Dr Miller is currently employed in a joint position as an assistant professor at Albany College of Pharmacy and as a clinical pharmacist/AIDS Education and Treatment Center faculty member for the Division of HIV Medicine at Albany Medical College in Albany, NY. Dr Miller presents extensively on the topics of antiretroviral therapy and HIV care. Additionally, he continues to be actively involved in clinical practice and clinical research. Dr Miller is affiliated with several professional organizations, including the Infectious Diseases Society of America (IDSA), the Society of Infectious Disease Pharmacists, and the American College of Clinical Pharmacists (ACCP). He is a board-certified pharmaceutical specialist through ACCP and is currently president-elect for the Northeastern New York Society of Health-System Pharmacists.

A senior clinical editor for University of Tennessee Advanced Studies in Pharmacy (UTAS iP) interviewed Dr Miller to discuss the challenges pharmacists face when managing HIV and opportunistic infections in a hospital setting.

UTAS iP: Looking at the recently released US Department of Health and Human Services Practice Guidelines on the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, what are some of the major points of interest for pharmacists? What are the major changes from the earlier version of these guidelines?

Dr Miller: The most recent version of the guidelines includes several important changes. In response to the increasing rates of transmitted drug resistance, the guidelines now recommend resistance testing for all patients, including those who are chronically infected with HIV. Previously, the guidelines only recommended that testing be considered for chronically infected patients. Also, in response to recent data from numerous studies, the guidelines have been amended to address scheduled antiretroviral treatment interruption. Because of poorer outcomes associated with treatment interruptions, this practice should generally be avoided unless absolutely necessary.

As a point of interest to pharmacists, the guidelines have included data on the new tablet formulation of lopinavir/ritonavir (Kaletra; Abbott Laboratories, Chicago, IL), the newest protease inhibitor Prezista (Tibotec, Mechelen, Belgium), and a newly highlighted drug interaction between ritonavir and fluticasone. Another area of interest is a focus on reducing pill burden, which is reflected by the development of once-daily and combination products. Most recently, Atripla (Bristol-Meyers Squibb and Gilead Sciences, LLC; Princeton, NJ, and Foster City, CA) was approved as a triple-combination antiretroviral product that can be taken as a once-daily single tablet and used as stand-alone therapy or in conjunction with other antiretroviral agents. The product combines a non-nucleoside transcriptase inhibitor, a nucleoside reverse transcriptase inhibitor, and a nucleotide reverse transcriptase inhibitor. Atripla is the first product to encompass an entire highly active antiretroviral therapy (HAART) regimen within a single pill.
UTAS/P: HIV is commonly referred to as a chronic illness, but that is only true for a subset of patients. One of the greatest challenges in HIV care is finding therapies for treatment-experienced patients with drug-resistant HIV strains. Finding drugs that are active for these patients is a still a struggle, despite the abundance of available antiretroviral agents. Can you comment on this issue?

Dr Miller: I agree. Although there are currently over 20 unique antiretroviral agents on the market, cross-resistance within drug classes can quickly reduce therapy options for treatment-experienced patients. We see patients whose HIV infection has little or no sensitivity to any of the available antiretroviral options. I think there is much work to be done in addressing this problem. It is of paramount importance to prevent drug resistance through optimization of medication adherence, in addition to employment of tolerable and efficacious drug regimens. As a result, we need to critically focus on improving patient counseling by setting up and utilizing more adherence clinics. We also need to optimize HIV management by increasing knowledge about the intricacies of HIV pharmacotherapy. Additionally, the expansion of novel agents and drug classes is essential in prolonging survival among treatment-experienced patients in whom drug resistance has developed. With the introduction of new protease inhibitors and newly identified targets for drug therapy (ie, integrase and chemokine C-C motif receptor 5), I think we are witnessing this needed drug development process. Although still in clinical study, agents from new therapeutic classes look potent and tolerable. Unfortunately, given the track record of the HIV virus, the work to expand therapy options and confront resistance may be a never-ending battle until a cure is found.

UTAS/P: With the ever-expanding number of available antiretroviral agents, pharmacists have become extensively involved in the pharmacotherapeutic care of patients infected with HIV. Can you speak about the role of the hospital pharmacist in the evaluation and management of HIV and opportunistic infections?

Dr Miller: As a hospital pharmacist, I can confidently say that pharmacists play a great role in the management of patients infected with HIV. Working as a hospital pharmacist in HIV management, it is of critical importance to ensure that antiretroviral agents are prescribed and dosed properly to optimize efficacy and avoid adverse events. Hospital pharmacists also take part in choosing the most appropriate antiretroviral regimens for patients and changing antiretroviral agents when necessary. With respect to opportunistic infections, we can ensure that patients are provided with appropriate prophylaxis for various opportunistic infections, based on their CD4 cell count and past medical history. When treatment of active opportunistic infections is indicated, we help choose appropriate therapy based on the offending pathogen, patient-specific characteristics, and the effectiveness and safety of the agent.

UTAS/P: With the advent of numerous powerful antiretroviral cocktails, which of the following opportunistic infections do you still worry about—Pneumocystis jiroveci pneumonia (PCP), Kaposi’s sarcoma, or toxoplasmosis? Are there other opportunistic infections that have surfaced recently?

Dr Miller: Out of these 3 opportunistic infections, PCP is the one we see most regularly, typically in patients who are poorly compliant with their HAART and PCP prophylaxis. For patients who present with respiratory complaints and low CD4 cell counts, we may empirically treat for PCP and community acquired pneumonia until a more definitive diagnosis can be made. One positive aspect of PCP, however, is that effective therapy exists. The majority of patients fare well after an appropriate course of high-dose sulfamethoxazole/trimethoprim or alternative therapy. Interestingly, we have also seen several patients within the last year who had initially presented with PCP and subsequently been diagnosed with HIV, a diagnosis pattern similar to that of the early years of HIV. Concerning additional opportunistic infections, we still see a fair amount of esophageal candidiasis, Cryptococcal meningitis, and disseminated Mycobacterium avium complex. In regard to esophageal candidiasis, rising rates of resistance to fluconazole and other azole agents have made it increasingly challenging to provide effective and convenient therapy.

UTAS/P: Please highlight some of the most significant changes that have occurred in recent years with respect to treatment and prophylaxis of the major opportunistic infections.

Dr Miller: There have not been many additions to the treatment armamentarium for opportunistic infec-
tions in recent years, but a few developments come to mind. First, we have seen numerous patients with refractory esophageal candidiasis caused by azole-resistant *Candida albicans*. To keep the disease under control in these patients, the echinocandin antifungals (caspofungin, micafungin, and anidulafungin) have been a necessary therapeutic option. Unfortunately, these agents are only available as intravenous formulations and are extraordinarily expensive. Thus, an expansion of more reasonably priced oral options would be welcome.

Secondly, the most recent US Public Health Service/IDSA treatment guidelines on opportunistic infections have included valganciclovir as an option for the treatment of cytomegalovirus disease. Valganciclovir achieves serum levels that are similar to those of intravenous ganciclovir, but valganciclovir has the benefits of oral administration and potentially less adverse effects. We have taken advantage of this therapy in order to send patients home sooner and potentially diminish some adverse drug effects.

**UTASiP:** By now, healthcare providers have learned to anticipate the occurrence of opportunistic infections by assessing the CD4+ cell count and HIV viral load. We know that when antiretroviral therapy leads to suppression of the HIV viral load to less than 50 copies/mL and to an increase in CD4+ cell count, the incidence of opportunistic infections decreases dramatically. Most recently, the SMART (Strategies for Management of Anti-Retroviral Therapy) study has highlighted the benefits of continuous therapy versus intermittent therapy with respect to preventing the occurrence of opportunistic infections. In this study, researchers enrolled 5472 patients with CD4+ cell counts >350 cells/mcL and randomized them to receive conventional antiretroviral regimens according to 2 strategies. One group received continuous therapy with the goal of suppressing viral load while the other group received intermittent therapy with the goal of maintaining the CD4+ cell count above 250 cells/mcL. This latter group stopped antiretroviral therapy until the CD4+ cell count fell to 250 cells/mcL, and then restarted therapy until the CD4+ cell count increased to >350 cells/mcL. The SMART study was stopped early because it became evident that the continuous therapy arm had significantly less progression of disease, serious AIDS events, and deaths. Can you comment on this study and its impact?

**Dr Miller:** The data from the SMART study really speak for themselves. When you look at the most recent analysis presented at the World AIDS Conference, it really seems to come down to differences in the CD4+ cell count response and viral suppression. Patients in the treatment interruption group spent more time with CD4+ cell counts below 350 cells/mcL and experienced higher viral loads. These factors were correlated with opportunistic infections and death. Another interesting finding is that more patients in the treatment interruption group experienced adverse events including myocardial infarctions, strokes, renal disease, and liver disease. These events have previously been blamed on the long-term use of antiretroviral therapy. Currently, these data suggest that once patients start on HAART, the treatment needs to become a lifelong commitment.

**UTASiP:** Can you address discontinuing primary and sometimes secondary prophylaxis for opportunistic infections in HIV patients experiencing a favorable response to antiretroviral therapy?

**Dr Miller:** As reflected in the US Public Health Service/IDSA Opportunistic Infection Prevention Guidelines, data support the safe discontinuation of primary and secondary prophylaxis for the majority of opportunistic infections. This recommendation goes back to the availability of effective HAART, which has increased our ability to restore immune function in patients with low CD4+ cell counts. For the patient, I think the option to discontinue prophylaxis is highly beneficial because, by doing so, we are able diminish pill burden and medication side effects, in addition to hopefully enhance a patient’s ability to focus on taking their HAART adherently. This is the ultimate goal.

**UTASiP:** Can you talk about the types of clinical interventions that hospital pharmacists perform in managing HIV and opportunistic infections in patients?

**Dr Miller:** Clinical interventions are often numerous and include appropriate dosing of antiretroviral agents, ensuring that antiretroviral regimens ordered within the hospital match those taken at home, identifying adverse drug effects, managing drug-drug interactions, and choosing appropriate antimicrobial therapy. Also, because I practice at an academic med-
ical center, I spend a lot of time educating and assisting house staff in the care of our patients infected with HIV. For medical residents with little experience in HIV and antiretroviral agents, the learning curve can be extraordinarily high and I do my best to help them through the process.

UTAS/iP: Antiretroviral agents are notoriously known for having numerous drug interactions. Many clinicians carry around pocket reference guides dedicated solely to drug interactions involving antiretroviral agents. How do you keep track of all these drug interactions? Do you have any tips for pharmacists?

Dr Miller: In truth, it is difficult to keep track of all antiretroviral drug interactions, even for those of us who specialize in this field. First, I think it is important to get a grasp of the most common drug interactions seen in treatment regimens for HIV-infected patients. Although hundreds of possible drug interactions exist, there are probably approximately 10 that account for the vast majority of interactions that we see with the commonly used regimens. Also, knowledge of how drugs are metabolized by, or affect, the CYP450 system is a great clue in identifying drug interaction potential. In the end, however, I think a good reference is vital. Typically, if I am not sure of a particular interaction, I look it up and hopefully add to my knowledge base by doing so. I most commonly use the Micromedex Healthcare Series database, which, in my experience, has up-to-date information on new interactions.

UTAS/iP: Pharmacists accomplish a great deal of their pharmaceutical care by simply speaking to patients about their medication concerns. Patient counseling can have a tremendous impact on compliance with, and correct use of, antiretroviral therapy. What are some of the challenges you face in counseling patients with HIV? Can you offer some advice on how to optimize pharmacy counseling sessions with patients infected with HIV?

Dr Miller: My biggest challenge in counseling patients is trying to alter a patient’s thinking and convincing them that medication adherence must be a priority in their life. We see numerous patients with difficult lifestyles and drug-abuse problems. For many of these patients, adherence with their antiretroviral agents is far from their primary concern. Regardless of the amount of scientific data we have, it comes down to getting patients into the right frame of mind and a stabilized lifestyle. Those factors make all the difference. I find that instead of rambling off facts and figures, it is more advantageous to ask the patient questions and identify specific steps that can be taken to optimize their compliance with medications.