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Gastrointestinal complications of HIV infection: changing priorities in the HAART era

C M Wilcox,1 M S Saag2

ABSTRACT

It has now been some 25 years since the initial description of AIDS. Following these observations, the epidemiology, natural history and manifestations of this disease have been well characterised. Intense investigation has better characterised HIV, resulting in the development of effective drug therapies to arrest disease progression. These multidrug combinations, termed highly active antiretroviral therapy or HAART, can suppress the viral load to the undetectable range and secondarily halt the destruction of CD4 T lymphocytes. This virological response is associated with a marked improvement in survival and absence of the many complications related to immunodeficiency. For patients who respond to HAART, the current emphasis is on treating side effects from the medications as well as treating other non-AIDS-related disorders. However, given the cost and complexities of medications as well as treating other non-AIDS-related disorders. However, given the cost and complexities of these regimens, there are many patients who continue to present with the classic manifestations of AIDS, and, especially in the developing world, we will continue to see these patients for years to come.

AIDS is one of the most devastating pandemics in history based on its worldwide scope and lethality. To date, an estimated 25 million deaths have been reported worldwide, 65 million people are believed to be infected, with approximately 14 000 new infections occurring daily.1 In sub-Saharan Africa, where 10% of the world’s population reside, HIV is particularly devastating. The prevalence of HIV in countries in the Southern region of Africa ranges from 10% to >20% of the population.1 Projected deaths from the years 2006–2050 will rise to an estimated 89–117 million.2 Since most HIV-infected patients are in their second to fourth decades of life, the pandemic has staggering implications for the social and economic stability of countries in the developing world. Furthermore, because of the number of parentless children and reduced life expectancy by ~50 years, the countries most affected will remain devastated for generations to come.

Worldwide, gastrointestinal (GI) disease continues to account for a high proportion of presenting symptoms of HIV infection, especially in the developing world.3 This may be in part related to the lack of diagnostic techniques to identify these disorders. Fortunately, the scientific community has made remarkable strides in elucidating the biology of the virus and translating these basic science observations into effective therapies (highly active antiretroviral therapy or HAART) against the virus. With the widespread use of antiretroviral therapy, the spectrum of complications of HIV disease has changed dramatically, including the presentation of GI disorders and complications of antiretroviral therapy itself. As such, gastroenterologists will continue to play a major role in the diagnosis and management of these patients and need to be aware of the novel presentations of GI disorders in the HAART era.

HISTORICAL PERSPECTIVE

In the late 1970s, patients worldwide were presenting with Pneumocystis carinii pneumonia (PCP), Kaposi’s sarcoma and other rare disorders linked to immune deficiencies. In the developed world, the afflicted were typically young, male, and most often homosexual or intravenous drug users. The first report of the AIDS epidemic was in 1981 when the Centers for Disease Control (CDC) described an apparent epidemic of PCP infection in gay men from New York and San Francisco.4 Shortly afterwards, the link to immune deficiency in general, and marked reduction in CD4+ T lymphocytes in particular, was recognised as a hallmark of disease and a predictor for opportunistic diseases and mortality.5 A large body of work documented the epidemiology of disease and the spectrum of complications associated with the immune deficiency of AIDS, and the GI tract was readily acknowledged as a prominent and common site for manifestations of the disorder. Following the identification of the virus in 1983, over the next decade, dramatic strides were made in developing antiretroviral therapy, culminating in the concept of combination antiretroviral therapy, termed highly active antiretroviral therapy or HAART, in 1995.

There was initial hope that HAART would cure HIV; however, the presence of viral DNA integrated into host lymphoid cells that reside as reservoirs in lymphoid tissue suggested that total eradication with HAART was not achievable with available therapy. Yet, infection can often be very well controlled with long-term antiviral therapy. Among responders, the level of HIV RNA in plasma (viral load) falls by several orders of magnitude within the first 2–4 weeks of therapy, becoming “undetectable” (<50 copies HIV RNA/ml) within 16–24 weeks (fig 1). The CD4 count may return to normal with maximal virological
Recent advances in clinical practice

Table 1  Current drugs used to treat HIV and their year of Food & Drug Administration approval

<table>
<thead>
<tr>
<th>Year approved</th>
<th>Agent (trade name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>Zidovudine (Retrovir)</td>
</tr>
<tr>
<td>1991</td>
<td>Didanosine (Videx)</td>
</tr>
<tr>
<td>1992</td>
<td>Zalcitabine (Hivid)</td>
</tr>
<tr>
<td>1994</td>
<td>Stavudine (Zerit)</td>
</tr>
<tr>
<td>1995</td>
<td>Saquinavir (Invirase)</td>
</tr>
<tr>
<td>1996</td>
<td>Lamivudine (Epivir)*</td>
</tr>
<tr>
<td>1996</td>
<td>Indinavir (Crixivan)</td>
</tr>
<tr>
<td>1997</td>
<td>Ritonavir (Norvir)</td>
</tr>
<tr>
<td>1998</td>
<td>Nevirapine (Viramune)</td>
</tr>
<tr>
<td>1999</td>
<td>Delavirdine (Rescriptor)</td>
</tr>
<tr>
<td>2000</td>
<td>Efavirenz (Sustiva)</td>
</tr>
<tr>
<td>2001</td>
<td>Abacavir (Ziagen)</td>
</tr>
<tr>
<td>2001</td>
<td>Amprenavir (Agenerase)</td>
</tr>
<tr>
<td>2002</td>
<td>Lopinavir/ritonavir (Kaletra)</td>
</tr>
<tr>
<td>2003</td>
<td>Tenviravir (Viread)*</td>
</tr>
<tr>
<td>2003</td>
<td>Emtricitabine (Emtriva)*</td>
</tr>
<tr>
<td>2004</td>
<td>Enfuvirtide (Fusion)</td>
</tr>
<tr>
<td>2004</td>
<td>Fosamprenavir (Lexiva)</td>
</tr>
<tr>
<td>2005</td>
<td>Tipranavir (Aptivus)</td>
</tr>
<tr>
<td>2005</td>
<td>Darunavir (Prezista)</td>
</tr>
<tr>
<td>2007 (expanded access)</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>2007 (expanded access)</td>
<td>Raltegravir (MK-0518)</td>
</tr>
<tr>
<td>2007 (expanded access)</td>
<td>Entravirene (TMC-125)</td>
</tr>
</tbody>
</table>

*Drugs with antiretroviral activity.

suppression if HAART is given for a prolonged period of time,5 and immunological activity may largely be restored.7 Over the last decade, newer agents continue to be developed as additional viral and cellular host targets are identified, with 25 agents currently approved and on the market, with >10 more promising drugs in development (table 1).

IMPLICATIONS OF HAART

The unrelenting natural history of HIV infection was dramatically altered following the widespread implementation of HAART. The use of HAART was associated with rapid and universal declines in the incidence of AIDS-defining illnesses and complications, crude mortality and AIDS-related mortality.5–10 For example, an observational study of >8500 patients documented an 86% reduction (15.6–2.7 deaths per 100 person-years of follow-up) in overall morality from 1994 to 2001, with a 25% annual reduction in HIV-related diseases.9

Numerous studies worldwide have confirmed these impressive results.9–16 Gastrointestinal complications have likewise fallen substantially. In a study of symptomatic patients undergoing endoscopy from 1995 to 1998, the prevalence of opportunistic infections fell from 69% to 13% coincident with the use of HAART, which increased from 0% to 82% of patients.17 The number of patients identified with cytomegalovirus (CMV) infection or oesophageal candidiasis fell 80% while the prevalence of gastro-oesophageal reflux disease rose eightfold.

The causes of death have also shown a dramatic shift away from AIDS-related causes. Indeed, recent studies suggest that approximately 50% of deaths in HIV-infected patients are unrelated to AIDS, whereas before HAART >90% deaths were AIDS related.8 9 11–13 18 Furthermore, as patients are living longer, especially those on HAART, other disorders not associated with immunodeficiency have assumed more importance. The best example is the rapid rise in complications of liver disease due to viral hepatitis in co-infected patients (see below).11–13 18

Discontinuation of primary and secondary prophylaxis for most opportunistic pathogens can now be recommended for those who respond to HAART with a sustained (>1 year) increase of CD4 cells to >200 cells.15 20 These data further support the concept that control of viral replication with HAART leads to a substantial degree of reconstitution of immune function.

Improvement in the immune system, even if only modest, may also serve as “therapy” for many AIDS-defining opportunistic disorders, particularly those lacking effective therapy such as microsporidia and cryptosporidiosis.21 Kaposi’s sarcoma, caused by human herpesvirus 8 (HHV-8), also may go into remission with combination antiretroviral therapy, and the response is durable when associated with marked reduction or absence of HHV-8 viraemia.22 23 These observations underscore the tremendous impact HAART can have in both the prevention and treatment of these opportunistic disorders.

Drug-induced side effects

The widespread use of HAART has also resulted in the appreciation of a number of drug-induced side...
effects. With this immune boost, however, a new syndrome of immune reconstitution has emerged.24 25 The so-called immune reconstitution inflammatory syndrome, or IRIS, results from a rapid rebound in immune function that responds to a variety of clinically occult infections that were present at the time of initiation of HAART. Typically, these presentations occur within 2–6 weeks after HAART initiation and consist of exaggerated symptoms and signs associated with the underlying disease, such as high fever, abdominal pain or inflammatory masses. Likewise, a boost in the immune system can also be associated with fulminant flare of hepatitis B virus (HBV) infection.26 Recognition of this phenomenon has now prompted appropriate screening for hepatitis B in those undergoing combination antiretroviral treatment.

A major shift in the management of HIV-infected patients is related to alleviating and preventing drug-induced side effects associated with HAART. In some centres, hospitalisation related to these side effects is considerable.27 Hypersensitivity reactions to drugs such as abacavir can be fatal if not recognised early and managed properly. This syndrome, occurring in 3–8% of patients taking the medication, presents with constitutional symptoms, fever, abdominal pain and rash.28 Onset is typically between 2 and 8 weeks after drug initiation. The syndrome is more common in Caucasians and is strongly associated with the human leucocyte antigen (HLA)-B5701 haplotype.29 Some centres are screening for this haplotype prior to prescribing abacavir, and this is likely to become common practice over the next year. Another potentially fatal complication of HAART is the lactic acidosis syndrome. This disorder is caused by nucleoside reverse transcriptase inhibitors (NRTIs), most commonly stavudine (D4T), didanosine (ddI) and zidovudine (AZT; ZDV), whereby progressive hepatic microvesicular steatosis results from mitochondrial DNA toxicity induced by these drugs.30 31 If not recognised when patients first become symptomatic, this disorder can lead to multiorgan dysfunction and death. Thus, the offending drugs must be stopped early to prevent a fatal outcome. The symptoms and signs associated with this syndrome include fatigue, abdominal pain, nausea or muscle aches; the liver is generally large on exam and the liver enzyme tests are abnormal. The so-called lipodystrophy syndrome has also been more widely observed. The primary clinical features include peripheral fat loss (lipoatrophy of the face, limbs and buttocks). In a few patients, central fat accumulation, gynaecomastia and hypertrophy of the dolicervical fat pad (“buffalo hump”) may occur.32 There is no direct association, however, of lipoatrophy and lipohypertrophy in a single, “fat redistribution”, syndrome as initially reported in the late 1990s. Many of the patients with lipodystrophy also have a metabolic component consisting of hypertriglyceridaemia, insulin resistance and impaired glucose tolerance.33 Some of these patients may also experience mild lactic acidaemia and hepatic dysfunction. The cause of this syndrome is unknown but may be due to the combination of toxic effects of protease inhibitors, particularly ritonavir, along with NRTI and NNRTI (non-nucleoside reverse transcriptase inhibitor) drugs. Given the improved survival and the spectrum of these drug-related side effects, cardiovascular complications leading to death are now increasingly documented.11–13 Exacerbation of underlying liver disease is also well recognised with HAART (see below). The effects of drug interactions are underappreciated. For example, use of proton pump inhibitor therapy is contraindicated when using indinavir and atazanavir.

Lastly, while the financial implications of these drugs are tremendous, cost-effectiveness analyses have shown their benefit in preventing complications and, most importantly, preventing hospitalisations.34 Nevertheless, the drug costs and need for monitoring associated with these agents is a major barrier to their optimal use worldwide.

**GENERAL GUIDELINES FOR MANAGEMENT**

HIV-infected patients can generally be divided into those who are treatment naïve or on HAART. For all patients, the CD4 lymphocyte count continues to be the best laboratory predictor for risk of an opportunistic disorder35 36 (see fig 2). In addition, there is increasing recognition that the HIV viral load is also helpful in predicting these risks.37 38 It is important to recognise that many of the suggested strategies outlined below are based upon studies before HAART was available. While the approach to the management of GI complications in the severely immunocompromised patient has changed very little, we know less about the prevalence of causes of disease and approach to the patient who is only a partial responder to HAART. In this section, we outline the general principles for diagnosis and management for the most common digestive complaints and disorders seen today in these patients.

**Upper GI disease**

The tropism of many pathogens for the squamous mucosa of the oesophagus (candida, herpes) as well as the appearance of heretofore new diseases (idiopathic oesophageal ulceration) established the upper GI tract as a common site for complications. Upper endoscopy in the symptomatic AIDS patient yields a specific diagnosis in ~75%, the majority related to immunodeficiency.39 40 Most of these patients have advanced disease with a CD4 count <100 cells/μl. Candida is the most common oesophageal pathogen in AIDS, followed by viral diseases. However, in the era of HAART, many of these previously common HIV-related disorders have essentially vanished.41–43 Nevertheless, these opportunistic disorders can be observed in patients who are failing HAART (low CD4, high viral load) or who are non-compliant.44 Indeed, today, when challenged by an HIV-infected patient with upper...
GI complaints, depending on the use of antiretrovirals, the vast majority will have causes unrelated to HIV-associated immunodeficiency.

In keeping with the theme outlined above, when approaching any patient, one must determine the stage of immunodeficiency as reflected by the CD4 lymphocyte count. Numerous studies continue to demonstrate that those patients with a CD4 count <200 cells/µl are those at greatest risk for opportunistic infections. Also, the risk of disease rises exponentially with this fall in CD4 cells <100 cells/µl (fig 2). As noted in fig 2, the frequency of a specific opportunistic infection is related to the CD4 count. For example, candida oesophagitis rises in incidence at a CD4 count of 100–200 whereas Mycobacterium avium complex is very uncommon until the CD4 count falls below 50. **However, in the era of HAART, there are patients with a modestly reduced CD4 count (<200 cells/µl) and undetectable viral load but in whom the CD4 count has risen from a very low level. These patients, in fact, are probably different from the untreated HIV-infected patient with a high viral load and a similar CD4 count <200 cells/µl. Nevertheless, a CD4 count <200 cells/µl remains an important marker for those patients in whom opportunistic infections and neoplasms should be suspected as a cause of symptoms.**

The approach to the HIV-infected patient with higher CD4 counts (>200 cells/µl) and upper GI complaints should parallel those of any other patient when immunodeficiency is not advanced. In the patient at risk for opportunistic disorders, oesophagitis strongly suggests oesophageal ulceration or severe candidiasis. A randomised trial comparing empirical fluconazole with endoscopy in patients with new onset oesophageal complaints showed that empiric therapy was the best strategy especially in patients with thrush. **These patients may still develop gastro-oesophageal reflux disease and, with a convincing history, a trial of proton pump inhibitor therapy may be warranted.**

**Diarrhoea**

Early in the epidemic, chronic diarrhoea was recognised as a hallmark of advanced HIV infection especially in developing countries, and was typically caused by infections. In this setting, the spectrum of causes is broad, significant morbidity is typical as is a reduced quality of life, mortality is high and, prior to or without treatment with HAART, chronic diarrhoea is responsible for many new cases of AIDS. **Studies have now demonstrated that during initial infection with HIV, heavy involvement in gut-associated lymphatic tissue (GALT) leads to rapid and probably permanent destruction of GALT.** More recent reports have shown that even with early and aggressive HAART initiated at the first signs of acute HIV infection, the GALT is not protected and still undergoes significant damage. Therefore, it is not surprising that in most of the world, where the availability of HAART is so limited, both acute and chronic diarrhoea remain substantial causes of morbidity and mortality, especially for children. Among patients with advanced HIV disease (CD4 counts <50 cells/µl), opportunistic infections are the most common cause of disease, particularly parasites such as Cryptosporidium and Microsporidium. In the developed world, CMV colitis is a significant cause of morbidity in those with advanced immunodeficiency.

In the era of HAART, opportunistic causes of diarrhoea have fallen dramatically. Yet, overall, the number of patients experiencing diarrhoea has changed very little. Experience at a single centre between 1995 and 1997 found that the occurrence of chronic diarrhoea remained constant (~8–10%/year) for those with CD4 counts <200 cells/µl. Opportunistic infections fell drastically from 53% to 15%, while other infections unrelated to immunodeficiency rose. The proportion of patients diagnosed with non-infectious causes increased from 52% to 70% over the 3-year period. Similar
Effective antimicrobial therapies are still lacking for many of the opportunistic infections resulting in diarrhea in AIDS. Paromomycin and, more recently, nitazoxanide have been evaluated in the therapy for cryptosporidiosis. Nitazoxanide shows efficacy as measured by oocyst clearance compared with placebo; however, these results have been limited primarily to the immunocompetent host. Therapy for Enterocytozoon bieneusi, the most common microsporidian species afflicting humans, is still lacking. In contrast, albendazole is an effective therapy for E. intestinalis. Therapy for non-tuberculous mycobacterial disease continues to consist of multidrug macrolide-containing regimens. For more in-depth discussion of the therapy of these opportunistic infections, the reader is referred to recent reviews.

Severe diarrhoea where no pathogen can be found despite intensive investigation with endoscopy and biopsy has been ascribed to HIV enteropathy. The exact pathogenesis of such diarrhoea remains unclear but has been attributed to dysregulation of local cytokine production and destruction of GALT, and HIV replication in residual GALT. In such patients, HAART has resulted in symptomatic improvement. Fortunately, in the era of HAART, this enteropathy is extremely uncommon today.

Although the incidence of the HIV wasting syndrome has fallen dramatically in the era of HAART, weight loss and wasting still occur and are associated with morbidity and increased mortality. In patients with AIDS, the mechanism(s) of wasting is multifactorial including reduction in nutritional intake, anorexia, medications and, importantly, GI diseases which are frequently infectious and often cause diarrhoea. Recent studies suggest that HIV-related wasting may still occur in approximately 17% of patients. A variety of therapies have been used with variable success. Nutritional supplements associated with counsel may improve caloric intake. Progressive resistance training and exercise have been found to be equivalent to other medical therapies. In selected patients, anabolic steroids and androgens may be effective but carry risk of hepatotoxicity. Megesterol remains a common therapy, and, while associated with weight gain, this consists primarily of fat rather than lean body mass. Supplementation with testosterone does not further enhance weight gain. Promising results have been shown for short-term use of growth hormone where placebo-controlled studies show an increase in lean body mass, body composition and quality of life. Identification and treatment of any opportunistic infection, particularly of the GI tract, continue to play a key role. In those who have poorly controlled HIV infection or are treatment naïve, institution of HAART remains a cornerstone of treatment, although it may be associated with alterations of body composition (see discussion on lipodystrophy).

The approach to diarrhoea in the HIV-infected patient should take into consideration the observations have been reported. One explanation for this rise in non-infectious causes is the fact that since these patients are now living longer, they have exposure to other pathogens which may result in disease. For example, antibiotic-induced diarrhoea from Clostridium difficile is now the most commonly identified bacterial pathogen, in one study accounting for 54% of all bacterial agents.

In contrast to the above discussion which centres around infectious causes of diarrhoea, in many patients today, however, drug-induced diarrhoea is the primary reason for the continuing high prevalence of diarrhoea in HIV-infected patients. Drug-induced diarrhoea has been most frequently attributed to the protease inhibitors, and studies suggest that diarrhoea occurs in up to 50% of patients taking nelfinavir and in up to 20% of those taking lopinavir/ritonavir and fosamprenavir/ritonavir. Often there is a temporal association between drug initiation and diarrhoea, and typically the diarrhoea is of mild to moderate severity. Given the prevalence of medication-induced diarrhoea, unless severe, many patients will not undergo routine evaluation (unpublished observation).

As noted above, in this setting, the likelihood of an opportunistic process is linked to the severity of immunodeficiency. Therefore, a search for typical HIV-associated processes should be undertaken based upon risk stratification of the patient. Specifically, patients with severe immunodeficiency (CD4 <100 cells/µl) are those most at risk for Cryptosporidium, Microsporidium and CMV disease. Mycobacterium avium complex, commonly seen in the pre-HAART era, is now very rare and is most likely to be found in the patient who first presents with end-stage HIV infection. Mycobacterium tuberculosis can involve the gut and is an important cause of disease in AIDS patients in the developing world.

Figure 3  Suggested algorithm for the management of upper gastrointestinal (UGI) tract symptoms in HIV-infected patients. PPI, proton pump inhibitor.
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following: the duration of the diarrhoea as the pathogenic spectrum of acute and chronic diarrhoea is different; the stage of immunodeficiency; the possibility of drug-induced diarrhoea; and the recent use of antibiotics or other epidemiological history to suggest *C. difficile* diarrhoea, *Giardia* or other pathogens. Routine stool testing is reasonable depending on the suspected cause and duration (acute vs chronic) of symptoms and has a yield of 13–75% depending on the epidemiological setting, CD4 count and number of stool tests performed.49 51

For patients at risk for opportunistic infection, in whom stool tests are repeatedly negative, the data are clear: prospective studies have shown the high yield of endoscopic examination with biopsy of the lower and upper GI tract in patients with negative stool tests, with a diagnosis established in 65–82%.73 For those with complaints referable to the distal colon (bright red rectal bleeding, tenesmus, urgency), examination of the distal bowel will often establish the diagnosis, with CMV being the most common cause found. However, one study suggested that CMV colitis may be limited to the right colon in a third of patients, supporting the use of full colonoscopy if the distal colon is endoscopically normal.74 Colonoscopic examination with biopsy will establish the diagnosis (fig 4). Small bowel biopsy, either at oesophagogastroduodenoscopy or ileoscopy at the time of colonoscopy, will help to exclude parasitic infections.

The above recommendations are taken from prior studies which have evaluated the investigation of HIV-infected patients in the pre-HAART era at risk for opportunistic infections. There is a paucity of data which investigate the best approach to the HIV-infected patient on HAART with diarrhoea at any stage of immunodeficiency. One would suspect that the patient with a CD4 count <200 cells/μl but with an undetectable viral load is different from a patient with the same CD4 count but poor response to HAART with a high viral load. The evaluation of acute and chronic diarrhoea in the patient with preserved immune function should parallel that in the normal host. Again, judgement should dictate the aggressiveness and timeliness of the evaluation (see fig 5 for suggested approach to evaluation.)

Liver disease

Co-infection with hepatotropic viruses is expected in HIV-infected patients, owing to the similar modes of viral acquisition through blood and sexual contact. Approximately 5–10% of HIV-infected patients have active HBV infection, with up to 35% having prior exposure as documented by HBV core antibodies.26 75 Co-infection with hepatitis C virus (HCV) varies from 13% to 80%, with the highest prevalence rates found among haemophiliacs and intravenous drug users.76 77 Co-infection with HCV was observed in 50% of hepatitis B surface antigen (HbsAg)-positive patients in one study.77 Seropositivity generally represents active infection, with HCV RNA typically found in high titres. Until HAART, the hepatotropic viruses played little role in the long-term outcome of these patients because the clinical course was so dominated by the opportunistic diseases associated with AIDS. Nevertheless, alterations in the natural history of viral hepatitis were documented early on due to HIV-associated immunodeficiency and its effect on hepatitis viral clearance. However, after HAART, and as these patients began living longer, end-stage liver disease has become a significant problem. Over the last decade, reports from Europe and the USA have shown liver disease to be a common reason for hospitalisation of HIV-infected patients, and to be the cause of death in 10–15% of patients.78 79 This is a marked departure from what was observed before HAART. Bica et al75 showed a rise in death rates from end-stage liver disease in HIV-infected patients from 10% in 1991, to 15% in 1996 and up to 50% in 1998. Likewise, patients with hepatocellular cancer related to HCV and/or HBV are being observed.80

It is now recognised that the natural history of HCV infection is altered by co-infection with HIV. In co-infected patients, HCV viral load is much higher than in HIV-negative patients. HCV-specific CD8+ T cell activity is reduced81 and there is more rapid progression of liver fibrosis and an accelerated progression to cirrhosis.72 For example, among immunocompetent hosts, progression to cirrhosis takes 20 years, yet in contrast approximately 10 years is all that is required for HIV-infected patients, similar to what is seen for HCV-infected patients postliver transplantation. Almost universally, liver-related toxicity rates with anti-retroviral therapy are higher for co-infected patients than HIV+/HCV− patients. Use of HAART is also associated with a rise in HCV RNA and aminotransferases.82 The cause of this more rapid progression remains speculative but has been attributed to reduced immune surveillance and CD8 activity. While more rapid progression to

Figure 4 Colonoscopic examination demonstrates diffuse subepithelial haemorrhage of the colon typical for cytomegalovirus colitis.
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Figure 5  Suggested strategy for the evaluation of diarrhoea in HIV-infected patients. OGD, oesophagastroduodenoscopy.

Risk factors for hepatotoxicity associated with highly active antiretroviral therapy

- Use of ritonavir
- Increase in CD4 cell count >50 cells during treatment
- Liver histological stage
- Stage F3 and F4 fibrosis
- Baseline elevation in serum aminotransferases
- Hepatitis C virus co-infection

Cirrhosis has been shown for HCV infection, recent studies suggest that HAART therapy reduces liver-related mortality. In this study, primarily of a haemophiliac population, liver-related mortality rates were 0.45 per 100 person-years in those receiving HAART as compared with 0.69 in the other antiretroviral treatments group and 1.7 in the untreated group. Despite these optimistic findings, such improvements have not been uniformly identified. In the D:A:D study, an increased risk of liver-related mortality was observed with longer exposure to combination antiretroviral therapy. In the EuroSIDA study, liver-related deaths showed an overall 7% decline per year. However, patients taking combination antiretroviral therapy for >2 years showed an increasing liver-related mortality rate, with a 12% increase in death rate with each additional year of exposure (95% CI 1.04 to 1.20). These differences in mortality associated with antiretroviral therapy are probably related to the underlying patient population (haemophiliac vs other), and perhaps the prevalence rates of HBV and HCV. In a multicentre cohort study of 1011 antiretroviral-naïve HIV/HCV-co-infected patients who started HAART, liver disease was the primary cause of death, yet higher increases of CD4 cell counts were associated with better hepatic outcomes. Improvement in immune function is likely to arrest or retard the underlying pathogenic mechanisms for progression to cirrhosis. Because of this more rapid progression, treatment of HCV infection has assumed more importance.

The natural history of HBV is also altered in the setting of HIV infection. Because of immunodeficiency, clearance of HBV is less efficient in the acute setting, resulting in increased rates of chronic infection (~20%) with subsequent high HBV viral loads, thus making the patient a reservoir for transmission. In addition, like HCV co-infection, the course of HBV infection is accelerated by HIV co-infection. When HAART is given to a patient with active HBV infection who is immunosuppressed, a flare of disease resulting in fulminant liver failure may result. Cautious use of the appropriate antiretrovirals which include efficacy toward HBV is essential to prevent this complication (see below).

With the availability of more effective antiretroviral therapies as well as antivirals directed toward these hepatotropic viruses, therapy for HCV and HBV has become a reality for co-infected patients. Pegalated interferon plus ribavirin has shown modest efficacy in HIV-infected patients co-infected with HCV. In the normal host, a sustained virological response (SVR) can be documented in ~55% of patients infected with genotype I, whereas in the HIV-infected patient, SVR rates of only 14–44% have been observed. As in the normal host, genotype I has been the most difficult to treat effectively. Predictors of response include genotypes 2 and 3, low HCV viral load (<800 000 IU/ml), absence of cirrhosis, age <40 years and higher alanine aminotransferase (ALT) levels (>3 times the upper limit of normal). Avoidance of AZT is prudent given its known bone marrow toxicity, and ddI should be avoided due to drug interaction (mitochondrial toxicity) with ribavirin. However, owing to the unique and significant toxicities of peg-interferon and ribavirin coupled with the rigour and commitment required to complete therapy, only a small proportion of patients are good candidates for specific treatment of HCV and will achieve a SVR.

The timing of treatment for HIV and HCV remains controversial. Recent recommendations suggest that HAART be instituted first in the patient with immunodeficiency, owing to significant reduced SVR rates when anti-HCV therapy is initiated when CD4 counts are <250 cells/μl. HCV treatment should ideally be instituted after a full effect from HAART, including an increase in CD4 count, has been achieved. The role of liver biopsy for staging prior to antiretroviral therapy has been suggested given the poor correlation between liver chemistry tests and histology.
Recent advances in clinical practice

Very recent, positive outcomes have been reported among HIV–HCV-co-infected patients undergoing liver transplantation for treatment of advanced cirrhosis and liver failure. The results demonstrate similar outcomes up to 36 months to those undergoing transplants who are HIV negative. A poor outcome was seen in those post-transplant with CD4 <200 cells and viral load >400 copies and those with HCV. Selection criteria for good candidates for transplant include undetectable HIV on a stable HAART regimen, demonstrated history of excellent adherence to medical treatment, absence of significant mental health disorders or recent substance use, and the presence of an effective social support network. Based on these data, HIV patients with advanced cirrhosis should be considered for liver transplantation in a similar fashion to those who are not co-infected.

Treatment of HBV in the setting of HIV co-infection has a number of nuances. Treatment with single agent therapy (lamivudine) leads to very rapid HIV drug resistance at the M184V position of reverse transcriptase. Newer available agents such as tenofovir and entecovir, when used in combination with lamivudine, have efficacy for both HIV and HBV. However, while the use of two drugs is adequate for the treatment of hepatitis B, a third drug (such as a NNRTI or a protease inhibitor) must be added to the HAART regimen to prevent HIV resistance to the nucleoside and nucleotide agents. Use of any dual combination or monotherapy of these agents is strongly discouraged. Similarly, owing to its partial anti-HIV activity, the use of adefovir should be avoided in HIV–HCV-co-infected patients. A case report of the development of an HIV resistance mutation (M184V) was observed in a single patient on entecavir, resulting in a ‘Dear doctor’ letter to providers. The clinical meaning and validation of this finding is currently under investigation. When placed in the context of the requirement for multiple anti-HBV drugs to prevent flares of disease, it seems prudent to use HAART therapy with three drugs, two of which have anti-HBV activity, whenever treatment of HBV is indicated in a co-infected patient. Recent recommendations for the treatment of hepatitis B and C in the HIV-infected patient have been published. Immunosuppression against hepatitis A and B is strongly recommended in all HIV patients, especially those with liver disease. However, immunisation is most likely to be effective when associated with an immune response. Therefore, immunisation should be given after HAART therapy has been initiated and an appropriate CD4 cell response documented. Following immunisation, one should consider checking antibody titres.

Drug-induced liver disease has become an important management issue with HAART. A number of risk factors have been linked to hepatotoxicity (box 1). Prospective studies document grades three and four drug toxicity in ~10% of patients, and these occur irrespective of the drug regimen. Drug-related mortality has been reported in 3% of patients experiencing hepatotoxicity. While a number of studies have identified these risk factors, it is important to recognise that the vast majority of patients have no significant hepatic complications from HAART therapy and should receive such treatment with very close monitoring. The issue of lactic acidosis and steatosis caused by antiretroviral agents has been discussed above.

CONCLUSIONS

The treatment of HIV infection has been revolutionised with HAART. Patients are living longer and now patients are free of the many HIV-associated complications including those of the GI tract. Nevertheless, with the advent of HAART, new challenges have arisen including drug-induced complications, and development of non-HIV-related diseases. Furthermore, whether patients will ultimately develop viral resistance to current antiretroviral therapies and then progress is unclear, but a paradigm of multidrug antiviral therapy will probably be necessary to maintain viral suppression and preserve immune function. As these patients are living longer and with a more normal life, we are now seeing older patients who will require management and screening for non-HIV-related disorders. Although patients with HIV will require management and screening for non-HIV-related disorders, we do not know if the disease course for these disorders will parallel that of the HIV-negative counterpart.

Key points

- The widespread use of highly active antiretroviral therapy (HAART) has altered the landscape for the management of HIV-infected patients such that gastrointestinal symptoms in treated patients who respond to therapy are less likely to be opportunistic infections and more likely to have drug-induced complications or disorders seen in a similar age-matched population.
- The CD4 count and HIV viral load help predict the risk of an opportunistic infection, with the highest risk seen in those with a CD4 count <100.
- Endoscopic evaluation of the gastrointestinal tract remains a cornerstone of diagnosis especially in those at risk for opportunistic infection.
- Appreciating the nuances of the treatment of HIV and viral hepatitis is critical to prevent flares of disease and drug resistance.

COMPETING INTERESTS: None.

REFERENCES

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