HIV and diabetes

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Abstract
Despite advances in HIV medicine people living with HIV (PLWH) continue to face many challenges. Addressing morbidity and mortality from concurrent and related conditions is a priority for all healthcare professionals working in this field. Diabetes in the general population is increasing in the developed world. Likewise, the numbers of PLWH who are diagnosed with the condition is escalating. This article provides an overview of the types of diabetes, outlines the various risk factors, describes screening measures and discusses the clinical management of this condition, with a focus on type 2 diabetes. The nurse’s role in diabetes prevention and care will be discussed, with specific reference to meeting the needs of PLWH.

Keywords: type 1 diabetes mellitus, type 2 diabetes mellitus, HIV, antiretroviral therapy, diagnosis, management

A. Revalidation
This article has been prepared with continuing professional development (CPD) in mind and can be used to support your revalidation. It is estimated that 2.5 hours of CPD activity will be required for completion of the reading, ‘time out’ activities, the quiz and writing a brief reflective account in relation to your learning and its applicability to your practice. There is a self-assessment quiz at the end of this article for you to assess what you have learnt.

B. Aims and intended learning outcomes
The article aims to increase your knowledge and confidence in assessing and caring for PLWH who may be at risk of, or diagnosed with, diabetes.

After reading this article, undertaking the activities and completing the self-assessment quiz you should be able to:

- Outline the differences between the main types of diabetes mellitus (DM);
- List the risk factors for developing type 2 diabetes mellitus (T2DM);
- Be aware of the criteria for diagnosing impaired glucose tolerance and diabetes;
- Describe the common symptoms seen in diabetes;
- Outline the various tests used in screening for and monitoring diabetes and the advantages and disadvantages of these;
- List the macro- and microvascular complications associated with DM;
- Know what investigations should be undertaken in order to prevent or identify these complications early; and
- Describe the specific considerations relevant to PLWH who receive a dual diagnosis of DM.

C. Introduction
Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic disorders in which blood glucose levels are raised over a prolonged period.

Diabetes is a common long-term health condition. In the 8 year period 2006–2014 the number of people in the UK diagnosed with diabetes increased from 1.9 million to 3.4 million [1]. For type 2 diabetes (defined later) NICE puts this as a prevalence rate of around 6% of the population in England and Wales [2]. If this trend continues it is estimated that 6 million people in UK will have diabetes by 2025 [1]. The condition is the single biggest cause of cerebrovascular accidents, retinopathy, peripheral vascular disease (potentially resulting in limb amputation), nephropathy, erectile dysfunction and coronary artery disease. Many people are unaware they have the condition [3].

D. Types of diabetes and causes

I. Type 1 diabetes
Previously referred to as ‘insulin-dependent diabetes mellitus’ (IDDM), type 1 diabetes (T1DM), is considered to be an autoimmune disorder with no lifestyle-related risk factors. There is ongoing debate about the causes but it is felt that the condition is likely to arise owing to genetic factors and/or viral infection, which prompt the immune system to attack the pancreas. The pancreas subsequently produces very little insulin or no insulin and is a lifelong condition. Onset of symptoms due to fluctuating glucose levels is rapid. T1DM is usually diagnosed before the age of twenty.

II. Type 2 diabetes
Type 2 diabetes (T2DM) is caused by a complex interplay of genetic and environmental factors. The condition was previously referred to as ‘non insulin-dependent diabetes mellitus’ (NIDDM) or ‘adult-onset diabetes’, although today, in some developed countries increasing numbers of children and young adults are being diagnosed [1]. About 90% of all cases of diabetes are Type 2.

In this condition there is a gradual reduction in insulin production and/or the body no longer responds efficiently to that which is produced; so-called ‘insulin resistance’. Lifestyle factors play a significant role, including obesity (note that among those who are not
obese, a high hip/waist ratio is often present) [4]. Smoking appears to increase risk as does a lack of physical activity in a significant proportion of cases [5,6]. A sedentary lifestyle [7] and dietary factors also influence the risk of developing the condition including high consumption of excessive sweetened drinks and a high intake of saturated and trans fats [8]. Genetics plays a part, as evidenced in several twin studies [9]. People of South Asian, African or Afro-Caribbean descent are at much higher risk of developing T2DM diabetes [10].

In addition prolonged use of some medications including: glucocorticoids, beta blockers, some antipsychotics and statins can increase diabetes risk [11]. Other health problems that are associated include Cushing’s syndrome and hyperthyroidism. Testosterone deficiency may also play a role [12].

III. Gestational diabetes

The third main type of diabetes is gestational diabetes, occurring in pregnancy, usually in the second trimester. About 4% of all pregnant women will develop gestational diabetes. Unlike type 1 and type 2 diabetes, gestational diabetes is due to the body’s significant increase in demand for insulin and the condition resolves after delivery. However, women are more likely to develop the condition again in subsequent pregnancies and are at higher risk of developing T2DM later in life. Women who are overweight, older, have had a very large baby in a previous pregnancy, or with a family history of diabetes are more at risk.

There are several other rarer types of diabetes mellitus, including maturity onset diabetes of the young, neonatal diabetes and Wolfram and Alström syndromes, however these are not covered in this article.

### Time out activity 1

Having looked at the causes and risk factors associated with diabetes spend a few minutes drafting a checklist for history-taking in PLWH, with the aim of identifying increased risk and early detection of diabetes. See Box 1 for suggested response.

### E. Symptoms of diabetes

People may present with a range of symptoms and T1DM onset is sudden. T2DM symptoms usually appear slowly over many months with many people unaware that they have the condition. Common symptoms of diabetes are listed in Box 2.

### F. Diagnostic tests

#### HbA1c

Once glucose attaches to haemoglobin it remains there until the red blood cell dies; an average of three to four months. The HbA1c blood test reports on the percentage of all haemoglobin that is glycated. The ‘A’ stands for ‘adult’ since after the first 6 months of age, nearly all haemoglobin is type A, about 98% of HbA is type 1, and two-thirds of this is subtype c.

An HbA1c result of 48 mmol/L (6.5%) or more is diagnostic of diabetes in most situations. The HbA1c test is also used to monitor diabetes and will normally be performed every 2–6 months. People with diabetes are usually advised to aim for a target range of 48–53 mmol/L (i.e. 6.5–7.0%) [13]. However, targets and goals will be negotiated between the individual and their specialist diabetes team, as acceptable levels vary by case. It is also important to note that the HbA1c test is inaccurate or inappropriate for use in the following individuals or scenarios:

- Children and young people
- Pregnancy
- Those suspected of having T1DM
- Those with symptoms of diabetes for less than two months
- People who are acutely unwell
- Those taking medication that may cause glycaemia, e.g. steroids
- Possible acute pancreatic damage, including post pancreatic surgery
- Patients with abnormal red blood cells such as thalassaemia

#### Random blood glucose test

In a medical emergency, in particular pre-diagnosis, a blood sample is taken to measure the glucose with no consideration of when the last meal was taken. A blood glucose level ≥11.1 mmol/L indicates diabetes; further tests are then done to confirm the diagnosis.

#### Fasting blood glucose test

A test using a blood sample obtained following a period of fasting for a minimum of 8 hours is called a fasting blood glucose test (FBG). A blood glucose level ≥7.0 mmol/L, after an overnight fast, indicates diabetes. To confirm the diagnosis, it is usually necessary to repeat the test a second time on a different day.

#### Oral glucose tolerance test

For an oral glucose tolerance test (OGTT) a baseline fasting blood glucose level measurement is taken. The
patient then consumes a drink that contains 75 g of glucose and blood levels are measured again after 2 hours. The test assists in determining the pancreatic response to the presence of glucose. A person with diabetes will see a sharp and sustained high level of glucose. A blood glucose level $\geq 11.1$ mmol/L, taken after 2 hours indicates diabetes.

Box 2. Symptoms of diabetes
- Unexplained weight gain or loss
- Unusual thirst
- Frequent urination and/or nocturia
- Extreme hunger
- Extreme fatigue and irritability
- Frequent infections, e.g. candidiasis
- Blurred vision
- Muscle cramps
- Tingling or numbness in the hands and feet
- Wounds appear slow to heal

G. Diagnosing diabetes
According to the World Health Organization a diagnosis of diabetes is made if an individual has:
- HbA1c $\geq 48$ mmol/L (6.5%)
- fasting blood glucose $\geq 7$ mmol/L; or
- blood glucose $\geq 11.1$ mmol/L after a 2-hour oral glucose tolerance test (OGGT) [14].

Impaired glucose tolerance is diagnosed with:
- fasting blood glucose $< 7$ mmol/L; and
- blood glucose of $\geq 7.8$ mmol/L, but $< 11.1$ mmol/L after a 2-hour OGTT [14].

Impaired fasting glycaemia is categorised as:
- fasting blood glucose 6.1–6.9 mmol/L; and
- blood glucose $< 7.8$ mmol/L after a 2-hour OGTT [14].

H. Blood glucose management
The target blood glucose ranges in Table 1 are given as a guide by NICE [2]. The number of times per day the individual should measure their blood glucose levels will vary depending entirely on their condition. The following is a useful general guideline, however, it does not apply to everyone and each case should be given individual advice by their specialist team. Adults with T1DM who are using insulin should check their blood glucose levels before every meal, sometimes as often as ten times per day.

Some people with T2DM may measure their glucose levels and would normally test daily. As this is a progressive condition and even with oral medication and diet control only, they may need to test their blood glucose periodically to observe trends.

Flash monitoring is a new technology that offers an alternative to finger-prick blood glucose testing. A sensor the size of a £2 coin sits on the back of the arm with a probe just under the skin. By scanning the sensor with a hand-held device the blood glucose level is displayed, indicating also whether the level is going up or down. The device stores data and makes it easy to view patterns over time.

I. Possible complications of diabetes mellitus
Diabetes is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy. Conditions associated with diabetes, in particular where blood glucose is poorly controlled over time, are listed in Box 3.

Box 2. Symptoms of diabetes
- Unexplained weight gain or loss
- Unusual thirst
- Frequent urination and/or nocturia
- Extreme hunger
- Extreme fatigue and irritability
- Frequent infections, e.g. candidiasis
- Blurred vision
- Muscle cramps
- Tingling or numbness in the hands and feet
- Wounds appear slow to heal

Box 3. Conditions associated with diabetes
- Cardiovascular disease
- Cerebral vascular accident
- Peripheral vascular disease (with potential need for amputations)
- Neuropathy
- Vision loss owing to retinopathy
- Nephropathy
- Erectile dysfunction and fertility problems
- Hypertension
- Disturbed blood lipid levels
- Thrombosis

Table 1: Target blood glucose ranges

<table>
<thead>
<tr>
<th>Adults with diabetes type</th>
<th>Time point</th>
<th>Target blood glucose range (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1DM</td>
<td>On waking</td>
<td>5–7</td>
</tr>
<tr>
<td></td>
<td>Before meals at other times of the day</td>
<td>4–7</td>
</tr>
<tr>
<td></td>
<td>90 minutes after meals</td>
<td>5–9</td>
</tr>
<tr>
<td>T2DM</td>
<td>Before meals</td>
<td>4–7</td>
</tr>
<tr>
<td></td>
<td>2 hours after meals</td>
<td>&lt;8.5</td>
</tr>
</tbody>
</table>


NICE recommends that people with diabetes undertake the following nine annual health checks in order to monitor and manage their condition, as well as to reduce the risk of these complications [15].

(1) Weight and body mass index measurements
(2) Blood pressure
(3) Smoking status
(4) HbA1c test
(5) Urinary albumin test
(6) Serum creatinine test
(7) Cholesterol levels
(8) Retinopathy screening
(9) Foot health check
J. HIV and diabetes

We know that people over the age of 40 years are more likely to develop diabetes. Now that PLWH are living into middle and older age, they are not an exception. The risk of developing diabetes alongside HIV infection consists primarily of traditional risk factors.

While autoimmune-related diabetes has been reported to develop after immune restoration with antiretroviral therapy (ART) this is rarely seen. In the few examples reported it is supposed that recovery of immune function predisposes to autoimmune disease, in the form of type 1 diabetes. There is no evidence to date of islet cell auto-immunity or beta cell destruction in PLWH [16].

Impaired glucose tolerance and insulin resistance are noted to precede weight loss in PLWH. Insulin resistance, rather than insulin deficiency, is usually implicated in the pathogenesis of diabetes in PLWH, i.e. T2DM. Increased accumulation of visceral fat with wasting of subcutaneous fat creates higher levels of inflammatory cytokines. These in turn can lead to impaired glucose tolerance by increasing insulin resistance. PLWH and metabolic syndrome show evidence of inflammation with, for example, higher CRP levels. This may also contribute to the pathogenesis of diabetes. In addition viraemia, a lower CD4 count, and longer duration of HIV infection makes developing diabetes more likely [16].

The British Medical Journal reported that – even when adjusted for a considerable range of variables including age, CD4 count, gender, ethnicity, poverty and hepatitis C infection – the diabetes risk was still significantly higher among adults with HIV than in the general population [17]. Also of note, in the D:A:D study group men were more likely to develop diabetes than women [18].

Hepatitis C infection has previously been described as a risk factor for diabetes mellitus in the general population [19], but this remains debatable. A meta analysis of treatment naive PLWH found that the known risk factors of black race, older age, and higher body mass index were associated with diabetes, but Hepatitis C co-infection was not, except possibly among people of black race [19].

There is also the possibility of risk of DM associated with the use of some of the older protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) [20], especially where their use has affected body fat distribution. Samad et al. found that individuals with HIV over 50 years are significantly more likely to develop T2DM if they started ART before 1999 or had longer exposure to older antiretroviral drugs such as stavudine (d4T) or first-generation protease inhibitors such as nelfinavir or indinavir [21]. These findings are backed by those found in the earlier D:A:D study cohort [18]. The authors’ conclusion was that diabetes in PLWH is chiefly a consequence of first-generation antiretroviral treatment. It may be then that, over time, numbers of PLWH who are newly diagnosed with diabetes will diminish significantly.

K. Management of diabetes mellitus

Prevention is obviously better than cure, but recent evidence also suggests that up to 50% of people with early T2DM can reverse it back to a pre-diabetic stage through dietary changes and weight loss [22]. We know that PLWH also have an increased risk of cardiovascular disease, independent of DM diagnosis [23], so this makes early identification of impaired insulin resistance and the effective management of hyperglycaemia especially important in this group of individuals. BHIVA guidelines recommend that monitoring and risk-reduction strategies for diabetes be employed in partnership with general practitioners and other healthcare providers [24]. The organisation recommends a metabolic screen at baseline, to include a random lipid profile and HbA1c. Subsequently all those aged over 40 years, on established ART are recommended to have a full metabolic assessment annually.

The management of diabetes in those with or without HIV aims to control blood glucose levels, thereby reducing the risk of related complications and associated disease. Effective management consists of the following five elements: patient education, dietary advice, blood pressure management, blood glucose management and drug treatment [25].

L. Recommended healthcare professional interventions

The following recommendations are adapted from NICE, BHIVA and American Diabetes Association advice [24–26].

I. Patient education

Patient information should be structured, evidence based, individualised, provided at and around the time of diagnosis, with annual reinforcement and review. This should include smoking cessation interventions, weight-loss advice where appropriate and information about how to monitor for symptoms of hyper and hypoglycaemia. People with diabetes should be advised to check their feet regularly for signs of injury or infection.

People with diabetes and HIV need to follow the clinical recommendations used for treating diabetes in the general population as already described.

II. Dietary advice

Advice should be personalised as part of a diabetes management plan, including other aspects of lifestyle modification, such as, increasing physical activity and
losing weight. Advice on healthy balanced eating is applicable as per the general population i.e. encourage high-fibre, low glycaemic-index sources of carbohydrate and to include low-fat dairy products and oily fish. Limiting the intake of foods containing saturated and trans fatty acids is also beneficial. For adults with T2DM who are overweight, a weight loss target of 5–10% is considered ideal but lesser degrees of weight loss may still be of benefit. Interestingly the use of foods marketed specifically for people with diabetes is discouraged. Reducing the risk of hypoglycaemia should be a particular aim for a person using insulin.

III. Blood pressure management

Hypertension is a frequent comorbid condition. If lifestyle advice does not reduce blood pressure to <140/80 mmHg (<130/80 mmHg if there is kidney, eye or cerebrovascular damage), anti-hypertensives should be prescribed. Note, however, that commonly used anti-hypertensives, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may not be optimal choices in patients with HIV, the latter potentially competing with other drugs that are metabolised by the cytochrome P450 isoenzyme [27].

IV. Blood glucose management

Active involvement of individuals with ‘ownership’ of HBA1c control is encouraged. Self-monitoring of blood glucose levels for adults with T2DM is not usually recommended unless the person is on insulin or there is history of, or increased risk of, hypoglycaemic episodes. Diabetics on insulin therapy are typically advised to check their blood glucose at least three times a day. This is used in conjunction with the HbA1c test performed every 3 months, then every 6 months once glucose levels are stable.

Given what we know about the role of ART in enhancing risk there is some debate about whether or not PI-based regimens should be avoided in PLWH who have pre-existing glucose abnormalities or a first-degree relative with diabetes, as is suggested by the American Diabetes Association (ADA) [26]. In patients who develop diabetes secondary to the use of an ART, a regimen switch may be advisable but balanced against the risk of ART treatment failure.

For those with diabetes before the diagnosis of HIV, and already taking a combination of medications and/or insulin to manage their blood glucose levels, it is possible that initiation of ART may affect glucose control and necessitate adjustments in therapy [26]. If not already being performed regularly then self-monitoring of blood glucose for a time can help determine when medication changes are needed.

Obviously all those who test their own blood at home should be taught to handle and dispose of contaminated supplies appropriately. The safe disposal of lancets, gauze and used glucose strips, as well as the proper cleaning of meters and lancet devices, must be reviewed at appropriate intervals.

V. Drug treatment

(i) Oral drug treatments are designed to reduce the amount of glucose released into the bloodstream (e.g. metformin), boost insulin production (e.g. gliclazide) or make body cells more sensitive to insulin (e.g. rosiglitazone). These can help control the condition for many years before there is a need to start using insulin.

Standard-release metformin is the initial drug choice for adults with T2DM especially in obese people. Studies in PLWH demonstrate that metformin use reduces insulin and triglyceride levels and decreases weight effectively, but note that ADA advise screening for lactic acidaemia and abnormal serum creatinine levels before prescribing this drug [26]. It is also important that people are educated about the clinical symptoms of lactic acidaemia (e.g. fatigue, weight loss, nausea, abdominal pain, dyspnoea) when prescribed metformin.

If metformin is contraindicated or not tolerated (it can cause GI disturbance), a dipeptidyl peptidase-4 (DPP-4) inhibitor, pioglitazone or a sulphonylurea is used. The sulphonylurea drugs, such as gliclazide, boost insulin production but can cause weight gain and hypoglycaemia. Third-line medications are the thiazolidinedione or ‘glitazone’ class of drugs [28]. These induce the cells to be more sensitive to insulin. There are also a few newer drug classes, including DPP-4 antagonists such as sitagliptin, which increase insulin production [29].

There is some evidence to suggest that PLWH achieve less robust responses to oral medication and that this may be more pronounced in people taking a PI-based regimen. The 2012 study investigators believe their overall findings of a poorer response could relate, in part, to persistent inflammation or immune activation, which has been associated with both HIV infection and insulin resistance [30].

(ii) Insulin was the first human hormone to be isolated and identified. The Nobel Prize was awarded to Banting and Best in 1923 for its discovery. They had succeeded in purifying insulin and treated a diabetic patient successfully that same year [31]. Insulin is an anabolic hormone produced by the beta cells of the pancreatic islets. It is considered to be the main hormone responsible for regulating metabolism of carbohydrates, fat and proteins. Beta cells are sensitive to blood glucose levels, secreting insulin when levels are high and inhibiting secretion of insulin when low. The neighbouring alpha cells respond by secreting glucagon in the opposite manner.

Time out activity 4

Take 15 minutes and go to the following website to remind yourself how and where insulin acts in relation to triglycerides, protein metabolism and electrolyte balance: www.verywell.com/how-insulin-works-in-the-body-1087716
Insulin is the only glucose-lowering therapy that is effective throughout the inevitable progression of beta cell dysregulation and reduced function seen in T2DM. Evidence suggests that early good glycaemic control in T2DM provides long-term protection [33]. It may also alter the course of disease progression. The American Association of Clinical Endocrinologists supports this early use of ‘modern insulins or insulin analogues’ in PLWH who are diagnosed as diabetic [34].

A range of injection devices are now available (and continue to be developed). Pre-filled and re-usable pens, pens with digital memory etc. have various advantages over conventional insulin delivery methods (see Figure 2 for some examples). These aim to improve patient safety and comfort, dosing accuracy and ease of use. Many users find them more discreet and socially acceptable, reporting enhanced QoL [35]. There are also subcutaneous implants available which contain a reservoir of insulin that is automatically released in response to blood glucose levels.

(iii) Other interventions: in addition, modification of risk factors such as dyslipidaemia and platelet function should be carried out through both non-pharmacological and pharmacological methods, as in the general population [32]. Dyslipidaemia is common in HIV and BHIVA advise on the appropriate use of statins as several are contraindicated with ART [36]. Annual screening for renal dysfunction, neuropathy and retinopathy is also recommended [20].

M. Nurse’s role

As always high-quality nursing care requires vigilance. Early detection and intervention can reverse T2DM in some and/or prevent a range of related complications. It is vital that nurses working in HIV have a sound knowledge base of the risk factors for DM as well as understanding subsequent health risks that come with this diagnosis. Furthermore, it is important to recognise that while psychosocial support is an integral part of effective diabetes management, it is arguably of even greater importance for those who have to handle the double burden of both an HIV and a diabetes diagnoses. As per the guidance given in Section L all interventions and strategies need to be individualised,
culture and age appropriate, negotiable, flexible and dynamic.

Adherence to treatment is already an area of expertise for many nurses working in HIV and this experience can be very useful for supporting PLWH who are subsequently diagnosed with DM. As with all long-term treatment regimens there are numerous factors affecting an individual’s ability to adhere, for example, self-efficacy, treatment expectations, health beliefs, and availability of social support. Diabetes management can evidently be quite complex, requiring lifelong commitment and in some cases considerable lifestyle changes. Empirical studies have shown positive and significant relationships between patient education and empowerment, social support and treatment adherence [37]. Armed with this knowledge and with existing applicable skills (such as motivational interviewing), nurses can support patients in their learning, decision-making and behavioural change as required.

Effective diabetes management requires a multidisciplinary approach with nurses working in conjunction with endocrinologists, diabetes specialists and dieticians. A philosophy of care that is based on empowerment and self-management models would appear best suited to this condition, supported by nurses working as educators and advocates where needed.

N. Useful resources
Nurses can facilitate access to a range of resources for people who are diagnosed with DM:
- Diabetes UK has a wealth of information targeted at both patients and health care professionals, including local support groups. Available at: www.diabetes.org.uk/professionals/information-support-for-your-patients
- HIV and Diabetes (HAD) – on line resources and support forums. Available at: haddsupport.uk/
- i-bASE. Available at: i-base.info/guides/side/increased-blood-sugar-levels-and-risk-of-type-2-diabetes
- DAFNE is a working collaborative of 75 UK based diabetes services. It is a structured education programme for T1DM in relation to glycaemic control through insulin use. Available at: www.dafne.uk.com
- DESMOND is a self-management programme for people with, or at risk of, T2DM. Available at: www.desmond-project.org.uk
- X-PERT Diabetes programme is for people with diabetes and aims to increase the knowledge, skills and understanding of the condition. Available at: www.xperthealth.org.uk
- Type 2 Diabetes and Me is an online step-by-step guide for people with type 2 diabetes provided by Diabetes UK. Available at: www.diabetes.org.uk/Guide-to-diabetes/Managing-your-diabetes/Education/Type-2-diabetes-and-me

O. Conclusion
While it is reassuring that modern HIV treatments appear to carry little risk of promoting the development of diabetes in people living with HIV, given the now near normal life expectancy [38] and longevity of contemporary ART regimens nurses will need to be alert to the possibility of DM occurring in this cohort and be well equipped to respond in a timely, effective and supportive manner.

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Q. References


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