Impact of highly active antiretroviral therapy on incidence and management of human immunodeficiency virus-related opportunistic infections

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We review the changes in incidences of HIV-related opportunistic infections and the safety of discontinuation of primary and secondary prophylaxis for HIV-related opportunistic infections in patients achieving immune restoration after the introduction of highly active antiretroviral therapy (HAART). HIV-related opportunistic infections continue to occur in patients who are newly diagnosed with HIV infection, those in the early course of HAART or non-adherent to HIV care and HAART, and those in whom non-HIV-related infections have emerged as a significant cause of morbidity and mortality in the post-HAART era. Clinical studies of patients with tuberculosis and HIV co-infection are reviewed to provide appropriate regimen combinations of rifamycins and antiretrovirals, which have varying degrees of drug–drug interactions that have posed challenges in the management of tuberculosis as well as HIV infection.

Keywords: HIV infection, AIDS, HAART, opportunistic infections, antimicrobial prophylaxis

Introduction

With the introduction of antimicrobial prophylaxis and highly active antiretroviral therapy (HAART), the morbidity and mortality of HIV-infected patients receiving HAART have declined,1,2 and the decline has been sustained.2 The incidences of nearly all AIDS-defining opportunistic infections (OIs) have decreased significantly.3 HAART has changed HIV infection from a debilitating fatal disease to a chronic manageable disease. Discontinuation of primary and secondary prophylaxis against several major AIDS-defining OIs has been recommended in patients with immune restoration after HAART.3 However, HIV-related OIs and deaths continue to occur in patients newly diagnosed with HIV infection, in those in the early course of HAART, or in those non-adherent to HIV care and HAART.3,5–9 and non-HIV-related infections, such as sepsis and chronic viral hepatitis, have emerged as significant causes of death in the post-HAART era.3,10,11 In addition, the complexity of drug–drug interactions between rifamycins and antiretrovirals has posed challenges in the management of tuberculosis (TB) and HIV co-infection. Our objective was to review the impact of HAART on the incidence and management of HIV-related OIs and to provide appropriate antituberculous therapy containing rifamycins and antiretroviral therapy combinations in patients with TB and HIV co-infection.

Bacterial infection

The proportion of recurrent bacterial pneumonia as an AIDS-defining OI of the respiratory tract appears to be stable or slightly in decline in the post-HAART era; Streptococcus pneumoniae remains the most common aetiologic agent of community-acquired bacterial pneumonia, although in a large number of cases the aetiologies are unidentified despite the use of extensive testing.7 With wider use of HAART and antimicrobial prophylaxis, the incidence of invasive pneumococcal disease among HIV-infected persons has declined in the post-HAART era.12 In a laboratory-based surveillance study conducted in San Francisco,12 the quarterly incidence of invasive pneumococcal disease decreased from 10.6 cases per 1000 person-years (PY) in 1994 to 4.2 cases per 1000 PY in patients with AIDS in 1997 (P = 0.004), with the most significant decrease occurring during 1996–1997.

Whether pneumococcal vaccination can reduce the risk of invasive pneumococcal disease in HIV-infected patients remains controversial. In patients without HAART, vaccination with a 23-valent polysaccharide pneumococcal vaccine in HIV-infected Ugandan adults showed an increase in the rate of pneumococcal disease in vaccine recipients,13 whereas vaccination with a 9-valent conjugate vaccine in HIV-infected and HIV-uninfected children in South Africa showed reduced rates.14 Although...
an observational study suggested that receipt of antiretroviral therapy, especially HAART, and pneumococcal vaccination were associated with a decreased risk for pneumococcal disease, more studies are needed to assess whether receipt of HAART will enhance the serological response to pneumococcal vaccination and clinical benefit.

The incidence of HIV-associated community-acquired bacteremia has declined in the post-HAART era. In an Italian university hospital for HIV care, the incidence of HIV-associated community-acquired bacteremia declined from six episodes per 100 PY in 1994–1995 to 3.8 episodes per 100 PY in 1997–1998; the most evident reduction occurred for non-typhoid Salmonella, whereas the rate of S. pneumoniae bacteremia remained constant over the two study periods.

Non-typhoid Salmonella bacteremia is associated with a high recurrence rate in HIV-infected patients despite suppressive therapy with ciprofloxacin in the pre-HAART era. Although the optimal duration of suppressive therapy to prevent recurrences of non-typhoid Salmonella bacteremia remains unclear in patients responding to HAART, it appears to be safe to discontinue ciprofloxacin 1 month after concurrent HAART.

**Fungal infection**

The incidence of *Pneumocystis jiroveci* pneumonia [formerly known as *P. carinii* pneumonia (PCP)] has declined, and survival following severe PCP has improved in patients receiving HAART. In the patients receiving primary or secondary prophylaxis against pneumocystosis and responding to HAART with resultant increases of CD4 lymphocyte counts to >200 cells/mm$^3$ for more than 3 months, the risk for pneumocystosis is sufficiently low to warrant discontinuation of prophylaxis.

However, pneumocystosis continues to be a leading cause of community-acquired pneumonia, resulting in mortality among AIDS patients in the post-HAART era because of patient non-adherence to antimicrobial prophylaxis and failure to use antiretroviral therapy.

Surveillance studies in the USA and France have documented the significantly decreasing incidence of cryptococcosis in the post-HAART era. In the Atlanta area, the incidence of cryptococcosis among patients with AIDS decreased from 66 cases per 1000 PY in 1992 to seven cases per 1000 PY in 2000, whereas in the Houston area, the incidence decreased from 23.6 cases per 1000 person-years to 1.6 cases per 1000 PY. In France, the incidence of HIV-associated cryptococcosis has decreased by 46% during the post-HAART era. However, HIV-infected patients with limited access to HIV care continue to develop cryptococcosis in the post-HAART era with the same incident mortality as seen earlier.

Infections due to endemic fungi, such as *Histoplasma capsulatum*, *Coccidioides immitis* and *Penicillium marneffei*, usually develop in patients at an advanced stage of HIV infection, and relapse rates are high in those patients not receiving maintenance antifungal prophylaxis. In case–control studies, use of antiretroviral therapy and antifungal prophylaxis has been found to be associated with a reduced risk, although the mortality did not improve in the patients who developed infections due to endemic fungi.

Studies supporting the discontinuation of maintenance antifungal therapy are emerging in selected cases of cryptococcosis and histoplasmosis. A multicentre study of discontinuation of suppressive antifungal therapy with fluconazole or itraconazole to prevent relapse of cryptococcal meningitis in patients receiving HAART demonstrated that discontinuation of antifungal therapy when the CD4 count increased to ≥100 cells/mm$^3$ was associated with a low risk of relapse, even in patients with detectable plasma viral load or cryptococcal antigenemia. Similarly, discontinuation of maintenance antifungal therapy was safe in patients with histoplasmosis who received at least 12 months of antifungal therapy and 6 months of antiretroviral therapy and had negative blood cultures, urine and serum *Histoplasma* antigen <4.1 units and CD4 count >150 cells/mm$^3$.

**Mycobacteriosis**

TB and HIV infection may be mutually detrimental in patients with co-infection; TB may accelerate the progression of HIV infection and be associated with a higher mortality rate and a shorter survival, whereas HIV infection increases the risk for development of active TB and TB recurrence in patients without HAART. In patients with access to HAART and rifampicin-containing antituberculous therapy, the incidence, recurrence and mortality rate of TB appear to be declining and survival improving. The use of HAART has been found to be associated with a >80% reduction in the risk of TB.

In patients with TB and HIV co-infection, the optimal management of these two diseases concurrently has been a challenge to HIV care providers, and the appropriate timing of initiation of HAART is not clear because of a high pill burden, toxicity and drug–drug interactions between rifamycins, protease inhibitors and non-nucleoside reverse transcriptase inhibitors. A high proportion of patients have had to change their antiretroviral therapy or antituberculous therapy because of toxicity. For patients with CD4 counts <100 cells/mm$^3$, antiretroviral therapy should be started early because delayed HAART in such TB patients may increase the risk for death or HIV progression; for patients with higher CD4 counts, HAART may be delayed until the continuation phase (after 2 months of antituberculous therapy), or until the end of antituberculous therapy.

Rifampcin may interact pharmacokinetically with protease inhibitors, accelerating their metabolism through the induction of P450 cytochrome oxidase (CYP 450), which may result in sub-therapeutic serum levels of protease inhibitors. In addition, protease inhibitors retard the metabolism of rifabutin, resulting in increased serum levels of rifabutin and an increased likelihood of drug toxicities. Rifabutin, with its lower induction capability of the CYP 450 enzyme, is recommended when combined with efavirenz or protease inhibitors (Table 1).

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Recent clinical studies have demonstrated that combinations of efavirenz or nevirapine plus two nucleoside reverse transcriptase inhibitors with rifampicin (10 mg/kg)-containing antituberculous therapy are good alternatives to HAART and antituberculous therapy combinations because of a lower pill burden and good clinical efficacy (Table 1). In addition, once-daily HAART containing efavirenz makes integration of directly observed therapy for TB and HIV infection possible.

Disseminated infection due to non-tuberculous mycobacteria occurs mostly in patients with CD4 lymphocyte counts <50 cells/mm$^3$, with *Mycobacterium avium* complex (MAC)
the most common aetiology. With the introduction of HAART, the incidence of disseminated MAC infection has declined,\textsuperscript{1,3} and the prognosis of patients with disseminated MAC infection has been significantly improved.\textsuperscript{52} In the Adult and Adolescent Spectrum of Disease (ASD) Project, the incidence of disseminated MAC infection decreased from 10 cases per 100 PY in 1992 to two cases per 100 PY in 1998.\textsuperscript{3} Studies have shown that primary prophylaxis can be safely discontinued in patients with an increase of CD4+ count to >100 cells/mm\textsuperscript{3}. Although the study design might be different and criteria for discontinuation of secondary prophylaxis varied, the rate of relapse of disseminated MAC infection was low in patients responding to HAART, with an increase in the CD4+ count to >100 cells/mm\textsuperscript{3}.\textsuperscript{2,45–47} Therefore, it has been recommended that secondary prophylaxis can also be discontinued in asymptomatic patients who complete a 12 month course of anti-MAC therapy and whose CD4+ cell count has been increased to >100 cells/mm\textsuperscript{3} for at least 6 months.\textsuperscript{4}

### Parasitic infections

Toxoplasma encephalitis (TE) is a life-threatening opportunistic infection of the central nervous system in patients at advanced stage of HIV infection. The incidence of TE in HIV-infected patients may depend on geography and ethnicity, the degree of immunosuppression and use of antimicrobial prophylaxis, such as trimethoprim/sulfamethoxazole and HAART. It is estimated that 20%–47% of the patients seropositive for *Toxoplasma gondii* in the pre-HAART era will ultimately develop TE. The risk for TE has declined in HIV-infected patients who receive trimethoprim/sulfamethoxazole prophylaxis and HAART with immune restoration.\textsuperscript{5,58} In a French hospital-based surveillance study, the incidence of TE decreased from 3.9 per 100 PY in the pre-HAART era to 1.0 per 100 PY; among patients whose CD4 cell counts increased to >200 cells/mm\textsuperscript{3} after HAART, the incidence decreased further to 0.1 per 100 PY.\textsuperscript{58} Although no randomized clinical trials have compared the safety of discontinuation of primary or secondary prophylaxis, many studies have demonstrated that the occurrence of TE was rare after discontinuation of primary and secondary prophylaxis against pneumocystosis and TE in patients with restoration of immunity.\textsuperscript{19–21,28,46}

*Cryptosporidium parvum* and microsporidia are the two common opportunistic parasites that cause chronic diarrhea and wasting in HIV-infected patients with CD4 counts <100 cells/mm\textsuperscript{3}, and antimicrobial agents have limited efficacy in preventing or eradicating infections with cryptosporidiosis or microsporidiosis among HIV-infected patients. Although studies assessing the changes of incidence of cryptosporidiosis and microsporidiosis are lacking, diarrhea due to microsporidia and cryptosporidia resolved spontaneously with immune restoration among HIV-infected patients who responded to HAART.\textsuperscript{50,60}

### Conclusions

To conclude, sufficient clinical data have demonstrated a decline in the incidence of nearly all HIV-related OIs,
and discontinuation of primary or secondary prophylaxis for pneumocystis, cryptococcal meningitis, histoplasmosis, disseminated MAC infection, CMV retinitis and TE is safe among HIV-infected patients responding to HAART. However, OIs continue to occur in patients who seek HIV care late, have limited access to HIV care or have poor compliance with antimicrobial prophylaxis and HAART. Therefore, more effort is needed to provide easy access to HIV care services, expand the availability of HAART and constantly reinforce patient adherence to antiretroviral and antimicrobial therapies.

Acknowledgements

We thank Dr Victor L. Yu, Section of Infectious Diseases, Veterans Affair Medical Center, Pittsburgh, for reviewing this manuscript.

References


