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In this issue:

Management of swallowing problems (oesophageal disorders) in people with HIV; *page 2*

- Case study
- Introduction
- Background on incidence
- Overview of causes
- Oesophageal candidiasis
- Ulcerative infections
- Neoplasms in the oesophagus
- Dual infections - a case study
- Diagnosis
- What to do without a diagnosis
- Managing symptoms while awaiting diagnosis and until effective treatment is delivered
- Treatment of oesophageal candidiasis
- Treatment of other serious oesophageal conditions
- Administering medication to people who can't swallow

Management of swallowing problems (oesophageal disorders) in people with HIV

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Case study

An HIV-positive mother brings her young malnourished and dehydrated 8 month-old into the clinic complaining that the boy won't eat or drink. Although the mother had tried to breastfeed exclusively for the first couple months of the child's life but she acknowledged that the child had been mixed fed for several months because she has still not disclosed her status to her family, and they have been interfering with her feeding choices. But, the boy had seemed well until a few weeks ago when he began to cry during feeding and then refused to eat.

The child was clearly malnourished and failing to thrive — and seemed at least a couple of kilograms underweight. But the mother claimed the child had had no diarrhoea or fever.

On oral examination, the nurse sees thrush and other sores. She suspects that the child may be HIV-positive and that his aversion to feeding could be due to oesophageal candidiasis or possibly some other HIV-related oesophageal infection.

Introduction

Disorders of the oesophagus or the food pipe, the tube that connects the mouth to the stomach, are common in people with HIV — and a range of problems caused by a variety of infections, ulcers, and neoplasms that may occur.¹ While many of these conditions are manageable, without proper care, fissures or fistulas may form in the oesophagus associated with upper gastrointestinal bleeding; and strictures can develop that narrow the oesophageal lumen — effectively blocking the passage of food or medication.^{2, 3, 4}

But even the less severe cases can have serious consequences in people or children with HIV. People are usually acutely aware of symptoms originating in the oesophagus ranging from epigastric pain, severe heartburn and other central chest pains to, perhaps most importantly, dysphagia (difficulty swallowing or the sensation of food or pills sticking in the chest), and odynophagia (painful — sometimes excruciatingly painful — swallowing).⁵

Having difficulty or being unable to swallow exerts a profound effect on the quality of life, often resulting in reduced nutritional intake, malnutrition and wasting syndrome — especially if health-seeking behaviour is delayed, as is often the case in resource-limited settings. Even if the oesophageal condition itself is not life-threatening, these sequelae weaken patients and make it more difficult to survive other AIDS-related complications.

Since diagnosis is difficult in most clinical settings in this part of the world, effective treatment is often delayed. But even when the proper treatment is readily available and prescribed, people need appropriate palliative and supportive care to relieve their symptoms and address related complications (such as the inability to eat) to achieve the best possible outcomes and improve prognosis.

This review will describe the epidemiology of opportunistic oesophageal conditions in HIV-infected patients, the clinical presentations and diagnosis, and the management of HIV-related

oesophageal disorders, with a specific focus on current practices in resource-poor settings.

Background on incidence

In resource-limited settings, there are few reliable data to describe the current frequency of oesophageal problems in people with HIV. But before antiretroviral therapy (ART) came into widespread use in industrialised countries, reports suggested oesophageal complaints were quite common, occurring in at least one-third of people with HIV at some point over the course of their illness.^{6, 7, 8} In fact, the most frequent oesophageal problem in people with HIV, oesophageal candidiasis, was reported to be the second most common AIDS-defining illness pre-ART in a large cohort study in France.⁹

Since the introduction of ART, the incidence of oesophageal diseases has fallen off dramatically.^{10, 11, 12} But oesophageal problems obviously still occur in people with HIV who are not yet on ART, or not yet enjoying good immunological reconstitution on ART, and in people who are not adherent or are failing on treatment.

But in sub-Saharan Africa, where many do not even qualify for ART or present to the ART clinic until after developing an AIDS-defining illness, the data are more limited. According to one prospective natural history cohort study conducted during the 1990s in rural Uganda, oesophageal candidiasis was the second most frequent AIDS-defining condition (after wasting syndrome).¹³ A study in Nigeria also reported it to be the most common oesophageal disorder in people with HIV.¹⁴

But many other disorders also cause oesophageal pain in people with HIV.

Overview of causes

In people with CD4 cell counts over 300 (including those responding well to ART), injuries to the oesophagus are most commonly caused by gastroesophageal reflux disease (GERD), though there are cases where specific pills, including AZT (zidovudine) and some common antibiotics, cause problems in the oesophagus^{15, 16}; and allergic reactions may also cause symptoms.¹⁷ In addition, some studies suggest that HIV infection can alter oesophageal motility and function in the absence of other infections or ulcers and lead to dysphagia.^{18, 19} One South African report on two cases of achalasia — where muscles in the oesophagus seize up — in people with HIV suggests that some changes in oesophageal function may be due to HIV-related neurologic damage.²⁰ Such incidents are quite rare, however.

This article will mainly focus on oesophageal diseases in people with advanced HIV disease that can be broadly divided into:

- Candidiasis: *Candida albicans* and other *Candida* species, which account for 50-70% of oesophageal infections²¹
- Ulcerative conditions, most commonly due to:
- Very rarely other infections;
- cytomegalovirus (CMV)
- idiopathic oesophageal ulcers
- herpes simplex virus (HSV)
- Neoplasms (Kaposi's sarcoma (KS), lymphoma's etc); ²²
- Dual complications or secondary infections of ulcers.

Aside from oesophageal candidiasis, few studies describe the frequency of other causes of oesophageal diseases in resource

limited settings — at least partly because it is harder to diagnose them. However, in one study at the Kenyatta National Hospital in Nairobi, 52 HIV/AIDS patients with oesophageal complaints underwent upper gastrointestinal (GI) endoscopy and biopsy. Again, the most common cause of lesions was oesophageal candidiasis (occurring in 51.9%), but a few cases of cytomegalovirus and herpes simplex oesophagitis were diagnosed, as were cases of upper GI Kaposi's sarcoma, and one gastric lymphoma.²³

Although there are a number of reports describing the development of oesophageal ulcers or candidiasis during acute seroconversion illness, oesophageal conditions generally signal the onset of the symptomatic stage of illness and, usually, very low CD4 cell counts.

Consequently, a number of studies from the pre-ART era suggest that oesophageal disease is associated with a poor prognosis — sometimes despite treatment. In one study of 100 subjects with oesophageal ulceration from the US in the early 1990s, survival from the time of diagnosis was poor — with a median survival of 8.9 months (range, 2 days to > 42 months) with some variability possibly depending upon the type of ulceration or CD4 cell count at diagnosis.²⁴ In a prospective study of 48 people with oesophageal symptoms at St Stephen's Hospital in London, the average survival time was only five months (range one to 13) after definitive diagnosis.²⁵

Outcomes in resource-constrained settings can be expected to be worse. In the Ugandan study, the median survival time after diagnosis of oesophageal candidiasis was even shorter — less than 3.5 months — much shorter than reported in industrialised countries.²⁶

Oesophageal candidiasis

Candidiasis, or thrush, is caused by an overgrowth of *Candida*, a yeast that is part of the normal “flora” of bacteria and fungi that live in or on the human body. *Candida albicans* is the most common species but a variety of *Candida* species have been shown to cause candidiasis, including *C. krusei*, *C. tropicalis*, *C. glabrata* (formerly *Torulopsis glabrata*) and others, particularly in people who have been taking azole antifungal drugs.²⁷

Candida can spread unchecked in people with reduced immune function or even when the immune system is suppressed for other reasons, such as stress, other viral infections or conditions such as diabetes, or if other normal micro-organisms that live in the body are killed by a course of antibiotics. However, initial colonization is often asymptomatic.

Oropharyngeal candidiasis (OPC), however, implies the presence of signs and symptoms of infection in the mouth and throat. It is the most common of all opportunistic infections. Mild oral candidiasis occurs in a third of people even while the CD4 cell count is between 200 and 400, while candidiasis can be found in 90% of those with AIDS.^{28, 29}

OPC is usually recognised by the presence of loosely adherent white-yellow films, plaques or curd-like patches that may be focal or scattered about on the tongue, roof of the mouth, gums, tonsils, or back of the throat. It can also present as angular cheilitis (fissures or ulcers at the corner of the mouth) or patches of erythema without plaques.

While OPC can alter the sense of taste, cause oral pain and sometimes make it difficult to eat, it is usually manageable. But if it goes untreated, as immune function continues to deteriorate (typically when the CD4 cell count falls below 100), colonisation can spread to the oesophagus.

Symptomatic oesophageal candidiasis is considered a serious AIDS-defining event — although in a few endoscopic surveys, some evidence of candidal oesophagitis was found in up to 40% of asymptomatic patients.³⁰

In Malawi, where Dr Anthony Harries says most cases are diagnosed based on a response to an empiric course of fluconazole (see below), “every year, about 6,000 patients are diagnosed and treated for oesophageal candida, so it is a common problem.”

Except in the latter cases, oesophageal candida infection involves the entire length of the oesophagus. As the fungus spreads, it infiltrates and disrupts the layers of squamous cells in the oesophageal mucosa.³¹ This sets off an exuberant inflammatory process, described as a “cottage cheese” oesophagus, which leads to a swollen oesophagus with a narrow passage, slowing the transit of solid foods and pills, and causing the sensation of dysphagia. Sometimes people also present with hiccups.

Although dysphagia is the most commonly reported symptom of candidiasis, as the infection becomes more advanced, ulcers or erosions can develop, leading to pain on swallowing. The degree of odynophagia experienced by the patient relates to the degree and extent of the mucosal erosion but affected patients typically report pain that is diffused along the entire length of the substernum, though it is sometimes localised within specific areas.³¹

It is important to note that while concurrent OPC is generally present, up to a third of people with oesophageal candidiasis may not have oral thrush.³² It is also important to remember that the habitual use of topical antifungal troches or rinses may eradicate oral thrush but not prevent isolated oesophageal involvement.

Ulcerative infections

Ulcers in the oesophagus generally cause odynophagia. Clues to the presence of severe oesophageal ulceration include extreme discomfort when eating solid foods or drinking acidic liquids, pain in lateral chest areas, and spontaneous chest pains.³⁴ Usually the pain is moderate to severe — so severe that in some cases, patients may drool or spit to avoid painful swallowing. Because pain may occur even when drinking water, people with oesophageal ulcers may become dehydrated as well as malnourished.

Cytomegalovirus (CMV)-related ulcerative oesophagitis

Cytomegalovirus (CMV) is a relatively ubiquitous herpes virus, with serological evidence of infection in over half of children by the age of 6 and over 90% of adults by the age of 80, according to one US study.³⁵ In most people, it causes a flu-like syndrome during acute infection and then lies dormant.

In people with HIV, CMV can become reactivated and cause serious disease once the CD4 cell count falls below 100 cells/mm³, and generally lower. The average CD4 cell count of people at the time they develop their first episode of CMV disease is below 30 cells/mm³ — and the oesophagus, where CMV can cause deep ulceration, is one of the most common sites of infection.³⁶

Due to poor diagnostic capacity, under-diagnosis of CMV oesophagitis is common, which makes it difficult to establish an accurate picture of CMV epidemiology in resource-poor countries.³⁷ However, in one Ghanaian study, among 99 patients with Centers for Disease Control (CDC) clinical stage IV disease, CMV oesophagitis was one of four major opportunistic infections detected.³⁸

CMV oesophagitis is characterised by deep ulceration, often in the distal third of the oesophagus, or just above the oesophago-gastric junction. Concurrent oral manifestations are rare.

However, smaller ulcers are occasionally seen in the oropharynx (in the middle of the part of the neck and throat behind the mouth and nasal cavity).

People with CMV oesophagitis usually present with odynophagia rather than dysphagia. They may localise their discomfort to the distal substernal area (below the breastbone) but it can sometimes be unclear whether the problem is in their oesophagus, or their stomach. Occasionally, ulceration in the distal oesophagus will cause pain in the cervical oesophagus (the part of the oesophagus in the neck) as well.

CMV may also be associated with low-grade fever; there can occasionally be vomiting and nausea; and CMV involvement in other organ systems, particularly the retina. However, CMV ulcers may develop without evidence of the infection elsewhere.

Case Study (adapted from a case reported in the European Journal of Paediatrics)³⁹

A 12-year old boy with HIV presented for care after a six month long episode of fatigue, fever of an unknown origin, low appetite, failure to thrive and weight loss from 45 to 37 kg – which the clinic initially responded to with enteral tube feeding. There was no diarrhoea and the cause of the illness was hard to determine.

The boy admitted not taking the nucleoside analogue component of his ART regimen, which his clinicians switched. But there was no improvement, and three months later the boy had a CD4 cell count of 40, and he was admitted to a hospital. An examination of the boy was unremarkable – he had some lymphadenopathy and oral candida but little else worth noting. His care providers screened him for a variety of conditions (stool tests, blood cultures, x-rays) but found nothing.

However, the boy finally reported that he had been having epigastric pain as well. So the hospital performed an upper GI endoscopy, which found severe ulcerative inflammation, and biopsied tissue showed strong evidence of CMV infection (see section on Diagnosis). CMV treatment affected a rapid improvement – the pain resolved, his fever went away and he began gaining weight. Then his clinicians switched him to a Kaletra-based second line regimen – his viral load became undetectable, CD4 cells jumped to 880, and he has been well for at least two years now.

The fact that the boy's pain was only belatedly reported complicated the case, and also illustrates how critically important it is to carefully question a patient about any pain they may be having.

However, it is also important to point out that the boy was seen in a well-resourced setting. Had he been seen in most of the settings in Africa, the approach to diagnosis and management would have been very different (see below).

HIV-associated idiopathic oesophageal ulcers

Deep ulcerations without evidence of CMV or other known infectious causes are encountered almost as commonly as CMV.⁴⁰ These idiopathic (without known cause) oesophageal ulcers are clinically indistinguishable from CMV ulcers in size, appearance, and location. These also occur primarily in people with low CD4 cell counts (under 100). Wilcox et al reported that the prognosis of people with idiopathic oesophageal ulcers was significantly better than those with CMV oesophagitis, though it was still poor (13.1 months compared with 7.6 months; $p = 0.03$).⁴¹

There is some debate whether HIV might directly cause these ulcers because they were not previously observed before HIV, and there are reports of idiopathic ulcers developing during acute HIV seroconversion.^{42, 43, 44, 45} However, HIV does not infect the squamous epithelial cells in the oesophageal mucosa, and one

study has reported that HIV can be found in inflammatory cells in ulcers in people with HIV – regardless of the cause.⁴⁶ In other words, HIV was just as commonly found in oesophageal ulcers caused by CMV or other infections as well. But the aetiology may be more complex – at least one study has suggested that apoptosis may play a role, with HIV-infected immune cells triggering bystander killing of uninfected mucosal cells.⁴⁷

Regardless of how the ulcers develop, determining whether or not they are indeed idiopathic (in other words, excluding the presence of CMV) is of crucial importance since the treatment of these two conditions is quite different. Notably, in contrast to CMV, these idiopathic ulcers may occur concurrently with aphthous ulcers in the mouth.

Herpes simplex virus (HSV)-related oesophagitis

HSV can directly infect the squamous mucosa and cause ulceration in HIV-infected patients – though its frequency varies by study.⁴⁸

HSV-oesophagitis is distinguished from the other ulcerative processes by its more widespread involvement, its typically shallow, erosive lesions, and its more abrupt onset.⁴⁹ There may also be fluid-filled vesicles which have not yet ruptured.⁵⁰

HSV infection causes intensely painful swallowing and, unlike CMV, is often associated with lesions on the lips or oral cavity (these tend to be bloodier than aphthous ulcers in the mouth); the latter are useful clues for oesophageal involvement.⁵¹

Other infections

On very rare occasions, other infections have been identified as the cause of ulcers in the oesophagus, including *Mycobacterium tuberculosis* (MTB), *Mycobacterium avium* and other bacteria, viruses, other fungal and protozoal infections.⁵²

MTB can infect any part of the GI tract but infections in the oesophagus are unusual. Still there have been a number of case reports of tuberculosis causing ulcers and even fistulas, typically in the middle in the oesophagus – so in settings with a high burden of TB/HIV, it is something that clinicians should be aware of.⁵³ When it does occur, the infection usually spreads from adjacent lymph nodes, but the lymph involvement is not always immediately evident. Patients with oesophageal tuberculosis may present with low-grade fever, epigastric pain, chest pains, dysphagia and odynophagia.

Atypical clinical manifestations of endemic infections could become more common as the HIV epidemic matures in different parts of the world. For instance, there are now reports of leishmaniasis causing oesophageal ulcers in Ethiopia,⁵⁴ and reports of histoplasmosis causing lesions in Latin America.⁵⁵

Neoplasms in the oesophagus

Neoplasms, especially KS, lymphoma and miscellaneous tumours can also occur in the oesophagus – though they are less common than candidiasis or the major causes of ulceration.^{56, 57}

KS appears to be the most common oesophageal neoplasm in people with HIV according to autopsy and endoscopic studies from the States.⁵⁸ Most of these studies were in men who have sex with men, who have a high burden of KSHV, the virus that triggers KS. However, KS is also widespread in Africa and many studies have indicated it has increased in frequency with the spread of HIV (see [HATIP #102](#)).

Although KS in the GI is often asymptomatic, patients with visceral KS seem to have a higher risk of death than those with KS

appearing only on the skin.⁵⁹ There is a good chance that dysphagia or odynophagia in someone with KS lesions may be due to KS in the oesophagus, as described in a [recently published case study](#).⁶⁰

In contrast to KS, lymphomas in the oesophagus in people with HIV (most commonly non-Hodgkin's lymphoma [NHL]) are symptomatic (causing dysphagia and odynophagia from oesophageal strictures), aggressive and rapidly progressive tumours.^{61, 62}

It is also important to consider oesophageal carcinomas (mostly squamous cell carcinoma or adenocarcinoma) which have a much higher incidence in Africa than the rest of the world, especially in South Africa and among men.^{63, 64} There are some suggestions that oesophageal cancer has become even more common since HIV. For instance, one analysis from the cancer registry in Kyadondo County, Uganda, which observed an increase in KS that paralleled the evolution of the epidemic of AIDS, also found that there was a marked increase in the incidence of oesophageal carcinoma during the same period.⁶⁵ Perhaps that is coincidental but there have also been reports of a higher incidence of laryngeal squamous cell carcinoma in people with HIV than the general population.⁶⁶

One possible factor to bear in mind is that human papillomavirus (HPV), which is also sexually transmitted, may also be involved in the development of these cancers. HPV types 16 and 18 are associated with most cervical cancers and can infect the oesophagus as well. At least one South African study has reported a statistically significant association with increased anti-HPV-16 IgG antibody levels and oesophageal cancer — although this was conducted in HIV-negative individuals.⁶⁷

Weight loss and dysphagia are the most common symptoms of oesophageal cancer, but as it progresses, it can lead to cough and stridor, coughing up blood and vocal cord paralysis.

Dual infections - a case study

It is important to remember that several disease processes can occur in the oesophagus at the same time. For example, candidiasis plaques may entirely mask an ulcer caused by something else, and a bacterial infection may become established in a deep ulcer.

Case study from Dr

Karilyn Collins, Tanzania

A young teacher in Tanzania, came to the female ward with a severely sore throat and inability to swallow. She had oral and oesophageal candidiasis and was started on fluconazole. She was also found to be HIV-positive and became acutely depressed after being given her diagnosis.

Her candidiasis improved but she continued to refuse to eat and complain bitterly of pain in the throat. On close examination, small vesicles could be seen on the tonsils and back of her throat, which were diagnosed as HSV ulcers. The pain at this stage was very severe and she was given oral morphine. She responded to aciclovir and made a full recovery. She was later started on ART and is now back teaching and leading a full and active life.

"This is really a good lesson of a double pathology," said Dr Collins. "Many of the clinical officers missed the herpes and continued treating the candida."

Diagnosis

In a recent review, Wilcox and Saag recommend taking an algorithmic approach to diagnosing oesophageal problems in people with HIV.⁶⁸ The approach is guided by the patient's

immunological status as well as clinical signs and symptoms — though it may have to be adapted somewhat for use in some resource-constrained settings.

Step 1 - what is the patient's immunological status?

Early in the course of HIV disease, the most likely causes of oesophageal symptoms in people with HIV are similar to those in the general population, but, as the immune system deteriorates, opportunistic infections and neoplasms become more likely.

CD4 cell counts are the best indicator of the risk of opportunistic infections and HIV-related neoplasms. However, in settings with limited access to CD4 cell count testing, it may be possible to use WHO's clinical disease staging system to approximate whether the patient has early, symptomatic or late-stage disease. It is important to remember that oesophageal candidiasis is sometimes a person's first AIDS-defining event.

Diagnostic approach in early HIV disease: CD4 cell counts over 200 or WHO Stage 1 or 2 disease

Early in HIV disease, oesophageal symptoms (usually heartburn or dysphagia) are more likely to be due to GERD, peptic disorders, or pill induced disorders).⁶⁹ GERD is by far the most common problem so rather than perform expensive and invasive investigations of the patient, the routine course of action is to prescribe a trial course of a proton pump inhibitor (or the best available treatment for reflux locally). Patients who fail to respond may require more involved diagnostic evaluations (see below).

Diagnostic approach in late HIV disease or AIDS: CD4 cell counts below 200 or WHO stage 3 or 4 disease

As CD4 cell counts decline, the index of suspicion shifts to opportunistic infections and neoplasms. Usually oesophageal candidiasis, often accompanied with oral thrush, is the first HIV-related oesophageal infection to appear when the CD4 cell count falls below 100 cells — although data from Uganda suggest earlier emergence in that setting.⁷⁰

However, GERD can still occur in patients with advanced HIV disease and may confound the diagnosis, so Wilcox and Saag recommend characterising the symptoms first.

If the person has symptoms of GERD — such as heartburn, dyspepsia (feeling bloated/too full or nauseous after eating) and slight regurgitation — they recommend prescribing a trial course of a proton pump inhibitor.

If the person has dysphagia or odynophagia, they recommend a therapeutic trial of fluconazole (or another azole drug where fluconazole is unavailable) as an appropriate diagnostic and therapeutic strategy. In fact, Wilcox et al conducted a prospective randomised controlled study in 134 people with HIV and oesophageal symptoms demonstrating that empiric therapy with fluconazole was an efficacious and cost-effective strategy compared to endoscopically determined therapy, with 82% of those randomized to fluconazole having a clinical improvement within the first week.⁷¹ Responses were even more consistent in those who also had oral thrush, though the approach was slightly less effective in people who had very severe symptoms or odynophagia alone.

Dr Harries describes how important this approach is in Malawi:

"In a resource-limited setting like Malawi the common presentation is pain on swallowing, and we put in our guidelines and teach to all healthcare workers that pain on swallowing in a young person is probably oesophageal candida. This presentation warrants an HIV test and if positive then the patient is treated presumptively with fluconazole. If the patient gets better, then we make the presumptive diagnosis of oesophageal candida and the patient is therefore in WHO Clinical Stage 4 and is eligible for ART. We only

have 2 or 3 endoscopy centres in the whole country, so the diagnosis has to be made clinically.”

This approach will work in most cases, though further investigations are advisable if there are danger signs (such as bleeding), or if there is clinical evidence or history strongly suggesting another condition. Dieterich et al recommend that all patients receive a general medical review, a proper physical exam and a screening for a history of oesophagitis.

Physical examination in a person with AIDS and oesophageal disorders

A physical examination should be an integral part of the diagnostic work-up for HIV-related oesophageal disorders.⁷² The following are recommended:

- Measurement of vital signs; body temperatures may be elevated with CMV but not with candidiasis, or idiopathic ulcers (recent reports are mixed about HSV)
- Record weight and compare with previous weights
- A careful oral examination, assessing for oral candidiasis, lesions, and masses
- Examine the optic fundi for CMV retinitis in patients with CD4 counts of <50-100 cells/mm³
- Palpate for thyroid enlargement
- Palpate the neck for lymphadenopathy
- Assess the abdomen for masses, tenderness, and organ enlargement (organomegaly)
- Obtain stool for occult blood
- Perform a neurologic examination
- Check the CD4 count and HIV viral load to determine the level of immunosuppression (or clinically stage the patient) and assess the risk of opportunistic infections as causes of oesophageal complaints.

Endoscopy, biopsy and laboratory investigations:

For those who fail to respond to azole therapeutic trials, or whose clinical presentation suggests a problem other than candidiasis, the standard of care in well-resourced settings is an upper GI endoscopy with aggressive tissue sampling for a definitive diagnosis.⁷³ (Imaging studies once used in some settings, such as barium swallow, can detect ulcers but can't diagnose specific causes).

An endoscope is a flexible tube containing optical fibres that allows the clinician or technician to see inside as the scope is passed down through the oesophagus. There are a number of advantages: it allows the clinician to see the shape and location of ulcers or neoplasms (which vary by type), helps detect when there is more than one problem, and makes it easier to biopsy the best possible tissue samples for laboratory investigation.

For instance, CMV may cause multiple oesophageal ulcers but sometimes there may only be one or two at the far end of the oesophagus. Dieterich et al describes these ulcers as typically oblong, with a sharply demarcated, "punched-out" appearance, and a bland base — however, idiopathic oesophageal ulcers can look exactly the same.⁷⁴

They recommend taking multiple biopsies from the densely inflamed granulation tissue of the ulcer margins or base — because that is where evidence of CMV (intranuclear inclusions), can be found by the lab after hematoxylin and eosin (H&E) staining. HSV

lesions, on the other hand, start out as rounded 1-3-mm vesicles whose centres later slough to form discrete well-defined ulcers with raised edges in the middle to distal oesophagus. But again, the best tissue to sample is from the edge of the ulcers, which can then be sent to a reference lab for H&E staining and other studies.

Unfortunately, idiopathic oesophageal ulcers is a diagnosis of exclusion but since the most common treatment for the condition are immunosuppressive corticosteroids — that might make any ulcer caused by an infection worse — multiple endoscopy-guided biopsies have to be performed before a diagnosis can be made safely.

In most resource-poor clinic settings, these procedures are not practical because of inadequate facilities, expensive laboratory reagents, and lack of trained personnel. Endoscopy is only available at better-equipped facilities, and is too expensive to use routinely.

Blind brush or balloon cytology?

Two inexpensive techniques could hold some promise in increasing diagnoses are blind cytology brushing, in which a cytology brush is passed through a nasogastric tube and swept through the oesophagus to collect tissue specimens, or a balloon cytology instrument, which is used in a similar way. Collected specimens can then be sent to the laboratory for evaluation.

Most studies from industrialised countries have demonstrated that these techniques don't add much to findings from conventional endoscopy/biopsy. However, a number of studies from resource-limited settings have reported promising results in detecting neoplasms, oesophageal cancer or detecting dysplasia before it becomes cancerous.⁷⁵ A large number of these studies are from China, which has a very high rate of oesophageal cancer.⁷⁶

Wilson et al conducted a study finding a number of techniques inferior to endoscopy/biopsy — brush cytology could not pick up CMV for instance — which was the most common cause of oesophageal ulcers in the study.⁷⁷ But brushing could detect HSV and incident candida, which is a useful diagnosis in people who have failed azole therapy as it could indicate an infection with a resistant organism.

Of note, researchers in South Africa have recently developed a new cheap brush device — a gelatine coated sponge on a string that can be swallowed by the patient.⁷⁸ After the gelatine dissolves, the sponge expands and can be withdrawn, collecting tissue samples on its way up. Although it is being developed for the early detection of oesophageal cancer, it would be interesting to see whether it could be useful in people with HIV and oesophageal problems (see <http://www.scienceinafrica.co.za/3cancer.htm>).

What to do without a diagnosis

In settings without the capacity to diagnose serious causes of oesophagitis that don't respond to azole therapy, the best course of action is unclear. In *A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa*, Seruyange and Adams write that, “sequential empiric therapy is a reasonable initial approach” (see *Treatment*).

It couldn't hurt to try an empiric course of aciclovir for HSV, which is readily available and well-tolerated. This is commonly done in Malawi.

“No response to fluconazole, we teach, is an indication for another possible problem,” Dr Harries told HATIP. “We recommend then either referring to endoscopy or an empirical course of aciclovir to treat oesophageal herpes. If still no better, then they have to be referred for endoscopy.” But patients with CMV or aphthous ulcers may have a long wait for diagnosis and treatment

since there are only two or three centres that offer endoscopy in the country.

However, an empiric course of treatment with IV ganciclovir for suspected CMV is expensive, has significant side effects, is not readily available in many settings, and many clinical teams have little experience in administering it.

If aphthous ulcers in the mouth are present at the same time, it may make more sense to provide a trial course of corticosteroids for idiopathic oesophagitis.

In fact, some palliative care experts working in resource-limited settings recommend this when nothing else works anyway. According to the *Palliative Care Toolkit: Improving care from the roots up in resource-limited settings*: “Where other measures have not helped, high dose [cortico]steroids can be used for severe oral or oesophageal inflammation that prevents swallowing: dexamethasone 8-12 mg once daily orally for a week. Always prescribe with an antifungal because steroids can worsen fungal infections.”⁷⁹

The only other available option in many settings may be to prescribe ART, and hope for the best. There has been at least one case reported of CMV oesophagitis that responded to ART without specific anti-CMV therapy.⁸⁰ However, it may be a challenge to administer the pills (see *Administering drugs* below).

Managing symptoms while awaiting diagnosis and until effective treatment is delivered

While waiting for a diagnosis or for treatment to have an effect, people with severe oesophageal problems may need immediate palliative and supportive care to deal with symptoms.

Dr Sarah Cox, currently at Chelsea & Westminster in the UK told HATIP that “Even in the context of ART, oral and oesophageal pain is experienced in 50% of individuals.^{81,82} Symptomatically the WHO ladder (paracetamol – weak opioids – strong opioids) is the backbone of treatment. NSAIDs may be useful except in ulcerative disease. Where thalidomide is available it has a place in the treatment of aphthous ulceration. Local measures include sucralfate, and in the UK cocaine 2% mouthwash [or similar products such as lidocaine] can be used if available.”

Although stressing that, it is usually ineffective to treat the symptoms without addressing the underlying pathology, Seruyange and Adams suggest in *A Clinical Guide to Supportive and Palliative Care* using standard analgesics or viscous lidocaine to help manage most odynophagia. They note however, that HSV ulcers can be especially painful “and usually require analgesics including morphine when available.”

Some cases of oesophageal discomfort may require much more, especially oesophageal cancer. Although the following case does not come from a person with HIV, it does illustrate symptomatic management of a common presumptive diagnosis for a condition that may also occur in people with HIV in Africa, but for which no effective treatment is available by the time it is usually detected.

Case Study 2 from Dr Karilyn Collins, Tanzania

The patient is a man in his late 60's, very emaciated, who has been unable to swallow anything for several months and has severe pain in the chest. He was HIV-negative and there was nothing to see orally. We have no endoscopy facility and the relatives refused to take him elsewhere as they had no finance for further investigation. We made a presumptive diagnosis of carcinoma of the oesophagus – which is a very common presumptive diagnosis in Tanzania.

We started him on oral morphine and prednisolone 60 mg daily and he was very quickly pain-free and able to swallow liquids. He went home with the hospice caring for him and had two months of reasonably good quality life. As the swallowing got more difficult again we gave concentrated morphine solution sublingually to control the pain. We did not have a syringe driver or IM / IV opiates.

Feeding people who can't swallow

Addressing malnutrition and managing weight loss can also be a pressing need for people who are or have been unable to eat. In some cases, this may require nasogastric feeding – giving liquidised food via a fine tube passing into the stomach through the nose. This can be used to boost nutritional intake in the short-term, perhaps for a couple of weeks during or after the period of illness. “This should be inserted by someone with appropriate training and should be regularly flushed with salt and water to prevent blockage,” write Lavy et al in the *Palliative Care Toolkit*.

“I use a dietician to assist with liquid supplements, soups, liquidise meals – in other words, a fluid diet,” Dr Halima Dawood of Greys Hospital in Pietermaritzburg, South Africa, told HATIP. “If this is not possible, we insert a feeding tube and on one occasion we used total parenteral nutrition [intravenous nutritional supplementation], but this is a luxury of working in a tertiary institution.”

Treatment of oesophageal candidiasis

Candidal oesophagitis

Oesophageal candidiasis requires systemic therapy with fluconazole or itraconazole tablets or solution, or ketoconazole where those are unavailable. Randomised trials have shown fluconazole to be superior to ketoconazole.⁸³ Fluconazole tablets and itraconazole solution have similar efficacy.⁸⁴ The largest study comparing the drugs found a higher clinical cure rate on fluconazole (81.5%) than itraconazole (75.2%) ($p < 0.001$); though about a quarter of the patients in both groups had their dosages increased at week two, and there was no difference between outcomes after one year of follow-up.⁸⁵ The absorption of ketoconazole and itraconazole is pH-dependent, so neither drug should be given at the same time as antacids or drugs that include an antacid such as some ddI tablet formulations. Fluconazole's absorption is not pH-dependent, however.

Fluconazole (or *Diflucan*) is by far the most commonly used drug, in part because Pfizer, the manufacturer of the branded version, provides the drug free of charge for the treatment of cryptococcal meningitis and oesophageal candidiasis, to governmental and non-governmental organizations in more than 80 eligible countries in need (those with a greater than 1 percent HIV/AIDS prevalence). According to the Diflucan® Partnership Program website (<http://www.diflucanpartnership.org/en/welcome/Default.aspx>), the programme has no time or dollar limit.

Fluconazole does have a couple of important drug interactions. First, it can double nevirapine exposure so care should be taken when giving the drug to people on or about to start nevirapine-containing regimens.⁸⁶ Studies also suggest it may decrease the clearance of AZT (zidovudine) increasing the potential for AZT toxicity.⁸⁷ Finally, rifampicin decreases fluconazole levels, so patients on TB treatment may need a higher dose of fluconazole.⁸⁸ (Note that levels of rifampicin may be reduced in people who are taking the anti-fungal drug ketoconazole).

One other concern about fluconazole is that it may cause congenital abnormalities if taken during pregnancy (during the first trimester). There is some evidence of this from animal studies but frankly, the human data on this are mixed. There have been some case reports of birth defects in infants whose mothers were taking fluconazole, and some experts believe that there is a clear phenotype of fluconazole teratogenicity.^{89,90} However, population-based cohort studies have failed to find any overall increased risk of congenital malformations after exposure to a short course of fluconazole.^{91,92,93} The danger may come from sustained treatment with higher doses (400-800 mg per day). Nevertheless, clinicians may wish to advise that women with childbearing potential practice birth control while taking fluconazole, and be cautious about its use in women who are pregnant.

Finally, the high cost of the azole drugs continues to limit access to them in some settings or in the private sector, although generic formulations of fluconazole are increasingly becoming available.

Before the DPP programme, there had been great interest in finding less expensive options such as the topical treatments nystatin and gentian violet, which are effective against OPC — but these are inadequate for oesophageal candidiasis. In a Ugandan study, nystatin had a very low cure rate for the treatment of oesophageal candidiasis in AIDS patients.⁹⁴ In patients with oesophageal candidiasis from the DRC, ketoconazole was twice as efficacious than gentian violet or nystatin in resolving oesophageal lesions.⁹⁵

On the other hand, miconazole, a medium-priced azolic drug that is not well absorbed systemically, was found to be effective and could be a valid alternative to more expensive azolic drugs in developing countries.⁹⁶ However, the oral drug would need to be taken four times a day — which could pose problems for adherence. In another Ugandan study, dysphagia as a surrogate marker of oesophageal candidiasis was significantly reduced, and to a comparable extent, in patients using either ketoconazole or a slow-release buccal patch formulation of miconazole.⁹⁷

People with oesophageal candidiasis should be prioritised for receiving ART. Without addressing their underlying immune suppression, the risk of recurrence may be as high as 80% within 10 weeks after stopping treatment.^{98,99} Except in cases where azole resistance has developed, retreatment is usually successful, however.

Although there is a paucity of studies on azole resistance in developing countries, studies from resource-rich countries provide evidence that emerging azole resistance is an important public health concern for the control of candidal oesophagitis.¹⁰⁰ Azole resistance may emerge as a result of advanced immunosuppression that leads to repeated courses of azole treatment for relapsing fungal infections, especially OPC, and chronic (maintenance) suppressive therapy with azole drugs.

In addition, very preliminary research using HIV-positive couples has suggested that in some cases, *Candida* strains can be transmitted from one person to another.¹⁰¹ As some strains can be resistant to anti-fungal treatment, this raises the possibility that drug-resistant strains could be passed on to people who have never received anti-fungal treatment themselves. (Use of gentian violet or nystatin for oral thrush instead could help avoid this — as would getting people onto ART sooner.) In addition, some species of *Candida*, such as *C. krusei* are intrinsically resistant to fluconazole.

In some cases, resistance may be overcome simply by increasing the dose of the drug, for instance Revankar et al reported high rates of response treating resistant oropharyngeal using doses up to 800

mg per day.¹⁰² Switching from fluconazole to itraconazole has also been demonstrated to work in a number of cases.^{103,104} Another option is to use intravenous amphotericin B, which is effective against most strains of *Candida* but due to its toxicity profile it is reserved for azole-resistant candidiasis.¹⁰⁵ Low doses (0.3-0.5 mg/kg/day) are usually adequate — and also represent an option for patients who are unable to swallow.

A host of new drugs have been developed with activity against fluconazole-resistant candidiasis, including new azoles, voriconazole and posaconazole, and a new class of drugs, the echinocandins, including micafungin, caspofungin and anidulafungin — which must all be given intravenously. Despite the fact that many of these drugs have been clinically evaluated in South Africa, it is not clear that they will be accessible or affordable in most resource-limited countries.

Dosages of drugs for oesophageal candidiasis

Fluconazole	Either 100-200 mg orally once a day (most commonly 200 mg, the dosage supplied by DPP). Higher doses may work in cases of resistance. or 200 mg intravenously vials per day A 50 mg/5 ml powder is available for oral suspension for paediatric use.
Itraconazole	100 mg, orally twice a day
Miconazole	250 mg orally four times a day
Amphotericin B	0.3-0.5 mg/kg/day, IV

Treatment of other serious oesophageal conditions

Cytomegalovirus

As noted earlier, the management of CMV oesophagitis is problematic in resource-limited settings. In a recent paper, Heiden et al noted there are three main issues: lack of access to ART for the majority of AIDS patients, the high costs of anti-CMV drugs, and poor diagnostic facilities for CMV.¹⁰⁶ However, they wrote that the offer of ART is attracting large numbers of patients with advanced disease and low CD4 counts. Three intravenous drugs are used in resource-rich countries: ganciclovir, foscarnet, and cidofovir. Ganciclovir is the most commonly available in resource limited settings and is effective in about 75% of the cases — though ART is needed for sustained benefit.^{107,108} The standard induction dose is usually 10-15 mg/kg given twice daily for 3-4 weeks.

Ganciclovir causes significant neutropenia in 25-68% of patients and thrombopenia in 5% of patients, so in some settings clinicians may prefer to use foscarnet, if it is available, for patients in whom ganciclovir is contraindicated.¹⁰⁹ Standard doses are 90 mg/kg IV twice a day daily for 14-21 days.

Herpes simplex virus

The treatment for HSV oesophagitis depends on whether the patient can tolerate oral therapy. If so, a dose of 15-30 mg/kg a day (usually 200-400 mg orally five times a day) for two weeks is given, if not intravenous acyclovir may be used until the patient can tolerate oral treatment.¹¹⁰ Famciclovir and valacyclovir are equally effective oral agents, while foscarnet may be an alternative for patients with acyclovir resistance.

Idiopathic oesophageal ulcer (IEU)

More than 90% of HIV-infected patients with IEU improve on systemic corticosteroid therapy.¹¹¹ As has already been noted, steroids may increase the risk of clinical CMV disease or oropharyngeal and oesophageal candidiasis if present. A short course of concomitant azole therapy is generally recommended.¹¹²

A placebo controlled comparison of thalidomide 200 mg found that it improves ulcer healing and discomfort.¹¹³ However, thalidomide has important side effects such as somnolence (and thus should be taken at night), peripheral neuropathy, skin rash, and – most importantly, severe birth defects in pregnancy. The birth defects are so severe that thalidomide was banned in many countries. Where it is available it is not be given to women with child-bearing potential who are not practicing adequate birth control.

Regardless of the treatment, there is a high relapse rate, so once again, ART is the only long term solution.

Others

In the cases of other infections causing oesophageal problems pathogen-specific treatment should be attempted, along with ART as soon as possible, since unusual infections are most commonly seen in patients with advanced AIDS.

Of note, a nine-month course of multi-drug therapy cures oesophageal tuberculosis and closes fistulas in the absence of drug resistance. However, there are alarming reports of multiple drug resistant tuberculosis (MDR TB) and if fistulas do not close due to recalcitrant MDR-TB, surgical intervention may be required.¹¹⁴

Neoplasms

Studies indicate that treatment for the most common AIDS-related cancers (KS and non-Hodgkin's lymphoma) may respond well to conventional chemotherapy given along with ART.^{115,116} However, most people with oesophageal carcinoma present too late for care, and generally the only options are surgery or palliation.

ART

With the exception of GERD, most of these conditions are indications for ART. To optimise adherence, it may be advisable to stabilise the oesophageal condition first, before administering ART.

"As soon as they can swallow meds, I usually start them on ART," Dr Halima Dawood told HATIP.

Administering medication to people who can't swallow

However, as noted earlier, there are some cases – such as presumptive CMV oesophagitis – where ART may be the only treatment option available. So clinicians may need to find an alternative way to supply the medications. In addition, healthcare workers may need to administer other medications (such as TB) to people who have difficulty swallowing.

It may be possible to administer an intravenous drug or oral solution to the patient. For instance, DPP provides access to an IV formulation of fluconazole and as a powder to that can be mixed and given as an oral solution for children. But when IV formulations are not possible, other strategies may have to be adopted.

The following section, excerpted from *Route of Administration* by Adams, Cohen and Orrell in *A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa*, provides some useful advice.

"Many palliative care patients and paediatric patients have difficulty swallowing tablets and capsules and require liquids or crushed tablets. Data on how these can affect both the efficacy and toxicity of drugs is limited.

Some general principles can be applied:

1. Slow-release or modified-release preparations have a special coating designed to release the drug slowly. Crushing will result in a higher peak concentration (potentially toxic) and a shorter duration of action (producing a sub-therapeutic state for a period) than is intended. Slow-release and modified-release preparations should not be crushed nor made into suspensions/syrups.

2. Enteric coated tablets are designed to prevent drug dissolution in the stomach and to promote absorption in the small intestine. Crushing enteric coated tablets can cause stomach irritation or decrease drug effectiveness.

3. Stability data (physical, chemical, and microbiological) for extemporaneously prepared products is very limited. It is unlikely quality control of the product and ingredients will be carried out. Give extemporaneous products the shortest practical expiry.

4. Take extra care to minimise exposure when crushing drugs which have a high incidence of allergic reactions e.g. antibiotics, chlorpromazine.

5. Crush tablets between two metal spoons; avoid plastic as some drugs adhere to plastic.

6. Do not use boiling or hot water to dissolve tablets as it may affect their bioavailability.

7. Hard gelatine capsules can often be opened and the powder mixed with a small amount of sterile water. With soft gelatine capsules, withdraw the contents using a needle and syringe, but note some may adhere to the gelatine leading to lower than anticipated levels.

8. If diluting commercial liquids stability may also be reduced as any preservative will be diluted.

Health care workers must be aware that administering drugs in another form will be 'off license' and thus they must be prepared to accept responsibility for any adverse effects and decreased efficacy.

In a few cases the oral route may not be the most suitable and an alternative route is preferable. For example, patients with:

- Severe oral pain or pain on swallowing
- Dysphagia
- Odynophagia
- Obstruction
- Uncontrollable vomiting
- Diminishing conscious level

If available, buccal, sublingual, and rectal preparations can be useful for patients unable to swallow. Absorption is rapid via these routes and avoids first pass metabolism. Buccal and sublingual preparations may not be suitable if the patient has an impaired mental state, dry mouth, or excessive salivation.

Within palliative care the use of some oral preparations rectally is recognised (e.g., morphine slow release tablets – but this is an ‘off-label’ use). Rectal preparations are limited by rectal discomfort, diarrhoea, local pathology, and patient acceptance.”

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