*Introduction*

**Over the last three decades HIV has been transformed from a terminal condition to one associated with a normal, or near normal, life expectancy (May et al, 2014; Wallender et al, 2016; Trickey et al, 2017). Today's HIV population is larger and older than ever before and this demographic shift brings fresh challenges to care providers.**

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 (PLWH). The number of PLWH engaged in care is 73% higher than 10 years ago and 34% (1 in 3) are now aged 50 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 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 out-patient 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. We review the evolution in treatments in the antiretroviral therapy (ART) era leading to the treatment options available currently, the principle health issues facing PLWH today and future

challenges for HIV care providers. We illustrate these issues in practice 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 (NRTI), became available in the mid-1980s but benefits were short-lived. Mono or dual-agent ART with NRTI was associated with rapid emergence of drug resistance mutations and ultimate treatment failure (Darbyshire et al, 2000). It was the advent of combination ART (cART) 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 (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), and combining two NRTI with a PI or NNRTI 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 (INI)), 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 NRTI plus one agent from another class remains preferred

in consensus guidelines for initial therapy (European AIDS Clinical Society (EACS), 2015; British HIV Association (BHIVA), 2016b; Department of Health and Human Services (DHHS); 2016 World Health Organization (WHO), 2016). The basic surrogate markers for monitoring HIV also remain largely unchanged; immune function is monitored using CD4+ lymphocytes (CD4 count) and ART efficacy by quantifying plasma HIV-RNA. The goal of cART 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 ART initiation*

The British HIV Association (BHIVA) produces guidelines relating to different aspects of the care of PLWH. Prior to 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 ART were largely CD4-based (Williams I et al, 2012). However, in 2015 the results of a large randomised control trial (RCT) demonstrated significant reductions in AIDS events, serious non-AIDS events and deaths in individuals with relatively preserved CD4 counts randomised to early versus deferred ART (INSIGHT START Study Group, 2015). The BHIVA 2016 treatment guidelines now recommend ART for all PLWH, regardless of CD4 count. Other major guidelines, including European and WHO guidelines, also recommend ART for all (European AIDS Clinical Society, 2015; World Health Organization 2016).

UNAIDS (2014) have set a target of '90:90:90' whereby 90% of all PLWH should be diagnosed, 90% of those on ART and 90% of those undetectable. 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 ART there is also a marked reduction in the risk of onward transmission from individuals on suppressive therapy. Observational data has long demonstrated a correlation between plasma viral load and transmission risk and in 2011 HPTN052, the first RCT to assess the impact of ART on transmission between serodifferent couples, demonstrated a 96% reduction in transmission events on ART (Cohen MS et al, 2011). Consequently, since 2012 most guidelines have recommended ART for the prevention of transmission to others. Cohen MS et al (2016) have recently published their final analysis of HPTN052 demonstrating a 93% reduction in transmission and no transmission where the positive partner was on ART and undetectable – the 8 transmissions on ART 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 ART) after over 58,000 condomless sex acts in 888 couples, of whom about 1/3 were men who have sex with men (Rodger et al, 2016).

In terms of what to start, current BHIVA guidelines (2016b), like most consensus guidelines, recommend two NRTI + a third drug (INI, NNRTI or PI) for initial therapy. In general, guidelines are moving towards INI-based regimens for first-line treatment; DHHS (2016), the major US guidelines, recommend only one non-INI-based combination first-line.

*Life expectancy*

UK cohort data from May et al (2014) show that HIV-positive individuals on suppressive ART 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 A 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 PLWH is driven by suboptimal HIV markers (low CD4 and/or detectable virus), other co-morbidities (such as hepatitis C), or lifestyle factors (such as alcohol or recreational drug use) (Obel et al, 2011).

*Co-morbidities*

As a consequence of the reduction in AIDS-related conditions the proportion of morbidity and mortality secondary to 'non-HIV related' co-morbidities has risen, as expected (Wada et al, 2014). Additionally PLWH seem to be at an increased risk of age-related co-morbidities 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 PLWH akin to those observed in controls that are about 10 years older (Schouten et al, 2014). Likely reasons include:

- <u>HIV per se:</u> even individuals with sustained viral suppression have higher markers of immune activation and inflammation than HIV-negative controls (Nou et al, 2016; Lichtfuss et al, 2012). Moreover, a legacy of prior immune

suppression and/or long duration of detectable viraemia are risk factors for some co-morbidities (Deeks, 2011; Deeks, 2009).

- Antiretrovirals: there are a number of associations between different drugs and co-morbidities. Examples include an increased risk of chronic kidney disease with tenofovir-DF (NRTI) and atazanavir (PI) (Ryom et al, 2013) and an association between myocardial infarction risk and use of abacavir (NRTI) (Sabin et al, 2016). Almost all first-line regimens are associated with a small, non-progressive decline in bone mineral density (BMD) but this is more marked with tenofovir-DF (McComsey et al, 2011). Tenofovir-DF and PI are 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 NRTI) were published 8 years after the drug was first approved in Europe (Bristol-Myers Squibb Pharmaceutical Limited, 2016; Maida et al, 2008). Didanosine is no longer recommended for HIV treatment (British HIV Association, 2016b).
- Co-infections: around 7% and 9% PLWH are co-infected with hepatitis B and C, respectively (Price et al, 2012; Turner et al 2010), both of which increase the risk of liver-related and all-cause mortality (Hernando et al, 2012; Nikopoulos et al, 2009). Evidence of prior cytomegalovirus (CMV) infection, in the absence of a history of CMV-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 PLWH (Obel et al, 2011). US 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 US and European cohort data from Helleberg et al (2015) show that more life years are lost to smoking than to HIV.

*Vaccinations*

BHIVA provides guidelines for the use of vaccines in PLWH. Key recommendations include annual influenza vaccine for all (British HIV Association, 2015). Two types of pneumococcal vaccination are recommended: all PLWH, regardless of age, should be offered a single dose of PCV-13; in addition, any who meet national criteria for pneumococcal vaccination (Public Health England, 2013) should also receive a single dose of PPV-23. PCV-13 and PPV-23 should be given at least 3 months apart.

*Quality of life, mental health & lifestyle*

PLWH are more likely to suffer mental health disorders then their HIV-negative counterparts (Janssen et al, 2015; Do et al, 2014; Sherr et al 2008). ASTRA, a cross sectional questionnaire study amongst PLWH 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 (QoL) scores in the 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 QoL over time is similar in both groups regardless of HIV status. Successfully treated PLWH still report high rates of symptoms such as insomnia, fatigue and sexual dysfunction (Erdbeer et al, 2014). Such data has led to a recent call to expand the '90:90:90' targets to include a fourth domain: 90% with good health-related QoL (Lazarus et al, 2016).

A recent meta-analysis from Park et al (2016) has demonstrated higher rates of smoking in PLWH 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 drugs use in the last 3 months (20% of these reported using 5 or more drugs).

*Stigma & social considerations*

Despite shifts in public attitudes, experience of stigma remains a significant obstacle for PLWH. Following interviews with 1576 participants, the UK Stigma Survey (2015) 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 due to their status (The People Living with HIV Stigma Survey, 2015). A recent survey showed that a significant proportion of the general public held misconceptions about HIV transmissibility (Sparrowhawk A, 2017).

*Challenges*

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

1) **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 ART 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 summarised in national guidelines (British HIV Association, 2016a). Wherever possible, once daily regimens are used and the choice of treatment individualised to take account of dose timing, food requirements and interactions with other medications. Barriers to ART adherence may evolve over time, for example due to changes in health, social circumstances or co-prescribed medication, therefore an ongoing proactive review of these challenges is essential as optimal treatment options may change.

**2) Managing drug-drug interactions (DDI)**

A major challenge for all PLWH, particularly older individuals, is managing DDI. Cohort data from Marzolini et al (2010) identified that of 1478 HIV positive patients, 68% had at least 1 non-ART co-medication and 40% at least 1 potential DDI. There are several mechanisms for interactions between antiretrovirals and other drugs; inhibition of the CYP3A4 isoenzyme by pharmokinetic 'boosters' is of particular importance. Since around 2000 we have utilised CYP3A4 inhibition 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 due to an 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 PIs and the INI elvitegravir. Potential 3A4-mediated DDI are manifold but important examples include a risk of rhabdomyolyisis with simvastatin (Aurobindo Pharma – Milpharm Limited, 2015) and a risk of iatrogenic Cushing's and secondary adrenal suppression with many steroids, including injected, inhaled and intranasal formulations (Saberi, Phengrasamy and Nguyen 2013). Other important sources of DDI include acid-reducing agents, antipsychotics and anticonvulsants. The University of Liverpool has developed an invaluable resource for checking potential DDI, the HIV Drug Interactions Checker website, and more recently its creators have developed a similar resource for hepatitis C drugs.

Preventing DDI is challenging, as demonstrated by Case Study 1. As HIV clinics are responsible for ART prescribing, they should include information and advice

regarding DDI in communications with GPs and other healthcare professionals as per BHIVA guidance (British HIV Association, 2016a). Although ensuring shared information across organisations is not always easy, two-way communication is key to ensuring patient safety. Patient education to enhance awareness of potential DDI, and empowerment to question prescribing decisions, provide an additional safeguard against inadvertent prescribing errors or self-sourced agents which may cause harm. Locally we document discussion about key DDI at each visit and provide patient information cards about important DDI, such as pharmacokinetic boosters and corticosteroids.

Potential for DDI is an important consideration when selecting an ART regimen. Although the avoidance of boosters does reduce the risk, many unboosted agents still have significant DDI potential. Whilst NRTIs are generally not associated with significant DDI, the exception is tenofovir-alefenamide, a novel formulation of the widely used NRTI tenofovir disproxil fumarate (TDF), which should not be co-administered with p-glycoprotein inducers (Gilead Sciences Limited, 2016). NNRTI and PI have complex DDI potential. Unboosted INI (raltegravir and dolutegravir) demonstrate a significantly lower propensity for DDI but there are still important interactions with some antacids, multivitamins and, for dolutegravir, metformin (Mercke Sharp & Dohme, 2015; Viiv Healthcare Limited, 2017).

**3) Co-morbidity screening and management**

Prevention and management of co-morbidities 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 ART choice (British HIV Association, 2016b). The frequency of monitoring thereafter will be guided by baseline results, existing co-morbidities, concomitant medications, and the ART regimen selected. The pre-existence, new onset or elevated risk of a comorbidity can be an indication for switching ART. Regardless of the mechanisms, the increased prevalence and younger age of onset of age-related illnesses in PLWH may warrant a lower threshold for investigation; providers of HIV care should ensure that primary care services, other clinical specialists and PLWH themselves are aware of this. Promoting a healthy lifestyle and signposting patients towards appropriate advice and support should also feature in HIV consultations. A dialogue with primary care can ensure that our messages are consistent.

**4) Optimal models of care**

Finally, how best to provide care for PLWH? Maintaining skills and providing training in the management of opportunistic diseases is challenging when hospital admissions for AIDS-defining conditions are infrequent. We 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 amongst the best HIV treatment outcomes in the world (Hill, 2015) and as HIV care evolves we must ensure that any changes to care models are evidence-based and do not compromise the high standards of care we have

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.

Case 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.**

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 shall all contribute to an elevated cardiovascular risk therefore abacavir should be avoided.

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

Case 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 and he has 2+ proteinuria on urine dipstick.**

The combination of a boosted protease inhibitor and intra-articular steroid may increase systemic exposure to the corticosteroid through CYP3A4 enzyme inhibition risking an iatrogenic Cushing's syndrome and, subsequently, life threatening adrenocortical suppression.

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

Conclusion

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 due to an unacceptable side effect and toxicity profile. Many will have been advised of a poor prognosis thus impacting on their psychological well-being, 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 their infection. Looking to the future, the needs of the population who are living into old age with HIV is constantly changing and our challenge as HIV care providers is to respond to their evolving needs.

**Key Points:**

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

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