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Managing meningitis in people with HIV in resource-limited settings: a clinical review

Introduction

"Samual Nzala is a 24-year-old gentleman brought by his family to the clinic because of a severe headache. The family reports that he has "malaria." His temperature is 39.7 degrees, but no parasites were seen on his MP (malaria parasite) slide. When the nurse spoke with him, he was lying on the bed in clinic with his eyes shut looking very uncomfortable. He keeps his eyes shut to the light and moves as little as possible. He did not feel well yesterday, but was working earlier this week with no problems. He has never had headaches before except when he has malaria. This is the worst headache he has ever had."

"His family says that he has had no recent head injuries, and the nurse cannot detect any focal problems (weakness or numbness in one part of the body) that might be evidence of a mass lesion in the brain, or signs of stroke. However, she finds he has a very stiff neck and is unable to flex his head forward."

She believes Samual most likely has some type of meningitis."
Adapted (with some details added) from Dr Gretchen Birbeck's *Where there is no neurologist* — see resource section)

Meningitis, inflammation of the membranes covering the spinal cord or brain, is common in people with HIV — but may be caused by a variety of things. Samual's symptoms: severe headache, fever, stiff neck, altered mental state or consciousness and sensitivity to light (photophobia) are hallmarks of meningitis—but not every symptom is always present and the clinical presentation may be non-specific. In people with HIV, meningitis may present with confusion only. On the other hand, depending on the cause or individual, there may be other complaints as well that could complicate diagnosis.

Symptoms may vary with the cause, which is most commonly an infection of some sort (either bacterial, mycobacterial (TB), amoebic, fungal or viral (see below)), but could also be due to physical injury (head trauma), subarachnoid haemorrhages, autoimmune conditions, cancers, or exposure to certain chemicals (Joynt). Some of these symptoms may not actually be due to involvement of the brain at all — for instance, sinusitis can cause a headache, severe dehydration due to malaria may cause altered mental state, and a stiff neck may occasionally be a feature of bacterial pneumonia.

This article will deal chiefly with the infections causing meningitis to which people with HIV may be more vulnerable—with a particular focus on cryptococcal, TB and pneumococcal meningitis.

Even with the roll-out of antiretroviral therapy (ART), being on the alert for meningitis is very important, because it may be the first illness that a person develops and is very dangerous.

Symptoms suggestive of meningitis must be treated as a medical emergency, since clinical deterioration can be very rapid and lead to death. Even when the initial presentation is initially subacute, as can be the case with cryptococcal meningitis, the consequences of delay are so grave that virtually any severe headache with a recent

onset in a person with HIV may warrant a closer examination (Hakim).

In either case, prompt and appropriate attention can improve survival and reduce the risk of serious long-term complications. But often in resource limited settings, diagnosing meningitis in a very ill person (or getting the person with meningitis to a place where he or she can be diagnosed), and providing effective care and treatment can present a number of difficult challenges. And even when a case is diagnosed and treated, few programmes adequately address how to manage the long-term consequences of meningitis in the children and adults who survive the condition.

Prevalence of meningitis in resource-limited settings

The spectrum of infectious meningitis in people with HIV

"In Sub-Saharan Africa, the commonest described HIV-associated CNS illnesses are infective conditions — and meningitis stands out as a very important problem," Professor James Hakim of the University of Zimbabwe said earlier this year at the Second HIV Infection and the Central Nervous System Meeting: Developed and Resource-Limited Settings, held in Venice, Italy.

Indeed, a review of the medical literature demonstrates an array of infections causing meningitis, although it is difficult to give the true prevalence of any condition because the frequency of some of the causes of meningitis varies by region and the local burden of infectious diseases, as well as the prevalence of HIV and the maturity of the local HIV epidemic (since some forms of meningitis, such as cryptococcal disease, tend to occur only in people with advanced HIV disease).

The strength of the local healthcare system also affects the prevalence of some causes of meningitis, particularly the local child health vaccination programmes and the HIV programme (since many conditions are much less common in people on antiretroviral therapy, while cotrimoxazole prophylaxis prevents some infections as well).

But as Prof Hakim and other neurologists stressed at the meeting in Venice, some infections may also be more common than people think — the capacity to diagnose certain infections is simply limited in many resource-limited settings. There are too few trained healthcare workers, especially neurologists, poor access to imaging equipment, and limited laboratory capabilities to do microbiology, culture, histology, etc, needed to confirm diagnoses in all cases (see also [HATIP #81](#)).

The following list describes the wide variety of organisms that have been reported to cause meningitis, bearing in mind that only some have been shown to be major causes of meningitis in people with HIV:

Causes	Frequency in HIV-positive people	Remarks
Cryptococcus neoformans	The most common cause of meningitis in people with HIV	Rarely seen as a cause prior to HIV
M.TB	Common cause of meningitis in populations with high TB/HIV coinfection rate	Meningitis is a more common TB presentation in people with HIV May occur on treatment

Causes	Frequency in HIV-positive people	Remarks
		Multidrug resistant (MDR)-TB strains are also a growing concern
Bacterial meningitis		Untreated, almost always results in death.
Haemophilus influenzae	Now less frequent cause due to childhood vaccination	Vaccination effective in children with HIV
Neisseria meningitidis	Not more frequent in HIV-positive	Cause of epidemic meningococcal meningitis in Africa Very rapid onset Rapid appropriate treatment can cure most cases Vaccine in short supply
Streptococcus pneumoniae	Greatly increased risk of pneumococcal meningitis	Children prone to recurrent disease Has a high rate of mortality and post-treatment complications, including irreversible brain damage, even where treatment is initiated timeously and correctly
Other common bacteria	Almost only seen in HIV or severely immunosuppressed	Bacterial infections that do not typically cause meningitis may disseminate to CSF in people with advanced HIV
Other causes		
Treponema pallidum	Common in people with HIV in many resource-limited settings	Neurosyphilis can present with signs and symptoms of acute meningitis soon after syphilis
Viral meningitis	Increased	Difficult to diagnose without viral tests such as PCR or culture, but most commonly associated with herpes viruses, or HIV seroconversion or progression.
IRIS	Frequency of meningitis as IRIS symptom unknown	ART may unmask a sub-clinical infection OR trigger a response in absence of active infection Most common in the setting of undiagnosed or recently treated cryptococcus or TB

It's important to keep in mind that multiple infections can occur at the same time in people with HIV and meningitis, especially TB and cryptococcal or bacterial meningitis.

The emergence of cryptococcal and TB meningitis since HIV

Several major studies have demonstrated how HIV has changed meningitis in resource-limited settings, especially increasing the prevalence of cryptococcal and TB meningitis, as well as the increased frequency of pneumococcal disease as the cause of bacterial pneumonia.

A study of 144 meningitis cases at the Pretoria Academic Hospital, South Africa found that between March 1994 and February 1998 "the HIV epidemic was responsible for a marked shift in the spectrum of meningitis seen at the hospital towards chronic infections such as TB and cryptococcal meningitis...Cryptococcal meningitis showed the most significant increase from 6% of cases in 1994/5 to... 26% in the last 2 years of the study" wrote Schutte et al.

More recently, a population-based surveillance study was performed to determine the burden of cryptococcosis (cryptococcal disease of any form – since the infection can disseminate to other body sites, causing pneumonia or skin lesions, for instance) by prospectively reviewing all the cases detected at laboratories (between March 2002 to February 2004) in Gauteng Province in South Africa (McCarthy). 2753 cases were identified. Among people with HIV, the case rate was 95/100 000, and among people living with AIDS 14/1000. 99% of the cases were in people over the age of 15 years. Almost all of the cases (97%) presented with meningitis.

Meanwhile, in Zimbabwe, Prof James Hakim and colleagues observed that the admission rate of cases of meningitis at Harare Central Hospital rose from 78 to 523 cases per 100 000 admissions per year between 1985 and 1995. So they performed a prospective cross-sectional study to determine the causative organisms and the characteristics of patients presenting with features of meningitis in their setting.

The study enrolled four hundred and six patients (predominantly adults) who presented to the referral hospitals in Harare with cases of suspected meningitis. Using what Prof. Hakim called "fairly crude diagnostic techniques" (see section on diagnosis), 200 cases were confirmed as meningitis: 89 (45%) had cryptococcal meningitis, 54 (27%) had mononuclear meningitis (aseptic), 31 (16%) had 'pyogenic' (purulent, and generally bacterial) meningitis (again, the most common organism was *S. pneumoniae* seen in 48%), 24 (12%) had TB meningitis and 2 (1%) had undefined meningitis (abnormal CSF not meeting any of the above criteria). HIV was detected in 90% of the confirmed cases –100% of those with cryptococcal meningitis.

"So cryptococcal meningitis became the predominant condition by the time that we published this, and now we probably see something of the order of 600 to 700 cases of cryptococcal meningitis per year in a one thousand bed hospital," said Prof Hakim. "And we went back into the records to see how many cases of cryptococcal meningitis have been diagnosed over the years and ten years earlier, there was just one case of cryptococcal meningitis diagnosed. So, clearly this is a very important issue in our environment as a direct consequence of HIV infection. But, also tuberculosis is becoming exceedingly important."

Likewise a study in Kigali, Rwanda reported that the incidence of cryptococcal meningitis increased from one case in 1983 to 130 new cases in 1992. The study examined the causes of meningitis in 2824 adults over the decade, and despite its recent emergence, cryptococcal meningitis was by far the leading cause of meningitis (Bogaerts). Similar findings have recently been reported in the Central African Republic (Békondi), in Kenya (Jowi) and Dar es Salaam, Tanzania (Matee and Matre).

Such reports aren't restricted to Africa. In Thailand, a national surveillance study during the pre-ART era found that cryptococcosis was the fourth most common opportunistic infection, accounting for 18.5% of all the AIDS-defining illnesses reported (Chariyalertsak). Another study from 1993 to 1999, reported that of 114 people admitted with chronic meningitis at a general hospital in Thailand,

54% of the cases were cryptococcal meningitis and 37% were TB meningitis (Helbok). Yet another study conducted in Thailand between 2001 and 2002, reported a cryptococcal meningitis case rate of 18 per 100 person years among people with AIDS admitted to hospital (Subsai).

Similarly high rates of cryptococcal meningitis and TB meningitis were reported in Southern and Western India, and throughout the Asia-Pacific Rim at the conference in Venice last April (Ghate) (see <http://www.aidsmap.com/en/news/E15D3AFF-1C6C-4909-A06E-04FB1785D21.asp>).

Increase in mortality from meningitis associated with HIV

Another relatively consistent finding across most resource-limited settings, regardless of the cause of infection, is the high rates of mortality associated with meningitis — though there are differences between settings that are probably related to the speed in diagnosing the condition and the adequacy of the treatments used (including ART).

One of the more striking findings in the Zimbabwean study was the high rate of in-hospital mortality from bacterial and TB meningitis despite providing treatment according to nationally accepted guidelines. In spite of this, the death rate in the hospital for bacterial and TB meningitis was 68% and 66.7%, respectively. “The use of benzyl penicillin and chloramphenicol as standard treatment appears not to significantly influence the outcome of patients with bacterial meningitis,” wrote Hakim et al (see section on treatment).

A study from Dar es Salaam, Tanzania reported an increased mortality associated with HIV infection in patients with bacterial meningitis, especially pneumococcal meningitis (Pallangyo). Of 36 patients with meningitis seen before a meningococcal epidemic affected Dar es Salaam, there was a statistically significant association with HIV infection ($P = 0.013$). 10 out of 19 (53%) people with HIV died, compared with 9 out of 59 (15%) of the people without HIV ($P = 0.028$).

Meningitis is the clinical presentation of TB with the highest mortality rate, even without HIV (Cecchini). In an Argentinian study of 141 cases with positive culture for *M. tuberculosis* (101 were people with HIV), the global mortality during hospitalisation was 63.3%. However, more than half of those cases were resistant to one or more TB drugs.

In another study of 528 adults treated for TB meningitis (96 with HIV and 432 without) in referral hospitals in Ho Chi Minh City, Vietnam, the 9-month survival rate was significantly decreased in people with HIV (relative risk of death from any cause, 2.91 [95% confidence interval, 2.14-3.96]; $P < .001$) (Thwaites). But the other aspects of response to treatment appeared similar regardless of HIV status, with no significant differences between time to fever clearance and coma clearance, “which suggests that HIV infection does not compromise anti-tuberculosis drug activity, despite its suppression of the immune system.”

“The median CD4 cell count for when these patients arrived and were started on treatment for TB meningitis was 55. So these patients undoubtedly will be dying of other things,” said Dr Guy E. Thwaites of Oxford University, who was the leading author of the study and who also spoke at the 2nd HIV Infection and the Central Nervous System Meeting in Venice in April. “And what is intriguing and what is very important, is what difference [ART] will make to these patients.”

But at the same meeting, Dr Mariana Croda reported a very high rate of mortality among people with HIV and TB meningitis in Sao Paulo, Brazil — where ART is readily available, but where people may still present late for treatment. Her findings were from a retrospective analysis and included 86 people with HIV and culture-proven TB meningitis, without any other additional CNS disease, who presented between 2000 to 2006. Drug sensitivity data were available for 63 of the participants and 9.5% of the patients had MDR-TB. Even so, the global mortality was 54% (30% in-hospital and 24% over the course of 9 month follow-up).

With the exception of MDR-TB, most people with TB meningitis should have access to TB drugs active against the infection. But the same cannot be said for people with cryptococcal meningitis in every setting.

Prof Hakim noted that the in-hospital mortality rate for cryptococcal meningitis in the Zimbabwe study was rather low — but that was because those patients were soon discharged without treatment. “National guidelines on the management of cryptococcal meningitis preclude the provision of anti-fungal agents in the public sector free-of-charge. The cost of anti-fungal agents, the numbers of patients with cryptococcal meningitis, and the need for continual therapy and monitoring make it unlikely that this policy will be altered in the foreseeable future. None of our patients with CM could afford the cost of medication, hence none was given specific anti-fungal treatment, though they received symptomatic treatment and relevant information concerning their disease.”

In another report from the early 90s, two physicians from Blantyre and Lilongwe, Malawi reported what became of similar cases of untreated cryptococcal meningitis (Maher and Mwandumba). “81% of the cases did not receive antifungal chemotherapy because they could not afford it. None of these untreated patients survived longer than 30 days after diagnosis of cryptococcal meningitis. Most died within the first 4 days. In fact, the median survival time after diagnosis for all 31 patients was 4 days. The patients who could afford antifungal chemotherapy survived four to at least nine months,” they wrote.

In a study in Senegal most people with HIV and cryptococcal meningitis were put onto fluconazole, which is not the most effective induction treatment but the only one that can be delivered in some settings (see *Treatments* below). The mortality rate was 71.1% overall (Soumaré).

Even worse outcomes were reported in 230 patients with cryptococcal meningitis seen at the University Teaching Hospital in Lusaka, Zambia — with or without treatment (Mwaba). 130 of the 230 (56%) patients received treatment with fluconazole monotherapy and 100 (43%) patients received palliative care only without any antifungal therapy. A 100% case fatality rate was observed in both groups at follow-up: by seven weeks in the untreated group and at six months in the fluconazole-treated group. The cumulative median survival from time of diagnosis was 19 days (range 1-164 days) for the fluconazole treated group and 10 days (range 0-42 days) for the untreated group.

Meanwhile, similar outcomes have been reported in South Africa, with up to 64% in-hospital mortality among HIV-positive cryptococcal meningitis patients in Durban (Moosa and Coovadia).

By the time of the Gauteng Province survey for cryptococcosis, outcomes had improved somewhat, at least in that province, with an in-hospital mortality of 27% — though long-term follow-up data were not reported. A higher percentage in this population received fluconazole, and at least 27% of the treated people also received amphotericin B, which has been demonstrated to achieve better outcomes.

Only a few received ART in most of these studies and one can hope that survival may be significantly improved now that ART is increasingly available.

Nevertheless, in many of the people presenting with meningitis, it is the first AIDS defining illness — and indeed may be the first indication that someone is HIV-infected.

Diagnosis of meningitis

Early detection is key regardless of the type of meningitis

“The high mortality rates observed among meningitis patients in this series reflect immunosuppression associated with HIV infection or malnutrition, late presentation at a hospital, lack of access to medical care, and failure on the part of some primary care providers to consider a diagnosis of meningitis,” wrote Bergemann and Karstaedt in the report from Baragwanath Hospital.

Experts agree on this regardless of the cause of meningitis.

“Bacterial meningitis remains an important cause of mortality and morbidity worldwide” wrote Scarborough and Njalale from the University of Malawi in Blantyre. “Health education, improved diagnostic speed and capacity, and ensuring appropriate antibiotic therapy may improve outcome amongst patients presenting with bacterial meningitis.”

“I think diagnosis and treatment early in the disease [TB meningitis] regardless of whether you’re HIV-positive or negative is the critical factor to getting a good outcome,” said Dr Thwaites.

“Because cryptococcal infection has become such an important cause of meningitis, appropriate diagnostic procedures, especially examination of CSF, are recommended early in individuals presenting with headache even if it is the sole symptom,” said Prof Hakim.

Early detection might be improved by educating healthcare workers, community based caregivers, communities and families to recognize the initial symptoms of meningitis — and to understand the need to quickly seek out medical attention.

Recognising the signs, symptoms and course of meningitis

While some symptoms are frequent in meningitis, they are not always present together.

Nor is it possible to definitively distinguish between the specific causes on the basis of symptoms alone.

However, the patterns of symptoms and the course of disease do vary somewhat by infection — and may increase the index of suspicion for some conditions.

General symptoms of meningitis

There are four classic symptoms of meningitis: headache, neck stiffness, change in mental status/ alertness, fever — but even these are not always present at the same time.

Other signs and symptoms include: sensitivity to light (photophobia), sensitivity to loud sounds (phonophobia), irritability, confusion, vomiting, seizures, delirium, myalgia, cranial nerve palsies, blindness and coma.

Many papers refer to ‘meningism’ that includes several signs (Nuchal rigidity, Kernig’s sign, Brudzinski’s sign) that can be assessed in a person lying supine and that might serve as indicators of meningitis. Nuchal rigidity is present if a person is

unable to flex their head forward due to rigidity of their neck muscles. A positive Kernig’s sign is when a person’s leg is bent in the hip and knee and there is pain when he or she tries to straighten or extend their knee. Brudzinski’s sign is when the patient involuntarily lifts their legs in reaction to lifting their head.

But while these signs may be ways to test for neck stiffness, a recent paper claims that they have only limited accuracy as a test for meningitis (Thomas).

“While these tests are commonly taught and regurgitated by medical students, simply noting neck stiffness in a patient who is as relaxed as possible by gently flexing the head is sufficient,” comments Dr. Francois Venter of the Reproductive Health and HIV Research Unit, of the University of the Witwatersrand, Johannesburg, South Africa.

It’s also important to note that neck stiffness may be absent in people with low CD4 cell counts.

Bacterial meningitis

In the major studies in people with HIV, the most commonly reported symptoms have been headache, high fever, stiff neck, vomiting, photophobia, confusion/delirium, seizures/convulsions (de Almeida, Almirante, Hakim) occurring over hours to days. Gordon et al reported that almost a third of patients had a pulse >100 bpm.

In infants, there may be swelling of the fontanelle (the soft spots between the cranial bones on the top of the skull). Molyneux et al report that children with HIV and bacterial meningitis are more often in shock when brought into the clinic than children without HIV.

Course:

One thing that many papers stress is that the course of disease can be extremely rapid, with up to 10% of patients dying within the first day or two after the onset of symptoms, even when it is diagnosed early and properly treated.

Gordon et al reported that the median time between the start of symptoms and presentation to the clinic was 3.96 (±5.4) days for bacterial meningitis versus 14.6 (±16.8) for cryptococcal meningitis ($p = 0.001$).

CD4 cell count:

Any (Janoff). A declining CD4 count appears to correlate with a greater risk of pneumococcal meningitis, but this infection occurs commonly at high CD4 counts.

Meningovascular syphilis

Neurosyphilis may be without symptoms altogether for a long time, but meningitis may start as soon as secondary syphilis (while there is a still a rash on the palms of the hands and soles of the feet) (Simon).

The most common clinical manifestations are headache, nausea, vomiting, stiff neck, delirium, cerebra and cranial nerve dysfunction, polyradiculopathy, fever and convulsions (Carmo, Johns).

Course:

May be either very gradual, but once meningitis begins the presentation may be acute (Carmo).

CD4 count:

Any. It is unclear what role immunosuppression plays in risk of meningovascular syphilis, response to treatment or progression.

TB meningitis

Variable but generally fever, reduced alertness, headache, meningism/neck stiffness, vomiting — and occasionally there may be focal deficits (weakness or problems on one side of the body) such as hemiplegia (paralysis on one side of the body) and cranial nerve palsies in people with HIV. In children, there may be hydrocephalus. The diagnosis is particularly difficult in children because signs and symptoms can be vague (Padayatchi). As with bacterial meningitis, both adults and children are usually very ill, as opposed to cryptococcal meningitis, where they may be surprisingly well.

Course:

According to Dr Thwaites, the duration of time from symptom to presentation is a median of 12 days versus 3 days for bacterial meningitis. The range for TB meningitis can be from a few days to a few months however.

CD4 cell count: Usually <350 and generally even lower. It was 55 in Thwaites et al, 131 in Hakim et al. However, it may occur at high CD4 counts as well.

Clue:

TB elsewhere in the body, such as the lymph nodes or on chest x-ray. Sputum specimens should be sent for smear and culture if there is evidence of TB elsewhere. Can occur even on treatment (break-through TBM) (Wilson, Karstaedt).

Cryptococcal meningitis

Headache or fever, perhaps without other clear symptoms — neck stiffness in particular is less common in patients. Still sometimes there is a mix of neck stiffness/meningism, sweats, nausea/vomiting; malaise, changes in mental status (irritability, changed behaviour, dementia, memory loss, even psychosis), altered consciousness. Less common are visual changes including blindness, cranial nerve deficits, or seizures.

Some of the African studies stress the importance of headache, while in other studies, fever is more prominent (Hakim, Maher and Mwandumba, French). To some extent the variability in symptoms may depend upon the sensitivity of the diagnostic techniques used to examine the cerebrospinal fluid — by the time less sensitive techniques (such as India Ink stains, see diagnosis) used in some settings detect the infection, headache may be virtually universal.

In a small percentage of people, there may also be cryptococcosis in other sites of the body, in particular skin lesions (nodules or papules) which if biopsied contain pearly white material that can be easily sent for laboratory investigations, or there could be also pneumonia that does not respond to conventional treatment. In fact, whenever, cryptococcosis is diagnosed in the lungs or skin lesions, the CSF should always be examined to rule out sub-clinical meningitis (see below) (Gluckman). “In fact, if skin lesions are present, CSF is almost always positive,” said Dr. Venter.

Course:

Generally, there is a more gradual onset of symptoms, increasing in intensity. People usually come in a median of two weeks after symptoms start but it can range from a few days to five months (Maher and Mwandumba).

“This is not acute meningitis. It doesn’t present in a day. If someone was well yesterday and they come in with a meningeal

syndrome today, it’s not going to be cryptococcal meningitis,” said Dr Steve Gluckman of the Botswana-Penn (University of Pennsylvania) collaboration, during a talk at the Botswana International HIV Conference in Gaborone in 2006.

“I agree, unless it presents after starting ART,” commented Dr. Graeme Meintjes of GF Jooste Hospital (see section on IRIS below).

CD4 cell count:

<100 or even lower. For instance, although the range in the study by French et al was between 1 and 365 cells, the median CD4 cell count was 16.

As a result, although cryptococcal meningitis may be the presenting AIDS-defining illness, Gordon et al noted that people with the condition were more likely to have a history of other serious infections and oral thrush than people with bacterial meningitis — which may provide a clue in a person whose HIV status is not immediately available.

In the McCarthy study, 24% had concomitant TB.

Viral meningitis

Headache (100%) and fever (93%) are the presenting symptoms in the majority of cases (Nowak). But other general signs of meningitis may also be present (Hakim). In cases of zoster, meningitis may occur weeks after the development of shingles — but herpes zoster can also occur in patients with no signs of shingles rash.

Course:

Typically chronic, though herpes can be acute.

CD4:

Any. And such meningitis can occur at high CD4 cell counts during acute HIV seroconversion.

Acute care for people presenting with symptoms of meningitis

People with meningitis may come in to a clinic or other facility that cannot adequately diagnose the condition, or may first be detected by teams providing home-based or palliative care.

Acute management can be crucial to a person’s survival and reduce their chances of long-term neurological consequences such as deafness or learning disabilities (more on those below).

Nurses should follow local guidelines for acute headache and/or fever of unknown origin (depending upon the presenting symptoms). If local guidelines aren’t available, Samuel’s case outlined at the beginning of this review highlights a few rules of thumb that can be used as a simple algorithm (Birbeck).

Is the headache of recent origin? If so, has there been a recent head trauma or any other easily identifiable cause such as sinusitis? Ask the family and examine for head injuries if the patient is not alert. If a common problem, manage accordingly.

Is there fever? If in a malaria endemic area, do a blood smear for malaria parasites. If present, manage according. If in a child, treat for malaria whether the smear is negative or not.

In addition, if the patient has advanced HIV disease, or if there are any of the signs or symptoms of meningitis, focal signs (problems, numbness or weakness in one distinct part of the body rather than the whole body which could be evidence of stroke or mass lesion in the brain), **the patient needs to be seen by a doctor**

or taken to a facility that can diagnose his or her condition as soon as possible.

But given the speed at which bacterial meningitis can kill or seriously disable someone, it may be necessary to start empirical antibiotic treatment.

"What you do for them in the beginning can make all the difference. Just recognizing their problem and referring them somewhere in time for them to receive important medicine can be the difference between life and death," wrote Dr Gretchen L. Birbeck in her book: *Where there is no neurologist*. But "if you suspect meningitis and a doctor cannot see the patient within one hour, begin antibiotic treatment yourself."

The antibiotic should be the broadest-spectrum antibiotic that is available, such as a third generation cephalosporin (check local guidelines). If possible, the nurse should also draw blood samples for further investigations, blood culture if available, at this time (since the antibiotic may clear initial evidence of bacteria by the time a doctor can see the patient).

"Send them to the doctor as quickly as possible. If the patient is too ill to travel, you may need to send for a doctor and treat the patient until the doctor has arrived. Continue to give the patient antibiotics as directed until help arrives. Keep the patient's head elevated. Do not let them lie flat. Use pillows or clothing to prop up the head of the patient. If you have bricks or blocks available, put some under the top part of the patient's bed and prop up the whole top half of the bed. If the sick patient is an infant or child being held by the parent, make certain they hold the child's head up too. Continue antibiotics (and antimalarials if you suspect malaria) until help arrives," Dr Birbeck writes.

Laboratory investigations to diagnose the cause of meningitis

The first steps to diagnosis are the same wherever the patient presents: checking whether there is a common problem and doing a blood smear for parasites in malaria endemic regions, and then managing accordingly.

However, in order to establish the cause of suspected meningitis, it is necessary to perform a lumbar puncture and examine the cerebrospinal fluid. If there is no focal weakness (in the limbs or cranial nerves) or signs of pressure on the optic nerve, a lumbar puncture should be performed in all patients if two or more of the following features are present:

- 1 Headache
- 2 Fever
- 3 Neck stiffness
- 4 Altered mental status (delirium or confused state)

OR: Persisting headache in HIV-infected patients with CD4 count <100 to rule out cryptococcal meningitis, after clinically excluding chronic sinusitis (Wilson).

If there are focal signs, there may be intracranial lesions (perhaps caused by toxoplasmosis, CNS lymphoma, tuberculomas, etc), and it may not be safe to do the lumbar puncture. If possible, a computed tomography (CT) scan of the brain should be arranged within 24 hours and if possible much sooner. If this reveals any lesions, manage accordingly (the management of toxoplasmosis and other intracranial lesions will be discussed in a future clinical review in HATIP).

And if a CT is not available or delayed, treat for likely causes and discuss with a senior colleague.

Again, while waiting, blood samples should be taken for culture and other tests and the patient should be treated with a broad spectrum antibiotic.

The lumbar puncture should be performed by experienced personnel under aseptic conditions (WHO). A description of how to perform the lumbar puncture, as well as good specimen collection and transport practices can be found in WHO's [Laboratory Manual for the Diagnosis of Meningitis caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*](#).

Lumbar puncture technique

Supplied by Dr. Douglas Wilson at Edendale Hospital in KwaZulu Natal, South Africa:

- 1 Give morphine 10 - 15 mg IMI 30 minutes before procedure if patient is anxious or restless
- 2 Position the patient in the left lateral position, with the spine fully flexed.
- 3 Locate the L4-5 or L5-S1 interspace, and mark the position over the interspinous ligament by gently indenting the skin with a pen-tip.
- 4 Sterile gloves should now be worn.
- 5 Clean the area with 10% povidone-iodine solution or 0.5% chlorhexidine solution in 70% alcohol, and infiltrate the skin with 1 ml 1-2% lignocaine (using an insulin syringe).
- 6 Insert the lumbar-puncture needle through the interspinous ligament into the subarachnoid space (identified by a 'flash-back' of CSF into the needle hub).
- 7 Immediately measure the CSF opening pressure using a disposable manometer, held vertically with the '0 cm' mark level with the needle.
- 8 Collect the CSF into three sterile white-topped tubes (labelled 1. 2. 3.):
 - 3 ml is sufficient for suspected bacterial meningitis;
 - 5 ml is required for the diagnosis of cryptococcal meningitis
 - 10 ml is required for the tuberculous meningitis
 - An additional 1 ml of CSF should be put into a grey-topped sodium fluoride tube, for glucose analysis.
- 9 Request chemistry, cell count, glucose, bacterial culture, cryptococcal agglutination test, India Ink stain, TB culture if TBM is suspected
- 10 Document capillary or plasma glucose immediately after procedure (for calculation of glucose ratio)

"In many countries in the developing world doctors are scared of doing lumbar punctures. I have encountered this from Namibia to Indonesia – it is seen as the preserve of the neurologist. Where there are no focal signs and a new headache or confusion in an HIV-infected person lumbar puncture should be encouraged," said Dr. Graeme Meintjes. "In the Jooste casualty, hundreds are done a month and the diagnostic yield is high."

When performing the lumbar puncture, it is important to measure the opening CSF pressure using a manometer. Normal pressure is below 20 cm CSF. This is important for two reasons: 1) to identify and managed raised intracranial pressure – increased intracranial pressure is associated with a higher risk of death in cryptococcal meningitis (van der Horst) (see more below); and because approximately 70% of people with cryptococcal meningitis have raised intracranial pressure (Graybill).

At least 10 ml of CSF will be needed (Wilson). Guidelines on cryptococcal meningitis from the South African HIV Clinician's Society (SAHCS) (see *Resources*) recommend collecting an extra tube of CSF and storing it at room temperature, just in case of a laboratory error.

Laboratory investigations to order

(adapted from the South African Handbook of HIV Medicine):

- A cell count and differential
- Protein and glucose concentrations
- An India ink stain (for cryptococcal meningitis), a stain for acid-fast bacilli (AFB) (for TB) and a Gram stain (for bacterial meningitis) for microscopy
- Mycobacterial, bacterial and fungal cultures
- A cryptococcal antigen test (this is the most sensitive and yet more expensive test, and some, including the SAHCS, recommend telling the lab to perform this only if the India ink stain is negative and no other diagnosis such as bacterial meningitis is made. On the other hand, not requesting the test could result in a delayed diagnosis and may increase the risk of death or increase hospitalisation costs, so these choices may vary from country to country)
- Syphilis serology (indicated by positive RPR or TPHA in blood)
- PCR for HSV or varicella zoster virus, where possible (it isn't in most settings) and if necessary

Blood samples should also be investigated for glucose and the VDRL and rapid plasma reagin (RPR) tests for syphilis, and sent for cultures if the CSF tests come back negative (especially if the patient was put on a course of antibiotics before the lumbar puncture was performed). If necessary, blood can also be evaluated for cryptococcal antigen, which is particularly useful when a lumbar puncture is considered.

Diagnosis: Bacterial meningitis

If the CSF is purulent, meningitis is likely due to a bacterial infection. The major causes of bacterial pneumonia should be identifiable by microscopy after the Gram staining, or by organism-specific testing in more sophisticated environments. Cultures can confirm the diagnoses, and may help identify if less typical bacteria are present (WHO 1997).

Diagnosis: Meningovascular syphilis

According to the Centers for Disease Control criteria, the presence of pleocytosis (WBC count $>10/\text{mm}^3$) and an elevation in CSF protein ($>0.50\text{g/l}$) is compatible with meningovascular syphilis, but a confirmed case would require a reactive syphilis serology in the CSF (CDC). (Pleocytosis and an elevated protein are usual in many meningeal conditions however). Unfortunately, even serology testing for syphilis in the CSF is not 100% sensitive (Brown and Frank). So in the presence of an otherwise unexplained pleocytosis, empiric treatment for neurosyphilis should be given to a person with a positive serum VDRL or RPR, even if the CSF serology comes back negative (Wilson).

Diagnosis: TB meningitis

There is no specific picture on the CSF examination, although a lymphocytosis and very high protein may be suggestive. Culture is definitive but takes weeks to months, and requires adequate volumes of CSF to be sent. A positive AFB smear allows for a clinical

diagnosis, but smears are often negative in extrapulmonary disease, even in overt cases of TB meningitis. Suspect TB meningitis if a high protein is present in CSF, even if AFB stain is negative. Given the difficulty in diagnosis, empiric treatment may be indicated when there is a high index of suspicion (Wilson).

"In a patient with a chronic history and lymphocytic meningitis in Africa, especially with altered mental status, the two commonest causes by far are cryptococcal meningitis and TB meningitis. If cryptococcal meningitis is excluded, *treat for TB*," said Dr. Meintjes. "You may need to start treatment for TB even before one has excluded cryptococcal disease then review when you have results. Clinical decline can be rapid with untreated TB meningitis in HIV. Seldom is the diagnosis of TB meningitis confirmed – it's usually empiric treatment."

Diagnosis: Cryptococcal meningitis

Again, culture is definitive, and, in people with HIV, usually grows within a few days to two weeks. The opening CSF pressure is usually high but could be normal. Low glucose and high protein levels are seen in only in 25% (Sungkanuparph). Cell counts are often in the normal range or only mildly elevated. India ink staining should identify most cases. The literature suggests that the Indian ink stain has a sensitivity of about 75%, though a recent study in Botswana found that it was as high as 95% (Gluckman). However, it is possible that this was related to later clinical presentation or more advanced disease than seen in other settings. Regardless, a negative result cannot be used to exclude diagnosis. Again, the antigen test is both more sensitive and specific.

Diagnosis: Viral meningitis

Typical CSF findings show clear CSF with pleocytosis and a modest elevation in protein. PCR is, again, rarely available so in most resource-limited settings, this is rather a diagnosis of aseptic meningitis, and management, aside from ART, is symptomatic.

Diagnosis in the real world

With limited diagnostic capacity, vague diagnostic criteria and symptoms that are sometimes not specific to any one infection, clinicians operating in the field often have to make their best guess about what infection they should try to treat, only to have treatment failure point them in a different direction:

Case study # 2, from Dr Karilyn Collins working in Tanzania

We had a case of a patient who stopped her ARVs after six months and was admitted unconscious and fitting. She had a left hemiplegia (paralysis on one side of the body) and a lumbar puncture that was normal pressure, with positive protein, low sugar (2.1), 36 cells phf and Indian ink negative. Nothing on culture. She was treated for cryptococcal meningitis and toxoplasmosis but remained semi-conscious and difficult to manage, screaming and confused.

After two weeks of no progress we decided to empirically treat for TB meningitis and she has steadily improved. We are now left with a patient who is blind; fundoscopy showed pale small discs but no signs of

CMV, with a hemiplegia. We are wondering when and if to restart ARVs?"

Treatment of the infectious cause of meningitis

Treatment for the identifiable (or suspected) cause of meningitis should be the first priority in each patient with meningitis and HIV. However, good long-term outcomes can only be achieved by also eventually putting people on ART (and perhaps other preventive therapy – see prevention below), and by managing the patient's increased intracranial pressure (through repeated lumbar punctures, appropriate analgesics for pain and other needs that may arise as a complication of meningitis (see caring for the patient below). However, the introduction of ART after a serious neurological infection does raise the potential for IRIS to develop – and as Dr Collin's case suggests, many clinicians are unsure when is the best time to initiate ART in someone who has had meningitis (see below).

Treatment: Bacterial meningitis

As already mentioned, empiric treatment for bacterial meningitis should be with a drug that treats a broad spectrum of infections or a combination that does so. Although the drugs used or stocked locally differ from one setting to the next, a range of antibiotics may be used for treatment including penicillin, ampicillin, vancomycin, chloramphenicol, and ceftriaxone.

Once the specific type of bacteria has been identified, different or fewer drugs may be preferred. Also, if there is no response after 48 hours (as assessed by purulent CSF on another lumbar puncture), there is a chance that the patient has been infected with a drug-resistant strain, or has more than one infection at once, and treatment may need to be adjusted accordingly.

Examples of bacteria specific treatment, all generally given at high doses:

- *H. influenzae*: treat with a third generation cephalosporin or chloramphenicol for at least 10 days
- *N. meningitidis*: treat with penicillin or a third generation cephalosporin for at least 7 days
- *S. pneumoniae* (penicillin sensitive): Treat with penicillin G potassium, a third generation cephalosporin or chloramphenicol for more than 10 days
- *S. pneumoniae* (penicillin resistant): treat with vancomycin with or without rifampicin
- *Listeria*: treat for two to three weeks with ampicillin +/- gentamicin or cotrimoxazole

Treatment of neurosyphilis

The WHO and CDC recommend treating neurosyphilis with IV Penicillin G 12-24 mU per day for 10 to 14 days or procaine penicillin (2.4mU per day) with oral probenecid (4x500) for 10 to 14 days (WHO 1997, CDC). But none of the intramuscular penicillin regimens reach adequate CSF concentrations, hence intravenous administration should be regarded as standard of care (Carmo).

However, after induction therapy, three weeks of treatment with benzathine benzylpenicillin 2.4 MU week is also recommended (Wilson).

Alternate regimens include: a third generation cephalosporin, such as ceftriaxone 2 g IM/IV per day for 14 days; doxycycline 200 mg bid for 28 days; or amoxicillin 2 g tid plus probenecid 500 mg qd for 28 days.

Clinical improvement and laboratory features should be used to gauge the response to treatment. Lumbar punctures should be

repeated every six months for the next two years to assess whether pleocytosis resolves (CSF white blood cell count should decline by six months and be normal after one or two years). VDRL (if positive and protein levels fall more slowly (Wilson, Carmo).

Treatment: TB meningitis

Unless drug sensitivity testing suggests otherwise, standard TB treatment is usually recommended to treat TB meningitis, provided treatment is started soon enough (Thwaites). But according to Dr Thwaites, obtaining a satisfactory response remains difficult.

"Those of you who've treated quite a lot of neurological TB will know it's rather frustrating because it waxes and wanes, it's very fluctuating and sometimes you have really quite severe clinical relapse of symptoms," he said at the conference in Venice earlier this year.

Drug resistant strains pose yet another challenge, particularly because second line TB drugs do not penetrate the CSF well (Cecchini).

Another issue is whether to use corticosteroids such as dexamethasone to improve responses in people with HIV. Dr Thwaites described a placebo-controlled study of dexamethasone that his team performed with 545 adults with TB meningitis (Thwaites 2004).

This group with HIV was small (98), and they had no access to ART (and as he previously noted, these people tended to die of other conditions). Treatment with dexamethasone reduced their risk of death by 22%, but the effect did not quite reach statistical significance ($p=0.08$).

Treatment: Cryptococcal meningitis

The recommended treatment options for cryptococcal meningitis in the US and Europe are not available or practical in many resource-limited settings:

Induction therapy: amphotericin B 0.7 mg/kg IV and flucytosine (100mg/kg orally) daily for 2 weeks, then consolidation phase with fluconazole (400mg) PO daily for 8 weeks, then fluconazole (200 mg) PO daily for secondary prophylaxis (Saag). (South African guidance differs, see below).

Studies have demonstrated that this is the most potent regimen against cryptococcal meningitis, according to Associate Professor Somnuek Sungkanuparph of Mahidol University, in Bangkok Thailand, who also spoke at the Second HIV Infection and the Central Nervous System in Venice earlier this year. Although the addition of flucytosine to amphotericin B did not significantly improve clinical outcomes over amphotericin B alone in the studies, there was a trend toward a better mycologic cure with this regimen and the combination has higher early fungicidal activity (van der Horst, Brouwer).

"With all this data giving amphotericin B combined with flucytosine may be a better choice. However, in most developing countries, you don't have flucytosine," he said.

So many programmes have opted for giving amphotericin B by itself (for instance, it is recommended by the SAHCS Guidelines). But even this is unavailable in most settings and is not accessible to every patient who needs it.

"Debate is not over regarding the induction regimens for cryptococcal meningitis in resource-poor countries facing a pandemic of HIV infection. Indeed, intravenous perfusions of amphotericin B are often difficult to manage, and amphotericin B toxicity is difficult to prevent, thereby precluding a complete induction therapy course in various areas," wrote Dr Olivier

Lortholary of the Institute Pasteur in *Clinical Infectious Diseases* earlier this year.

However, Dr Venter strongly disagrees with this view.

"Clinicians are needlessly scared of amphotericin B. If you hydrate the patients properly, and use a big line, it's safe. This could be read as encouraging giving second-rate therapy due to inability to manage the consequences. We all need to give lots more amphotericin B – the outcomes are much better," he said.

In many settings, the only available treatment is fluconazole but this treatment has not been shown to produce adequate responses (as the high mortality rates in some of the studies mentioned above demonstrate). More recently, a retrospective study in Cape Town reported high early mortality whether using fluconazole 200 mg daily (for those thought to have a better prognosis or 400 mg daily (Schaars). And earlier this year, another study from Cape Town demonstrated a marked difference in early fungicidal activity for amphotericin B over fluconazole (Bicanic). "At a dosage of 400 mg/day, fluconazole dosage is almost static over the first two weeks of therapy," the authors noted.

If using amphotericin B, the patient and their family should be counselled, if possible, that it can greatly improve mortality outcomes, but that it can initially also cause side effects such as fever, chills, shaking and nausea. In addition, it has the potential to cause kidney damage (usually only during the second week of treatment) – thus patients need to be monitored closely and the doctor advised about all medications that they are taking (since some may increase the risk of kidney damage).

Since flucytosine is not available, the SAHCS Guidelines suggest that a slightly higher dose of amphotericin B, 1 mg/kg, should be used in African settings. They also make the following recommendations on how to prevent and or manage its side effects. First, the first daily dose should be "run slowly over the first half hour of administration."

"Nephrotoxicity and electrolyte abnormalities may be prevented by avoiding amphotericin B in patients with renal impairment, by prehydration (1 litre normal saline containing 20 mmol KCl (1 ampoule), by avoiding concurrent use of other nephrotoxins (non-steroidal anti-inflammatory agents (NSIADs), aminoglycosides including streptomycin) and by routine administration of potassium and magnesium supplements.

"Phlebitis may be prevented by rotation of the drip site every 2 - 3 days and by flushing of lines after the amphotericin B infusion is complete.

"Febrile reactions may be prevented when subsequent doses of amphotericin B are given by administration of paracetamol 1 g 30 minutes prior to dose. Severe febrile reactions may require hydrocortisone 25 mg ivi at the start of the infusion.

"If nephrotoxicity occurs, manage as follows:

- If creatinine increases by 2-fold or more, omit a dose and/or increase prehydration to 1 litre 8-hourly
- If creatinine fails to decrease after the above intervention, stop amphotericin B therapy and use fluconazole."

was done and apart from very high pressure it was completely clear, no protein, normal sugar and Indian ink stain negative. On the strength of the high pressure she started oral fluconazole and we are at present using a generic rather than Diflucan.

She went home on the fluconazole and was admitted six weeks later semi-conscious. I repeated the LP and the pressure was very low but this time pandy protein (a test to determine the presence of protein in the cerebrospinal fluid) was positive, there were 32 cells /hpf and Indian ink stain was positive. She is at present on I/V fluconazole. My worry is that the generic oral drug is not effective! She is improving slowly, her severe pain is relieved by morphine and steroids.

This may not be a problem with the generic; it could just be a case of failed therapy – as the studies above show, fluconazole is often not potent enough to treat cryptococcal meningitis.

Reducing intracranial pressure

Finally, if the patient has high intracranial pressure, repeated lumbar punctures to drain off pressure has also been shown to improve survival in patients with cryptococcal meningitis.

"If the pressure is elevated, they should have a daily spinal tap to lower the pressure until they've had several days in a row with a normal pressure, then we could stop. That may be two days, it may be three days, it can be a week or more sometimes. But pressure needs to be aggressively managed," said Dr Gluckman.

The SAHCS guidelines recommend "draining not more than 20 - 30 ml of CSF (to decrease opening pressure by 20 - 50%) at initial LP. Thereafter the need for pressure relief should be dictated by recurrence of symptoms of raised intracranial pressure. Patients may require daily LPs."

When to start ART in patients with meningitis and the risk of IRIS

Ultimately ART is needed in order to prevent relapse of meningitis, and to keep the patient from dying from other causes.

For instance, in one study that Associate Professor Sungkanuparph co-authored, the impact of ART on relapse and survival rates was investigated in patients who had had a diagnosis of cryptococcal meningitis (Jongwutiwes). Out of 127 patients, 52 received ART, and the median time of ART initiation after cryptococcal diagnosis was 2.6 months. By six months, CD4 cell counts had increased by 97 cells and 87.9% achieved undetectable HIV-RNA. But the impact on survival was even more striking. The median time it took for one-quarter of patients to experience relapse was 10.4 months in the group without ART and 41.9 months in the ART group (P<0.01). The 75% survival from cryptococcal-related mortality in the group without ART was only 6.4 months versus more than 54 months for the ART group (P<0.01). ART was the only factor that was associated with a lower relapse and mortality rate.

However, Assoc. Prof. Sungkanuparph also published an early study showing that IRIS can occur in people with cryptococcal meningitis who are put on ART (Sungkanuparph 2003). The study involved 60 patients, 14 of whom had opportunistic infections a median of 16 weeks after going on ART. "After receiving ART there are a lot of opportunistic infections that happened that fit with the

Case Study #3 Treatment in the real world, from Dr Karilyn Collins

"A 24 year old girl was admitted with severe headache in the middle of October. She is HIV- positive and had started on ARVs in September with a CD4 of 32. An LP

criteria of IRIS, and because Thailand is an epidemic area of tuberculosis, it is not surprising that tuberculosis is the most common IRIS in this cohort (8 episodes) and cryptococcal meningitis (3 episodes) is also another cause of IRIS." Similar data have been reported in South Africa (Lawn).

Clearly the risk of IRIS must be balanced with the risk of progression and death without ART, but when is the best time to start ART in people who have had meningitis?

In one retrospective cohort study of 120 patients with cryptococcal disease, the risk of IRIS was significantly higher in those who started ART within two months of their diagnosis (Lortholary 2005). In another retrospective review, the risk was reported to be higher in those who initiated ART within 30 days of their cryptococcal diagnosis (Shelburne). But there was no statistical difference in mortality between those who had IRIS and those who did not over 18 months of follow-up.

The SAHCS guidelines believe that ART should begin sooner. "We believe ART is most appropriately started 2 – 4 weeks after treatment for cryptococcal disease has commenced. Although no prospective evidence exists in this regard, given these patients' advanced immunosuppression, delaying ART introduction beyond 4 weeks to reduce the risk of IRIS may increase the risk of mortality."

There is some disagreement whether all ART regimens are equally appropriate. The SAHCS guidelines recommend caution using a nevirapine-based regimen while the patient is on fluconazole, since at least one study in 24 patients has shown that adding fluconazole to a stable nevirapine regimen can increase nevirapine levels and the risk of liver toxicity by 25% (Pitt). In a pharmacokinetic study that Assoc. Prof. Sungkanuparph was involved with, coadministration doubled nevirapine trough levels – and yet, in a larger study in 686 subjects in Thailand, there was no difference between the rates of hepatitis or other adverse events between people who were taking nevirapine with or without fluconazole (at either 400 mg per week or 200 mg per day) (Manosuthi W 2005 and 2007).

One possible difference between the South African and Thai studies could have been that the CD4 cell counts in the patients in Thailand were extremely low. Hypersensitivity reactions have been shown to be more likely in people with CD4 cell counts over 200.

Regardless of the regimen, people placed on ART still have to be counseling about the risk of IRIS and the need to seek medical attention should it occur. Closer monitoring of people who have previously had meningitis is advisable, though it is unclear for how long. In another recent study from Assoc. Prof. Sungkanuparph found that cryptococcal IRIS could develop as much as 27 months after antiretroviral therapy was initiated, and he could not identify any factors to identify which patients were at particular risk, or predict when the IRIS might occur (<http://www.aidsmap.com/en/news/3381844F-7EB1-4379-B25B-15A6258191AD.asp>).

"Close monitoring after initiation of ART is needed and we don't know how long – maybe two to four years or longer," concluded Assoc. Prof. Sungkanuparph.

Reducing suffering in a person with meningitis and managing its long-term consequences

One thing that literature sometimes neglects to mention is the intense suffering that people with meningitis go through – such as the screaming patient that Dr Collins was caring for.

As frightening as lumbar punctures may sound to some, in the case of cryptococcal meningitis, they do provide real pain relief

since much of the pain is due to high pressure around the brain. In fact, "simply relieving the pressure is the most potent and immediate form of pain relief," said Dr. Venter.

But appropriate pain medication must be prescribed as well, commensurate to the level of pain that the individual is enduring (See the WHO analgesic ladder in the *Resources* section). (NSAIDs however should be avoided in patients on amphotericin B due to a risk of kidney toxicity).

In addition, *A clinical guide to supportive and palliative care for HIV/AIDS in sub-Saharan Africa* (see *Resources* section) recommends "other measures such as being in a quiet, dark room, having a cool cloth over the eyes, and having the neck massaged may be helpful." It also stresses that adopting a palliative care approach also extends to addressing psychosocial issues related to the illness.

"Consider the implications of the person's condition for his or her ability to continue to work. In addition, there have been unfortunate incidences of patients with dementia or delirium being thrown out of their homes or of being locked up in a small shed."

This would likely result in the rapid death of someone with meningitis.

In addition, meningitis can also result in permanent brain damage, hearing loss, blindness, partial paralysis or learning disabilities in survivors – especially if diagnosis and treatment are delayed. Health systems aren't prepared to manage such individuals, as the following case submitted by Dr Natalya Dinat, Director of Wits Palliative Care, at the University of Witwatersrand illustrates:

Case Study #4 Treatment in the real world, from Dr Karilyn Collins

The patient was a 26 year old on her first visit. She was diagnosed with RVD (retroviral disease) and TB meningitis that had involved her spine, and referred by the hospital team. She had paraparesis (partial paralysis of the lower limbs) because of her TB, and had an indwelling catheter.

The patient was on TB medication, rifampin 5 daily; pyridoxine 25 daily, amitriptyline 10mg, daily Bactrim prophylaxis. She was not yet ready to disclose her status to her family.

On examination, she had painful feet and diarrhoea. On 3rd July 2003, amitriptyline was increased to 25mg each night, and Imodium prescribed. The patient was also referred for home-based care. Amitriptyline was increased to 50mg on 20th July 2003, and a wheelchair issued.

On 20th August 2003, she complained of severe back pain, for which treatment was prescribed. A follow up visit on the 9th September 2003 found the patient still in severe pain, with depressed mood. The left leg was also painful, and she had difficulty in walking. The prescribed medication had not been issued by the clinic, the patient was continuing with TB medication.

Dr Dinat says that the case illustrates several specific challenges:

- 1 There is no proper referral system between different health facilities, no proper communication channel. This results in patients defaulting in their medication.
- 2 The system does not cater for patients who are either bedridden or cannot walk. TB patients have to be weighed to determine the dose of treatment; most of these patients either do not have transport or money to get to the nearest health facility.
- 3 The delays in disability grant applications affect availability of resources which assist the family.
- 4 Lack of medication due to introduction of the EDL. The primary health care EDL did not have amitriptyline as they did not offer psychiatric services.
- 5 Medication prescribed by the palliative care team not issued promptly, this resulted in delayed initiation of treatment which impacts on patient outcome.
- 6 When the patient required ARVs, she had to be started on dual therapy through the private health system as the ARV treatment was not yet available in the public health sector.

The longterm consequences in children can be even more devastating, according to Dr. Joan Marston, who is the paediatric palliative care manager for the Hospice Palliative Care Association of South Africa and Chair of the International Children's Palliative Care Network in South Africa.

"I can report anecdotally on children diagnosed with meningitis in a children's hospice programme. Each case was reported late and was left with severe residual disability. All families have rejected the children and there are few suitable facilities for children with disabilities, from whatever cause, in South Africa," she said.

"Children with severe disabilities fall into one of the categories of children requiring paediatric palliative care which is the care of the child's body, mind and spirit and support for the family into the bereavement period. It includes developmental support and may continue over many years as there are a number of children with severe life-limiting conditions that may live into their 30s such as Duchenne's Muscular Dystrophy; genetic conditions, severe disabilities."

Case Study #5 and #6, from Dr Marston.

A girl of 4 years living on a farm with a mother with reduced mental capacity was admitted to hospital after a few epileptic episodes and found to have cryptococcal meningitis which has left her blind and deaf and developmentally delayed. At 8 years she is not able to walk, sit alone or talk but does respond to touch, laughs often, and is able to eat. She was referred for paediatric palliative care by the medical team and is on a chronic programme providing regular visits, developmental stimulation (with little success) loving emotional and social support and regular chaplaincy visits. The hospice placed the child in a registered place of Care with regular admissions to an in-patient unit for intensive physiotherapy and clinical evaluation.

The family received regular visits on the farm but the mother did not have the capacity to care for her child and had another baby to care for. The family later left the farm and had no further contact with the child.

A boy of 3 was admitted to a hospice in-patient unit from a district hospital after a late diagnosis of AIDS-related cryptococcal meningitis, semi-comatosed, blind and deaf. His mother was unable to care for him as he was fed through a naso-gastric tube. He appeared to have pain with muscle spasms which was treated successfully with an anti-spasmodic and paracetamol and daily full-body massage, and was also treated for epilepsy with Epilim and Phenobarb as a result of the meningitis. The child remained in the in-patient unit as there was no place that could care for him, and he remained semi-comatosed although he appeared to respond to touch and loud noises, but died in the district hospital after developing pneumonia. Attempts were made to encourage the mother to visit her child and spend time with him but she refused to care for him unless she received payment and then disappeared from his life.

"Children are often diagnosed late, and are often left with disabilities which make them difficult to care for at home," said Dr Marston. "They require long-term palliative interventions to improve their quality of life. Sadly, there are few facilities to care for these children properly and they often are placed in places of safety/shelters without suitably trained staff. I also wonder how many children actually die before reaching medical help."

She notes that the Association for People with Disabilities or APD, is a national association in South Africa that provides a very good service to disabled adults with some accommodation in certain centres. Unfortunately, there are few similar facilities caring for disabled children. A more activist and community-based approach may be called for.

"The need for constant care, added to the stigma of AIDS, can be an overwhelming prospect to families," according to *A clinical guide to supportive and palliative care for HIV/AIDS in sub-Saharan Africa*. "Adopting a team approach to care is a good strategy to facilitate optimal care in such difficult circumstances. The team should include the patient, the family, members of the community, and all the relevant care providers, including traditional healers and spiritual leaders if desired by the family."

Prevention of meningitis

Given such challenges, as the old adage goes, prevention would certainly be better than a cure.

"Approaches to reducing the incidence include the deployment of effective antiretroviral therapy in areas where HIV co-infection is common, vaccination, and prophylactic antibiotic therapy," wrote Scarborough and Njalale from Malawi.

- Vaccination for the major causes of bacterial pneumonia is recommended in people with HIV, even though the protection offered may not be as great as in the general population, particularly in those with lower CD4 cell counts (Spach). However, data from one study with the 23-valent pneumococcal polysaccharide vaccine in Africa found that vaccination was associated with an increased risk of pneumococcal disease (French). However, recent studies have shown PCV-7 (7-serotype conjugate pneumococcal vaccine) to be safe and efficacious when used in children infected with HIV, and WHO now recommends that countries with a high prevalence of HIV

prioritise the introduction of this vaccine (<http://www.who.int/entity/wer/2007/wer8212.pdf>). In addition, good national vaccination policies could also reduce the overall burden of bacterial pneumonia through “the herd effect.” (Klugman)

- Cotrimoxazole prophylaxis has been shown to reduce the frequency of bacterial infections — even in Zambia, where there is a high level of background antibiotic resistance (Mulenga <http://www.aidsmap.com/en/news/DFC83829-056C-4C24-94FE-BAB37FA7BDE0.asp>).
- Isoniazid preventive therapy (IPT) reduces the incidence of TB and making it a part of the essential package of care offered to people with HIV could potentially reduce the risk of TB meningitis as well (see [HATIP # 96](#)).
- Fluconazole prophylaxis: The use of prophylaxis to prevent cryptococcal meningitis and other infections is more controversial. Although several randomised studies have shown that fluconazole and itraconazole reduces the incidence of cryptococcal disease in people with advanced HIV disease, and one study even demonstrated a survival benefit, none of these studies have been conducted in sub-Saharan Africa (Chang, Chetchotisakd). In addition, concerns have been raised about the potential drug interactions (as with nevirapine), the potential for teratogenicity, and the risk of developing fluconazole-resistant thrush infections.

So WHO's draft guidelines on the Essential Prevention and Care Interventions for PLHIVs, includes a recommendation to consider fluconazole prophylaxis in areas where cryptococcal disease is common for severely immunocompromised people with HIV (WHO clinical stage 4 or CD4 < 100 cells) but the level of recommendation is ‘optional.’

The SAHCS guidelines stress that the priority should rather be to get people with such low CD4 cell counts on ART as soon as possible.

“ART is the most effective intervention to treat AIDS, and is the most potent mechanism to prevent both primary and secondary recurrences of cryptococcosis.” However, it concedes that “primary prevention... with fluconazole may have a limited role in patients with CD4 counts below 100 cells where delays in access to ART are anticipated.”

Unfortunately, such delays are common in South Africa... and can have serious consequences, as the final case from Dr Dinat illustrates.

Case Study #7 - Dr Natalia Dinat, South Africa

A forty four year old female patient referred to us by the Mpumelelo ARV Clinic with a diagnosis of RVD (retroviral or HIV disease), and CD4 count was 80 cells/mm³.

The patient was first seen by the outreach team in 7th December 2006 and found to have the following: difficulty in speaking and comprehending, incontinent, bed sores with ECOG scale of 4 (ECOG is a scale used to assess disease progression as well as how the disease affects the daily living abilities of the patient — a scale of 4 means the subject is completely disabled, unable to care for themselves, and confined to bed or chair).

The family had insight into the condition of the patient. The wound was dressed and the family

counselled. Follow up visits were done between December 2006 and March 2007, during which time she was started on ART.

On May 2nd 2007, the patient was visited by the team. She indicated that she had been to the local clinic because of a severe headache. She was given pethidine 50mg stat (an opioid analgesic) and ibuprofen 200mg tds. She was also advised to go to the hospital if there was no improvement on the headache. The palliative care nurse clinician examined her and found that she had positive Kernig signs.

A single dose of Voltaren 75mg (diclofenac) was given intramuscularly. The patient was presented and discussed at the clinical review meeting and the palliative care doctor had to review the patient.

The patient was reviewed on the 7th May 2007 by the palliative care doctor, and confirmed that the patient had neck stiffness and positive Kernig sign. A provisional diagnosis of meningitis was done and the patient referred for admission through the hospital casualty department.

Upon arrival at casualty the patient was returned home as the admitting doctor felt that the patient did not have meningitis. A lumbar puncture was not done.

The patient was continued on Spectrapain 2 tabs tds with no improvement. The patient deteriorated and was admitted on the 28th May 2007. A diagnosis of cryptococcal meningitis was confirmed and the patient put on fluconazole. The patient was discharged prematurely because of the industrial action in the public hospitals and continued on fluconazole 400mg orally, and follows up at the local clinic.

On the 10th July, the patient was visited by the team. She was found sleeping, complaining of vomiting, weakness, photophobia and conjunctivitis. She still had neck stiffness. She was referred to St John's Hospital for assessment by ophthalmologists. She was to continue with the other medication. After three months of follow up, the patient had improved but still had some weakness. The patient died 11th November 2007.

Resources for palliative and supportive care for people with disabilities

- The AIDSMap Palliative Care Portal: <http://www.aidsmap.com/cms1038390.asp>
- The African Palliative Care Association: <http://www.apca.co.ug/>
- The Hospice Palliative Care Association South Africa: <http://www.hospicepalliativecaresa.co.za/>
- The International Association for Hospice and Palliative Care: <http://www.hospicecare.com>
- The International Children's Palliative Care Network: <http://www.icpcn.org.uk/> (in particular, see their international directory)
- The Association for the Physically Disabled (APD) helps South Africans with physical disabilities: <http://www.apd.org.za/>

- The Child Rights Information Network:
<http://www.crin.org/index.asp>
- Foundation for Hospices in Sub-Saharan Africa (FHSSA):
www.fhssa.org
- The International Federation of Red Cross and Red Crescent Societies: <http://www.ifrc.org>
- The Elizabeth Glaser Pediatric AIDS Foundation:
<http://www.pedaids.org>
- The WHO pain ladder:
<http://www.who.int/cancer/palliative/painladder/en>
- A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa addresses the many aspects of palliative care that are key in caring for the person living with HIV/AIDS from an African perspective: to read online:
<http://www.fhssa.org/i4a/pages/Index.cfm?pageID=3361>
- A very clear and easy to use resource manual for nurses and other cadre of health staff: "Where there is no neurologist," by Dr Gretchen Birbeck is available online:
http://neurology.msu.edu/downloads/where%20there%20is%20no%20neurologist_whole%20book.pdf

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A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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