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Enteric viruses in HIV-related diarrhoea

Richard C.G. Pollok and Michael J.G. Farthing

HIV-related diarrhoea is an important cause of morbidity and mortality in HIV infection. Cytomegalovirus is a well-established cause of diarrhoea, but the role of other enteric viruses is less clear and will be discussed here. The clinical manifestations, disease mechanisms, diagnostic techniques and current treatments for the management of these infections are reviewed.

OPPORTUNISTIC viral enteritis is a potentially important gastrointestinal (GI) manifestation of HIV-related disease. However, with the exception of cytomegalovirus (CMV) and human herpes simplex virus (HSV), which are established aetiological agents of disease in the GI tract in patients with HIV, the role of other enteric viruses remains controversial.

Between 44% and 82% of HIV patients with chronic diarrhoea have a pathogen that is readily identifiable using a well-established diagnostic protocol that includes stool culture, microscopy and histological examination of biopsies obtained by endoscopy of the upper and lower GI tract[1–4]. For example, using such a protocol, 82% of 155 cases of persistent diarrhoea were related to infection with identifiable bacteria, parasite or CMV, with CMV alone accounting for 18% of these cases[4]. The additional techniques of stool electron microscopy and specific immunological staining implicated other enteric viruses in a further 11% of cases. The role of these other viruses in so-called 'pathogen-negative' diarrhoea remains uncertain. The clinical importance of HIV enteropathy is probably limited. Several viruses, including astrovirus, picobirnavirus, small round structured virus (SRSV) and rotavirus, are implicated in HIV-related diarrhoea. In addition, adenovirus is associated with persistent diarrhoea in patients with characteristic adenovirus colitis. The evidence for a pathological role for these viruses will be discussed (Table 1).

It is well established that CMV can infect the GI tract and cause diarrhoea and methods of diagnosis and current treatments are reviewed. The spectrum of disease morbidity and mortality among HIV patients has altered dramatically since the widespread introduction of highly active antiretroviral therapy (HAART). Opportunistic infections, including CMV infection of the GI tract, in patients with AIDS have diminished greatly. Following the initiation of HAART, AIDS patients with CMV can successfully discontinue antiCMV treatment without reactivation of the disease and with a parallel reduction in CMV **viraemia**.

Richard C.G. Pollok* BSc, MRCP, DTM&H
Wellcome Trust Research Training Fellow

Michael J.G. Farthing MD, FRCP
Professor Gastroenterology

Digestive Diseases Research Centre, St Bartholomew's and the Royal London School of Medicine and Dentistry, Turner St, London, UK E1 2AT.
Tel: +44 20 7882 7191
Fax: +44 20 7882 7192
***e-mail: r.c.pollok@mds.qmw.ac.uk**

CMV infection of the GI tract

The pathogenic role of CMV infection is well established. Although **retinitis** is the most common manifestation of infection, before the introduction of combination antiretroviral therapy, GI infection of the oesophagus, stomach, small bowel and colon occur in 5–15% of patients during the course of HIV infection. The incidence of CMV retinitis has declined following the introduction of HAART, with a concomitant increase in survival[5]. This is also presumably true of GI CMV, although published data are limited. Although CMV can infect any part of the GI tract, the most common site of infection is the colon[6], and the most common manifestation of CMV colitis is chronic or intermittent diarrhoea in association with abdominal pain. The disease is also associated with mild or severe rectal bleeding or abdominal pain in the absence of diarrhoea and, in addition, fever is common at presentation. Pain can precede the development of **toxic megacolon**, and intestinal perforation is rare but clearly life threatening. Colonic CMV infection can occur in association with infection elsewhere in the GI tract including the oesophagus, which usually results in **dysphagia** and **odynophagia**, and the pancreatico-biliary tree, which results from AIDS-related **cholangiopathy** or **pancreatitis** and manifests as pain in the upper abdomen. GI infection can also herald CMV retinitis and careful retinal assessment is, therefore, essential in this group.

Mechanisms of disease

The mechanisms by which CMV induces GI disease are poorly understood. CMV infection of the mucosa is associated with a marked local inflammatory response, which might have a role in inducing mucosal ulceration. Wilcox and colleagues found that mRNA levels of the pro-inflammatory cytokine tumour necrosis factor α (TNF-α) were elevated in oesophageal mucosa of patients with CMV **oesophagitis**, but returned to normal following treatment of CMV (Ref. 7). Similarly, Sharpstone *et al.* noted increased levels of TNF-α in faecal samples from patients with GI CMV (Ref. 8). The enteric ischaemia that results from CMV-associated vasculitis might conceivably play a role in GI CMV (Ref. 9). Although this hypothesis remains unexplored in CMV enteritis, a similar mechanism has been invoked to explain the aetio-pathogenesis of the

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Table 1. Evidence supporting an association between enteric viruses and diarrhoea in HIV infection

Virus	Association	Refs
CMV	Strong	1–4
HIV	Possible	44,45
Adenovirus	Possible	35–38
Rota, calci-, astro-, corona-, picobirnavirus	Weak	See Table 3

inflammatory enteritis, **Crohn's disease**. The role of CMV-specific T cells in GI disease is unclear. Patients with serological evidence of CMV but without clinical disease have $CD8^+$ T cells that are specific for pp65, the CMV lower matrix protein, in gut-associated lymphoid tissue[10]. By contrast, systemic CMV-specific $CD4^+$ cells wane in patients treated with long-term HAART (Ref. 11). Further studies are required to determine the role of CMV specific T-cell responses in patients with HIV.

Diagnosis of CMV

A spectrum of both upper and lower GI manifestations of CMV infection have been described and a definitive diagnosis of CMV **enterocolitis** requires intestinal biopsy. In a prospective study, Wilcox and colleagues evaluated 55 patients with HIV by sigmoidoscopy and colonoscopy. Chronic diarrhoea and abdominal pain occurred in 80% and 50% of patients respectively and 9% presented with lower GI bleeding with a previous history of diarrhoea[12]. Endoscopically, appearances were heterogeneous. Three main categories were identified: (1) colitis associated with ulceration (39%); (2) ulceration alone (38%); or (3) colitis alone (20%). Subepithelial haemorrhage was common in all groups. A total of 31 patients underwent complete endoscopy to the caecum. Of these, four (9%) had disease that was proximal to the splenic flexure without distal involvement that was therefore inaccessible by flexible sigmoidoscopy. This contrasts with early reports suggesting higher rates of right-sided colitis[13]. The same group has assessed the varied endoscopic appearances of CMV infection of the oesphagus[14]. Multiple ulcers, located in the middle or lower oesophagus, were identified in 58% of patients. These were usually less than 1 cm in diameter and superficial. The heterogeneous manifestation of CMV disease in both the colon and oesophagus makes biopsy essential for accurate diagnosis.

A histologically based diagnosis of CMV enterocolitis depends largely on identification of characteristic cytomegalovirus inclusion bodies in samples usually obtained from the base of CMV ulcers. In addition, specific immunoperoxidase staining for CMV is also useful in identifying GI disease[15]; positive staining is more likely from the edge of ulcers and some authors claim greater sensitivity compared to conventional histology, although it is unclear from these reports how rigorously inclusions bodies have been excluded[16,17]. The value of a viral culture of intestinal biopsies is limited as this is a time-consuming procedure. Furthermore, CMV **viraemia** can occur in the absence of mucosal disease, which can lead to a false-positive diagnosis if biopsies are contaminated with blood. Although using *in situ* hybridization to assess GI CMV disease is both sensitive and specific, it probably offers little additional benefit over conventional histology[18]. Using the PCR for the detection of CMV might also be more sensitive than using standard histological techniques; however, evidence suggests that this technique lacks specificity, with 28% of normal GI biopsies positive by PCR. Furthermore, as with *in situ* hybridization, there is the risk of PCR giving a false-positive result in patients with viraemia. The sensitivity of conventional histology, viral culture, PCR and immunohistochemistry are summarized in Table 2 (Ref. 19). Cotte and colleagues monitored CMV DNA levels during treatment and levels broadly reflected clinical response[20].

Newer techniques are now available to monitor the natural history and progression of CMV disease in the post-HAART era. Salmon-Ceron and colleagues have compared three blood markers of CMV, levels of pp65 antigenaemia in viral culture, plasma levels of CMV DNA and levels of late CMV mRNA, in the assessment of CMV-disease progression in patients on HAART. In a multivariate analysis, plasma CMV DNA, raised pp65 antigenaemia or a CD4 count of 75 cells μl^{-1} were identified as independent risk factors in the development of CMV disease[21]. Others have compared these techniques with retinal assessment in the evaluation of CMV **retinitis**. The Digene hybrid capture CMV DNA system was 85% as sensitive as retinal assessment, which is similar to the more cumbersome pp65 antigenaemia assay (80% as sensitive)[22].

Glossary

Cholangiopathy – Pathology relating to the biliary tree.

Crohn's disease – Chronic inflammatory condition of the gastrointestinal tract, the cause of which remains unknown.

Dysphagia – Difficulty in swallowing.

Enteric virus – Virus with a tissue tropism for the intestinal tract.

Enterocolitis – Inflammation of the upper intestine and colon.

Odynophagia – Pain on swallowing.

Oesophagitis – Inflammation of the oesophagus.

Pancreatitis – Inflammation of the pancreas.

Retinitis – Inflammation of the retina that can lead to visual impairment or blindness.

Toxic megacolon – Pathological dilatation of colon associated with certain infections and inflammatory conditions of the bowel.

Viraemia – Blood-borne carriage of virus.

Table 2. CMV positivity identified by different techniques in gastrointestinal biopsies[a,b]

Tissue	Histology	Virus culture	PCR	IHC
Abnormal	6.4%	11%	67%	3.6%
Normal	3%	17%	28%	0

[a]Adapted from Ref. 19.
[b]Abbreviation: IHC, immunohistochemistry.

These newer techniques have not yet been evaluated in the management of GI CMV disease, however.

Drug treatment

Treatment of CMV enterocolitis requires parenteral therapy with either ganciclovir (5 mg kg^{-1} twice daily) or foscarnet (90 mg kg^{-1} twice daily), both of which can cause severe side effects. Although these agents improve both endoscopic and symptomatic markers of CMV disease, the survival benefit is uncertain and needs to be re-evaluated following the introduction of HAART (Ref. 23). Ganciclovir can cause severe bone marrow depression with resultant anaemia and neutopaenia, and foscarnet can cause severe renal impairment (although a concomitant infusion of normal saline largely diminishes the risk of renal damage). In an open label, randomized study comparing a two-week course of foscarnet with ganciclovir, at the doses stated above, there was no significant difference in response of GI CMV disease between the two therapies[24]. Approximately 75% of patients had good clinical and endoscopic responses with disappearance of inclusion bodies as determined histologically. Relapse occurred within ten weeks in at least 50% of patients and survival without HAART was ≈20 weeks. Surprisingly, Blanshard and colleagues found that maintenance therapy did not increase the time taken for relapse of GI disease, although numbers were small and allocation of maintenance therapy was not randomized. The use of oral ganciclovir in maintenance therapy for retinitis is effective but has not been specifically evaluated for GI disease[25]. The efficacy of treatment with oral ganciclovir for primary prophylaxis of CMV disease is disputed and concerns about the development of viral resistance have been raised[26,27]. It is hoped that newer agents, such as cidofovir, famiclovir, valganciclovir and formivirsen, will have a role in the management of CMV disease[28].

HAART

Encouragingly, the advent of HAART has led to a marked reduction in mortality and morbidity of HIV patients[29]. HAART can result in remission of previously persistent opportunistic infections, including CMV infection[5]. However, the development of viral resistance and difficulties with compliance could lead to breakthrough HIV viraemia and the re-emergence or reacquisition of opportunistic GI infections. Unfortunately, combination antiretroviral therapy is costly and, consequently, unavailable to the vast majority of HIV patients worldwide. Patients on HAART with stable CMV retinitis and CD4 counts of 150 cells μl^{-1} were able to successfully discontinue antiCMV maintenance therapy without relapse of retinitis or development of extraocular disease over a mean follow-up period of 16 months[30]. Importantly, immune reactivation retinitis occurred in 90% of patients started on HAART before discontinuation of antiCMV treatment, with substantial visual loss in the minority of patients. MacDonald and colleagues report similar findings, although the follow-up period was considerably shorter, and they do not comment on immune reactivation retinitis[31]. Others find that HAART causes a significant and progressive decline in CMV viraemia in the absence of specific antiCMV treatment[32]. It is intriguing to speculate about the possible occurrence of immune reactivation enteritis in patients with GI CMV; this has not been described to date.

Many questions remain about the host immune response to opportunistic infections following immune reconstitution with HAART. What are the specific immune mechanisms leading to disease resolution following HAART? Does the T-cell repertoire expand following reconstitution to recognize 'new' CMV antigens? When can secondary prophylaxis be discontinued in patients that respond to HAART? What are the immune consequences of retroviral rebound when HAART fails? How can CMV indices be monitored to predict relapse in patients on HAART?

Adenovirus

Adenovirus is reported to cause infection in other immunosuppressed groups, including individuals with primary immunodeficiency and bone-marrow-transplant patients[33]. In HIV patients, Dionisio and colleagues report increasing stool carriage of subgenus F type 40 adenovirus with increasing immunosuppression[34]. Janoff and colleagues first described adenovirus colitis[35]. Electron microscopy or culture of colonic biopsies from 67 HIV patients investigated for diarrhoea identified adenovirus in five patients. Colonoscopy revealed mild inflammatory change in two of these patients. Focal necrosis and amphophilic nuclear inclusions within degenerating epithelial cells were shown using light microscopy, and electron microscopy revealed characteristic hexagonal adenovirus particles within the inclusions (Fig. 1). Maddox *et al.* have confirmed these characteristic features and found that specific immunostaining for adenovirus is both sensitive and specific for the identification of adenovirus inclusions[36]. The pathogenic role of adenovirus remains unclear as this group of patients is frequently co-infected with other known pathogens. Thomas and co-workers report that adenovirus colitis is significantly more likely to be associated with chronic diarrhoea[37], while Schmidt and colleagues were able to detect adenovirus only in AIDS patients who are severely immunosuppressed[38]. Although in the severely immunosuppressed group, adenovirus was detected more frequently in patients with diarrhoea than without (10% vs 3.3%), both positive and negative correlations between adenovirus and diarrhoea have been reported by other groups (Table 1)[37–43]. Most studies indicate a strong association between infection with adenovirus and co-infection with other pathogens, in particular CMV. It is difficult, therefore, to ascribe a pathogenic role to this virus with any certainty[37–39].

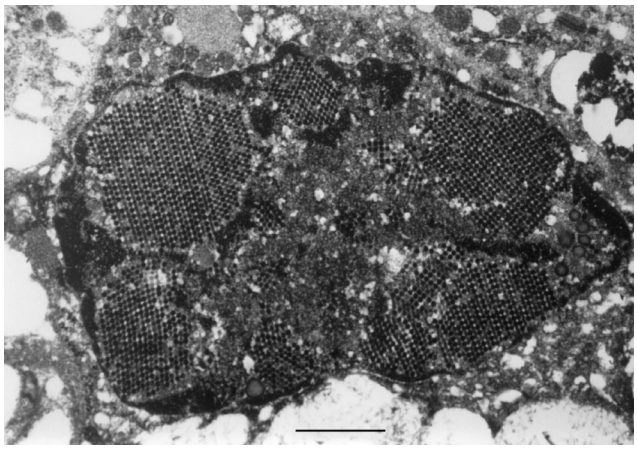

Figure 1. Enteric adenovirus. Transmission electron microscograph of typical hexagonal arrays of intranuclear adenovirus particles within an inclusion body from a rectal biopsy specimen taken from an HIV patient with light microscopic features of 'adenovirus colitis' (courtesy of Dr Christine Blanshard). Paraffin wax sections were dewaxed and post-fixed with 2% osmium tetroxide and embedded in Spurr's resin. Ultra-thin sections were stained with uranyl acetate and Reynold's lead acetate and examined by transmission electron microscopy. Scale bar = 1 μm.

HIV

Infection of enterocytes by HIV is well documented and is implicated as the cause of so-called 'HIV enteropathy', in which morphological and functional abnormalities of the gut are described in the absence of any other detectable pathogen[44]. The clinical importance of HIV enteropathy is probably limited, certainly 'pathogen-negative' diarrhoea is comparatively short lived and associated with a good prognosis[45].

Other enteric viruses

Several other enteric viruses are associated with HIV-related diarrhoea. Grohman and colleagues examined stool specimens from patients with or without diarrhoea[39]. Electron microscopy, polyacrylamide-gel electrophoresis and enzyme immunoassay were used to examine samples for rotavirus, adenovirus, calcivirus and picobirnavirus. Paired sera were also analysed for antibodies to Norwalk and picobirnavirus. Overall, virus was detected in 35% of patients with diarrhoea and 12% without diarrhoea. Astrovirus, picobirnavirus, calcivirus (including SRSV) and adenovirus were identified significantly more often in patients with diarrhoea. Unfortunately, co-infection with other known pathogens was not evaluated systematically and no information regarding the relative distribution of acute and chronic diarrhoea was provided. Schmidt and colleagues detected virus in 17% of stool samples from 256 HIV-infected patients[38]. Adenovirus and coronavirus were detected more frequently in patients with diarrhoea than without (10% vs 3.3% and 15% vs 6.6% respectively) and both were associated with severe immunosuppression. Thea *et al.* found no association between **enteric virus** shedding and diarrhoea in a study performed in Zaire[40]. Overall, this group identified enteric virus, including rotavirus, SRSV, coronavirus and adenovirus in 17% of samples analysed. They noted a trend towards increased shedding with greater immunosuppression, a finding in common with Cunningham and colleagues[43]. An association of rotavirus with prolonged diarrhoea in HIV patients, as detected by enzyme immunoassay was also reported, although other groups do not support this finding[41]. Data from selected studies that have evaluated enteric virus carriage in HIV patients are summarized in Table 3.

In summary, data regarding the association of non-CMV enteric virus infection and diarrhoea is conflicting. The best evidence relates to adenovirus infection although its pathogenic role is far from certain. We speculate that many of these viruses cause only self-limiting acute diarrhoea or, as in the case of adenovirus, act as a cofactor in CMV infection. Little is known about therapeutic options for these putative pathogens, although ribavarin might be effective in the treatment of adenovirus (R.C.G. Pollok, unpublished). The impact of HAART on non-CMV enteric virus infection has not yet been evaluated and warrants study.

The outstanding questions

- What are the mechanisms by which CMV infection of the gut causes diarrhoea?
- What are the specific immune mechanisms leading to disease resolution following HAART?
- What role do non-CMV enteric viruses, particularly adenovirus, have in HIV-related diarrhoea?
- What is the significance of pathological change associated with 'adenovirus colitis'?
- What role does HAART play in the control of non-CMV enteric virus infection?

Table 3. Prevalence of enteric viruses, and their association with diarrhoea

Methods	Overall prevalence (%)	n	Viruses identified	Association with diarrhoea	Ref.
EM, bx, culture	34	23	HSV CMV Adenovirus	No No No	42
EM, EIA	17	197	Rotavirus	No	40
EIA	19	101	Rotavirus	Yes	41
EM, bx, culture	7.4	67	Adenovirus	Yes	43
EM, EIA, PAGE	29	110	Astrovirus Picobirnavirus Calcivirus Adenovirus	Yes – Yes Yes	39
EM, bx	17	256	Adenovirus Coronavirus	Yes Yes	38
EM, bx	16	377	Adenovirus Rotavirus Calcivirus	Yes –	37

[a]Abbreviations: bx, endoscopic biopsy; EIA, enzyme immunoassay; EM, electron microscopy; PAGE, polyacrylamide gel electrophoresis.

Future prospects

New developments in the diagnosis and treatment of CMV are being established. Assays for CMV DNA and the CMV pp65 antigen assay offer the prospect of CMV surveillance before the development of end-organ disease, which will allow the tailored introduction of prophylaxis. Oral ganciclovir and valganciclovir (which, of the two, has greater bioavailability) are potentially useful prophylactic agents. Second generation CMV treatments are becoming available and are being evaluated, largely in transplant patients. The advent of HAART has dramatically reduced the occurrence of all opportunistic infections, including CMV. Consequently, this has made evaluation of these newer agents difficult in patients with HIV. HAART is unlikely to be widely available in the developing world in the immediate future and diarrhoeal disease continues to contribute to the death toll of HIV patients in these countries. The role of non-CMV enteric infection in HIV-related diarrhoea remains uncertain and unless further research is undertaken the importance of these viruses in HIV-related diarrhoea is unlikely to be established.

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