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BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010

Y Gilleece, DR Chadwick, J Breuer, D Hawkins, E Smit, LX McCrae, D Pillay, N Smith and J Anderson on behalf of the BHIVA Guidelines Subcommittee*

British HIV Association (BHIVA), BHIVA Secretariat, Mediscript Ltd, London, UK

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Introduction and epidemiology

HIV-2, which is closely related to SIV from sooty mangabeys, was first identified in 1986 in patients with AIDS in Guinea-Bissau and Cape Verde, West Africa. Like HIV-1, HIV-2 is an immunodeficiency virus that causes AIDS in humans. However, although HIV-1 and HIV-2 are related, there are important structural differences between them which influence pathogenicity, natural history and therapy.

The HIV-2 epidemic has its epicentre in West Africa, and is also found in those countries that have had historical colonial links with the region, in particular Portugal and France. Sociocultural issues such as civil war and migration have had major impacts on the spread of HIV-2. Recent data from Guinea-Bissau suggest that the incidence of HIV-2 is now falling, in contrast to that of HIV-1, which has remained stable since 1999 [1]. Diagnoses of HIV-2 are increasing in India but in Europe and the United States the prevalence remains low [2–4]. HIV-2 does not protect against HIV-1 and dual infection is observed. In the United Kingdom, approximately 137 HIV-2 monoinfections and 35 HIV-1 and HIV-2 dual infections have been reported to the Health Protection Agency (HPA) [5].

Modes of transmission

The most common mode of transmission is through heterosexual sex. HIV-2 is less infectious early in the course of infection than HIV-1, with a 5–10-fold lower rate of heterosexual transmission [6,7] and a 20–30-fold lower rate of vertical transmission [8–10]. This is likely to be a result of the lower level of viraemia observed in HIV-2 than in HIV-1 [11]. The rate of sexual transmission of HIV-2 is increased in the presence of other sexually transmitted infections, particularly ulcerative conditions such as herpes simplex and syphilis [12,13]. Vertical transmission has been reported in association with primary HIV-2 infection during pregnancy [8–10]. Other transmission routes are blood transfusion [14,15], and probably injecting drug use and homosexual sex.

Correspondence: Dr Yvonne Gilleece, Lawson Unit, Royal Sussex County Hospital, Eastern Road, Brighton BN2 5BE, UK. Tel: 01273 664731; fax: 01273 674720; e-mail: yvonne.gilleece@bsuh.nhs.uk

*See Appendix for list of members of the BHIVA Guidelines Writing Group on HIV-2.

Natural history

Both HIV-1 and HIV-2 are associated with similar opportunistic infections and AIDS. Natural history studies indicate that HIV-2 is less pathogenic than HIV-1 [16–18]. Although the mortality rate in individuals infected with HIV-2 is two-to-three times that seen in HIV-negative populations, this compares with a 10-fold higher mortality rate in those infected with HIV-1 than in those who are HIV negative. HIV-2 infection has a longer asymptomatic phase than HIV-1 infection and some patients with HIV-2 may never develop AIDS [19]. A cohort study of seroconverter women in Senegal found that the incidence of AIDS-defining illness was 0.95 [95% confidence interval (CI) 0.2–3.8] per 100 person-years among HIV-2-infected women as compared with 5.6 (95% CI 3.3–9.8) in HIV-1-infected women [16]. In practice, it is not unusual to see patients who remain asymptomatic for 10–20 years without treatment [20]. There are, however, patients in whom disease progresses as rapidly as in those who have HIV-1. AIDS-defining illnesses have been noted to occur at higher CD4 cell counts in individuals infected with HIV-2 than in those infected with HIV-1, although this is unusual [21].

Plasma viral loads are lower in HIV-2-infected individuals, suggesting that HIV-2 replication is restricted in comparison to that of HIV-1. An *in vivo* study has clearly demonstrated that, like HIV-1, HIV-2 can establish a stable, integrated proviral infection but that HIV-2 produces less mRNA, which may attenuate HIV-2 replication and

pathogenesis [22]. HIV-2 is less infectious than HIV-1 early in the course of infection and, although infectivity increases as the disease advances, in general HIV-2 has significantly lower infectivity than HIV-1 [23].

Dual infection with HIV-1 and HIV-2

HIV-2 infection does not protect against HIV-1 infection and dual infection is well documented [24–26] although it is still uncommon in the United Kingdom. Studies from West Africa demonstrate that dual infection is more common in older women [25]. Dually infected patients tend to present at a more advanced stage of disease than those with HIV-2 only. Infection with both HIV-1 and HIV-2 generally carries the same prognosis as HIV-1 monoinfection [19].

Diagnosis of HIV-2 infection

It is important to note that HIV-2 has a different capsid antigen from the HIV-1 p24 antigen and that this capsid antigen may result in a prolonged seroconversion window period for HIV-2, but there is no current evidence from human studies that it is longer than the 3-month period described for HIV-1. Detection of HIV-2 infection is based on the demonstration of virus-specific antibodies using enzyme-linked immunosorbent assay-based techniques. It is recommended that all HIV-confirmatory laboratories use appropriate discriminatory assays such as Immunocomb HIV 1&2 (Orgenics Ltd, Yavne, Israel) or Genie II HIV-1/2 (Bio-Rad, Marnes la Coquette, France) to differentiate HIV-1 and HIV-2 infections, and to diagnose dual infection, as part of their HIV confirmation algorithm. These dot blot assays should be confirmed with a line immune assay such as Inno-LIA HIV 1/2 (Innogenetics, Gent, Belgium) or Western blot. In cases of doubt, for instance faint bands or blots against HIV-2 antigens, blood should be sent on to the HPA's Centre for Infections, Colindale (London, UK) for further investigation in their in-house HIV-2 specific antibody assays.

Historically in the United Kingdom, not all laboratories have had universal access to HIV-2 diagnostic tests. It is therefore good practice to re-evaluate the serology of any individual who is positive for HIV-1 with an undetectable HIV-1 viral load while not on treatment to ensure that HIV-2 infection is not overlooked, particularly in patients from an HIV-2-endemic area.

Where infection with both HIV-1 and HIV-2 is suspected, dual sero-reactivity for both HIV-1 and HIV-2 alone is not diagnostic. Dual infection can be proven only by the isolation of both viruses from the same individual or by demonstration of HIV-1 and HIV-2 proviral DNA in peripheral blood monocytes by polymerase chain reaction [27]. Because HIV-2 RNA may be negative it cannot be used as a diagnostic test. HIV-2 proviral DNA may be low or repeatedly negative in some asymptomatic individuals, making confirmation of diagnosis difficult [28].

Surrogate markers

HIV-2 RNA viral load

Although assays for quantifying HIV-2 exist they are variable and none is available commercially [29]. There is therefore limited access to these data in laboratories in the United Kingdom. HIV-2 plasma viral load is approximately 30-fold lower than that of HIV-1 [30]. The median HIV-2 plasma viral load has been documented as being 3 $\log_{10}$ HIV-2 RNA copies/mL [31]. Baseline HIV-2 RNA load, when detectable, significantly predicts the rates of disease progression as determined by CD4 cell decline or death [20,32]. HIV-2-infected individuals with high RNA loads experience rapid CD4 cell count declines and death, as seen in HIV-1-positive individuals, whereas those with low or undetectable HIV-2 RNA viral loads have decreased or indeed no disease progression [32]. In practice, however, HIV-2 viral load is detectable in only 8% of individuals with CD4 counts >500 cells/μL, in 62% of those with CD4 counts <300 cells/μL and in only 53% of individuals with an AIDS-defining illness [33]. Thus, in patients with CD4 counts <300 cells/μL, where it is detectable, measurement of HIV-2 RNA viral load may be used to identify individuals most at risk of disease progression. Conversely, in patients in whom HIV RNA is not detectable or even low, HIV-2 RNA should be interpreted together with CD4 cell count both when considering and when monitoring treatment.

A Collaboration on HIV-2 Infection (ACHIEV2E) study group has evaluated various HIV-2 RNA assays employed in nine different centres and found considerable variation between laboratories, particularly for HIV-2 group B. This may make comparison of outcome between cohort studies difficult, which may in turn reduce the reliability of interpretation of HIV-2 RNA results [29]. The additional difficulty of obtaining a timely viral load assay makes monitoring the response to antiretroviral therapy difficult. Regular CD4 cell count monitoring is therefore very helpful to identify individuals with rapid progression. It is also important to note that treatment response may be poorer in those with HIV-2 infection, with significantly lower viral load drops reported when compared with HIV-1-infected patients with similar baseline characteristics [34]. The genome of HIV-2 is very variable and there is a possibility of under-quantification with the viral load assays; thus this response may be poorer still. Regardless of whether HIV-2 RNA is detectable or not, blood should be sent to a specialist HIV-2 viral load testing laboratory for quantification in an

alternative assay in all patients where there is a low CD4 cell count.

Viral load testing in the United Kingdom is performed at the following centres:

Prof. Deenan Pillay/Dr Bridget Ferns
Department of Virology
Royal Free & University College London Medical School
Windeyer Building
46 Cleveland St
London W1T 4JF
Tel: 0207 6799490/9483
Fax: 0207 5805896
E-mail: d.pillay@ucl.ac.uk

Dr Duncan Clark/Dr David Bibby
Department of Virology
Barts and The London NHS Trust
Pathology and Pharmacy Building
80 Newark St
London E1 2ES
Tel: 02032460358
Fax: 02032460325
E-mail: duncan.clark@bartsandthelondon.nhs.uk

The UK HIV-2 reference laboratory is based at the HPA in Colindale and is led by:

Dr Jennifer Tosswill
Health Protection Agency
Sexually Transmitted and Blood Borne Virus Laboratory
61 Colindale Avenue
London NW9 5HT
Tel: 020 8327 6274
E-mail: jennifer.tosswill@hpa.org.uk

HIV-2 genotyping can be performed by:

Dr Erasmus Smit
Consultant Virologist
West Midlands Public Health Laboratory
Health Protection Agency
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham B9 5SS
Tel: 0121 424 1239
Fax: 0121 772 6229
E-mail: erasmus.smit@heartofengland.nhs.uk

The laboratories should be contacted in advance of sending specimens to discuss appropriate samples and the conditions for transporting them.

CD4 cell count and percentage

In individuals with undetectable HIV-2 RNA, CD4 cell count may be the only method to identify whether an individual with HIV-2 infection needs treatment and whether that treatment regimen is effective. When detectable, the CD4 cell count decline correlates with HIV-2 RNA viral load and therefore, because of the undetectable or low viral load observed in HIV-2-infected patients, CD4 cell counts can remain stable for many years. However, CD4 cell counts can decline rapidly in those with a high viral load, the rate of decline being the same as in HIV-1-infected patients at comparable viral loads. High CD4 percentage is significantly associated with survival [20]. CD4 cell count rise in response to antiretroviral therapy is well documented [33,35,36]; however, it is often blunted when compared with the treatment response in HIV-1-infected patients [34]. Mean CD4 count rises of 40–71 and 60–136 cells/μL, respectively, have been reported using cohort data [37].

Treatment

Because of limited treatment experience and difficulties in organizing HIV-2 RNA and resistance assays, it is advisable for patients to be referred to an HIV-2-experienced treatment centre. There are no randomized control trials and treatment response is assessed using results obtained from small cohort and clinical case studies.

HIV-2 structure and genotype

HIV-2 shows significant genetic diversity and at least eight different groupings (designated A–H) have been described, with each representing a distinct cross-species transmission of the virus from its primate reservoir. However, despite all groupings exhibiting pathogenicity in humans, to date only groups A and B have become established as human epidemics [38]. All groups of HIV-2 differ significantly in structure from HIV-1, with an array of polymorphisms in areas that are associated with antiretroviral drug susceptibility in HIV-1 algorithms. Like HIV-1, HIV-2 exhibits mutations which may be found either as baseline polymorphisms or as secondary responses to antiretroviral agents. A baseline genotype prior to treatment should be carried out on all patients (contact Dr E. Smit). The specific mutations encountered following failed antiretroviral therapy in HIV-2-infected patients have similarities to those seen in HIV-1-infected patients. However, the pathways of resistance development differ and there are additional mutational changes which influence drug susceptibility. Because of this, and because of the lack of large data sets with which to clarify HIV-2 pathways, caution must be exercised in interpreting HIV-2 genotypic resistance.

Nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance

The structure of the NNRTI-binding pocket of HIV-2 differs from that of HIV-1 [39], conferring innate resistance to this class of drugs. NNRTIs should not be used [40].

Nucleoside reverse transcriptase inhibitor (NRTI) resistance

In vitro susceptibility of HIV-2 to NRTIs is similar to that of HIV-1 in spite of wild-type polymorphisms at NRTI HIV-1 mutation codons. However, there seems to be a low genetic barrier to resistance in HIV-2, with equivalent mutations in HIV-1 and HIV-2 reverse transcriptase (RT) having different effects on substrate susceptibility, with as few as two mutations in HIV-2 conferring full zidovudine and lamivudine resistance, which makes choices for salvage therapy very difficult [41].

Q151M (+ / − V111I) [33,42–48] and K65R [24,44,49] may develop much more rapidly in HIV-2-infected individuals than in those infected with HIV-1, and are the main resistance pathways. M184V/I appears upon treatment failure in patients treated with lamivudine/emtricitabine and has been reported to occur *in vitro* in as little as 6 weeks [50].

Patients failing treatment with thymidine analogues do not always exhibit classic thymidine analogue mutations (TAMs), suggesting that HIV-2 may have a different resistance pathway from that observed in HIV-1. Codon mutations K70R, S215Y and Q151M have been documented in HIV-2-positive individuals treated with zidovudine, causing NRTI treatment failure [33,42–46]. Q151M has been noted to occur with increased frequency in HIV-2-infected patients (16–27% *vs*. 2–5% in HIV-1-infected patients) treated with didanosine combined with either stavudine or zidovudine [35,36,40,46,49,51,52], resulting in low-level phenotypic resistance to didanosine, zidovudine and zalcitabine [35] but not multidrug resistance to almost all NRTIs. This may be a consequence of the lack of association with the other mutations of the multidrug resistance Q151M complex (A62V, V75I, F77L and F116Y) [46].

The mutation K65R was previously reported only in combination with and subsequent to the presence of Q151M and M184V in a patient receiving stavudine, abacavir and didanosine [36]. There are now conflicting data with respect to K65R. Recent data have highlighted the more frequent selection of the K65R mutation in HIV-2 than HIV-1, which can emerge as rapidly as 3 months after treatment initiation in NRTI-experienced patients in the presence of low (but not undetectable) HIV-2 viral loads [47,48,51]. *In vitro*, however, the K65R mutation was not detected despite the use of ultrasensitive genotyping after exposure to NRTI combinations as used in the clinical studies above [50]. It is possible that the interplay of TAMS and the K65R mutation seen in HIV-1 may also occur in HIV-2, causing reversion of mutations, but clearly more data are needed to assess this further. It is notable that tenofovir is effective in the presence of significant primary nucleoside-associated resistance mutations, including Q151M [36].

Protease inhibitor (PI) resistance

HIV-2 has natural polymorphisms at many of the HIV-1 primary and secondary PI codon positions which may play an important role in early treatment failure with the acquisition of more PI mutations. Cell culture experiments have shown early resistance mutation selection, even though the 50% inhibitory concentration (IC_{50}) values of some PIs for HIV-2 are similar to those for HIV-1 [53]. For this reason it is important to select the most potent PIs for therapy, because the NRTI backbone is already compromised. Careful follow-up and a timely change to second-line therapy must be a priority given that not many options are available.

Development of resistance mutations in HIV-2 protease may be similar to that in HIV-1 protease, and thus HIV-1 data may be used to help predict HIV-2 susceptibility [40]; however, some important differences exist. Resistance mutations known to confer resistance to PIs in HIV-1, but which can occur as natural polymorphisms in HIV-2, are 10I/V, 20V, 32I, 33V, 36I, 46I, I47V, 63E/K, 71V, 73A, 77T, 82I and 93L [35,36,42,53,54]. These mutations may be implicated in emergent drug resistance in HIV-2. Mutations in the protease of HIV-2 found to be selected with various PIs are W6F, T12A, E21K, I50V, I54M, V62A, I64V, V71I, I82F, I82L, I84V, L90M and L99F, some of which will show cross-resistance across the PI class (I54M, 82F and L99F) [54]. Several novel mutational pathways have been found to be associated with HIV-2 resistance to different PIs and have not been described in HIV-1 PI resistance pathways (W6F, T12A and E21K) [53]. Baseline genotypic testing of HIV-2 prior to treatment is therefore essential.

In vitro studies have shown the IC_{50} values of atazanavir (sevenfold), nelfinavir and tipranavir (eightfold) to be significantly higher than those for HIV-1, suggesting the hypothesis that these compounds have lower activities against HIV-2 [55–58]. Treatment with nelfinavir is associated with frequent virological failure and the emergence of I54M, I82F, V71L and L90M, and it is not recommended for use in HIV-2-infected patients [33]. *In vitro* data on tipranavir are in conflict, with one study finding tipranavir to be effective against HIV-2 [56] and another finding it to be as ineffective as atazanavir [55]. With no clinical data

available for tipranavir, its use in the treatment of HIV-2 should be considered with caution. A reduction in susceptibility to amprenavir to a level similar to that observed in HIV-1 following amprenavir-based regimen failure has been reported. This is likely to be clinically relevant, and therefore amprenavir is not recommended for HIV-2 [59]. M46I has been shown to occur frequently in PI-naïve HIV-2-infected patients and is associated with significant phenotypic resistance to indinavir, thus reinforcing the need for baseline genotyping prior to deciding on treatment [60].

There are few data on the use of saquinavir in HIV-2-infected patients, but two studies included seven patients treated with saquinavir in combination with one ($n = 1$) or two ($n = 3$) NRTIs, with a second PI, ritonavir ($n = 2$), or with two NRTIs and a second PI ($n = 1$). None of these treatments was effective, but it should be noted that saquinavir was used after patients had been exposed to other, suboptimal drug regimens. *In vitro* the IC_{50} of saquinavir has been found to be similar for HIV-1 and HIV-2 using both phenotypic and kinetic inhibition assays. Therefore saquinavir may be useful in the treatment of HIV-2 infection but should be monitored closely [36,55,57,61].

Lopinavir has been shown to be effective in the treatment of HIV-2 infection (see 'What to start treatment with') [62]. Of concern are more recent data suggesting an increased frequency of the proV47A mutation in HIV-2-infected patients failing lopinavir/ritonavir as their first PI [63,64]. This single mutation conferred high-level resistance to lopinavir and cross-resistance to indinavir and amprenavir. Hypersusceptibility to saquinavir was noted and susceptibility to tipranavir and atazanavir was maintained. This mutation does not occur in naïve patients and occurs in only 0.14% of PI-experienced HIV-1-infected patients, in whom it is associated with reduced viral replication [65]. In contrast, its reported frequency in HIV-2-infected patients is 8.6% and in these patients it is associated with lopinavir failure and increased viral replication (101.5%). When lopinavir fails with the emergence of the V47A mutation, treatment with saquinavir may be successful as a result of the hypersusceptibility conferred by this mutation [66]. More data are, however, needed to evaluate this further.

HIV-2 has *in vitro* sensitivities to lopinavir that are similar to those of HIV-1 [55,67]. There are no clinical studies comparing the efficacies of the different PIs. There is a good body of evidence that boosted lopinavir is clinically effective whereas there is less information on tipranavir and darunavir.

Fusion inhibitors

Reduced susceptibilities of 20- to 100-fold have been observed in viruses containing the envelope gene of HIV-2, which would suggest that an *in vivo* response is unlikely [68]; use of fusion inhibitors is therefore not recommended.

Integrase inhibitors

One *in vitro* study demonstrated that the phenotypic susceptibility of 19 wild-type samples of HIV-2 to raltegravir and elvitegravir was similar to that of HIV-1, in spite of the natural polymorphisms observed at secondary HIV-1 sites [69]. These changes may influence the rate at which primary mutations occur. The only published data available, in two patients, have shown raltegravir to be highly effective in heavily pretreated HIV-2-infected patients when used in combination with drugs selected based on RT and protease gene sequencing, which in both cases were abacavir, tenofovir and darunavir [70]. Further data are needed to evaluate this further as a long-term strategy, but integrase inhibitors are included in our current recommendations.

Chemokine (C-C motif) receptor 5 (CCR5) antagonists

One phenotypic *in vitro* susceptibility study has shown that small molecule inhibitors are effective against wild-type HIV-2 isolates. The HIV-2 strains were slightly less sensitive than the HIV-1 strains to these inhibitors, but the order of efficiency of the compounds tested remained the same [71]. However, there is the distinct possibility that HIV-2 may use co-receptors other than CCR5 or CXCR4 for productive infection *in vitro* [72]. The clinical efficacy of the CCR5 antagonists remains unknown at this stage.

When to start treatment

There are no randomized controlled trials for the treatment of HIV-2 infection and few patients world-wide have received antiretroviral therapy. The available data suggest that initiation of antiretroviral therapy in HIV-2-infected patients should be based on CD4 cell count and clinical status. As HIV-2 viral load is often undetectable until CD4 count <300 cells/μL, and it is the viral load that drives disease progression in HIV-2 infection, it may be advisable to start treatment earlier than in HIV-1-positive individuals, where a threshold CD4 count of 350–500 cells/μL is used [37]. An HIV-2 plasma viral load above 1000 copies/mL is considered high and is predictive of clinical progression; therefore treatment should be recommended at this level of viral load [73]. CD4 recovery in treated HIV-2-infected individuals seems to be poorer than might be expected from HIV-1 data, which may also justify earlier treatment in HIV-2-infected patients. In patients dually infected with HIV-1 and HIV-2, HIV-1 may be considered the dominant virus; however,

Table 1. Preferred first-line regimens

Regimen	A	B	C
Preferred	Lopinavir/ritonavir	Tenofovir*	Emtricitabine*
Alternative	Darunavir/ritonavir	Zidovudine†	

*Coformulated as Truvada (Gilead, Cambridge, UK).
†May be coformulated as Combivir (ViiV Healthcare UK Ltd, Uxbridge, Middlesex, UK).
Choose one drug each from columns A, B and C [Licensing is based on the European Medicines Agency (EMEA)].

Table 2. Preferred second-line regimens

Initial regimen	Options to consider
2 NRTIs + lopinavir/ritonavir	2 NRTIs + saquinavir/ritonavir + raltegravir 2 NRTIs + darunavir/ritonavir + raltegravir

There are no data on chemokine (C-C motif) receptor 5 (CCR5) inhibitors but they may be considered as part of a third-line regimen.
NRTI, nucleoside reverse transcriptase inhibitor.

careful consideration should be given when choosing treatment for dual-infected patients to ensure activity against both viruses and to reduce the risk of drug resistance developing [47]. A small data series suggests that treatment of dual infection in this way can be effective [47,74,75].

What to start treatment with (see Table 1)

Therapy should consist of two NRTIs and one or more PIs. World Health Organization guidelines suggest that three NRTIs may also be effective [76]; however, recent data from an observational study in Europe [77] showed an inferior CD4 cell response when treatment with three NRTIs was compared with a PI-based regimen, and therefore the preferred recommendation in this guideline is for treatment consisting of a combination of classes. Once therapy has been started, HIV-2 viral load should be periodically monitored.

Patients treated successfully have so far been treated mainly with two NRTIs plus lopinavir/ritonavir or indinavir/ritonavir [35,36,62,74]. A good first-line regimen would be tenofovir/emtricitabine/boosted lopinavir, for which there are published data proving efficacy with a response rate of 60% out to 96 weeks, based on CD4 and HIV-2 RNA composite endpoints [62]. Truvada and saquinavir (particularly with the development of V47A on failure of lopinavir) or darunavir in combination with raltegravir should be the preferred second-line therapy (see Table 2). It is important to note that there are few data on the outcome of second-line treatment in HIV-2 infection. Recent data, on two highly treatment-experienced patients only, showed a combination, selected based on RT and protease genotyping, of abacavir, tenofovir, darunavir and raltegravir to be very effective; however, this needs to be evaluated in higher numbers of patients longer term [70].

There are not many NRTI choices available for second- and third-line therapy. Tenofovir or zidovudine must be used as the NRTI backbone with lamivudine or FTC in spite of the fact that an M184V mutation may be present. The final choice will depend on whether Q151M and/or K65R has developed on treatment failure.

The choice should ultimately be based on the genotypic resistance report, but one should always bear in mind that the interpretations of HIV-2 mutations are based on a few clinical cases and *in vitro* studies, and not on randomized controlled trials.

The clinical efficacy of CCR5 inhibitors is still unknown, but they can be considered as part of a third-line regimen.

It is unclear whether double-boosted PI regimens would be more efficacious, but at least for HIV-1 it has been shown that darunavir outperforms double-boosted PI regimens. Therefore, the current recommendation would be to use darunavir.

Antiretroviral agents known to have reduced efficacy in treating HIV-2 infection and which are therefore *not* recommended in the treatment of HIV-2 infection are all NNRTIs, nelfinavir, amprenavir, atazanavir and enfuvirtide. Reduced efficacy has also been observed in triple nucleoside combinations and these should also be avoided [77].

In the case of dual infection, a baseline genotypic resistance test for HIV-1, and if possible for HIV-2, should be performed. Antiviral drugs known to be active against both viruses should be given and both HIV-1 and HIV-2 RNA levels should be measured periodically [78]. Treatment failure despite low baseline HIV-2 viral load is not uncommon [47,51] and viral load response is significantly lower than that seen in HIV-1 [34].

Opportunistic infections

Prophylaxis and treatment should be given as for HIV-1.

Pregnancy

Please refer to the BHIVA guidelines for Pregnancy, 1.11 section 14 [79].

Appendix: the BHIVA Guidelines Writing Group on HIV-2

Group chair: Jane Anderson, Homerton University Hospital NHS Foundation Trust, London, UK.

Group deputy chair: Yvonne Gilleece, Brighton and Sussex University Hospital NHS Trust, Brighton, UK.

Members: Judith Breuer, University College, London, UK; David Hawkins, Chelsea and Westminster Hospital, London, UK; Erasmus Smit, West Midlands Public Health Laboratory, Birmingham, UK; Li Xu McCrae, West Midlands Public Health Laboratory, Birmingham, UK; David Chadwick, The James Cook University Hospital, Middlesbrough, UK; Deenan Pillay, University College London, London, UK; Nicola Smith, Chelsea and Westminster Hospital, London, UK.

References

1 Månsson F, Biague A, da Silva ZJ *et al*. Prevalence and incidence of HIV-1 and HIV-2 before, during and after a civil war in an occupational cohort in Guinea-Bissau, West Africa. *AIDS* 2009; **23**: 1575–1582.

2 Pfutzner A, Dietrich U, von Eichel U *et al*. HIV-1 and HIV-2 infections in a high-risk population in Bombay, India: evidence for the spread of HIV-2 and presence of a divergent HIV–1 subtype. *J Acquir Immune Defic Syndr* 1992; **5**: 972–977.

3 Cazein F, Hamers F, Alix J, Brunet JB. Prevalence of HIV-2 in Europe. *Euro Surveill* 1996; **1**: 21–23.

4 CDC. Update: HIV-2 infection among blood and plasma donors–United States, June 1992–June 1995. *Morb Mortal Wkly Rep* 1995; **44**: 603–606.

5 Health Protection Agency Centre for Infections, Health Protection Scotland and UCL Institute of Child Health. Unpublished HIV Diagnoses Surveillance Tables 01:2010. Available at www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1237970242135 (accessed 27 April 2010).

6 Horsburgh CR Jr, Holmberg SD. The global distribution of human immunodeficiency virus type 2 (HIV-2) infection. *Transfusion* 1988; **28**: 192–195.

7 Kanki PJ, Travers KU, MBoup S *et al*. Slower heterosexual spread of HIV-2 than HIV-1. *Lancet* 1994; **343**: 943–946.

8 Adjorlolo-Johnson G, De Cock KM, Ekpini E *et al*. Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. *JAMA* 1994; **272**: 462–466.

9 Morgan G, Wilkins HA, Pepin J *et al*. AIDS following mother-to-child transmission of HIV-2. *AIDS* 1990; **4**: 879–882.

10 Matheron S, Courpotin C, Simon F *et al*. Vertical transmission of HIV-2. *Lancet* 1990; **335**: 1103–1104.

11 Gueudin M, Damond F, Braun J *et al*. Differences in proviral DNA load between HIV-1- and HIV-2-infected patients. *AIDS* 2008; **22**: 211–215.

12 Pepin J, Dunn D, Gaye I *et al*. HIV-2 infection among prostitutes working in The Gambia: association with serological evidence of genital ulcer diseases and with generalized lymphadenopathy. *AIDS* 1991; **5**: 69–75.

13 Pepin J, Quigley M, Todd J *et al*. Association between HIV-2 infection and genital ulcer diseases among male sexually transmitted disease patients in The Gambia. *AIDS* 1992; **6**: 489–493.

14 Miyazaki M. Epidemiological characteristics of human immunodeficiency virus type-2 infection in Africa. *Int J STD AIDS* 1995; **6**: 75–80.

15 Harrison LH, da Silva AP, Gayle HD *et al*. Risk factors for HIV-2 infection in Guinea-Bissau. *J Acquir Immune Defic Syndr* 1991; **4**: 1155–1160.

16 Marlink R, Kanki P, Thior I *et al*. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science* 1994; **265**: 1587–1590.

17 Jaffar S, Wilkins A, Ngom PT *et al*. Rate of decline of percentage CD4 + cells is faster in HIV-1 than in HIV-2 infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **16**: 327–332.

18 Whittle H, Morris J, Todd J *et al*. HIV-2 infected patients survive longer than HIV-1 infected patients. *AIDS* 1994; **8**: 1617–1620.

19 Schim van der Loeff M, Jaffar S, Aveika A *et al*. Mortality of HIV-1, HIV-2 and HIV-1/HIV-2 dually infected patients in a clinic-based cohort in the Gambia. *AIDS* 2002; **16**: 1775–1783.

20 Berry N, Jaffar S, Schim van der Loeff M *et al*. Low level viraemia and high CD4 % predict normal survival in a cohort of HIV type-2-infected villagers. *AIDS Res and Human Retr* 2002; **18**: 1167–1173.

21 Matheron S, Mendoza-Sassi G, Simon F *et al*. HIV-1 and HIV-2 AIDS in African patients living in Paris. *AIDS* 1997; **11**: 934–936.

22 MacNeil A, Sarr AD, Sankale JL, Meloni ST, Mboup S, Kanki P. Direct evidence of lower viral replication rates *in vivo* in human immunodeficiency virus type 2 (HIV-2) infection than in HIV-1 infection. *J Virol* 2007; **81**: 5325–5330.

23 Gilbert PB, McKeague IW, Eisen G *et al*. Comparison of HIV-1 and HIV-2 infectivity from a prospective cohort study in Senegal. *Stat Med* 2003; **22**: 573–593.

24 Otten RA, Adams DR, Kim CN *et al*. Chronic HIV-2 infection protects against total CD4 + cell depletion and rapid disease progression induced by SHIV89.6p challenge. *AIDS* 2004; **18**: 1127–1135.

25 Holmgren B, da Silva Z, Larsen O *et al*. Dual infections with HIV-1, HIV-2 and HTLV-1 are more common in older women than in men in Guinea-Bissau. *AIDS* 2003; **17**: 241–253.

26 Koblavi-Deme S, Kestens L, Hanson D *et al*. Differences in HIV-2 plasma viral load and immune activation in HIV-1 and HIV-2 dually infected persons and those infected with HIV-2 only in Abidjan, Cote d'Ivoire. *AIDS* 2004; **18**: 413–419.

27 Peeters M, Gershy-Damet GM, Fransen K *et al*. Virological and polymerase chain reaction studies of HIV-1/HIV-2 dual infection in Cote d'Ivoire. *Lancet* 1992; **340**: 339–340.

28 Damond F, Loussert-Ajaka I, Apetrei C *et al*. Highly sensitive method for amplification of human immunodeficiency virus type 2 DNA. *J Clin Microbiol* 1998; **36**: 809–811.

29 Damond F, Benard A, Ruelle J *et al.* Quality control assessment of human virus type 2 immunodeficiency (HIV-2) viral load quantification assays: results from an international collaboration on HIV-2 infection in 2006. *J Clin Microbiol* 2008; **46**: 2088–2091.
30 Andersson S, Norrgren H, da Silva Z *et al.* Plasma viral load in HIV-1 and HIV-2 singly and dually infected individuals in Guinea-Bissau, West Africa: significantly lower plasma virus set point in HIV-2 infection than in HIV-1 infection. *Arch Intern Med* 2000; **160**: 3286–3293.
31 Matheron S, Pueyo S, Damond F *et al.* for the French HIV-2 Cohort Study Group. Factors associated with clinical progression in HIV-2-infected patients: the French ANRS cohort. *AIDS* 2003; **17**: 2593–2601.
32 Ariyoshi K, Jaffar S, Alabi AS *et al.* Plasma RNA viral load predicts the rate of CD4 T cell decline and death in HIV-2 infected patients in West Africa. *AIDS* 2000; **14**: 339–344.
33 Smith NA, Shaw T, Berry N *et al.* Antiretroviral therapy for HIV-2 infected patients. *J Infect* 2001; **42**: 126–133.
34 Drylewicz J, Matheron S, Lazaro E *et al.* Comparison of viro-immunological marker changes between HIV-1 and HIV-2-infected patients in France. *AIDS* 2008; **22**: 457–468.
35 Adjé-Touré CA, Cheingsong R, Garcia-Lerma JG *et al.* Antiretroviral therapy in HIV-2 infected patients: changes in plasma viral load, CD4 + cell counts, and drug resistance profiles of patients treated in Abidjan, Côte d'Ivoire. *AIDS* 2003; **17** (Suppl. 3): S49–S54.
36 Van der Ende ME, Prins JM, Brinkman K *et al.* Clinical, immunological and virological response to different antiretroviral regimens in a cohort of HIV-2 infected patients. *AIDS* 2003; **17** (Suppl. 3): S55–S61.
37 Matheron S, Damond F, Benard A, Taieb A, Campa P. CD4 recovery in treated HIV-2 infected adults is lower than expected: results from the France ANRS CO5 HIV-2 cohort. *AIDS* 2006; **20**: 459–462.
38 Damond F, Collin G, Descamps D *et al.* Improved sensitivity of human immunodeficiency virus type 2 subtype B plasma viral load assay. *J Clin Microbiol* 2005; **43**: 4234–4236.
39 Ren J, Bird LE, Chamberlain PP, Stewart-Jones GB, Stewart DI, Stammers DK. Structure of HIV-2 reverse transcriptase at 2.35 – A resolution and the mechanism of resistance to non-nucleoside inhibitors. *Proc Natl Acad Sci USA* 2002; **99**: 14410–14415.
40 Parkin NT, Schapiro JM. Antiretroviral drug resistance in non-subtype B HIV-1, HIV-2 and SIV. *Antivir Ther* 2004; **9**: 3–12.
41 Smith RA, Anderson DJ, Pyrak CL, Kiviat NB, Gottlieb GS, Preston BD. Low genetic barrier to nucleoside analogue resistance in HIV-2. *Antivir Ther* 2007; **12**: S137.
42 Rodes B, Holguin A, Soriano V *et al.* Emergence of drug resistance mutations in human immunodeficiency virus type 2-infected subjects undergoing antiretroviral therapy. *J Clin Microbiol* 2000; **38**: 1370–1374.
43 Van der Ende ME, Schutten M, Ly TD *et al.* HIV-2 infection in 12 European residents: virus characteristics and disease progression. *AIDS* 1996; **10**: 1649–1655.
44 Van der Ende ME, Guillon C, Boers PH *et al.* Antiviral resistance of biologic HIV-2 clones obtained from individuals on nucleoside reverse transcriptase inhibitor therapy. *J Acquir Immune Defic Syndr* 2000; **25**: 11–18.
45 Tantillo C, Ding A, Jacobo-Molina A *et al.* Location of anti-AIDS drug binding site and resistance mutations in the three dimensional structure of HIV-1 reverse transcriptase. *J Mol Biol* 1994; **243**: 369–387.
46 Descamps D, Damond F, Matheron S *et al.* High frequency of selection of K65R and Q151M mutations in HIV-2 infected patients receiving nucleoside reverse transcriptase inhibitors containing regimen. *J Med Virol* 2004; **74**: 197–201.
47 Rodes B, Toro C, Jimenez V *et al.* Viral response to antiretroviral therapy in a patient coinfected with HIV type 1 and type 2. *CID* 2005; **41**: e19–e21.
48 Damond F, Matheron S, Peytavin G *et al.* Selection of K65R mutation in HIV-2 infected patients receiving tenofovir-containing regimen. *Antivir Ther* 2004; **9**: 635–636.
49 Van Vaerenbergh K, Van Laetham K, Albert J *et al.* Prevalence and characteristics of multinucleoside-resistant human immunodeficiency virus type 1 among European patients receiving combinations of nucleoside analogues. *Antimicrob Agents Chemother* 2000; **44**: 2109–2017.
50 Ntemgwa ML, Toni T, Brenner BG *et al.* Nucleoside and nucleotide analogs select in culture for different patterns of drug resistance in human immunodeficiency virus types 1 and 2. *Antimicrob Agents Chemother* 2009; **53**: 708–715.
51 Schmit JC, Van Laetham K, Ruiz L *et al.* Multiple dideoxynucleoside analogue-resistant (MddNR) HIV-1 strains isolated from patients from different European countries. *AIDS* 1998; **12**: 2007–2015.
52 Rodriguez-Rosado R, Briones C, Soriano V. Introduction of drug resistance testing in clinical practice. *AIDS* 1999; **13**: 1007–1014.
53 Ntemgwa M, Brenner BG, Oliveira M, Moisi D, Wainberg MA. Natural polymorphisms in the HIV-2 protease can accelerate time to development of resistance to Protease Inhibitors (PIs). *Antimicrob Agents Chemother* 2007; **51**: 604–610.
54 Cavaco-Silva J, Miranda AC, Cabanas J *et al.* for the Portuguese HIV-2 Study Group. Amino acid substitutions selected by therapy in HIV-2 protease and reverse transcriptase. *16th Conference on Retroviruses and Opportunistic Infections*. Montreal, Canada, February 2009 [Abstract 633].
55 Desbois D, Roquebert B, Peytavin G *et al.* for the French ANRS HIV-2 Cohort (ANRS CO 05 VIH-2). In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. *Antimicrob Agents Chemother* 2008; **52**: 1545–1548.

56 Brower ET, Bacha UM, Kawasaki Y, Freire E. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. *Chem Biol Drug Des* 2008; **71**: 298–305.
57 Witvrouw M, Pannecouque C, Switzer WM, Folks TM, De Clercq E, Heneine W. Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: implications for treatment and postexposure prophylaxis. *Antivir Ther* 2004; **9**: 57–65.
58 Rodes B, Sheldon J, Toro C, Jimenez V, Alvarez MA, Soriano V. Susceptibility to protease inhibitors in HIV-2 primary isolates from patients failing antiretroviral therapy. *J Antimicrob Chemother* 2006; **57**: 709–713.
59 Maguire M, Shortino D, Klein A *et al*. Emergence of resistance to protease inhibitor amprenavir in human immunodeficiency virus type-1 infected patients: selection of four alternative viral protease genotypes and influence of viral susceptibility to coadministered reverse transcriptase nucleoside inhibitors. *Antimicrob Agents Chemother* 2002; **46**: 731–738.
60 Jallow S, Kaye S, Alabi A *et al*. Virological and immunological response to Combivir and emergence of drug resistance mutations in a cohort of HIV-2 patients in The Gambia. *AIDS* 2006; **20**: 1455–1458.
61 Mullins C, Eisen G, Popper S *et al*. Highly active antiretroviral therapy and viral response in HIV type 2 infection. *Clin Infect Dis* 2004; **38**: 1771–1779.
62 Bénard A, Damond F, Campa P *et al*. for the ANRS CO5 HIV-2 Cohort Study Group. Good response to lopinavir/ritonavir-containing antiretroviral regimens in antiretroviral-naive HIV-2-infected patients. *AIDS* 2009; **23**: 1171–1173.
63 Rodes B, Toro C, Sheldon J *et al*. High rate of proV47A selection in HIV-2 patients failing lopinavir-based HAART. *AIDS* 2006; **20**: 127–129.
64 Brandin E, Lindborg L, Gyllensten K *et al*. Pol gene sequence variation in Swedish HIV-2 patients failing antiretroviral therapy. *AIDS Res Hum Retroviruses* 2003; **19**: 543–550.
65 Parkin N, Chappey C, Petropoulos C. Improving lopinavir genotype algorithm through phenotype correlations; novel mutation patterns and amprenavir cross-resistance. *AIDS* 2003; **17**: 955–961.
66 Masse S, Lu X, Dekhtyar T *et al*. In vitro selection and characterization of human immunodeficiency virus type 2 with decreased susceptibility to lopinavir. *Antimicrob Agents Chemother* 2007; **51**: 3075–3080.
67 Koh Y, Nakata H, Maeda K *et al*. Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro. *Antimicrob Agents Chemother* 2003; **47**: 3123–3129.
68 Whitcomb J, Huang W, Fransen S *et al*. Analysis of baseline enfuvirtide (T-20) susceptibility and co-receptor tropism in two phase III study populations. *10th Conference on Retroviruses and Opportunistic Infections*. Boston, MA, February 2003 [Abstract 557].
69 Roquebert B, Damond F, Collin G *et al*. for the French ANRS HIV-2 Cohort (ANRS CO 05 VIH-2). HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir in vitro. *J Antimicrob Chemother* 2008; **62**: 914–920.
70 Damond F, Lariven S, Roquebert B *et al*. Virological and immunological response to HAART regimen containing integrase inhibitors in HIV-2-infected patients. *AIDS* 2008; **22**: 665–666.
71 Willey S, Peters PJ, Sullivan WM, Dorr P, Perros M, Clapham PR. Inhibition of CCR5-mediated infection by diverse R5 and R5X4 HIV and SIV isolates using novel small molecule inhibitors of CCR5: effects of viral diversity, target cell and receptor density. *Antivir Res* 2005; **68**: 96–108.
72 Owen SM, Ellenberger D, Rayfield M *et al*. Genetically divergent strains of human immunodeficiency virus type 2 use multiple coreceptors for viral entry. *J Virol* 1998; **72**: 5425–5432.
73 Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach. Available at www.who.int/hiv/pub/arv/adult/en/index.html (accessed 4 February 2010).
74 Jallow S, Alabi A, Sargee-Njie R *et al*. Virological response to highly active antiretroviral therapy in patients infected with human immunodeficiency virus type 2 (HIV-2) and in patients dually infected with HIV-1 and HIV-2 in the Gambia and emergence of drug-resistant variants. *J Clin Microbiol* 2009; **47**: 2200–2208.
75 Landman R, Damond F, Gerbe J, Brun-Vezinet F, Yeni P, Matheron S. Immunovirological and therapeutic follow-up of HIV-1/HIV-2-dually seropositive patients. *AIDS* 2009; **23**: 426–428.
76 Gilks CF, Crowley S, Ekpini R *et al*. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet* 2006; **368**: 505–510.
77 Benard A, Taieb A, van Sighem A *et al*. for the ACHIEV2E study group. Immuno-virological response to triple NRTI and boosted PI in treatment-naïve HIV-2-infected patients. *European AIDS Clinical Society Conference*. Cologne, November 2009 [Abstract PS10/5].
78 Schutten M, van der Ende M, Osterhaus A *et al*. Antiretroviral therapy in patients with dual infection with human immunodeficiency virus types 1 and 2. *NEJM* 2000; **23**: 1758–1760.
79 De Ruiter A, Mercey D, Anderson J *et al*. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Medicine* 2008; **9**: 452–502.