Chronic obstructive pulmonary disease in patients with HIV: an emerging problem

People with well-controlled HIV now have normal life expectancies and physicians managing these patients are increasingly encountering co-existing chronic obstructive pulmonary disease. This article reviews similarities with this disease in the general population and highlights key differences including significant drug–drug interactions.

Clinicians faced with an human immunodeficiency virus (HIV)-infected patient reporting progressive dyspnoea and chronic cough may be familiar with the management of common infectious complications of HIV infection such as *Pneumocystis jirovecii* pneumonia and bacterial pneumonia. However, since the advent of combination antiretroviral therapy there has been a marked reduction in the incidence of these infectious complications (Heffernan et al, 2005; Grubb et al, 2006).

In the HIV-uninfected population, chronic obstructive pulmonary disease is a leading cause of mortality and morbidity in the developed world and its economic burden is increasing (Lopez et al, 2006; Mathers and Loncar, 2006). There are around 900 000 people currently diagnosed with chronic obstructive pulmonary disease in the UK and an estimated 2 200 000 people with chronic obstructive pulmonary disease who remain undiagnosed. This is the equivalent to 13% of the population of England aged 35 years and over (Shahab et al, 2006).

With the improved survival seen since the introduction of combination antiretroviral therapy, chronic obstructive pulmonary disease is emerging as a significant problem in stable HIV disease. This article describes the epidemiology, pathogenesis, clinical presentation and management of HIV-infected patients with chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease is defined as an irreversible airflow limitation, which is usually progressive and associated with an exaggerated chronic inflammatory response to noxious particles in the airways or lung (Vestbo et al, 2013). The chronic airflow limitation that occurs in chronic obstructive pulmonary disease is caused by a combination of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The disease course is characterized by frequent exacerbations of symptoms, which also contribute to an accelerated decline in lung function.

Spirometry is the most widely available and reproducible test of lung function and can demonstrate evidence of airflow obstruction required to diagnose chronic obstructive pulmonary disease. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are measured and a post-bronchodilator FEV_1/FVC ratio of <0.70 confirms airflow obstruction. In those with evidence of irreversible airways obstruction with an FEV_1/FVC of <0.70, the predicted FEV_1 can be used to give an estimation of disease severity (Vestbo et al, 2013). With progressive destruction of lung parenchyma, gas exchange, as measured by diffusion capacity of the lung for carbon monoxide (also known as transfer factor), is impaired and is a manifestation of emphysema. Small airways collapse can be measured by assessing the speed of air leaving the lung during the middle portion of a forced expiration, called forced expiratory flow 25–75%. Gas trapping on expiration can be measured by increased residual volumes on lung function testing.

Epidemiology

Respiratory symptoms such as cough and dyspnoea were commonly reported among HIV-infected patients early in the epidemic. The high prevalence was attributed to pulmonary infection, HIV-related inflammation and high rates of cigarette smoking. Early studies of pulmonary function revealed that levels of transfer factor declined with progression of HIV disease, in keeping with this hypothesis. In the early 1990s, pre-combination antiretroviral therapy, a case series (Diaz et al, 1992) reported emphysematous changes on computed tomography and abnormal lung function testing in four individuals (aged <55 years) in the absence of pulmonary infection with limited smoking history. The same group performed a subsequent case controlled study of 114 HIV-infected individuals without pulmonary infections matched for age and smoking with 44 HIV-uninfected controls. This showed the presence of emphysema in 15% compared with 2% in the non-HIV infected group (Diaz et al, 2000).

Abnormalities in diffusion capacity have also been noted in the combination antiretroviral therapy era. A cross-sectional analysis of 300 HIV-infected men and

Dr Andrew T Scourfield *is Respiratory Registrar in the Department of Respiratory Medicine, University College Hospital London, London NW1 2BU,*
Dr Sarah R Doffman *is Consultant in Respiratory Medicine in the Department of Respiratory Medicine, Brighton and Sussex University Hospital, Brighton, and* **Professor Robert F Miller** *is Honorary Consultant in HIV Medicine at Camden Provider Services and UCL Hospitals, London*

Correspondence to: Dr AT Scourfield (andrew.scourfield@nhs.net)

289 HIV-uninfected men enrolled from 2009–11 in the Lung HIV Study at several study sites in the USA showed that, despite most participants having normal airflow, there was a significant reduction in transfer factor in HIV infected compared with HIV-uninfected men (mean predicted 69% *vs* 76%). A moderate to severe reduction of transfer factor (≤60%) was observed in 30% of HIV-infected compared with 18% of HIV-uninfected men, despite the fact that 89% of those with HIV were on combination antiretroviral therapy. A reduced level of transfer factor was significantly associated with being HIV infected and with lower CD4 cell count (<200 cells/μl), after adjusting for smoking and other confounders. Respiratory symptoms of cough, sputum and dyspnoea were more prevalent in HIV-infected patients, particularly those with abnormal pulmonary function compared with HIV-uninfected patients (Crothers et al, 2013).

In the post-combination antiretroviral therapy era, a prospective observational study from the USA of 1014 HIV-infected and 713 HIV-uninfected men from the Veterans Aging Cohort Study assessed prevalence of chronic obstructive pulmonary disease as determined by the *International Classification of Diseases* (ninth revision). After adjusting for age, race/ethnicity, pack-years of cigarette smoking, intravenous drug user and alcohol misuse, HIV infection was an independent risk factor, with chronic obstructive pulmonary disease 50–60% more likely in those with HIV (Crothers et al, 2006). This finding was confirmed in a larger follow-up study of the same cohort (Crothers et al, 2011). Several studies from North America and one from Europe have assessed the prevalence and risk factors for obstructive airways disease in HIV-infected individuals in the combined antiretroviral therapy era. These studies and their key findings are shown in *Table 1*. Data from Brighton, UK have shown 15% prevalence of airflow obstruction (FEV_1/FVC <0.7) post-bronchodilator in 133 consecutive patients recruited from an HIV outpatient clinic (Dickson et al, 2013).

Pathogenesis

The respiratory tract serves as an interface between the host and the environment; pulmonary immune defences encompass both innate and acquired responses. Pathogens entering the respiratory tract are phagocytosed by alveolar macrophages, the main component of the innate immune system in the lung. Alveolar macrophages are generally immunosuppressive to prevent an inflammatory response. If the innate host defence is impaired, persistence of the antigen stimulates specific acquired immune responses. This occurs in the lymphoid tissue of the lung and results in production of antigen-specific T

Table 1. Studies of pulmonary function testing in HIV-infected individuals in the combined antiretroviral therapy era

Location	Study period	Reference	Study type	Population and demographics	Key findings
Los Angeles, United States	2003–4	George et al (2009)	Cross sectional, spirometry	234 HIV clinic outpatients, 60% current smokers	31.5% respiratory symptoms, airflow obstruction. Increasing age, smoking pack-year history, previous bacterial pneumonia and use of combined antiretroviral therapy
Copenhagen, Denmark	2000–7	Kristoffersen et al (2012)	Prospective cohort study median follow up 4.4 years of spirometry and TLCO	63 patients with previous lung function testing followed up, 48% current smokers	FEV_1/FVC <0.7 10% at baseline, 19% at follow up. Reduced TLCO in smoking HIV-infected patients, decline during follow up also in non-smokers
Pittsburgh, United States	2007–9	Gingo et al (2010)	Cross sectional, spirometry pre and post bronchodilator and TLCO	167 HIV clinic outpatients, 53% current smokers	64% respiratory symptoms (dyspnoea>cough) TLCO <80% predicted in 64% airflow obstruction: smoking pack-year history, intravenous drug use and use of combined antiretroviral therapy
Baltimore, United States	2007–9	Drummond et al (2012)	Retrospective cross-sectional review of spirometry	1077 people in inner city area with history of intravenous drug user (303 HIV), 86% current smokers	HIV 16% FEV_1/FVC<0.7, airflow obstruction: Higher viral load (>200 000 copies/ml)
Philadelphia, United States	2008–9	Hirani et al (2011)	Cross sectional, spirometry	98 HIV clinic outpatients 55% current smokers	16% FEV_1/FVC <0.7 and 14% airflow obstruction in never smokers. Association with: increasing age, intravenous drug use, smoking pack-year history and previous *Pneumocystis jirovecii* pneumonia
Hamilton, Canada	<2010	Cui et al (2010)	Cross sectional, spirometry	119 HIV clinic outpatients 44% current smokers	20% abnormal spirometry, 12% airway obstruction (FEV_1/FVC <0.7)
Baltimore, United States	2007–10	Drummond et al (2013)	Longitudinal analysis of spirometry in AIDS Linked to the Intravenous Experience study (median follow up 2.75 years)	1064 (316 HIV infected) 85% current smokers	No significant decline in HIV compared to non-HIV group. HIV-infected patients with CD4 >200 cells/ml had no difference to HIV uninfected. Decline in FEV_1 and FVC associated with HIV viral load >75 000 copies/ml and CD4 <100 ml/litre

FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; HIV = human immunodeficiency virus; TLCO = transfer factor of the lung for carbon monoxide.

and B cells; under the control of local chemokine production, these migrate to the sites of the initial challenge. Studies have demonstrated the accumulation of CD8+ T cells in the lungs of patients with severe chronic obstructive pulmonary disease; HIV-positive smokers also have a higher percentage of CD8+ T cells detectable on bronchoalveolar lavage. HIV infection causes activation of alveolar macrophages, a reduction in CD4 T-cell count, increased number and percentage of CD8 T cells and an increased CD4:CD8 ratio in the alveolar space with generalized CD4 and CD8 T-cell activation (Beck, 2013; Twigg and Knox, 2013). This leads to a cycle of pulmonary inflammation and damage.

Role of *Pneumocystis jirovecii* colonization

The lung microbiome is a rapidly expanding area of research and studies have shown wide variability in the microbiological population in the lungs of HIV-infected as compared with uninfected individuals (Twigg et al, 2010, 2011; Ireland et al, 2012).

P. jirovecii is a well-recognized cause of pneumonia in those with HIV infection. In HIV-uninfected individuals, colonization with *P. jirovecii* is a risk factor for chronic obstructive pulmonary disease severity, independent of smoking history or corticosteroid use. In HIV-infected patients the frequency of *P. jirovecii* colonization has been reported as 40–58%. While those with lower CD4 counts appear to have increased rates of colonization, other studies have suggested that this still occurs in those on antiretroviral therapy, with higher CD4 counts and in those taking *P. jirovecii* pneumonia prophylaxis (Morris and Norris, 2012).

A study of HIV-infected individuals showed worse airflow obstruction in those colonized with *P. jirovecii*, even adjusting for smoking history. Animal studies also suggest colonization with pneumocystis may play a role in the development of chronic obstructive pulmonary disease. One study in primates revealed macaques infected with simian immunodeficiency virus developed pneumocystis colonization and these animals had higher rates of airflow obstruction and increased emphysematous changes. Immunocompetent mice colonized by pneumocystis and exposed to cigarette smoke were more likely to develop emphysema than non-colonized mice or those not exposed to cigarette smoke, implying these two factors are synergistic (Morris and Norris, 2012).

The inflammatory response to pneumocystis in the lung is similar to that seen in chronic obstructive pulmonary disease, even when *P. jirovecii* is detected at low levels, as occurs in colonization. These changes include increased numbers of CD8 lymphocytes, neutrophils and macrophages. It remains to be determined if colonization with pneumocystis in those with chronic obstructive pulmonary disease is a cause of ongoing inflammation or a marker of structural lung damage and use of corticosteroids (Morris and Norris, 2012).

Clinical presentation

A diagnosis of chronic obstructive pulmonary disease should be considered in any HIV-infected patient who reports dyspnoea, chronic cough or sputum production, particularly in those with a history of exposure to a risk factor such as cigarette smoke, occupational exposure to dust and chemicals, irrespective of the CD4 count and whether or not the patient is taking combination antiretroviral therapy.

Chronic cough is often the first symptom of chronic obstructive pulmonary disease to develop. The cough may be dry, but commonly patients with chronic obstructive pulmonary disease produce small amounts of sputum. Large volume sputum production should raise the suspicion of underlying bronchiectasis.

Dyspnoea is another common symptom in individuals with chronic obstructive pulmonary disease and is frequently encountered in HIV-infected persons with a wide differential diagnosis. In the early stages dyspnoea may be reported on exertion but as lung function deteriorates increasing breathlessness may occur at rest and cause significant disability and anxiety. *P. jirovecii* pneumonia should always be considered in those who are not receiving combination antiretroviral therapy and who have low CD4 counts (<250 cells/μl). Wheezing and chest tightness are non-specific symptoms that may also be present, usually after exertion, but their absence does not exclude chronic obstructive pulmonary disease.

The differential diagnosis for HIV-infected patients with chronic cough and dyspnoea is shown in *Table 2*.

It is important to assess for other features of severe chronic obstructive pulmonary disease such as ankle swelling which may suggest the development of right heart failure from cor pulmonale. Careful attention should also be paid to detecting anxiety or depression, which are associated with worse outcomes and are more frequent in individuals with HIV (Rabkin, 2008). Weight loss and anorexia may represent advanced chronic obstructive pulmonary disease or suggest an alternative pathology.

Imaging

Chest radiograph

In those with chronic cough and shortness of breath chest radiography should be a first-line investigation. It is useful to exclude other causes such as malignancy or tuberculosis, and during exacerbations to exclude complications of chronic obstructive pulmonary disease such as pneumonia and pneumothorax. In chronic obstructive pulmonary disease the chest radiograph may show hyperexpanded lung fields (>7th anterior rib intersecting the diaphragm at the mid-clavicular line), flattening of the hemidiaphragms, and if bullous lung disease is present this may be seen as a hyperlucency in lung fields (*Figure 1*).

Computed tomography of the chest

In the late 1980s a high prevalence of bullous lung disease was noted on computed tomography scans of HIV-

infected individuals, occurring at a younger age (mean 37 years) than other immunocompromised individuals (Kuhlman et al, 1989). Features of chronic obstructive pulmonary disease seen on chest computed tomography include prominent small airways, emphysema (which can be centriacinar, panacinar or para-septal) and mosaic attenuation as a result of gas trapping from obstructive bronchiolitis. Expiratory phase high resolution computed tomography scan can show evidence of air trapping, which in some patients may be the only sign of early-stage small airways disease in an otherwise normal lung. More severe disease is characterized by the development of thin-walled bullae (*Figure 2*).

Managing chronic obstructive pulmonary disease in HIV patients: considerations

Pharmacotherapy and drug–drug interactions

In the absence of data specific to the HIV population, pharmacotherapy for chronic obstructive pulmonary disease is in line with guidelines for the HIV-uninfected population. Inhaled bronchodilators (beta-2 agonists and anticholinergics) are the preferred initial therapy with inhaled corticosteroids reserved for those with severe disease.

There are several important interactions for prescribers to be aware of:

Table 2. Differential diagnosis for chronic cough and dyspnoea in HIV-infected individuals

Condition		Usual CD4 count cell/mm^3	Dyspnoea	Additional features	Chest radiograph
Obstructive spirometry	Chronic obstructive pulmonary disease	Any	On exertion	Wheeze, history of cigarette smoking, obstructive spirometry reduced TLCO	Hyperinflated lung fields, flattening of diaphragm, increased bronchial wall thickening, hyperlucency (if bullous change)
	Asthma	Any	On exertion or identifiable trigger	Wheeze, history of atopy, reversible obstructive spirometry	May be normal or show features of bronchial wall thickening and hyperinflation
	Bronchiectasis	Any	If airway obstruction	Previous respiratory infections	Increase in bronchovascular markings, ring shadows of bronchi seen 'end-on', tram-track opacities or air fluid levels
Restrictive spirometry	Sarcoidosis	>200 (may be caused by immune reconstitution inflammatory syndrome)	On exertion	Fever, arthralgia, lymphadenopathy, hepatosplenomegaly, skin nodules, uveitis, neurological or cardiac disease	Hilar lymphadenopathy +/- reticulonodular opacities
	Non-specific interstitial pneumonitis	<200 May be normal	Often remains stable over years	Fever (often prolonged)	Interstitial or alveolar infiltrates, normal in up to 50%
	Lymphocytic interstitial pneumonia	>350	Progressive exertional dyspnoea	Fever, weight loss, fatigue, if occurs as part of DILS xerophthalmia and xerostomia	Reticular or nodular shadowing
	Cryptogenic organizing pneumonia	Any	Exertional dyspnoea	Fevers, weight loss, restrictive defect on spirometry with reduced TLCO	Consolidation
	Hypersensitivity pneumonitis	Usually >350	Acute or subacute dyspnoea depending on allergen exposure	Fever, rash, weight loss	Normal or diffuse nodules
Infectious causes	*Pneumocystis jirovecii* pneumonia	<200, not on combined antiretroviral therapy	Progressive dyspnoea on exertion	Fever, oxygen desaturation with exercise	Normal or bilateral infiltrates
	Bacterial pneumonia	Any, incidence increased with lower CD4	Short history of dyspnoea	Fever, chest pain	Focal consolidation, may be diffuse, pleural effusion
	Tuberculosis	Any, incidence increased with lower CD4	Not a prominent feature	Weight loss, fevers, superficial lymphadenopathy, hepatosplenomegaly	Parenchymal infiltrates +/- cavitation, hilar and/or mediastinal lymphadenopathy, pleural effusion
Other causes	Lung cancer	Any	Not a prominent feature	Weight loss, anaemia, history of cigarette smoking	Mass lesion, hilar and/or mediastinal lymphadenopathy, pleural effusion
	Gastro-oesophageal reflux	Any	Not a feature	Dyspepsia or acid reflux	Often normal, may show features of hiatus hernia or aspiration
	Chronic allergic rhinitis	Any	Not a feature	Rhinorrhoea, nasal congestion, sneezing	Normal

DILS = diffuse infiltrative lymphocytosis syndrome; HIV = human immunodeficiency virus; TLCO = transfer factor of the lung for carbon monoxide.

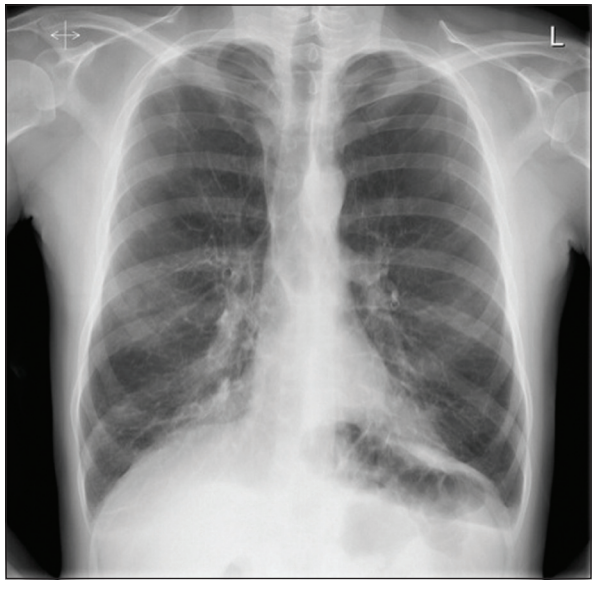

Figure 1. Radiograph of a 50-year-old male ex-smoker, diagnosed with human immunodeficiency virus in 1998, who had recurrent pneumonia. He started combined antiretroviral therapy in 2006. His current CD4 count is 300 cells/μl, and HIV-1 viral load <50 copies/ml.

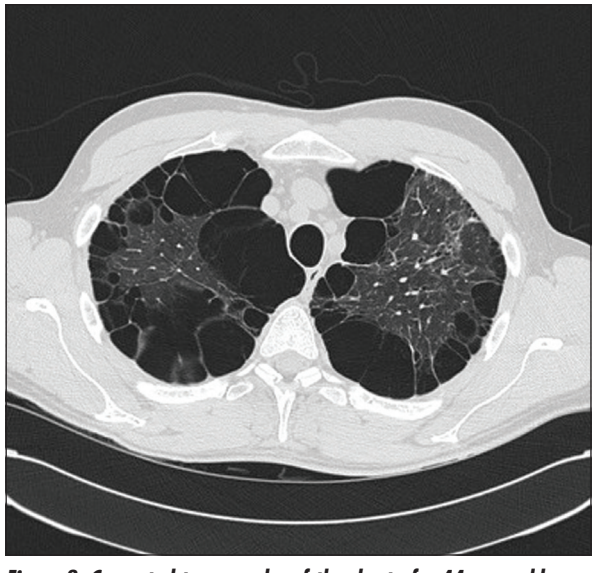

Figure 2. Computed tomography of the chest of a 44-year-old man, current smoker. He was diagnosed with human immunodeficiency virus in 2004 when he presented with a Pneumocystis jirovecii *pneumonia infection. He started combined antiretroviral therapy in 2009 but has poor compliance. His CD4 count is 170 cells/μl, HIV-1 viral load >100 000 copies/ml.*

Inhaled corticosteroids

Multiple case reports describe iatrogenic Cushing's syndrome in individuals on ritonavir-boosted protease inhibitor antiretroviral regimen treated with fluticasone (a component of Seretide) as a result of reduced steroid metabolism (Foisy et al, 2008). Ritonavir is a potent inhibitor of the hepatic CYP3A4 isoenzyme. Other inhaled steroids metabolized by this route include budesonide and mometasone; beclomethasone is not and can be safely administered with ritonavir-containing antiretroviral therapy. Of note, the new pharmacoenhancer cobicistat, currently only available as part of a fixed dose combination called Stribild, is also a potent CYP3A4 inhibitor and therefore should not be administered with inhaled steroids other than beclomethasone. Inhaled corticosteroids should be used with caution in HIV-infected individuals as these increase the risk of bacterial pneumonia (Calverley et al, 2007) and this risk remains elevated despite the use of combination antiretroviral therapy (Heffernan et al, 2005).

Long acting beta-agonists

Co-administration of salmeterol (also contained in Seretide) with ritonavir is not recommended as a result of increased salmeterol concentrations that may cause QT prolongation, palpitations and sinus tachycardia (Abbvie Ltd, 2012).

Anticholinergics

Short- and long-acting anticholinergics are thought to be safe with combination antiretroviral therapy although this interaction has not been studied.

Prednisolone

Oral prednisolone is frequently used in short courses to treat chronic obstructive pulmonary disease exacerbations. A study of co-administration of prednisolone 20 mg once daily with ritonavir 200 mg twice daily (a higher dose than used in clinical practice) showed that the area under the curve of the active metabolite prednisolone increased by 37% and 28% after 4 and 14 days of ritonavir respectively (Abbvie Ltd, 2012). This is unlikely to be clinically significant in short courses but monitoring for therapeutic and adverse effects is advised with prolonged courses.

Theophylline

Theophylline is mainly metabolized by CYP1A2, therefore when co-administered with ritonavir and cobicistat (at standard dosing) levels are not significantly affected. However, given the narrow therapeutic window drug monitoring should be considered.

Role of antiretroviral therapy

Owing to the early onset of chronic obstructive pulmonary disease in HIV, surrogate markers have been investigated; the most studied factor is the impact of HIV viral load. Poorly controlled HIV has been associated with worse lung function; the aforementioned Veterans Aging Cohort Study cohort study showed chronic obstructive pulmonary disease was less likely in those with suppressed HIV RNA levels (<400 copies/ml) and those on combination antiretroviral therapy at baseline (Crothers et al, 2011). Another study of 1077 former intravenous drug users demonstrated that airway obstruction was

associated with HIV viral loads >200 000 copies/ml. In a longitudinal follow-up study of this cohort over a median 2.75 years, high HIV viral load (>75 000 copies/ml) and low CD4 count (<100 cells/μl) were associated with reduced FEV_1 and FVC (Drummond et al, 2013).

With the initiation of combination antiretroviral therapy there is a trend to normalization of pulmonary immune function. Despite this, two studies have suggested worse airflow obstruction in patients on combination antiretroviral therapy (George et al, 2009; Gingo et al, 2010). Possible explanations for this observation might be the timing of combination antiretroviral therapy in different populations or immune response to subclinical infections.

Similarities to managing chronic obstructive pulmonary disease in the general population

Smoking cessation

The prevalence of cigarette smoking among HIV-infected individuals ranges from 44–86% depending on the population studied. Smoking cessation in the non-HIV population delays decline in lung function (Fletcher and Peto, 1977) and should be the main focus of any treatment strategy. Most smoking cessation trials use motivational interviewing with or without nicotine replacement therapy. Smoking cessation interventions in individuals with HIV have shown variable results. A study of 474 HIV-positive smokers, randomized to usual care or counselling via mobile phone intervention, demonstrated significantly greater abstinence up to 3 months, but the effect diminished after 6 and 12 months (Gritz et al, 2013). Another study of 209 HIV-positive smokers randomized to nicotine replacement combined with counselling, self-help or internet-based treatment, and showed comparable results in all arms (Humfleet et al, 2013). The largest study of varenicline compared it to nicotine replacement therapy, both with telephone counselling, in 228 HIV-positive smokers. This showed promising results with biochemically confirmed abstinence rates at 3 months of 25.6% *vs* 11.8% respectively. The adverse event profile was similar to the general population and there was no association of adverse events with use of combination antiretroviral therapy (Ferketich et al, 2013).

Pulmonary rehabilitation

The combination of chronic obstructive pulmonary disease and HIV is associated with higher rates of self-reported physical disability and decreased physical functioning (Oursler et al, 2011). In HIV-uninfected individuals with chronic obstructive pulmonary disease, pulmonary rehabilitation significantly improves physical functioning. Systemic effects of inflammation from HIV can contribute to reduction in muscle mass and exercise capacity. Aerobic exercise appears to be safe and may be beneficial for HIV-infected adults but the optimal exercise regimen for those with HIV and chronic obstructive pulmonary disease is yet to be determined (Nixon et al, 2010).

Conclusions and future perspectives

Chronic obstructive pulmonary disease is a major cause of morbidity and mortality in the UK. With the ageing HIV population and as a result of the insidious onset of symptoms, physicians managing those with HIV should enquire routinely about smoking habits and pay particular attention to eliciting symptoms of chronic obstructive pulmonary disease such as cough, dyspnoea, sputum production and wheezing.

Even after controlling for known risk factors chronic obstructive pulmonary disease appears to be more prevalent in individuals with HIV. This may be related to chronic inflammatory changes that occur as well as the immune response to subclinical microorganisms colonizing the respiratory tract.

The prevalence of cigarette smoking in the HIV population is extremely high and the key focus of any treatment strategy should be smoking cessation. Pharmacotherapy is in line with national guidance for management of chronic obstructive pulmonary disease, but there are significant drug–drug interactions which patients, GPs and specialists need to be aware of (particularly those taking CYP3A4 inhibitors, such as ritonavir and cobicistat). Complex patients may benefit from early involvement of a respiratory specialist with an interest in HIV.

Novel treatment strategies may look at using anti-inflammatory agents and assessing response to eradication of *P. jirovecii* pneumonia in those who are colonized. Antiretroviral therapy is important to prevent pulmonary opportunistic infections and to reverse systemic and intrapulmonary inflammation. It will be interesting to see how the trend for earlier initiation of combination antiretroviral therapy will impact on the incidence of chronic obstructive pulmonary disease in HIV-infected individuals. **BJHM**

Conflict of interest: Dr AT Scourfield and Dr SR Doffman: none. Professor R Miller is Editor in Chief of British Journal of Hospital Medicine. *He took no part in the peer review process nor in the decision to accept it for publication.*

Abbvie Ltd (2014) Norvir Summary of Product Characteristics. Abbvie Ltd, Maidenhead

Beck JM (2013) Abnormalities in host defense associated with HIV infection. *Clin Chest Med* **34**(2): 143–53 (doi: 10.1016/j.

KEY POINTS

- Physicians caring for HIV (human immunodeficiency virus)-infected patients should be alert for chronic obstructive pulmonary disease.
- Even after controlling for cigarette smoking chronic obstructive pulmonary disease appears to be more prevalent among HIV-infected persons than among the general population.
- Treatment is as for the general population – smoking cessation and pharmacological interventions.
- Clinically significant drug–drug interactions can occur – check for these at www.hiv-druginteractions.org.

ccm.2013.01.003)
Calverley PM, Anderson JA, Celli B et al (2007) Salmeterol and fluticasone proprionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* **356**(8): 775–89
Crothers K, Butt AA, Gibert CL et al (2006) Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* **130**(5): 1326–33
Crothers K, Huang L, Goulet JL et al (2011) HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med* **183**(3): 388–95 (doi: 10.1164/rccm.201006-0836OC)
Crothers K, McGinnis K, Kleerup E et al (2013) HIV infection is associated with reduced pulmonary diffusing capacity. *J Acquir Immune Defic Syndr* **64**(3): 271–8 (doi: 10.1097/QAI.0b013e3182a9215a)
Cui Q, Carruthers S, McIvor A et al (2010) Effect of smoking on lung function, respiratory symptoms and respiratory diseases amongst HIV-positive subjects: a cross-sectional study. *AIDS Res Ther* **7**: 6 (doi: 10.1186/1742-6405-7-6)
Diaz PT, Clanton TL, Pacht ER (1992) Emphysema-like pulmonary disease associated with human immunodeficiency virus infection. *Ann Intern Med* **116**(2): 124–8
Diaz PT, King MA, Pacht ER et al (2000) Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* **132**(5): 369–72
Dickson N, Hollington R, Malbon R et al (2013) Prevalence of chronic obstructive pulmonary disease in an HIV infected population. *HIV Med* **14** (suppl 2): 12–77 (abstr P95)
Drummond MB, Kirk GD, Astemborski J et al (2012) Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax* **67**(4): 309–14 (doi: 10.1136/thoraxjnl-2011-200702)
Drummond MB, Merlo CA, Astemborski J et al (2013) The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS* **27**(8): 1303–11 (doi: 10.1097/QAD.0b013e32835e395d)
Ferketich AK, Diaz P, Browning KK et al (2013) Safety of varenicline among smokers enrolled in the lung HIV study. *Nicotine Tob Res* **15**(1): 247–54 (doi: 10.1093/ntr/nts121)
Fletcher C, Peto R (1977) The natural history of chronic airflow obstruction. *BMJ* **i**: 1645–8
Foisy MM, Yakiwchuk EM, Chiu I et al (2008) Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV Med* **9**(6): 389–96 (doi: 10.1111/j.1468-1293.2008.00579.x)
George MP, Kannass M, Huang L et al (2009) Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. *PLoS One* **4**(7): e6328 (doi: 10.1371/journal.pone.0006328)
Gingo MR, George MP, Kessinger CJ et al (2010) Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. *Am J Respir Crit Care Med* **182**(6): 790–6 (doi: 10.1164/rccm.200912-1858OC)
Gritz ER, Danysh HE, Fletcher FE et al (2013) Long-term outcomes of a cell phone-delivered intervention for smokers living with HIV/AIDS. *Clin Infect Dis* **57**(4): 608–15 (doi: 10.1093/cid/cit349)
Grubb JR, Moorman AC, Baker RK et al (2006) The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. *AIDS* **20**(8): 1095–107
Heffernan RT, Barrett NL, Gallagher KM et al (2005) Declining incidence of invasive Streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. *J Infect Dis* **191**(12): 2038–45
Hirani A, Cavallazzi R, Vasu T et al (2011) Prevalence of obstructive lung disease in HIV population: a cross sectional study. *Respir Med* **105**(11): 1655–61 (doi: 10.1016/j.rmed.2011.05.009)
Humfleet GL, Hall SM, Delucchi KL et al (2013) A randomized clinical trial of smoking cessation treatments provided in HIV clinical care settings. *Nicotine Tob Res* **15**(8): 1436–45 (doi: 10.1093/ntr/ntt005)
Ireland AW, Ghedin E, Pop M et al (2012) Comparison of the respiratory microbiome in HIV-infected and HIV-uninfected individuals. *Am J Resp Crit Care Med* **185**(Meeting abstracts): A4045
Kristoffersen US, Lebech AM, Mortensen J et al (2012) Changes in lung function of HIV-infected patients: a 4.5-year follow-up study. *Clin Physiol Funct Imaging* **32**(4): 288–95 (doi: 10.1111/j.1475-097X.2012.01124.x)
Kuhlman JE, Knowles MC, Fishman EK et al (1989) Premature bullous pulmonary damage in AIDS: CT diagnosis. *Radiology* **173**: 23–6
Lopez AD, Shibuya K, Rao C et al (2006) Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* **27**: 397–412
Mathers CD, Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* **3**: e442
Morris A, Norris K (2012) Colonization by *Pneumocystis jirovecii* and its role in disease. *Clin Microbiol Rev* **25**(2): 297–317 (doi: 10.1128/CMR.00013-12)
Nixon S, O'Brien K, Glazier RH et al (2010) Aerobic exercise interventions for adults living with HIV/AIDS. *Cochrane Database Syst Rev* (8): CD001796
Oursler KK, Goulet JL, Crystal S et al (2011) Association of age and comorbidity with physical function in HIV infected and uninfected patients: results from the Veterans Aging Cohort Study. *AIDS Patient Care STDS* **25**(1): 13–20
Rabkin JG (2008) HIV and Depression: review and update. *Curr HIV/AIDS Rep* **5**(4): 163–71
Shahab L, Jarvis MJ, Britton J et al (2006) Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax* **61**(12): 1043–7
Twigg HL, Nelson D, Dong Q et al (2010) Analysis of the respiratory microbiome using bronchoalveolar lavage from HIV-infected and uninfected subjects. *Am J Respir Crit Care Med* **181**(Meeting abstracts): A5629
Twigg HL, Nelson D, Dong Q et al (2011) Analysis of the respiratory microbiome using bronchoalveolar lavage from HIV-infected and uninfected subjects. *Am J Respir Crit Care Med* **183**(Meeting abstracts): A6257
Twigg HL 3rd, Knox KS (2013) Impact of antiretroviral therapy on lung immunology and inflammation. *Clin Chest Med* **34**(2): 155–64 (doi: 10.1016/j.ccm.2013.01.004)
Vestbo J, Hurd S, Agusti A et al (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **187**(4): 347–65 (doi: 10.1164/rccm.201204-0596PP)