

H

Human immunodeficiency virus treatment

H

The management of human immunodeficiency virus (HIV) is continually progressing and over the last decade has seen vast improvements in the drug options available to patients. These newer drugs are associated with significantly less toxicity than some of the older ones and are also associated with reduced tablet burden, which improves adherence and patient tolerability.

HIV is now managed as a chronic condition, with life expectancy significantly improved in recent years.¹ The main aim of treatment is to reduce the mortality and morbidity associated with the condition by:

- suppressing the virus – measured by checking the patients viral load (copies/mL) with a target of <50 copies/mL or ‘undetectable’
- restoring and maintaining the patient’s immune system – measured by the patient’s CD4 count (cells/ μ L). In non-HIV patients this should be >500 cells/ μ L.

When treatment should be started

The WHO recommends starting treatment at CD4 counts <500 cells/ μL .² The British HIV Association (BHIVA) recommends that treatment with antiretroviral therapy (ART) should be initiated in all HIV-positive patients with CD4 count <350 cells/ μL .³ To date there have been no published randomised trials that directly assess whether treatment-naïve people with higher CD4 cell counts should initiate ART immediately rather than defer to <350 cells/ μL . In addition, BHIVA recommends starting treatment regardless of CD4 count if there is active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; a high risk for cardiovascular disease, in pregnant women, symptomatic primary HIV infection, HIV-associated nephropathy (HIVAN) and in serodiscordant couples.³

Antiretroviral therapy

There are six different classes of antiretroviral drugs that can be used in combination to treat HIV:

- 1 nucleoside reverse transcriptase inhibitors (NRTIs)
- 2 non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- 3 protease inhibitors (PIs)
- 4 entry inhibitors
- 5 fusion inhibitors
- 6 integrase inhibitors.

Drug summaries, including information on adult doses and side effects, can be found in Tables H1–H5. The relevant product SPC should be consulted for further information and for guidance on dosing in children.

TABLE H1
Nucleoside reverse transcriptase inhibitors

Generic name	Trade name	Adult dose/dose adjustment in renal impairment	Counselling points/side effects
Abacavir	Ziagen ⁴ tablets and solution (abacavir) Combination products Trizivir ⁴ tablets (abacavir/ lamivudine /zidovudine) Kivexa ⁴ tablets (abacavir/ lamivudine) Triumeq ⁴ (lamivudine/ abacavir/ dolutegravir)	300 mg every 12 hours or 600 mg once daily Dose modification in renal impairment: none ⁵	May be taken with or without food Contraindicated in patients positive for the human leukocyte antigen (HLA)-B*5701 allele, which is associated with increased risk of hypersensitivity reaction Lactic acidosis, hepatomegaly, hepatic steatosis, lipodystrophy, dyslipidaemia, hypersensitivity reactions
Emtricitabine	Emtriva ⁴ capsules and solution (emtricitabine) Combination products Atripla ⁴ (tenofovir/efavirenz/ emtricitabine) Eviplera ⁴ (tenofovir / emtricitabine/ rilpivirine) Stribild ⁴ (tenofovir/ emtricitabine, elvitegravir, cobicistat) Truvada ⁴ (tenofovir/emtricitabine)	200 mg daily (as oral solution: 240 mg daily) Dose modification in renal impairment ⁵	May be taken with or without food Lactic acidosis, hepatomegaly, hepatic steatosis, lipodystrophy, dyslipidaemia
		eGFR (mL/min)	
		Dose	
		30–50	200 mg every 48 hours
		15–30	200 mg every 72 hours
		<15	200 mg every 96 hours

(continued)

TABLE H1
(Continued)

Generic name	Trade name	Adult dose/dose adjustment in renal impairment	Counselling points/side effects
Lamivudine	Epivir ⁴ tablets and solution (lamivudine) N.B.: generic lamivudine products are now available	300 mg daily or 150 mg 12-hourly Dose modification in renal impairment in HIV ⁵	May be taken with or without food Lactic acidosis, hepatomegaly, hepatic steatosis, lipodystrophy, dyslipidaemia
	Combination products		
	Combivir ⁴ (lamivudine/zidovudine)	eGFR (mL/min) Dose 30–50 150 mg stat then 150 mg daily	
	Kivexa ⁴ (abacavir/lamivudine)	15–30 150 mg stat then 100 mg daily	
	Triumeq ⁴ (lamivudine/ abacavir/ dolutegravir)	5–15 150 mg stat then 50 mg daily	
	Trizivir ⁴ (lamivudine, zidovudine, abacavir sulfate)	<5 50 mg stat then 25 mg daily ⁷ (SPC licensed dose) or 150 mg stat then 25–50mg daily ^{1,6}	
Tenofovir	Viread ⁴ tablets and granules (tenofovir) Combination products Atripla ⁴ (tenofovir/efavirenz/ emtricitabine) Evipera ⁴ (tenofovir / emtricitabine/ rilpivirine) Stribild ⁴ (tenofovir/ emtricitabine, elvitegravir, cobicistat) Truvada ⁴ (tenofovir /emtricitabine)	245 mg daily Dose modification in renal impairment: eGFR (mL/min) Dose 30–50 245 mg every 48 hours 10–30 245 mg every 72–96 hours <10 245 mg every 7 days	To be taken with food Proximal renal tubulopathy, renal impairment, renal failure, lactic acidosis, hepatomegaly, hepatic steatosis, lipodystrophy, dyslipidaemia

TABLE H2
Non-nucleoside reverse transcriptase inhibitors

Generic name	Trade name	Adult dose/ dose adjustment in renal impairment	Counselling points/ side effects
Efavirenz	Sustiva ⁴ capsules, tablets and solution (efavirenz) Combination products Atripla ⁴ (tenofovir/efavirenz/ emtricitabine)	600 mg daily (as oral solution: 720 mg daily) Dose modification in renal impairment: none ⁵	To be taken on an empty stomach, preferably at bedtime Rash, central nervous system effects – dizziness, depression. abnormal dreams, sleep disturbances, psychosis
Etravirine	Intelence ⁴ tablets (etravirine)	200 mg 12-hourly Dose modification in renal impairment: none ⁴	To be taken with food Rash
Nevirapine	Viramune ⁴ tablets and suspension (nevirapine) N.B.: generic nevirapine products now also available	200 mg daily for 14 days, increased to 200 mg 12-hourly maintenance dose Dose modification in renal impairment: none ⁵	2-week lead in recommended to reduce the incidence of rash May be taken with or without food Rash, allergic reactions, hepatitis, abnormal liver function tests
Rilpivirine	Edurant ⁴ (rilpivirine) Combination products Eviplera ⁴ (tenofovir / emtricitabine/ rilpivirine)	25 mg daily Dose modification in renal impairment: none ⁴	Must be taken with food for maximum absorption Should only be used in patients with a viral load <100 000 copies/mL Dyslipidaemia, insomnia, raised amylase, raised transaminase

TABLE H3

Protease inhibitors

Generic name	Trade name	Adult dose/ dose adjustment in renal impairment	Counselling points/side effects
Atazanavir	Reyataz ⁴ tablets (atazanavir)	300 mg daily taken with ritonavir 100 mg daily Dose modification in renal impairment: none ⁵	To be taken with food Jaundice, rash
Darunavir	Prezista ⁴ tablets and suspension (darunavir)	ART-naive patients – 800 mg daily with ritonavir 100 mg daily ART-experienced patients with no evidence of resistance/resistant mutations – 800 mg daily with ritonavir 100 mg daily ART-experienced patients – 600 mg 12-hourly with ritonavir 100 mg 12-hourly Dose modification in renal impairment: none ⁵	To be taken with food Insomnia, rash, increased alanine aminotransferase, diabetes, dyslipidaemia, peripheral neuropathy
Lopinavir/ritonavir	Kaletra ⁴ tablets and suspension (lopinavir/ritonavir)	400/100 mg lopinavir/ritonavir 12-hourly Dose modification in renal impairment: none ⁵	To be taken with food Dyslipidaemia, pancreatitis, diabetes, anxiety, hypertension, hepatitis, erectile dysfunction, menstrual disorders
Ritonavir	Norvir ⁴ tablets and solution (ritonavir) Combination products Kaletra ⁴ tablets and suspension (lopinavir/ritonavir)	Only to be used as a pharmacokinetic enhancer with other PIs – see information on previous PIs for dosing advice	To be taken with food Hypersensitivity, dyslipidaemia, dysgeusia, peripheral neuropathy, oral and peripheral paraesthesia, rash, pharyngitis, cough (refer also to side effects of the co-administered PI)

TABLE H4

Entry inhibitors

Generic name	Trade name	Adult dose/ dose adjustment in renal impairment	Counselling points/ side effects
Maraviroc	Celsentri ⁴ tablets (maraviroc)	300 mg 12-hourly – will need dose adjustment if on interacting medication: consult SPC Dose modification in renal impairment may be required if patient on potent CYP3A4 inhibitors: consult SPC ⁴	Should only be used in patients with CCR5 tropic virus. May be taken with or without food Anaemia, anorexia, depression, rash, increases in alanine transaminase (ALT), increases in aspartate transaminase (AST)

TABLE H5

Integrase inhibitors

Generic name	Trade name	Adult dose/dose adjustment in renal impairment	Counselling points/ side effects
Dolutegravir	Tivicay ⁴ tablets (dolutegravir) Combination products Triumeq ⁴ (lamivudine/ abacavir/ dolutegravir)	No/not suspected integrase resistance – 50 mg daily Known/suspected integrase resistance – 50 mg 12-hourly Dose modification in renal impairment: none ⁵	May be taken with or without food. In the presence of known integrase resistance, take with food to enhance exposure Insomnia, abnormal dreams, rash, pruritus, raised ALT, raised AST, raised creatine phosphokinase
Raltegravir	Isentress ⁴ tablets (raltegravir)	400 mg tablet 12-hourly (N.B. other formulations are not bioequivalent) Dose modification in renal impairment: none ⁵	May be taken with or without food Decreased appetite, abnormal dreams, insomnia, depression, vertigo, rash, raised AST, raised ALT, hypertriglyceridaemia
Elvitegravir/ cobicistat	Stribild ⁴ (elvitegravir, cobicistat, emtricitabine, tenofovir)	Each tablet contains: elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir 245 mg Dose: one tablet daily Dose modification in renal impairment ⁴	To be taken with food Rash – but see also side effects of tenofovir and emtricitabine for combination tablet side effects
		CrCl (mL/min)	Dose
		70–90	Only use if other treatment options have been discussed and Stribild is still the preferred option
		<70	Do not use

Which antiretrovirals should be used?

In treatment-naïve patients standard therapy should be initiated with a backbone of two NRTIs plus a third agent, which can be a ritonavir-boosted PI, an NNRTI or an integrase inhibitor³ (Figure H1). The current BHIVA first-line treatment algorithms are also summarised in Figure H1.

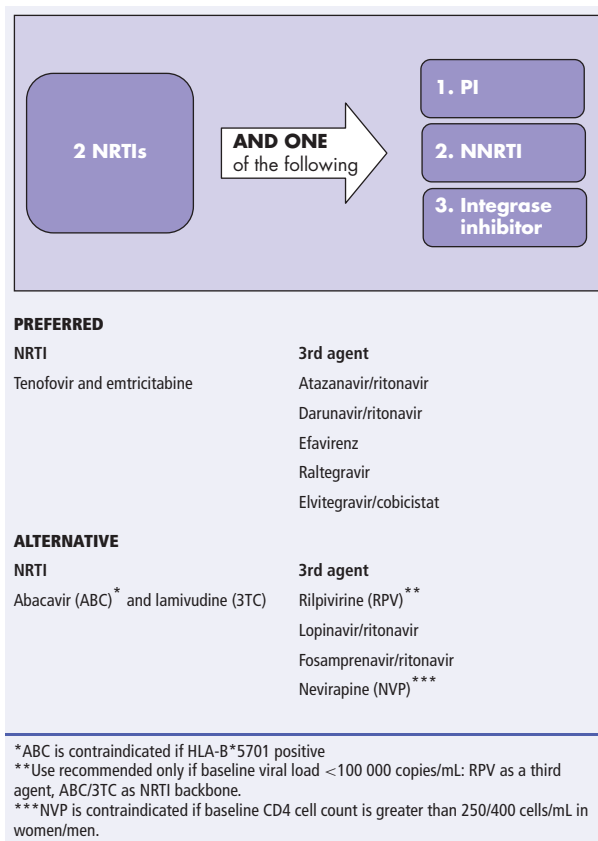


FIGURE H1 Standard antiretroviral therapy. NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor

Drug choice should be tailored to the individual patient, with considerations of:

- efficacy
- toxicity/side effect profile
- pill burden – both the number of tablets per day and the frequency with which they need to be taken
- comorbidities, that could contraindicate/caution some ART
- drug interactions
- patient preference.

Side effects

Minor side effects common to all antiretroviral drugs include nausea, vomiting, diarrhoea, headache and fatigue – these are generally worse in the first few weeks after initiation and usually subside with continued treatment. Important side effects specific to certain antiretrovirals are summarised below and in Tables H1–H5; consult the relevant SPC for a complete list of all side effects for each drug.

- Tenofovir is associated with renal impairment and osteoporosis.
- Zidovudine can cause macrocytic anaemia and lipodystrophy.
- Abacavir is associated with life-threatening hypersensitivity rash.
- NNRTIs, particularly efavirenz, may cause neuropsychiatric symptoms like dizziness and insomnia.
- Nevirapine has a risk of hepatotoxicity and Stevens–Johnson syndrome/toxic epidermal necrolysis.
- PIs are associated with a wide range of side effects, including hyperlipidaemia, hepatitis, diarrhoea and insulin resistance.
- Integrase inhibitors may cause headache and nausea, although this is rare.

Drug interactions

Antiretrovirals have the potential to interact with each other and with other medications. Before initiating ART, or introducing other medicines to patients already stable on ART, drug interactions should be checked, as some may be clinically significant. Interactions may be managed with dose modification or increased monitoring, or may even necessitate a change in therapy. The use of herbal remedies and ‘recreational drugs’ should also be considered as these often interact with antiretrovirals. The University of Liverpool has a comprehensive website that can be used to check interactions of HIV medicines (available at <http://www.hiv-druginteractions.org>, and also available to download as an app). Information on interactions is also available in the SPC for each drug.

Nucleoside reverse transcriptase inhibitors

(Abacavir, didanosine, emtricitabine, lamivudine (3TC), rilpivirine (RPV), stavudine, tenofovir, zidovudine)

NRTIs work by inhibiting the reverse transcriptase enzyme, preventing the formation of proviral DNA from the viral RNA. This is achieved by acting as nucleoside substrates during the formation of proviral DNA, resulting in termination of the DNA chain and therefore preventing replication. The most commonly used NRTIs are detailed in Table H1.

H**Non-nucleoside reverse transcriptase inhibitors**

(Efavirenz, etravirine, nevirapine, rilpivirine)

NNRTIs also work by inhibiting the reverse transcriptase enzyme, preventing the formation of viral DNA. This is via a different mechanism – attaching directly to the reverse transcriptase enzyme, preventing it from working. The most commonly used NNRTIs are detailed in Table H2.

Protease inhibitors

(Atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir)

PIs work by blocking the protease enzyme that is needed to break large chains of viral protein into smaller building blocks that are used in the assembly of new HIV particles. This results in the production of an immature, less infectious HIV. The most commonly used PIs are detailed in Table H3. All PIs are used in combination with ritonavir, which acts as a booster to increase levels.

Entry inhibitors

(Maraviroc)

In order to fuse with the host cell the HIV virus must first bind to the CD4 receptor and a chemokine receptor 4 or 5 (CXCR4 or CCR5). The CCR5 inhibitor maraviroc is the only licensed drug in its class and works by binding to the CCR5 receptor. This prevents the virus from binding and fusing with the host cell. This will only work in patients who have CCR5 tropic virus, so tropism testing should be carried out before initiating maraviroc – dual tropic or CXCR4 tropic virus will not be successfully suppressed with maraviroc. More detail can be found in Table H4.

Fusion inhibitor

(Enfuvirtide)

This works by binding to a surface protein on the HIV particle, preventing fusion with and entry of the virus into the host cell. This drug is only available as an injection and has had limited use – it will not be discussed further in this chapter.

Integrase inhibitors

(Raltegravir, dolutegravir, elvitegravir/cobicistat)

Integrase inhibitors work by blocking the viral integrase enzyme, which is responsible for inserting and integrating viral DNA into the host DNA, preventing replication. Elvitegravir is the newest of the integrase inhibitors and must be co-administered with a pharmacokinetic enhancer (usually cobicistat), and is used as part of a single fixed-dose tablet regimen with tenofovir and emtricitabine – this is called Stribild or ‘quad’ because of its four drug components.

The most commonly used integrase inhibitors are detailed in Table H5.

H

REFERENCES

- 1 May M *et al.* (2011). Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *BMJ* 343: d61016.
- 2 WHO (2014). *Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations*. http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf?ua=1&ua=1 (accessed 13 December 2014).
- 3 Williams I *et al.* (2014). British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (2013 update). *HIV Med* 15(Suppl 1): 1–85.
- 4 eMC (2014). www.medicines.org.uk (accessed 20 October 2014).
- 5 Ashley C, Currie, A (eds) (2009). *The Renal Drug Handbook* (3rd edn). Oxford: Radcliffe Publishing.

Hyperosmolar hyperglycaemic state

Hyperosmolar hyperglycaemia state (HHS) is a medical emergency characterised by hypovolaemia, marked hyperglycaemia and raised serum osmolality.

HHS was formerly known as hyperosmolar non-ketotic syndrome (HONS or HONK).

HHS typically occurs in the elderly but, as the diabetes pandemic widens, HHS may now also be the initial presentation of type 2 diabetes mellitus in younger adults and teenagers.

A precise definition of HHS does not exist; it has different features to diabetic ketoacidosis (DKA) and it is therefore treated differently (see *Diabetic ketoacidosis* entry). Whilst DKA presents within hours of onset, HHS may develop over many days and consequently dehydration and metabolic disturbances are more extreme. HHS has a higher mortality than DKA and may be more complex, with vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis. Other uncommon complications of HHS include seizures, cerebral oedema and central pontine myelinolysis, the latter possibly being precipitated by rapid changes in osmolality during treatment. Some patients present a mixed picture of both DKA and HHS.

Diagnosis of HHS

The following are characteristic features of HHS:

- hypovolaemia
- marked hyperglycaemia (30 mmol/L or more) without significant blood ketones (<3 mmol/L) or acidosis (pH > 7.3; bicarbonate > 15 mmol/L)
- serum osmolality – usually ≥ 320 mosmol/kg.

Management of HHS in adults

In 2012, the JBDS Inpatient Care Group published guidance on treating HHS in adults¹ so all trusts should aim to have a policy or care pathway in place. The main focus of treatment is to treat the underlying cause and gradually and safely to normalise osmolality, replace fluid and electrolyte losses and normalise blood glucose levels. Additionally clinicians should aim to prevent arterial or venous thrombosis, avoid complications such as cerebral oedema and prevent foot ulceration.

Early escalation to High Dependency Unit (HDU) should be considered if *one or more of the following is present*:

- osmolality > 350 mosmol/kg
- sodium > 160 mmol/L

- venous/arterial pH <7.1
- hypokalaemia <3.5 mmol/L or hyperkalaemia >6 mmol/L on admission
- hypoxia, (oxygen saturation <92%, assuming normal baseline)
- altered consciousness (GCS <12 or abnormal AVPU)
- systolic BP <90 mmHg or
- pulse outside 60–100 bpm.

For management in young people (<16 years), refer to published paediatric guidance.²

Fluid

These patients are severely dehydrated because of prolonged osmotic diuresis (Table H6) and fluid replacement is the first priority. Sodium chloride 0.9% with ready-mixed potassium as required is currently recommended as the fluid of choice because the majority of electrolyte losses are sodium, chloride and potassium.

TABLE H6

Typical fluid and electrolyte deficits in hyperosmolar hyperglycaemic state³

Water	100–220 mL/kg
Sodium	5–13 mmol/kg
Chloride	5–15 mmol/kg
Potassium	4–6 mmol/kg

Serum osmolality is a useful indicator of severity of illness, and also for monitoring rate of change with treatment. Because frequent measurement is not usually available in UK hospitals, calculated osmolality¹ is used to guide treatment, where:

$$\text{Osmolality} = 2\text{Na}^+ + \text{glucose} + \text{urea}$$

(normal range = 280–300 mosmol/kg)

- The rate of rehydration is determined by assessing initial severity plus any pre-existing comorbidities. Caution is needed, particularly in the elderly, where too rapid rehydration may precipitate heart failure but insufficient rehydration may fail to reverse acute kidney injury.
- Intravenous fluid replacement aims to achieve a positive balance, with 3–6 litres of fluid to be given over the first 12 hours and the remaining replacement of estimated fluid losses within the next 12 hours, although it may take up to 72 hours for complete normalisation of biochemistry.
- Calculate (or measure) osmolality every hour initially and adjust the rate of fluid replacement to ensure a positive fluid balance sufficient to promote a gradual decline in osmolality.

- Use intravenous sodium chloride 0.9% to reverse severe dehydration. The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours. N.B.: fluid replacement (without insulin) will lower blood glucose and reduce osmolality, shifting water into the intracellular space. This inevitably results in a rise in serum sodium, which is not necessarily a reason to give hypotonic fluids. A fall in blood glucose of 5.5 mmol/L causes a 2.4 mmol/L rise in sodium; a greater rise than this indicates insufficient fluid replacement.
- Maintain an accurate fluid balance chart and aim for a minimum urine output of 0.5 mL/kg/hour.
- Only switch to sodium chloride 0.45% if the osmolality is not declining despite adequate positive fluid balance and an adequate rate of fall in blood glucose level.
- Patients should be allowed to take oral fluids as soon as they are able.

Intravenous insulin

A safe rate of fall in blood glucose should be between 4 and 6 mmol/L per hour to a target of 10–15 mmol/L in the first 24 hours.

- An intravenous insulin infusion should *only* be commenced once the blood glucose is no longer falling with fluid replacement alone or at the start of treatment for HHS if there is significant ketonaemia (blood ketones > 1 mmol/L).
- Insulin may be infused in the same line as the intravenous replacement fluid, provided that a Y-connector with a one-way, antisiphon valve is used, and a large-bore cannula has been placed.
- A syringe pump should be set up containing 50 units of soluble insulin in 50 mL sodium chloride 0.9% (i.e. 1 unit/mL) and this should be infused at the lower starting rate of 0.05 unit/kg/hour because most patients with HHS are insulin-sensitive.
- Avoid hypoglycaemia: if blood glucose falls below 14 mmol/L, commence glucose 5% or 10% at 125 mL/hour while continuing the sodium chloride 0.9% infusion.
- Subcutaneous insulin is usually given to provide stability for a short time (weeks or months) following an episode of HHS. In the longer term most patients will be able to control their diabetes with either diet and oral therapy or diet alone.

Potassium

Patients with HHS are potassium-depleted but less acidotic than those with DKA, so potassium shifts are less pronounced. Patients with acute kidney injury may present with hyperkalaemia but patients on diuretics may be profoundly hypokalaemic. Potassium should be replaced or omitted as required (Table H7).

Anticoagulation

A major cause of death in HHS is thromboembolic disease. Prophylactic anticoagulation with low-molecular-weight heparin is

TABLE H7

Suitable potassium replacement levels in hyperosmolar hyperglycaemic state

Potassium level in first 24 hours	Potassium chloride to be added
<3.5 mmol/L	Senior review as additional potassium is essential (if necessary, via a central line in HDU)
3.5–5.5 mmol/L	40 mmol/L of fluid
>5.5 mmol/L	None

indicated for the full duration of admission, unless specifically contraindicated.⁴

Antibiotics

Infection is often difficult to exclude in patients with HHS. Antibiotics should be prescribed according to local guidelines when there are clinical or other signs to suggest infection.

Aftercare

- The underlying cause of HHS should be determined to minimise recurrence.
- The patient should have appropriate diabetes education and follow-up by the diabetes team.
- Prior to discharge there must be a plan in place for ongoing management and follow-up of diabetes depending on the patient's lifestyle and home circumstances.

REFERENCES

- 1 Joint British Diabetes Societies Inpatient Care Group (2012). *The Management of the Hyperosmolar Hyperglycaemic State (HHS) in Adults with Diabetes*. London: Diabetes UK. http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_HHS_Adults.pdf (accessed 30 January 2015).
- 2 Zeitler P *et al.* (2011). Hyperglycaemic hyperosmolar syndrome in children: pathophysiological considerations and guidelines for treatment. *J Pediatr* 158: 9–14.
- 3 Kitabachi AE *et al.* (2009). Hyperglycaemic crises in adult patients with diabetes. *Diabetes Care* 32: 1335–1343.
- 4 NICE (2015). *Venous Thromboembolism: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital* (CG 92). <http://www.nice.org.uk/guidance/cg92> (accessed 3 February 2015).

Hypodermoclysis

This is a technique used to administer fluids and electrolytes subcutaneously to achieve fluid maintenance or replacement in mildly dehydrated patients or in patients at risk of dehydration, when the oral or intravenous routes are not available. This might include patients in the first few days after a stroke, patients with poor venous access, palliative care patients or those who are agitated or confused and continually remove venous access devices.

It is not suitable for patients with severe dehydration, patients in shock, where more than 3 litres of fluid are required in a 24-hour period, or where precise control of the volume and rate of infusion is required.

Normally 500 mL of fluid is given over 8 hours, up to a maximum of 2 litres over a 24-hour period.

Solutions for hypodermoclysis

Solutions suitable for hypodermoclysis should ideally be isotonic (or close to isotonicity) with extracellular fluid. The suitability of a solution for subcutaneous administration must be established before use. Examples of solutions that have been used are:

- sodium chloride 0.9% or 0.45% solution
- glucose 5% solution (not more than 2 litres should be given in 24 hours, and the rate of administration should not exceed 2 mL/min. Higher rates or higher strengths have led to shock. The site should be inspected regularly for signs of irritation and inflammation due to the low pH of glucose solutions)
- sodium chloride 0.18% with glucose 4% solution
- potassium solutions up to 40 mmol/L (20 mmol/500mL) in isotonic glucose or saline (ulceration can sometimes occur due to low pH and high osmolarity, so regular observation of the infusion site is required).¹

Solutions unsuitable for hypodermoclysis

The following solutions are *not* suitable for hypodermoclysis:

- colloids
- total parenteral nutrition
- potassium solutions greater than 40 mmol/L
- glucose solutions greater than 5%
- solutions containing ions other than sodium, potassium or chloride, unless the solution's physiological characteristics are completely understood, e.g. pH and tonicity.²

Administration

Solutions are administered using a standard giving set through a subcutaneous needle and should always be gravity-fed. The choice of site should be healthy, clean, non-oedematous and convenient for the patient's comfort. Commonly used sites are the abdomen, thigh, scapula, axillary and subclavicular chest wall.³

Care should be taken in young children and the elderly to control the speed and total volume of fluid administered and to avoid overhydration, especially in renal impairment.

Hyaluronidase may be used to increase the rate of absorption of subcutaneous fluids. In clinical practice, there are three strategies for

its use in hypodermoclysis:

- 1 routinely every 24 hours
- 2 when required only, e.g. if an infusion is running very slowly, or there is swelling at the infusion site
- 3 at the start of the infusion only, and then only on resiting or as required.

The licensed dose of hyaluronidase is 1500 units per site every 24 hours.⁴ This dose is dissolved in 1 mL of water for injections, or sodium chloride 0.9%, and is injected subcutaneously into the site before the infusion is set up. Alternatively, it can be injected into the tubing of the infusion set, about 2 cm back from the needle, at the start of the infusion. 1500 units is sufficient for administration of 500–1000 mL of most fluids.

Monitoring the infusion site

The infusion site should be checked when the bag is changed. More regular monitoring is required for solutions other than sodium chloride 0.9%. The site should be changed if pain is experienced at the infusion site, the site becomes inflamed, white or hard, or if blood is observed in the giving set.

REFERENCES

- 1 *Can potassium be given by subcutaneous infusion?* UKMI Q&A 45.6 (accessed via www.evidence.nhs.uk 19 August 2014).
- 2 *Can magnesium sulphate be given subcutaneously?* UKMI Q&A 14.5 (accessed via www.evidence.nhs.uk 19 August 2014).
- 3 Hypodermoclysis Working Group (1998). *Hypodermoclysis – Guidelines on the technique*. Wrexham: CP Pharmaceuticals.
- 4 SPC (2011). *Hyalase November 2011 revision*. <http://emc.medicines.org.uk/> (accessed 19 August 2014).

Hypopituitarism

Overview

Definition	<p>Hypopituitarism is the complete or partial deficiency of one or more of the pituitary hormones and can occur in adults or children.</p> <p>Causes of pituitary insufficiency include:</p> <ul style="list-style-type: none"> ● pituitary tumours ● radiotherapy or surgery ● pituitary infarction ● infection ● head injury. <p>The symptoms of hypopituitarism depend on the hormones involved and the degree of insufficiency^{1,2}</p>
------------	---

Risk factors	<p>Initially, a patient with any hormone deficiency may be asymptomatic. Individuals with the following deficiencies present with the indicated condition.</p> <ul style="list-style-type: none"> • Adrenocorticotrophic hormone (ACTH) deficiency: adrenal (cortisol) insufficiency • Thyroid-stimulating hormone (TSH) deficiency: hypothyroidism • Gonadotrophin deficiency: hypogonadism • Growth hormone deficiency: failure to thrive and short stature in children; most adults are asymptomatic, but some may experience fatigue and weakness and decreased quality of life • Antidiuretic hormone deficiency (ADH) – polyuria and polydipsia
Differential diagnosis	Differential diagnosis depends on the hormones affected
Diagnostic tests	<p>Hormonal studies should be performed in pairs of target gland and their respective stimulatory pituitary hormone for proper interpretation.²</p> <ul style="list-style-type: none"> • Thyroid: TSH, thyroxine (T4), triiodothyronine (T3) • Adrenal function: ACTH stimulation test (or morning cortisol and ACTH) • Fertility: follicle-stimulating hormone (FSH), luteinising hormone (LH) and either oestradiol (if amenorrhoeic) or morning testosterone (as appropriate for sex) • Prolactin • Growth hormone-provocative testing
Treatment goals	<ul style="list-style-type: none"> • Replacement of affected hormones to physiological levels
Treatment options	<ul style="list-style-type: none"> • Pituitary hormone deficiencies are treated by replacing either the pituitary hormone itself, e.g. growth hormone, or the target hormone, e.g. levothyroxine, corticosteroids
Pharmaceutical care and counselling	
Essential intervention	<ul style="list-style-type: none"> • Glucocorticoids are required if the ACTH–adrenal axis is impaired • Hypothyroidism is treated with levothyroxine • Gonadotrophin deficiency is treated with sex-appropriate hormones. Testosterone replacement is used in men and oestrogen replacement is used in women, with progesterone in women with an intact uterus • Growth hormone is replaced in children. It is not routinely replaced in adults unless the patient is symptomatic of growth hormone deficiency after all other pituitary hormones have been replaced. The use of growth hormone is advised by the National Institute of Health and Care Excellence via two technology appraisals for adults and children^{3,4} • Diabetes insipidus is treated using desmopressin. See <i>Diabetes insipidus (cranial)</i> entry
Continued monitoring	<p>Hormone levels should be monitored to determine complications of under- or overreplacement. Hormone treatment may need to be adjusted to physiological maintenance levels, using the lowest dose</p>

REFERENCES

- 1 Jorn Schneider H (2007). Hypopituitarism. *Lancet* 369: 1461–1470.
- 2 Corenblum B (2013). *Hypopituitarism (panhypopituitarism)*. Medscape. <http://emedicine.medscape.com/article/122287-overview> (accessed 28 August 2014).
- 3 NICE (2010). *Human Growth Hormone (Somatropin) for the Treatment of Growth Failure in Children (TA188)*. London: National Institute for Health and Care Excellence.
- 4 NICE (2003). *Human Growth Hormone (Somatropin) in Adults with Growth Hormone Deficiency (TA64)*. London: National Institute for Health and Care Excellence.