The changing face of an epidemic: healthy old age with HIV

ABSTRACT

The demographics of the HIV epidemic in the UK have changed significantly. Owing to a steady rate of new diagnoses and improved survival, the population of individuals living with HIV continues to increase. HIV is now widely considered to be a chronic condition and HIV-positive individuals are expected to live into old age. Increasing rates of age-related comorbidities challenge HIV care providers to deliver durable viral suppression, ensure long-term adherence to antiretroviral treatment and promote wellbeing into old age. High rates of mental health disorders and social stigma continue to have a negative impact on the quality of life of people living with HIV. Models of care must adapt to this evolving epidemic.

There are an estimated 88 769 individuals accessing HIV care in the UK (Kirwan et al, 2016). This figure has increased year on year, a function of improved life expectancy, a relatively static rate of new diagnoses and a steady decline in all-cause mortality in people living with HIV. The number of people living with HIV engaged in care is 73% higher than 10 years ago and 34% (1 in 3) are now aged 50 years or over, compared to 1 in 7 a decade earlier (Kirwan et al, 2016). In addition, 17% of 6095 new HIV diagnoses in 2016 were in adults aged 50 years or over (Kirwan et al, 2016). Although late diagnosis and opportunistic infections remain a significant problem, HIV is now widely considered a chronic condition with the mainstay of care delivered to stable patients in an outpatient setting.

In addition to an ageing patient cohort, HIV has in itself been linked to a variety of age-related comorbidities such as cardiovascular disease, cognitive dysfunction and osteoporosis. As a result, multimorbidity and polypharmacy are now commonplace in patients attending for care with HIV physicians obliged to adapt to this paradigm shift.

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This article reviews the evolution of treatments in the antiretroviral therapy era leading to the treatment options available currently, the principal health issues facing people living with HIV today and future challenges for HIV care providers. These issues are illustrated through two clinical case vignettes.

Antiretroviral therapy

Effective antiretroviral therapy suppresses viral replication to promote immune reconstitution and thereby avert the inexorable immune decline, AIDS-related illness and eventual death associated with untreated HIV. The first HIV drugs, nucleoside reverse transcriptase inhibitors, became available in the mid-1980s but benefits were short-lived. Mono or dual-agent antiretroviral therapy with nucleoside reverse transcriptase inhibitors was associated with rapid emergence of drug resistance mutations and ultimate treatment failure (Darbyshire et al, 2000).

It was the advent of combination antiretroviral therapy in the mid-1990s that, providing patients could tolerate the complex dosing schedules and challenging side effects of early drugs, provided durable viral suppression, immune reconstitution and dramatic reductions in HIV-related morbidity and mortality (Centers for Disease Control and Prevention, 2015). The mid to late 1990s saw the licensing of two new drug classes, protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and combining two nucleoside reverse transcriptase inhibitors with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor as a triple-drug combination greatly reduced the risk of HIV resistance development, and much improved outcomes (Hammer et al, 1997; Montaner et al, 1998).

Since then we have seen the development of further drug classes (most notably integrase inhibitors), new agents in existing classes, co-formulations, single tablet regimens and marked improvements in drug convenience, tolerability and toxicity. Despite this, the basic 'recipe' for first-line treatment remains unchanged and the triple combination of two nucleoside reverse transcriptase inhibitors plus one agent from another class remains preferred in consensus guidelines for initial therapy (European AIDS Clinical Society, 2015; British HIV Association, 2016b; Department of Health and Human Services, 2016; World Health Organization, 2016). The basic surrogate markers for monitoring HIV also remain largely unchanged: immune function is monitored using CD4+ lymphocytes (CD4 count) and antiretroviral therapy efficacy by quantifying

plasma HIV-RNA. The goal of combination antiretroviral therapy is to suppress HIV-RNA below limits of detection (less than 20–200 copies/ml depending on the assay), a so-called 'undetectable viral load'.

Guidelines on antiretroviral therapy initiation

The British HIV Association produces guidelines relating to different aspects of the care of people living with HIV. Before 2015, in the absence of robust trial evidence for individual clinical benefit in asymptomatic HIV at relatively high CD4 counts, recommendations around when to start antiretroviral therapy were largely CD4-based (Williams et al, 2012). However, in 2015 the results of a large randomized controlled trial demonstrated significant reductions in AIDS events, serious non-AIDS events and deaths in individuals with relatively preserved CD4 counts randomized to early *vs* deferred antiretroviral therapy (INSIGHT START Study Group, 2015). The British HIV Association (2016b) treatment guidelines now recommend antiretroviral therapy for all people living with HIV, regardless of CD4 count. Other major guidelines, including European (European AIDS Clinical Society, 2015) and World Health Organization (2016) guidelines, also recommend antiretroviral therapy for all.

UNAIDS (2014) have set a target of '90:90:90' whereby 90% of all people living with HIV should be diagnosed, 90% of those on antiretroviral therapy and 90% of those with undetectable viral load. Although some populations are close to meeting, or even exceeding, those targets, global figures fall well short across all three domains (UNAIDS, 2014). Beyond the individual health benefits of prompt antiretroviral therapy there is also a marked reduction in the risk of onward transmission from individuals on suppressive therapy. Observational data have long demonstrated a correlation between plasma viral load and transmission risk and in 2011 HPTN052, the first randomized controlled trial to assess the impact of antiretroviral therapy on transmission between serodifferent couples, demonstrated a 96% reduction in transmission events in those on antiretroviral therapy (Cohen et al, 2011). Consequently, since 2012 most guidelines have recommended antiretroviral therapy for the prevention of transmission to others.

Cohen et al (2016) have published their final analysis of HPTN052 demonstrating a 93% reduction in transmission and no transmission where the positive partner was on antiretroviral therapy and undetectable – the eight transmissions on antiretroviral therapy were all from individuals with detectable HIV-RNA. PARTNER, a European observational cohort study, demonstrated no transmissions within serodifferent partnerships (where the positive partner was on suppressive antiretroviral therapy) after over 58 000 condomless sex acts in 888 couples, of whom about one third were men who have sex with men (Rodger et al, 2016).

In terms of what to start, current British HIV Association (2016b) guidelines, like most consensus guidelines, recommend two nucleoside reverse transcriptase inhibitors plus a third drug (integrase inhibitor, non-nucleoside reverse transcriptase inhibitor or protease inhibitor) for initial therapy. In general, guidelines are moving towards integrase inhibitor-based regimens for first-line treatment; Department of Health and Human Services (2016), the major American guidelines, recommend only one non-integrase inhibitor-based combination first line.

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Life expectancy

UK cohort data from May et al (2014) show that HIV-positive individuals on suppressive antiretroviral therapy with a CD4 greater than 350 cells/μl have the same life expectancy as the general UK population; more recently an analysis of European and North American cohorts has demonstrated similar findings (Trickey et al, 2017). Individuals with lower CD4 counts or detectable HIV viraemia have impaired life expectancy. Danish cohort data show that any excess mortality in people living with HIV is driven by suboptimal HIV markers (low CD4 count and/or detectable virus), other comorbidities (such as hepatitis C), or lifestyle factors (such as alcohol or recreational drug use) (Obel et al, 2011).

Comorbidities

As a consequence of the reduction in AIDS-related conditions the proportion of morbidity and mortality secondary to 'non-HIV-related' comorbidities has risen, as expected (Wada et al, 2014). Additionally people living with HIV seem to be at an increased risk of age-related comorbidities including cardiovascular disease, liver disease, chronic kidney impairment and non-AIDS cancers compared to HIV-negative controls (Schouten et al, 2012). Potential confounders abound but even well-controlled cohorts demonstrate rates of age-related disease in people living with HIV akin to those observed in controls that are about 10 years older (Schouten et al, 2014). Likely reasons include:

HIV per se

Even individuals with sustained viral suppression have higher markers of immune activation and inflammation than HIV-negative controls (Lichtfuss et al, 2012; Nou et al, 2016). Moreover, a legacy of prior immune suppression and/or long duration of detectable viraemia are risk factors for some comorbidities (Deeks, 2009, 2011).

Antiretrovirals

There are a number of associations between different drugs and comorbidities. Examples include an increased risk of

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chronic kidney disease with tenofovir DF (nucleoside reverse transcriptase inhibitor) and atazanavir (protease inhibitor) (Ryom et al, 2013) and an association between myocardial infarction risk and use of abacavir (nucleoside reverse transcriptase inhibitor) (Sabin et al, 2016). Almost all first-line regimens are associated with a small, non-progressive decline in bone mineral density but this is more marked with tenofovir DF (McComsey et al, 2011). The combination of tenofovir DF and a protease inhibitor is associated with an increased fracture risk (Bedimo et al, 2012). It can take years of post-marketing surveillance before the longer term health impact of a drug emerges; the first reports of non-cirrhotic portal hypertension association with didanosine (a nucleoside reverse transcriptase inhibitor) were published 8 years after the drug was first approved in Europe (Maida et al, 2008; Bristol-Myers Squibb Pharmaceutical Limited, 2016). Didanosine is no longer recommended for HIV treatment (British HIV Association, 2016b).

Co-infections

Around 7% and 9% people living with HIV are co-infected with hepatitis B and C respectively (Turner et al, 2010; Price et al, 2012), both of which increase the risk of liver-related and all-cause mortality (Nikopoulos et al, 2009; Hernando et al, 2012). Evidence of prior cytomegalovirus infection, in the absence of a history of cytomegalovirus-related disease, is associated with a higher risk of non-AIDS morbidity and mortality (Lichtner et al, 2015).

Traditional risk factors

These likely account for a significant proportion, and in those with well-treated HIV the majority, of the excess morbidity observed in people living with HIV (Obel et al, 2011). American data from Althoff et al (2015) show that smoking is the most important population factor for non-AIDS cancers, even when lung cancer is excluded (29% attributable to smoking, 5% to detectable HIV viraemia) and American and European cohort data from Helleberg et al (2015) show that more life years are lost to smoking than to HIV.

Vaccinations

The British HIV Association provides guidelines for the use of vaccines in people living with HIV. Key recommendations include annual influenza vaccine for all (British HIV Association, 2015). Two types of pneumococcal vaccination are recommended: all people living with HIV, regardless of age, should be offered a single dose of PCV13; in addition, any who meet national criteria for pneumococcal vaccination (Public Health England, 2013) should also receive a single dose of PPV23. PCV13 and PPV23 should be given at least 3 months apart.

Quality of life, mental health and lifestyle

People living with HIV are more likely to suffer mental health disorders than their HIV-negative counterparts (Sherr et al, 2008; Do et al, 2014; Janssen et al, 2015). ASTRA, a cross-sectional questionnaire study among people living with HIV in the UK, demonstrated that a longer time with diagnosed HIV but not age per se was associated with symptoms of anxiety and depression (McGowan et al, 2017).

A comparison between ASTRA and the Health Survey for England showed significantly lower health-related quality of life scores in HIV-positive participants compared to the general population across all domains, particularly anxiety and depression (Miners et al, 2014). In terms of ageing this study showed that decline in health-related quality of life over time is similar in both groups regardless of HIV status. Successfully treated people living with HIV still report high rates of symptoms such as insomnia, fatigue and sexual dysfunction (Erdbeer et al, 2014). Such data have led to a call to expand the '90:90:90' targets to include a fourth domain: 90% with good health-related quality of life (Lazarus et al, 2016).

A meta-analysis from Park et al (2016) demonstrated higher rates of smoking in people living with HIV compared to the general population. Rates of recreational drug use in UK HIV-positive gay men are high (Daskalapoulou et al, 2014), with 51% reporting any drug use in the last 3 months (20% of these reported using five or more drugs).

Stigma and social considerations

Despite shifts in public attitudes, experience of stigma remains a significant obstacle for people living with HIV. Following interviews with 1576 participants, the UK Stigma Survey found that in the previous 12 months around half had feelings of shame, guilt or self-blame in relation to their HIV status, 12% had decided against applying for or turned down a job or promotion because of HIV and 20% reported sexual rejection because of their status (Stigma Survey UK 2015, 2015). A recent survey showed that a significant proportion of the general public held misconceptions about HIV transmissibility (Sparrowhawk, 2017).

Challenges

As people living with HIV can anticipate living into old age there are a number of key challenges facing patients, care providers and society:

Maintaining long-term treatment adherence

For any condition, poor concordance with treatment is associated with suboptimal disease control and adverse outcomes. For HIV, poor adherence may also result in viral rebound and can drive the development of drug resistance and limitation of future treatment options. The prevalence of both transmitted and acquired antiretroviral therapy resistance in the UK has fallen, likely a function of drugs

that are more convenient and tolerable as side effects are a common reason for missed doses. There is also greater availability of treatment options with a high barrier to resistance development. Viral rebound is associated with an increased risk of onward transmission, HIV-related symptoms and risk of rapid CD4 decline.

Regular adherence review and tips for adherence support are essential and interventions are summarized in national guidelines (British HIV Association, 2016a). Wherever possible, once-daily regimens are used and the choice of treatment individualized to take account of dose timing, food requirements and interactions with other medications. Barriers to antiretroviral therapy adherence may evolve over time, for example as a result of changes in health, social circumstances or co-prescribed medication, so an ongoing proactive review of these challenges is essential as optimal treatment options may change.

Managing drug–drug interactions

A major challenge for all people living with HIV, particularly older individuals, is managing drug–drug interactions. Cohort data from Marzolini et al (2010) identified that of 1478 HIV positive patients, 68% had at least one non-antiretroviral therapy co-medication and 40% at least one potential drug–drug interaction. There are several mechanisms for interactions between antiretrovirals and other drugs; inhibition of the cytochrome P450 3A4 (CYP3A4) isoenzyme by pharmokinetic 'boosters' is of particular importance. Since around 2000 CYP3A4 inhibition has been used to augment plasma concentrations and prolong the half-life of some key antiretrovirals (Kilby et al, 2000) to facilitate less frequent dosing schedules. Ritonavir, an antiretroviral no longer used for therapy because of its unacceptable side-effect profile, is a potent CYP3A4 inhibitor used at sub-therapeutic doses to boost other drugs (AbbVie Limited, 2016). More recently cobicistat has been licensed for the same purpose (Gilead Sciences Limited, 2016b); boosting is required for protease inhibitors and the integrase inhibitor elvitegravir (Gilead Sciences Limited, 2016c).

Potential CYP3A4-mediated drug–drug interactions are manifold but important examples include a risk of rhabdomyolysis with simvastatin (Aurobindo Pharma – Milpharm Limited, 2015) and a risk of iatrogenic Cushing's syndrome and secondary adrenal suppression with many steroids, including injected, inhaled and intranasal formulations (Saberi et al, 2013). Other important sources of drug–drug interactions include acid-reducing agents, antipsychotics and anticonvulsants. The University of Liverpool has developed an invaluable resource for checking potential drug–drug interactions, the HIV Drug Interactions Checker website (www.hiv-druginteractions.org/), and more recently its creators have developed a similar resource for hepatitis C drugs (www.hep-druginteractions.org/).

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Preventing drug–drug interactions is challenging, as demonstrated by *case study 1*. As HIV clinics are responsible for antiretroviral therapy prescribing, they should include information and advice regarding drug–drug interactions in communications with GPs and other health-care professionals as per British HIV Association (2016a) guidance. Although ensuring shared information across organizations is not always easy, two-way communication is key to ensuring patient safety. Patient education to enhance awareness of potential drug–drug interactions, and empowerment to question prescribing decisions, provide an additional safeguard against inadvertent prescribing errors or self-sourced agents which may cause harm. Locally the authors document discussion about key drug–drug interactions at each visit and provide patient information cards about important drug–drug interactions, such as pharmacokinetic boosters and corticosteroids.

Potential for drug–drug interactions is an important consideration when selecting an antiretroviral therapy regimen. Although the avoidance of boosters does reduce the risk, many unboosted agents still have significant drug–drug interactions potential. While nucleoside reverse transcriptase inhibitors are generally not associated with significant drug–drug interactions, the exception is tenofovir-alefenamide, a novel formulation of the widely used nucleoside reverse transcriptase inhibitor tenofovir DF, which should not be co-administered with p-glycoprotein inducers (Gilead Sciences Limited, 2016a). Non-nucleoside reverse transcriptase inhibitors

CASE STUDY 1

Mrs Y is a 65-year-old woman with HIV treated with Truvada (a fixed dose combination of tenofovir DF and emtricitabine), darunavir and ritonavir. She has no history of antiretroviral resistance and has excellent adherence. Her co-medications include Adcal D3. She has widespread osteoarthritis. She now requires a corticosteroid injection for knee pain.

The combination of a boosted protease inhibitor and intra-articular steroid may increase systemic exposure to the corticosteroid through cytochrome P450 3A4 enzyme inhibition, risking an iatrogenic Cushing's syndrome and, subsequently, life-threatening adrenocortical suppression.

A switch to an unboosted integrase inhibitor would avoid this. In view of the potential for divalent cations to bind to integrase inhibitor in the digestive tract reducing their absorption she should be counselled to dose space the integrase inhibitor from her calcium supplement by at least 4 hours. A once-daily integrase inhibitor is therefore preferable to promote long-term adherence.

KEY POINTS

- An ageing cohort of people living with HIV brings fresh challenges to HIV care providers including maintaining long-term treatment adherence, managing drug-drug interactions and comorbidity screening and management.
- In people living with HIV, the proportion of morbidity and mortality secondary to 'non-HIV related' comorbidities has risen.
- High rates of mental health disorders, experience of social or internalized stigma and lower health-related quality of life scores in people living with HIV relative to the general population highlight that HIV care must extend beyond viral suppression.
- Models of HIV care in the UK must evolve without compromising the high standards already achieved.

CASE STUDY 2

Mr X is a 56-year-old smoker who was recently diagnosed with type 2 diabetes. He has commenced metformin and simvastatin in primary care. He is currently taking Kivexa (a fixed dose combination of abacavir and lamivudine) and efavirenz for HIV and his viral load is undetectable. His fasting blood tests show an elevated cholesterol level and he has 2+ proteinuria on urine dipstick.

Regular assessment of cardiovascular risk, including screening for type 2 diabetes, is an important component of Mr X's HIV care. His age, gender, smoking history and diabetes all contribute to an elevated cardiovascular risk so abacavir should be avoided.

His proteinuria requires investigation but may be caused by diabetic nephropathy. In view of the increased risk of kidney injury, specifically a proximal tubulopathy, associated with tenofovir DF, a tenofovir alafenamide-containing nucleoside reverse transcriptase inhibitor backbone is preferable. Efavirenz can lower simvastatin levels, so cholesterol levels should be monitored and the dose of simvastatin increased in the event of a suboptimal response. He should receive smoking cessation support and advice on weight loss through dietary modification and exercise.

and protease inhibitors have the potential for complex drug–drug interactions. Unboosted integrase inhibitors (raltegravir and dolutegravir) demonstrate a significantly lower propensity for drug–drug interactions but there are still important interactions with some antacids, multivitamins and, for dolutegravir, metformin (Merck Sharp and Dohme, 2015; Viiv Healthcare Limited, 2017).

Comorbidity screening and management

Prevention and management of comorbidities are an increasingly important element of HIV care, as illustrated in *case study 2*. Basic assessment of renal function (including urine protein), liver function and estimates of fracture and cardiovascular risk should be performed and used to help guide choice of antiretroviral therapy (British HIV Association, 2016a). The frequency of monitoring thereafter will be guided by baseline results, existing comorbidities, concomitant medications and the antiretroviral therapy regimen selected. The pre-existence, new onset or elevated risk of a comorbidity can be an indication for switching antiretroviral therapy.

Regardless of the mechanisms, the increased prevalence and younger age of onset of age-related illnesses in people living with HIV may warrant a lower threshold for investigation; providers of HIV care should ensure that primary care services, other clinical specialists and people living with HIV themselves are aware of this possibility. Promoting a healthy lifestyle and signposting patients towards appropriate advice and support should also feature in HIV consultations. A dialogue with colleagues in primary care can ensure that the messages given are consistent.

Optimal models of care

Finally, how best to provide care for people living with HIV? Maintaining skills and providing training in the management of opportunistic diseases is challenging when hospital admissions for AIDS-defining conditions are infrequent. Doctors see patients less frequently, perform fewer tests and rely more on telephone, email and other 'virtual' mechanisms for follow up to manage increasing capacity with declining funds. Intermittently there are calls for HIV management to be shifted to primary care but evidence that this would be more efficient, or better for patients, is lacking. Ultimately the UK has among the best HIV treatment outcomes in the world (Hill, 2015) and as HIV care evolves it is important to ensure that any changes to care models are evidence based and do not compromise the high standards of care achieved. HIV, relative to other long-term conditions, remains uncommon in the UK and as such may be best led by specialist services. However, better engagement with primary care, two-way dialogue and shared decision making or monitoring could ensure patients have access to optimal management of both HIV and their general health.

Conclusions

The management, prognosis and societal response to HIV have evolved significantly. Today's cohort of older adults with HIV will include many who commenced treatment at lower CD4 counts after a prolonged period of HIV viraemia. Their treatment history may include agents no longer used because they have an unacceptable side-effect and toxicity profile. Many will have been advised of a poor prognosis thus impacting on their psychological wellbeing, lifestyle choices and preparation for later life. Many will have experienced significant and debilitating social stigma resulting from their diagnosis. Conclusions drawn about ageing in HIV from today's cohort of older adults may not therefore apply to a younger patient diagnosed early in the course of the infection. Looking to the future, the needs of the population who are living into old age with HIV is constantly changing and the challenge for HIV care providers is to respond to their evolving needs. **BJHM**

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AbbVie Limited (2016) Norvir Summary of Product Characteristics. www.medicines.org.uk/emc/medicine/22952 (accessed 20 May 2017)
Althoff KN, Gange SJ, Achenbach C et al (2015) Smoking outweighs HIV-related risk factors for non-AIDS-defining cancers. Unpublished poster presentation. 2015 Conference on Retroviruses and Opportunistic Infections, Seattle, USA: 23–26 February
Aurobindo Pharma – Milpharm Limited (2015) Simvastatin summary of product characteristics. www.medicines.org.uk/emc/medicine/23055 (accessed 20 May 2017)
Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P (2012) Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* **26**(7): 825–831. https://doi.org/10.1097/QAD.0b013e32835192ae
Bristol-Myers Squibb Pharmaceutical Limited (2016) Videx summary of product characteristics. www.medicines.org.uk/emc/medicine/3596 (accessed 20 May 2017)
British HIV Association (2015) British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. www.bhiva.org/documents/Guidelines/Vaccination/2015-Vaccination-Guidelines.pdf (accessed 20 May 2017)
British HIV Association (2016a) British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals 2016. www.bhiva.org/documents/Guidelines/Monitoring/2016-BHIVA-Monitoring-Guidelines.pdf (accessed 20 May 2017)
British HIV Association (2016b) British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf (accessed 20 May 2017)
Centers for Disease Control and Prevention (2015) HIV Mortality (through 2014). www.cdc.gov/hiv/pdf/library/slidesets/cdc-hiv-mortality.pdf (accessed 20 May 2017)
Cohen MS, Chen YQ, McCauley M et al; HPTN 052 Study Team (2011) Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **365**(6): 493–505. https://doi.org/10.1056/NEJMoa1105243
Cohen MS, Chen YQ, McCauley M et al.; HPTN 052 Study Team (2016) Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med* **375**(9): 830–839. https://doi.org/10.1056/NEJMoa1600693
Darbyshire J, Foulkes M, Peto R et al (2000) Zidovudine (AZT) versus AZT plus didanosine (ddI) versus AZT plus zalcitabine (ddC) in HIV infected adults. *Cochrane Database Syst Rev* (**3**): CD002038. https://doi.org/10.1002/14651858.CD002038
Daskalapoulou M, Rodger A, Phillips AN et al (2014) Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study *Lancet HIV* **1**(1): e22–31. https://doi.org/10.1016/S2352-3018(14)70001-3)
Deeks SG (2009) Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. *Top HIV Med* **17**(4): 118–123.
Deeks SG (2011) HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* **62**(1): 141–155. https://doi.org/10.1146/annurev-med-042909-093756
Department of Health and Human Services (2016) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed 20 May 2017)
Do AN, Rosenberg ES, Sullivan PS et al (2014) Excess burden of depression among HIV-infected persons receiving medical care in the united states: data from the medical monitoring project and the behavioral risk factor surveillance system. *PLoS ONE* **9**(3): e92842. https://doi.org/10.1371/journal.pone.0092842
Erdbeer G, Sabranski M, Sonntag I et al (2014) Everything fine so far? Physical and mental health in HIV-infected patients with virological success and long-term exposure to antiretroviral therapy. *J Int AIDS Soc* **17**(4) Suppl 3: 19673. https://doi.org/10.7448/IAS.17.4.19673
European AIDS Clinical Society (2015) Guidelines Version 8.0 October 2015. www.eacsociety.org/files/guidelines_8.0-english-revised_20160610.pdf (accessed 20 May 2017)
Gilead Sciences Limited (2016a) Descovy summary of product characteristics. www.medicines.org.uk/emc/medicine/31764 (accessed 20 May 2017)
Gilead Sciences Limited (2016b) Tybost summary of product characteristics. www.medicines.org.uk/emc/medicine/28298 (accessed 20 May 2017)
Gilead Sciences Limited (2016c) Vitekta summary of product characteristics. www.medicines.org.uk/emc/medicine/28410 (accessed 20 May 2017)
Hammer SM, Squires KE, Hughes MD et al (1997) A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* **337**(11): 725–733. https://doi.org/10.1056/NEJM199709113371101
Helleberg M, May MT, Ingle SM et al (2015) Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. *AIDS* **29**(2): 221–229. https://doi.org/10.1097/QAD.0000000000000540
Hernando V, Perez-Cachafeiro S, Lewden C et al (2012) All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. *J Hepatol* **57**(4): 743–751. https://doi.org/10.1016/j.jhep.2012.06.010)
Hill A (2015) Generics: the facts. Unpublished oral presentation. 21st Annual Conference of the British HIV Association, Brighton: 21–24 April
INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F et al (2015) Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* **373**: 795–807. https://doi.org/10.1056/NEJMoa1506816
Janssen MA, Meulenbroek O, Steens SC et al (2015) Cognitive functioning, wellbeing and brain correlates in HIV-1 infected patients on long-term combination antiretroviral therapy *AIDS* **29** (16): 2139–2148. https://doi.org/10.1097/QAD.0000000000000824
Kilby JM, Skaflanos G, Gizzi N et al (2000) Safety and pharmacokinetics of once-daily regimens of soft-gel capsule saquinavir plus minidose ritonavir in human immunodeficiency virus-negative adults. *Antimicrob Agents Chemother* **44**(10): 2672–2678. https://doi.org/10.1128/AAC.44.10.2672-2678.2000
Kirwan PD, Chau C, Brown AE et al (2016) HIV in the UK - 2016 report. www.gov.uk/government/uploads/system/uploads/attachment_data/file/602942/HIV_in_the_UK_report.pdf (accessed 20 May 2017)
Lazarus JV, Safreed-Harmon K, Barton SE et al (2016) Beyond viral suppression of HIV - the new quality of life frontier. *BMC Med* **14**(1): 94. https://doi.org/10.1186/s12916-016-0640-4
Lichtfuss GF, Cheng WJ, Farsakoglu Y et al (2012) Virologically suppressed HIV patients show activation of NK cells and persistent innate immune activation. *J Immunol* **189**(3): 1491–1499. https://doi.org/10.4049/jimmunol.1200458
Lichtner M, Cicconi P, Vita S et al (2015) Cytomegalovirus co-infection is associated with an increased risk of severe non-AIDS defining events in a large cohort of HIV-infected patients. *J Infect Dis* **211**(2): 178–186. https://doi.org/10.1093/infdis/jiu417
Maida I, Garcia-Gasco P, Sotgiu G et al (2008) Antiretroviral-associated portal hypertension: a new clinical condition? Prevalence, predictors and outcome. *Antivir Ther* **13**(1): 103–107.
Marzolini C, Elzi L, Gibbons S et al (2010) Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* **15**(3): 413–423. https://doi.org/10.3851/IMP1540
May MT, Gompels M, Delpech V et al (2014) Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* **28**(8): 1193–1202. https://doi.org/10.1097/QAD.0000000000000243
McComsey GA, Kitch D, Daar ES et al (2011) Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis* **203**(12): 1791–1801. https://doi.org/10.1093/infdis/jir188
McGowan JA, Sherr L, Rodger AJ et al (2017) Age, time living with diagnosed HIV infection, and self-rated health. *HIV Med* **18**(2): 89–103. https://doi.org/10.1111/hiv.12398
Merck Sharp & Dohme Limited (2015) Isentress summary of product characteristics. www.medicines.org.uk/emc/medicine/20484 (accessed 20 May 2017)

Miners A, Phillips A, Kreif N et al (2014) Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: a cross-sectional comparison with the general population. *Lancet HIV* **1**(1): e32–40. https://doi.org/10.1016/S2352-3018(14)70018-9

Montaner JS, Reiss P, Cooper D et al (1998) A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA* **279**(12): 930–937. https://doi.org/10.1001/jama.279.12.930

Nikolopoulos GK, Paraskevis D, Hatzitheodorou E et al (2009) Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clin Infect Dis* **48**: 1763–1771. https://doi.org/10.1086/599110

Nou E, Lo J, Grinspoon SK (2016) Inflammation, immune activation, and cardiovascular disease in HIV. *AIDS* **30**(10): 1495–1509. https://doi.org/10.1097/QAD.0000000000001109

Obel N, Omland LH, Kronborg G et al (2011) Impact of non-HIV and HIV risk factors on survival in HIV-infected patients on HAART: a population-based nationwide cohort study. *PLoS One* **6**(7): e22698. https://doi.org/10.1371/journal.pone.0022698

Park LS, Hernández-Ramírez RU, Silverberg MJ, Crothers K, Dubrow R (2016) Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. *AIDS* **30**(2): 273–291. https://doi.org/10.1097/QAD.0000000000000922

Price H, Bansi L, Sabin CA et al (2012) Hepatitis B virus infection in HIV-positive individuals in the UK collaborative HIV cohort (UK CHIC) study. *PLoS One* **7**(11): e49314. https://doi.org/10.1371/journal.pone.0049314

Public Health England (2013) Pneumococcal. www.gov.uk/government/uploads/system/uploads/attachment_data/file/263318/Green-Book-Chapter-25-v5_2.pdf (accessed 20 May 2017)

Rodger AJ, Cambiano V, Bruun T et al (2016) Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA* **316**(2): 171–181. https://doi.org/10.1001/jama.2016.5148

Ryom L, Mocroft A, Kirk O et al (2013) Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis* **207**(9): 1359–1369. https://doi.org/10.1093/infdis/jit043

Saberi P, Phengrasamy T, Nguyen DP (2013) Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management *HIV Med* **14**(9): 519–529. https://doi.org/10.1111/hiv.12039

Sabin CA, Reiss P, Ryom L et al (2016) Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration. *BMC Med* **14**: 61. https://doi.org/10.1186/s12916-016-0588-4

Schouten J, Wit FW, Stolte IG et al; for the AGEhIV Cohort Study Group (2014) Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* **59**(12): 1787–1797. https://doi.org/10.1093/cid/ciu701

Sherr L, Lampe F, Fisher M et al (2008) Suicidal ideation in UK HIV clinic attenders. *AIDS* **22**(13): 1651–1658. https://doi.org/10.1097/QAD.0b013e32830c4804

Sparrowhawk A (2017) Perceptions of HIV within the general public. Oral abstract O26. 23rd Annual Conference of the British HIV Association, Liverpool: 4–7 April

Stigma Survey UK 2015 (2015) HIV in the UK: Changes and Challenges; Actions and Answers. The People Living with HIV Stigma Survey UK 2015. National findings. www.stigmaindexuk.org/reports/2016/NationalReport.pdf (accessed 20 May 2017)

Trickey A, May MT, Vehreschild JJ et al (2017) Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* https://doi.org/10.1016/S2352-3018(17)30066-8

Turner J, Bansi L, Gilson R et al (2010) The prevalence of hepatitis C virus (HCV) infection in HIV-positive individuals in the UK - trends in HCV testing and the impact of HCV on HIV treatment outcomes. *J Viral Hepat* **17**(8): 569–577. https://doi.org/10.1111/j.1365-2893.2009.01215.x

UNAIDS (2014) 90-90-90 An ambitious treatment target to help end the AIDS epidemic. www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf (accessed 20 May 2017)

Viiv Healthcare Limited (2017) Tivicay summary of product characteristics. www.medicines.org.uk/emc/medicine/28545 (accessed 20 May 2017)

Wada N, Jacobsen LP, Cohen M, French A, Phair J, Muñoz A (2014) Cause-specific mortality among HIV-infected individuals, by CD4(+) cell count at HAART initiation, compared with HIV-uninfected individuals *AIDS* **28**(2): 257–265. https://doi.org/10.1097/QAD.0000000000000078

Williams I, Churchill D, Anderson J et al (2012) British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. *HIV Med* **13** (Suppl 2): 1–85. https://doi.org/110.1111/j.1468-1293.2012.01029

World Health Organization (2016) Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1 (accessed 28 June 2016)