Research Review Speaker Series™

Beyond HIV – endocrine comorbidities and ageing

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About the speaker

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Dr. Brown is an Associate Professor of Medicine and Epidemiology in the Division of Endocrinology, Diabetes and Metabolism at Johns Hopkins University, where he is also the primary endocrine consultant to the Johns Hopkins HIV Clinic. His research focuses on metabolic, endocrine and skeletal abnormalities observed in patients with HIV infection, particularly as related to ageing. He is a co-investigator in the Multicenter AIDS Cohort Study and the AIDS Clinical Trial Group. In the MACS, he is the Chair of the Metabolic Working Group. In the ACTG, he is a member of the Inflammation/End organ Disease Transformative Science Group and serves in leadership positions on multiple studies.

In this review:

Abbreviations used in this review

BMD = bone mineral density
BP = blood pressure
COPD = chronic obstructive pulmonary disease
CRP = C-reactive protein
CV = cardiovascular
DPP = dipeptidyl peptidase
DXA = dual energy x-ray absorptiometry
GI = gastrointestinal
GLP = glucagon-like peptide
HbA_{1c} = glycosylated haemoglobin
H/LDL = high/low-density lipoprotein
HIV = human immunodeficiency virus
MI = myocardial infarction
NNRTI = non-nucleoside reverse transcriptase inhibitor
NPH = neutral protamine Hagedorn
OR = odds ratio
PI = protease inhibitor
PSA = prostate specific antigen
PTH = parathyroid hormone
QOL = quality of life
SGLT = sodium-glucose transport protein
TSH = thyroid stimulating hormone
TNF = tumour necrosis factor

This review summarises a webinar presented by Dr. Todd Brown in Sydney, Australia, on Sept 03, 2015. Dr. Brown addressed issues faced by physicians when deciding on the optimal evaluation and treatment of endocrine and metabolic problems in patients with HIV infection.

Endocrine and metabolic conditions are prevalent among HIV-infected persons

Endocrine and metabolic abnormalities are common in patients with HIV infection. The problems of osteoporosis, diabetes, dyslipidaemia and hypogonadism are also problems that increase in frequency with ageing. Indeed, many commonalities exist between chronic HIV infection and ageing, including inflammation, which is currently a major area of research. We know that, even with effective metabolic therapy and suppressed viral loads, chronic inflammation arises, which may lead to a host of problems and may influence some of the metabolic problems that were covered in the webinar.

Osteoporosis, diabetes, dyslipidaemia and hypogonadism lead to clinical problems that are quite severe and of concern: fracture, CV disease, frailty and decreased QOL. The hope is that by controlling some of these outcomes, endocrine and metabolic abnormalities can be mitigated.

BONES

Osteoporosis and fractures are quintessential diseases of ageing. US fracture incidence data show an exponential increase in the risk of fracture among women from around 65 years of age; the same phenomenon occurs in men from around 70 years.[1] Fracture prevalence rates differ among patients with HIV infection. Data from a large US healthcare system identified an increased risk of fracture in HIV-positive patients from age ~40 years in women and ~30 years in men (Figure 1).[2] These data also showed how the difference in fracture prevalence between HIV-infected and non-HIV-infected patients appeared to increase with increasing age. For patients approaching their 60s and 70s, this interaction between age and HIV infection can be of great concern.

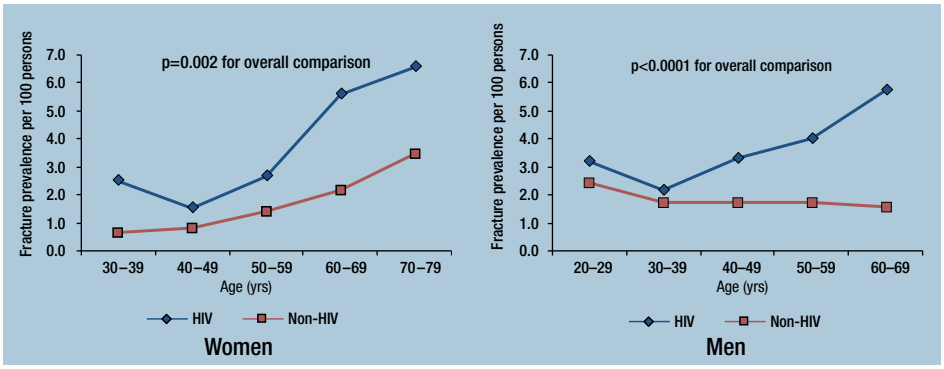

Figure 1. Fracture prevalence in HIV-infected and non-HIV-infected individuals in MGH/Partners Healthcare System: 1996–2008[2]

One of the underlying problems with fracture is osteoporosis. This is a common problem in patients with HIV infection. A meta-analysis performed in 2006 involving data from 20 clinical studies concluded that the overall prevalence of osteoporosis in HIV-infected patients was ~15% – a >3-fold greater prevalence compared with HIV-uninfected controls.[3] This suggests that fracture is a real problem, which may underlie at least some of the risk of fracture in HIV infection.

Pathophysiology and risk factors

Comorbidities associated with HIV infection that conspire to increase the risk of low bone density include HIV disease factors (inflammation and viral proteins, leading to increased bone resorption and decreased bone formation), medication factors (tenofovir, certain PIs, and antiretroviral therapy initiation is associated with a decrease in BMD of ~2–6% over 96 weeks) and patient-related factors (low bodyweight, smoking, alcohol use, opioid use, hepatitis C co-infection, physical inactivity, hypogonadism, low vitamin D).

To screen or not to screen? Who to screen?

A case presentation illustrated dilemmas around decisions to screen for osteoporosis. A 62-year-old white male was referred to the lipodystrophy clinic for bodyfat changes. He was diagnosed with HIV infection in 1987, with a nadir CD4 count of 22 cells/mm^3. He received stavudine/lamivudine/indinavir (d4T/3TC/IDV) from 1997 to 2002, and his regimen

at the time of reporting consisted of tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV). He had a history of hypogonadism on transdermal testosterone. He also had a history of COPD as well as a 60-pack-year smoking history treated with multiple steroid courses. He had no history of fracture and no height loss.

Guidelines for DXA screening issued in 2014 by the US NOF (National Osteoporosis Foundation) recommend including:[4]

- individuals with a fragility fracture after age 50 years
- women aged ≥65 years and men aged ≥70 years
- younger postmenopausal women and men aged 50–69 years with clinical risk factors for fracture
- adults with a condition (e.g. rheumatoid arthritis) or taking a medication (e.g. glucocorticoids in a daily dose ≥5mg prednisone or equivalent for ≥3 months) associated with low bone mass or bone loss.

Similar screening recommendations for the prevention and treatment of osteoporosis in postmenopausal women and older men were issued in 2010 by the RACGP (Royal Australian College of General Practitioners).[5]

- Any fracture following minimal trauma.
- Presence of major risk factors (e.g. age >60 years, hypogonadism, >3 months glucocorticoid use and other conditions associated with low bone density).

In 2014, a multinational group of HIV specialists agreed on a set of recommendations regarding the screening, diagnosis and monitoring of bone disease in adults with HIV infection.[6]

- DXA should be performed in all postmenopausal women and in men aged ≥50 years, patients with a history of fragility fracture, chronic glucocorticoid use (≥5mg × 3 months) or at high risk of falls (at any age).

In patients aged 40–50 years, the 10-year risk of fracture should be assessed using FRAX (Fracture Risk Assessment Tool);[7] those with a FRAX score of >10% should also undergo BMD measurement by DXA.

A DXA scan of the man in the case presentation revealed low bone density T-scores (–2.2 in the L1–L4 spine; –2.2 femoral neck; –2.3 total hip). Using DXA in a functional definition, the WHO categorises osteoporosis as a T-score of <–2.5, osteopenia as a T-score of –1.0 to –2.5 and normal bone mass as a T-score of >–1.0. The following caveats exist with DXA scans:

- the Z-score (<–2.0) is preferable over the T-score in men aged <50 years and in premenopausal women
- although DXA predicts a 1.5- to 3-fold increased risk of fracture for each standard deviation decrease, BMD explains only ~50% of fracture risk
  - DXA fails to detect other bone factors, such as bone quality, and falls, which are critical considerations in the overall risk of fracture.

When the DXA score indicates low BMD, the 2010 RACGP guidelines advise excluding and treating causes of secondary osteoporosis. Dr. Brown's clinical practice is to look for:

- vitamin D deficiency (blood 25-hydroxyvitamin D)
- hyperparathyroidism (PTH, dietary calcium)
- subclinical hyperthyroidism (TSH)
- hypogonadism in males (free testosterone)
- phosphate wasting (fractional excretion of phosphate).

Whenever there is any clinical indication, testing also includes:

- idiopathic hypercalciuria (24-hour urinary calcium)
- coeliac sprue (tissue transglutaminase)
- multiple myeloma (serum protein electrophoresis)
- mastocytosis (serum tryptase)
- Cushing's syndrome (24-hour urinary free cortisol).

Dr. Brown stressed the critical importance of vitamin D deficiency and phosphate wasting among secondary causes of low BMD. In this setting, a low BMD may not be osteoporosis; the bone matrix might be adequate. The clinical syndrome of osteomalacia is associated with impaired bone mineralisation and may be accompanied by weakness, fracture, pain, anorexia and weight loss. Importantly, the condition is treated with vitamin D, dietary calcium, with or without phosphate, and stopping tenofovir. Bisphosphonates are contraindicated. Osteomalacia is the most important differential diagnosis for low BMD.

For cases without any secondary causes, the 2014 US NOF guidelines outline which patients should be treated (applies to postmenopausal women and men aged ≥50 years).

- Those with hip or vertebral fractures.
- Those with BMD T-scores ≤–2.5 at the femoral neck, total hip or spine on DXA.
- Those with T-scores between –1 and –2.5 (osteopenia) at above sites AND 10-year hip fracture probability ≥3% or 10-year all major osteoporosis-related fracture ≥20% based on FRAX model.

Based on FRAX scores, the case patient has a risk of major osteoporotic fracture of 18% (below the threshold) and a hip fracture risk of 4.1% (above the threshold), so in the US, he would probably be treated.

In Australia, the PBS (Pharmaceutical Benefits Scheme) funds alendronate and risedronate for women and men with osteoporotic fracture, and for women and men aged ≥70 years without prevalent fracture, but with a T-score of ≤–2.5 at the lumbar spine or femoral neck.

Various management options are available for increasing BMD and decreasing fracture risk. General recommendations include:

Calcium/vitamin D supplementation (i.e. vitamin D_3 1000IU)

- Smoking cessation, alcohol reduction
- Weight-bearing exercise
- Assess fall risk (ask 'are you worried about falling?')
  – refer to physical therapy for strength/balance training.

Treatment options include:

- Bisphosphonates
- Selective oestrogen receptor modulator
- Oestrogen
- PTH analogue
- Strontium ranelate.

Is it appropriate to switch from tenofovir to another reverse transcriptase inhibitor in the case patient, who has a high FRAX score and other risk factors? Dr. Brown and colleagues recommend switching from TDF to abacavir or raltegravir instead.[6] In patients on a PI-based regimen, switching to an alternative such as raltegravir may be appropriate.[8] The available data that support these recommendations are from the OsteoTDF pilot study (switching from tenofovir to abacavir resulted in increases in hip and decreases in spine BMD at week 48),[9] the TROP study (switching from tenofovir to raltegravir significantly increased spine and hip BMD at week 48 in patients with osteopenia/osteoporosis taking a ritonavir-boosted PI),[10] and a study of a single-tablet antiretroviral regimen without dose adjustment in HIV-positive patients with mild-to-moderate renal impairment (switching from tenofovir- and non-tenofovir-containing regimens to elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide significantly increased hip and spine BMD at week 48).[11]

TAKE HOME MESSAGES

- DXA screen HIV-infected men aged >50 years and postmenopausal women
- Treatment guidelines should follow those established for the general population
- Remember secondary causes
- Consider switches of TDF in those at higher risk

DIABETES

Diabetes is a very common condition with rapidly increasing prevalence, particularly in the developing world. Diabetes is a leading cause of CV disease, blindness, end-stage renal disease, amputations and hospitalisations. It is common in HIV-infected populations. While diabetes can be controlled, management is complicated by the plethora of medications available and must be individualised to the patient.

Pathogenesis of diabetes in HIV-infected patients

- Antiretroviral medication factors
  - thymidine analogues and older PIs (strong effects upon glucose metabolism)
- HIV factors
  - residual immune activation/inflammation (affect glucose uptake)
- Host factors
  - adiposity
  - hepatitis C virus infection
  - genetic factors (family history, race)
  - concomitant medications: corticosteroids/ atypical antipsychotics

Case presentation

- 53 year-old African American male, HIV-positive for 20 years, on ART since 2000
- Viral load <50 copies/mL
- TDF/FTC/EFV
- Mild/moderate lipoatrophy of face/buttocks/ thighs
- Mild hypertension, normal lipids, no smoking
- Strong family history of diabetes
- BMI 27 kg/m^2

Who should be screened for diabetes?

The IDSA (Infectious Diseases Society of America) guidelines advise screening for diabetes prior to ART, within 4–6 weeks after ART initiation and every 6–12 months thereafter.[12] These guidelines have remained essentially unchanged for the last decade. In Dr. Brown's opinion, it may not be necessary to screen so often, as the newer ART regimens are less diabetogenic; he recommends yearly fasting glucose assessments. The RACGP diabetes screening guidelines focus on individuals who are at excess risk for type 2 diabetes.[13]

How to screen for diabetes?

RACGP diagnostic criteria for type 2 diabetes stipulate:

- Fasting plasma glucose level ≥7.0 mmol/L, on two separate occasions
- 2-hour postprandial glucose level ≥11.0 mmol/L on oral glucose tolerance test, on two separate occasions
- HbA_{1c} level ≥48 mmol/mol (≥6.5%), on two separate occasions

The HbA_{1c} has several advantages over fasting plasma glucose level and oral glucose tolerance tests, including greater convenience (fasting is not required), evidence to suggest greater pre-analytical stability and less day-to-day perturbations during periods of stress and illness. However, HbA_{1c} measurements can be problematic. Clinical practice recommendations issued by the American Diabetes Association in 2013 contained the caveat that *"for conditions with abnormal red cell turnover..., the diagnosis of diabetes must employ glucose criteria exclusively"*.[14] People with abnormal red cell turnover include HIV-infected patients on ribavirin, which is associated with haemolytic anaemia. Moreover, HbA_{1c} testing underestimates glycaemia in HIV infection (Figure 2).[15] Such findings make Dr. Brown hesitant about using HbA_{1c} as a diagnostic criteria in people who are not very hyperglycaemic.

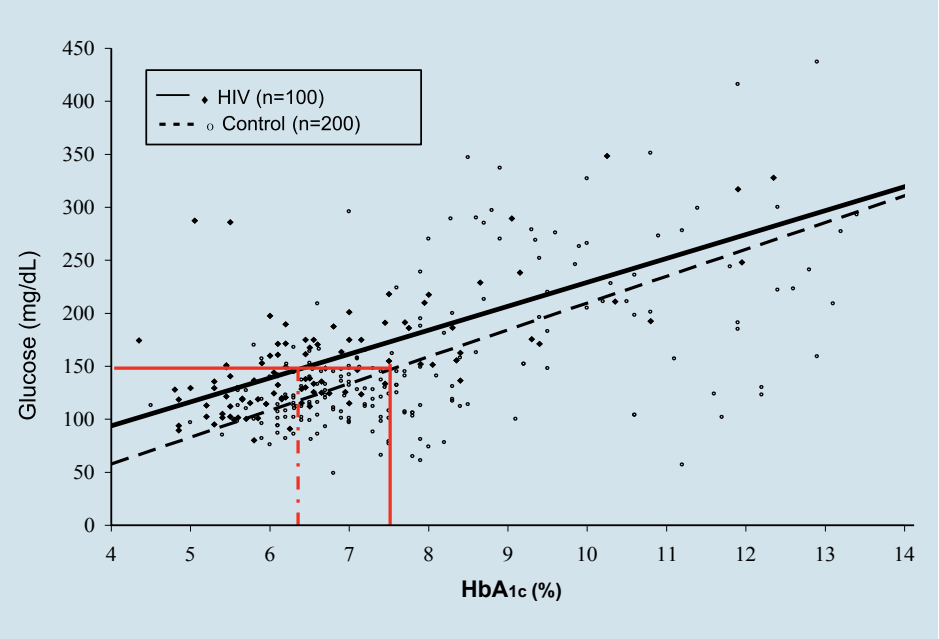

Figure 2. HbA_{1c} underestimation of glycaemia in HIV-infected patients

For diabetes screening in HIV-infected persons, Dr. Brown performs a fasting glucose. If the glucose level is 5.7–6.9 mmol/L (100–125 mg/dL), consider 75g oral glucose tolerance test. He tends to avoid HbA_{1c} for screening (particularly in those on abacavir, low CD4 count, PIs, high MCV concentration).

The man in the case presentation had a fasting glucose level of 8.05 mmol/L (145 mg/dL) and an HbA_{1c} level of 51 mmol/mol (6.8%).

Following a diagnosis of diabetes mellitus, what are the next steps?

Universal agreement supports lifestyle modification. An important message for patients is that weight loss does not have to be substantial to be metabolically relevant. In one study, a modest goal weight loss of 7% decreased the incidence of diabetes by 58% among people on a diabetes prevention programme participating in 150 minutes per week of exercise and caloric restriction.[16] Similarly, a 7% weight loss was associated with a 57% reduction in TNF-α and a 30% reduction in CRP levels among obese persons who reduced their dietary intake by 500 calories per day over 8 weeks.[17]

There is also universal agreement for metformin as the first-line drug for diabetes. Advantages include a decrease in HbA_{1c} level of ~1%, a long track record of no hypoglycaemia, no weight gain and possible CV disease benefit. Disadvantages include GI side effects, rare cases of lactic acidosis and the following contraindications:

- chronic kidney disease (serum creatinine level >1.4 in women and >1.5 men)
- hypoxia
- decompensated liver disease
- severe congestive heart failure
- alcohol abuse
- past history of lactic acidosis.

In Dr. Brown's opinion, reports of worsening lipoatrophy are small in magnitude (imperceptible to the patient) and do not merit avoidance of metformin.

Uncertainty surrounds the use of combination therapy. Choices consist of sulfonylureas, glitazones, acarbose, insulin and the incretins (GLP-1 analogues, DPP-4 inhibitors, SGLT-2 inhibitors).

The 2014 Australian Diabetes Society Position Statement supports the use of lifestyle measures (diet, exercise, bodyweight control), metformin as first-line therapy unless contraindicated or not tolerated, with sulfonylureas the recommended initial second-line agent to add to metformin, or if contraindicated or not tolerated, another agent is recommended (DPP-4 inhibitor, GLP-1 receptor agonist, SGLT-2 inhibitor, insulin, acarbose or a thiazolidinedione).[18] Choice depends on the individual patient's risk factor profile and factors associated with each drug (see table 1.)

Table 1. Advantages and disadvantages of antidiabetic medications

Advantages	Disadvantages
Sulfonylureas	
HbA_{1c} level decrease of ~1% Proven clinical utility Decrease in microvascular events Cheap	Bodyweight gain Hypoglycaemia High failure rate
Pioglitazone	
HbA_{1c} level decrease of ~1% No hypoglycaemia Possible CV disease benefit Increase in HDL cholesterol level Lowering of triglyceride levels Decrease in liver fat Some decreases in inflammation Low failure rate May have a modest effect on lipoatrophy (~200–500g)	Bodyweight gain (max 0.5kg) Fluid retention/congestive heart failure Macular oedema Osteoporosis/fracture Bladder cancer
Acarbose	
Lack of hypoglycaemia Possible CV disease benefit	Small lowering in HbA_{1c} level (~0.5%) Flatulence Diarrhoea Elevations in liver function tests
Insulin	
Unlimited HbA_{1c} level lowering Decreased incidence of microvascular events	Hypoglycaemia Bodyweight gain Lingering concerns about mitogenic effects Psychological barrier to use of an injectable
GLP-1 analogues	
HbA_{1c} level decrease of ~1% No hypoglycaemia Bodyweight loss Some evidence for decreases in inflammatory markers (independently of their weight loss properties)	GI side effects Possible increased risk of pancreatitis/pancreatic cancer (data are conflicting) No CV disease benefit
DPP-4 inhibitors	
No hypoglycaemia Bodyweight neutral Possible decrease in inflammation	Smaller decrease in HbA_{1c} level (~0.5%) GI side effects Possible increased risk of pancreatitis/pancreatic cancer (data are conflicting) Hypersensitivity reactions No CV disease benefit Heart failure
SGLT-2 inhibitors	
Some weight loss (~2kg) Reduction in BP No hypoglycaemia (when used as monotherapy)	Urinary tract infections/candidiasis Polyuria Potential for dehydration

Insulin is the recommended first-line therapy if HbA_{1c} level >75 mmol/mol (>9%) or if patient has severe liver disease or kidney disease or hypertriglyceridaemia. In clinical practice, Dr. Brown starts with bedtime glargine, detemir or NPH (10–15U, increased by 2–3U every 3 days until fasting glucose level is <6.6 mmol/L [120 mg/dL]). Prandial insulin is added if not at goal.

GLP-1 is an important regulator of glucose homeostasis. Neuroendocrine cells in the gut release GLP-1, which increases β-cell response in the pancreas by enhancing glucose-dependent insulin secretion. GLP-1 promotes satiety and reduces appetite. The GLP-1 pathway can be manipulated in one of two ways: i) with an injectable GLP-1 analogue (exenatide, liraglutide, exenatide LAR, dulaglutide, albiglutide, lixisenatide); or ii) with an oral DDP-4 inhibitor (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin).

SGLT-2 inhibitors, or 'gliflozins', are the newest class of drugs (dapagliflozin, canagliflozin, empagliflozin). They lower glucose via an insulin-independent mechanism; blocking SGLT-2 increases glucose excretion. Recently, the US FDA has reported cases of diabetic ketoacidosis, which need further investigation. Emerging evidence indicates CV disease benefit in phase 4 trials involving empagliflozin. As yet, it is unclear as to where these drugs will fit into the therapeutic armamentarium. Dr. Brown generally chooses sulfonylureas when selecting the next drug to add to metformin.

What should be the glycaemic target?

Clinical data support a target of <7%. The UKPDS demonstrated that an increased incidence of microvascular and macrovascular complications of diabetes was associated with rising HbA_{1c} levels; the incidence was greatly increased with HbA_{1c} levels ≥7%.[19] A meta-analysis of clinical data has shown that intensive glucose control (target <6%) in adults with type 2 diabetes reduces the risk for some CV disease outcomes (e.g. nonfatal MI) but does not reduce the risk for CV death or all-cause mortality, and increases the risk for severe hypoglycaemia.[20] Moreover, long-term follow-up data demonstrate a 'legacy effect' of hypoglycaemia associated with intensive glucose control in patients with type 2 diabetes.[21] Dr. Brown emphasised an important message for patients is illustrated by the outcomes from the 10-year follow-up of the UKPDS.[21] Over time, the HbA_{1c} curves for the two treatment groups (conventional therapy, sulfonylurea-insulin) decreased and converged. However, the risk of MI remained lower at 10 years of follow-up in those who were intensively treated. This suggests that current glycaemic control has a huge impact on health outcomes in the long-term.

The Australian Diabetes Society recommends that individualisation of HbA_{1c} level goal is key. Tighter control (6.0–6.5%) is recommended for younger, healthier individuals, whereas looser control (7.5–≥8.0%) can be considered for older people and those who are prone to hypoglycaemia or have comorbidities.

Prevention of complications is multifaceted

Prevention of microvascular problems: retinopathy (yearly ophthalmological exams), nephropathy (BP control, spot urine microalbumin every 6–12 months, ACE inhibitor/ARB with microalbuminuria or hypertension, lipid control), neuropathy (foot exams every 6–12 months, instruction in foot care, podiatry if evidence of neuropathy).

To prevent macrovascular problems, pay attention to the 'ABCDS' CV risk factors: Antiplatelet therapy, BP, Cholesterol, Diabetes/glucose management and Smoking cessation. A target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of CV and microvascular events by about 50%.[22]

TAKE HOME MESSAGES

- Regularly screen for diabetes
- Avoid HbA_{1c} level for diagnosis
- Lifestyle changes are critical
- Metformin first
- Individualise second- and third-line drugs
- HbA_{1c} level goal is <53 mmol/mol (<7%) in most, but should be individualised
- Use multipronged approach to prevent complications

DYSLIPIDAEMIA

HIV infection is associated with an increased risk of CV disease. This section focused on lipids as one of the possible causes. The following case presentation illustrated questions around lipid control. A 53-year-old white male, diagnosed with HIV in 1990 was started on stavudine/lamivudine/indinavir (d4T/3TC/IDV) in May 1996 and was receiving tenofovir/emtricitabine/lopinavir/ritonavir (TDF/FTC/LPV/r) at the time of reporting. His CD4 count was 460 cells/mm^3 and his viral load was undetectable. His course was complicated by lipoatrophy and hyperlipidaemia. He was treated with rosuvastatin 5 mg/day and gemfibrozil 600mg twice daily. His coronary artery risk factors were 2 pack/day smoking and a family history of MI (father at age 55 years). His total cholesterol level was 7.31 mmol/L (283 mg/dL), his triglyceride level was 3.7 mmol/L (330 mg/dL) and his HDL, LDL and non-HDL cholesterol levels were 0.91 mmol/L (35 mg/dL), 4.7 mmol/L (182 mg/dL) and 6.67 mmol/L (258 mg/dL), respectively.

How best to treat the lipid profile?

The initial ATP (Adult Treatment Panel) III guidelines issued in 2001 prioritise lowering triglycerides in patients with elevated triglycerides (>5.6 mmol/L [500 mg/dL]) to reduce the risk of pancreatitis.[23] If triglyceride level is not elevated, the primary focus should be LDL cholesterol.[23] These guidelines were supported for many years in the US and worldwide by clinical trial data confirming the benefit of the ATP III treatment goals.[24] However, in 2013, the ACC/AHA (American College of Cardiology and American Heart Association) issued guidelines that discarded the ATP III treatment goals.[25] These new guidelines recommend intensity of statin therapy (see table 2) in the following four groups:

- Individuals with known atherosclerotic CV disease (high-intensity statin therapy)
- Individuals with LDL cholesterol level ≥190 mg/dL (high-intensity statin therapy)
- Individuals aged 40–75 years with diabetes and LDL cholesterol level 70–189 mg/dL (moderate-intensity statin therapy; high-intensity reasonable if risk >7.5%)
- Individuals aged 40–75 years with estimated 10-year atherosclerotic CV disease risk ≥7.5% and LDL cholesterol level 70–189 mg/dL (moderate- to high-intensity statin therapy)

Table 2. High-, moderate- and low-intensity statin treatment

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL cholesterol by ~≥50%	Daily dose LDL cholesterol by ~30–50%	Daily dose lowers LDL cholesterol by <30%
Atorvastatin (40)–80mg Rosuvastatin 20 (40)mg	Atorvastatin 10 (20)mg Rosuvastatin (5) 10mg Simvastatin 20–40mg Pravastatin 40 (80)mg Lovastatin 40mg Fluvastatin XL 80mg Fluvastatin 40mg twice daily Pitavastatin 2–4mg	Simvastatin 10mg Pravastatin 10–20mg Lovastatin 20mg Fluvastatin 20–40mg Pitavastatin 1mg

The ACC/AHA guidelines have been controversial. The major differences between the prior and new guidelines follow:

- risk calculator is derived from four different cohorts and includes both MI and stroke
- no LDL cholesterol or non-HDL cholesterol treatment initiation thresholds or treatment targets
- sole focus on statins
- focus on adherence
- no recommendations regarding combination therapy for hypertriglyceridaemia or high non-HDL cholesterol.

In contrast, the Australian guidelines for the assessment and management of absolute CV disease risk have retained the treatment targets.[26] People are stratified by risk (i.e. high, moderate, or low) – those at high risk should be treated to target; moderate risk should be treated to target if fails to achieve target after 6 months of lifestyle intervention, has a family history of CV disease or of Aboriginal/Torres Strait Islander, South Asian, Middle Eastern, Māori, Pacific Islander ethnicity. Statins are considered to be first-line. If LDL cholesterol is not at goal, the guidelines advise adding ezetimibe, a bile acid sequestrant or niacin. If triglyceride level is elevated, consider fenofibrate, niacin or omega-3 fatty acids.

In reference to the cholesterol panel of the case patient, the AHA/ACC 10-year risk of first atherosclerotic CV disease event was 19.6% (clincalc.com), whereas the Australian 5-year risk was 15% (cvdcheck.org.au) – statin therapy is necessary. Atorvastatin and rosuvastatin are probably the most appropriate, but their interaction with CYP3A4 inhibitors limits the dose of atorvastatin to 40 mg/day and rosuvastatin to 20 mg/day.[27–31] Management steps include diet and exercise, smoking cessation, increasing the rosuvastatin dose (maximum dose on PI, 20mg), switching from lopinavir/ritonavir to either darunavir/ritonavir or atazanavir/ritonavir, integrase inhibitor or an NNRTI, e.g. rilpivirine, etravirine (not efavirenz, which tends to decrease statin levels).[32] If fibrate therapy is retained, switch to fenofibrate to avoid the risk of muscle toxicity.

TAKE HOME MESSAGES

- Risk stratification is critical
- Statins are first-line – role of other lipid-lowering therapies is unclear
- Switching off PIs/efavirenz may be a good strategy in conjunction with statins
- Integrase inhibitors and newer NNRTIs are the most lipid-friendly and have the fewest interactions with statins

HYPOGONADISM

Changes that occur in the hypothalamic-pituitary-gonadal axis with ageing include:

- testosterone decrease with increasing age
  - it is unclear whether this is an ageing effect or due to accumulation of comorbidities
- low testosterone in the ageing population is associated with multiple adverse outcomes (e.g. fracture, CV disease)
  - is this a causal role or disease marker?
- testosterone has a diurnal rhythm with peak levels 6–8am
  - variation decreases with ageing
- testosterone is 98% protein-bound (sex hormone-binding globulin, albumin)
  - In conditions that alter sex hormone-binding globulin (HIV, ageing), free testosterone may be more accurate than total testosterone.

For a diagnosis of androgen deficiency in HIV-infected men, start with symptoms consistent with androgen deficiency with no other obvious explanation. Obtain morning free testosterone levels (repeat to confirm).[33] After diagnosing hypogonadism, establish the cause (low testosterone level, low or normal luteinising hormone plus follicle-stimulating hormone = secondary hypogonadism; low testosterone, high luteinising hormone plus follicle-stimulating hormone = primary hypogonadism).[34]

It is uncertain as to whether testosterone replacement will benefit or harm an older patient with a low testosterone level. Potential benefits of testosterone therapy in older men include decreased fat mass, increased lean mass, increased muscle strength, improvements in physical function, bone health, QOL, sexual function and cognition. Adverse effects include male pattern balding, acne/sebum, lower spermatogenesis, gynecomastia, erythrocytosis, sleep apnoea and, of most concern, prostate and CV events. Meta-analysis data show a higher rate of prostate events among middle-aged and older

men in testosterone replacement trials.[35] The prevailing view is that testosterone replacement does not cause prostate cancer but may unmask a dormant tumour. In another meta-analysis of CV events in testosterone trials, the data indicate that testosterone use is harmful with a pooled OR of 1.82 (not statistically significant).[36] Good-quality data from large-scale clinical trials are lacking.

Suggested monitoring during testosterone replacement therapy includes measurement of testosterone levels, PSA level, haematocrit/haemoglobin, digital rectal exam and IPSS (International Prostate Symptom Score) or equivalent.

TAKE HOME MESSAGES

- Presenting signs and symptoms of hypogonadism are nonspecific
- Use quality free testosterone assays to make a diagnosis with a morning measurement
- Long-term benefits/risks unclear
- Consider a trial of testosterone therapy in men with signs/symptoms of hypogonadism AND a low free testosterone level

CASE STUDY

The final session presented the case of a 56-year-old man diagnosed with HIV infection in 1985 who developed an AIDS-defining illness of Pneumocystis pneumonia in 1994 and HIV-associated neurological disease in 2012. Comorbidities included hepatitis B virus infection (1999), peripheral neuropathy (2003), lipodystrophy (2005), insulin-dependent diabetes (2005) and acute MI (2010), and he consumes alcohol and smokes cigarettes on a daily basis. Early treatment included stavudine, lamivudine, saquinavir, nelfinavir and ritonavir-boosted indinavir. He was switched to efavirenz, ritonavir-boosted atazanavir and enfuvirtide after developing resistance in 2005, with tenofovir added soon after. In 2007 he had virological suppression and his CD count had increased to ~650 cells/μL, and he started a regimen of tenofovir, lamivudine, etravirine, ritonavir-boosted darunavir and raltegravir.

Bone problems

The man fractured his left foot with minimal trauma in 2009. Suggested investigations were FRAX score, Framingham score, DXA scan, urinalysis, and calcium phosphate, urea, creatinine and vitamin D levels. Spinal plain film for silent vertebral fracture could also be considered, as these can be quite common in the absence of clinical osteoporosis. DXA scan revealed total hip and spine T-scores of –2.2 and –1.2, respectively. He experienced stress fractures in his right distal tibia and cuboid in 2010 and in his right foot in 2011.

Kidney disease

The man developed mild chronic renal failure in 2010 with mild proteinuria, and his estimated GFR at the time of reporting was <60 mL/min/1.73m^2. Switching off tenofovir was discussed, but problems were identified, including his hepatitis B virus status and his probable lamivudine resistance. It was generally agreed that there is no feasible alternative ART regimen currently available for this man, but waiting for TAF (tenofovir alafenamide fumarate) to become available was suggested.

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MSD

Disclosures

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