clinical trial (KAMON 2 Study). *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Rome, Italy. July 2011 [Abstract: CDB358].
13 Waters L, Jackson A, Singh K *et al.* The impact of continued HAART versus lopinavir/ritonavir monotherapy (mLPV/r) on body fat and bone mineral density (BMD) as measured by DEXA: 48 week results of a randomised study. *XVII International AIDS Conference*. Mexico City, Mexico. August 2008 [Abstract CDB0193].
14 Mathis S, Khanlari B, Pulido F *et al.* Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. *PLoS ONE* 2011; **6**: e22003.
15 Gazzard B, Hill A, Anceau A. Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices. *Appl Health Econ Health Policy* 2011; **9**: 217–223.
16 United Kingdom Medical Research Council. A randomised controlled trial of a strategy of switching to boosted PI monotherapy versus continuing combination ART for the long-term management of HIV-1 infected patients who have achieved sustained virological suppression on HAART (PIVOT). Available at http://clinicaltrials.gov/ct2/show/NCT01230580 (accessed May 2012).
17 Karlström O, Josephson F, Sönnerborg A. Early virological rebound in a pilot trial of ritonavir boosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr* 2007; **44**: 417–422.
18 Vernazza P, Daneel S. Schiffer V *et al.* Risk of CNS compartment failure on PI monotherapy (ATARITMO study). *XVI International AIDS Conference*. Toronto, Canada. August 2006 [Abstract WEPE0073].

6.4 Stopping therapy

6.4.1 Recommendation

- We recommend against treatment interruption or intermittent therapy in patients stable on a virally suppressive ART regimen (1A).

6.4.1.1 Auditable measure

Proportion of patients with a CD4 cell count <350 cells/μL not on ART.

6.4.2 Rationale

Several RCTs have investigated the efficacy of CD4 cell count-guided intermittent therapy as a potential strategy to reduce long-term risk of drug toxicity and drug resistance [1–4]. In the largest of these, patients were randomly allocated to either CD4 cell count-guided intermittent therapy (stopping ART once CD4 cell count >350 cells/μL, restarting when CD4 cell count falls to 250 cells/μL) compared with a continuous ART [1]. The trial showed intermittent therapy was associated with a significantly higher rate of opportunistic disease and all-cause mortality and a higher rate of major cardiovascular, renal or hepatic disease. The effect was seen at all CD4 cell count levels. The study showed for the first time that continuous ART with virological suppression is associated with a reduction in the risk of non-AIDS co-morbidities and all-cause mortality as well as HIV disease progression. For this reason, treatment interruption or intermittent therapy is not recommended.

Once ART has been started in a patient with HIV infection, it should be continued. Temporary interruptions of 1–2 days can usually be managed and are unlikely to be associated with adverse outcomes. Longer interruptions of ART should only be considered in exceptional circumstances. These may include:

- After pregnancy, in women who have taken ART during pregnancy to prevent mother-to-child transmission, but do not otherwise require treatment.
- After early initiation of ART (CD4 cell counts >500 cells/μL) (e.g. when started to reduce infectiousness).
- Severe drug toxicity (e.g. hepatotoxicity).
- Severe psychological distress.

Guidance on pharmacokinetic considerations when stopping ART is contained in Section 6.2.3 Stopping therapy: pharmacological considerations.

6.4.3 References

1 El-Sadr WM, Lundgren JD, Neaton JD *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355**: 2283–2296.
2 Danel C, Moh R, Minga A *et al.* CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet* 2006; **367**: 1981–1989.
3 Cardiello PG, Hassink E, Ananworanich J *et al.* A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis* 2005; **40**: 594–600.
4 Ananworanich J, Gayet-Ageron A, Le Braz M *et al.* CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. *Lancet* 2006; **368**: 459–465.

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7.0 Managing virological failure

7.1 Introduction

For detailed guidance on HIV VL, resistance and genotropism testing, the reader should consult *BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011* [1] (http://www.bhiva.org/Monitoring.aspx).

The following recommendations concern the management of patients experiencing virological failure on ART. Patient populations at the time of virological failure will include those with no or limited HIV drug resistance through to those with three-class failure and either no or limited treatment options. For the assessment and evaluation of evidence, priority questions were agreed and outcomes were ranked (critical, important and not important) by members of the Writing Group. For patients with no or limited HIV drug resistance the following were ranked as critical outcomes: viral suppression <50 copies/mL at 48 weeks, development of resistance, discontinuation rates for clinical and laboratory adverse events. For patients with three-class failure/few therapeutic options: clinical progression, median CD4 cell count change at 48 weeks, and development of new resistance. Treatments were compared where data were available and differences in outcomes assessed. Details of the search strategy and literature review are contained in Appendix 2.

In the UK, the virological failure rate on current first-line regimens in 2008–2009 was approximately 10% at 1 year [2]. The options for switch depend on the most recent and past ARV treatments as well as current and archived resistance results. As genotypic testing in ARV-naïve patients is now performed routinely and is recommended practice, detection of resistance at virological failure is rarely a result of transmitted drug resistance and failure to adapt first-line treatment [3,4].

The general principles for the management of patients experiencing virological failure are outlined in Boxes 7.1 and 7.2 as GPPs. Details of typical patterns of HIV drug resistance found in patients with a history of or presenting with virological failure are outlined in Box 7.3. For guidance on HIV VL, drug resistance and tropism testing, the reader should consult the BHIVA routine investigation and monitoring guidelines [1].

7.1.1 Summary of auditable measures

- Record in patient's notes of resistance result at ART initiation (if available) and at first VL >400 copies/mL and/or before switch.
- Record in patient's notes of adherence assessment and tolerability/toxicity to ART in patients experiencing virological failure or repeated viral blips.
- Number of patients experiencing virological failure on current ART regimen.
- Proportion of patients experiencing virological failure switched to a new suppressive regimen within 6 months.
- Proportion of patients on ART with previously documented HIV drug resistance with VL <50 copies/mL.
- Record of patients with three-class virological failure with or without three-class resistance referred/discussed in multidisciplinary team with expert advice.

7.2 Blips, low-level viraemia and virological failure

7.2.1 Recommendations

In patients on ART:

- A single VL 50–400 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern (GPP).
- We recommend a single VL >400 copies/mL is investigated further, as it is indicative of virological failure (1C).
- We recommend in the context of repeated viral blips, resistance testing is attempted (1D).

7.2.2 Rationale

7.2.2.1 Blips

Optimal HIV control is ordinarily reflected by complete viral suppression with an undetectable VL. A virological blip is variably defined but for the purposes of these guidelines the definition that has been adopted is a detectable VL <400 copies/mL, which is preceded and followed by an undetectable result without any change of

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therapy. Blips are frequent and represent random variation around a mean undetectable VL [5–7]. Many patients have at least one at some time [8] when they are not predictive of virological failure or associated with emergent resistance in most studies [5,9,10]. VL assay variation and laboratory processing artefacts account for many blips (i.e. no 'true' increase in viral replication), which partly explains why blips do not appear to compromise long-term outcomes [9,11–13]. However, those with sustained low-level increases in VL run a higher risk of virological failure. Most blips are low level [median magnitude 79 copies/mL in one study (range 51–201)] and short lived [median 2.5 days (range 2–11.5)] [7]. In a retrospective study, 28.6% of patients, experienced VL increases from 50 to 500 copies/mL over 8 years; 71% of these were blips [8].

Review and reiteration of the importance of full adherence, as well as looking for any tolerability/toxicity issues, DDIs/food interactions, and archived resistance should take place. However, blips do not appear to be related to intercurrent illness, vaccination, baseline CD4 cell count/VL, duration of preceding suppression or level of adherence [7,14,15]. Therefore, it is the recommendation of the Writing Group that a VL result of 50–400 copies/mL preceded and followed by an undetectable VL should not be a cause of clinical concern. In the context of repeated blips, it may then be useful to test for resistance [16,17].

7.2.2.2 Low-level viraemia

Low-level viraemia (LLV) is defined as a repeatedly detectable but low level of viraemia over a sustained period of time. For the purposes of these guidelines, <400 copies/mL is used although it is recognized that some patients have VLs up to 1000 copies/mL without development of resistance and with therapeutic drug levels. LLV is observed in up to 8% of individuals [18] and is associated with an increased risk of virological rebound (>400 copies/mL) [6,19]. The likelihood of resuppression after LLV is greater for lower magnitudes of viraemia: 41% after two consecutive VLs >50 copies/mL compared with 12% after two VLs >200 copies/mL [20]. LLV is associated with resistance (37% in one study [21]) that may be associated with LLV magnitude; in one analysis, maximum VL was higher in those with who developed resistance (368 *vs*. 143 copies/mL; P=0.008). LLV is also associated with immune activation [10]. Low-level antigenic exposure differentially affects T-cell activation and HIV-specific T-cell response. In cohort studies [19] and clinical trials [21], patients on PI/r-based ART are more likely to experience detectable viraemia than those on NNRTI. In the absence of clear data, the Writing Group believes LLV on a low-genetic barrier regimen warrants prompt regimen change. This is especially true where ART combination without a boosted PI is being used [22,23]. Further evaluation should follow as for that set out in Box 7.1.

7.2.2.3 Virological failure

Failure is defined as 'failure to achieve a VL <50 copies/mL 6 months after commencing ART or following viral suppression to <50 copies/mL a VL rebound to >400 copies/mL on two consecutive occasions'. In the UK, approximately 18% of those achieving an undetectable VL in 2008–2009 experienced VL rebound. In the same database, among drug-experienced patients the overall prevalence of resistance was 44% in 2007 [1]]. Confirmation of virological failure at any stage should lead to the practice set out in Box 7.1.

Box 7.1 Best practice for the management of patients with virological failure

- Factors affecting adherence and drug exposure, including tolerability/toxicity issues, DDIs/food interactions, ARV potency, significant renal/liver disease and mental health/drug dependency problems are evaluated.
- Resistance testing is performed while on failing therapy or within 4 weeks of discontinuation.
- Past ART and resistance tests are reviewed for archived mutations.
- Tropism testing is performed if MVC is being considered.
- Intensification with an additional active ARV is not recommended.
- Once virological failure is confirmed and a resistance result available, the regimen is changed as soon as possible to avoid accumulation of resistance mutations.

The choice of the new ART regimen will primarily depend on the results of resistance testing and the patient's preference. Additional considerations include the results of tropism and HLA-B*57 testing, DDIs/food interactions, co-morbidities and future therapy options. The goal of the new combination is to re-establish a VL <50 copies/mL.

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Box 7.2 Best practice for the management of patients with three-class virological failure

- In patients with ongoing viraemia and with few options to construct a fully suppressive regimen, referral for specialist advice and/or discussion in a multidisciplinary team 'virtual' clinic.
- Include at least two and preferably three fully active agents with at least one active PI/r (e.g. DRV/r) and one agent with a novel mechanism of action (CCR5 antagonist/integrase or fusion inhibitor).
- Treatment interruption is not recommended.

Box 7.3 Typical resistance patterns on virological failure

- No resistance (WT virus).
- 3TC/FTC resistance (M184V/I) following any first-line therapy, including TDF/FTC or ABC/3TC.
- NNRTI resistance (e.g. K103N or Y181C/I/V) and/or 3TC/FTC resistance (following first-line therapy with NNRTI-based regimen, including TDF/FTC or ABC/3TC).
- INI resistance (e.g. Q148 or N155H) and/or 3TC/FTC resistance (following first-line therapy with RAL-based regimen, including TDF/FTC or ABC/3TC).
- Extended RT resistance (e.g. K65R/L74V or thymidine analogue mutations) (following suboptimal regimens/patients with more extensive drug history associated with virological failure).
- Three-class resistance (indicating NRTI, NNRTI and PI) (following multiple failing regimens).
- Limited or no therapeutic options (following multiple failing regimens, including the newer drugs with novel actions).

7.3 Patients with no or limited drug resistance

7.3.1 Recommendations

- We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and without emergent resistance mutations at failure switch to a PI/r-based combination ART regimen (1C).
- We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure switch to a new PI/r-based regimen with the addition of at least one, preferably two, active drugs (1C).
- We recommend patients experiencing virological failure on first-line PI/r plus two-NRTI-based regimens, with major protease mutations, switch to a new active PI/r with the addition of at least one, preferably two, active agents of which one has a novel mechanism of action (1C).
- We recommend against switching a PI/r to an INI or NNRTI as the third agent in patients with historical or existing RT mutations associated with NRTI resistance or past virological failure on NRTIs (1B).

7.3.2 Rationale

7.3.2.1 First-line treatment failure with no resistance

A significant minority of patients have WT virus despite failing on therapy [24–30]. Failure here is usually attributable to poor treatment adherence with drug levels that are both insufficient to maintain VL suppression and inadequate to select out viral mutations associated with drug resistance detectable on standard tests. Factors affecting adherence such as tolerability/toxicity issues, regimen convenience, drug–food interactions and mental health/drug dependency problems should be fully evaluated and where possible corrected before initiation of the new regimen. Additional adherence support should be considered and careful discussion with the patient take place. TDM may be of benefit in individual patients in confirming low/absent therapeutic drug levels and enabling discussion with the patient.

A priority question the Writing Group addressed was whether patients failing an NNRTI-based ART without detectable resistance should receive a PI/r-based regimen.

The absence of detectable resistance mutations does not exclude the presence of mutations in minor virus populations, especially with the NNRTIs [9–11]. This may lead to subsequent failure if the same first-line drugs, or drugs in the same class, are prescribed [31,32]. Testing for minority resistance is a specialist test and expert interpretation by a virologist is essential. There is no indication for routine minority species testing in patients failing with WT virus on therapy.

The recommendation of the Writing Group is that, following NNRTI/two NRTIs virological failure when no resistance mutations exist, a switch to a PI/r-based regimen should lead to virological suppression and is unlikely to lead to emergent resistance. The decision as to whether to restart the same NNRTI-based combination or switch to another NNRTI, RAL or MVC (where CCR5 tropism has been confirmed) has to be individualized to the patient, their history of virological failure, and to whether further switches in the combination are occurring.

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No supportive data exist for management of virological failure when this has developed on first-line therapy with RAL/two NRTIs but the general principles set out for NNRTI-based failure would still apply. However, the high genetic barrier of PI/r reduces the risk of low-level resistance developing.

7.3.2.2 First-line treatment failure with non-nucleoside reverse transcriptase inhibitor resistance

Up to two-thirds of virologically failing patients harbour viruses with NNRTI and half NRTI mutations at 48 weeks [27–30,33]: with increasing time, there will be accumulation of resistance mutations that may compromise second-line regimens [34]. Although potential options for second-line therapy after failure on an NNRTI-containing regimen include RAL, ETV and MVC as the third agent (RPV is not licensed for this indication), evidence supports the use of a PI/r. A switch to any PI/r-based regimen should lead to virological suppression and is unlikely to lead to further emergent resistance and should be considered whenever possible. Where NRTI resistance has been documented or likely, these should be replaced and new active NRTIs or other ARVs should be incorporated. There are no direct comparisons of the boosted PIs in second-line treatment after first-line failure on an NNRTI-based regimen and choice would be individualized to the patient. Sequencing from an EFV or NVP-based regimen to ETV is not recommended [35] although it remains an option when switched as part of a new combination when only K103N is present. Switching to RAL or MVC with two active NRTIs is an option but is also not recommended in a patient with historical or existing RT mutations/previous NRTI virological failure [36].

7.3.2.3 First-line treatment failure on a ritonavir-boosted protease inhibitor-based two nucleoside reverse transcriptase inhibitor regimen with or without protease inhibitor resistance

Less than 1% of patients harbour viruses with primary PI mutations and 10–20% NRTI mutations at 48 weeks, with 75% having WT virus [24,27–29,37,38]. There are currently limited data regarding the efficacy of switching to another PI/r, NNRTI, MVC or RAL-based regimen and again the decision is individualized to the patient. However, switching to RAL, MVC or NNRTI in a patient with historical or existing RT mutations is not recommended because of an increased risk of virological failure and further emergence of resistance [36]. By contrast, because of the high genetic barrier of PI/r, sequencing to a regimen that includes a new PI/r is unlikely to lead to further emergent resistance and is recommended. Where PI/r mutations exist, DRV/r is the preferred agent unless resistance is likely.

7.3.2.4 First-line treatment failure with integrase inhibitor-based resistance

Up to one-half of patients harbour viruses with primary integrase mutations and 25% NRTI mutations at 48 weeks: approximately half have WT virus [26,33,37,39]. Again, there are no data supporting a switch to PI/r, NNRTI or MVC but sequencing to a new regimen that includes PI/r is unlikely to lead to further emergent resistance and is recommended. Switching to NNRTI or MVC with two active NRTIs is an option but is also not recommended in a patient with historical or existing RT mutations/previous NRTI virological failure. Patients experiencing virological failure on RAL should switch to a new regimen as soon as possible to reduce the risk of accumulating resistance mutations that may affect susceptibility to newer INIs such as dolutegravir.

7.4 Patients with triple-class (non-nucleoside reverse transcriptase inhibitor, nucleoside reverse transcriptase inhibitor, protease inhibitor) virological failure with or without triple-class resistance

7.4.1 Recommendations

- We recommend patients with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed/referred for expert advice (or through virtual clinic referral) (GPP).
- We recommend patients with triple-class resistance switch to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as DRV/r or TPV/r and one agent with a novel mechanism (CCR5 receptor antagonist or integrase/fusion inhibitor) with ETV an option based on viral susceptibility (1C).

7.4.2 Rationale

Risk of development of triple-class virological failure is relatively low at about 9% at 9 years from start of ART [40]. Until the last few years, limited treatment options have been available for people with HIV who have had virological failure with the three original classes of HIV ARV drugs (triple-class virological failure) of whom many have developed triple-class resistance. Most of these patients have received suboptimal ARV treatment, often from the pre-HAART era, or have adhered poorly to multiple regimens and have accumulated resistance. However, with the introduction of several new agents active

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against resistant virus, many of which have novel sites of action, the potential for virological control akin to that achieved with naïve patients has now become a probability [41,42].

Consequent to more active ARVs and improved strategies of management, there has been substantial improvement in the proportion of people who had virological response after triple-class virological failure between 2000 and 2009 [43]. However, despite improvements in treatments, VLs cannot be suppressed for some people. In most patients, this is a result of poor adherence but some patients do have extended drug resistance and minimal treatment options and achieving viral suppression is not possible.

The drugs now most commonly used in triple-class failure are boosted PIs, DRV/r and TPV/r, the INIs RAL and elvitegravir (ELV), the CCR5 chemokine receptor antagonist MVC, the NNRTI ETV, and the fusion inhibitor enfuvirtide. The available data for DRV/r, TPV/r, RAL, ELV, ETV and enfuvirtide show that they are most effective when used with other active drugs to which the virus is susceptible based on resistance testing and antiviral experience [44–52]. When used as the only effective agent, the likelihood of achieving virological suppression is significantly reduced and the development of emergent resistance to the drug greater, and a future opportunity for constructing an effective regimen is often lost.

A priority question the Writing Group addressed was whether two or three fully active drugs should be included in the new regimen. In a meta-analysis of 10 trials of patient with triple-class virological failure and virological resistance where the study drug was added to optimized background therapy and compared with placebo, associations were demonstrated with increased virological suppression (pooled OR 2.97) and larger CD4 cell count increases for the active agent [53]. Optimized background therapy genotypic sensitivity scores (GSSs) were also associated with larger differences in virological suppression ($P < 0.001$ for GSS = 0, ≤ 1 and ≤ 2) and CD4 cell count increase (GSS = 0, $P < 0.001$; GSS $\leq$ 1, $P < 0.002$; GSS $\leq$ 2, $P = 0.015$) between the two groups. In a further non-inferiority study, ELV was found to be non-inferior to RAL when accompanied by a boosted PI and a third agent [45].

This supports the use of at least two and possibly three of these agents in the new regimen and with this strategy, the goal of an undetectable VL is now achievable even in most patients with multi-regimen failure. A priority question addressed in this group was whether regimens with at least three fully active drugs should include NRTIs. The recommendation from the Writing Group is that in constructing an optimized background, continuing/commencing NRTIs may contribute partial ARV activity to a regimen, despite drug resistance [55,56].

For those drugs with a novel mode of action (integrase and fusion inhibitors, and CCR5 antagonists), the absence of previous exposure indicates susceptibility although MVC is only active against patients harbouring CCR5 tropic virus. For DRV, TPV and ETV, the number and type of mutations inform the degree to which these drugs are active [56–58]. The potential for DDIs is also important. ETV can be paired with DRV/r (but not TPV/r) and MVC dosing is variable depending on the other drugs in the new regimen; however, RAL and enfuvirtide require no alteration.

Some patients can have a successfully suppressive fully active three-drug regimen constructed without a PI/r [59]. Nevertheless, where feasible, a PI/r such as DRV/r should be included because of its protective effect on emergent resistance to the other drugs in the regimen although this can be given DRV/r 800 mg/100 mg once daily in treatment-experienced patients without DRV resistance associated mutations [60]. Enfuvirtide is an option in some patients despite the inconvenience of subcutaneous injection and injection site reactions. With the availability of the newer agents, dual PI/r are not recommended [61].

The same principles regarding reviewing adherence, tolerability/toxicity issues, DDIs/food interactions, and mental health/drug dependency problems apply. Additional adherence support is important in these patients as the reason triple-class failure has occurred often relates to past poor adherence. Additionally, the pill burden is increased and careful discussion with the patient should take place.

7.5 Patients with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

7.5.1 Recommendations

- We recommend accessing newer agents through research trials, expanded access and named patient programmes (GPP).
- We suggest continuing/commencing NRTIs as this may contribute partial ARV activity to a regimen, despite drug resistance (2C).
- We recommend the use of 3TC or FTC to maintain a mutation at codon position 184 of the RT gene (1B).
- We recommend against discontinuing or interrupting ART (1B).
- We recommend against adding a single, fully active ARV because of the risk of further resistance (1D).

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- We recommend against the use of MVC to increase the CD4 cell count in the absence of CCR5 tropic virus (1C).

7.5.2 Rationale

This situation usually occurs following attempts in patients with triple-class failure to achieve virological suppression with the newer agents and often indicates adherence issues have not been addressed successfully or sequential addition of the newer agents has occurred without incomplete viral suppression and selection of resistance to the new drug.

There is evidence from cohort studies that continuing therapy, even in the presence of viraemia and the absence of CD4 T-cell count increases, reduces the risk of disease progression [62,63] whereas interruption may lead to a rapid fall in CD4 cell count and a rise in VL [64,65]. Other studies suggest continued immunological and clinical benefits if the HIV RNA level is maintained <10 000–20 000 copies/mL [66]. Continuing or commencing NRTIs, even in the presence of known resistance may contribute partial ARV activity [54,55]. Hence, if the CD4 cell count is well maintained (>200 cells/μL), it may be better to continue the failing regimen and not change treatment until investigational agents are available that can be put together with drugs, which may have only partial activity at best, to increase the likelihood of constructing virologically suppressive and durable regimen options.

In general, adding a single, fully active ARV to a failing regimen is not recommended because of the risk of rapid development of resistance. However, in patients with a high likelihood of clinical progression (e.g. CD4 cell count <100 cells/mL) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits [67]. Potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations and patients should maintain that regimen for the shortest period possible [68,69].

Where feasible, patients should be given the opportunity to enrol in research studies or expanded access programmes evaluating investigational new drugs. Some drugs are likely to be available in the near future that might be sequenced in the same class (e.g. dolutegravir) although others with novel sites of action (e.g. maturation inhibitors, CD4 receptor antagonists, etc.) are still in earlier phases of development and some years off randomized trials. Drugs developed for, and used in, other settings such as pegylated interferon that have been incidentally demonstrated to decrease VL should not be used without discussion with an experienced HIV physician as data are either too limited or contradictory.

Several studies and an early meta-analysis suggested that CCR5 receptor antagonists were associated with significant gains in CD4 cell counts even in the presence of C-X-C chemokine receptor type 4 tropic virus. However, a more recent meta-analysis refuted this finding (P=0.22) when comparing with other new drugs [53].

A priority question that the Writing Group addressed was whether 3TC/FTC should be used in maintaining an RT mutation at codon 184 in patients with limited or no therapeutic options.

Although the M184V mutation is associated with resistance to 3TC/FTC, the mutation has a broad influence on the RT enzyme. *In vitro* studies have shown that M184V-possessing enzymes have lower processivity and higher fidelity and replicate more slowly than WT enzymes [70]. These observations have led to the hypothesis that maintaining this mutation using 3TC/FTC would provide clinical benefit through the replication deficit provided by the M184V mutation combined with the residual antiviral activity of 3TC/FTC [71,72]. It has been shown that patients harbouring M184V due to 3TC failure who continue on 3TC monotherapy maintain lower VLs than at baseline and rarely develop new RT or protease mutations [73]. Moreover, ceasing 3TC monotherapy has been demonstrated to result in replication capacity recovery and a reduction in CD4/CD8 ratio driven by the de-selection of the M184V mutation [74]. This strategy is supported by the E-184 study which was a small but randomized, open-label study of 3TC monotherapy *vs*. no therapy in patients failing ART [75]. Monotherapy was associated with significant smaller increases in VL, smaller declines in CD4 cell counts, and no selection of additional RT mutations.

Finally, the presence of M184V mutation enhances *in vitro* susceptibility to TDF and this translated into a significant HIV RNA response in clinical trials of TDF intensification [76,77].

7.6 References

1 Asboe D, Aitken C, Boffito M *et al*. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012; **13**: 1–44. Available at http://www.bhiva.org/PublishedandApproved.aspx (accessed April 2012).

2 Pillay D, Dunn D. UK HIV Drug resistance database. Annual Report 2008/09. Available at http://www.ctu.mrc.ac.uk/pdf/HIV_Res_Report09.pdf (accessed June 2012).

3 Wittkop L, Günthard HF, de Wolf F *et al*. Effect of transmitted drug resistance on virological and

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immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. *Lancet Infect Dis* 2011; **11**: 363–371.

4 Kuritzkes DR, Lalama CM, Ribaudo HJ *et al.* Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis* 2008; **197**: 867–870.

5 Havlir D, Bassett R, Levitan D *et al.* Prevalence and predictive value of intermittent viremia with combination HIV therapy. *JAMA* 2001; **286**: 171–179.

6 Greub G, Cozzi-Lepri A, Ledergerber B *et al.* Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy. *AIDS* 2002; **16**: 1967–1969.

7 Nettles RE, Kieffer TL. Update on HIV-1 viral load blips. *Curr Opin HIV AIDS* 2006; **1**: 157–161.

8 Garcia-Gasco P, Maida I, Blanco F *et al.* Episodes of low level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. *J Antimicrob Chemother* 2008; **61**: 699–704.

9 Nettles RE, Kieffer TL, Kwon P *et al.* Intermittent HIV-1 viremia (Blips) and drug resistance in patients. *JAMA* 2005; **293**: 817–829.

10 Karlsson A, Younger S, Martin J *et al.* Immunologic and virologic evolution during periods of intermittent and persistent low-level viraemia. *AIDS* 2004; **18**: 891–989.

11 Roche Diagnostics GmbH, Mannheim, Germany. COBAS Amplicor HIV-1 MONITOR Test, version 1.5. June 2007, Package Insert. Available at http://www.fda.gov/Cber/sba/hiv1roc122002S.htm (accessed September 2008).

12 Lima V, Harrigan R, Montaner J. Increased reporting of detectable plasma HIV-1 RNA levels at the critical threshold of 50 copies per milliliter with the Taqman assay in comparison to the Amplicor assay. *J Acquir Immune Defic Syndr* 2009; **51**: 3–6.

13 Stosor V, Palella FJ Jr, Berzins B *et al.* Transient viremia in HIV-infected patients and use of plasma preparation tubes. *Clin Infect Dis* 2005; **41**: 1671–1674.

14 Miller LG, Golin CE, Liu H *et al.* No evidence of an association between transient HIV viremia ('blips') and lower adherence to the antiretroviral medication regimen. *J Infect Dis* 2004; **189**: 1487–1496.

15 Di Mascio M, Markowitz M, Louie M *et al.* Dynamics of intermittent viremia during highly active antiretroviral therapy in patients who initiate therapy during chronic versus acute and early human immunodeficiency virus type 1 infection. *J Virol* 2004; **78**: 10566–10573.

16 Pozniak A, Gupta RK, Pillay D, Arrivas J, Hill A. Causes and consequences of incomplete HIV RNA suppression in clinical trials. *HIV Clin Trials* 2009; **10**: 289–298.

17 Easterbrook PJ, Ives N, Waters A *et al.* The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to <400 copies/ml. *AIDS* 2002; **16**: 1521–1527.

18 Cohen C. Low-level viremia in HIV-1 infection: consequences and implications for switching to a new regimen. *HIV Clin Trials* 2009; **10**: 116–124.

19 Geretti AM, Smith C, Haberl L *et al.* Determinants of virological failure after successful virological suppression in first-line highly active antiretroviral therapy. *Antivir Ther* 2008; **13**: 927–936.

20 Staszewski S, Sabin C, Dauer B, Lepri A, Phillips A. Definition of loss of virological response in trials of antiretroviral drugs. *AIDS* 2003; **17**: 1997–1998.

21 Taiwo B, Gallien S, Aga E *et al.* Antiretroviral drug resistance in HIV-1 infected patients experiencing persistent low-level viraemia during first-line therapy. *J Infect Dis* 2011; **204**: 515–520.

22 Prosperi MCF, Mackie N, Di Giambenedetto S *et al.* Detection of drug resistance mutations at low plasma HIV-1 RNA load in a European multicentre cohort study. *J Antimicrob Chemother* 2011; **66**: 1886–1896.

23 Galliena S, Delaugerreb C, Charreau I *et al.* Emerging integrase inhibitor resistance mutations in raltegravir-treated HIV-1-infected patients with low-level viraemia. *AIDS* 2011; **25**: 665–669.

24 Ortiz R, DeJesus E, Khanlou H *et al.* Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS* 2008; **22**: 1389–1397.

25 Molina J-M, Andrade-Villanueva J, Echevarria J. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008; **372**: 646–655.

26 Lennox JL, DeJesus E, Lazzarin A *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374**: 796–806.

27 Riddler SA, Haubrich R, DiRienzo AG *et al.*; AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358**: 2095–2106.

28 Daar ES, Tierney C, Fischl MA *et al.* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1 a randomized trial. *Ann Intern Med* 2011; **154**: 445–456.

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29 Soriano V, Arasteh K, Migrone H *et al*. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther* 2011; **16**: 339–348.

30 Rimsky L, Vingerhoets J, Van Eygen V *et al*. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the Phase 3 ECHO and THRIVE Studies: 48-week analysis. *J Acquir Immune Defic Syndr* 2012; **59**: 39–46.

31 Li JZ, Paredes R, Ribaudo HJ *et al*. Low-frequency HIV-1 drug resistance mutations and risk of NNRTI-based antiretroviral treatment failure: a systematic review and pooled analysis. *JAMA* 2011; **305**: 1327–1335.

32 Paredes R, Lalama CM, Ribaudo HJ *et al*. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis* 2010; **201**: 662–671.

33 Sax P, DeJesus E, Mills A *et al*. Elvitegravir/cobicistat/emtricitabine/tenofovir (Quad) has non-inferior efficacy and favorable safety compared to efavirenz/emtricitabine/tenofovir in treatment-naive HIV-1+ subjects. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA. March 2012 [Abstract 101].

34 Cozzi-Lepri A, Paredes R, Phillips AN *et al*. The rate of accumulation of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in patients kept on a virologically failing regimen containing an NNRTI. *HIV Med* 2011; **12**: 1–11.

35 Ruxrungtham K, Pedro RJ, Latiff GH *et al*. Impact of reverse transcriptase resistance on the efficacy of TMC125 (etravirine) with two nucleoside reverse transcriptase inhibitors in protease inhibitor-naıve, nonnucleoside reverse transcriptase inhibitor-experienced patients: study TMC125-C227. *HIV Med* 2008; **9**: 883–896.

36 Eron JJ, Young B, Cooper DA *et al*. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 2010; **375**: 396–407.

37 Dejesus E, Rockstroh J, Henry K *et al*. Week 48 results of an ongoing global phase 3 study comparing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate with atazanavir/ritonavir-boosted plus emtricitabine/tenofovir disoproxil fumarate in treatment naive HIV-1+ subjects showing efficacy, safety, and pharmacokinetics. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA. March 2012 [Abstract 627].

38 Molina JM, Andrade-Villanueva J, Echevarria J *et al*. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr* 2010; **53**: 323–332.

39 Eron JJ Jr, Rockstroh JK, Reynes J *et al*. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. *Lancet Infect Dis* 2011; **11**: 907–915.

40 Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years. *Arch Intern Med* 2010; **170**: 410–419.

41 Yazdanpanah Y, Fagard C, Descamps D *et al*. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV: results of the ANRS 139 TRIO Trial. *Clin Infect Dis* 2009; **49**: 1441–1449.

42 Wittkop L, Breilh D, Da Silva D *et al.*; ANRS CO3 Aquitaine Cohort. Virological and immunological response in HIV-1-infected patients with multiple treatment failures receiving raltegravir and optimized background therapy, ANRS CO3 Aquitaine Cohort. *J Antimicrob Chemother* 2009; **63**: 1251–1255.

43 The Pursuing Later Treatment Option II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Group. Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study. *Lancet Infect Dis* 2012; **12**: 119–127.

44 Hicks CB, Cahn P, Cooper DA *et al*. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet* 2006; **368**: 466–475.

45 Molina JM, Lamarca A, Andrade-Villanueva J *et al*. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet* 2012; **12**: 27–35.

46 Lalezari JP, Henry K, O'Hearn M *et al*. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; **348**: 2175–2185.

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47 Lazzarin A, Clotet B, Cooper D *et al*. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; **348**: 2186–2195.
48 Katlama C, Haubrich R, Lalezari J *et al*. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS* 2009; **23**: 2289–2300.
49 Gulick R, Lalezari J, Goodrich J *et al*. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; **359**: 1429–1441.
50 Grinsztejn B, Nguyen BY, Katlama C *et al*. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet* 2007; **369**: 1261–1269.
51 Clotet B, Bellos N, Molina J *et al*. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369**: 1169–1178.
52 Steigbigel R, Cooper D, Kumar P *et al*. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008; **359**: 339–354.
53 Pichenot M, Deuffic-Burban S, Cuzin L *et al*. Efficacy of new antiretroviral drugs in treatment experienced HIV-infected patients: a systematic review and meta-analysis of recent randomized controlled trials. *HIV Med* 2011; **12**: 1–8.
54 Eron JJ Jr, Bartlett JA, Santana JL *et al*. Persistent antiretroviral activity of nucleoside analogues after prolonged zidovudine and lamivudine therapy as demonstrated by rapid loss of activity after discontinuation. *J Acquir Immune Defic Syndr* 2004; **37**: 1581–1583.
55 Scherrer AU, von Wyl V, Boni J *et al*. Viral suppression rates in salvage treatment with raltegravir improved with the administration of genotypic partially active or inactive nucleoside/tide reverse transcriptase inhibitors. *J Acquir Immune Defic Syndr* 2011; **57**: 24–31.
56 Vingerhoets J, Peeters M, Azijn H *et al*. An update of the list of NNRTI mutations associated with decreased virologic response to etravirine (ETR): multivariate analyses on the pooled DUET -1 and DUET 2 clinical trial data. X*VII International Drug Resistance Workshop*. Sitges, Spain, June 2008 [Abstract 24].
57 Lambert-Niclot S, Flandre P, Canestri A *et al*. Factors associated with the selection of mutations conferring resistance to protease inhibitors (PIs) in PI-experienced patients displaying treatment failure on darunavir. *Antimicrob Agents Chemother* 2008; **52**: 491–496.
58 Parkin N, Vhappey C. Protease mutations associated with higher or lower than expected tipranavir (TPV) susceptibility based up on the TPV mutation score. *13th Conference on Retroviruses and Opportunistic Infections*. Denver, CO. February 2006 [Abstract 637].
59 Nozza S, Galli L, Visco F *et al*. Raltegravir, maraviroc, etravirine: an effective protease inhibitor and nucleoside reverse transcriptase inhibitor-sparing regimen for salvage therapy in HIV-infected patients with triple class experience. *AIDS* 2010; **24**: 924–928.
60 Cahn P, Fourie J, Grinsztejn B *et al*. Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. *AIDS* 2011; **25**: 929–939.
61 Landman R, Capitant C, Descamps D *et al*.; ANRS127 Study Group. Efficacy and safety of ritonavir-boosted dual protease inhibitor therapy in antiretroviral-naive HIV-1-infected patients: the 2IP ANRS 127 study. *J Antimicrob Chemother* 2009; **64**: 118–125.
62 Miller V, Sabin C, Hertogs K *et al*. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS* 2000; **14**: 2857–2867.
63 Raffanti SP, Fusco JS, Sherrill BH *et al*. Effect of persistent moderate viremia on disease progression during HIV therapy. *J Acquir Immune Defic Syndr* 2004; **37**: 1147–1154.
64 Deeks SG, Wrin T, Liegler T *et al*. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med* 2001; **344**: 472–480.
65 Lawrence J, Mayers DL, Hullsiek KH *et al*. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med* 2003; **349**: 837–846.
66 Ledergerber B, Lundgren JD, Walker AS *et al*. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* 2004; **364**: 51–62.
67 Murray JS, Elashoff MR, Iacono-Connors LC *et al*. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 1999; **13**: 797–804.
68 Kristiansen TB, Pedersen AG, Eugen-Olsen J *et al*. Genetic evolution of HIV in patients remaining on a stable HAART regimen despite insufficient viral suppression. *Scand J Infect Dis* 2005; **37**: 890–901.
69 Hatano H, Hunt P, Weidler J *et al*. Rate of viral evolution and risk of losing future drug options in heavily pretreated, HIV-infected patients who continue to receive a stable, partially suppressive treatment regimen. *Clin Infect Dis* 2006; **43**: 1329–1336.
70 Petrella M, Wainberg MA. Might the M184V substitution in HIV-1 RT confer clinical benefits? *AIDS Rev* 2002; **4**: 224–232.

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71 Larder BA, Kemp SD, Harrigan PR. Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science* 1995; **269**: 696–699.
72 Quan Y, Brenner BG, Oliveira M, Wainberg MA. Lamivudine can exert a modest antiviral effect against human immunodeficiency virus type 1 containing the M184V mutation. *Antimicrob Agents Chemother* 2003; **47**: 747–754.
73 Eron JJ, Benoit SL, Jemsek J *et al.* Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimetre. North American Working Party. *N Engl J Med* 1995; **333**: 1662–1669.
74 Gianotti N, Tiberi S, Menzo S *et al.* HIV-1 replication capacity and genotypic changes in patients undergoing treatment interruption or lamivudine monotherapy. *J Med Virol* 2008; **80**: 201–208.
75 Castagna A, Danise A, Mezo S *et al.* Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomised pilot study (E-184V study). *AIDS* 2006; **20**: 795–803.
76 Wainbery MA, Miller MD, Quan Y *et al. In vitro* selection characterisation of HIV-1 with reduced susceptibility to PMPA. *Antivir Ther* 1999; **4**: 87–94.
77 Miller MD, Margot N, Lu B *et al.* Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. *J Infect Dis* 2004; **189**: 837–846.

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8.0 Antiretroviral therapy in specific populations

For some patient populations, specific considerations need to be taken into account when deciding when to start and the choice of ART. The following sections outline specific recommendations and the supporting rationale for defined patient populations. In parallel to guidelines on ART in adults, BHIVA also publishes guidelines on the management and treatment of specific patient populations, including coinfection with TB, coinfection with viral hepatitis B or C, and HIV-positive pregnant women. An outline of the recommendations for when to start and choice of ART, from the BHIVA guidelines for TB and viral hepatitis is summarized below. The reader should refer to the full, published guidelines for these patient populations for more detailed information and guidance on the BHIVA website (http://www.bhiva.org/publishedandapproved.aspx) and be aware that BHIVA clinical practice guidelines are periodically updated.

For these current guidelines, new guidance on when to start and choice of ART has been developed for HIV-related cancers, HIV-associated NC impairment, CKD, CVD and women. The guidance only considers specific issues concerning the initiation and choice of ART in these patient populations. Guidance on the management of pregnancy in HIV-positive women has not been included.

8.1 HIV with tuberculosis coinfection

This guidance provides a brief summary of the key statements and recommendations regarding prescribing ART in HIV-positive patients co-infected with TB. It is based on the *BHIVA guidelines for the treatment of TB/HIV coinfection 2011* [1], which should be consulted for further information. The full version of the guidelines is available on the BHIVA website (http://www.bhiva.org/TB-HIV2011.aspx).

8.1.1 When to start antiretroviral therapy

8.1.1.1 Recommendations

Timing of initiation of ART during TB therapy:

CD4 cell count (cells/μL)	When to start HAART	Grade
<100	As soon as practical within 2 weeks after starting TB therapy	1B
100–350	As soon as practical, but can wait until after completing 2 months TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities	1B
>350	At physician's discretion	1B

Auditable measure. Proportion of patients with TB and CD4 cell count <100 cells/μL started on ART within 2 weeks of starting TB therapy.

8.1.1.2 Rationale

Most patients with TB in the UK present with a low CD4 cell count, often <100 cells/μL. In such patients, ART improves survival, but can be complicated by IRD and drug toxicity. Data suggest that ART can be delayed until the first 2 months of TB therapy has been completed but at CD4 cell counts <50 cells/μL the short-term risk of developing further AIDS-defining events and death is high, and ART should be started as soon as practicable and within 2 weeks of initiation of TB therapy [2–5]. Starting ART early in severely immunosuppressed HIV-positive patients presenting with TB is associated with decreased mortality and a lowering of the rates of disease progression but rates of IRD are high.

Patients with HIV and a CD4 cell count >350 cells/μL have a low risk of HIV disease progression or death during the subsequent 6 months of TB treatment, depending on age and VL [6]. They should have their CD4 cell count monitored regularly and ART can be withheld during the short-course of TB treatment.

One study performed in HIV-associated TB meningitis in the developing world, where 90% of the patients were male, the majority drug users, many with advanced disease and the diagnosis being made clinically, showed no difference in mortality starting ART early or late [7].

8.1.2 What to start

8.1.2.1 Recommendations

We recommend EFV in combination with TDF and FTC as first-line ART in TB/HIV coinfection	1B
We recommend that when rifampicin is used with EFV in patients over 60 kg, the EFV dose is increased to 800 mg daily. Standard doses of EFV are recommended if the patient weighs <60 kg	1C
We recommend that rifampicin is not used with either NVP or PI/r	1C
We recommend that where effective ART necessitates the use of PI/r, that rifabutin is used instead of rifampicin	1C

Auditable measure. Proportion of patients with active TB on anti-TB therapy started on ART containing EFV, TDF and FTC.

8.1.2.2 Rationale

Preferred antiretroviral therapy. HIV-related TB should be treated with a regimen, including rifamycin for

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the full course of TB treatment, unless there is rifamycin resistance or intolerance. Rifamycins frequently interact with ARV medications and can lead to similar toxicities, notably rash and hepatitis. We recommend EFV as the preferred therapy for ART because of its confirmed potency when used in TB/HIV coinfection [8–10], and its efficacy in RCT. We recommend that EFV be given with TDF and FTC due to the availability of a once-daily co-formulation, a reduced risk of rash compared with NVP and improved efficacy at higher HIV VLs (commonly occurring in this setting). ABC-3TC is an alternative acceptable NRTI backbone in patients with lower HIV VLs and that are HLA-B*57:01 negative (see Section 5.3 Which NRTI backbone).

There is significant variability in the effect that rifampicin has on EFV concentrations because of liver enzyme induction, especially of CYP450 3A4 [8,11–13]. Subtherapeutic EFV concentrations may occur among patients who weigh more than 60 kg who are taking standard dose EFV together with rifampicin, and increasing the dose of EFV from 600 mg daily to 800 mg daily may be necessary; however, there is a risk of increasing adverse effects. A cohort study and a small RCT have shown that the standard adult EFV dose (600 mg daily) together with two NRTIs is well tolerated and was efficacious in achieving complete viral suppression among adults on concomitant rifampicin-based TB treatment, although the majority of patients were of low body weight [9,10,14].

In summary, we recommend that when EFV is used with rifampicin, and in patients over 60 kg, the EFV dose is increased to 800 mg daily. Standard doses of EFV are recommended if the patient weighs <60 kg. We suggest that TDM be performed at about the week of starting EFV if side effects occur and the dose adjusted accordingly.

Nevirapine. NVP taken with TB treatment is complicated by pharmacokinetic interactions and by overlapping toxicities, especially skin rash and hepatitis. One study showed that patients co-infected with HIV and TB who initiated NVP-based ART during TB treatment had a nearly twofold higher risk of having a detectable HIV VL after 6 months compared with those taking NVP who did not have TB. However, those patients who were established on NVP at the time of initiation of TB treatment did not have a higher risk of HIV virological failure [11]. Using a higher maintenance dose of NVP (300 mg bd) to overcome drug interactions has been associated with higher rates of hepatotoxicity [15]. In one randomized trial comparing NVP 200 mg twice daily at initiation with EFV 600 mg once daily among patients with TB and HIV and CD4 cell counts <250 cells/μL, non-inferiority of NVP was not demonstrated compared with EFV [16].

Protease inhibitors. When co-administered with rifampicin, concentrations of standard-dose PIs are decreased below therapeutic targets and cannot, therefore be recommended [17–19]. Changing the dosing of PI/r has resulted in unacceptable rates of hepatotoxicity [20–22].

Rifabutin has little effect on the concentrations of PI/r but rifabutin concentrations are increased when the drug is taken together with PIs. Current recommendations are to give rifabutin at a dose of 150 mg thrice weekly to adults taking PI/r. Some data suggest that 150 mg once daily can be given to reduce the theoretical risk of rifamycin resistance due to subtherapeutic rifabutin concentrations, but this strategy may be associated with increased side effects [23–30].

Other drugs. There are few clinical data to support the use of newer NNRTIs, INIs and CCR5 receptor antagonists with rifampicin or rifabutin. We recommend that physicians review pharmacokinetic and other data summarized in the current BHIVA guidelines for treatment of TB/HIV coinfection [1].

8.1.3 References

1 Pozniak AL, Coyne KM, Miller RF *et al.*; BHIVA Guidelines Subcommittee. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.

2 Dean GL, Edwards SG, Ives NJ *et al.* Treatment of tuberculosis in HIV-1 infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002; **16**: 75–83.

3 Abdoolkarim SS, Naidoo K, Grobler A *et al.* Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; **362**: 697–706.

4 Havlir DV, Kendall MA, Ive P *et al.* Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011; **365**: 1482–1491.

5 Blanc F-X, Sok T, Laureillard D *et al.* Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; **365**: 1471–1481.

6 Gazzard BG, on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med* 2008; **9**: 563–608.

7 Torok ME, Yen NT, Chau TT *et al.* Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis* 2011; **52**: 1374–1383.

8 Friedland G, Khoo S, Jack C *et al.* Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients

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treated for tuberculosis and HIV. *J Antimicrob Chemother* 2006; **58**: 1299–1302.
9 Manosuthi W, Kiertiburanakul S, Sungkanuparph S *et al.* Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS* 2006; **20**: 131–132.
10 Boulle A, Van Cutsem G, Cohen K *et al.* Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when co-administered with rifampicin-based antitubercular therapy. *JAMA* 2008; **300**: 530–539.
11 Lopez-Cortes LF, Ruiz-Valderas R, Viciana P *et al.* Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet* 2002; **41**: 681–690.
12 Manosuthi W, Sungkanuparph S, Thakkinstian A *et al.* Efavirenz levels and 24-week efficacy in HIV-infected patients with tuberculosis receiving highly active antiretroviral therapy and rifampicin. *AIDS* 2005; **19**: 1481–1486.
13 Ngaimisi E, Mugusi S, Minzi O *et al.* Effect of rifampicin and CYP2B6 genotype on long-term efavirenz auto induction and plasma exposure in HIV patients with or without tuberculosis. *Clin Pharmacother* 2011; **90**: 406–413.
14 Manosuthi W, Sungkanuparph S, Tantanathip P *et al.* A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N2R Study. *Clin Infect Dis* 2009; **48**: 1752–1759.
15 Avihingsanon A, Manosuthi W, Kantipong P *et al.* Pharmacokinetics and 48-week efficacy of nevirapine: 400 mg versus 600 mg per day in HIV-tuberculosis co-infection receiving rifampicin. *Antivir Ther* 2008; **13**: 529–536.
16 Bonnet M, Bhatt N, Baudin E *et al.* Results of the CARINEMO-ANRS 12146 randomized trial comparing the efficacy and safety of nevirapine versus efavirenz for treatment of HIV-TB co-infected patients in Mozambique. *6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention.* Rome, Italy. August 2011 [Abstract WELBX05].
17 Laporte C, Colbers E, Bertz R *et al.* Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother* 2004; **48**: 1553–1560.
18 Acosta EP, Kendall MA, Gerber JG *et al.* Effect of concomitantly administered rifampin on the pharmacokinetics and safety of atazanavir administered twice daily. *Antimicrob Agents Chemother* 2007; **51**: 3104–3110.
19 Ribera E, Azuaje C, Lopez RM *et al.* Pharmacokinetic interaction between rifampicin and the once-daily combination of saquinavir and low-dose ritonavir in HIV-infected patients with tuberculosis. *J Antimicrob Chemother* 2007; **59**: 690–697.
20 Schmitt C, Riek M, Winters K, Schutz M, Grange S. Unexpected hepatotoxicity of rifampin and saquinavir/ritonavir in healthy male volunteers. *Arch Drug Inf* 2009; **2**: 8–16.
21 Haas DW, Koletar SL, Laughlin L *et al.* Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr* 2009; **50**: 290–293.
22 Nijland HM, l'homme RF, Rongen GA *et al.* High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS* 2008; **22**: 931–935.
23 Narita M, Stambaugh JJ, Hollender ES *et al.* Use of rifabutin with protease inhibitors for human immunodeficiency virus-infected patients with tuberculosis. *Clin Infect Dis* 2000; **30**: 779–783.
24 Boulanger C, Hollender E, Farrell K *et al.* Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis* 2009; **49**: 1305–1311.
25 Jenny-Avital ER, Joseph K. Rifamycin-resistant Mycobacterium tuberculosis in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis* 2009; **48**: 1471–1474.
26 Naiker S, Conolly C, Weisner L *et al.* Pharmacokinetic evaluation of different rifabutin dosing strategies in African TB patients on lopinavir/ritonavir-based ART. *18th Conference on Retroviruses and Opportunistic Infections.* Boston, MA. February 2011 [Abstract 650].
27 Weiner M, Benator D, Burman W *et al.* Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005; **40**: 1481–1491.
28 Khachi H, O'Connell R, Ladenheim D, Orkin C. Pharmacokinetic interactions between rifabutin and lopinavir/ritonavir in HIV-infected patients with mycobacterial co-infection. *J Antimicrob Chemother* 2009; **64**: 871–873.
29 Tseng AL, Walmsley SL. Rifabutin-associated uveitis. *Ann Pharmacother* 1995; **29**: 1149–1155.
30 Cato A 3rd, Cavanaugh J, Shi H *et al.* The effect of multiple doses of ritonavir on the pharmacokinetics of rifabutin. *Clin Pharmacol Ther* 1998; **63**: 414–421.

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8.2 HIV and viral hepatitis coinfection

8.2.1 Introduction

The following guidance provides a brief summary of the key statements and recommendations regarding prescribing ART in patients with HIV/hepatitis B and C coinfection. It is based on the *BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013* [1], which should be consulted for further information and to the BHIVA web site for latest updates (http://www.bhiva.org/publishedandapproved.aspx).

Where viral hepatitis B or C chronic infection has been diagnosed, all individuals should be referred and subsequently managed by a clinician experienced in the management of both HIV and hepatitis or should be jointly managed by clinicians from HIV and hepatitis backgrounds. Those with end-stage liver disease (ESLD) should be managed in centres where potential complications can be dealt with and where a close link to a transplant unit exists.

8.2.1.1 Summary of when to start recommendations

CD4 cell count (cells/μL)	HBV requiring treatment*	HBV not requiring treatment	HCV with immediate plan to start HCV treatment*	HCV with no immediate plan to start HCV treatment
>500	Start ART (1C) (Include TDF and FTC)	Consider ART (2C) (Include TDF and FTC)	Consider ART before HCV treatment commenced (2C)	Consider ART (2D)
≤500	Start ART (1B) (Include TDF and FTC)	Start ART (1B) (Include TDF and FTC)	Start ART before HCV treatment commenced (1C) Discuss with HIV and viral hepatitis specialist	Start ART (1C)

*See *BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013* [1] for indications to treat hepatitis B and C

8.2.2 Hepatitis B

8.2.2.1 When to start *antiretroviral therapy*

Recommendations

- We recommend patients with HIV and hepatitis B virus coinfection who have a CD4 cell count <500 cells/μL are treated with fully suppressive ART inclusive of anti-HBV active antivirals (1B).
- We recommend patients with HIV and HBV coinfection who have a CD4 cell count ≥500 cells/μL and who have an HBV-DNA ≥2000 IU/mL and/or evidence of more than minimal fibrosis (Metavir ≥F2) are treated with fully suppressive ART inclusive of anti-HBV active antivirals (1C).

Auditable measure. Proportion of patients with a CD4 cell count ≥500 cells/μL and an HBV DNA ≥2000 IU/mL and/or evidence of more than minimal fibrosis commencing ART inclusive of anti-HBV antivirals.

Rationale. Because of the negative effect of immune depletion on HBV disease progression, the availability of single drugs with high level dual hepatitis B and HIV antiviral activity, and the increased risk of liver-related deaths in patients with CD4 cell counts ≥500 cells/μL, coinfected patients with active HBV disease (HBV viral load ≥2000 IU/mL or Metavir F2 or above) and those with CD4 cell counts below 500 cells/μL should start ART inclusive of anti-HBV active antivirals [2]. Patients with CD4 cell counts ≥500 cells/μL and HBV DNA of <2000 IU/mL, minimal or no evidence of liver inflammation or fibrosis, and a repeatedly normal ALT should be given the option to commence treatment or defer and be monitored not less than 6-monthly with HBV DNA and ALT and at least yearly for evidence of fibrosis.

For more information on the indications to start treatment for hepatitis B infection please refer to the *BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013* [1].

8.2.2.2 What to start

Recommendations

- We recommend TDF/FTC as part of a fully suppressive ART combination should be given to all patients where HBV treatment is deemed necessary (1C).
- We recommend neither 3TC nor FTC be used as the sole active drug against HBV in ART due to the rapid emergence of HBV resistant to these agents (1B).
- We recommend 3TC/FTC may be omitted from the ART regimen and tenofovir be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of 3TC/FTC-resistant HBV or HIV (1D).

Auditable measures. Proportion of patients with a CD4 cell count <500 cells/μL receiving TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen.

Proportion of patients receiving 3TC or FTC as the sole active drug against HBV in ART.

Rationale. TDF, FTC and 3TC are agents that have good antiviral activity against both HIV and hepatitis B. The efficacy of these drugs against hepatitis B has been assessed in randomized trials extending out to 5 years in mono-infected patients [3]. They are recommended agents in these guidelines for the treatment of HIV-1 infection.

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All hepatitis B coinfected individuals who start ART, should commence a regimen containing TDF and FTC. Hepatitis B treatment options for patients declining ART are discussed elsewhere [1].

If an individual becomes intolerant or is unable to commence a TDF-containing regimen, entecavir should be used if retaining activity. Because entecavir demonstrates modest anti-HIV activity and can select for HIV resistance, it should only be used in addition to a fully suppressive combination ART regimen. No individual coinfected with hepatitis B should receive a regimen containing 3TC or FTC monotherapy as its use may result in the selection of the YMDD mutation [4,5]. TDF resistance has not been clearly described and resistance is unlikely to provide an explanation for most cases of suboptimal responses to TDF. In combination with 3TC or FTC, it has been demonstrated to be effective at suppressing HBV DNA, inducing HBeAg seroconversion, and reducing the risk of HBV breakthrough [6].

Where there is primary non-response or partial response to HBV-active antivirals, or where there is virological breakthrough, assessment of drug adherence and HBV resistance testing should be undertaken. Coinfected individuals who need to start a new ART regimen for reasons such as ART virological failure should ensure that effective anti-hepatitis B therapy is continued in addition to their new ART regimen. Abrupt withdrawal of effective treatment may lead to a flare in hepatitis B replication with liver damage. This may be particularly severe in patients with cirrhosis.

8.2.3 Hepatitis C

8.2.3.1 When to start *antiretroviral therapy*

Recommendations

- We recommend all patients with HIV and hepatitis C virus coinfection be assessed for HCV treatment (GPP).
- We suggest commencing ART when the CD4 cell count is greater than 500 cells/μL in all patients who are not to commence HCV treatment immediately (2D).
- We recommend commencing ART when the CD4 cell count is less than 500 cells/μL in all patients who are not to commence anti-HCV treatment immediately (1B).
- We recommend commencing ART to optimize immune status before anti-HCV therapy is initiated when the CD4 cell count is between 350 and 500 cells/μL unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilized on HCV therapy (GPP).
- We recommend commencing ART to allow immune recovery before anti-HCV therapy is initiated when the CD4 cell count is less than 350 cells/μL (GPP).

Auditable measure Proportion of patients with a CD4 cell count <500 cells/μL commencing ART.

Rationale. HIV has an impact on hepatitis C infection. Individuals with HCV coinfection have higher HCV viral loads, faster rates of fibrosis progression and an increased risk of cirrhosis compared to those with HCV alone. End-stage liver disease, HCC and liver-related death occur more frequently, at an earlier age, and within a shorter time period with the risk of liver-related mortality and HCC increasing as the CD4 cell count declines. Successful treatment outcome with pegylated interferon (PEG-IFN) and ribavirin (RBV) lessens as the CD4 cell count declines and although ART slows the progression of liver disease it is still faster than in HCV monoinfection.

For these reasons, patients with HIV and hepatitis C infection with CD4 cell counts <500 cells/μL should start ART. This should be immediate irrespective of whether HCV treatment is planned or not. For patients with CD4 cell counts between 350 and 500 cells/μL, initiation of anti-HCV treatment should be delayed until after start of ART unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilized on HCV therapy.

Individuals with a CD4 cell count greater than 500 cells/μL who defer hepatitis C therapy, should be given the option to commence ART. If they opt to defer, they should be monitored closely for HIV or hepatitis C disease progression, including at least an annual assessment of liver fibrosis.

8.2.3.2 What to start

Recommendations

- We recommend if patients are commencing ART, and DAAs are not being considered, standard first-line ART should be commenced (GPP).
- We recommend when DAAs are to be used there is careful consideration of possible DDIs (1C) and current or archived HIV resistance. All drug interactions should be checked with an expert source (e.g., www.hiv-druginteractions.org).
- We recommend if boceprevir is to be used, RAL with TDF plus FTC should be the treatment of choice for those with wild-type HIV (1C): pharmacokinetic data would support ETV, RPV and MVC as alternatives.
- We recommend if telaprevir is to be used either RAL or standard-dose ATV/r should be used (1C): pharmacokinetic data would support ETV, RPV and MVC as alternatives. EFV may be used but the telaprevir dose needs to be increased to 1125 mg tds.

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- We suggest that if ABC is to be used with ribavirin, the ribavirin should be weight-based dose-adjusted (2C).

Auditable measure. Among patients receiving DAAs for HCV genotype 1 with ART for wild type HIV, the percentage on a recommended regimen, i.e. RAL with TDF plus FTC with boceprevir; or RAL or boosted ATV with standard dose telaprevir; or EFV with increased dose 1125 mg tds telaprevir.

Rationale. When DAAs are chosen, some restriction on first-line ARV choice exists due to drug–drug interactions. Boceprevir and telaprevir are currently licensed DAAs for the treatment of hepatitis C genotype 1 infection and are substrates and inhibitors of cytochrome P (CYP) 3A4/5 and p-glycoprotein (p-gp), and therefore interact with several ARVs. Boceprevir is also metabolized by aldo-ketoreductase. Choice of available, safe third agents differs with use of boceprevir and telaprevir. From the limited data and drug–drug interaction studies, we recommend that if boceprevir is to be used, RAL with TDF/FTC should represent first-line ART in the presence of wild-type HIV. For telaprevir, we recommend that standard-dose ATV/r or RAL should be used – EFV can also be used but telaprevir dose needs to be increased to 1125 mg tds. Alternative ARVs when treating with either boceprevir or telaprevir are ETV, RPV and MVC, based on available pharmacokinetic (PK) data. Multiple DAAs are currently in Phase III trials in coinfected patients. Each drug has particular DDIs when combined with ART agents, and expert opinion should be sought on possible PK interactions. Clinicians should refer to an online information resource (such as http://www.hep-druginteractions.org) or seek expert opinion on possible PK interactions.

8.2.4 References

1 Wilkins E , Nelson M for the BHIVA Hepatitis Guidelines Writing Group. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. *HIV Medicine* 2013; **14** (Suppl 4): 1–71.

8.3 HIV-related cancers

8.3.1 Summary of auditable measures

Proportion of patients with an AIDS-defining malignancy on ART.

Proportion of patients with a non-AIDS-defining malignancy on ART.

Record in patient's notes of potential pharmacokinetic drug interactions between ARVs and systemic anticancer therapy.

8.3.2 When to start antiretroviral therapy: AIDS-defining malignancies

KS, high-grade B-cell NHL and invasive cervical cancer are all AIDS-defining illnesses and are thus indications to commence ART regardless of CD4 cell count or HIV VL.

8.3.2.1 Kaposi sarcoma

Recommendation

- We recommend starting ART in HIV-positive patients with KS (1A).

Rationale. ART has been shown to reduce the incidence of KS in HIV cohort studies [1–4], to prevent KS in patients on ART [3], and, in addition, increases the time to disease progression in KS [5], improves prognosis in KS and prolongs survival in KS [6–8]. When initiating ART for KS, there appears to be no difference in response or outcome of KS between different HIV treatment regimens [3,9]. Therefore, no recommendation can be made on choice of HIV therapy for patients with KS.

8.3.2.2 Non-Hodgkin lymphoma

Recommendation

- We recommend starting ART in HIV-positive patients with NHL (1B).

Rationale. ART has been shown to reduce the incidence of NHL [1,2,10–18] and to improve the outcome [8,19–22]. Before ART was available, the treatment of NHL with standard doses of chemotherapy produced marked toxicity and a high incidence of opportunistic infections [23]. In an attempt to decrease toxicity, modified-dose chemotherapy regimens were used by the AIDS Clinical Trials Group (ACTG). However, the reduced opportunistic infections were offset by the lower response rates [24]. Since the widespread availability of ART, two retrospective studies reported higher tumour response rates and overall survival in HIV seropositive patients with systemic NHL who were treated with CHOP chemotherapy and concomitant ART compared with those who were treated with CHOP alone [19,20]. Similarly, in a separate study of liposomal doxorubicin in combination with cyclophosphamide, vincristine and prednisolone in HIV-associated NHL, improvement in survival was associated with HIV viral control, although complete remission rates were independent of HIV VL [25].

Further evidence to support the use of ART with chemotherapy in both KS and NHL is the finding from historical

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comparisons that the fall in CD4 cell count during chemotherapy is less profound when ART is prescribed concomitantly and that the duration of lymphocyte subset suppression is briefer [4,26–28].

However, a number of US intergroup studies have either withheld ART during chemotherapy [29,30] or delayed the initiation of ART [31]. The rationale for this approach includes avoiding adverse pharmacokinetic and pharmacodynamic interactions between ART and chemotherapy and the theoretical concern that PIs may inhibit lymphocyte apoptosis and thus contribute to chemoresistance of lymphomas [32]. Although no new HIV mutations were identified, these studies were small and ART was promptly reinstituted after abbreviated chemotherapy. Nevertheless, it took 12–18 months after completing chemotherapy for plasma HIV viraemia to become undetectable in many patients [30]. Importantly, patients with NHL frequently present with CD4 cell counts <200 cells/μL and thus the reduction in CD4 cell count associated with systemic chemotherapy and structured suspension of ART is not ideal.

8.3.2.3 Cervical cancer

Recommendation

- We suggest starting ART in HIV-positive patients with cervical cancer (2C).
- We recommend starting ART in HIV-positive patients who are commencing radiotherapy or chemotherapy for cervical cancer (1D).

Rationale. There is less clear evidence to support starting ART in women diagnosed with invasive cervical cancer, despite its status as an AIDS-defining illness. Co-registration studies have shown that ART has not reduced the incidence of cervical cancer [33–35], moreover the effects of ART on pre-invasive cervical dysplasia have been variable with some studies suggesting that ART causes regression of cervical intraepithelial neoplasia [36–42] and others showing no beneficial effect of ART [43–46]. The effects of ART on outcomes in HIV-positive women with invasive cervical cancer have not been reported but analogies with anal cancer may be drawn as the malignancies share common pathogenesis and treatment modalities. Combined chemoradiotherapy in anal cancer has been shown to cause significant and prolonged CD4 suppression even when ART is administered concomitantly [47–50]. Similarly the toxicity of chemoradiotherapy for HIV-associated anal cancer appears to be less profound among patients given ART compared to historical controls [48,49,51–56].

8.3.3 When to start antiretroviral therapy: non-AIDS-defining malignancies

8.3.3.1 Recommendation

- We suggest starting ART in HIV-positive patients with non-AIDS-defining malignancies (2C).
- We recommend starting ART in HIV-positive patients who are commencing immunosuppressive radiotherapy or chemotherapy for non-AIDS-defining malignancies (1C).

8.3.3.2 Rationale

While ART has little effect on the incidence of NADMs [2,57–64] and there is no evidence that ART alone causes regression of NADMs, the immunosuppressive effects of both chemotherapy [4,26–28] and radiotherapy [47–50] may justify starting ART in HIV-positive individuals who are commencing systemic anticancer therapy or radiotherapy.

8.3.4 What to start

8.3.4.1 Recommendation

- We recommend that potential pharmacokinetic interactions between ARVs and systemic anticancer therapy are checked before administration (with tools such as: http://www.hiv-druginteractions.org) (GPP).

8.3.4.2 Rationale

Significant pharmacokinetic and pharmacodynamic interactions have been reported between ARV drugs and systemic anticancer therapies. The mechanisms of the pharmacokinetic interactions include the inhibition and induction by ARV agents of enzymes, especially the CYP450 family and uridine diphosphoglucuronosyl transferase isoenzymes, involved in the catabolism and activation of cytotoxic chemotherapy agents. In addition, competition for renal clearance, intracellular phosphorylation and ABC (ATP-binding cassette) transporters, has been hypothesized to contribute to these drug interactions [65]. Similarly, pharmacodynamic interactions, in particular overlapping toxicities between ARVs and systemic anticancer therapy, suggest that some drug combinations should be avoided in patients with HIV-associated cancers. Much of the guidance on the use of individual ARV agents with systemic anticancer therapy comes from reviews of potential drug interactions rather than from clinical studies [65–67]. The pharmacokinetic interactions between ARVs and systemic anticancer therapy are not confined to cytotoxic chemotherapy agents and extensive interactions with newer targeted therapies such as imatinib, erlotinib, sorafenib, bortezomib and temsirolimus have been described [67].

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8.3.4.3 Recommendation

- We suggest avoiding ritonavir-boosted ART in HIV-positive patients who are to receive cytotoxic chemotherapy agents that are metabolized by the CYP450 enzyme system (2C).

8.3.4.4 Rationale

In general, clinically important pharmacokinetic drug interactions with systemic anticancer therapies are most common with PI/r-based ART and most clinicians avoid these combinations where possible. For example, in a cohort study, the rates of severe infections and severe neutropenia following chemotherapy for AIDS-related NHL were significantly higher among patients receiving concomitant PI (mainly ritonavir boosted) than in those on NNRTI-based ART regimens, although there was no difference in survival between the groups [68]. Furthermore, case reports of clinically significant life-threatening interactions between ritonavir-boosted-based ART and docetaxel [69], irinotecan [70] and vinblastine [71] have been published.

8.3.4.5 Recommendation

- We recommend against the use of ATV in HIV-positive patients who are to receive irinotecan (1C).

8.3.4.6 Rationale

The camptothecin cytotoxic agent irinotecan is extensively metabolized by uridine diphosphoglucuronosyl transferase 1A1 isoenzymes that are inhibited by ATV [72]. In patients with Gilbert's syndrome, who have a congenital deficiency of uridine diphosphoglucuronosyl transferase 1A1, irinotecan administration has led to life-threatening toxicity [73].

8.3.4.7 Recommendation

- We suggest avoiding ARV agents in HIV-positive patients who are to receive cytotoxic chemotherapy agents that have overlapping toxicities (2C).

8.3.4.8 Rationale

Both ARV agents and systemic anticancer therapies have substantial toxicity and where these overlap it is likely that the risk of toxicity is greater. For example, ZDV commonly causes myelosuppression and anaemia [74], which are also frequent side effects of cytotoxic chemotherapy and so these should not be co-prescribed where possible. Similarly, dideoxynucleosides cause peripheral neuropathy [75], a common toxicity of taxanes and vinca alkaloids, so co-prescribing should be avoided. Both ZDV and dideoxynucleosides are no longer recommended for initiation of ART but some treatment-experienced patients may still be receiving these drugs and alternatives should be considered.

8.3.5 References

1 Jacobson LP, Yamashita TE, Detels R *et al.* Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals. Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 1999; **21** (Suppl 1): S34–S41.

2 International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* 2000; **92**: 1823–1830.

3 Portsmouth S, Stebbing J, Gill J *et al.* A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. *AIDS* 2003; **17**: F17–F22.

4 Clifford GM, Polesel J, Rickenbach M *et al.* Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005; **97**: 425–432.

5 Bower M, Fox P, Fife K *et al.* Highly active anti-retroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma. *AIDS* 1999; **13**: 2105–2111.

6 Stebbing J, Sanitt A, Nelson M *et al.* A prognostic index for AIDS-associated Kaposi's sarcoma in the era of highly active antiretroviral therapy. *Lancet* 2006; **367**: 1495–1502.

7 Holkova B, Takeshita K, Cheng DM *et al.* Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. *J Clin Oncol* 2001; **19**: 3848–3851.

8 Tam HK, Zhang ZF, Jacobson LP *et al.* Effect of highly active antiretroviral therapy on survival among HIV-infected men with Kaposi sarcoma or non-Hodgkin lymphoma. *Int J Cancer* 2002; **98**: 916–922.

9 Bower M, Weir J, Francis N *et al.* The effect of HAART in 254 consecutive patients with AIDS-related Kaposi's sarcoma. *AIDS* 2009; **23**: 1701–1706.

10 Stebbing J, Gazzard B, Mandalia S *et al.* Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol* 2004; **22**: 2177–2183.

11 Kirk O, Pedersen C, Cozzi-Lepri A *et al.* Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy. *Blood* 2001; **98**: 3406–3412.

12 Besson C, Goubar A, Gabarre J *et al.* Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood* 2001; **98**: 2339–2344.

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13 Grulich AE, Li Y, McDonald AM. Decreasing rates of Kaposi's sarcoma and non-Hodgkin's lymphoma in the era of potent combination anti-retroviral therapy. *AIDS* 2001; **15**: 629–633.
14 Carrieri MP, Pradier C, Piselli P *et al.* Reduced incidence of Kaposi's sarcoma and of systemic non-Hodgkin's lymphoma in HIV-infected individuals treated with highly active antiretroviral therapy. *Int J Cancer* 2003; **103**: 142–144.
15 Franceschi S, Dal Maso L, Pezzotti P *et al.* Incidence of AIDS-defining cancers after AIDS diagnosis among people with AIDS in Italy, 1986–1998. *J Acquir Immune Defic Syndr* 2003; **34**: 84–90.
16 Diamond C, Taylor TH, Im T, Miradi M, Anton-Culver H. Improved survival and chemotherapy response among patients with AIDS-related non-Hodgkin's lymphoma receiving highly active antiretroviral therapy. *Hematol Oncol* 2006; **24**: 139–145.
17 Engels EA, Pfeiffer RM, Goedert JJ *et al.* Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS* 2006; **20**: 1645–1654.
18 Bower M, Fisher M, Hill T *et al.* CD4 counts and the risk of systemic non-Hodgkin's lymphoma in individuals with HIV in the UK. *Haematologica* 2009; **94**: 875–880.
19 Navarro JT, Ribera JM, Oriol A *et al.* Influence of highly active anti-retroviral therapy on response to treatment and survival in patients with acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma treated with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone. *Br J Haematol* 2001; **112**: 909–915.
20 Vaccher E, Spina M, di Gennaro G *et al.* Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. *Cancer* 2001; **91**: 155–163.
21 Lim ST, Karim R, Tulpule A, Nathwani BN, Levine AM. Prognostic factors in HIV-related diffuse large-cell lymphoma: before versus after highly active antiretroviral therapy. *J Clin Oncol* 2005; **23**: 8477–8482.
22 Lim ST, Karim R, Nathwani BN *et al.* AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. *J Clin Oncol* 2005; **23**: 4430–4438.
23 Kaplan LD, Abrams DI, Feigal E *et al.* AIDS-associated non-Hodgkin's lymphoma in San Francisco. *JAMA* 1989; **261**: 719–724.
24 Kaplan LD, Straus DJ, Testa MA *et al.* Low dose compared with standard dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. *N Engl J Med* 1997; **336**: 1641–1648.
25 Levine AM, Tulpule A, Espina B *et al.* Liposome-encapsulated doxorubicin in combination with standard agents (cyclophosphamide, vincristine, prednisone) in patients with newly diagnosed AIDS-related non-Hodgkin's lymphoma: results of therapy and correlates of response. *J Clin Oncol* 2004; **22**: 2662–2670.
26 Bower M, Stebbing J, Tuthill M *et al.* Immunologic recovery in survivors following chemotherapy for AIDS-related non-Hodgkin lymphoma. *Blood* 2008; **111**: 3986–3990.
27 Powles T, Imami N, Nelson M, Gazzard BG, Bower M. Effects of combination chemotherapy and highly active antiretroviral therapy on immune parameters in HIV-1 associated lymphoma. *AIDS* 2002; **16**: 531–536.
28 Little R, Pearson D, Steinberg S *et al.* Dose-adjusted EPOCH chemotherapy in previously untreated HIV-associated non-Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1999; **18**: 10a.
29 Little RF, Pittaluga S, Grant N *et al.* Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood* 2003; **101**: 4653–4659.
30 Dunleavy K, Little RF, Pittaluga S *et al.* The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. *Blood* 2010; **115**: 3017–3024.
31 Sparano JA, Lee JY, Kaplan LD *et al.* Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood* 2010; **115**: 3008–3016.
32 Phenix BN, Lum JJ, Nie Z, Sanchez-Dardon J, Badley AD. Antiapoptotic mechanism of HIV protease inhibitors: preventing mitochondrial transmembrane potential loss. *Blood* 2001; **98**: 1078–1085.
33 Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst* 2009; **101**: 1120–1130.
34 Engels EA, Biggar RJ, Hall HI *et al.* Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008; **123**: 187–194.
35 Dal Maso L, Polesel J, Serraino D *et al.* Pattern of cancer risk in persons with AIDS in Italy in the HAART era. *Br J Cancer* 2009; **100**: 840–847.
36 Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine MD. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS* 1998; **12**: 1459–1464.
37 Minkoff H, Ahdieh L, Massad LS *et al.* The effect of highly active antiretroviral therapy on cervical cytologic changes

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associated with oncogenic HPV among HIV-infected women. *AIDS* 2001; **15**: 2157–2164.

38 Heard I, Tassie JM, Kazatchkine MD, Orth G. Highly active antiretroviral therapy enhances regression of cervical intraepithelial neoplasia in HIV-seropositive women. *AIDS* 2002; **16**: 1799–1802.

39 Schuman P, Ohmit SE, Klein RS *et al.* Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. *J Infect Dis* 2003; **188**: 128–136.

40 Ahdieh-Grant L, Li R, Levine AM *et al.* Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Natl Cancer Inst* 2004; **96**: 1070–1076.

41 Del Mistro A, Bertorelle R, Franzetti M *et al.* Antiretroviral therapy and the clinical evolution of human papillomavirus-associated genital lesions in HIV-positive women. *Clin Infect Dis* 2004; **38**: 737–742.

42 Soncini E, Zoncada A, Condemi V *et al.* Reduction of the risk of cervical intraepithelial neoplasia in HIV-infected women treated with highly active antiretroviral therapy. *Acta Biomed* 2007; **78**: 36–40.

43 Lillo FB, Ferrari D, Veglia F *et al.* Human papillomavirus infection and associated cervical disease in human immunodeficiency virus-infected women: effect of highly active antiretroviral therapy. *J Infect Dis* 2001; **184**: 547–551.

44 Moore AL, Sabin CA, Madge S *et al.* Highly active antiretroviral therapy and cervical intraepithelial neoplasia. *AIDS* 2002; **16**: 927–929.

45 Heard I, Potard V, Costagliola D. Limited impact of immunosuppression and HAART on the incidence of cervical squamous intraepithelial lesions in HIV-positive women. *Antivir Ther* 2006; **11**: 1091–1096.

46 Sirera G, Videla S, Lopez-Blazquez R *et al.* Highly active antiretroviral therapy and incidence of cervical squamous intraepithelial lesions among HIV-infected women with normal cytology and CD4 counts above 350 cells/mm^3. *J Antimicrob Chemother* 2008; **61**: 191–194.

47 Wichmann MW, Meyer G, Adam M *et al.* Detrimental immunologic effects of preoperative chemoradiotherapy in advanced rectal cancer. *Dis Colon Rectum* 2003; **46**: 875–887.

48 Wexler A, Berson AM, Goldstone SE *et al.* Invasive anal squamous-cell carcinoma in the HIV-positive patient: outcome in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2008; **51**: 73–81.

49 Fraunholz I, Weiss C, Eberlein K, Haberl A, Rodel C. Concurrent chemoradiotherapy with 5-fluorouracil and mitomycin C for invasive anal carcinoma in human immunodeficiency virus-positive patients receiving highly active antiretroviral therapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 1425–1432.

50 Alfa-Wali M, Allen-Mersh T, Antoniou A *et al.* Chemoradiotherapy for anal cancer in HIV patients causes prolonged CD4 cell count suppression. *Ann Oncol* 2011; **23**: 141–147.

51 Blazy A, Hennequin C, Gornet JM *et al.* Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2005; **48**: 1176–1181.

52 Oehler-Janne C, Huguet F, Provencher S *et al.* HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. *J Clin Oncol* 2008; **26**: 2550–2557.

53 Seo Y, Kinsella MT, Reynolds HL. Outcomes of chemoradiotherapy with 5-fluorouracil and mitomycin C for anal cancer in immunocompetent versus immunodeficient patients. *Int J Radiat Oncol Biol Phys* 2009; **75**: 143–149.

54 Hogg ME, Popowich DA, Wang EC. HIV and anal cancer outcomes: a single institution's experience. *Dis Colon Rectum* 2009; **52**: 891–897.

55 Vatra B, Sobhani I, Aparicio T *et al.* [Anal canal squamous-cell carcinomas in HIV positive patients: clinical features, treatments and prognosis]. *Gastroenterol Clin Biol* 2002; **26**: 150–156.

56 Abramowitz L, Mathieu N, Roudot-Thoraval F *et al.* Epidermoid anal cancer prognosis comparison among HIV+ and HIV- patients. *Aliment Pharmacol Ther* 2009; **30**: 414–421.

57 Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; **370**: 59–67.

58 Herida M, Mary-Krause M, Kaphan R *et al.* Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol* 2003; **21**: 3447–3453.

59 Bedimo R, Chen RY, Accortt NA *et al.* Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989–2002. *Clin Infect Dis* 2004; **39**: 1380–1384.

60 Bower M, Powles T, Nelson M *et al.* HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS* 2003; **17**: 371–375.

61 Hessol NA, Seaberg EC, Preston-Martin S *et al.* Cancer risk among participants in the women's interagency HIV study. *J Acquir Immune Defic Syndr* 2004; **36**: 978–985.

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62 Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS* 2008; **22**: 489–496.
63 Patel P, Hanson DL, Sullivan PS *et al.* Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med* 2008; **148**: 728–736.
64 Powles T, Robinson D, Stebbing J *et al.* Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol* 2009; **27**: 884–900.
65 Rudek MA, Flexner C, Ambinder RF. Use of antineoplastic agents in patients with cancer who have HIV/AIDS. *Lancet Oncol* 2011; **12**: 905–912.
66 Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet* 2005; **44**: 111–145.
67 Deeken JF, Pantanowitz L, Dezube BJ. Targeted therapies to treat non-AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations and research outlook. *Curr Opin Oncol* 2009; **21**: 445–454.
68 Bower M, McCall-Peat N, Ryan N *et al.* Protease inhibitors potentiate chemotherapy-induced neutropenia. *Blood* 2004; **104**: 2943–2946.
69 Mir O, Dessard-Diana B, Louet AL *et al.* Severe toxicity related to a pharmacokinetic interaction between docetaxel and ritonavir in HIV-infected patients. *Br J Clin Pharmacol* 2010; **69**: 99–101.
70 Corona G, Vaccher E, Sandron S *et al.* Lopinavir-ritonavir dramatically affects the pharmacokinetics of irinotecan in HIV patients with Kaposi's sarcoma. *Clin Pharmacol Ther* 2008; **83**: 601–606.
71 Kotb R, Vincent I, Dulioust A *et al.* Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. *Eur J Haematol* 2006; **76**: 269–271.
72 Fujita K, Sparreboom A. Pharmacogenetics of irinotecan disposition and toxicity: a review. *Curr Clin Pharmacol* 2010; **5**: 209–217.
73 Wasserman E, Myara A, Lokiec F *et al.* Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. *Ann Oncol* 1997; **8**: 1049–1051.
74 Moyle G, Sawyer W, Law M, Amin J, Hill A. Changes in hematologic parameters and efficacy of thymidine analogue-based, highly active antiretroviral therapy: a meta-analysis of six prospective, randomized, comparative studies. *Clin Ther* 2004; **26**: 92–97.
75 Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Saf* 1998; **19**: 481–494.

8.4 HIV-associated neurocognitive impairment

8.4.1 Introduction

With the widespread use of effective combination ART, the incidence of severe HIV-associated cerebral disease has declined dramatically [1]; however, more subtle forms of brain disease, known as HIV-associated NC disorders are reported to remain prevalent [2]. This NC deficit may present with a wide spectrum of clinical symptoms, but typically includes patterns involving ineffective learning and problems with executive function, rather than pure difficulties in formulating new memory (the cortical defect typical of Alzheimer's disease [3]).

Given the changing picture of this disease, a revised nomenclature system has been proposed classifying subjects with abnormal neuropsychological testing results in to three categories based on patient's symptoms, measured via the activities of daily living scale [2]. Subjects with abnormal neuropsychiatric testing results, who are otherwise asymptomatic, are classified as having HIV-associated asymptomatic NC impairment; those who are mildly symptomatic are classified as having HIV-associated mild NC disorder; and those who are severely symptomatic are classified as having HIV-associated dementia. The clinical relevance of asymptomatic NC impairment, namely asymptomatic subjects with abnormal results on neuropsychological testing, remains unclear.

Reports describing rates of NC impairment vary with some groups describing that up to 50% of HIV-positive subjects meet the above diagnostic criteria [4]. However, such reports should be interpreted with caution as asymptomatic subjects are often included and not all reports correct for effective ARV use. A Swiss cohort has reported 19% of aviraemic HIV-positive subjects meet the classification for mild NC disorder or above [5].

Risk factors for the development of NC disorders are poorly understood and are likely to be multifactorial, including both HIV disease factors [6] and concomitant diseases [7]. Although it is possible the choice of combination ART a subject receives may influence NC function, this is a controversial area without definitive evidence. The following recommendations apply to patients with symptomatic HIV-associated NC disorders.

8.4.2 When to start antiretroviral therapy

8.4.2.1 Recommendation

- We recommend patients with symptomatic HIV-associated NC disorders start ART irrespective of CD4 lymphocyte count (1C).

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Auditable measure. Proportion of patients with symptomatic HIV-associated NC disorders on ART.

8.4.2.2 Rationale

Current evidence suggests NC function improves after commencing ART for the first time [8] in both cognitively symptomatic [9] and asymptomatic [10] subjects. However, these studies have been undertaken in individuals with other indications to commence ART, in general with CD4 lymphocyte counts in the designated range where treatment is recommended. For subjects with higher CD4 lymphocyte counts, the ongoing START study will prospectively assess NC function in HIV-positive subjects commencing ART at an earlier stage of HIV disease.

Therefore, ART is recommended in NC symptomatic subjects whose CD4 lymphocyte count itself is an indication to commence therapy.

In the absence of scientific data, in cognitively symptomatic subjects with higher CD4 lymphocyte counts in whom ART would not be otherwise indicated, a recommendation to consider commencing ART is based (i) on observed improvements in cognitive function reported in subjects with lower CD4 lymphocyte counts commencing therapy [8], and (ii) to avoid a future decline in CD4 lymphocyte count in such subjects, given the well-described association between low nadir CD4 lymphocyte count and NC impairment [6].

Suboptimal adherence to therapy may occur more frequently in subjects with NC impairment, hence adequate support services to optimize adherence are essential.

8.4.3 What to start

8.4.3.1 Recommendation

- We recommend patients with HIV-associated NC disorders start standard combination ART regimens (1C).

Auditable measure. Proportion of patients with HIV-associated NC disorders on ART containing two NRTIs and one of an NNRTI, a PI/r or an INI.

8.4.3.2 Rationale

Although during the earlier years of ART, clear benefits on cerebral function of individual ARV drugs such as ZDV were reported [11] and the benefits of combination therapy overall are well described [8], data are sparse regarding any differences in these benefits between individual agents or combinations. Within cohort studies, the use of the NRTI class within ARV regimens has been associated with a reduced risk of severe HIV-associated dementia [12] compared with the use of other regimens; however, the confounders of a cohort study limit interpretation of these data.

Recently, attempts have been made to establish a relationship between cognitive function and CNS ARV drug delivery based on an ARV scoring system known as the clinical penetration effectiveness (CPE) score [13]. The CPE score aims to rationally score the cerebral effects of individual ARV agents. However, the system is predominantly designed around pharmacokinetic modelling rather than pharmacodynamic endpoints such as data describing changes in NC function. Studies that have assessed the correlation between the CPE scores of ARV regimens with NC function report conflicting findings with some cohorts reporting a positive association [14,15], and others describing a negative association [16]. Given the potential flaws outlined in the design of the CPE score, a lack of prospective clinical data and discrepancies in findings within cohort studies, the CPE score should not influence therapeutic decisions in subjects with NC impairment commencing ART.

One small prospective study has assessed the cerebral effects of three different ARV regimens in neurologically asymptomatic subjects reporting greater improvement in NC function in subjects commencing a quadruple nucleoside regimen compared with an EFV- or ATV/r-containing regimen [17]. However, subjects were asymptomatic from a neurological point of view, limiting the relevance of these findings to neurologically symptomatic subjects.

The improvements in NC function observed with ZDV monotherapy [11] and the greater improvements in NC function observed with a ZDV-containing quadruple nucleoside regimen compared with other ART regimens [17], raise the possibility of selecting a ZDV-containing ARV regimen in subjects with NC impairment. Conversely, a lack of comparator data for ZDV monotherapy and potential toxicities arising from ZDV use may limit the relevance of these data. Of note, further to peripheral toxicities, which are well described with ZDV use, biomarker data suggest there may also be CNS toxicities associated with the use of ZDV-containing regimens [18].

In summary, we recommend patients with NC impairment start standard combination ART regimens and the choice should be determined, as with other patients, by different factors, including baseline VL, side effect profile, tolerability, DDIs and patient preference.

8.4.3.3 Novel antiretroviral strategies and NC function

Novel ARV strategies, including protease-inhibitor monotherapy continue to be assessed in clinical trials as cost-beneficial treatment regimens with the potential for reduced long-term toxicities. Concerns have been raised

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regarding the cerebral effects of PI monotherapy [19], with such concerns based on the hypotheses that PI monotherapy comprises only one effective ARV agent that may not adequately suppress ongoing HIV replication in sanctuary sites such as the CNS, and on pharmacokinetic modelling that suggests that not all PIs have optimal penetration across the blood–brain barrier [13]. Furthermore, isolated cases describing the evolution of CNS disease in previously stable HIV-positive subjects receiving PI monotherapy have been reported [20].

One study was specifically designed to assess the cerebral effects of LPV/r monotherapy [21]; however, it was terminated early due to a lack of efficacy in the plasma compartment. Although cases of CNS disease were reported within this study, such results must be interpreted with caution as virological endpoints in the plasma compartment were not met and therefore such cases may be driven by poor ARV efficacy *per se*, rather than distinct CNS disease itself [22].

In the MONET study assessing DRV/r *vs*. standard therapy, no differences in patient-reported cognitive function are observed between the study treatment arms over 3 years of therapy [23]. Although reassuring, these data represent changes in patient-reported observations rather than observations from formal neuropsychological testing. Interestingly, in a small substudy within MONET, improvements in detailed neuropsychological testing and improvements in cerebral biomarkers measured via imaging techniques, were reported in both treatment arms [24].

In the ongoing UK PIVOT study, detailed neuropsychological testing is being assessed prospectively in subjects on PI monotherapy *vs*. standard therapy, the results of which will be of great interest to this field.

Given the above theoretical concerns regarding the CNS activity of PI monotherapy, and for the majority of HIV-positive subjects it may be possible to select other ARV regimens, we suggest this approach is currently avoided in neurologically symptomatic subjects.

8.4.4 Modification of antiretroviral therapy

8.4.4.1 Recommendation

In patients with ongoing or worsening NC impairment despite ART, we recommend the following best practice management (GPP):

- Reassessment for confounding conditions.
- Assessment of CSF HIV RNA, CSF HIV genotropism and genotyping of CSF HIV RNA.
- In subjects with detectable CSF HIV RNA, modifications to ART should be based on plasma and CSF genotypic and genotropism results.

8.4.4.2 Rationale

Several published randomized controlled studies, assessing both intensification of ART with a new ARV agent [25] and with adjunctive therapies [26–29] have been published. Unfortunately, none of these studies describe improvements in cognition subsequent to the study interventions. Without evidence-based interventions, the Writing Group outlines below a best practice approach based on the current literature.

As HIV-associated NC disorders are a diagnosis of exclusion, re-evaluation of subjects with ongoing NC impairment despite ART for confounding conditions, with expert input from other clinical specialties such as psychiatry, neurology and neuropsychology, is recommended and, where possible, input from an HIV neurology service.

Assessment of CSF HIV RNA, CSF HIV genotropism and genotypic analysis of CSF RNA may be useful tools in the management of subjects with ongoing NC for the following reasons. First, data from cohorts of untreated HIV-positive subjects would suggest CSF HIV RNA to be greater in subjects with HIV-associated dementia and cognitive decline [30,31] and therefore suppression of CSF HIV RNA may be beneficial for cognitive function. Secondly, in subjects with ongoing NC impairment, higher degrees of genetic diversity between HIV viral strains in the CSF and plasma compartment may exist [32], even in subjects with undetectable plasma HIV RNA [33]. Therefore, assessment for CSF HIV resistance may be worthwhile to tailor ART.

8.4.5 References

1 Dore GJ, Correll PK, Li Y *et al*. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS* 1999; **13**: 1249–1253.
2 Antinori A, Arendt G, Becker JT *et al*. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; **69**: 1789–1799.
3 Valcour V, Paul R, Chiao S, Wendelken LA, Miller B. Screening for cognitive impairment in human immunodeficiency virus. *Clin Infect Dis* 2011; **53**: 836–842.
4 Heaton RK, Clifford DB, Franklin DR Jr *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2011; **75**: 2087–2096.
5 Simioni S, Cavassini M, Annoni JM *et al*. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010; **24**: 1243–1250.
6 Ellis RJ, Badiee J, Vaida F *et al*. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS* 2011; **25**: 1747–1751.

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7 Wright EJ, Grund B, Robertson K *et al.* Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. *Neurology* 2011; **75**: 864–873.

8 Al-Khindi T, Zakzanis KK, van Gorp WG. Does antiretroviral therapy improve HIV-associated cognitive impairment? A quantitative review of the literature. *J Int Neuropsychol Soc* 2011; **17**: 1–14.

9 Cysique LA, Vaida F, Letendre S *et al.* Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology* 2009; **73**: 342–348.

10 Winston A, Puls R, Kerr SJ *et al.* Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: a randomized, controlled study. *HIV Med* 2012; **13**: 245–251.

11 Schmitt FA, Bigley JW, McKinnis R *et al.* Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. *N Engl J Med* 1988; **319**: 1573–1578.

12 d'Arminio Monforte A, Cinque P, Mocroft A *et al.* Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol* 2004; **55**: 320–328.

13 Letendre S, Marquie-Beck J, Capparelli E *et al.* Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol* 2008; **65**: 65–70.

14 Tozzi V, Balestra P, Salvatori MF *et al.* Changes in cognition during antiretroviral therapy: comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders. *J Acquir Immune Defic Syndr* 2009; **52**: 56–63.

15 Smurzynski M, Wu K, Letendre S *et al.* Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS* 2011; **25**: 357–365.

16 Marra CM, Zhao Y, Clifford DB *et al.* Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS* 2009; **23**: 1359–1366.

17 Winston A, Duncombe C, Li PC *et al.* Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. *Clin Infect Dis* 2010; **50**: 920–929.

18 Schweinsburg BC, Taylor MJ, Alhassoon OM *et al.* Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. *J Neurovirol* 2005; **11**: 356–364.

19 Perez-Valero I, Bayon C, Cambron I, Gonzalez A, Arribas JR. Protease inhibitor monotherapy and the CNS: peace of mind? *J Antimicrob Chemother* 2011; **66**: 1954–1962.

20 Katlama C, Valantin MA, Algarte-Genin M *et al.* Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS* 2010; **24**: 2365–2374.

21 Gutmann C, Cusini A, Günthard HF *et al.* Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. *AIDS* 2010; **24**: 2347–2354.

22 Paton NI, Meynard JL, Pulido F *et al.* Inappropriate claim of 'failure of ritonavir-boosted lopinavir monotherapy in HIV' in the Monotherapy Switzerland/Thailand (MOST) trial. *AIDS* 2011; **25**: 393–394.

23 Winston A, Fätkenheuer G, Arribas J *et al.* Neuropsychiatric adverse events with ritonavir-boosted darunavir monotherapy in HIV-infected individuals: a randomised prospective study. *HIV Clin Trials* 2010; **11**: 163–169.

24 Garvey L, Higgs C, Mohammed P *et al.* Changes in cerebral function parameters in HIV type 1-infected subjects switching to darunavir/ritonavir either as monotherapy or with nucleoside analogues. *AIDS Res Hum Retroviruses* 2011; **27**: 701–703.

25 Brew BJ, Halman M, Catalan J *et al.* Factors in AIDS dementia complex trial design: results and lessons from the abacavir trial. *PLoS Clin Trials* 2007; **2**: e13.

26 Schifitto G, Navia BA, Yiannoutsos CT *et al.* Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. *AIDS* 2007; **21**: 1877–1886.

27 Schifitto G, Yiannoutsos CT, Ernst T *et al.* Selegiline and oxidative stress in HIV-associated cognitive impairment. *Neurology* 2009; **73**: 1975–1981.

28 Schifitto G, Zhong J, Gill D *et al.* Lithium therapy for human immunodeficiency virus type 1-associated neurocognitive impairment. *J Neurovirol* 2009; **15**: 176–186.

29 Schifitto G, Peterson DR, Zhong J *et al.* Valproic acid adjunctive therapy for HIV-associated cognitive impairment: a first report. *Neurology* 2006; **66**: 919–921.

30 Ho DD, Rota TR, Schooley RT *et al.* Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med* 1985; **313**: 1493–1497.

31 Sönnerborg AB, Ehrnst AC, Bergdahl SK *et al.* HIV isolation from cerebrospinal fluid in relation to immunological deficiency and neurological symptoms. *AIDS* 1988; **2**: 89–93.

32 Soulié C, Fourati S, Lambert-Niclot S *et al.* HIV genetic diversity between plasma and cerebrospinal fluid

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in patients with HIV encephalitis. *AIDS* 2010; **24**: 2412–2414.
33 Canestri A, Lescure FX, Jaureguiberry S *et al.* Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis* 2010; **50**: 773–778.

8.5 Chronic kidney disease

8.5.1 When to start antiretroviral therapy

8.5.1.1 Recommendation

- We recommend patients with HIVAN start ART immediately irrespective of CD4 cell count (1C).
- We recommend patients with end-stage kidney disease who are suitable candidates for renal transplantation start ART irrespective of CD4 cell count (1C).

Auditable measure. Proportion of patients with HIVAN started on ART within 2 weeks of diagnosis of CKD.

8.5.1.2 Rationale

The use of ART has been associated with a decline in the incidence of HIVAN in HIV cohort studies [1], with renal histological improvement in case reports [2,3], and with delayed progression to end-stage kidney disease in case series [4,5]. In the UK, most HIVAN cases are encountered in patients with advanced immunodeficiency who were not previously known to be HIV positive, or who disengaged from care or who declined ART [6]. HIVAN is rare in patients with CD4 cell counts >350 cells/μL or with undetectable HIV RNA levels [7]. Patients presenting with higher levels of proteinuria (urine albumin–creatinine ratio >70 mg/mmol or urine protein–creatinine ratio >100 mg/mmol or urine protein excretion >1 g/24 h) or proteinuria with haematuria (urine albumin–creatinine ratio >30 mg/mmol or urine protein–creatinine ratio >50 mg/mmol) or stage 4–5 CKD should be referred for specialist assessment and a renal biopsy considered; those found to have HIVAN should start ART immediately, irrespective of CD4 cell count.

For CKD other than HIVAN, there is limited information on the natural history *per se* and on whether ART confers renal benefit. Immunodeficiency is a potent risk factor for CKD [8,9]. The majority of patients with CKD have (nadir) CD4 cell counts <350 cells/μL and thus qualify for ART as per current treatment guidelines. There are no data to provide guidance on whether HIV-positive patients with (or at risk of developing) CKD benefit from earlier ART initiation. None the less, HIV replication, immune activation and inflammation may play a role in the pathogenesis of kidney diseases or contribute to kidney disease progression in some patients [10]. For this reason, ART should be considered in those presenting with CKD other than HIVAN.

Renal transplantation is the treatment of choice for those requiring renal replacement therapy. Patients to be considered for renal transplantation are required to have suppressed HIV RNA levels and to have CD4 cell counts >200 cells/μL [11], and should start ART, irrespective of CD4 cell count.

8.5.2 What to start

8.5.2.1 Recommendations

- We recommend against the use of ARV drugs that are potentially nephrotoxic in patients with stages 3–5 CKD if acceptable alternative ARV agents are available (GPP).
- We recommend dose adjustment of renally cleared ARV drugs in patients with reduced renal function (GPP).

Auditable measure. Number of patients with CKD stages 3–5 on ARVs that are potentially nephrotoxic and a record of the rationale.

Record in patient's notes of calculated dose of renally cleared ARVs in patients with CKD stage 3 or greater.

8.5.2.2 Rationale

There are no data from clinical RCTs to inform ART decisions in patients with CKD. The risk of CKD is increased with older age, reduced estimated glomerular filtration rate (eGFR), hypertension, diabetes and with cumulative exposure to indinavir, TDF, ATV and, to a lesser extent, LPV [12,13]. Indinavir use is no longer recommended in view of the high incidence of renal complications: crystalluria and pyuria are reported in 20–67% [14–16] and nephrolithiasis, tubulointerstitial nephritis and gradual loss of renal function in 4–33% of patients [14,17–20].

TDF has been associated with falls in eGFR [12,21,22], accelerated decline in eGFR [9], acute renal failure [23], tubulointerstitial nephritis [24], CKD [9,12], renal tubular dysfunction [13,25] and Fanconi syndrome [26,27]. The incidence of TDF-associated renal toxicity is low in clinical trials and cohort studies of the general HIV population [28,29]. Older age, pre-existing renal impairment, co-administration of didanosine or (ritonavir-boosted) PIs, advanced HIV infection and low body mass appear to increase the risk of renal complications [9,13,25,27,30,31].

ATV has been associated with reductions in eGFR [32], nephrolithiasis and tubulointerstitial nephritis [13,24,33], and CKD [12]. The incidence of renal stones with ATV in one cohort was 7.3 per 1000 person-years, with almost half

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of those who developed renal stones having eGFR <60 at the time of ATV initiation [34].

The nephrotoxic potential of both TDF and ATV is low in patients with normal renal function. However, in patients with CKD and impaired renal function (eGFR <75 mL/min/1.73m^2), alternative ARVs should be considered.

In patients undergoing renal transplantation, PIs give rise to challenging DDIs with calcineurin inhibitors (http://www.hiv-druginteractions.org). Post-transplantation, acute allograft rejection and impaired renal function are common [35]. We suggest TDF and ATV are avoided in patients who are waiting or who have undergone, renal transplantation, and that specialist advice is sought regarding choice and appropriate dose of ARVs.

NNRTIs, INIs, ABC and 3TC have not been associated with CKD and can be used in HIV-positive patients with CKD. In patients with impaired renal function, specific ARV drugs (all NRTIs except ABC) may need to be dose-adjusted [36]. Impaired survival has been reported with ART prescription errors in patients undergoing dialysis [37]. We recommend dose adjustment of renally cleared ARVs in patients with renal failure but caution against the risk of overinterpreting estimates of renal function for this purpose as true measures of renal function may be substantially higher in patients with mild–moderate renal impairment. Specific ARVs that require dose adjustment in patients with reduced renal function include 3TC, FTC, TDF, DDI, ZDV and MVC (depending on PI use). For further information and advice, the reader should refer to the summary of product characteristics for each ARV.

8.5.3 References

1 Lucas GM, Eustace JA, Sozio S *et al*. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS* 2004; **18**: 541–546.

2 Scheurer D. Rapid reversal of renal failure after initiation of HAART: a case report. *AIDS Read* 2004; **14**: 443–447.

3 Kirchner JT. Resolution of renal failure after initiation of HAART: 3 cases and a discussion of the literature. *AIDS Read* 2002; **12**: 103–105, 110–102.

4 Szczech LA, Gupta SK, Habash R *et al*. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* 2004; **66**: 1145–1152.

5 Atta MG, Gallant JE, Rahman MH *et al*. Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant* 2006; **21**: 2809–2813.

6 Post FA, Campbell LJ, Hamzah L *et al*. Predictors of renal outcome in HIV-associated nephropathy. *Clin Infect Dis* 2008; **46**: 1282–1289.

7 Estrella M, Fine DM, Gallant JE *et al*. HIV type 1 RNA level as a clinical indicator of renal pathology in HIV-infected patients. *Clin Infect Dis* 2006; **43**: 377–380.

8 Mocroft A, Kirk O, Gatell J *et al*. Chronic renal failure among HIV-1-infected patients. *AIDS* 2007; **21**: 1119–1127.

9 Campbell LJ, Ibrahim F, Fisher M *et al*. Spectrum of chronic kidney disease in HIV-infected patients. *HIV Med* 2009; **10**: 329–336.

10 Choi AI, Shlipak MG, Hunt PW, Martin JN, Deeks SG. HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy. *AIDS* 2009; **23**: 2143–2149.

11 Bhagani S, Sweny P, Brook G. Guidelines for kidney transplantation in patients with HIV disease. *HIV Med* 2006; **7**: 133–139.

12 Mocroft A, Kirk O, Reiss P *et al*. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. *AIDS* 2010; **24**: 1667–1678.

13 Dauchy FA, Lawson-Ayayi S, de La Faille R *et al*. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. *Kidney Int* 2011; **80**: 302–309.

14 Kopp JB, Miller KD, Mican JAM *et al*. Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997; **127**: 119–125.

15 Gagnon RF, Tecimer SN, Watters AK, Tsoukas CM. Prospective study of urinalysis abnormalities in HIV-positive individuals treated with indinavir. *Am J Kidney Dis* 2000; **36**: 507–515.

16 Dieleman JP, van Rossum AM, Stricker BC *et al*. Persistent leukocyturia and loss of renal function in a prospectively monitored cohort of HIV-infected patients treated with indinavir. *J Acquir Immune Defic Syndr* 2003; **32**: 135–142.

17 Malavaud B, Dinh B, Bonnet E *et al*. Increased incidence of indinavir nephrolithiasis in patients with hepatitis B or C virus infection. *Antivir Ther* 2000; **5**: 3–5.

18 Dieleman JP, Sturkenboom MC, Jambroes M *et al*. Risk factors for urological symptoms in a cohort of users of the HIV protease inhibitor indinavir sulfate: the ATHENA cohort. *Arch Intern Med* 2002; **162**: 1493–1501.

19 Voigt E, Wickesberg A, Wasmuth JC *et al*. First-line ritonavir/indinavir 100/800 mg twice daily plus nucleoside reverse transcriptase inhibitors in a German multicentre study: 48-week results. *HIV Med* 2002; **3**: 277–282.

20 Herman JS, Ives NJ, Nelson M, Gazzard BG, Easterbrook PJ. Incidence and risk factors for the development of indinavir-associated renal complications. *J Antimicrob Chemother* 2001; **48**: 355–360.

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21 Fux CA, Simcock M, Wolbers M *et al.* Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir Ther* 2007; **12**: 1165–1173.
22 Goicoechea M, Liu S, Best B *et al.* Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 2008; **197**: 102–108.
23 Herlitz LC, Mohan S, Stokes MB *et al.* Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney Int* 2010; **78**: 1171–1177.
24 Schmid S, Opravil M, Moddel M *et al.* Acute interstitial nephritis of HIV-positive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. *Virchows Arch* 2007; **450**: 665–670.
25 Labarga P, Barreiro P, Martin-Carbonero L *et al.* Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. *AIDS* 2009; **23**: 689–696.
26 Woodward CL, Hall AM, Williams IG *et al.* Tenofovir-associated renal and bone toxicity. *HIV Med* 2009; **10**: 482–487.
27 Zimmermann AE, Pizzoferrato T, Bedford J *et al.* Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006; **42**: 283–290.
28 Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005; **40**: 1194–1198.
29 Nelson MR, Katlama C, Montaner JS *et al.* The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS* 2007; **21**: 1273–1281.
30 Calza L, Trapani F, Tedeschi S *et al.* Tenofovir-induced renal toxicity in 324 HIV-infected, antiretroviral-naive patients. *Scand J Infect Dis* 2011; **43**: 656–660.
31 Brennan A, Evans D, Maskew M *et al.* Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir. *AIDS* 2011; **25**: 1603–1609.
32 Daar ES, Tierney C, Fischl MA *et al.* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med* 2011; **154**: 445–456.
33 Couzigou C, Daudon M, Meynard JL *et al.* Urolithiasis in HIV-positive patients treated with atazanavir. *Clin Infect Dis* 2007; **45**: e105–e108.
34 Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. *AIDS* 2011; **25**: 1671–1673.
35 Stock PG, Barin B, Murphy B *et al.* Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 2010; **363**: 2004–2014.
36 Izzedine H, Deray G. The nephrologist in the HAART era. *AIDS* 2007; **21**: 409–421.
37 Tourret J, Tostivint I, Tezenas Du Montcel S *et al.* Antiretroviral drug dosing errors in HIV-infected patients undergoing hemodialysis. *Clin Infect Dis* 2007; **45**: 779–784.

8.6 Cardiovascular disease

8.6.1 Introduction

CVD is a leading cause of non-AIDS morbidity and mortality among HIV-positive individuals [1,2] and an increased risk of CVD events has been observed when compared with HIV-negative populations [3–8]. This has been attributed to the increased prevalence of surrogate markers of CVD (such as dyslipidaemia) and the proinflammatory state associated with HIV infection. However, because ART may not mitigate (or indeed may exacerbate) these effects, caution is required in extrapolating from these makers to effects on overall mortality. The following recommendations apply to patients with, or at high risk, of CVD.

8.6.2 Definition and assessment of cardiovascular disease risk

For the purposes of these guidelines, patients with an elevated CVD risk are as defined in the JBS2 guidelines [9] and include:

- People with any form of established atherosclerotic CVD.
- Asymptomatic people who have an estimated multifactorial CVD risk >20% over 10 years.
- People with diabetes mellitus (type 1 or 2).
- People with elevated blood pressure >160 mmHg systolic or >100 mmHg diastolic, or lesser degrees of blood pressure elevation with target organ damage.
- People with elevated total cholesterol to high-density lipoprotein cholesterol ratio >6.0.
- People with familial dyslipidaemia.

NICE does not recommend a specific CVD risk calculation for the UK population [10]. Cohort data have demonstrated that the observed myocardial infarction (MI) rates in HIV-seropositive people in developed countries paralleled those predicted by the Framingham risk equation [11] but the

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extent to which this can be extrapolated to women and men of non-European ethnicity is unknown. Therefore, there is insufficient evidence to recommend a specific CVD risk calculation for the population of HIV-positive adults in UK.

The Framingham CVD risk calculator works reasonably well in HIV-positive populations, although it is worth noting that it was not developed for use in non-white groups. Other algorithms may be better suited to these populations. A CVD risk calculator has been developed for use in HIV-positive populations (http://www.chip.dk/TOOLS) [12], although it should be noted that this provides 5-year risk estimates rather than the usual 10-year estimates. Alternatively, the QRISK calculator (http://www.qrisk.org) or the QIntervention tool (http://qintervention.org), which also provides an estimate of the risk of developing type II diabetes, can be used.

8.6.3 When to start antiretroviral therapy

There are insufficient data to inform whether CVD risk should affect the decision to start ART.

The SMART trial provides the only randomized data about the effect of ART on CVD risk, but was not powered for a CVD endpoint. Fewer major CVD events were observed in the viral suppression arm but the difference was not statistically significant [13]. In a *post hoc* analysis, HIV VL <400 copies/mL was associated with fewer CVD events suggesting that suppression of viraemia may have been protective; CD4 cell count was not significantly associated with CVD events [14,15].

Several cohort studies have examined changes in rate of cardiovascular events in HIV-positive populations over time since the introduction of ART but no clear protective effect was found [16–19]. In the HIV Outpatients Study cohort, baseline CD4 cell count <350 cells/μL was associated with increased CVD risk, but 350–500 cells/μL and use of ART were not; in a parallel case–control study, cases were more likely to have a current (but not baseline or nadir) CD4 cell count of 350–500 cells/μL [20]. The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study found that untreated patients had a lower incidence of MI than those on ART [21] and risk increased with longer exposure to combination therapy [22].

While there is uncertainty as to whether treating HIV infection reduces CVD risk, there is good evidence from RCTs that interventions targeted at modifiable CVD risk factors are of benefit. For this reason, all HIV-positive adults should be assessed for CVD risk annually and interventions targeted at improving modifiable risk factors.

8.6.4 What to start

8.6.4.1 Recommendations

- We suggest avoiding ABC (2C), FPV/r (2C) and LPV/r (2C) in patients with a high CVD risk, if acceptable alternative ARV drugs are available.

Auditable measure. Number of patients with high CVD risk on either ABC or FPV/r or LPV/r and record of rationale.

8.6.4.2 Rationale

Modifiable risk factors should be addressed in all patients with high CVD risk.

No RCT has been powered to assess the CVD risk associated with the use of individual ARVs and a history of CVD may be an exclusion criteria. A meta-analysis of all RCTs where ABC was assigned randomly found no association with MI, but the event rate in the population was low; the extent to which these findings can be extrapolated to a population with high CVD risk is unknown [23]. Although a *post hoc* analysis of the SMART study did find such an association, use of ABC was not randomized [24].

Two cohorts have found a strong association between recent ABC use and MI [25,26] while another did not [27,28]; all were limited in their ability to adjust for presence of CVD risk factors. An analysis of the manufacturer's trial registry found no association [29], but the trials only enrolled patients with low CVD risk. One case–control study, which did not adjust for important CVD risk factors, did find an elevated risk of MI associated with ABC use [7] but another did not [12]. Cerebrovascular events were more common in patients exposed to ABC in two cohort studies [8,28] while another found a protective effect [27]. In view of the uncertainty about the safety of ABC in patients with a high CVD risk, we suggest the use of alternative agents where possible.

Early studies of PI exposure and risk of MI gave conflicting results, some reporting an increased risk [5,30] while others did not [3,16,31]. The D:A:D cohort, with longer follow-up, reported an increasing risk of MI with years of PI exposure (independent of measured metabolic effects) [22]. Cumulative exposure to indinavir and LPV/r were associated with increasing risk of MI [adjusted relative risk per year for LPV/r 1.13 (95% CI 1.05–1.21); relative risk at 5 years 1.84] [26]. Case–control studies reported similar associations for LPV/r [7,12] and FPV/r [12] but in one of these, important CVD risk factors were not included [7]. A further study found no association between PI exposure and all cerebrovascular events [8].

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An updated analysis has recently reported no association between ATV/r use and an increased risk of MI [32]. Although there has been insufficient data to include DRV/r in these analyses, in patients with a high CVD risk, we suggest the use of alternatives to LPV/r and FPV/r where possible.

In the MOTIVATE studies for treatment-experienced patients, coronary artery disease events were only reported in the MVC arm (11 in 609 patient years), while there were none in the placebo arm (0 in 111 patient years); those affected generally had pre-existing CVD risk. No such signal was found in the MERIT study for treatment-naïve patients. MVC has also been associated with postural hypotension when used at higher than recommended doses in healthy volunteers; patients with a history of postural hypotension, renal impairment or taking antihypertensive agents may be at increased risk [33]. In view of the limited data available, special caution should be exercised in the use of MVC in patients with a high CVD risk and use of alternative agents, where possible, considered.

8.6.5 References

1 Mocroft A, Reiss P, Gasiorowski J *et al.* Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr* 2010; **55**: 262–270.

2 Smith C. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS* 2010; **24**: 1537–1548.

3 Klein D, Hurley LB, Quesenberry CP Jr *et al.* Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr* 2002; **30**: 471–477.

4 Currier J, Taylor A, Boyd F *et al.* Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003; **33**: 506–512.

5 Mary-Krause M, Cotte L, Simon A *et al.* Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS* 2003; **17**: 2479–2486.

6 Triant V, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007; **92**: 2506–2512.

7 Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Québec's public health insurance database. *J Acquir Immune Defic Syndr* 2011; **57**: 245–253.

8 Rasmussen LD, Engsig FN, Christensen H *et al.* Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. *AIDS* 2011; **25**: 1637–1646.

9 British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association. Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91** (Suppl 5): v1–52.

10 National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE CG67. London, 2008, reissued 2010. Available at http://www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf (accessed May 2012).

11 Law MG, Friis-Møller N, El-Sadr WM *et al.* The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med* 2006; **7**: 218–230.

12 Lang S, Mary-Krause M, Cotte L *et al.* Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med* 2010; **170**: 1228–1238.

13 El-Sadr WM, Lundgren JD, Neaton JD *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355**: 2283–2296.

14 Phillips AN, Carr A, Neuhaus J *et al.* Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther* 2008; **13**: 177–187.

15 Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS* 2008; **22**: 2409–2418.

16 Bozette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003; **348**: 702–710.

17 Crum NF, Riffenburgh RH, Wegner S *et al.* Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006; **41**: 194–200.

18 Palella FJ Jr, Baker RK, Moorman AC *et al.* Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006; **43**: 27–34.

19 Bonnet F, Chene G, Thiebaut R *et al.* Trends and determinants of severe morbidity in HIV-infected patients:

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the ANRS CO3 Aquitaine Cohort, 2000–2004. *HIV Med* 2007; **8**: 547–554.
20 Lichtenstein KA, Armon C, Buchacz K *et al*. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV Outpatient Study. *Clin Infect Dis* 2010; **51**: 435–447.
21 Friis-Moller N, Sabin CA, Weber R *et al*. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349**: 1993–2003.
22 Friis-Moller N, Reiss P, Sabin CA *et al*. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; **356**: 1723–1735.
23 Ding X, Andraca-Carrera E, Cooper C *et al*. No Association of myocardial infarction with ABC use: an FDA meta-analysis. *18th Conference on Retroviruses and Opportunistic Infections*. Boston, MA. February 2011 [Abstract 808].
24 SMART/INSIGHT and D:A:D. Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008; **22**: F17–F24.
25 Obel N, Farkas DK, Kronborg G *et al*. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med* 2010; **11**: 130–136.
26 Worm SW, Sabin C, Weber R *et al*. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* 2010; **201**: 318–330.
27 Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the HAART era. *Clin Infect Dis* 2011; **53**: 84–91.
28 Choi AI, Vittinghoff E, Deeks SG *et al*. Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons. *AIDS* 2011; **25**: 1289–1298.
29 Brothers CH, Hernandez JE, Cutrell AG *et al*. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr* 2009; **51**: 20–28.
30 Holmberg SD, Moorman AC, Williamson JM *et al*. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002; **360**: 1747–1748.
31 Iloeje UH, Yuan Y, L'Italien G *et al*. Protease inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. *HIV Med* 2005; **6**: 37–44.
32 d'Arminio Monforte A, Reiss P, Ryom L *et al*. ATV-containing ART is not associated with an increased risk of cardio- or cerebrovascular events in the D:A:D study. *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, WA. March 2012 [Abstract 823].
33 European Medicines Agency. Celsentri Summary of Product Characteristics. 2007. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000811/WC500022190.pdf (accessed May 2012).

8.7 Women

8.7.1 Introduction

The following guidance considers issues concerning the initiation and choice of ART for HIV-positive women who are not currently pregnant. For guidance on the management of pregnancy in HIV-positive woman please refer to the *BHIVA guidelines for the management of HIV infection in pregnant women 2012* [1].

There are few specific data on ART treatment in women other than in pregnancy. Data available are largely from a meta-analysis, *post hoc* analyses or derived from cohort studies. The majority of the randomized clinical trial data on ART comes from studies that have enrolled mostly male subjects. If RCTs do enrol women, the numbers are often too small to draw significant gender-based conclusions.

Approximately one-third of people diagnosed with, and accessing care, for HIV in the UK are women [2]. The majority are of childbearing age but the age range is increasing, adding the complexity of menopause and its sequelae to the management of HIV-positive women. Many HIV-positive women in the UK are of African heritage and face overlapping challenges to their health and well-being [3].

Women's experience of HIV reflects multiple social and cultural influences, which when combined with sex-specific biological factors influence individual responses to HIV.

8.7.2 When to start

8.7.2.1 Recommendations

- We recommend therapy-naïve HIV-positive women who are not pregnant start ART according to the same indicators as in men (see Section 4: When to start) 1A.

Auditable measure. Proportion of HIV-positive women with CD4 cell count <350 cells/μL not on ART.

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8.7.2.2 Rationale

Gender differences in HIV VL and CD4 cell count at different stages of infection have been observed [4] but have not been consistently associated with long-term clinical outcomes for HIV-positive women. Based on current data, the indications for starting ART do not differ between women who are not pregnant and men.

Gender-specific socio-economic and cultural factors may impact on women's ability to access care and manage their medication, compromising their ability to initiate and adhere to therapy, and they may require support from the multidisciplinary team.

8.7.3 What to start

8.7.3.1 Recommendations

- We recommend therapy-naïve HIV-positive women start ART containing two NRTIs and one of the following: PI/r, NNRTI or INI (1A), as per therapy-naïve HIV-positive men.
- We recommend therapy-naïve HIV-positive women start ART with preferred or alternative NRTI backbone and third agent as per therapy-naïve HIV-positive men (See Section 5.1: What to start: summary recommendations) (1A).
- Factors such as potential side effects, co-morbidities, drug interactions, patient preference and dosing convenience need to be considered in selecting ART in individual women.
- We recommend both HIV-positive women of childbearing potential and healthcare professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV-positive woman and for that of an unborn child (GPP).
- We recommend that potential pharmacokinetic interactions between ARVs, hormonal contraceptive agents and hormone replacement therapy are checked before administration (with tools such as: http://www.hiv-druginteractions.org) (GPP]).

8.7.3.2 Rationale

Efficacy. There are few data to guide prescribing of initial ART specifically for women, as no RCT in patients starting ART has been powered to detect sex differences in efficacy. From the limited data available, virological outcomes within clinical trial settings generally appear to be no different between men and women.

A meta-analysis of FDA registrational RCTs analysed data from 22 411 HIV-positive patients participating in 43 trials for 16 ARVs. Overall, 20% of study participants were women. No significant differences in treatment response at week 48 were reported between men and women. Rates of ART discontinuation for virological failure were higher in men (8.15%) than in women (4.25%) [5].

A subanalysis of an RCT comparing ATV/r and LPV/r in ART-naïve patients of whom 31% were women, showed comparable virological efficacy at week 96 between the two treatment arms in women [6], although virological response rates were lower in women when compared with men.

In a study comparing ATV/r and EFV in 1857 ART-naïve patients of whom 17% were women, female sex was associated with increased virological failure on ATV/r compared with EFV [7]. No difference was seen with EFV between men and women.

The efficacy and tolerability of RAL were shown not to be different between men and women at 48 weeks in one study of a diverse cohort of both treatment-naïve and -experienced patients [8]. RPV in ART-naïve men and women showed no difference in rates of virological suppression at 48 and 96 weeks between men and women, but the number of women included was low and the study was not designed to investigate sex differences [9,10].

Cohort studies in the UK have reported similar virological outcomes during the first year of treatment in heterosexual men and women [11]. An Italian cohort study reported no significant effect of gender on clinical progression or the risk of developing a clinical event [12]. Data from Spain, which included both naïve and ARV-experienced women patients, showed them with similar virological responses to men [13].

HIV-positive women starting ART should use ARVs from the list of preferred and alternative drugs outlined in Section 5.1 (What to start: summary recommendations). Factors, including potential for side effects, drug interactions, patient preference, co-morbidities and dosing convenience need to be taken into consideration when selecting ART regimens in individual women.

Toxicity, discontinuation and adherence. Adverse events and treatment discontinuations within ART clinical trials and cohort studies published between 2002 and 2007 have been systematically reviewed. The overall event rate is often the same but the adverse event profile may be different. Women were reported to be more likely than men to experience ART-related lipodystrophy, rash and nausea, and to discontinue therapy [4].

Data from the USA have shown that women are more likely than men to discontinue ART for poor adherence, dermatological symptoms, neurological reasons, constitutional symptoms and concurrent medical conditions [14]. UK cohort data found 88.6% of men compared with 80.7% of women spent 100% of the first year after starting

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HAART actually on therapy [11].

Comparison of ATV/r with LPV/r found poorer virological outcomes in treatment-naïve women compared with men. Gender differences in efficacy were due to higher discontinuation rates in women than men in both treatment arms [6]. CNS side effects of varying severity can occur with EFV, particularly at the initiation of therapy. This may be partly explained by the greater EFV exposure associated with a CYP2B6 variant, more commonly found in Africans and African Americans [15]. In the UK population, this is of particular relevance to women, the majority of whom are of African ethnicity. NVP-associated rash occurs more frequently in women than men [16]. Hepatotoxicity associated with NVP is more common in women with a CD4 cell count >250 cells/μL, restricts women's use of the drug [17].

A systematic review of studies on gender and ART adherence published between 2000 and 2011 in the resource-rich world concluded that overall reported adherence is lower in women than men [18]. However, of over 1000 studies initially identified for review, only 44 had adequate data on gender to allow any comparisons to be made. The authors identified the particular factors for lower adherence in women were depression, lack of supportive interpersonal relationships, young age, drug and alcohol use, black ethnicity, ART of six or more pills per day, higher numbers of children, self-perception of abdominal fat gain, sleep disturbances and increased levels of distress.

Fetal safety. Concerns about potential fetal toxicity of ARVs have influenced prescribing practice in HIV-positive women. Of note, other than ZDV in the third trimester, no ARV drug has a licence for use in pregnancy.

Pregnancy in women living with HIV who are already on effective therapy is increasing; 70% of HIV-positive pregnant women in the UK in 2010 were diagnosed before the current pregnancy, of which 60% were already on ART at conception [19]. Where newer drugs are available, women are conceiving on these agents, with ZDV now rarely used as first-line therapy for adults. European cohort data comparing pregnancies that were managed with ZDV-containing regimens *vs*. those without ZDV found no difference in risk of detectable VL at delivery, vertical transmission or congenital abnormality when comparing ZDV-sparing with ZDV-containing ART [20].

The most robust data on teratogenicity and first trimester ART exposure are from the Antiretroviral Pregnancy Registry (APR) [21]. This international prospective reporting system records rates of congenital birth defects in babies born to women with exposure to ART at any stage of pregnancy. Approximately 200 or more reports need to be received for a particular compound before data are reported for that compound by the APR. There are now over 200 prospective reports in the APR of first trimester exposure for ABC, ATV, EFV, FTC, 3TC, LPV, NVP, ritonavir, TDF and ZDV. No signal of increased risk of congenital abnormality has been demonstrated, and a greater than twofold higher rate than in the general population has been excluded. There are, so far, fewer than 200 prospective reports for DRV, RAL and RPV within the APR and hence no reports on these agents are yet available.

Despite previous concerns over the safety of EFV based on preclinical animal studies and retrospective case reports in human subjects, the current data do not provide evidence of excess teratogenicity above the expected baseline for infants exposed to EFV in the first trimester. Sufficient numbers of first trimester exposures of EFV have been monitored to detect at least a twofold increase in risk of overall birth defects within the APR, and no such increases have been detected to date [21].

Data from Côte d'Ivoire found no significant increased risk of unfavourable pregnancy outcome in women with first-trimester exposure to EFV compared with NVP [22]. A systematic review and meta-analysis of observational cohorts carried out in 2010 [23] and further updated in 2011 [24] reported birth outcomes among women exposed to EFV during the first trimester. No increased risk of overall birth defects among the babies of women exposed to EFV during the first trimester compared with exposure to other ARV drugs was found. The prevalence of overall birth defects with first-trimester EFV exposure was similar to the ranges reported in the general population.

A review of live births to women with HIV in a large unselected UK population between 1990 and 2007 found no increased risk of abnormalities in infants exposed to EFV in the first trimester, providing further reassurance that ART *in utero* does not pose a major risk of fetal anomaly [25]. Mathematical modelling using North American cohort data has demonstrated a theoretical loss of life expectancy in women who delay EFV at initiation of ARV [26].

Based on current evidence, EFV can be initiated in women of childbearing potential, can be continued in women who conceive on the drug and commenced in pregnancy but the data should be discussed in detail with the individual woman when deciding on her preferred treatment regimen. Given that no ARV drug is licensed for use in pregnancy apart from ZDV in the third trimester, a discussion regarding the potential unknown long- and short-term effects on an unborn child should be had with any woman of childbearing potential who commences any ARV drug regimen. Further details can be found in the BHIVA pregnancy guidelines [1].

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Hormone interactions. Significant pharmacokinetic and pharmacodynamic interactions have been reported between ARV drugs and hormonal agents. Inducers of hepatic enzymes by ARVs may result in increased breakdown of ethinyl oestradiol and progestogens that can compromise contraceptive and hormone replacement therapy efficacy. Additional contraceptive measures or different ARV regimens may be required in these circumstances. Potential DDIs should be checked using various resources, including specialist HIV pharmacists, web-based tools such as the University of Liverpool website on HIV drug interactions and medical information departments in pharmaceutical companies. There is no significant interaction between ETV and the combined oral contraceptive pill, and no interaction is anticipated with RAL. Hormonal contraceptive agents, which have been shown not to have a significant interaction or where there is no anticipated interaction include depot medroxyprogesterone acetate, and the levonorgestrol IUS (Mirena coil).

8.7.4 HIV-positive women experiencing virological failure

There is very little evidence to guide prescribing ART in HIV-positive women experiencing virological failure on ART, with most studies recruiting approximately 10% of women. One study investigating DRV/r in ART-experienced patients recruited a large proportion of women and was powered to show a difference in virological efficacy between men and women; this showed higher discontinuation rates among women than men, with nausea being cited as a particular problem, but overall there was no difference in virological efficacy [27]. A further study has reported similar efficacy and tolerability of RAL in ART-experienced HIV-positive women [8].

In HIV-positive women experiencing virological failure on ART, the same principles of management and recommendations apply as per HIV-positive men experiencing virological failure (see Section 7: Management of virological failure).

8.7.5 References

1 Taylor GT, Clayden P, Dhar J *et al.* BHIVA guidelines for the management of HIV infection in pregnant women 2012. *HIV Med* 2012; **13** (Suppl. 2): 87–157.

2 Health Protection Agency. *HIV in the United Kingdom: 2010 Report.* London, Health Protection Agency, 2010.

3 Doyal L. Challenges in researching life with HIV/AIDS: an intersectional analysis of black African migrants in London. *Cult Health Sex* 2009; **11**: 173–188.

4 Nicastri E, Leone S, Angeletti C *et al.* Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. *J Antimicrob Chemother* 2007; **60**: 724–732.

5 Soon G, Min M, Struble K *et al.* Meta-analysis of efficacy outcomes for treatment-naïve and experienced HIV-infected women in randomized controlled clinical trials (RCTs) (2000–2008). *50th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Boston, September 2010 [Abstract H-1812].

6 Squires KE, Johnson M, Yang R *et al.* Comparative gender analysis of the efficacy and safety of atazanavir/ritonavir and lopinavir/ritonavir at 96 weeks in the CASTLE study. *J Antimicrob Chemother* 2011; **66**: 363–370.

7 Smith K, Tierney C, Daar E *et al.* Association of race/ethnicity and sex on outcomes in ACTG A5202. *18th Conference on Retroviruses and Opportunistic Infections.* Boston, MA. February 2011 [Abstract 536].

8 Squires K, Bekker L, Eron J *et al.* Safety, tolerability, and efficacy of raltegravir (RAL) in a diverse cohort of HIV-infected patients: 48-week results from the REALMRK study. *51st Interscience Conference on Antimicrobial Agents and Chemotherapy.* Chicago, IL. September 2011 [Abstract H2-789].

9 Cohen CJ, Andrade-Villanueva J, Clotet B *et al.* Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; **378**: 229–237.

10 Martorell C, Mayer CA, Northland R *et al.* Week 96 safety and efficacy by gender and race subgroups in treatment-naïve HIV-1-infected patients in the Phase III ECHO and THRIVE trials. *Annual Meeting of the Infectious Diseases Society of America.* Boston, MA. September 2011 [Abstract 404].

11 Barber TJ, Geretti AM, Anderson J *et al.* Outcomes in the first year after initiation of first-line HAART among heterosexual men and women in the UK CHIC Study. *Antivir Ther* 2011; **16**: 805–814.

12 Murri R, Lepri A, Phillips A. Access to antiretroviral treatment, incidence of sustained therapy interruptions, and risk of clinical events according to sex: evidence from the ICoNA. Study. *J Acquir Immune Defic Syndr* 2003; **34**: 184–189.

13 Collazos J, Asensi V, Carton JA. Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART. *AIDS* 2007; **21**: 835–843.

14 Kempf MC, Pisu M, Dumcheva A *et al.* Gender differences in discontinuation of antiretroviral treatment regimens. *J Acquir Immune Defic Syndr* 2009; **52**: 336–341.

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15 Haas DW, Ribaudo HJ, Kim RB *et al*. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004; **18**: 2391–2400.
16 Mazhude C, Jones S, Murad S. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor induced rash. *AIDS* 2002; **16**: 1566–1568.
17 Sanne I, Mommeya-Marin H, Hinkle J, Bartlett JA, Lederman MM, Maartens G. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis* 2005; **191**: 825–829.
18 Puskas CM, Forrest JI, Parashar S *et al*. Women and vulnerability to HAART non-adherence: a literature review of treatment adherence by gender from 2000 to 2011. *Curr HIV/AIDS Rep* 2011; **8**: 277–287.
19 National Study of HIV in Pregnancy and Childhood. National surveillance data. Available at http://www.nshpc.ucl.ac.uk (accessed April 2012).
20 Tariq S, Townsend CL, Cortina-Borja M *et al*. Use of zidovudine-sparing HAART in pregnant HIV-infected women in Europe: 2000–2009. *J Acquir Immune Defic Syndr* 2011; **57**: 326–333.
21 Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2011*. Wilmington, NC, Registry Coordinating Center, 2011. Available at http://www.APRegistry.com (accessed April 2012).
22 Ekouevi DK, Coffie PA, Ouattara E *et al*. Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the IeDEA West Africa and ANRS Databases, Abidjan, Côte d'Ivoire. *J Acquir Immune Defic Syndr* 2011; **56**: 183–187.
23 Ford N, Mofenson L, Kranzer K *et al*. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS* 2010; **24**: 1461–1470.
24 Ford N, Calmy A, Mofensen L. Safety of efavirenz in first-trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS* 2011; **25**: 2301–2304.
25 Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990–2007. *AIDS* 2009; **23**: 519–524.
26 Hsu H, Rydzak C, Cotich K *et al*. Quantifying the risks and benefits of efavirenz use in HIV-infected women of childbearing age in the USA. *HIV Med* 2011; **12**: 97–108.
27 Currier J, Averitt Bridge D, Hagins D *et al*. Sex-based outcomes of darunavir-ritonavir therapy: a single-group trial. *Ann Intern Med* 2010; **153**: 349–357.

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Dr Duncan Churchill has no conflicts of interest to declare.

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Professor Jose Arribas has a financial interest/relationship or affiliation: Tibotec, Janssen, Abbott, BMS, Gilead Sciences, MSD, ViiV Healthcare.

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Dr Mike Youle has received lecture and consultancy fees from Abbott and Gilead.

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10.0 List of abbreviations

3TC	2′,3′-dideoxy-3′-thiacytidine, lamivudine
ABC	Abacavir
ACTG	AIDS Clinical Trials Group
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
BHIVA	British HIV Association
BPS	British Psychological Society
CCR5	C–C chemokine receptor type 5
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy regimen
CI	Confidence interval
CKD	Chronic kidney disease
Cmin	Minimum concentration
CNS	Central nervous system
CPE	Clinical penetration effectiveness
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
CYP450	Cytochrome P450
DDI	Drug–drug interaction
DRV	Darunavir
DRV/r	Darunavir/ritonavir
ECG	Electrocardiogram
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
ELV	Elvitegravir
ETV	Etravirine
FDC	Fixed-dose combination
FPV	Fosamprenavir
FPV/r	Fosamprenavir/ritonavir
FTC	Emtricitabine
GPP	Good practice point
GRADE	Grading of recommendations assessment, development and evaluation
GSS	Genotypic sensitivity score
HAART	Highly active anti-retroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HLA	Human leukocyte antigen
INI	Integrase inhibitor
IQR	Interquartile range
IRD	Immune reconstitution disorder
KS	Kaposi sarcoma
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MVC	Maraviroc
MI	Myocardial infarction
NADM	Non-AIDS-defining malignancy
NC	Neurocognitive
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Clinical Excellence
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
NVP	Nevirapine
PHI	Primary HIV infection
PI	Protease inhibitor
PI/r	Ritonavir-boosted protease inhibitor
RAL	Raltegravir
RCT	Randomized clinical trial
RPV	Rilpivirine
RT	Reverse transcriptase
RR	Relative risk
SQV/r	Saquinavir/ritonavir
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TDM	Therapeutic drug monitoring
TPV	Tipranavir
TPV/r	Tipranavir/ritonavir
UK CAB	UK Community Advisory Board
VL	Viral load
WT	Wild type
ZDV	Zidovudine

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11.0 List of appendices

The appendices can be found on the BHIVA website (http://www.bhiva.org/TreatmentofHIV1_2012.aspx)

Appendix 1 Summary modified GRADE system
Appendix 2 Literature search
A2.1 Questions and PICO criteria
A2.2 Search protocols
Appendix 3 GRADE tables
A3.1 Choice of nucleoside reverse transcriptase inhibitor backbone
A3.2 Choice of third agent
A3.3 Protease inhibitor monotherapy
Appendix 4 BHIVA Treatment Guideline update 2013

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CORRIGENDUM

In the British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (2013 update)[1], the following text amendment should be noted:

On page 32, right-hand column, paragraph 3, with a yellow background, the text reads as:

> RPV **is also recommended as a preferred third agent** but only in patients with baseline VL < 100 000 copies/mL.

This should be changed to:

> RPV **remains an alternative agent**, and should only be used in patients with baseline VL < 100 000 copies/mL.

We apologise for this error.

Reference

1 Williams I, Churchill D, Anderson J *et al*. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (2013 update). *HIV Medicine* 2014; **15** (Suppl 1): 1–85.