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What is This?
A dedicated clinic for HIV-positive individuals over 50 years of age: a multidisciplinary experience

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Summary: The HIV-infected population is ageing. Issues including polypharmacy and co-morbidities led us to develop a dedicated clinic for HIV-infected individuals over 50. We describe our service evaluation after two years. The over 50 clinic commenced in January 2009. The team comprises a registrar, consultant, nurse practitioner and is supported by a pharmacist and mental health services. Patients undergo a full medication and drug interactions review, neurocognitive assessment, adherence self-assessment and investigations including therapeutic drug monitoring (TDM), coronary artery calcium scores (CACS) and bone mineral density.

Over two years of activity, 150 patients attended the service. Median (range) age was 58 (50–88), all were on combined antiretroviral therapy and 38% (57/150) were on ≥3 non-HIV drugs. CACS was high (>90th centile) in 14%. Thirty-eight percent had osteopaenia and 18% had osteoporosis requiring treatment. Thirteen out of 125 men had an increased prostate specific antigen, four were diagnosed with prostate cancer. Drug interaction, TDM and neurocognitive assessments were useful for several patients.

Asymptomatic patients over 50 in long-term follow-up had new pathologies detected through targeted screening. The clinic has improved general practitioner (GP) liaison and facilitated closer working relationships with other specialties. Patients have reacted positively to the clinic, particularly as many do not routinely access their GP.

Keywords: HIV infection, ageing with HIV, multidisciplinary HIV clinic

INTRODUCTION

Since the advent of combined antiretroviral therapy (cART) in the mid-1990s, HIV-infected individuals have enjoyed progressive reductions in HIV-associated morbidity and mortality. Recent studies show marked improvements in life-expectancy for patients with HIV and patients experiencing sustained immune re-constitution on cART have a risk of mortality similar to that of the general population. There has been a shift from HIV-related to ‘non-HIV-related’ morbidities and HIV treating clinicians are dealing increasingly with an ageing population. This is partly due to marked improvements in life-expectancy but, in addition, patients are becoming infected with HIV at an older age. Indeed, the Centers for Disease Control and Prevention (CDC) have predicted that by 2015, 50% of HIV-infected individuals in the USA will be older than 50 years of age.

Older age is not a barrier to successful cART; in general, older patients demonstrate better adherence, better virological response rates but lower CD4 responses on cART. However, age-related changes in drug absorption, distribution, metabolism and excretion may render older HIV-infected patients more susceptible to drug-related adverse events. Moreover, older patients are more likely to be receiving multiple drugs for co-morbid conditions, increasing the risk of drug–drug interactions, particularly when more than one prescriber is involved.

HIV-infected individuals are at greater risk of the morbidities classically associated with increased age including cardiovascular disease (CVD), reduced bone mineral density (BMD) and neurocognitive impairment (NCI). The precise mechanisms for this increased risk are uncertain and likely multifactorial, but chronic inflammation, a well-established risk factor for CVD, almost certainly plays a role. The role of immune senescence, or accelerated immune ageing, is also unclear. HIV-positive patients have more immune activation and more immune senescence than HIV-negative controls, even on suppressive ART, and both immune activation and senescence are independently associated with surrogate markers of CVD.

Although depression is not age-related, it is under-diagnosed and older adults may be at greater risk of factors associated with depression, such as social isolation. Additionally, depression is associated with cognitive abnormalities and older HIV-infected patients with NCI are more likely to have past or current depression than those without.

Since 2003 our department has run a weekly ‘Virtual Clinic’; this was set up to review patients failing therapy and treatment complications. Over recent years the caseload has shifted from reviewing virological failures and resistance, more to managing antiretroviral (ARV) complications and co-morbidities; the outpatient team meetings, held prior to each clinical session, also focused increasingly on the same challenges.
In the face of the issues outlined above, and an increasing proportion of older patients in our HIV cohort, we have developed a dedicated outpatient clinic for HIV-infected individuals aged 50 or older. We describe the development of this service, our current clinic protocols and a summary of selected service outcomes following the introduction of enhanced physical and psychological screening.

METHODS

A multidisciplinary team consisting of a consultant, HIV nurse practitioner, specialist trainee doctor and pharmacist were tasked with setting up an ‘over 50 clinic’. Several meetings were held in conjunction with other members of the department as well as other specialties and from these a clinic template and protocol was developed; the clinic started in January 2009. The clinic consultant, specialist trainee and nurse practitioner each run a weekly clinic in conjunction, and a specialist pharmacist and dietician provide support. Patients are referred in by their regular clinic doctor or nurse with age the only entry criterion.

At each appointment a thorough medical history, careful medication history and review of previous blood and urine results are performed. Additional assessments and investigations are listed in Table 1 with additional details described in the following text:

**Blood tests**

A very high prostate specific antigen (PSA) is strongly suggestive of cancer; the significance of mild elevations is less clear. PSA levels are interpreted according to age-related cut-offs and referral to Urology services made if elevated. Data suggest prostate cancer may be less common in HIV-infected men, although this may be secondary to reduced use of PSA screening. Hypogonadism is common in HIV-infected men and our local clinic policy recommends testing total and free testosterone levels in all male patients. Fasting lipids are used to estimate CV risk by the Joint British Societies (JBS)-2 method. Elevated fasting glucose (>6 mmol/L) prompts oral glucose tolerance testing and if impaired glucose tolerance or diabetes is confirmed, specialist referral made. Therapeutic drug monitoring (TDM) of selected ARVs (tenofovir, non-nucleoside reverse transcriptase inhibitors, protease inhibitor [PI], maraviroc and raltegravir) is performed if indicated by nucleoside reverse transcriptase inhibitors, protease inhibitor 

**CV assessments**

Several tools are available to estimate CV risk. Framingham over-estimates CV risk in the general UK population; Framingham-based assessments include JBS-2 which is preferred in our clinic as it includes more additional risk factors. Framingham estimation may underestimate CV risk in HIV-infected populations and HIV-specific models may perform better. Because of this we elected to perform additional CV risk assessment in our clinic. Surrogate markers of CVD risk including serum inflammatory markers, measure of blood vessel reactivity and coronary artery calcium score (CACS). CACS is predictive of future CV events in large, prospective studies in the general population and correlates well with estimated CV risk in HIV-infected subjects. CACS has limitations such as failing to detect non-calcified coronary plaques and may not be the optimal marker of CV risk in HIV; however, after detailed discussion with the cardiology team at our centre, CACS was deemed the most suitable method in the first instance. Patients undergo CT

<table>
<thead>
<tr>
<th>Test category</th>
<th>Details</th>
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<tbody>
<tr>
<td>Blood tests</td>
<td>Vitamin D (+ PTH if low), PSA (if not checked by GP), testosterone (free and total), fasting glucose and lipids, TDM as indicated</td>
</tr>
<tr>
<td>Other clinical data</td>
<td>Urine (uPCR and uACR) as per EACS guidelines, height, weight, body mass index and hip:waist ratio (with referral to the dietician within the MDT if indicated), chest X-ray, faecal occult bloods (if &gt;60 and not registered with GP) as per national guidelines, sexual health risk assessment and screening if indicated</td>
</tr>
<tr>
<td>Cardiovascular assessment (Figure 1)</td>
<td>Estimated risk (JBS-2), coronary artery calcium score (CACS)</td>
</tr>
<tr>
<td>Bone assessments (Figure 2)</td>
<td>Bone mineral density (BMD), bloods as listed – see Figure 2</td>
</tr>
<tr>
<td>HIV-associated neurocognitive disorder (HAND) assessment (Figure 3)</td>
<td>Generalized anxiety disorder questionnaire (GAD-7), depression questionnaire (PHQ-9), direct questioning to ascertain concerns about memory/attention/cognition (patient or others), revised every day memory questionnaire (EMQ-R), International HIV Dementia Scale (IHDS)</td>
</tr>
<tr>
<td>Medication assessments</td>
<td>Adherence review (medication self-assessment, locally devised questionnaire), careful polypharmacy and drug–drug interaction review</td>
</tr>
<tr>
<td>Others</td>
<td>Psycho social assessment, referral to smoking cessation service as appropriate. Female patients: review of cervical cytology and breast screening</td>
</tr>
</tbody>
</table>

**Table 1 Routine assessments within the over 50 clinic**

**Figure 1** Coronary artery calcium score (CACS) flowchart. TC = total cholesterol in mmol/L; LDL = low-density lipoprotein-cholesterol in mmol/L.
scanning of the coronary vasculature and CACS is reported as a centile by comparing the absolute score with an age- and gender-matched cohort; further management or referral depends on centile score as outlined in Figure 1. Only asymptomatic patients are referred for CACS; any patient with symptoms or signs suggestive of coronary artery disease are investigated and referred in the usual manner.

**Bone assessment**

Low BMD is common in HIV-infected individuals and, following meetings with the rheumatology team and careful literature review, a local algorithm was devised (Figure 2). This remains under regular review and will be adapted as new evidence and guidance emerges.

**Psychological and HIV-associated neurocognitive disorder assessments**

In the absence of clear consensus guidelines on how best to investigate and manage NCI in HIV-infected individuals we developed a protocol (Figure 3) in collaboration with our psychology and psychiatry colleagues over a series of meetings. The first step is assessment of anxiety and depression (both can be associated with NCI and may require correction before further assessment is undertaken). All patients are briefly questioned regarding any concerns (their own or others’) about memory, attention and cognitive function.

GAD-7 is a short, patient-completed questionnaire developed as a screening tool for generalized anxiety disorder and has been shown to be reliable and accurate when compared with formal anxiety assessments. GAD-7 shows excellent internal consistency (Cronbach’s α = 0.92), good test–re-test reliability (intraclass correlation = 0.83) and good correlation whether self- and mental health professional (MHP)-administered (intraclass correlation = 0.83). GAD-7 also correlates well with two other anxiety scales: the Beck Anxiety Inventory (r = 0.72) and the anxiety subscale of the Symptom Checklist-90 (r = 0.74). Finally, increasing GAD-7 scores correlate strongly with multiple domains of functional impairment. The questionnaire also performs moderately well with regard to other common anxiety disorders: panic disorder, social anxiety disorder and post-traumatic stress disorder. Patients are asked to grade 7 anxiety-related symptoms from 0 to 3; a score >10 prompts referral to psychology.

PHQ-9 (patient health questionnaire) is also self-administered and scores each of the nine Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for depression in a similar way to GAD-7, from 0 (not at all) to 3 (nearly every day). The internal reliability of PHQ-9 is excellent (Cronbach’s α = 0.86–0.89) in different studies as is test–re-test reliability. Self-completed PHQ-9 completed correlated well with repeat questionnaire via telephone with an MHP (r = 0.84, mean scores 5.08 versus 5.03). PHQ-9 score correlates well with depression severity as assessed by MHP interview: 93% of patients with no depressive disorder had a PHQ-9 score <10 and 88% with major depression had scores of ≥10. There is a strong association between increasing PHQ-9 score and worsening functional ability.

Depending on the score different courses of action are recommended. In our service a score greater than 5 prompts...
repeat assessment in six months, a score of 10 or more referral to psychology and greater than 15 or more, referral to psychiatry services to consider pharmacotherapy.

Patients are then questioned directly about their or others’ concerns regarding memory, cognition or attention. Depending on the outcome of this discussion, symptomatic patients undergo further assessment with EMQ-R and International HIV Dementia Scale (IHDS). With the EMQ-R, patients rate 13 symptoms on a scale of 0 to 4 (0 = once or less in the last month; 4 = once or more in a day); this is a simplified version of the original 28-point version and was shown to be valid and reliable in a retrospective study; the original EMQ is very reliable (Cronbach’s $\alpha$ 0.91) and sensitive to memory differences across different patient groups; the revised version correlates very highly with the original ($r = 0.97$). With EMQ-R, each question is divided into retrieval (R) and attentional (A) items and cut-offs are provided for the total, R and A mean scores. The IHDS questionnaire screens for HIV-related dementia; as diagnosis depends on formal neuropsychometric testing, screening questionnaires have been developed to identify patients who require time-consuming formal assessment. Both the HDS and the IHDS were developed to evaluate subcortical brain function as opposed to the mini mental state examination, which predominantly assesses cortical function. The IHDS was developed from the HDS as a cross-cultural tool to screen for HIV-associated neurocognitive disorder; a cut-off of 10 yields a sensitivity of 80% for diagnosing dementia, compared with psychometric testing, in resource-rich and poor settings.

Patients with abnormal scores on EMQ-R and IHDS are referred to psychology services for neuropsychometric testing; those with abnormalities on one test only are reassured but if still concerned may be offered further assessment.

Pharmacokinetics and drug interactions

Whether we should tailor antiretroviral dosing depending on age is unclear. However, it is well known that ageing is associated with changes in body functions and with a relative loss of water and an increase in adipose tissue. The most important pharmacokinetic change characterizing old age is a decrease in the kidney excretory capacity. Tenofovir, which is renally excreted, has been shown to cause toxicity more frequently in older HIV-infected individuals. Alteration in the rate of hepatic drug metabolism with advancing age is less clear and data on antiretroviral concentrations in older patients are scarce. However, lopinavir, atazanavir and darunavir have all been shown to achieve higher exposures in older individuals. The clinical consequences of these findings are unclear and no recommendations, to date, exist on individual dose adjustment in the ageing population. Nevertheless, the increased drug exposure in the elderly raises interest in the measurement of ARV drug plasma concentrations to monitor pharmacotherapy in this age group.

Furthermore, TDM is useful in a population where polypharmacy and the increased risk of significant drug interaction are common. Because of polypharmacy, collaboration with patients’ regular doctors is vital and one of the main objectives of the dedicated clinic is to strengthen communications with general practitioners (GPs) and social services when needed.

RESULTS

General

From the time of clinic inception (January 2009) to August 2011 we have seen 150 patients. Seven percent were women...
and median (range) age was 58 (50–88) years. The commonest ethnicity was white Caucasian (89%) followed by black African (9%) and Asian (2%). Median (range) duration of HIV infection was 14 (2–26) years, suggesting that the population included both individuals with long-term infection and others with more recent HIV acquisition. All patients seen were on cART and 38% (57/150) were on three or more non-HIV medications.

**Coronary artery calcium score**

Seventy individuals with no prior history of ischaemic heart disease underwent assessment by CACS. CAC scores revealed significant correlation with age ($P = <0.001$) and Framingham risk scores ($P = 0.047$). In our care pathway, those with a CAC score greater than 75th percentile on age and sex matching qualify for lipid lowering therapy. Fifteen (21%) individuals met these criteria, of these eight (53%) had 10 year Framingham risk scores less than 20% so may have been deemed otherwise of too low CV risk and eight (53%) were not on lipid-lowering agents.

**Neuropsychometric assessment**

The current neuropsychometric algorithm was introduced in September 2010; after careful discussion, considering the lack of guidance on screening for, and lack of interventions to treat, NCI, we elected to screen only patients for whom concerns had been noticed (by themselves or others). It was felt screening asymptomatic individuals could lead to undue distress. If guidance changes or new evidence emerges this will be revised. Forty-six HIV-infected individuals were evaluated between September 2010 and August 2011. Of these, median age was 58 (range 50–74) years, 93% were men and 98% were on ART. All were administered GAD-7 and PHQ-9 questionnaires. Twenty-four percent exhibited moderate to severe anxiety by GAD-7 and of the three with severe anxiety, one had already commenced amitryptiline and was experiencing improvement, one was referred to psychiatry (outcome pending) and one declined psychiatric assessment but did agree to formal neuropsychometric testing (result pending). By PHQ-9, 32% had moderate to severe depressive symptoms were referred to their GP or to psychology services. Twenty-one individuals reported concerns (theirs or others) regarding memory, attention and cognition so were also administered EMQ and IHDS. EMQ scores were impaired in four (19%) and IHDS scores were low ($\leq 10$) in six (30%). To date, six have undergone brain magnetic resonance imaging scanning (all normal) and have been referred for formal neuropsychometric testing (results pending); for the remainder repeat testing is planned. Longer-term follow-up is not available at present but will be reviewed at a future date.

**Bone mineral density**

To date, 120 individuals have undergone dual-energy X-ray absorptiometry scanning for the first time, 118 men and eight women. The rates of osteoporosis and osteopaenia, overall and by gender, are shown in Table 2. Low BMD appears very common in women although these results should be interpreted with caution due to low numbers of female patients.

**Table 2 Bone mineral density results**

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 111)</th>
<th>Female (n = 8)</th>
<th>Overall (n = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>17 (15%)</td>
<td>4 (50%)</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Osteopaenia</td>
<td>41 (37%)</td>
<td>3 (38%)</td>
<td>44 (36%)</td>
</tr>
<tr>
<td>Normal</td>
<td>53 (48%)</td>
<td>1 (12%)</td>
<td>54 (45%)</td>
</tr>
</tbody>
</table>

**PSA results**

Of 127 men seen in the clinic since the introduction of routine PSA measurement, 125 have results available. Using age-adjusted cut-offs (age 50–59, PSA 3 ng/mL or more; age 60–69, PSA 4 ng/mL or more; age 70 plus, PSA more than 5 ng/mL), 13 men had PSA values greater than the upper limit of normal for their age. Outcomes are as follows:

- Four continue to be monitored in the over 50 clinic;
- Four diagnosed with prostate adenocarcinoma, who were referred for specialist management;
- One repeated after three months and PSA normal;
- Four treated with 30 days antibiotics:
  - One normalized;
  - One awaiting outcome;
  - Two PSA remained high and under urology follow-up.

**Polypharmacy and drug–drug interaction assessment**

Overall, 50% of the patients seen were on polypharmacy. Examples of significant drug–drug interactions are as follows:

- Simultaneous intake of omeprazole 40 mg daily and atazanavir/ritonavir 300/100 mg once daily;
- Simvastatin 40 mg daily with and nevirapine 400 mg daily and no cholesterol response;
- Darunavir/ritonavir 800/100 mg once daily with concomitant amlodipine 10 mg once daily or other calcium channel blockers, resulting in CV adverse effects.

**Therapeutic drug monitoring**

TDM results for tenofovir ($n = 52$), efavirenz ($n = 77$) and darunavir ($n = 34$) were reviewed. In our small cohort of older HIV-infected individuals, plasma concentrations of efavirenz were not markedly different when compared with data in younger patients.

On the other hand, the predicted clearance of ritonavir-boosted darunavir was lower and drug exposure was higher for patient’s older than 50 years of age, following once daily dosing, confirming that it is essential to continue collecting data for all currently used antiretrovirals over a wide age range.

Tenofovir plasma concentrations correlated inversely with estimated glomerular filtration rate, consistent with data in the literature. Furthermore, increasing age was significantly associated with lower tenofovir clearance and higher plasma drug exposure. Patients older than 60 years showed higher drug concentrations than younger individuals.
suggesting the need for close renal function monitoring in this population.

In terms of drug–drug interactions, to date 21% of individuals attending the clinic have undergone an intervention (dose adjustment or medication change to either their antiretroviral or the co-administered non-antiretroviral drug).

SERVICE DEVELOPMENT

Our over 50 clinic remains under regular review and screening procedures are updated regularly. As well as optimizing current, and introducing new, screening procedures, this clinic provides an ideal opportunity to carry out age-related research, audit and service evaluation. All individuals attending the clinic are offered the possibility of signing a written consent form to allow publication of data emerging from the Clinic. Planned service developments include the possibility of introducing routine anal cytology and we are planning to commence a research project investigating serological markers of inflammation among clinic attendees. Finally, as we plan to continue and expand the service we will be consulting with GPs and plan to involve primary care representatives on an ongoing basis.

CONCLUSIONS

HIV-infected individuals aged 50 years or older in long-term follow-up at Chelsea and Westminster Hospital have the opportunity of attending a dedicated over 50 clinic. This clinic enables the ongoing assessment of targeted screening tests in HIV-infected patients to best define their clinical utility and cost-effectiveness. Improved knowledge on HIV and ageing through such methods will facilitate clearer screening guidelines for HIV-infected patients and development of future care pathways, particularly in community and GP settings.

In our two-year experience, HIV-infected patients over 50 years of age were found to have pathologies only detected by targeted screening. The clinic has served to improve GP liaison and closer working relationships with other specialties.

Important limitations include lack of longer-term follow-up, particularly with regard to CV and neurocognitive assessment; these data will be reviewed regularly and we expect more information on outcomes with time. In addition, in the absence of a formal comparative study we cannot state that outcomes have improved within this service. However, most of the assessments are recommended in consensus guidelines and we have highlighted cases where a serious condition may have remained otherwise undetected.

The majority of patients reacted positively to the clinic, particularly as many do not routinely access their GP.

ACKNOWLEDGEMENTS

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