

BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals (2019 interim update)

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1. Introduction

This guideline is an update of that produced in 2011 to reflect the advances in knowledge made in the last 5 years. As with the previous monitoring guideline, the aim is to present a consensus regarding the standard assessment and investigation of HIV infection from the time of diagnosis and to describe the appropriate monitoring of HIV-positive individuals both on and off ART. This guideline does not address the investigation and management of specific conditions related to HIV infection nor does it look at the choice of ART as these are all covered in other specific BHIVA guidelines.

Systematic literature searches were performed within Medline and Pre-Medline, Embase and the Cochrane library. All study types were included between 2011 and May 2015, although animal studies, case reports, letters and editorials were excluded. In addition, limited use was made of peer-reviewed research abstracts from the major HIV conferences. Results were limited to English language material.

Within this guideline, assessment and monitoring of HIV-positive individuals have been categorised into the following areas: initial diagnosis; asymptomatic individuals not yet on ART; ART initiation; initial assessment following commencement of ART; routine monitoring on ART and monitoring in special circumstances.

Summary tables of assessment/monitoring at each of these stages can be found in section 4 of the guideline. Following these tables, the evidence underpinning these recommendations, including the strength of evidence, is given in the main text.

We have tried to reduce greatly the length of the guideline, especially by heavily relying on other BHIVA guidelines for reference, in order to make it as user-friendly as possible.

Significant changes include the recommendations to reduce/stop CD4 cell count testing in stable patients and to stop performing tests that are no longer of value in an age where most HIV-positive patients are fit and well. We also suggest more consideration for monitoring for age-related conditions such as cardiovascular and bone health using QRISK2 and FRAX scores. Part and parcel of this guideline's recommendations is the provision of cost-effective care and collaborating with primary care services.

2. Auditable targets

The following suggested targets for audit are considered to be important areas of practice/patient care. The percentages represent the targets for the minimum proportion of patients meeting each specific criterion. These targets were reviewed by the British HIV Association (BHIVA) Audit and Standards subcommittee.

Patients newly diagnosed within the HIV service should have HIV-1 status discriminated from HIV-2 or a documented reason why this is not possible (e.g. elite controller) (97%)

Patients newly diagnosed within the HIV service should have genotypic resistance test performed within 3 months of first diagnosis or a documented reason why this is not possible (e.g. elite controller) (97%)

New patients (transferred in or diagnosed within the HIV service) should have a genotypic resistance test performed, baseline resistance status recorded or a documented attempt to obtain this information from previous care provider(s) (95%).

Patients on ART should have a list of all current medication, or note that no medication other than ART is being taken, recorded within the past 15 months (97%)

Patients with HIV viral load assessed within 6 weeks of commencing ART (80%).

Patients on ART with HIV viral load measured within the last 9 months or within the last 15 months if taking a PI (90%)

Patients aged ≥ 40 years with 10-year cardiovascular disease (CVD) risk calculated within 1 year of first presentation (90%), and within the last 3 years if taking ART (90%).

Patients with a smoking history documented in the last 2 years (90%) and blood pressure (BP) recorded in the last 15 months (90%).

3. Tables summarising the monitoring of patients at different stages of their HIV care

3.1 Baseline/initial assessment for all newly diagnosed HIV-positive patients

<p>History</p> <ul style="list-style-type: none"> • General medical (including symptoms) • Psychosocial • Sexual and reproductive health • Past and current comorbidities • Concomitant medications • Lifestyle • HIV status of sexual partners and children • Conception issues • Knowledge and beliefs about HIV infection, HIV transmission and HIV treatment • Partner notification • HIV testing of children • Current or previous intimate partner violence • Vaccination • Lifetime travel <p>Examination</p> <p>General physical examination including: weight, height, BMI, blood pressure, waist circumference</p> <p>Investigations</p> <ul style="list-style-type: none"> • Confirmation of HIV-1/-2 status • Test for primary HIV infection (PHI) • HIV-1 plasma viral load • HIV-1 drug-resistance test¹ • CD4+ T cell count (absolute and percentage) • Hepatitis A virus IgG (or total) • Hepatitis B tests • Hepatitis C virus antibody • Offer full STI screen (including syphilis serology) • Measles/varicella antibodies (according to vaccination/infection history) 	<ul style="list-style-type: none"> • Full blood count • Renal profile • Liver profile • Bone profile • Dipstick urinalysis and urine protein/creatinine ratio if protein positive in the urine dipstick <p style="text-align: center;">Additionally for women</p> <ul style="list-style-type: none"> • Cervical cytology (if not done in the last 12 months and aged 25–65 years or never had cervical cytology) • Rubella in women of child-bearing potential if no history of previous test/vaccination <p>Other investigations</p> <ul style="list-style-type: none"> • HLA-B*57:01 if abacavir therapy being considered • Viral tropism test if a CCR5 inhibitor being considered • Cardiovascular risk assessment for patients >40 years old (QRISK2) • Bone fracture risk assessment (FRAX tool) for all patients >50 years, post-menopausal women, or other high risk patients • Interferon-gamma release assay (IGRA) in the situations recommended in the BHIVA tuberculosis guidelines • Test patients for parasitic infections if persistent eosinophilia on FBC and relevant travel history • Within first 3 months assess current or previous mental health problems, neurocognitive problems, current social and welfare situation, employment status, immigration status
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¹ Integrase resistance testing not recommended unless background resistance rate rises to >3%, or history suggesting possible transmission from a patient with likely or proven integrase resistance.

Routine screening for toxoplasma IgG, mumps IgG, CMV serology, *Schistosoma* serology, stool for ova, cysts and parasites, serum vitamin D, serum amylase, creatine kinase and parathyroid hormone are not recommended.

Transfers: as above if information is not present in any transfer letter.

3.2 Monitoring asymptomatic patients who currently do not want ART

<p>History</p> <ul style="list-style-type: none"> General health and wellbeing enquiry to be performed at least annually <p>Since last visit any new or changes in:</p> <ul style="list-style-type: none"> Symptoms Contraception/pregnancy Sexual history Mental health Newly diagnosed comorbidities and treatment changes Smoking status Alcohol/drugs including over the counter/recreational drugs Vaccines: flu/HPV vaccine Safeguarding Children/partner status and whether tested Housing, occupation/student, income/benefits Vaccinations Travel plans and history Patient's ideas about HIV and its treatment <p>Examination</p> <p>Only if new symptoms or signs</p>	<p>Investigations</p> <p><i>Annually if CD4 cell count >500 cells/mm³</i></p> <ul style="list-style-type: none"> HIV viral load CD4 count FBC / renal / liver profiles STI screen Hepatitis A/B /C infection/immunity status Cervical smear for women if not done by GP <p><i>6-monthly</i></p> <ul style="list-style-type: none"> CD4 if previous result <500 cells/mm³ <p><i>3-monthly</i></p> <ul style="list-style-type: none"> CD4 if previous result <350 cells/mm³ STI/hepatitis screen for higher risk patients¹ <p><i>Other</i></p> <ul style="list-style-type: none"> Annual lipids in patients ≥ 40 years, if smoker and /or BMI >30 Cardiovascular risk assessment for patients >40 years old (QRISK2) Bone fracture risk assessment using FRAX tool in everyone aged >50 years, post-menopausal women, or other high-risk patients every 3 years
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¹ MSM + frequent partner change /IDU/chaotic lifestyle/adolescent/CSW/other drug use/chemsex/other risk.

3.3 Monitoring of patients who are now starting ART who did not start soon after the baseline visit

<p>History</p> <ul style="list-style-type: none"> Patient's ideas about HIV and its treatment; screening for depression <p>Examination</p> <ul style="list-style-type: none"> Only if new symptoms <p>Assessments</p> <ul style="list-style-type: none"> Assessment of the common complications of treatment such as diabetes, heart disease and osteopenia Cardiovascular risk Bone fracture risk (see baseline assessment) 	<p>Investigations</p> <ul style="list-style-type: none"> CD4 count if a test had not been done within the previous three months <p><i>If not done within the last 6 months, test for:</i></p> <ul style="list-style-type: none"> HIV viral load Full blood count Renal profile Liver profile Bone profile Dipstick urinalysis with urine protein/creatinine ratio if protein positive in the urine dipstick analysis HIV resistance test if was not done previously or recent high risk of superinfection with resistant virus Tropism test if CCR5 therapy considered HLA-B*57:01 test if not previously done and abacavir therapy considered
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3.4 Monitoring in the first 6 months after starting ART

<p>History</p> <ul style="list-style-type: none"> • First done 2–4 weeks after starting ART and then at each subsequent visit • Adherence and tolerability check <p>Examination</p> <ul style="list-style-type: none"> • According to any symptoms <p>Investigations</p> <ul style="list-style-type: none"> • After 2–4 weeks, 3 months and 6 months • Renal profile • Liver profile • Dipstick urinalysis • May test urinalysis and renal profile more frequently if starting TDF or there is an indication of renal impairment • FBC: only if patient is unwell or has started zidovudine (test after 6 and 12 weeks then 3 monthly) 	<p><i>CD4 cell count</i></p> <ul style="list-style-type: none"> • After 3 months ART if baseline was <350 cells/mm³ • Repeat at 6 months after starting ART if it was still <350 cells/mm³ at 3 months post-ART. If the VL is suppressed on ART, see section 4.7 • If >350 cells/mm³ and VL suppressed on ART see section 4.7 <p><i>HIV viral load</i></p> <ul style="list-style-type: none"> • Measure at 1, 3 and 6 months after starting ART • If VL does not fall at least 10-fold (1.0 log₁₀) after 1 month, repeat at 2 months post-ART start • If VL not fully suppressed at 6 months or any increase in VL at any time, see section 4.7.2
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3.5 Monitoring of patients established on ART and with the viral load suppressed

<p>Cover all annual issues as outlined in Table 3.2: In addition:</p> <p>History at each visit:</p> <ul style="list-style-type: none"> • Full medication history and recreational drug use • Understanding of dosing instructions • Adherence • Mood • Adverse effects • Patients' concerns about medication <p>Examination</p> <ul style="list-style-type: none"> • According to any symptoms <p>Investigations</p> <p><i>HIV viral load</i></p> <ul style="list-style-type: none"> • Every 6 months – could be up to 12 months if on a protease inhibitor 	<p><i>CD4 cell count</i></p> <ul style="list-style-type: none"> • If <200 cells/mm³, test 3–6-monthly. If 200–350 cells/mm³, test annually • If >350 cells/mm³ on two occasions >1 year apart, no further CD4 cell counts required¹ <p><i>6–12 monthly:</i></p> <ul style="list-style-type: none"> • Full blood count • Renal profile • Liver profile • Bone profile • Dipstick urinalysis <p><i>Annually:</i></p> <ul style="list-style-type: none"> • Urine protein/creatinine ratio if protein positive in the urine dipstick analysis (may be more frequent if other comorbidities that affect renal function) • Metabolic assessment: (if aged ≥40 years) lipid profile, HbA1c
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¹Unless there is subsequent treatment failure or new HIV-related symptoms.

Additional monitoring in specific situations

3.6 Additional monitoring of patients presenting with advanced disease (CD4 cell count <200 cells/mm³ at first presentation)

<p>In addition to standard baseline tests:</p> <p>History</p> <ul style="list-style-type: none"> To ascertain any symptoms indicative of HIV-related problems Assessment for CMV retinitis (fundoscopy or retinal photography) if CD4 cell count is <50 cells/mm³ 	<p>Investigations</p> <ul style="list-style-type: none"> Tests for <i>Toxoplasma</i>, <i>Cryptococcus</i> and mycobacterial infection are only indicated if patient has relevant symptoms Monitor for IRIS, especially within 3 months of starting ART
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3.7 Monitoring of people who inject drugs (PWID) (including those injecting during chemsex)

<p>History</p> <p>Review and discussed at each visit:</p> <ul style="list-style-type: none"> Injection drug practice, including current use of recreational and illicit drugs and access to needle exchange programmes. Additional adherence support is offered to injecting drug users who commence antiretroviral therapy, particularly for those actively injecting and with chaotic lifestyles 	<p>Examination</p> <p>At each visit:</p> <ul style="list-style-type: none"> Injection sites for signs of infection
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3.8 Monitoring of immigrants from the tropics

<p>History</p> <ul style="list-style-type: none"> A lifetime travel history and vaccination history should be obtained as part of the routine work-up at diagnosis for all individuals newly diagnosed with HIV 	<p>Investigations</p> <ul style="list-style-type: none"> In individuals with eosinophilia or symptoms compatible with tropical illness, further investigation should be tailored according to geographical exposure and clinical features Individuals who spend further time in the tropics should have investigations repeated as necessary, preferably >3 months after travel
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3.9 Monitoring of older patients

<p>History</p> <ul style="list-style-type: none"> All medications (prescribed and non-prescribed) are reviewed and documented at every clinic visit 	<p>Investigations</p> <ul style="list-style-type: none"> Fragility fracture risk assessment in all patients over 50 years every 3 years Screening for colorectal and breast cancers should be offered in accordance with national guidelines Do an annual cardiovascular risk assessment in all patients over 40
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3.10 Some specific issues relating to monitoring of women not covered above

<p>History</p> <ul style="list-style-type: none"> • Check HPV vaccination history <p>Investigations</p> <p><i>Cervical smears</i></p> <ul style="list-style-type: none"> • Do not perform under age 25 • An initial colposcopy can be performed, but only if resources permit • Perform annual cytology • Do not perform cervical screening after age 65 unless they fulfil the criteria for ongoing surveillance or follow up as indicated in national guidelines <p><i>Breast cancer</i></p> <ul style="list-style-type: none"> • Screen following the 2016 national guidelines <p><i>Other female cancers</i></p> <ul style="list-style-type: none"> • Screen according to national guidelines 	<p><i>Menopause</i></p> <ul style="list-style-type: none"> • Monitor according to relevant guidelines (also see section 5.5) <p><i>Pregnancy</i></p> <p>Monitor according to relevant guidelines (also see section 5.5)</p>
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3.11 Monitoring of patients with low-level HIV viraemia

<p>History</p> <ul style="list-style-type: none"> • Adherence check and a viral load repeated when above 50 copies/mL to ensure this comes back to undetectable <p>Investigations</p> <p><i>VL 50–200 copies/mL</i></p> <ul style="list-style-type: none"> • If the repeat is <50 copies/mL, continue routine monitoring. This is considered a single blip. • If the initial viral load measurement is below 200 copies/mL and subsequent measurement again between 50 and 200 copies/mL, check adherence and possible drug interactions. Do a resistance test • 3–4 monthly viral load follow-ups of individuals with stable unsuppressed (<200 copies/mL) viral loads if they are managed as low level viraemic patients 	<ul style="list-style-type: none"> • Genotypic resistance testing should be attempted and acted upon especially if there is a gradual increase in viral load • No need for repeat genotypic resistance testing at a frequency greater than once a year if the viral load is stable and there is no need for routine TDM <p><i>VL >200 copies/mL</i></p> <ul style="list-style-type: none"> • Action is taken if a second repeat viral load is above 200 copies/mL and if both measurements are above 200 copies/mL, refer to BHIVA treatment guidelines (1A) • Careful assessment of patients with frequent ‘blips’ and/or one measurement above 200 copies/mL as these can sometimes be associated with viral rebound and virological failure
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3.12 Monitoring of patients with hepatitis B, C or tuberculosis

Please see the relevant BHIVA guidelines.

3.13 Monitoring of patients with mental health problems, social care issues, prisoners, metabolic disease

Please see main text

4. Evidence and discussion on the choice of recommendations for monitoring

4.1 The GRADE system

In the following sections the evidence is scored using the GRADE system [1,2].

A **Grade 1** recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients 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. 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 is defined as follows:

Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence from another source (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 randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias.

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

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

In addition to graded recommendations, we have included good practice points (GPP), which are recommendations based on the clinical judgement and experience of the working group. GPPs emphasise 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 emphasised that GPPs are not an alternative to evidence-based recommendations.

References

1. Guyatt GH, Oxman AD, Vist GE *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924–926.
2. Development and Evaluation (Short GRADE) Working Group. The grading of recommendations assessment. Available at: <http://www.gradeworkinggroup.org/publications/> (accessed May 2016).

4.2 Models of care and practical considerations

Recommendations

- We suggest that for stable asymptomatic patients monitoring can be carried out by healthcare professionals (including nurses and GPs) with appropriate training and competence (GPP).
- We suggest the creation of case-note proformas to cover the common clinical situations. Increasingly this will be using electronic patient records (GPP).
- We suggest that in order to reduce the need for in-person clinic visits, for those who desire this, consultations can take place in hospital outpatient clinics, or in the community provided the convenience and confidentiality of patients is ensured (GPP).
- We recommend that patients are encouraged to register with a GP, if not already registered, and that the HIV service regularly communicates with the GP about their patient, including the creation of a care plan if appropriate (GPP).
- We suggest that, unless results of investigations are of serious prognostic significance, for example malignancy, results do not have to be given in person and can be communicated via alternative modalities such as email/phone/or other electronic means (GPP).
- We suggest that options for checking of test results could include a computer-based system for picking up abnormalities, a healthcare professional (HCP)-based system for checking results or, if investigations are very important and urgent, the HCP who initiated the tests should monitor the results (GPP).
- We suggest that for all routine consultations, the HCPs who conducted the consultation should monitor that results have been received for all tests taken (GPP).
- We suggest that the results of investigations and other matters of clinical importance should be provided to the patient and others involved with their care or wellbeing (with patient consent) at least annually, or more immediately if action is required by another party, e.g. general practitioner or another HCP involved in their care such as another hospital specialty, CPN/CNS or occupational health (GPP).

Evidence

The available staff skill mix should be used to the best advantage for the patient. Eliciting patients' views on how to redesign services is invaluable to tailor services to the needs of local populations [1,2].

References

1. Kegg S, Goddard S, Russell J. Learning from patients to redesign an HIV service. *Sex Transm Infect* 2012; **88** (suppl 1): A48.
2. British HIV Association. Standards of Care for People Living with HIV. 2013. Available at: <http://www.bhiva.org/documents/Standards-of-care/BHIVASTandardsA4.pdf> (accessed May 2016).

4.3 Baseline/initial assessment for all newly diagnosed HIV-positive patients

4.3.1 History

Recommendations

- We recommend that a full history is obtained at the first clinic visit (GPP).
- We recommend asking patients how they identify their gender (GPP).
- We recommend that within the first 3–6 months, a history of current or previous mental health problems, neurocognitive problems, current social and welfare situation, employment status, immigration status, current partners and children and social supports is performed (GPP).

Evidence

A full history should comprehensively evaluate the medical, psychosocial, sexual and reproductive health of the HIV-positive patient. Particular emphasis should be placed on past and current comorbidities, concomitant medications, lifestyle habits, HIV status of sexual partners and children, and conception issues. Knowledge and beliefs about HIV infection, HIV transmission and HIV treatment should be assessed. Partner notification, HIV testing of children and current or previous intimate partner violence should be discussed.

In patients who have transferred care, permission should be sought to obtain clinical information including immuno-virological status, vaccination and antiretroviral treatment history if not already received.

4.3.2 Examination

Recommendation

We recommend that a general physical examination including weight, height, BMI, blood pressure and waist circumference is performed in patients with newly diagnosed HIV infection (GPP).

4.3.3 Investigations

4.3.3.1 Confirmation of HIV status

Recommendations

- We recommend confirming HIV-positive serology. Confirm positive serology and distinguish between HIV-1 and HIV-2 infections (1A).
- We recommend that new transfers should have written confirmation that HIV-2 infection has been excluded; otherwise another typing assay needs to be performed (1A).
- We recommend that primary HIV infection (PHI) needs to be excluded, which will help with contact tracing and the decision on whether rapid ART is necessary (1B).

Evidence

HIV confirmatory serological testing safeguards against sample mix-ups or specimen contamination, but is not necessary if an HIV viral load or typing assay has already confirmed HIV. HIV-2 ART differs substantially and therefore HIV-2 infection needs to be excluded to prevent therapy failure and drug resistance [1]. HIV-1 avidity assays are helpful to diagnose recent infections, but seroconverting HIV serology +/- positive p24 Ag, or detectable HIV viral load in the absence HIV serology can also identify PHI and have a better positive predictive value than an avidity test. Patients with PHI are highly infectious and contact tracing may reduce onward transmission. Rapid treatment may be indicated: see BHIVA guidelines for treatment of HIV-1 positive adults with antiretroviral therapy 2015 [2].

References

1. Gilleece Y, Chadwick DR, Breuer J *et al.* British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med* 2010; **11**: 611–619.
2. Churchill D, Waters L, Ahmed N *et al.* BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).

4.3.3.2 HIV viral load

Recommendations

- We recommend that an HIV viral load should be performed at the first visit following serological diagnosis (1A).
- We recommend that undetectable viral load result whilst not on treatment needs repeating, review of serology to exclude HIV-2 and measurement on a different viral load assay (1D).
- We recommend a repeat HIV viral load in all new transfers prior to repeat prescriptions if it is not possible to confirm a recent viral load from the previous clinic (1A).

Evidence

HIV viral load is the highest during PHI and then usually declines to a steady state within 4–6 months [1]. It has limited predictive value for the rate of HIV progression [2] and correlates with the risk of sexual or mother-to-child transmission. Although there is generally a good correlation in the measurements between different manufacturers' assays, their lower limit of quantitation differs (range 20–75 copies/mL) as do their ability to detect diverse subtypes, most notably non-group M viruses.

References

1. Sabin CA, Devereux H, Phillips AN *et al.* Course of viral load throughout HIV-1 infection. *J Acquir Immune Defic Syndr* 2000; **23**: 172–177.
2. Rodriguez B, Sethi AK, Cheruvu VK *et al.* Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection. *JAMA* 2006; **296**: 1498–1506.

4.3.3.3 Resistance testing

Recommendations

- We recommend that a baseline genotypic resistance test should be performed on the first available sample (1A).
- We recommend that baseline integrase resistance testing should currently not be performed since there is currently little evidence of transmission of integrase strand transfer inhibitor (INSTI)-resistant virus. However, it is recommended if there are other baseline transmitted drug resistant mutations present, or the patient's partner has evidence of INI resistance (1C).

Evidence

See also Appendix 1. A baseline genotypic resistance test (protease and reverse transcriptase genes) needs to be performed on the earliest available sample in order to exclude transmitted drug resistant (TDR) mutations since mutations can disappear (revert back to wildtype amino acids) over time [1-3]. Detection of TDR minority variants by more sensitive sequencing technology (next generation sequencing) has been shown to predict a higher risk of virological failure with low genetic barrier drugs [4,5]. No clinical cut offs have yet been established, but a high genetic barrier ART regimen should probably be selected when

low-level minority variants are detected in a UKAS accredited assay. There is currently no evidence of circulating transmitted drug resistant INSTI mutations [6].

References

1. Castro H, Pillay D, Cane P *et al.* Persistence of HIV-1 transmitted drug resistance mutations. *J Infect Dis* 2013; **208**: 1459–1463.
2. Gandhi RT, Wurcel A, Rosenberg ES *et al.* Progressive reversion of human immunodeficiency virus type 1 resistance mutations in vivo after transmission of a multiply drug-resistant virus. *Clin Infect Dis* 2003; **37**: 1693–1698.
3. Pao D, Andrady U, Clarke J *et al.* Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. *J Acquir Immune Defic Syndr* 2004; **37**: 1570–1573.
4. Ghosn J, Pellegrin I, Goujard C *et al.* HIV-1 resistant strains acquired at the time of primary infection massively fuel the cellular reservoir and persist for lengthy periods of time. *AIDS* 2006; **20**: 159–170.
5. Li JZ, Paredes R, Ribaldo 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.
6. Casadella M, van Ham PM, Noguera-Julian M *et al.* Primary resistance to integrase strand-transfer inhibitors in Europe. *J Antimicrob Chemother* 2015; **70**: 2885–2888.

4.3.3.4 CD4+ T cell count

Recommendation

- We recommend that CD4+ T cell count and percentage should be taken for clinical staging at the initial visit (1A).

Evidence

CD4 count monitoring is crucial in patients before starting ART since it correlates with the level of immune dysfunction and suppression, which in turn dictate the urgency of starting ART [1]. It should be taken into account that the CD4 cell count can fluctuate widely especially following PHI, but also during other acute illnesses such as HCV and tuberculosis (TB). The CD4 percentage is usually less variable. CD4 cell counts are used to determine the risk of certain infections and cancers and to guide chemoprophylaxis to prevent opportunistic infections. It is also used to decide when vaccination with live vaccines is safe and when to investigate for latent TB [2,3].

References

1. Mellors JW, Munoz A, Giorgi JV *et al.* Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; **126**: 946–954.
2. Geretti AM, Brook G, Cameron C *et al.* British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Available at: <http://www.bhiva.org/vaccination-guidelines.aspx> (accessed May 2016).
3. Pozniak AL, Coyne KM, Miller RF *et al.* British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.

4.3.3.5 HLA-B*57:01 testing

Recommendation

- We recommend that all patients should be screened prior to prescribing abacavir (1A).

Evidence

HLA-B*57:01 testing identifies patients at risk of abacavir hypersensitivity reaction (HSR) with a negative predictive value of 99.4–100% [1,2]. The prevalence of HLA-B*57:01 in black sub-Saharan Africans is low (<1%) whereas it is higher (6.49%) in white Europeans [3]. HLA-B*57:01 testing is best performed at the initial visit, even if abacavir is not going to be used, so that the result is available should an urgent switch be necessary. HLA-B*57:01 negative patients who initiate abacavir should still be told to look out for the symptoms of HSR.

References

1. Mallal S, Phillips E, Carosi G *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–579.
2. Martin AM, Nolan D, Gaudieri S *et al.* Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci U S A* 2004; **101**: 4180–4185.
3. Orkin C, Sadiq ST, Rice L, Jackson F. Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. *HIV Med* 2010; **11**: 187–192.

4.3.3.6 Hepatitis A, B and C

Recommendations

- We recommend that all new patients should be screened for hepatitis A immunity (1A), hepatitis B virus surface antigen (HBsAg), anti-core total antibody (anti-HBc), anti-surface antibody (anti-HBs) status (1B), and hepatitis C antibody status (1C).
- We recommend that all HCV antibody-positive patients require measurement of HCV viral load (at least twice if initially negative) (1A).
- We recommend referral of HCV RNA-positive patients to a hepatitis specialist (1A).

Evidence

Hepatitis A and B are vaccine preventable infections that HIV-positive patients are at risk of acquiring and hepatitis B and C are treatable diseases that are common in HIV-positive individuals [1,2].

References

1. Geretti AM, Brook G, Cameron C *et al.* British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Available at: <http://www.bhiva.org/vaccination-guidelines.aspx> (accessed May 2016).
2. Wilkins E, Nelson M, Agarwal K *et al.* British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. *HIV Med* 2013; **14 Suppl 4**: 1–71.

4.3.3.7 Sexual health screen including syphilis serology

Recommendations

We recommend a full STI screen is offered to all HIV-positive individuals at baseline, to be directed by the sexual history. The screen should include syphilis serology for all, vulvo-vaginal swabs for chlamydia and gonorrhoea NAAT for all women, urine testing for chlamydia and gonorrhoea NAAT for men, and pharyngeal and rectal swabs for chlamydia and gonorrhoea NAAT for MSM and heterosexual women with a history of oral or anal sex (1B).

Evidence

Sexually transmitted infections are common in people with HIV infection and some of these can increase the risk of HIV transmission **in people who do not have an undetectable viral load on treatment** [1-4]. HIV-positive individuals are more at risk of complications from STIs.

References

1. British HIV Association. Standards of Care for People Living with HIV. 2013. Available at: <http://www.bhiva.org/documents/Standards-of-care/BHIVASTandardsA4.pdf> (accessed May 2016).
2. Fakoya A, Lamba H, Mackie N *et al.* British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.
3. Malek R, Mitchell H, Furegato M *et al.* Contribution of transmission in HIV positive men who have sex with men to evolving epidemics of sexually transmitted infections in England: an analysis using multiple data sources, 2009–2013. 2015. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21093> (accessed May 2016).
4. Rodger A, Cambiano V, Bruun T *et al.* Risk of HIV transmission through condomless sex in MSM couples with suppressive ART: The PARTNER2 Study extended results in gay men. *AIDS* 2018, 23–27 July 2018, Amsterdam. Late breaking oral abstract WEAX0104LB.

4.3.3.8 Cervical cytology

Recommendations

We recommend cervical cytology in all newly diagnosed women aged 25–65 years if it has not been performed within past 12 months or the individual has never had cervical cytology (1D) (See section 5.5.1).

4.3.3.9 Infection screening

Baseline screening of the following organisms is required in order to decide whether vaccination is necessary, unless there is a reliable history of infection or immunisation: varicella zoster virus IgG, measles IgG and rubella IgG (women of child-bearing age) (1B).

We recommend screening for tuberculosis using an interferon-gamma release assay (IGRA) in the situations recommended in the BHIVA tuberculosis/HIV co-infection guidelines (1B).

We suggest testing patients for parasitic infections if there is persistent eosinophilia (defined as an absolute eosinophil count of >500 cells/mL (>0.5 x 10⁹/L)) present on the full blood count (FBC) and if a relevant travel history is given (2C).

We recommend that the following tests for infections **should not** be performed routinely and should only be performed in specific circumstances, dictated by the clinical situation: toxoplasma IgG, mumps IgG, *Schistosoma* serology, stool for ova, cysts and parasites (1D).

Evidence

Opportunistic infection immunity screening guides the prescription of chemoprophylaxis or vaccination [1]. Tuberculosis is a common co-infection in people from high prevalence areas and in people with low CD4 cell count [2]. *Toxoplasma* serology is only of value in patients with suspected cerebral infection or a minority of

patients with a low CD4 cell count who cannot tolerate co-trimoxazole. There is no evidence to support the routine testing for mumps or tropical infections without a clinical indication.

References

1. Geretti AM, Brook G, Cameron C *et al.* British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Available at: <http://www.bhiva.org/vaccination-guidelines.aspx> (accessed May 2016).
2. Pozniak AL, Coyne KM, Miller RF *et al.* British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.

4.3.3.10 Metabolic screen

Recommendation

We recommend the following tests at baseline (1B):

- * Full blood count;
- * Renal profile: including creatinine, estimated glomerular filtration rate (eGFR), urinalysis (and protein/creatinine ratio if protein positive in the urine dipstick);
- * Liver profile: bilirubin, ALT or AST, alkaline phosphatase, (and GGT and albumin if other tests abnormal);
- * Bone profile: calcium, phosphate and alkaline phosphatase;
- * Random lipid profile: total cholesterol, LDL, HDL and triglycerides and HbA1c.
- We do not recommend routine testing of blood vitamin D levels or serum amylase and creatine kinase.

Evidence

A limited number of additional tests is indicated to detect common complications of HIV infection or to serve as reference if metabolic disease is subsequently diagnosed.

Anaemia, neutropenia and/or thrombocytopenia are common in patients with advanced immunosuppression, severe (opportunistic) infections or malignancy. Acute kidney injury (AKI) and chronic kidney disease (CKD) are relatively common in patients with HIV, especially in those with advanced disease; assessment of renal function (estimated glomerular filtration rate; eGFR) allows appropriate dosing of antiretroviral and other medications and identification of those at greatest risk of kidney disease progression and AKI due to nephrotoxic medications [1]. Dipstick urinalysis for haematuria, proteinuria and glycosuria and quantification of urinary protein (protein/creatinine ratio; PCR) provides additional information on kidney function and the risk of kidney disease progression [1].

Liver enzyme elevations and/or abnormalities of liver function are common in patients with viral hepatitis and opportunistic infections such as tuberculosis, cytomegalovirus and *Cryptosporidium*. Non-infectious causes of liver disease such as hepatic steatosis are also relatively common and many drugs used to treat or prevent opportunistic infections, including rifamycins, isoniazid, pyrazinamide, co-trimoxazole, fluconazole, co-amoxiclav and cephalosporins may cause liver injury.

Dyslipidaemia is common in HIV-positive patients and an important risk factor for ischaemic heart disease. Acute illness may affect plasma lipid concentrations and glucose homeostasis; lipid measurements are best deferred in these patients. Decisions on lipid-lowering therapy should be based on overall cardiovascular risk rather than lipid levels in isolation [2]. Elevations of serum amylase and creatine kinase are common but rarely clinically significant in asymptomatic individuals; we recommend against their routine evaluation.

References

1. Yombi JC, Jones R, Pozniak A *et al.* Monitoring of kidney function in HIV-positive patients. *HIV Med* 2015; **16**: 457–467.

2. NICE. CVD risk assessment and management. Clinical knowledge summaries. 2014. Available at: <http://cks.nice.org.uk/cvd-risk-assessment-and-management> (accessed May 2016).

4.3.3.11 Cardiovascular risk assessments

Recommendation

- We recommend baseline assessment of cardiovascular risk on HIV-positive patients who are aged >40 years and/or have significant CVD risk factors using QRISK2, taking into account that it will underestimate risk (1B).

Evidence

With the advent of ART and an increasing number of older people being diagnosed with HIV, there is increasing morbidity from cardiovascular disease in HIV-positive individuals [1]. As chronic infection with HIV increases cardiovascular risk, tools used to assess risk often underestimate the risk for HIV-positive patients. QRISK2 tool for CVS risk assessment has been validated on the UK population [2], and is widely used in primary care however it underestimates risk in HIV-positive patients and other chronic conditions [3].

References

1. Shah MR. The broad spectrum of HIV-related cardiovascular disease. *JACC Heart Fail* 2015; **3**: 600–602.
2. ClinRisk. Welcome to the QRISK®2-2016 risk calculator. 2016. Available at: <http://www.qrisk.org/> (accessed May 2016).
3. Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *BMJ* 2009; **339**: b2584.

4.3.3.12 Bone health and fracture risk

Recommendations

- We recommend that fracture risk is assessed at baseline in all patients over 50 and post-menopausal women, or in the presence of other risk factors using the FRAX score (1C).
- We suggest that routine testing of vitamin D and parathyroid hormone is not required (2D).

Evidence

A study looking into the effect of HIV seroconversion found no effect on vitamin D levels pre- and post-seroconversion [1]. There is no strong evidence of what age fracture risk assessments should start, with 58% of fractures in one cohort occurring in patients under 50; however, the overall fracture rate was low (0.53 per 100 person years) [2]. The same study did show a significant increase in fractures in HIV-positive patients with a CD4 cell count under 200 cells/mm³, those with a history of corticosteroid use and antiepileptic medication. Tools for assessing fracture risk include FRAX and QFracture [3,4]. See section 5.7 for a fuller discussion.

References

1. Achhra AC, Amin J, Law MG *et al*. Changes in metabolic, inflammatory and coagulation biomarkers after HIV seroconversion – the Health in Men (HIM) Biomarker Substudy. *Antivir Ther* 2013; **18**: 355–359.
2. Yong MK, Elliott JH, Woolley IJ, Hoy JF. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. *J Acquir Immune Defic Syndr* 2011; **57**: 205–210.

3. NICE. Osteoporosis: assessing the risk of fragility fracture. NICE guidelines CG146. 2012. Available at: <https://www.nice.org.uk/guidance/cg146> (accessed May 2016).
4. WHO. FRAX WHO fracture risk assessment tool. Version 3.10. 2016. Available at: <https://www.shef.ac.uk/FRAX/index.aspx> (accessed May 2016).

4.4 Monitoring asymptomatic patients who currently do not want ART

4.4.1 Frequency of screening/attendance

Recommendations

We recommend that patients are reviewed at the following frequency based on the CD4 cell count (1B):

- * CD4 <350 cells/mm³: 3–6 monthly;
- * CD4 350–500 cells/mm³: 6 monthly;
- * CD4 >500 cells/mm³: 6–12 monthly.

We suggest that if patients do not attend for appointments, contact them within 2 weeks to re-engage (GPP).

Evidence

Most patients will start ART soon after diagnosis of HIV and only a minority might wish to defer treatment. More frequent visits (3 monthly or whenever at risk) are desirable for those at high risk of STI or hepatitis virus acquisition to allow early diagnosis and management to reduce morbidity and onward transmission [1]. The frequency of follow up otherwise is stratified according to the risk of HIV-related complications [2]. There is also some evidence that a formal annual review improves clinical care and documentation of certain parameters such as smoking and alcohol intake, vaccination and offer of an STI screen [3].

References

1. Brook G, McSorley J, Shaw A. Retrospective study of the effect of enhanced systematic sexually transmitted infection screening, facilitated by the use of electronic patient records, in an HIV-infected cohort. *HIV Med* 2013; **14**: 347–353.
2. Reekie J, Gatell JM, Yust I *et al.* Fatal and nonfatal AIDS and non-AIDS events in HIV-1-positive individuals with high CD4 cell counts according to viral load strata. *AIDS* 2011; **25**: 2259–2268.
3. Atha L, Fearnley N, Brady S. Formal annual reviews for HIV-infected adults: is clinical care improved? *Int J STD AIDS* 2013; **24 (Suppl 1)**: 14–15.

4.4.2 History and examination

4.4.2.1 History

Recommendation

- We recommend a general health and wellbeing enquiry annually (GPP).

Since the last visit, have there been any new, or changes in:

- * Symptoms;
- * Contraception;
- * Sexual history risk factors;
- * Mental health new symptoms;
- * Newly diagnosed comorbidities and treatment changes;
- * Risk factors for osteoporosis if under 50, e.g. corticosteroids, hypogonadism;
- * Smoking status;
- * Alcohol/drugs including over the counter/recreational drugs;
- * Allergies;
- * Safeguarding;
- * Children/partner status and whether tested;
- * Housing;
- * Occupation/student;
- * Income/benefits;
- * Partner/s;
- * Vaccines course progress/completion hepatitis A and B/flu vaccine/HPV vaccine;
- * Pneumococcal vaccine completion;
- * Travel plans and history, e.g. malaria prophylaxis;
- * Patient's expectations;
- * Patient's questions.

4.4.2.2 Examination and assessments

Recommendation

- We recommend a physical examination is performed only if the physician notices new symptoms or signs indicating new pathology.

Evidence

Monitoring visits allow changes in disease status, risk factors for STIs and hepatitis virus acquisition [1,2] vaccine course completion, mental health issues [3] and lifestyle and recreational substance use changes [4] to be documented and managed. They also allow monitoring of adherence to appointments and engagement in care [5], which may be of relevance when considering ART [6-13].

With regard to hepatitis A and B infections, a rigorous approach is required to ensure vaccine courses are completed [14], especially in those co-infected with hepatitis C [15] as there is an ongoing incidence of hepatitis B infection in the UK HIV-positive cohort [16]. There is also evidence of continuing high rates of hepatitis C re-infection rates among HIV-positive MSM [17,18].

References

1. Brook G, McSorley J, Shaw A. Retrospective study of the effect of enhanced systematic sexually transmitted infection screening, facilitated by the use of electronic patient records, in an HIV-infected cohort. *HIV Med* 2013; **14**: 347–353.

2. Bayley J, Macdonald F, Brookes R *et al*. A cross-sectional survey looking at uptake rates of sexually transmitted infection screening in an HIV-positive cohort in an inner city London cohort. Abstract P208. *HIV Med* 2013; **14 (Suppl 2)**: 77.
3. Thorley N, Grima E, Sellers P *et al*. Screening for depression, excessive alcohol intake, recreational drug use and adherence to antiretrovirals within an HIV outpatient clinic: a pilot service evaluation. Abstract P22. *HIV Med* 2014; **15 (Suppl 3)**: 24.
4. Cohn SE, Jiang H, McCutchan JA *et al*. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. *AIDS Care* 2011; **23**: 775–785.
5. Dean BB, Hart RL, Buchacz K *et al*. HIV laboratory monitoring reliably identifies persons engaged in care. *J Acquir Immune Defic Syndr* 2015; **68**: 133–139.
6. Kegg S, Goddard S, Russell J. Learning from patients to redesign an HIV service. *Sex Transm Infect* 2012; **88 (suppl 1)**: A48.
7. Gutierrez EB, Sartori AM, Schmidt AL *et al*. Measuring adherence to antiretroviral treatment: the role of pharmacy records of drug withdrawals. *AIDS Behav* 2012; **16**: 1482–1490.
8. Centers for Disease Control. Compendium of evidence-based interventions and best practices for HIV prevention. Available at: <http://www.cdc.gov/hiv/research/interventionresearch/compendium/lrc/index.html> (accessed May 2016).
9. Aberg JA, Gallant JE, Anderson J *et al*. Primary care guidelines for the management of persons infected with human immunodeficiency virus: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2004; **39**: 609–629.
10. Fakoya A, Lamba H, Mackie N *et al*. British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.
11. NICE. Generalised anxiety disorder and panic disorder in adults: management. NICE guidelines CG113. 2011. Available at: <https://www.nice.org.uk/guidance/cg113> (accessed May 2016).
12. NICE. Depression in adults: recognition and management. NICE guidelines CG90. 2009. Available at: <http://guidance.nice.org.uk/CG90> (accessed May 2016).
13. NICE. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE guidelines CG76. 2009. Available at: <https://www.nice.org.uk/guidance/CG76> (accessed May 2016).
14. Bhaduri S, Roberts M, Williams N. Audit of hepatitis B vaccination in a semi-urban HIV-positive cohort. Abstract P366. *HIV Med* 2014; **15 (Suppl 3)**: 134.
15. Bray J, Leen C. Immunisation in co-infected HIV-hepatitis C patients: an audit of practice. Abstract P334. *HIV Med* 2014; **15 (Suppl 3)**: 123–124.
16. Thornton A, Bhagani S, Burroughs A *et al*. Viral hepatitis testing patterns among HIV-positive individuals in the UK Collaborative HIV Cohort (UKCHIC) study. Abstract P234. *HIV Med* 2014; **15 (Suppl 3)**: 91–92.
17. El-Hayek C, Doyle JS, Cuevas M *et al*. New hepatitis C infection and re-infection among HIV co-infected men in Melbourne, Australia. Abstract P733. *J Hepatol* 2014; **60**: S314.
18. Peters L, Mocroft A, Soriano V *et al*. High rate of hepatitis C virus (HCV) recurrence in HIV-infected individuals with spontaneous HCV RNA clearance. *HIV Med* 2014; **15**: 615–620.

4.4.3 Investigations

Recommendations

We recommend 3-monthly screening for STIs if the patient has high risk factors for acquisition, e.g. MSM with frequent partner change or chemsex/IVDU with chaotic lifestyle/CSW/patients who frequently use intranasal cocaine/recent tattoo abroad/recent blood transfusion abroad/other risk (1B)

We recommend that in such patients the following will be performed (1B):

- * Screen for gonorrhoea and chlamydia at all exposed sites;
- * Syphilis serology.

Also consider at least annually in patients with high risk:

- * Hepatitis B surface antigen or core antibody if not known to be core antibody positive or vaccinated with an adequate surface antibody response (>10 MIU/mL);
- * Hepatitis C antibody (HCV antigen or RNA if ALT abnormal).

• We recommend the following tests be performed annually for those with a CD4 cell count >500 cells/mm³ (2C):

- * HIV viral load;
- * CD4;
- * FBC, renal/liver profile;
- * Random lipids, only if smoker and/or BMI >30 or aged >40 years. If normal, repeat after 2 years;
- * Screen for gonorrhoea and chlamydia all exposed sites if partner change since the last test (self-taken swabs if asymptomatic);
- * Syphilis serology if partner change since the last test;
- * Hepatitis B (for infection or immunity) and C screening (in at-risk patients).

Also every 3 years

- * Bone fragility risk assessment in patients aged >50, post-menopausal women as determined by the FRAX score and NOGG guidance.

Evidence

Evidence as to how frequently laboratory investigations should be carried out is lacking and practice is usually dictated by availability of staff, facilities and costs and previous guidelines [1-3]. What evidence there is suggests that for many stable patients, especially if CD4 cell count is >500 cells/mm³, annual testing is adequate [4-6].

Earlier studies have suggested that the HIV viral load (which increases slowly over time and then rapidly prior to the onset of advanced immunosuppression or AIDS) [1-3,7,8] should be measured every 6 months in asymptomatic stable patients not receiving ART [9]; however, no studies have looked at annual viral load measurements in resource-rich settings. Two early measurements to establish the set point viral load are recommended [9] and the viral load may also influence the choice of ART [10].

For fracture risk, see section 4.3.3.12

Evidence for hepatitis B and C screening and vaccination for hepatitis B comes from the BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013 (updated September 2014) [11].

There is no evidence to support yearly testing for serum vitamin D level or serum parathyroid hormone (PTH) level (see section 4.3.3.12).

Screening for STIs and hepatitis viruses should be available in the HIV clinic [11-14].

References

1. Garcia-Diaz A, Clewley GS, Booth CL *et al.* Comparative evaluation of the performance of the Abbott real-time human immunodeficiency virus type 1 (HIV-1) assay for measurement of HIV-1 plasma viral load following automated specimen preparation. *J Clin Microbiol* 2006; **44**: 1788–1791.
2. Schutten M, Peters D, Back NK *et al.* Multicenter evaluation of the new Abbott RealTime assays for quantitative detection of human immunodeficiency virus type 1 and hepatitis C virus RNA. *J Clin Microbiol* 2007; **45**: 1712–1717.
3. Labbett W, Garcia-Diaz A, Fox Z *et al.* Comparative evaluation of the ExaVir Load version 3 reverse transcriptase assay for measurement of human immunodeficiency virus type 1 plasma load. *J Clin Microbiol* 2009; **47**: 3266–3270.
4. Buclin T, Telenti A, Perera R *et al.* Development and validation of decision rules to guide frequency of monitoring CD4 cell count in HIV-1 infection before starting antiretroviral therapy. *PLoS One* 2011; **6**: e18578.
5. Chow EP, Read TR, Chen MY *et al.* Routine CD4 cell count monitoring seldom contributes to clinical decision-making on antiretroviral therapy in virologically suppressed HIV-infected patients. *HIV Med* 2015; **16**: 196–200.
6. Doyle A, Kegg S. Routine laboratory monitoring in the HIV out-patient setting – what does the full blood count add? *HIV Med* 2014; **15 (Suppl 3)**: 133–134.
7. Bruisten SM, Oudshoorn P, van Swieten P *et al.* Stability of HIV-1 RNA in blood during specimen handling and storage prior to amplification by NASBA-QT. *J Virol Methods* 1997; **67**: 199–207.
8. Vandamme AM, Van Laethem K, Schmit JC *et al.* Long-term stability of human immunodeficiency virus viral load and infectivity in whole blood. *Eur J Clin Invest* 1999; **29**: 445–452.
9. Giordano M, Kelleher T, Colonna RJ *et al.* The effects of the Roche AMPLICOR HIV-1 MONITOR UltraSensitive Test versions 1.0 and 1.5 viral load assays and plasma collection tube type on determination of response to antiretroviral therapy and the inappropriateness of cross-study comparisons. *J Clin Virol* 2006; **35**: 420–425.
10. Griffith BP, Mayo DR. Increased levels of HIV RNA detected in samples with viral loads close to the detection limit collected in Plasma Preparation Tubes (PPT). *J Clin Virol* 2006; **35**: 197–200.
11. Wilkins E, Nelson M, Agarwal K *et al.* British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. *HIV Med* 2013; **14 Suppl 4**: 1–71.
12. Brook G, McSorley J, Shaw A. Retrospective study of the effect of enhanced systematic sexually transmitted infection screening, facilitated by the use of electronic patient records, in an HIV-infected cohort. *HIV Med* 2013; **14**: 347–353.
13. Ismail M, Baguley S. Audit in the routine investigation and monitoring of adult HIV-1-infected individuals. *Int J STD AIDS* 2013; **24 (Suppl 1)**: 10–11.
14. Flagg EW, Weinstock HS, Frazier EL *et al.* Bacterial sexually transmitted infections among HIV-infected patients in the United States: estimates from the Medical Monitoring Project. *Sex Transm Dis* 2015; **42**: 171–179.

4.4.4 Other assessments

Recommendations

- We recommend that the following assessments be made annually (2C):
 - * QRISK2 only if smoker or diabetic and/or BMI>30 and age >40 years (unnecessary if there is already established vascular disease);
 - * Hepatitis A/B vaccine course completed, any boosters required;
 - * Vaccines Flu annual;
 - * Check annual cervical smear (if resources permit) is done by GP or at HIV centre of care, and results and follow up plan if indicated;
 - * A HPV vaccine course has been completed where indicated.
- We recommend that the following assessments be made every 3 years (2C).
 - * Bone fracture risk assessment using the FRAX tool in all patients >50 years, post-menopausal women or other high-risk patients (see section 5.7).

Evidence

Evidence as to how frequently laboratory investigations should be carried out is lacking and practice is usually dictated by availability of staff, facilities and costs and previous guidelines [1,2]. QRisk2 scores may be useful in identifying those at risk of heart disease especially in the context that HIV-positive persons may have an older 'heart age' than their actual age would suggest due to the pro-inflammatory state induced by HIV infection [3].

The vaccination evidence is from the BHIVA vaccination guidelines [4].

National Osteoporosis Guideline Group (NOGG) guidelines [5] should be followed regarding bone mineral density (BMD) screening in conjunction fracture risk assessment using tools such as FRAX. One study [6] suggested that measuring BMD by DEXA in all HIV patients regardless of any further specification may help identify 20% of patients with early BMD disorders which would not be identified using current criteria for selective screening of BMD. Larger studies with analysis of confounding factors are required before this can be implemented as evidence-based policy. Several studies have tried to address questions such as the ideal interval between DEXA scans [7], the extent to which low BMD in HIV is explained by low body weight and smoking [8], and the role of HIV in progression to low BMD [9]. Clinical guidance on management has also been produced [10]. However, many aspects of the relationship between HIV and low BMD remain unclear.

References

1. British HIV Association. Standards of Care for People Living with HIV. 2013. Available at: <http://www.bhiva.org/documents/Standards-of-care/BHIVASTandardsA4.pdf> (accessed May 2016).
2. Fakoya A, Lamba H, Mackie N *et al*. British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.
3. Davies T, May M, Gompels M. Too old too soon? Heart age compared with actual age in HIV-positive individuals. Abstract P27. *J Int AIDS Soc* 2012; **15 (Suppl 4)**: 18152.
4. Geretti AM, Brook G, Cameron C *et al*. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Available at: <http://www.bhiva.org/vaccination-guidelines.aspx> (accessed May 2016).
5. National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. 2014. Available at: https://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf (accessed May 2016).

6. Mazzotta E, Ursini T, Agostinone A *et al.* Prevalence and predictors of low bone mineral density and fragility fractures among HIV-infected patients at one Italian center after universal DXA screening: sensitivity and specificity of current guidelines on bone mineral density management. *AIDS Patient Care STDS* 2015; **29**: 169–180.
7. Negro E, Bonjoch A, Gomez-Mateu M *et al.* Time of progression to osteopenia/osteoporosis in chronically HIV-infected patients: screening DXA scan. *PLoS One* 2012; **7**: e46031.
8. Kooij KW, Wit FW, Bisschop PH *et al.* Low bone mineral density in patients with well-suppressed HIV infection: association with body weight, smoking, and prior advanced HIV disease. *J Infect Dis* 2015; **211**: 539–548.
9. Bonjoch A, Figueras M, Estany C *et al.* High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. *AIDS* 2010; **24**: 2827–2833.
10. McComsey GA, Tebas P, Shane E *et al.* Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis* 2010; **51**: 937–946.

4.5 Starting ART for patients who do not start soon after the baseline visit

4.5.1 History and examination

4.5.1.1 History

Recommendations

We recommend that patient's ideas about HIV and its treatment should be discussed in detail (1C).

We recommend that screening for depression using standard tools is done to avoid increased risk of adverse effects with efavirenz-based regimens (1C).

Evidence

There is evidence that patient ideas about treatment are important determinants of subsequent adherence with therapy and consequently with outcome. Open questions should be used to explore patients' ideas about HIV disease and its treatment: these are more likely to uncover their concerns. Non-verbal clues may indicate undisclosed concerns; these should be explored further [1]. A tool to assess readiness to commence ART has been proposed by the European AIDS Clinical Society (EACS) [2].

There is an association between depression risk in HIV patients and the risk of subsequent depression diagnosis after exposure to efavirenz [3].

4.5.1.2 Examination

Recommendations

We recommend that physical examination should include a focused clinical examination related to complications of treatment (2C).

We recommend that cardiovascular risk be assessed using an appropriate tool such as QRISK2 (1B).

We recommend that bone fracture risk is assessed in patients >50 years, post-menopausal women or with other risks using an appropriate tool such as FRAX (1B).

Evidence

See also section 4.3.3.11. The NICE recommendation for cardiovascular risk assessment is the QRISK2 score [4,5]. This includes details about the person: age, sex, ethnicity, postcode, smoking status, and selected

medical and family history, values of current blood pressure and body mass index (BMI). The total cholesterol/high-density lipoprotein (HDL)-cholesterol ratio is taken from a non-fasting blood sample. Consider also taking blood to assess HbA1c and kidney function [6]. QRISK2 does not cover cardiovascular risk assessment in people with dyslipidaemias or type 1 diabetes mellitus. For fracture risk, see section 4.3.3.12

References

1. NICE. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE guidelines CG76. 2009. Available at: <https://www.nice.org.uk/guidance/CG76> (accessed May 2016).
2. European AIDS Clinical Society. European guidelines for treatment of HIV-infected adults in Europe. 2015. Available at: <http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html> (accessed May 2016).
3. Wong BJO, Zachry WM, Tsai K-T *et al*. The effect of depression risk in HIV patients on antiretroviral therapy (ART) choice and the risk of subsequent depression diagnosis after exposure. Abstract 225. *Pharmacoepidemiol Drug Saf* 2012; **21** (Suppl 3): 106–107.
4. NICE. CVD risk assessment and management. Clinical knowledge summaries. 2014. Available at: <http://cks.nice.org.uk/cvd-risk-assessment-and-management> (accessed May 2016).
5. ClinRisk. Welcome to the QRISK®2-2016 risk calculator. 2016. Available at: <http://www.qrisk.org/> (accessed May 2016).
6. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE guidelines CG181. 2014. Available at: <https://www.nice.org.uk/guidance/cg181> (accessed May 2016).

4.5.2 Investigations: HIV-specific tests

4.5.2.1 CD4 cell count

Recommendation

We recommend that a CD4 cell count be performed prior to the start of ART if a test has not been done within the previous 3 months (1A).

Evidence

Previously, the CD4 cell count played an important part in deciding whether to start ART but BHIVA guidelines now recommend offering ART to all HIV-positive patients, either for their own health or for treatment as prevention [1]. The CD4 cell count still has a useful role to play in terms of understanding disease prognosis and also in helping asymptomatic patients to decide whether they wish to start ART [2-4].

References

1. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. May MT, Gompels M, Delpech V *et al*. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* 2014; **28**: 1193–1202.
3. Mocroft A, Furrer HJ, Miro JM *et al*. The incidence of AIDS-defining illnesses at a current CD4 count \geq 200 cells/ μ L in the post-combination antiretroviral therapy era. *Clin Infect Dis* 2013; **57**: 1038–1047.

4. Nelson M, Dockrell D, Edwards S *et al.* British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Med* 2011; **12 Suppl 2**: 1–140.

4.5.2.2 Viral load

Recommendations

We recommend that all patients starting ART should have HIV viral load measured immediately prior to starting treatment (1A).

We recommend that any of the commercially available viral load assays are suitable to measure viral load (see also sections 4.3 and 5.10) (1B).

Evidence

The viral load level immediately prior to starting ART influences the choice of agents used in ART, in that several treatments have reduced efficacy at a viral load >100,000 copies/mL and are best avoided if the viral load is higher [1]. Also, adequate response to treatment is accurately measured by measuring the subsequent rate of fall of viral load on treatment (see section 4.6)

4.5.2.3 Resistance testing

Recommendations

We recommend that all patients starting ART should have an HIV resistance test taken prior to starting ART (usually taken at the baseline visit) (1A). If there is an urgent need to start ART (e.g. an AIDS-defining illness) then suitable ART can be commenced before the resistance result is available (1D).

We recommend resistance testing using a genotypic resistance assay that should include the polymerase and protease genes only (see sections 4.3 and 5.10) (1B). Testing for integrase resistance is not recommended unless there is a known high risk of acquired resistance in a patient and there is a plan to use agents from this class or if there are baseline TDR mutations (1D).

We suggest that if the resistance test was performed more than 6 months before the start of ART, a repeat test is generally not recommended unless the risk of superinfection is considered to be high, although this is, in fact, rare (2D).

Evidence

See Appendix 1. The BHIVA treatment guidelines [1] require resistance testing before initiating therapy, which is recommended to contain two nucleos(t)ide RTIs with a third agent that is an NNRTI, PI or integrase inhibitor. This is in order to avoid any agent to which the virus is resistant. The proportion of untreated patients with transmitted resistance has been falling in recent years although it varies in different UK cohorts from 7% to 19% [2-4]. Recent evidence from the START trial showed baseline resistance in only 4.7% of UK participants [5]. Resistance detected in these cohorts affects NRTIs, NNRTIs and PIs but not integrase inhibitors [2-5]. There is little evidence for repeating the resistance test after the baseline assay before ART is commenced, apart from the occasional case report of superinfection of an HIV-positive patient with a second strain of HIV with ART resistance [6]. However, a study in a large cohort of 4425 patients found evidence of superinfection in about 2% of patients, but there was only one possible case of a newly acquired resistant strain [7].

References

1. Churchill D, Waters L, Ahmed N *et al.* BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. Castro H, Pillay D, Sabin C, Dunn DT. Effect of misclassification of antiretroviral treatment status on the prevalence of transmitted HIV-1 drug resistance. *BMC Med Res Methodol* 2012; **12**: 30.

3. Dolling D, Sabin C, Delpech V *et al.* Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study. *BMJ* 2012; **345**: e5253.
4. McFaul K, Lim C, Jones R *et al.* Transmitted antiretroviral drug resistance in treatment naïve HIV-infected persons in London in 2011 to 2013. Abstract O315. *J Int AIDS Soc* 2014; **17 (Suppl 3)**: 19747.
5. Baxter JD, Dunn D, White E *et al.* Global HIV-1 transmitted drug resistance in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV Med* 2015; **16 Suppl 1**: 77–87.
6. Pinggen M, Nouwen JL, Dinant S *et al.* Therapy failure resulting from superinfection by a drug-resistant HIV variant. *Antivir Ther* 2012; **17**: 1621–1625.
7. Bartha I, Assel M, Sloot PM *et al.* Superinfection with drug-resistant HIV is rare and does not contribute substantially to therapy failure in a large European cohort. *BMC Infect Dis* 2013; **13**: 537.

4.5.2.4 Tropism testing

Recommendation

We do not recommend tropism testing before starting ART unless the patient is going to receive treatment with a CCR5 inhibitor (1D).

Evidence

The BHIVA treatment guidelines do not recommend the use of maraviroc (or other unlicensed CCR5 inhibitors) in first-line therapy for HIV [1]. However, it may be used in rare circumstances as a first-line drug [1]. A test to confirm that the majority strain of virus is CCR5 tropic is required before using a CCR5 inhibitor as this class is ineffective if the patient's virus is CXCR4 tropic or dual CCR5 and CXCR4 tropic [2,3].

References

1. Churchill D, Waters L, Ahmed N *et al.* BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. Gulick RM, Lalezari J, Goodrich J *et al.* Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; **359**: 1429-1441.
3. Moyle GJ, Wildfire A, Mandalia S *et al.* Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. *J Infect Dis* 2005; **191**: 866-872.

4.5.2.4 HLA-B*57:01

Recommendation

We recommend that if abacavir is going to be part of the new ART regimen, then the patient's HLA-B*57:01 status should be known before starting therapy (1B).

Evidence

Abacavir is an 'alternative' starting agent in the BHIVA treatment guidelines if the viral load is <100,000 copies/mL although there are situations when it can be used first line, such as in combination with lamivudine and dolutegravir [1]. Patients who are HLA-B*57:01 positive have a high rate of abacavir hypersensitivity, which can be fatal, but this can be prevented through screening [2,3]. See section 4.3.

References

1. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. Mallal S, Phillips E, Carosi G *et al*. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–579.
3. Rauch A, Nolan D, Martin A *et al*. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* 2006; **43**: 99–102.

4.5.3 Investigations: non-HIV-specific tests

4.5.3.5 Hepatitis B and C testing

Recommendation

We recommend that a test for hepatitis B infection (if the patient is non-immune) and for hepatitis C infection be performed within 3 months of starting ART if this was not previously tested or the patient has been at risk of acquisition of either infection since their previous test (1B).

Evidence

The choice of antiretroviral agents is influenced by the patient's hepatitis infection status [1]. For patients with HIV/hepatitis B co-infection the ART regimen would normally include tenofovir and emtricitabine or lamivudine as effective treatment for both infections [1]. In patients with HIV/hepatitis C co-infection, the choice of antiretrovirals is influenced both by the potential interactions with any hepatitis C treatment being considered, but also by the potential hepatotoxicity of some antiretroviral agents [2].

4.5.3.6 Liver function

Recommendation

We recommend that liver function tests (LFTs), including ALT or AST, ALP, albumin and bilirubin, (plus GGT, if other parameters are abnormal) should be performed at ART initiation (1C).

Evidence

Elevation of liver enzymes is frequently associated with the use of antiretroviral therapy, as some of these medications can cause liver damage [3,4].

References

1. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. Wilkins E, Nelson M, Agarwal K *et al*. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. *HIV Med* 2013; **14 Suppl 4**: 1–71.
3. Law WP, Dore GJ, Duncombe CJ *et al*. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996–2001. *Aids* 2003; **17**: 2191–2199.
4. Wit FW, Weverling GJ, Weel J *et al*. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis* 2002; **186**: 23–31.

4.5.3.7 Renal function

Recommendation

We recommend that an assessment of renal function, eGFR, urinalysis (and urine protein/creatinine ratio if urinalysis 1+ positive for protein) should be performed at ART initiation (1B).

Evidence

The purpose of screening is early detection of CKD or drug-induced renal injury. In patients with glomerular disease, the bulk of urinary protein is albumin and may be picked up on dipstick [1,2].

References

1. Campbell LJ, Ibrahim F, Fisher M *et al.* Spectrum of chronic kidney disease in HIV-infected patients. *HIV Med* 2009; **10**: 329–336.
2. de Silva TI, Post FA, Griffin MD, Dockrell DH. HIV-1 infection and the kidney: an evolving challenge in HIV medicine. *Mayo Clin Proc* 2007; **82**: 1103–1116.

4.5.3.8 Full blood count

Recommendation

FBC should be performed prior to starting ART (1B).

Evidence

In patients on ART, blood count abnormalities are rare with antiretrovirals other than zidovudine. In individuals with advanced disease, more frequent haematological monitoring is indicated because of an increased risk of drug toxicity and also an increased risk of developing opportunistic infections (for example disseminated *Mycobacterium avium* complex infection) with haematological involvement. Haemoglobin level is an independent prognostic factor in both ART-naïve individuals and in those commencing therapy [1-3].

References

1. Harris RJ, Sterne JA, Abgrall S *et al.* Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. *Antivir Ther* 2008; **13**: 959–967.
2. Kowalska JD, Mocroft A, Blaxhult A *et al.* Current hemoglobin levels are more predictive of disease progression than hemoglobin measured at baseline in patients receiving antiretroviral treatment for HIV type 1 infection. *AIDS Res Hum Retroviruses* 2007; **23**: 1183–1188.
3. Shah S, Smith CJ, Lampe F *et al.* Haemoglobin and albumin as markers of HIV disease progression in the highly active antiretroviral therapy era: relationships with gender. *HIV Med* 2007; **8**: 38–45.

4.5.3.9 Other biomarkers

Recommendation

Amylase, creatine kinase, lactate dehydrogenase and lactate should be measured if clinical disease is present or suspected, but are not recommended for routine monitoring of stable patients (GPP).

4.6 Soon after starting ART (first 6 months)

4.6.1 History and examination

Recommendation

We recommend that patients be seen after 2–4 weeks to check for drug-associated adverse effects (2C).
We recommend that ART adherence should be assessed at each clinic visit (1A).

Evidence

The majority of adverse drug effects occur in the first 2 weeks after starting therapy and so patients should be seen soon after. However, there is no evidence of a link to subsequent poor outcome in the long term [1,2].

See BHIVA treatment guidelines [3]. Poor adherence has been associated with higher mortality [4,5] and also with increased risk of virological failure in many different cohorts [6-8]. The number of daily pills counted was related to self-reported health status but not to self-reported adherence [9].

Successful interventions to improve adherence have included: adherence counselling; a once-daily regimen (compared to twice daily); text messaging; web-based cognitive behavioural intervention; face-to-face multi-session intensive behavioural interventions (two studies); contingency management; modified directly observed therapy; and nurse-delivered home visits combined with telephone calls [10,11].

References

1. Shet A, Antony J, Arumugam K *et al*. Influence of adverse drug reactions on treatment success: prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India. *PLoS One* 2014; **9**: e91028.
2. Sumana SH, Shashikumar NS, H N *et al*. Study of antiretroviral drug induced adverse drug reactions in patients visiting A.R.T centre. Abstract CLP/OP-24. *Indian J Pharmacol* 2013; **45 (Suppl)**: S47.
3. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
4. Kiwuwa-Muyingo S, Oja H, Walker A *et al*. Dynamic logistic regression model and population attributable fraction to investigate the association between adherence, missed visits and mortality: a study of HIV-infected adults surviving the first year of ART. *BMC Infect Dis* 2013; **13**: 395.
5. Kiwuwa-Muyingo S, Walker AS, Oja H *et al*. The impact of first year adherence to antiretroviral therapy on long-term clinical and immunological outcomes in the DART trial in Uganda and Zimbabwe. *Trop Med Int Health* 2012; **17**: 584–594.
6. Court R, Leisegang R, Stewart A *et al*. Short term adherence tool predicts failure on second line protease inhibitor-based antiretroviral therapy: an observational cohort study. *BMC Infect Dis* 2014; **14**: 664.
7. De Beudrap P, Thiam M, Diouf A *et al*. Risk of virological failure and drug resistance during first and second-line antiretroviral therapy in a 10-year cohort in Senegal: results from the ANRS 1215 cohort. *J Acquir Immune Defic Syndr* 2013; **62**: 381–387.
8. Genberg BL, Wilson IB, Bangsberg DR *et al*. Patterns of antiretroviral therapy adherence and impact on HIV RNA among patients in North America. *Aids* 2012; **26**: 1415–1423.

9. Gianotti N, Galli L, Bocchiola B *et al.* Number of daily pills, dosing schedule, self-reported adherence and health status in 2010: a large cross-sectional study of HIV-infected patients on antiretroviral therapy. *HIV Med* 2013; **14**: 153–160.
10. Mannheimer S, Hirsch-Moverman Y. What we know and what we do not know about factors associated with and interventions to promote antiretroviral adherence. *Curr Infect Dis Rep* 2015; **17**: 466.
11. Mbuagbaw L, Sivaramalingam B, Navarro T *et al.* Interventions for enhancing adherence to antiretroviral therapy (ART): a systematic review of high quality studies. *AIDS Patient Care STDS* 2015; **29**: 248–266.

4.6.2 Investigations

4.6.2.1 CD4 cell count

Recommendations

- We recommend that a CD4 cell count should be taken 3 months after starting ART (1D).
- We recommend that the frequency of subsequent testing depends on the baseline and 3-month CD4 cell count and response to treatment (1D).

In patients with a CD4 count >350 cells/mm³ 3 months after starting ART who subsequently successfully suppress HIV viral load on ART, a repeat CD4 cell count is not required for 1 year (see section 4.7) (1D).

Patients with a CD4 count <350 cells/mm³ at 3 months should have a further CD4 cell count 6 months after starting ART (1D). Providing the viral load is fully suppressed at 6 months after starting ART, for the subsequent frequency see section 4.7.

For patients who do not have a fully suppressed viral load at 6 months, see section 5.10.

Evidence

In patients on ART, the level of the CD4 cell count has a role in guiding the use of prophylaxis against opportunistic infections and also in providing prognostic information for the patient and their healthcare worker. BHIVA guidelines for the treatment of opportunistic infections recommend that maintenance therapy for, and prophylaxis against, a range of OIs should be continued until the CD4 cell count is established as >200 cells/mm³ [1]. In addition, patients with a CD4 cell count <200 cells/mm³ have a worse prognosis in terms of risk of both AIDS-defining illnesses (ADI) and non-ADI as compared to patients with higher CD4 counts, both off and on ART [2-7]. This is also true for patients whose CD4 cell increase is slow or absent even when on effective ART [5,7]. Although the risk is smaller, this poorer prognosis remains at CD4 cell counts in the range 200–350 cells/mm³ [2-7]. There is therefore a need to monitor the CD4 cell count more intensively in patients with a CD4 cell count <350 cells/mm³. Although there is potentially a small difference in prognosis between CD4 cell counts in the ranges 350–500 and >500 cells/mm³, this difference is so small [4-7] as to not warrant additional CD4 monitoring over and above a single count at 3 months post ART. A small proportion of patients ($<3\%$) will suffer a fall in CD4 cell count when on effective ART [4,6,8] and these patients are at increased risk of cardiovascular disease, cancer, and death [8].

References

1. Nelson M, Dockrell D, Edwards S *et al.* British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. *HIV Med* 2011; **12 Suppl 2**: 1–140.
2. May MT, Gompels M, Delpech V *et al.* Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* 2014; **28**: 1193–1202.
3. Mocroft A, Furrer HJ, Miro JM *et al.* The incidence of AIDS-defining illnesses at a current CD4 count ≥ 200 cells/ μ L in the post-combination antiretroviral therapy era. *Clin Infect Dis* 2013; **57**: 1038–1047.

4. Gale HB, Gitterman SR, Hoffman HJ *et al.* Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts ≥ 300 cells/ μ L and HIV-1 suppression? *Clin Infect Dis* 2013; **56**: 1340–1343.
5. Gilson RJ, Man SL, Copas A *et al.* Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborative HIV Cohort (UK CHIC) Study. *HIV Med* 2010; **11**: 152–160.
6. Girard PM, Nelson M, Mohammed P *et al.* Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS* 2013; **27**: 2759–2763.
7. Zoufaly A, Cozzi-Lepri A, Reekie J *et al.* Immuno-virological discordance and the risk of non-AIDS and AIDS events in a large observational cohort of HIV-patients in Europe. *PLoS One* 2014; **9**: e87160.
8. Helleberg M, Kronborg G, Larsen CS *et al.* CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. *Clin Infect Dis* 2013; **57**: 314–321.

4.6.2.2 Viral load

Recommendations

We recommend that viral load measurements be taken at 1, 3 and 6 months after starting ART (1B).

We recommend that additional viral load measurements are taken between 2 and 5 months after starting ART if viral load has not decreased at least 10-fold after 1 month of ART or there are concerns about the patient's adherence to therapy (1D).

For patients who do not have a fully suppressed viral load at 6 months, or whose viral load rises after an initial fall, see section 5.10.

Evidence

ART response is accurately predicted by a three-fold or more ($0.5 \log_{10}$) viral load decrease at 4 weeks after starting therapy, as compared with the pre-treatment viral load [1] although much higher falls are expected [2–5]. The time taken to achieving an undetectable viral load will depend on the efficacy of the ART and the starting viral load. The majority of patients responding to ART will have a VL below the level of detection of available commercial assays (20–50 copies/mL) by 6 months ART [1–5] and it usually remains below the level of detection subsequently [6].

References

1. Smith CJ, Staszewski S, Sabin CA *et al.* Use of viral load measured after 4 weeks of highly active antiretroviral therapy to predict virologic outcome at 24 weeks for HIV-1-positive individuals. *J Acquir Immune Defic Syndr* 2004; **37**: 1155–1159.
2. 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.
3. Hughes RA, Sterne JA, Walsh J *et al.* Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. *HIV Med* 2011; **12**: 583–593.
4. O'Connor J, Smith C, Lampe F *et al.* Rate of viral load failure over time in people on ART in the UK Collaborative HIV Cohort (CHIC) study. *J Int AIDS Soc* 2014; **17**: 19527.
5. Ribaldo HJ, Smith KY, Robbins GK *et al.* Racial differences in response to antiretroviral therapy for HIV infection: an AIDS clinical trials group (ACTG) study analysis. *Clin Infect Dis* 2013; **57**: 1607–1617.

6. Doyle T, Smith C, Vitiello P *et al.* Plasma HIV-1 RNA detection below 50 copies/ml and risk of virologic rebound in patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2012; **54**: 724–732.

4.6.2.3 Liver function

Recommendation

We recommend that liver function tests (LFTs), including ALT or AST, ALP, and bilirubin (plus GGT, albumin if other parameters are abnormal), should be performed at 2–4 weeks follow up after ART initiation or modification, during routine clinic visits and when clinically indicated (e.g. acute illness) (1B).

Evidence

See section 4.5.3.6.

4.6.2.4 Renal function

Recommendations

We recommend renal function monitoring after 2–4 weeks of treatment, and after 3 and 6 months in patients without renal risk factors. More frequent monitoring is required in patients at risk of renal impairment (e.g. patients on TDF) (1B).

We recommend that dipstick urinalysis should be performed at all routine clinic visits in patients on TDF (1D).

Evidence

Although most antiretroviral drugs may cause renal injury, TDF has been most frequently associated with nephrotoxicity [1-6]. TDF has been implicated in the development of acute renal failure, progressive decline in renal function, hypophosphataemia, renal tubular acidosis, Fanconi syndrome, nephrogenic diabetes insipidus, hypokalaemia, osteomalacia, and urinary concentration defects [2-6]. Discontinuation of TDF usually leads to improvement of the renal abnormalities. Patients who receive TDF together with didanosine or (ritonavir-boosted) protease inhibitors, and those with advanced HIV infection, old age, low body mass and pre-existing renal impairment appear to be at increased risk [2,3,5,6], although the incidence of renal toxicity in randomized clinical trials has generally been low (less than 1%). Atazanavir/ritonavir and, to a lesser extent, lopinavir/ritonavir have also been associated with CKD.

Renal function in patients on TDF should be monitored more closely by assessing eGFR, serum phosphate and urinalysis at each clinic visit. A progressive decline in eGFR, or the presence of severe hypophosphataemia (phosphate less than 0.64 mmol/L) or new-onset haematuria, glycosuria (in the presence of normoglycaemia) or proteinuria may indicate ART toxicity. The presence of hypophosphataemia should be confirmed on a fasting specimen. Proteinuria of tubular origin, which predominates in drug-induced renal injury, may not be detected by dipstick testing [4]. Proteinuria on dipstick should be quantified by uPCR measurement.

References

1. de Silva TI, Post FA, Griffin MD, Dockrell DH. HIV-1 infection and the kidney: an evolving challenge in HIV medicine. *Mayo Clin Proc* 2007; **82**: 1103–1116.
2. 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.
3. Parsonage MJ, Wilkins EG, Snowden N *et al.* The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. *HIV Med* 2005; **6**: 341–346.

4. Siedner MJ, Atta MG, Lucas GM *et al.* Poor validity of urine dipstick as a screening tool for proteinuria in HIV-positive patients. *J Acquir Immune Defic Syndr* 2008; **47**: 261–263.
5. 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.
6. Staszewski S PA, Lu B, Enejosa J, Cheng A for the Study 903 team. Similar renal safety profile between tenofovir DF (TDF) and stavudine (d4T) using modification of diet in renal disease (MDRD) and Cockcroft-Gault (CG) estimation of glomerular filtration rate (GFR) in antiretroviral-naïve patients through 144 week. *10th European AIDS Conference*. November 2005. Dublin, Ireland. Abstract PE9.7/10.

4.6.2.5 Full blood count

Recommendation

We recommend FBC monitoring (at 6 and 12 weeks, and then 3-monthly) in patients who have recently commenced zidovudine or who become unwell (e.g. with a rash)(1B).

Evidence

In patients on ART, blood count abnormalities are rare with antiretrovirals other than zidovudine [1-3].

References

1. 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.
2. Parsonage MJ, Wilkins EG, Snowden N *et al.* The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. *HIV Med* 2005; **6**: 341–346.
3. Staszewski S PA, Lu B, Enejosa J, Cheng A for the Study 903 team. Similar renal safety profile between tenofovir DF (TDF) and stavudine (d4T) using modification of diet in renal disease (MDRD) and Cockcroft-Gault (CG) estimation of glomerular filtration rate (GFR) in antiretroviral-naïve patients through 144 week. *10th European AIDS Conference*. November 2005. Dublin, Ireland. Abstract PE9.7/10.

4.7 Monitoring of patients established on ART

4.7.1 History and examination

Recommendation

We recommend that the issues recommended for annual review with treatment-naïve individuals should also be covered with patients on ART (see section 4.4). The following topics should also be reviewed at each prescription (GPP):

Full medication history and recreational drug use;

Understanding of dosing instructions;

Adherence;

Contraception and plans for conception;

Mood;

Adverse effects using open questions (e.g. 'Tell me about problems you have had with bowel disturbance' or 'What do you find most difficult about taking your medications?');

Patients' concerns about medication.

Evidence

Routine clinical appointments should aim at understanding whether any of the following factors have changed over time: risk factors for STIs and hepatitis virus acquisition (in view of the high rates of hepatitis C re-infection rates among HIV-positive MSM [1-4]); need for a hepatitis B vaccine booster [5]; lifestyle and mental health issues [6]; recreational substance use [7]; adherence to ART [6-11]; and to appointments [8]. All these should be documented and managed when necessary.

References

1. Bayley J, Macdonald F, Brookes R *et al*. A cross-sectional survey looking at uptake rates of sexually transmitted infection screening in an HIV-positive cohort in an inner city London cohort. Abstract P208. *HIV Med* 2013; **14** (Suppl 2): 77.
2. Brook G, McSorley J, Shaw A. Retrospective study of the effect of enhanced systematic sexually transmitted infection screening, facilitated by the use of electronic patient records, in an HIV-infected cohort. *HIV Med* 2013; **14**: 347–353.
3. El-Hayek C, Doyle JS, Cuevas M *et al*. New hepatitis C infection and re-infection among HIV co-infected men in Melbourne, Australia. Abstract P733. *J Hepatol* 2014; **60**: S314.
4. Peters L, Mocroft A, Soriano V *et al*. High rate of hepatitis C virus (HCV) recurrence in HIV-infected individuals with spontaneous HCV RNA clearance. *HIV Med* 2014; **15**: 615–620.
5. Geretti AM, Brook G, Cameron C *et al*. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Available at: <http://www.bhiva.org/vaccination-guidelines.aspx> (accessed May 2016).
6. Thorley N, Grima E, Sellers P *et al*. Screening for depression, excessive alcohol intake, recreational drug use and adherence to antiretrovirals within an HIV outpatient clinic: a pilot service evaluation. Abstract P22. *HIV Med* 2014; **15** (Suppl 3): 24.
7. Cohn SE, Jiang H, McCutchan JA *et al*. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. *AIDS Care* 2011; **23**: 775–785.
8. Dean BB, Hart RL, Buchacz K *et al*. HIV laboratory monitoring reliably identifies persons engaged in care. *J Acquir Immune Defic Syndr* 2015; **68**: 133–139.
9. Gutierrez EB, Sartori AM, Schmidt AL *et al*. Measuring adherence to antiretroviral treatment: the role of pharmacy records of drug withdrawals. *AIDS Behav* 2012; **16**: 1482–1490.

10. NICE. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE guidelines CG76. 2009. Available at: <https://www.nice.org.uk/guidance/CG76> (accessed May 2016).

11. 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.

4.7.2 Investigations: HIV-specific tests

4.7.2.1 Viral load

Recommendations

We recommend that viral load testing should be performed routinely every 6 months (1A) and might be at intervals of up to 12 months for patients established on ART that includes a PI (GPP).

We recommend that viral load rebound to above 50 copies/mL should be confirmed by testing a subsequent sample (2A). Repeat testing of the same sample is not recommended.

We recommend that if there is confirmed viraemia, the patient should be seen promptly to assess the underlying determinants and avoid accumulation of resistance (1A).

Evidence

Routine follow-up has been 3–4-monthly and in most clinical trials, 12-weekly is standard. However, with better-tolerated and more effective treatments, reducing the frequency of follow-up to 6-monthly has been shown to be adequate for people on ART with stable viral suppression [1,2].

References

1. Sanasi K, Seshadri V, Parker D *et al*. Randomized-controlled trial of every 4 month versus every 6 months monitoring in HIV-infected patients controlled on highly active antiretroviral therapy. *IDWeek 2013*. October 2013. San Francisco, CA, USA. Abstract 673.
2. Young B, Hart RL, Buchacz K *et al*. HIV viral load monitoring frequency and risk of treatment failure among immunologically stable HIV-infected patients prescribed combination antiretroviral therapy. *J Int Assoc Provid AIDS Care* 2015; **14**: 536-543.

4.7.2.2 CD4 count

Recommendations

We suggest that if the CD4 cell count is <200 cells/mm³ and the viral load is suppressed, the CD4 cell count is measured 6-monthly or more frequently if cessation of prophylactic antimicrobials is being considered (2A).

We recommend that the frequency of CD4 T cell count measurements could be reduced to once a year in patients who have maintained a viral load below 50 copies/mL for more than 1 year and have a CD4 T cell count above 200 cells/mm³ (1A).

We recommend that if the CD4 cell count has been >350 cells/mm³ and the viral load has been suppressed on two occasions a year or more apart then a CD4 cell count is not required unless there is subsequent treatment failure or new onset of HIV-related symptoms. For patients starting ART with a CD4 cell count >350 cells/mm³, there is no need to repeat the CD4 cell count unless there is subsequent treatment failure or new onset of HIV-related symptoms (1A).

Evidence

See section 4.6 [1-6].

References

1. Ford N, Stinson K, Gale H *et al.* CD4 changes among virologically suppressed patients on antiretroviral therapy: a systematic review and meta-analysis. *J Int AIDS Soc* 2015; **18**: 20061.
2. Gale HB, Gitterman SR, Hoffman HJ *et al.* Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts ≥ 300 cells/ μ L and HIV-1 suppression? *Clin Infect Dis* 2013; **56**: 1340–1343.
3. Gilson RJ, Man SL, Copas A *et al.* Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborative HIV Cohort (UK CHIC) Study. *HIV Med* 2010; **11**: 152–160.
4. Girard PM, Nelson M, Mohammed P *et al.* Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS* 2013; **27**: 2759–2763.
5. Zoufaly A, Cozzi-Lepri A, Reekie J *et al.* Immuno-virological discordance and the risk of non-AIDS and AIDS events in a large observational cohort of HIV-patients in Europe. *PLoS One* 2014; **9**: e87160.
6. Helleberg M, Kronborg G, Larsen CS *et al.* CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. *Clin Infect Dis* 2013; **57**: 314-321.

4.7.3 Investigations: non-HIV-specific tests

Recommendation

We suggest other investigations in patients established on ART be performed at the following frequency (2A):

6–12 monthly

- * Biochemistry: renal profile (eGFR), liver profile, bone profile;
- * Syphilis serology (may be more frequent as informed by a sexual health assessment).

Annually

- * Full blood count;
- * Urinalysis: dipstick for blood, protein and glucose;
- * Urine protein/creatinine ratio if protein + in the urine (may be more frequent if other comorbidities that affect renal function or on TDF);
- * Metabolic assessment: random lipid profile (total and HDL cholesterol), HbA1c (if aged >40 years).

Evidence

Elevation of liver enzymes may be associated with the chronic use of antiretroviral therapy, non-alcoholic steatohepatitis (NASH), alcohol and/or recreational drug use, other viral infections, syphilis or other STIs [1-5].

Abnormal renal function can be caused by TDF and or causes of nephropathy linked to HIV. See sections 4.5.3.7 and 4.6.2.4

References

1. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. Law WP, Dore GJ, Duncombe CJ *et al*. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. *Aids* 2003; **17**: 2191–2199.
3. Wit FW, Weverling GJ, Weel J *et al*. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis* 2002; **186**: 23–31.
4. Justice AC, Wagner JH, Fusco GP *et al*. HIV survival: liver function tests independently predict survival. *XIV International AIDS Conference*. July 2002. Barcelona, Spain. Abstract MoOrB1058.
5. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of liver chemistry tests. *Gastroenterology* 2002; **123**: 1364–1366.

5. Special circumstances

5.1 Patients with advanced disease (CD4 cell count <200 cells/mm³)

People who present with CD4+ T cell counts <200 cells/mm³ are considered to have advanced HIV disease. In 2013, this group accounted for 24% new diagnoses [1]. Late presentation is associated with increased mortality, particularly for those with an AIDS-defining condition and during the first year of follow-up [2].

5.1.1 History and examination

Recommendations

- We recommend fundoscopic examination or retinal photography for the detection of CMV retinitis in individuals with CD4 cell counts <50 cells/mm³ (1D).
- Routine screening for CMV IgG is not recommended (GPP).

Evidence

CMV disease is mostly seen at CD4 counts <50 cells/mm³ [3,4] but antiviral primary prophylaxis had no clear benefit in HIV-positive individuals, albeit in a trial in the pre-ART era, that assessed oral ganciclovir, a drug with limited oral bioavailability [5].

References

1. Yin Z, Brown AE, Hughes G *et al*. HIV in the United Kingdom 2014 Report: data to end 2013. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf (accessed May 2016).
2. Montlahuc C, Guiguet M, Abgrall S *et al*. Impact of late presentation on the risk of death among HIV-infected people in France (2003-2009). *J Acquir Immune Defic Syndr* 2013; **64**: 197–203.
3. Ford N, Shubber Z, Saranchuk P *et al*. Burden of HIV-related cytomegalovirus retinitis in resource-limited settings: a systematic review. *Clin Infect Dis* 2013; **57**: 1351-1361.
4. Baldassano V, Dunn JP, Feinberg J, Jabs DA. Cytomegalovirus retinitis and low CD4+ T-lymphocyte counts. *N Engl J Med* 1995; **333**: 670.
5. Brosgart CL, Louis TA, Hillman DW *et al*. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV-infected individuals. Terry Beinr Community Programs for Clinical Research on AIDS. *AIDS* 1998; **12**: 269–277.

5.1.2 Investigations

Recommendation

- We recommend tests for *Toxoplasma*, *Cryptococcus* and mycobacterial disease (MAC/TB) are not performed routinely but if the patient has relevant symptoms (GPP). Screening for latent TB is recommended (1B).

Evidence

See BHIVA TB/HIV co-infection guidelines for the indications for screening for TB [1].

Recommendation

- We recommend that the patient be assessed for clinical features of immune reconstitution inflammatory syndrome (IRIS) at follow-up visits after starting ART, especially within 3 months of starting ART (1B).

Evidence

Although BHIVA treatment guidelines recommend immediate ART for all, many patients will start ART with a low CD4+ T cell count (see section 4.5). Monitoring in patients initiating ART with a co-incident opportunistic infection or malignancy should be in accordance with the relevant guidelines. Such individuals are at risk of developing immune reconstitution inflammatory syndrome (IRIS) (16% of unselected patients in a large meta-analysis), particularly during the first 3 months of therapy, although risk is greatest in patients with a CD4 nadir of <50 cells/mm³ [2,3].

References

1. Pozniak AL, Coyne KM, Miller RF *et al*. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.
2. Muller M, Wandel S, Colebunders R *et al*. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 251–261.
3. Laureillard D, Marcy O, Madec Y *et al*. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome after early initiation of antiretroviral therapy in a randomized clinical trial. *Aids* 2013; **27**: 2577–2586.

5.2 Injecting drug users

5.2.1 History and examination

5.2.1.1 History

Recommendations

- We suggest that injection drug practice, including current use of recreational and illicit drugs and access to needle exchange programmes, is reviewed and discussed at each visit (GPP).
- We suggest that additional adherence support is offered to injecting drug users who commence antiretroviral therapy, particularly for those actively injecting and with chaotic lifestyles. This recommendation includes patients who inject as part of chemsex (GPP).

5.2.1.2. Examination

Recommendation

We suggest that injection sites are examined for signs of infection at each visit (GPP).

Evidence

People who inject drugs (IDUs) are at high risk of acquiring and transmitting blood-borne viruses. Easy access to needle exchange programmes should be facilitated for those actively injecting, and discussion about the use of clean needles, syringes and mixing equipment is important not only to influence the risk of acquisition of other infections but also to reduce the risk of onward transmission of HIV to injecting partners [1].

Antiretroviral therapy in IDUs is complicated by lower rates of retention in care, poor adherence and the potential for drug–drug interactions between recreational and illicit drugs or opiate substitution therapy and

NNRTIs/Pis [2]. IDUs, particularly those actively injecting and with chaotic lifestyles, may benefit from additional adherence support.

Injection site infections are common; staphylococcal, streptococcal and fungal blood-stream infections are frequent complications that may give rise to endocarditis and osteomyelitis [1].

References

1. Public Health England. Shooting up. Infections among people who inject drugs in the United Kingdom 2013. 2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/370707/Shooting_Up_2014.pdf (accessed May 2016).
2. Morris JD, Golub ET, Mehta SH *et al*. Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts. *AIDS Res Ther* 2007; **4**: 12.

5.3 Immigrants from the tropics

5.3.1 History

Recommendation

- We suggest a lifetime travel history and vaccination history should be obtained as part of the routine work-up at diagnosis for all individuals newly diagnosed with HIV (GPP).

5.3.2 Investigations

Recommendations

- We suggest that in individuals with eosinophilia or symptoms compatible with tropical illness, further investigation should be tailored according to geographical exposure and clinical features (GPP).
- We suggest that individuals who spend further time in the tropics should have investigations repeated as necessary, preferably >3 months after travel (GPP).

Evidence

There is an increasing body of evidence on the interactions between helminth and tropical infections and HIV and the prevalence of these infections in HIV-positive immigrants, although study participants are geographically heterogeneous, with relatively few data from immigrants of Asian origin.

Although presence of eosinophilia is associated with parasitic illness, eosinophilia and/or symptoms are not uniformly present in HIV-positive immigrants [1-3]. Immigrants will also be at risk of other diseases more prevalent in the tropics and not necessarily related to HIV status such as malaria, filariasis, leishmaniasis and HTLV. Routine screening is not recommended for these infections, but in the presence of symptoms or eosinophilia investigation as appropriate to exposure should be undertaken [4,5].

References

1. Costiniuk CT, Cooper CL, Doucette S, Kovacs CM. Parasitic disease screening among HIV patients from endemic countries in a Toronto clinic. *Can J Infect Dis Med Microbiol* 2012; **23**: 23–27.
2. Whitty CJ, Carroll B, Armstrong M *et al*. Utility of history, examination and laboratory tests in screening those returning to Europe from the tropics for parasitic infection. *Trop Med Int Health* 2000; **5**: 818–823.

3. Rodriguez-Guardado A, Rodriguez M, Martinez M *et al.* Screening for strongyloidiasis in HIV-positive immigrants from endemic areas. Abstract P2135. *Clin Microbiol Infect* 2012; **18 (Suppl 3)**: 621.
4. Checkley AM, Chiodini PL, Dockrell DH *et al.* Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. *J Infect* 2010; **60**: 1–20.
5. Whetham J, Day JN, Armstrong M *et al.* Investigation of tropical eosinophilia; assessing a strategy based on geographical area. *J Infect* 2003; **46**: 180–185.

5.4 Older patients (50 years and over)

Recommendations

- We recommend that all medications (prescribed and non-prescribed) are reviewed and documented at every clinic visit to identify potential drug–drug interactions (1C).
- We recommend that there is close liaison with the patient’s GP, including regular information exchange (GPP).
- We suggest that a fragility fracture risk assessment (FRAX score) is undertaken (GPP).
- We suggest that in the investigation of patients with symptoms of cognitive impairment, cardiovascular risk factors and current/prior alcohol dependence should be considered (2C).
- We recommend that screening for colorectal and breast cancers should be offered in accordance with guidelines for HIV-negative individuals (1C).

Evidence

Approximately 25% of HIV-positive adults accessing care in the UK are aged ≥ 50 years. Over 16% of new diagnoses were in this age group in 2013, of whom the majority were late diagnoses (CD4 < 350 cells/mm³) [1]. Several recent observational studies have shown significantly lower CD4 cell count gains and higher mortality after initiation of ART in older versus younger patients [2,3]. An impaired immunological response may increase the risk of both HIV- and non-HIV-related morbidities.

Drug absorption and metabolism are altered with increasing age due to changes in total body fat and fat distribution, decreased liver and renal function, all of which may potentiate drug toxicity [4]. HIV-positive individuals aged ≥ 50 years are more likely to receive multiple medications (in addition to antiretroviral agents) than younger patients and are therefore at greater risk of drug–drug interactions [5,6]. Therapeutic drug monitoring may play a role in the investigation of drug toxicity and/or serious drug–drug interaction; increased plasma concentrations of PIs, but not NNRTIs, has been reported in older patients, although the clinical significance of this finding is not known [7].

Bone mineral density is reduced and bone resorption is increased in older patients [8] (see section 4.3.3.12 and 4.4.4)

Neurocognitive impairment in older patients may have HIV- and non-HIV-related aetiologies, with a higher prevalence of metabolic and cardiovascular risk factors than younger patients [9]. Prior alcohol dependence may also contribute to cognitive impairment in later life [10].

Cancer screening should be offered in accordance with recommendations for age-matched HIV-uninfected populations and undertaken in general practice: faecal occult blood testing for colorectal cancer every 2 years in men and women aged 60–74 years (England, Wales, N. Ireland) [11]; mammography every 3 years for breast cancer in women aged 50–70 years (earlier if indicated by family history) [12]. Extended screening for breast cancer in women aged 47–49 and 71–73 is under evaluation [13] (see section 5.5.2).

References

1. Public Health England. HIV data tables. 2016. Available at: <https://www.gov.uk/government/statistics/hiv-data-tables> (accessed May 2016).
2. Blanco JR, Jarrin I, Vallejo M *et al.* Definition of advanced age in HIV infection: looking for an age cut-off. *AIDS Res Hum Retroviruses* 2012; **28**: 1000–1006.
3. Fatti G, Mothibi E, Meintjes G, Grimwood A. Antiretroviral treatment outcomes amongst older adults in a large multicentre cohort in South Africa. *PLoS One* 2014; **9**: e100273.
4. Kinirons MT, O'Mahony MS. Drug metabolism and ageing. *Br J Clin Pharmacol* 2004; **57**: 540–544.
5. Marzolini C, Back D, Weber R *et al.* Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011; **66**: 2107–2111.
6. Yiu P, Nguyen NN, Holodniy M. Clinically significant drug interactions in younger and older human immunodeficiency virus-positive patients receiving antiretroviral therapy. *Pharmacotherapy* 2011; **31**: 480–489.
7. Winston A, Jose S, Gibbons S *et al.* Effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring. *J Antimicrob Chemother* 2013; **68**: 1354–1359.
8. Biver E, Calmy A, Delhumeau C *et al.* Microstructural alterations of trabecular and cortical bone in long-term HIV-infected elderly men on successful antiretroviral therapy. *AIDS* 2014; **28**: 2417–2427.
9. Ciccarelli N, Grima P, Fabbiani M *et al.* Baseline CD4(+) T-cell count and cardiovascular risk factors predict the evolution of cognitive performance during 2-year follow-up in HIV-infected patients. *Antivir Ther* 2015; **20**: 433–440.
10. Gongvatana A, Morgan EE, Iudicello JE *et al.* A history of alcohol dependence augments HIV-associated neurocognitive deficits in persons aged 60 and older. *J Neurovirol* 2014; **20**: 505–513.
11. UK Government. NHS bowel cancer screening (BCSP) programme. Population screening programmes. Available at: <https://www.gov.uk/topic/population-screening-programmes/bowel> (accessed May 2016).
12. UK Government. NHS breast screening (BSP) programme. Population screening programmes. Available at: <https://www.gov.uk/topic/population-screening-programmes/breast> (accessed May 2016).
13. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; **380**: 1778-1786.

5.5 Pregnancy and issues that affect women

5.5.1 Cervical screening [1]

Recommendations

We recommend that national guidelines for cervical screening in HIV-positive women be followed and cervical screening is not performed under the age of 25 (1A).

We recommend that the HPV vaccine history, type of vaccine (Gardasil or Cervarix) and number of doses given be ascertained (GPP).

We recommend that all women newly diagnosed with HIV should have cervical surveillance performed by the GP, the medical team managing their HIV infection or other suitable service (1B).

We suggest that cervical cytology should be performed annually until evidence from larger studies indicates the optimum frequency of cervical screening in women with HIV infection (2C).

Cervical screening should not be performed after age 65 unless women fulfil the criteria for ongoing surveillance or follow up as indicated in national guidelines

An initial colposcopy at diagnosis can also be performed, if resources permit (2C).

We recommend that subsequent colposcopy for cytological abnormality should follow UK national guidelines, and the age range screened should be the same as for HIV-negative women (1B) [1].

We suggest that HIV-positive women follow national guidelines and should not have cervical screening after age 65 unless they fulfil the criteria for ongoing surveillance or follow up as indicated above (2B).

Evidence

There is no evidence in HIV-negative women that cervical screening under the age of 25 reduces cervical cancer rates and it may do more harm than good in younger women [2]. Women with HIV infection are more likely to have infection with HPV 16 or 18 than women who are HIV negative [3,4] and have a higher prevalence [5,6] and incidence [5,7] of CIN than HIV-negative women.

While there is some evidence that HIV-positive women are at increased risk of false-negative cytology [8], other studies have shown that cytology performed at 2-yearly intervals is sufficiently sensitive for cervical surveillance in women with HIV [9]. At present, annual smears are recommended but a small study has indicated they may not be necessary in women on ART with well-controlled HIV and a CD4 cell count greater than 350 cell/mm³ [10]. Further larger studies are awaited to clarify the optimal smear frequency in this group of women. HIV-negative women aged 65 and over are taken out of the call/recall system unless they need ongoing surveillance or follow up. This is generally required if a woman has had an abnormal result in any of her three most recent tests or is recommended for early repeats owing to a previous abnormality.

Generally speaking, the natural history and progression of cervical cancer means it is highly unlikely that women of 65 and over will go on to develop the disease. Women aged 65 and over who have never had a test are entitled to one.

References

1. Bower M, Palfreeman A, Alfa-Wali M *et al*. British HIV Association guidelines for HIV-associated malignancies 2014. *HIV Med* 2014; **15 Suppl 2**: 1-92.
2. UK Government. Cervical screening programme. Population screening programmes – guidance. 2015. Available at: <http://www.cancerscreening.nhs.uk/cervical/index.html> (accessed May 2016).
3. Minkoff H, Feldman J, DeHovitz J *et al*. A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. *Am J Obstet Gynecol* 1998; **178**: 982–986.
4. Palefsky JM, Minkoff H, Kalish LA *et al*. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. *J Natl Cancer Inst* 1999; **91**: 226–236.

5. Six C, Heard I, Bergeron C *et al.* Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS* 1998; **12**: 1047–1056.
6. Wright TC, Jr., Ellerbrock TV, Chiasson MA *et al.* Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol* 1994; **84**: 591–597.
7. Ellerbrock TV, Chiasson MA, Bush TJ *et al.* Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA* 2000; **283**: 1031–1037.
8. Maiman M, Fruchter RG, Sedlis A *et al.* Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Gynecol Oncol* 1998; **68**: 233–239.
9. Kitchener H, Nelson L, Adams J *et al.* Colposcopy is not necessary to assess the risk to the cervix in HIV-positive women: an international cohort study of cervical pathology in HIV-1 positive women. *Int J Cancer* 2007; **121**: 2484–2491.
10. Davies O, Rajamanoharan S, Balachandran T. Cervical screening in HIV-positive women in the East of England: recent CD4 as the predictive risk factor. *Int J STD AIDS* 2015; **26**: 945–950.

5.5.2 Breast cancer and other cancer screening

Recommendations

We recommend that women be screened for breast cancer following the 2016 national guidelines (GPP). We suggest screening for other cancers according to national guidelines for HIV-negative women (GPP).

Evidence

National guidelines recommend women aged 50–70 receive breast screening via their GP every 3 years [1]. This will be extended to age 47–73 in the 2016 National Breast Screening programme. Screening in women aged <50 is recommended when there is a history of breast cancer in a first-degree relative (mother or sister at a young age). There is currently no evidence that increased frequency of screening for breast cancer or starting screening at a young age will reduce the incidence of breast cancer in HIV-positive women.

At present, there is no evidence that HIV-positive women are at higher risk of breast, uterine or ovarian cancers (see section 5.4). There are currently no recommendations about any new screening methods.

Reference

1. UK Government. NHS breast screening (BSP) programme. Population screening programmes. Available at: <https://www.gov.uk/topic/population-screening-programmes/breast> (accessed May 2016).

5.5.3 Contraception

Recommendations

We suggest family planning and contraception discussion at baseline, annually, postnatally, and when age appropriate, in adolescent clinics (GPP).

We suggest discussion of the following, with provision of written information in the appropriate language (GPP):

- * Sex and risk of pregnancy;
 - * Contraception options including long-acting reversible contraceptives;
 - * Condoms, and prevention of STI transmission;
 - * Stopping contraception;
 - * Contraception and ART drug interactions;
 - * Prescribers of contraception should be aware of potential drug interactions with future ART (GPP).
- We recommend use of condoms to decrease STI risk and HIV transmission to HIV-negative partners (1A).
 - We recommend including male partners in family planning discussions (1C).

Evidence

There is a high rate of unwanted pregnancies among HIV-positive women. Partner approval is an important factor in a woman's likelihood of using contraception [1]. We have taken our guidance from NICE contraception guidelines [2] and BHIVA/BASHH/FSRH guidelines [3].

There is no strong evidence to suggest that women with HIV are any different from HIV-negative women in their contraceptive use and requirements [4].

NICE Contraception guidance 2014 [2] recommends:

Providing contraceptive services for young people;
Providing contraceptive services after a pregnancy;
Providing contraceptive services after an abortion;
Providing school and education-based contraceptive services;
Providing emergency contraception;
Providing condoms in addition to other methods of contraception.

There are many potential drug interactions between ART and contraception options and prescribers should be aware of these [5,6]. Use of hormonal contraception methods alone without condoms leads to an increased risk of HIV transmission to HIV-negative partners [7].

References

1. Akelo V, Girde S, Borkowf CB *et al.* Attitudes toward family planning among HIV-positive pregnant women enrolled in a prevention of mother-to-child transmission study in Kisumu, Kenya. *PLoS One* 2013; **8**: e66593.
2. NICE. Contraceptive services for under 25s. NICE guidelines PH51. 2014. Available at: <https://www.nice.org.uk/guidance/ph51> (accessed May 2016).
3. Fakoya A, Lamba H, Mackie N *et al.* British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.
4. Lopez LM, Hilgenberg D, Chen M *et al.* Behavioral interventions for improving contraceptive use among women living with HIV. *Cochrane Database Syst Rev* 2013; **1**: Cd010243.
5. University of Liverpool. HIV drug interactions. 2016. Available at: <http://www.hiv-druginteractions.org> (accessed August 2016).

6. Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. *Infect Dis Obstet Gynecol* 2012; **2012**: 890160.
7. Heffron R, Donnell D, Rees H *et al*. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012; **12**: 19–26.

5.5.4 Conception

Recommendations

Please refer to BHIVA/BASHH/FSRH guidelines for the management of sexual and reproductive health of people living with HIV 2017 [1]. (Please note that these guidelines are a consultation version).

We suggest that family planning and conception issues should be routinely discussed with all patients at baseline, including MSM and WSW and people who are not in relationships who still wish to conceive and parent, and if this arises in subsequent consultations (GPP).

We recommend discussion should cover the following topics as outlined in the BHIVA treatment guidelines [2] (GPP):

- * How to prevent HIV transmission to partner;
- * How to prevent HIV transmission to baby;
- * Chance of having HIV negative baby;
- * Safety of ART in pregnancy.

We recommend discussion of the available options and the possible risks of each method. All discussions should be documented clearly in clinical notes (1D).

Evidence

Evidence from observational studies and randomised controlled trials has now clearly established that there is no risk of transmission when a person with HIV has sustained viral suppression to undetectable levels. Thus, people who have maintained viral suppression for at least 6 months can be advised that natural conception carries no transmission risk (see sexual and reproductive health guidelines for consultation on the BHIVA website [1]).

References

1. Waters L, Lord E, Mackie N *et al*. BHIVA, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV 2017. <https://www.bhiva.org/file/zryuNVwnXcxMC/SRH-guidelines-for-consultation-2017.pdf> (accessed February 2019).
2. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).

5.5.5 Pregnancy

Recommendation

We recommend following national guidelines: BHIVA pregnancy guidelines and NICE antenatal care guidelines (1A) [1,2].

References

1. de Ruiter A, Taylor GP, Clayden P *et al*. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med* 2014; **15 Suppl 4**: 1-77.

2. NICE. Antenatal care for uncomplicated pregnancies. NICE guidelines CG62. 2016. Available at:
<https://www.nice.org.uk/guidance/cg62> (accessed May 2016).

5.5.6 Menopause and bone health

Recommendation

We recommend 3-yearly bone fracture risk assessment using the FRAX tool in women aged >50, post-menopausal women or with other risks, e.g. excess alcohol intake.

Evidence

See section 4.4.4.

5.5.7 Discussion relating to menstruation problems or menopause

Recommendation

We recommend following the NICE Menopause Guideline, which includes:

Baseline

- * Ask about LMP, cycle, contraception, abnormal bleeding, discharge, pelvic pain;
- * If over age 45, menopausal symptoms: hot flushes, sweats, menorrhagia, depression, tiredness, dry skin, loss of libido (GPP).

Annually

- * Enquire if any changes (GPP).

Evidence

NICE has recently produced guidelines [1].

Reference

1. NICE. Menopause: diagnosis and management. NICE guidelines NG23. 2015. Available at: <https://www.nice.org.uk/guidance/ng23> (accessed May 2016).

5.6 Patients with chronic kidney disease/kidney transplantation

Recommendations

We recommend that patients with chronic kidney disease be reviewed at 6–12-monthly intervals with monitoring of renal function (GPP).

We recommend that blood pressure, lipid profile, BMI, smoking status, antiretroviral therapy and other medications are reviewed annually in patients with chronic kidney disease (GPP).

We suggest that kidney transplant recipients are reviewed at 6–12-monthly intervals with monitoring of renal function and CD4 cell count (GPP).

We recommend that monitoring and risk-reduction strategies be employed in partnership with general practitioners and renal physicians to avoid duplication (GPP).

Evidence

Chronic kidney disease (CKD), defined by the presence of eGFR <60 mL/min/1.73m² or proteinuria, is present in approximately 15% of HIV-positive patients (although the majority of these have modest amounts of proteinuria with preserved eGFR) [1]. Both eGFR <60 mL/min/1.73m² and albuminuria are cardiovascular risk factors and identify individuals at risk of progression to end-stage kidney disease [2,3]. Hypertension, obesity, dyslipidaemia and smoking are modifiable risk factors. As for the general population, the target blood pressure for patients with CKD is $<140/90$ mmHg, and $<130/80$ mmHg if albuminuria (albumin/creatinine ratio [ACR] >70 mg/mmol) is present. Patients with CKD and ACR >70 mg/mmol (>30 mg/mmol with hypertension, and >3 mg/mmol with diabetes) should be offered an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker [4].

Several HIV drugs TDF, atazanavir and lopinavir have been associated with CKD [5,6] and these drugs are best avoided in patients with CKD [7]; other drugs (ritonavir, cobicistat, dolutegravir and rilpivirine) may inhibit creatinine secretion resulting in non-progressive reductions in eGFR without other signs of renal toxicity [8]. Several antiretrovirals (including TDF, lamivudine and emtricitabine) may need to be dose reduced in subjects with renal impairment [7].

Kidney transplantation is an increasingly used treatment strategy for end-stage kidney disease with excellent overall outcomes [9]. Patients with HIV, however, are at increased risk of graft rejection, which may require high-dose glucocorticoids or lymphocyte inhibiting/depleting therapies [10]. Furthermore, protease inhibitors have major drug interactions with calcineurin inhibitors (i.e. tacrolimus requires a 95–99% dose reduction) and any changes in antiretroviral therapy need to be carefully considered [10]. Poor HIV control may compromise graft function and impair host resistance to infection.

NICE guidelines for the general population suggest annual monitoring of renal function in patients with eGFR >45 mL/min/1.73m² and/or ACR <30 mg/mmol, and 6-monthly monitoring for most of those with eGFR 15–45 mL/min/1.73m² or ACR >30 mg/mmol [11]. This frequency of monitoring is appropriate for most HIV-positive patients with CKD [12].

Trends in renal function (eGFR and quantified albuminuria [uACR] or proteinuria [uPCR]) should be reviewed to allow detection of kidney-disease progression. Patients with progressive loss of renal function (eGFR decline >5 – 10 mL/min/1.73m²/year, unexplained or severe CKD (confirmed eGFR <30 – 45 mL/min/1.73m² and/or ACR >30 – 50 or PCR >50 – 100 mg/mmol) should be referred for renal evaluation.

References

1. Post FA, Holt SG. Recent developments in HIV and the kidney. *Curr Opin Infect Dis* 2009; **22**: 43–48.
2. Choi AI, Li Y, Deeks SG *et al*. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation* 2010; **121**: 651–658.

3. Jotwani V, Li Y, Grunfeld C *et al.* Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors. *Am J Kidney Dis* 2012; **59**: 628–635.
4. NICE. Management of chronic kidney disease. NICE Pathways. Available at: <http://pathways.nice.org.uk/pathways/chronic-kidney-disease - path=view%3A/pathways/chronic-kidney-disease/management-of-chronic-kidney-disease.xml&content=view-node%3Anodes-blood-pressure-control-and-antihypertensive-treatment> (accessed May 2016).
5. 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.
6. Scherzer R, Estrella M, Li Y *et al.* Association of tenofovir exposure with kidney disease risk in HIV infection. *Aids* 2012; **26**: 867–875.
7. Churchill D, Waters L, Ahmed N *et al.* BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
8. Yombi JC, Pozniak A, Boffito M *et al.* Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity. *Aids* 2014; **28**: 621–632.
9. Gathogo E, Jose S, Jones R *et al.* End-stage kidney disease and kidney transplantation in HIV-positive patients: an observational cohort study. *J Acquir Immune Defic Syndr* 2014; **67**: 177–180.
10. Gathogo EN, Hamzah L, Hilton R *et al.* Kidney transplantation in HIV-positive adults: the UK experience. *Int J STD AIDS* 2014; **25**: 57–66.
11. NICE. Chronic kidney disease in adults: assessment and management. NICE guidelines CG182. 2014. Available at: <https://www.nice.org.uk/Guidance/CG182> (accessed May 2016).
12. Yombi JC, Jones R, Pozniak A *et al.* Monitoring of kidney function in HIV-positive patients. *HIV Med* 2015; **16**: 457–467.

5.7 Monitoring for, and assessing osteoporosis and fracture risk

Recommendations

We suggest that a FRAX score is calculated, and a history of falls elicited, in all patients >50 years (GPP).

We recommend that patients at increased risk of fracture have their bone mineral density (BMD) measured, their vitamin D/parathyroid hormone status assessed and optimised, and their antiretroviral therapy and other medications reviewed (GPP).

We recommend against the evaluation of BMD, vitamin D and/or parathyroid hormone status in the absence of elevated fracture risk (GPP).

Evidence

See also section 4.3.3.12. Osteopenia, osteoporosis and fractures are more common in HIV-positive patients compared to the general population [1,2]. HIV is an independent risk factor for low bone mineral density (BMD) [2], along with older age, white ethnicity, hypogonadism or post-menopausal status, low body mass, smoking, high alcohol intake and glucocorticoid use. In the UPBEAT study, osteoporosis at the femoral neck was present in <5% of HIV-positive patients >50 years [3]. The presence of osteoporosis is a risk factor for subsequent fracture [4].

Several HIV drugs (TDF, protease inhibitors) have been associated with low BMD [5-8]. In randomised controlled trials, initiation of TDF/FTC is associated with approximately 2% greater reduction in BMD at the hip and lumbar spine [9] and initiation of a PI/r with a 0.8% greater reduction in total BMD [10], and discontinuation of TDF may result in 2–3% increase in BMD [11,12]. TDF may be best avoided in patients with osteoporosis and those at increased risk of fracture [13].

Although not specifically validated for people living with HIV, we recommend the use of FRAX (see section 4.3.3.12) to calculate the risk of fracture in HIV-positive patients >50 years (>40 years if major risk factors are present). This is consistent with NICE guidance if HIV is considered a risk factor [14]. Dual X-ray absorptiometry (DEXA) scanning provides a BMD measurement that allows refinement of fracture risk as calculated by the FRAX tool and should be performed in those at increased risk (10-year risk of major osteoporotic fracture >10%). The estimate provided by the FRAX tool allows the identification of patients whose fracture risk exceeds the intervention threshold as defined by the National Osteoporosis Guideline Group (see section 4.4.4). Biochemical parameters (calcium, phosphate and alkaline phosphatase) have very limited use as screening tools for reduced BMD.

Low vitamin D status is common in HIV-positive patients in the UK, and one-third of patients may have severe vitamin D deficiency (25[OH]D less than 10 mg/L [15]). Risk factors for vitamin D deficiency include sampling in winter, black ethnicity and exposure to efavirenz [16]. Whereas calcium and vitamin D supplementation mitigate the modest BMD reductions associated with TDF/FTC/EFV initiation [17], vitamin D supplementation alone had no effect on BMD in stable patients on ART [18].

FRAX can be used to stratify patients aged >50 according to fracture risk (any osteoporotic fracture):

- <10%: reassure and repeat FRAX after 3 years;
- 10–20%: consider DEXA scan to refine risk estimate; if >10% fracture risk, provide lifestyle advice and optimise risk factors including vitamin D deficiency;
- >20%: optimise risk factors, review ART (TDF) and lifestyle factors, and refer for osteoporosis treatment.

References

1. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; **20**: 2165–2174.

2. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab* 2008; **93**: 3499–3504.
3. Cotter AG, Sabin CA, Simelane S *et al.* Relative contribution of HIV infection, demographics and body mass index to bone mineral density. *AIDS* 2014; **28**: 2051–2060.
4. Winston A, Jose S, Gibbons S *et al.* Effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring. *J Antimicrob Chemother* 2013; **68**: 1354–1359.
5. Battalora L, Buchacz K, Armon C *et al.* Low bone mineral density and risk of incident fracture in HIV-infected adults. *Antivir Ther* 2016; **21**: 45–54.
6. Kinai E, Nishijima T, Mizushima D *et al.* Long-term use of protease inhibitors is associated with bone mineral density loss. *AIDS Res Hum Retroviruses* 2014; **30**: 553–559.
7. Mary-Krause M, Viard JP, Ename-Mkoumazok B *et al.* Prevalence of low bone mineral density in men and women infected with human immunodeficiency virus 1 and a proposal for screening strategy. *J Clin Densitom* 2012; **15**: 422–433.
8. Yin MT, Zhang CA, McMahon DJ *et al.* Higher rates of bone loss in postmenopausal HIV-infected women: a longitudinal study. *J Clin Endocrinol Metab* 2012; **97**: 554–562.
9. 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.
10. Grant PM, Kitch D, McComsey GA *et al.* Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. *Clin Infect Dis* 2013; **57**: 1483–1488.
11. Bloch M, Tong WW, Hoy J *et al.* Switch from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48 weeks. *HIV Med* 2014; **15**: 373–380.
12. Hamzah L, Tiraboschi JM, Iveson H *et al.* Effects on vitamin D, bone and the kidney of switching from fixed-dose tenofovir disoproxil fumarate/emtricitabine/efavirenz to darunavir/ritonavir monotherapy: a randomized, controlled trial (MIDAS). *Antivir Ther* 2015.
13. Churchill D, Waters L, Ahmed N *et al.* BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
14. NICE. Fragility fracture risk assessment. NICE Pathways. Available at: <http://pathways.nice.org.uk/pathways/osteoporosis - path=view%3A/pathways/osteoporosis/fragility-fracture-risk-assessment.xml&content=view-index> (accessed May 2016).
15. Childs K, Welz T, Samarawickrama A, Post FA. Effects of vitamin D deficiency and combination antiretroviral therapy on bone in HIV-positive patients. *Aids* 2012; **26**: 253–262.
16. Welz T, Childs K, Ibrahim F *et al.* Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *Aids* 2010; **24**: 1923–1928.
17. Overton ET, Chan ES, Brown TT *et al.* Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: a randomized trial. *Ann Intern Med* 2015; **162**: 815–824.

18. van den Bout-van den Beukel CJ, van den Bos M, Oyen WJ *et al*. The effect of cholecalciferol supplementation on vitamin D levels and insulin sensitivity is dose related in vitamin D-deficient HIV-1-infected patients. *HIV Med* 2008; **9**: 771–779.

5.8 Monitoring of patients with diabetes mellitus

Recommendation

We recommend that monitoring and risk-reduction strategies be employed in partnership with general practitioners and other healthcare providers to avoid duplication (GPP).

5.9 Monitoring of patients with, or at high risk of, cardiovascular disease

Recommendations

We recommend that patients with established CVD and those at increased risk of CVD (10 year CVD risk >10%) are screened annually for hypertension, diabetes, dyslipidaemia and chronic kidney disease, and that BMI, smoking status and antiretroviral therapy are reviewed annually (GPP).

We recommend against the evaluation of inflammatory or coagulation biomarkers and imaging studies as part of routine clinical care (GPP).

Evidence

HIV-positive patients are at increased risk of myocardial infarction (MI) and other manifestations of cardiovascular disease [1,2], although the CVD incidence may be decreasing due to better control of modifiable risk factors such as hypertension and dyslipidaemia [3]. Hypertension, dyslipidaemia, diabetes and smoking are major, modifiable risk factors [4]. In addition, some studies have identified an association between MI or cardiovascular disease (CVD) events and exposure to abacavir, didanosine and/or lopinavir [5-7], and these drugs may be best avoided in patients at high CVD risk [8]. Poor HIV control may further contribute to the heightened risk of cardiovascular complications in this population [9].

NICE guidelines recommend that patients with established CVD receive advice on restricting dietary salt, saturated fat, cholesterol and alcohol intake, weight reduction, physical activity and smoking cessation, and receive high-dose (80 mg) atorvastatin [10]. Although firm evidence in HIV populations is lacking, we endorse this recommendation for HIV-positive patients.

References

1. Currier JS, Taylor A, Boyd F *et al*. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003; **33**: 506–512.
2. Klein D, Hurley LB, Quesenberry CP, Jr., Sidney S. 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.
3. Triant VA, 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.
4. NICE. Cardiovascular disease prevention. NICE guidelines PH25. 2010. Available at: <https://www.nice.org.uk/guidance/ph25> (accessed May 2016).
5. Friis-Moller N, Weber R, Reiss P *et al*. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. *AIDS* 2003; **17**: 1179–1193.
6. Sabin CA, Worm SW, Weber R *et al*. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; **371**: 1417–1426.

7. Triant VA. HIV infection and coronary heart disease: an intersection of epidemics. *J Infect Dis* 2012; **205 Suppl 3**: S355–361.
8. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
9. El-Sadr WM, Lundgren J, Neaton JD *et al*. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355**: 2283–2296.
10. NICE. CVD risk assessment and management. 2014. Available at: <http://cks.nice.org.uk/cvd-risk-assessment-and-management-!topicsummary> (accessed May 2016).

5.10 Extra viral load monitoring needed in special circumstances

5.10.1 Low level viraemia (intermittent or persistent)

Recommendations

For patients stable on ART we recommend that:

An adherence check is performed and a viral load is repeated when above 50 copies/mL to ensure this comes back to undetectable (1B).

If the repeat is <50 copies/mL, continue routine monitoring (1B). This is considered a single blip.

If the initial viral load measurement is below 200 copies/mL and subsequent measurement again between 50 and 200 copies/mL that adherence and DDIs are reviewed, a resistance test performed and acted upon (1D).

Frequent (3–4 monthly) viral load follow-ups of individuals with stable unsuppressed (<200 copies/mL) viral loads if they are managed as low-level viraemic patients according to the BHIVA treatment guidelines (1D).

Genotypic resistance testing should be attempted and acted upon especially if there is a gradual increase in viral load (1C).

There is no need for repeat genotypic resistance testing at a frequency greater than once a year if the viral load is stable (2D) and there is no need for routine TDM (2C).

CSF HIV viral load measurement should be considered to exclude compartmentalisation (1C).

Urgent action (as above) is taken if the second repeat viral load is above 200 copies/mL and if both measurements are above 200 copies/mL refer to BHIVA treatment guidelines for managing virological failure (1A).

A careful assessment (as above) of patients with frequent ‘blips’ and/or one measurement above 200copies/mL as these can sometimes be associated with viral rebound and virological failure (1C).

Evidence

Low-level viraemia (LLV, blips) refers to viral load measurements repeatedly between 50 and 200 copies/mL. It is not always associated with an increased risk of virological failure and the current BHIVA treatment guidelines suggest that in the absence of strong data that patients are permitted to carry on with their current regimen providing they are not on a low genetic barrier NNRTI regimen [1]. The mechanism is not yet fully understood; however, the following factors need to be taken into account: (a) the well-documented low-level variability of assays used to measure HIV-1 RNA. Artefacts that relate to the way samples are processed have also been found to play a role in the frequency ‘blips’ are reported [2]; (b) the frequency of viral load monitoring; (c) adherence; (d) drug levels; (e) immune activation; and (f) possible ongoing viral replication. Research data indicate that blips do not have clinical consequences and do not necessarily lead to virological failure including in patients who initiate treatment during PHI [2,3]. This seems especially true if the viral loads are below 200 copies/mL where assay variation can play a role. Genotypic drug resistance mutations can be detected at low viral loads but there is also a higher risk of stochastically not amplifying the drug resistance quasispecies, i.e. false negative results [4]. There is, however, a concern that frequent blips might lead to viral rebound and some recent evidence suggests higher amplitude blips (>500 copies/mL) also increase the risk of viral rebound [5]. Recent data suggest that residual viraemia <50

copies/mL predicts blips and low-level viraemia [6,7]. In the absence of evidence that detectable HIV-1 RNA below 50 copies/mL is predicting virological rebound and/or failure, this cut-off continues to be clinically used.

There is no good data looking at the viral load monitoring frequency, but the writing group is of the opinion that monitoring should not be relaxed in these patients since some studies have shown that they are at a higher risk of virological failure. In patients with fully suppressed viral load it takes around 1–2 weeks for HIV to rebound, which gives a greater adherence tolerance than for patients who have already a baseline viral load above 50 copies/mL. The PARTITION study has found that a high proportion of patients with PLLV had detectable HIV-1 in their CSF and it is therefore necessary to exclude CNS replication as a cause [8].

There is concern that frequent episodes of LLV could increase the size of the reservoir especially if these represent ongoing viral replication [9]; however, recent data suggest that reservoir replenishment does not occur even in patients on monotherapy [10]. More definitive data will be required in this area. HIV-1 total proviral DNA quantitation emerges as a potential tool [11] offering a glimpse of the size of the reservoir. However, there is not yet enough evidence for this to guide clinical decisions and the assay is currently only used in research. We expect more data in the near future as there is a growing body of evidence around the degree to which the reservoir determines virological control and disease progression [12].

References

1. Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Available at: <http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf> (accessed May 2016).
2. Lee PK, Kieffer TL, Siliciano RF, Nettles RE. HIV-1 viral load blips are of limited clinical significance. *J Antimicrob Chemother* 2006; **57**: 803–805.
3. Fidler S, Olson A, Fox J *et al*. The importance of viral blips and duration of therapy initiated in primary infection in maintaining viral control after stopping cART. *J Int AIDS Soc* 2014; **17**: 19820.
4. Aleman S, Soderbarg K, Visco-Comandini U *et al*. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS* 2002; **16**: 1039–1044.
5. Grennan JT, Loutfy MR, Su D *et al*. Magnitude of virologic blips is associated with a higher risk for virologic rebound in HIV-infected individuals: a recurrent events analysis. *J Infect Dis* 2012; **205**: 1230–1238.
6. Doyle T, Smith C, Vitiello P *et al*. Plasma HIV-1 RNA detection below 50 copies/ml and risk of virologic rebound in patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2012; **54**: 724–732.
7. Hofstra LM, Mudrikova T, Stam AJ *et al*. Residual viremia is preceding viral blips and persistent low-level viremia in treated HIV-1 patients. *PLoS One* 2014; **9**: e110749.
8. Nightingale S, the PARTITION Study Group. HIV-1 RNA detection in CSF in ART-treated subjects with incomplete viral suppression in plasma. *Conference on Retroviruses and Opportunistic Infections*. Boston, MA, USA. Abstract 442.
9. Jones LE, Perelson AS. Transient viremia, plasma viral load, and reservoir replenishment in HIV-infected patients on antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007; **45**: 483–493.
10. Torres-Cornejo A, Benmarzouk-Hidalgo OJ, Gutierrez-Valencia A *et al*. Cellular HIV reservoir replenishment is not affected by blip or intermittent viremia episodes during darunavir/ritonavir monotherapy. *Aids* 2014; **28**: 201–208.
11. Bruner KM, Hosmane NN, Siliciano RF. Towards an HIV-1 cure: measuring the latent reservoir. *Trends Microbiol* 2015; **23**: 192–203.
12. Williams JP, Hurst J, Stohr W *et al*. HIV-1 DNA predicts disease progression and post-treatment virological control. *Elife* 2014; **3**: e03821.

5.11 Monitoring of HIV-positive patients with chronic viral hepatitis B or C co-infection

Recommendations

We recommend that all patients should be 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 (GPP).

We recommend that patients be monitored based on the recommendations in the BHIVA hepatitis guidelines (1A).

Evidence

These recommendations are based on the BHIVA hepatitis guidelines [1].

Reference

1. Wilkins E, Nelson M, Agarwal K *et al.* British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. *HIV Med* 2013; **14 Suppl 4**: 1–71.

5.12 Monitoring HIV-positive patients who have tuberculosis

Recommendations

We recommend that persons being treated for HIV and TB should be cared for by a specialist multidisciplinary team that has experience of managing TB/HIV co-infection (GPP).

We recommend that patients be monitored based on the recommendations in the BHIVA guidelines for the treatment of HIV/TB coinfection 2011 and NICE TB guidelines 2015 (1A).

Evidence

These recommendations are based on the 2011 BHIVA guidelines [1] and the 2015 NICE TB guidelines [2].

References

1. Pozniak AL, Coyne KM, Miller RF *et al.* British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Med* 2011; **12**: 517–524.
2. NICE. Tuberculosis. NICE guidelines NG33. 2016. Available at: <https://www.nice.org.uk/guidance/ng33> (accessed May 2016).

5.13 Screening for, and managing mental health problems

Recommendations

We recommend that in line with Standards for psychological support for adults living with HIV, that all HIV-positive patients have regular screening to identify psychological support needs (GPP).

We recommend HIV-positive patients should have access to screening for the presence of symptoms of depression, anxiety, drug and alcohol misuse, acute stress disorder and risk of self-harm within the first 3 months of receiving an HIV diagnosis. It is essential for pathways to be in place for further assessment following screening (GPP).

We recommend that HIV-positive patients should have access to screening for cognitive difficulties within the first 3 months of receiving an HIV diagnosis (GPP).

We recommend HIV-positive patients should have access to repeated screening following events that are known to trigger or exacerbate psychological distress or cognitive difficulties, and otherwise on an annual basis (GPP).

We recommend HIV-positive patients whose screen suggests significant difficulties should be offered referral to a suitably competent practitioner for further assessment (GPP).

We recommend HIV-positive patients with current mental health problems have access to HIV care through close coordination between mental health and HIV services (GPP).

Evidence

The Standards for psychological support for adults living with HIV identify the importance of assessing and managing psychological support [1]. It recommends a stepped care model that describes four essential levels of psychological support provision for HIV-positive patients based on levels of complexity of need.

The wellness thermometer can be useful as an aid to communication [2]. Pre-consultation screening tools enable patients' agendas to shape the consultation and enable better communication of any concerns.

References

1. British Psychological Society, British HIV Association, Medical Foundation for AIDS & Sexual Health. Standards for psychological support for adults living with HIV. 2011. Available at: http://www.bhiva.org/documents/Publications/Standards_for_psychological_support_for_adults_living_with_HIV.pdf (accessed May 2016).
2. Croston M, Whitehead T, Benn P *et al.* The wellness thermometer: healthcare professionals' experiences of using the tool in practice. *National HIV Nurses Conference*. June 2015. Leeds, UK. Abstract P11.

5.14 Patients with social care needs

Recommendations

Additional monitoring in this group is not recommended. However, services should be aware of local services and how to refer HIV-positive individuals for social care support (GPP).

Services should be aware of safeguarding issues relating to their clients and how to access support (GPP).

Evidence

A National AIDS Trust survey [1] found that a high proportion of people with HIV have, at some point, social care needs. These include home and personal care support, and emotional/psychological support, but the most frequently cited needs relate to poverty and its associated issues. Services may consider adding social care issues to clinic proformas or annual reviews to identify needs.

Reference

1. National AIDS Trust. The impact of social care support for people living with HIV. The results of NAT's snapshot survey of healthcare professionals. 2011. Available at: http://www.nat.org.uk/MediaLibrary/Files/Policy/2011/Social_Care_Survey_June_2011_FINAL.pdf (accessed May 2016).

5.15 Monitoring of patients in prison

Recommendations

We suggest that HIV-positive patients who are in prison are provided with timely information regarding current medication and other current health issues so the prison health authorities can facilitate appropriate HIV care without delay (GPP).

We suggest that HIV providers that have a prison in their locality have robust pathways in place to allow rapid registration for patients who are imprisoned in order to ensure uninterrupted HIV care (GPP).

We recommend HIV-positive patients have access to STI screening including for other blood-borne viruses while in prison (1D).

Prisoners who also have a history of injecting drug use should be offered additional support (see section 5.2) (GPP).

We suggest that HIV-positive patients who are in prison are given appropriate access to healthcare in privacy, whether that is at the prison or at a clinic (GPP).

Evidence

Continuity of HIV care for patients who are in prison is the aim. Prisoners also have other additional sexual health needs that can be addressed. A comparison of male prisoners seen in STI clinics compared to other male attendees in 2011 demonstrated that compared with other male STI clinic attendees, prisoners' standardised new diagnosis rates were higher for genital warts (5.5% vs 4.6%); hepatitis B (0.4% vs 0.1%); and hepatitis C (2.0% vs 0.0%). However comprehensive sexual health screens (48% vs 64%) were offered less frequently to prisoners [1].

A questionnaire survey of clients leaving prison ($n=35$) demonstrated that 82.9% felt HIV/HCV testing should be offered in prison; 71.1% felt this should be done using a mouth swab; 35% had no concerns regarding HIV/HCV testing but in those who did, dislike of needles, receiving a positive result and concerns regarding confidentiality were the commonest barriers to testing [2].

References

1. Marsh K, Chan S, Wheatley N *et al*. Missed STI and HIV Testing Opportunities Among Male Prisoners in England. Abstract P3.444. *Sex Transm Dis* 2013; **89** (Suppl 1): A287.

2. Williams H, Axten D, Makia F *et al.* HIV and hepatitis C prevalence in individuals leaving prison and entering drug and alcohol services in the area of highest HIV prevalence in the UK. Abstract LBP-1.12. *Sex Transm Dis* 2011; **87** (Suppl 1): A356–357.

5.16 Transgender issues

Recommendations

All patients should be asked about which gender they identify with and whether this is the gender they were given at birth (GPP).

Supplementary questions for patients identifying as trans, should include (GPP):

How long has patient been living in the gender with which they identify?

Social transition (binding, tucking), hormone use, dose, duration, obtained 'online' or prescription;

Silicone;

Future plans for surgery/hormones;

Sexual History (sex with men, women, both);

Psychosocial issues: depression, PTSD, intimate partner violence, support network; employment, sex work and substance use;

Legal concerns: gender recognition certificate, ID;

NHS records.

Evidence

Accurately monitoring the progression of the HIV epidemic is essential for determining public health priorities, designing and assessing the efficacy of interventions, and understanding current health needs [1]. However, there is currently no reliable data concerning the incidence of HIV infection in trans populations in the UK.

HIV prevalence and incidence among trans women is extremely high. Meta-analyses of studies in the USA, six Asia-Pacific, five Latin American, and three European countries suggests a 49% higher likelihood of becoming HIV positive for transgender women, in comparison with all other populations of reproductive age; this equates to an estimated 19% global prevalence of HIV in trans women [2]. There are no estimates for HIV prevalence in transgender men or non-binary people.

Trans people living with HIV are more likely than non-trans HIV-positive individuals to avoid seeking care in various medical settings for fear of being treated differently. Trans people are also more likely to experience discrimination, and disclosure of their HIV status by health professionals without their consent [3]. There is evidence that trans women are less likely to receive ART and that they experience lower adherence [4,5]

Transgender patients may have had previous negative healthcare experiences (70% mistreatment, >19% denied care). Developing trust and rapport may take longer than doctors are used to and may have different priorities. Care should be taken to pay attention to pronouns the patient uses, avoid genital and rectal exams on first visit, if possible, and avoid using the terms 'pre-op' and 'postop'.

References

1. UNAIDS. Report on the global AIDS epidemic. A UNAIDS 10th anniversary special edition. Executive summary. Geneva, Switzerland: UNAIDS; 2006. Available at: http://www.unaids.org/sites/default/files/media_asset/2006_gr-executivesummary_en_0.pdf (accessed June 2016).
2. Baral SD, Poteat T, Stromdahl S *et al.* Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13**: 214–222.

3. Stigma Index UK. HIV in the UK: changes and challenges; actions and answers. The people living with HIV stigma survey UK 2015. National findings. 2015. Available at:
<http://www.stigmaindexuk.org/reports/2016/NationalReport.pdf> (accessed June 2016).
4. Melendez RM, Exner TA, Ehrhardt AA *et al.* Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health* 2006; **96**: 1034–1037.
5. Sevelius JM, Carrico A, Johnson MO. Antiretroviral therapy adherence among transgender women living with HIV. *J Assoc Nurses AIDS Care* 2010; **21**: 256–264.

Appendix 1: resistance testing

5.16 Resistance testing

5.16.1 When should patients have a resistance test? (See also section 4.3.3.3)

At baseline, we recommend that:

All newly diagnosed patients should have a baseline resistance test with a genotyping test that includes sequencing of the part of the polymerase (pol) gene that encodes the reverse-transcriptase (RT) and protease (PR) proteins (1A). Baseline genotypic resistance test should be performed on the first available sample at diagnosis. If treatment is deferred, testing should only be repeated when ART exposure or superinfection is suspected (1A).

Baseline integrase resistance testing should currently not be performed since there is not enough evidence of transmitted integrase strand transfer inhibitor (INSTI)-resistant mutations occurring. However, it is recommended if there are other baseline transmitted drug resistance (TDR) mutations present or when transmitted INSTI resistance is suspected, for example when the patient's partner has evidence of such resistance (1C).

A genotypic tropism test should only be performed just prior to a patient initiating a CCR5 co-receptor antagonist (1A).

5.16.2 Recommendations at virological failure

We recommend that:

Resistance testing should be performed in all patients experiencing suboptimal viral load response to therapy initiation ($<1 \log_{10}$ in 4 weeks) virological failure (confirmed viral load >200 copies/mL on two samples while on ART) (1A). In all cases, the test should include sequencing of all genes encoding proteins that are targeted by current and future treatment agents in order to optimise treatment combinations (1B).

Resistance testing should be performed after each event of virological failure in order to guide the new therapy selection or just before therapy switch in known poorly adherent patients to exclude any new mutations (1B).

In complex salvage patients all previous drug resistance reports should be taken into account when a new regimen is constructed. Resistance reports from previous clinics should also be obtained and a cumulative Stanford HIV drug resistance report should be generated in order to predict drug sensitivities (1B).

A repeat tropism test should be performed to exclude tropism switch in those who fail on CCR5 co-receptor antagonist (maraviroc). The risk of CCR5 co-receptor antagonist resistance is small in those cases where there is no tropism switch (1A).

A genotyping test should be performed for patients failing on INSTIs in order to optimise design of the following regimen (1B).

In special circumstances, we recommend that:

A resistance test should be performed on a CSF sample if CSF viral load is detectable during therapy (1C).

In pregnancy, resistance testing should be performed prior to ART initiation (1A). Clinicians should have a lower threshold to perform resistance tests in pregnant women and should request a resistance test if the viral load is detectable by week 36 (1D).

Expert clinical virology advice should be sought with complex or unusual resistance profiles (1B).

5.16.3 What samples should be tested?

The samples available while patients have detectable viraemia while on ART should be selected for resistance testing in patients whose therapy is failing (1B), as in the absence of ART, mutations might be missed.

Most laboratories are able to perform standard HIV-1 genotyping in samples where viral load is >500 copies/mL.

Performance of HIV-1 genotyping when the viral load is below 500 copies/mL differs between laboratories but testing is

certainly recommended and should be attempted when changes in therapy are contemplated, and in all cases of virological failure (3B).

HIV-1 genotyping assays require HIV-1 RNA extraction from plasma and EDTA samples should be used. For tropism assays whole blood might be necessary; this is in case sequencing of proviral DNA is required (i.e. when viral load is <500 copies/mL).

CSF: in cases of viral load discordance between plasma and CSF when patients are on treatment in order to ensure optimisation of therapy.

5.16.4 Which method should be used?

Current HIV-1 genotyping assays mostly rely on dideoxynucleotide sequencing using the Sanger method that allows detection of mutations when present at a level of 20–25% of the virus quasispecies population.

There are assays available based on sequencing the pol (encoding the RT, PR, IN proteins) and envelope genes as well as genotyping tests predicting co-receptor usage.

A variety of methods is commercially available in the UK but in-house assays are also widely used. It is critical for laboratories performing resistance testing to be accredited, participate in a variety of quality assurance schemes, ensure tight quality-control programmes within the laboratory, and make the results of their performance available to users.

Detection of minority variants by deep sequencing is becoming available in many laboratories; however, reporting of those is not yet part of standard clinical algorithms. More laboratories will have validated next-generation sequencing methods in the near future and only tests validated by UKAS accredited laboratories should be used. In the absence of clinical cut-off data all minority variants should be interpreted with extreme caution and should be discussed with an expert before being acted upon (2B). Next-generation sequencing methods seem more sensitive in predicting CCR5 co-receptor antagonist failure (2B).

Phenotyping assays used to predict response to ART in cases of complex resistance profiles are not readily available (see section 5.16.5)

5.16.5 How should results be interpreted?

There is a variety of online tools available that aid interpretation of HIV-1 genotyping results. The Stanford database (<http://hivdb.stanford.edu>), ANRS (<http://www.hivfrenchresistance.org>) and REGA (<http://rega.kuleuven.be/cev/regadb/download>) are the most commonly used data-interpretation systems.

Additionally, the International AIDS Society (IAS-USA) provides updates on significant drug resistant mutations.

HIV physicians should be familiar with these online tools as well as with the basics of result interpretation and clinical significance of most common mutations.

Specialist virology input by a clinical virologist is necessary for interpretation of complex patterns of mutations, for selection of alternative assays and tests in clinical dilemmas and ensuring quality control is clinically adequate in the diagnostic services responsible for resistance testing (1B).

When a resistance test is performed by sequencing HIV-1 RNA, the subtype information is also automatically provided in the resistance report. Subtyping is of limited direct clinical use for managing the individual patient although it might aid interpretation of sequencing results. It provides, however, important epidemiological information.

Evidence

Testing at baseline: performing a genotypic resistance test (sequencing of pol gene that encodes RT and PR proteins) at time of diagnosis/entry to care is recommended for patients diagnosed with primary HIV infection as well as those with chronic infection by all clinical guidelines, although implementation capacity differs in different parts of the world [1-3]. There is consensus on discriminating TDR mutations as opposed to naturally occurring polymorphisms [4] and the estimated prevalence of TDR mutations in the UK remains stable at 10%. Recent evidence suggests that it is self-sustained and sequences with TDR mutations are mainly derived from treatment-naïve patients, the main group of patients contributing to this phenomenon [5].

Testing needs to be performed on the earliest available sample close to time of infection, since TDR mutations can disappear (revert back to wildtype) over time [6]. However, specific TDR mutations can be detected years after transmission [6-9]. This is particularly true for thymidine analogue mutations (TAMs)

like M41L and T215F/Y, as opposed to K65R and M184V and mutations conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Persistent revertants therefore, such as those containing M41L are observed more frequently [10,11]. Detection of TDR minority variants by more sensitive next-generation sequencing (NGS, detecting variants present in frequencies as low as 0.1–1%) has been shown to predict a higher risk of virological failure with low genetic barrier drugs such as NNRTIs [12,13]. Clinical thresholds have not yet been established, but an ART regimen with a high barrier to resistance (e.g. a boosted PI regimen) should probably be selected when low minority variants compromising susceptibility to NNRTIs are detected in a validated assay. In a recent large meta-analysis NNRTI-associated TDR was associated with cases of high-level resistance [14]. The impact of TDR to NRTI use in therapeutic schemes containing INSTIs is not known. High genetic barrier agents like boosted PIs seem unaffected by TDR. Finally, there is currently no evidence of circulating transmitted drug resistant INSTI mutations [15]. As the use of INSTIs becomes widespread, this position might need to be reviewed and sequencing of the integrase gene might be required.

Testing at virological failure: the understanding that viruses and in particular RNA viruses exist in the infected host as quasispecies (from the Latin *quasi* – as if; almost) provides an important conceptual background in explaining resistance in virological failure [16]. HIV-1 replication is associated with a high mutation rate as the RT lacks proofreading capacity, leading to errors during replication and generation of a swarm of genetically distinct viruses. Genetic recombination when viruses infect the same cell, and proviral variants accumulated over time, also contribute [17,18]. When patients' adherence to ART is suboptimal there is ongoing viral replication under drug pressure; selection of fit minor variants bearing drug resistance mutations is then possible and these can become dominant, leading to virological failure. There are several studies exploring the clinical utility of genotyping [19,20] and resistance testing at failure is a well-established practice in resource rich settings [1,2]. A public health approach, however, has been adopted in parts of the world with high prevalence [3,21] and new modelling approaches have been explored as an alternative to genotyping testing [22]. Modern ART is highly effective and new compounds are becoming available allowing more choice at failure. New patterns of resistance are however noted in clinical trials and *in vitro*. Therefore, resistance surveillance and database schemes need to be continuously updated.

Boosted protease inhibitors (bPIs) represent a potent class of ART. Mutants resistant to bPIs even in patients failing therapy are rather rare. Emerging evidence suggests that sequencing of genes not currently part of standard testing algorithms like the gag and envelope (in particular the part of the genome encoding the cytoplasmic tail of gp41) might be required and mutations detected in cleavage sites (CS) in particular might be detrimental in virological failure experienced by patients on ritonavir-boosted protease inhibitors [23,24]. After release from the host cell membrane, the viral protease (PR) cleaves the gag and gagpol precursor proteins to form the mature, infectious virion and the structural proteins are produced: matrix (MA), capsid (CA), nucleocapsid (NC), p6, and spacer peptides p1 and p2 [25,26]. HIV-1's PR also processes the gagpol precursor polypeptide, releasing the PR, integrase (IN), and reverse transcriptase (RT) enzymes. Indeed, multiple mutations within all gag and spacer proteins have been linked to PI exposure, reduced susceptibility, and resistance [27]. The high genetic variability observed in the gag, however, translates to the need for comparison of individual patient gag sequences between baseline and failure.

Tropism assays can be performed on peripheral blood mononuclear cells (PBMCs) if the viral load is less than 500 copies/mL when maraviroc switch is considered. Most laboratories prefer to perform it on the last stored plasma (VL >500 copies/mL) because of technical difficulties of working with PBMCs and some concerns about the sensitivity of PBMCs in picking up minority X4 virus [28]. NGS genotypic tropism tests have been shown to have better sensitivity at predicting maraviroc virological failure due to minority X4 tropic virus and it would be the preferred test should a validated and accredited test be available [29]. Phenotypic tropism assays are not readily available in the UK. Upon virological failure around two-thirds of patients will have a tropism switch from R5 to X4 and therefore the tropism test needs to be repeated [30].

Of those who remain R5 tropic, one-third will have maraviroc-specific resistance but because there are no genotypic signature mutations associated with this phenotypic resistance there are no clinical laboratories in UK that perform maraviroc resistance testing [31-33].

A resistance test should be performed at the time of virological failure and preferably within 4 weeks of stopping ART. Most laboratories will attempt resistance testing on low viral loads (down to 200 copies/mL, some even lower), but the risk of amplification bias is increased at viral loads below 1000 copies/mL. Not detecting drug resistant mutations does not exclude their existence. In the UK, laboratories test using population (Sanger sequencing), however, next-generation sequencing methodologies are becoming available. NGS emerges as a powerful new tool in managing patients with HIV [34] as well as providing unique insights in the pathogenesis and epidemiology of the infection [35]. NGS does not increase the sensitivity for detecting mutations at low viral loads and suffers the same amplification bias problem. NGS however has the potential to detect minority drug resistant variants where the patients have stopped their medication and wildtype virus has become the dominant virus with viral rebound, i.e. high viral loads. The multiple technical considerations, cost efficiency issues and more importantly clinical utility considerations will probably be overcome as these technologies advance [36], laboratories are centralised and our knowledge about the impact of minority variants is enhanced [37,38].

Phenotyping assays measure the 'fold resistance': this is the ratio of the IC₅₀ (drug concentration that inhibits 50% of patient virus population) to IC₅₀ of reference strains. The cost, turnaround time and limitations in clinical interpretation explain why these assays are not widely available.

Result interpretation of genotyping testing relies on tools available online that are based on large databases of sequences. Quality control systems and ongoing evaluation of these data interpretation tools especially as larger more complicated NGS data become available is of paramount importance [38].

5.16.8 References

1. European AIDS Clinical Society. European guidelines for treatment of HIV-infected adults in Europe. 2015. Available at: <http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html> (accessed May 2016).
2. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016. Available at: <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf> (accessed May 2016).
3. Jordan MR, Bennett DE, Wainberg MA *et al.* Update on World Health Organization HIV drug resistance prevention and assessment strategy: 2004-2011. *Clin Infect Dis* 2012; **54 Suppl 4**: S245-249.
4. Bennett DE, Camacho RJ, Otelea D *et al.* Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PLoS One* 2009; **4**: e4724.
5. Mbisa JL, Fearnhill E, Dunn DT *et al.* Evidence of self-sustaining drug resistant HIV-1 lineages among untreated patients in the United Kingdom. *Clin Infect Dis* 2015; **61**: 829-836.
6. Gandhi RT, Wurcel A, Rosenberg ES *et al.* Progressive reversion of human immunodeficiency virus type 1 resistance mutations in vivo after transmission of a multiply drug-resistant virus. *Clin Infect Dis* 2003; **37**: 1693-1698.
7. Little SJ, Frost SD, Wong JK *et al.* Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *J Virol* 2008; **82**: 5510-5518.
8. Pao D, Andraday U, Clarke J *et al.* Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. *J Acquir Immune Defic Syndr* 2004; **37**: 1570-1573.

9. Smith DM, Wong JK, Shao H *et al.* Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. *J Infect Dis* 2007; **196**: 356–360.
10. Baxter JD, Dunn D, White E *et al.* Global HIV-1 transmitted drug resistance in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV Med* 2015; **16 Suppl 1**: 77–87.
11. Castro H, Pillay D, Cane P *et al.* Persistence of HIV-1 transmitted drug resistance mutations. *J Infect Dis* 2013; **208**: 1459–1463.
12. Li JZ, Paredes R, Ribaud 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.
13. Pou C, Noguera-Julian M, Perez-Alvarez S *et al.* Improved prediction of salvage antiretroviral therapy outcomes using ultrasensitive HIV-1 drug resistance testing. *Clin Infect Dis* 2014; **59**: 578–588.
14. Rhee SY, Blanco JL, Jordan MR *et al.* Geographic and temporal trends in the molecular epidemiology and genetic mechanisms of transmitted HIV-1 drug resistance: an individual-patient- and sequence-level meta-analysis. *PLoS Med* 2015; **12**: e1001810.
15. Casadella M, van Ham PM, Noguera-Julian M *et al.* Primary resistance to integrase strand-transfer inhibitors in Europe. *J Antimicrob Chemother* 2015; **70**: 2885–2888.
16. Domingo E, Sheldon J, Perales C. Viral quasispecies evolution. *Microbiol Mol Biol Rev* 2012; **76**: 159–216.
17. Ghosn J, Pellegrin I, Goujard C *et al.* HIV-1 resistant strains acquired at the time of primary infection massively fuel the cellular reservoir and persist for lengthy periods of time. *AIDS* 2006; **20**: 159–170.
18. Mansky LM. Retrovirus mutation rates and their role in genetic variation. *J Gen Virol* 1998; **79 (Pt 6)**: 1337–1345.
19. Baxter JD, Mayers DL, Wentworth DN *et al.* A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beinr Community Programs for Clinical Research on AIDS. *AIDS* 2000; **14**: F83–93.
20. Cingolani A, Antinori A, Rizzo MG *et al.* Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *Aids* 2002; **16**: 369–379.
21. Gupta RK, Jordan MR, Sultan BJ *et al.* Global trends in antiretroviral resistance in treatment-naïve individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. *Lancet* 2012; **380**: 1250–1258.
22. Revell AD, Wang D, Wood R *et al.* An update to the HIV-TRePS system: the development of new computational models that do not require a genotype to predict HIV treatment outcomes. *J Antimicrob Chemother* 2014; **69**: 1104–1110.
23. Rabi SA, Laird GM, Durand CM *et al.* Multi-step inhibition explains HIV-1 protease inhibitor pharmacodynamics and resistance. *J Clin Invest* 2013; **123**: 3848–3860.
24. Sutherland KA, Goodall RL, McCormick A *et al.* Gag-Protease Sequence Evolution Following Protease Inhibitor Monotherapy Treatment Failure in HIV-1 Viruses Circulating in East Africa. *AIDS Res Hum Retroviruses* 2015; **31**: 1032–1037.
25. Maguire MF, Guinea R, Griffin P *et al.* Changes in human immunodeficiency virus type 1 Gag at positions L449 and P453 are linked to I50V protease mutants in vivo and cause reduction of sensitivity to amprenavir and improved viral fitness in vitro. *J Virol* 2002; **76**: 7398–7406.

26. Prabu-Jeyabalan M, Nalivaika EA, King NM, Schiffer CA. Structural basis for coevolution of a human immunodeficiency virus type 1 nucleocapsid-p1 cleavage site with a V82A drug-resistant mutation in viral protease. *J Virol* 2004; **78**: 12446–12454.
27. van Maarseveen NM, Andersson D, Lepsik M *et al.* Modulation of HIV-1 Gag NC/p1 cleavage efficiency affects protease inhibitor resistance and viral replicative capacity. *Retrovirology* 2012; **9**: 29.
28. Swenson LC, Dong WW, Mo T *et al.* Use of cellular HIV DNA to predict virologic response to maraviroc: performance of population-based and deep sequencing. *Clin Infect Dis* 2013; **56**: 1659–1666.
29. Tsibris AM, Korber B, Arnaout R *et al.* Quantitative deep sequencing reveals dynamic HIV-1 escape and large population shifts during CCR5 antagonist therapy in vivo. *PLoS One* 2009; **4**: e5683.
30. Lewis M, Simpson P, Fransen S *et al.* XCR4-using virus detected in patients receiving maraviroc in the Phase 3 studies MOTIVATE1 and MOTIVATE2 originates from a pre-existing minority of CXCR4-using virus. Abstract 56. *Antivir Ther* 2007; **12 (Suppl 1)**: S65.
31. Westby M, Smith-Burchnell C, Mori J *et al.* Reduced maximal inhibition in phenotypic susceptibility assays indicates that viral strains resistant to the CCR5 antagonist maraviroc utilize inhibitor-bound receptor for entry. *J Virol* 2007; **81**: 2359–2371.
32. Jubb R, Lewis M, Simpson P *et al.* CCR5-tropic resistance to maraviroc is uncommon even among patients on functional MVC monotherapy or with ongoing low-level replicatio. *Conference on Retroviruses and Opportunistic Infections*. February 2009. Montreal, Canada. Abstract 639.
33. Nelson M, Fisher M, Gonzalez-Garcia J *et al.* Impact of baseline antiretroviral resistance status on efficacy outcomes among patients receiving maraviroc plus optimized background therapy in the MOTIVATE 1 and 2 trials. *HIV Clin Trials* 2010; **11**: 145–155.
34. Van Laethem K, Theys K, Vandamme AM. HIV-1 genotypic drug resistance testing: digging deep, reaching wide? *Curr Opin Virol* 2015; **14**: 16–23.
35. Geretti AM, Paredes R, Kozal MJ. Transmission of HIV drug resistance: lessons from sensitive screening assays. *Curr Opin Infect Dis* 2015; **28**: 23–30.
36. McElroy K, Thomas T, Luciani F. Deep sequencing of evolving pathogen populations: applications, errors, and bioinformatic solutions. *Microb Inform Exp* 2014; **4**: 1.
37. Cozzi-Lepri A, Noguera-Julian M, Di Giallonardo F *et al.* Low-frequency drug-resistant HIV-1 and risk of virological failure to first-line NNRTI-based ART: a multicohort European case-control study using centralized ultrasensitive 454 pyrosequencing. *J Antimicrob Chemother* 2015; **70**: 930–940.
38. Frentz D, Boucher CA, Assel M *et al.* Comparison of HIV-1 genotypic resistance test interpretation systems in predicting virological outcomes over time. *PLoS One* 2010; **5**: e11505.

Appendix 2: list of abbreviations

25[OH]D	25-hydroxy vitamin D
ACR	albumin/creatinine ration
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BHIVA	British HIV association
BMD	bone mineral density
bPis	boosted protease inhibitors
c/mL	copies per millilitre
CA	capsid
ART	antiretroviral therapy
CKD	chronic kidney disease
CMV	cytomegalovirus
CSF	cerebrospinal fluid
CSW	commercial sex worker
CVD	cardiovascular disease

DEXA	dual energy X-ray absorptiometry
EFV	efavirenz
eGFR	estimated glomerular filtration rate
FBC	full blood count
FRAX	tool for fracture risk assessment
FTC	emtricitabine
GGT	gamma glutamyl transferase
GPP	good practice point (see GRADE/evidence section 4.1)
HSR	hypersensitivity reaction
IC ₅₀	drug concentration that inhibits 50% of virus population
IGRA	interferon-gamma release assay
IN	integrase
INI	integrase inhibitor
INSTI	integrase strand transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
IVDU/IDU	intravenous/injecting drug user
LFTs	liver function tests
LLV	low level viraemia

NRTI	nucleos(t)ide reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear
MA	matrix
MI	myocardial infarction
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAAT	nucleic acid amplification test
NC	nucleocapsid
NGS	next-generation sequencing
NNRTI	non-nucleos(t)ide reverse transcriptase inhibitor
NOGG	National Osteoporosis Guideline Group
PCR	polymerase chain reaction
PHI	primary HIV infection
PI	protease inhibitor
PI/r	ritonavir boosted protease inhibitor
PLLV	persistent low level viraemia
PLWH/ PLWHIV	people living with HIV
Pol	polymerase

PR	protease
PrEP	pre-exposure prophylaxis
PrEP-C	pre-exposure prophylaxis for conception
PWID	people who inject drugs
PYFU	person years follow up
QRISK2	cardiovascular risk assessment tool
R5	CCR5, lymphocyte tropism
RT	reverse transcriptase
STI	sexually transmitted infection
TAF	tenofovir alafenamide
TAMs	thymidine analogue mutations
TasP	treatment as prevention
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TDR	transmitted drug resistance
UKAS	United Kingdom Accreditation Service