DECISIONS

A 65-year-old HIV-positive man with acute diarrhea

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A 65-year-old man with chronic HIV infection presents with a one-week history of diarrhea. He describes six to eight loose bowel movements daily. His most recent CD4 count is 0.22×10^9/L, with an undetectable viral load. His current anti-retroviral (ARV) regimen consists of ritonavir-boosted atazanavir, tenofovir and emtricitabine.

What are the key components of history to obtain for this patient?

In addition to onset and duration of the diarrhea, details such as volume and frequency of stools, nocturnal symptoms, abdominal pain, fever and weight loss may provide clues to the underlying cause.[1] Sexual activities, food and water exposures, recent travel and antibiotic use should also be assessed. In any patient with HIV, the history should also include the duration of HIV infection, past HIV-related complications, current and past ARV regimens (and adherence), and most recent T-lymphocyte CD4 count, as these details can provide insight into the susceptibility to opportunistic pathogens.[1]

What is the differential diagnosis of acute diarrhea in this patient?

Potential complications of HIV infection can be divided into HIV-related and HIV-unrelated causes (i.e., conditions that commonly occur in HIV-negative individuals) (Figure 1). Causes related to HIV occur almost exclusively in immuno-compromised or HIV-positive patients, and include opportunistic infections or malignant diseases, ARV-related effects and HIV infection itself.

In patients with diarrhea and a CD4 count below 0.10×10^9/L, potential opportunistic infections include *Cryptosporidium* species and micro-sporidia.[1] Below a CD4 count of 0.05×10^9/L, patients are at risk of acquiring cytomegalovirus (CMV) colitis and disseminated *Mycobacterium avium* complex disease.[1] Opportunistic malignant diseases such as non-Hodgkin lymphoma and Kaposi sarcoma can present with diarrhea when the gastrointestinal tract is involved.

Diarrhea caused by ARV agents is common. Incidence of diarrhea is highest with protease inhibitors (13.6%), followed by nucleoside reverse transcriptase inhibitors (10.0%) and non-nucleoside reverse transcriptase inhibitors (2.2%).[2] The incidence of diarrhea also varies among ritonavir-boosted protease inhibitors, ranging from 2% (ritonavir-boosted atazanavir) to 11% (ritonavir-boosted lopinavir).[2]

Diarrhea caused by HIV itself (known as HIV enteropathy) should be considered when other causes have been excluded.

Causes unrelated to HIV, such as infectious (e.g., *Escherichia coli*, *Campylobacter*, *Shigella*, *Clostridium difficile*, viral), drug-induced (e.g., laxatives), dietary and immunologic causes, remain important considerations as well. A broader differential diagnosis exists in patients who present with chronic diarrhea, and includes inflammatory bowel disease, irritable bowel syndrome and gluten-sensitive enteropathy.
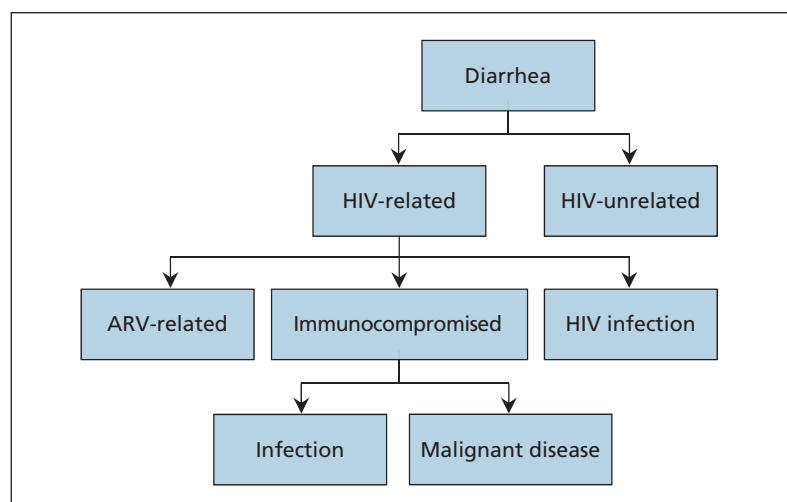
What initial investigations should be ordered?

After a clinical assessment of volume status and stability, serum electrolytes and creatinine should be measured to assess for metabolic or renal abnormalities secondary to volume depletion. Depending on the severity of diarrhea, and the presence of

Figure 1: Approach to the diagnosis of diarrhea in a patient with HIV infection. ARV = antiretroviral therapy.

metabolic derangements, admission to hospital for intravenous fluid replacement may be necessary.

Recommendations from the Panel on Antiretroviral Guidelines for Adults and Adolescents suggest that initial investigations include a CD4 count if previous results from blood tests are unavailable or tests were done more than three months previously.[3] A stool sample should be sent for bacterial culture and to test for ova, cysts and parasites; the latter test should be run on samples collected on at least two separate days.[4] Specimen requisitions should identify the patient as HIV-positive or request acid-fast (to detect *Cryptosporidium*, *Isospora* and *Cyclospora*) and trichrome staining (to detect microsporidia) because these are not routinely performed.[1] A stool sample should also be collected to test for *Clostridium difficile*.[1] Depending on the extent of depletion of CD4 lymphocytes and the clinical history, additional tests to be considered include blood cultures, as well as blood and stool cultures for acid-fast bacilli.

If symptoms persist despite negative stool investigations, a referral to a gastroenterologist should be made for consideration of endoscopy.[1] Direct visualization of the gastrointestinal mucosa and histopathology from biopsy samples can improve diagnostic yield. In addition, the diagnosis of CMV colitis is based on histopathologic findings, because it can occur in the absence of detectable CMV viremia.[5] Current guidelines based on expert opinion suggest flexible sigmoidoscopy or colonoscopy when laboratory investigations are nondiagnostic, with consideration for upper endoscopy if symptoms persist.[6]

Should ARV be withheld at this time?

When considering temporary discontinuation of ARV regimens, clinicians must weigh the likelihood of ARV toxicity, severity of illness and potential harm if an offending agent is continued against the potential harms of treatment interruption. Factors suggesting ARV-related diarrhea include an ARV regimen known to cause diarrhea and a temporal relation between diarrhea and ARV initiation. Current guidelines recommend short-term interruption of ARV only when a patient experiences severe or life-threatening toxicity or cannot take oral medications.[3] If a decision is made to interrupt treatment, the entire ARV regimen should be withheld. Long-term interruption of ARV therapy is not recommended.[3] Management of ARV-associated diarrhea should be carried out in consultation with a clinician who has experience managing the treatment of patients with HIV.

Case revisited

On further history, no unique exposures were identified. Results of routine laboratory investigations were normal. Stool cultures isolated *Shigella* species. Because of his immunocompromise, and based on susceptibility testing, the patient received ciprofloxacin 500 mg orally twice daily for seven days, and his symptoms resolved. The patient was also counselled on the risks of *Shigella* transmission with sexual activity, and the importance of safe sexual practice and proper hand hygiene.

References

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