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FOLLOW-UP TO MANAGEMENT STRATEGIES FOR CANDIDATES FOR PROTEASE INHIBITORS AND REQUIRING TREATMENT FOR *MYCOBACTERIUM TUBERCULOSIS*

As stated in "Management strategies for candidates for protease inhibitors and requiring treatment for *Mycobacterium tuberculosis",* which appeared in a recent issue of the *Canada Communicable Disease Report* (CCDR)[1], there is potential for significant interaction between HIV protease inhibitors and rifamycins. Rifamycins are potent inducers of the cytochrome P450 enzyme system, and may dramatically decrease protease inhibitor concentrations. In addition, protease inhibitors may also increase rifamycin concentrations, and thus increase the risk of toxicity. These effects have been extensively reviewed in the literature[2-5]. The article in the CCDR suggests that alternative antiretroviral therapy be considered for patients requiring treatment for both HIV and *M. tuberculosis* infections. Specifically, the option of replacing a protease inhibitor with a non-nucleoside reverse transcriptase inhibitor (NNRTI) is offered. However, we would like to point out that all members of the NNRTI class (i.e. delavirdine, nevirapine, efavirenz) are also extensively metabolized by the cytochrome P450 system[6-8], and therefore are susceptible to similar interactions with rifamycin agents (Table 1); these compounds would not be ideal alternatives in this setting, especially if rifampin is used.

For example, delavirdine concentrations are virtually undetectable in the presence of rifampin[9]. With rifabutin, delavirdine concentrations are decreased by 50% to 60%[10]. Attempts have been made to determine whether higher doses of delavirdine were able to compensate for the inductive effects of rifabutin[11]. Even with a median delavirdine dose of 600 mg three times daily (range: 400 mg to 1 g three times daily), trough concentrations were often still not adequate, and rifabutin concentrations were significantly elevated[11]. Thus, the authors concluded that this combination should be avoided because of lower than normal delavirdine concentrations and the possibility of toxicity related to increased rifabutin exposure.

Resistance may develop extremely rapidly with NNRTIs [12,13]; therefore, it is imperative to avoid concomitant therapy with agents including rifamycins that may reduce NNRTI concentrations to subtherapeutic concentrations. In such situations, alternative antiretroviral and/or antimycobacterial agents need to be considered.

Table 1
Rifamycin interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors

	Rifabutin	Rifampin
Protease inhibitors		
Amprenavir (Code: 141W94)	14% ↓ amprenavir, 3- to 6-fold ↑ minimum drug concentration of rifabutin. Therefore, decrease dose of rifabutin to avoid toxicity[16].	81% ↓ AUC and 91% ↓ minimum drug concentration of amprenavir[16]. Therefore, **avoid combination**.
Indinavir (Crixivan®)	Interaction study of half-dose rifabutin + indinavir: 155% ↑ rifabutin AUC, 33% ↓ indinavir AUC. Therefore, **↑ indinavir to 1000 mg every 8 hours and ↓ rifabutin to 150 mg daily**[14].	May reduce indinavir concentrations. Therefore, **avoid combination**[14].
Nelfinavir (Viracept®)	32% ↓ nelfinavir AUC, 3-fold ↑ rifabutin AUC. Therefore, reduce rifabutin dose by 50%[17].	82% ↓ nelfinavir AUC. Therefore, **avoid combination**[17].
Ritonavir (Norvir®)	400% ↑ rifabutin AUC, risk of toxicity. Therefore, **avoid combination**[18].	35% ↓ ritonavir AUC. Therefore, may need to ↑ ritonavir dose[19].

Saquinavir (Invirase®, Fortovase®)	40% ↓ saquinavir AUC. Therefore, **avoid combination if possible, or ↑ saquinavir dose**[19].	80% ↓ saquinavir AUC. Therefore, **avoid combination**[20].
Non-nucleoside reverse transcriptase inhibitors		
Delavirdine (Rescriptor®)	50% to 60% ↓ delavirdine concentrations[10] (not adequately compensated with 600 mg three times a day); also > 200% ↑ rifabutin AUC[11]. Therefore, **avoid concomitant use.**	Virtually undetectable delavirdine concentrations; **combination contraindicated**[9].
Efavirenz (Sustiva®)	Potential for ↓ efavirenz concentrations and ↑ / ↓ rifabutin concentrations.	26% ↓ efavirenz concentrations[21]; clinical significance unknown. Therefore, rifampin dosage adjustment not required.
Nevirapine (Viramune®)	16% ↓ nevirapine concentrations[7].	37% ↓ nevirapine concentrations[7].
↓ = decrease concentration ↑ = increase concentration AUC = area under concentration curve		

In some instances, interactions between retrovirals and rifamycins may be managed by appropriate dosage adjustment. For example, to adequately adjust for the interaction between indinavir and rifabutin, indinavir should be increased to 1 g every eight hours and rifabutin should be decreased to 150 mg daily[14]. This can be done with no additional dosing times and a minimal increase in pill burden (i.e. three additional 200 mg indinavir capsules and one less rifabutin 150 mg capsule per day). Other agents that may be co-administered with full or one-half dose rifabutin include amprenavir, nelfinavir, and nevirapine (Table 1). A study to evaluate the approximate dose of rifabutin to be used concurrently with ritonavir and saquinavir is ongoing.

Therefore, the following amendments to the recommendations as published in the CCDR (for HIV-infected persons diagnosed with active TB and who are being treated with regimens that include protease inhibitors) are recommended.

1. **Treatment for active TB**. Consider using rifabutin instead of rifampin in a multi-drug regimen. Rifabutin is a less potent inducer of the cytochrome P450 enzyme system. The usual dosage of rifabutin is 300 mg daily, but may be reduced to 150 mg daily depending upon the concurrent antiretroviral agent being used (see Table 1).

2. **Patients who are being satisfactorily treated with an antiretroviral therapy that includes a protease inhibitor**. If the patient is currently taking indinavir, the dosage should be increased. If the patient is taking saquinavir and/or ritonavir, another antiretroviral agent (e.g. nelfinavir, amprenavir, nevirapine) should be substituted, with appropriate dosage adjustments to compensate for concomitant rifabutin therapy.

3. **Patients who are having incomplete viral suppression with a regimen that includes a protease inhibitor**. In the setting of incomplete viral suppression, changing at least two or all components of an antiretroviral regimen is recommended[15]. Agents that may be combined with two new nucleoside analogues include indinavir, nelfinavir, amprenavir, and nevirapine. Appropriate dosage adjustments should be made to compensate for concomitant rifabutin therapy.

We hope that the above information will provide additional guidance for clinicians managing patients with concurrent HIV and TB infection.

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MORE ON MANAGEMENT STRATEGIES FOR CANDIDATES FOR PROTEASE INHIBITORS AND REQUIRING TREATMENT FOR *MYCOBACTERIUM TUBERCULOSIS*

In the preceding article, Drs. Tseng and Walmsley have nicely expanded on the potential interactions of several antiretrovial agents with rifabutin and rifampin. As they pointed out, delavirdine has a clearly established interaction with rifabutin and rifampin. The clinical significance of the pharmacokinetic interactions between nevirapine or efavirenz with rifabutin and rifampin are less clear. A new option not covered in the original article[1] or in the follow-up by Tseng and Walmsley was recently discussed during the recent World AIDS Conference in Geneva. This involves a potent new nucleoside analogue, abacavir, also known as 1592 or Ziagen™. Preliminary data suggest that the antiviral effect which can be achieved with triple nucleoside combination including AZT, 3TC/ZDV, and abacavir is of similar magnitude to that described for triple drug combination regimens using two nucleosides plus a potent protease inhibitor or two nucleosides plus a non-nucleoside reverse transcriptase inhibitor in antiretroviral therapy naïve patients[2]. If and when these results are confirmed, this approach may offer a valid treatment option which will be unlikely to create problems when used concomitantly with rifampin or rifabutin.

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Source: *J Montaner, MD, Chair, AIDS Research, Professor of Medicine, University of British Columbia, Vancouver BC.*

International Notes

STATEWIDE SURVEILLANCE FOR EHRLICHIOSIS – CONNECTICUT AND NEW YORK, 1994-1997

In the United States, human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE) represent two clinically indistinguishable yet epidemiologically and etiologically distinct diseases caused by *Ehrlichia chaffeensis* and a bacterium similar or identical to *E. equi*, respectively. Infection with these emerging tickborne pathogens results in acute, influenza-like illnesses with fever, headache, malaise, and frequently leukopenia and/or thrombocytopenia. Connecticut and New York have initiated statewide laboratory-based surveillance to determine the magnitude and geographic extent of ehrlichiosis. This report summarizes results from the first 3 years of surveillance, which showed that rates of ehrlichiosis were similar in counties in both states where the disease occurs, and highest age-specific rates occurred among persons aged > 40 years.

In New York, since 1994, physicians have been encouraged to submit serum specimens and clinical data from patients with signs and symptoms consistent with ehrlichiosis. Ehrlichiosis became reportable in Connecticut in January 1995 and in New York in March 1996; public-health laboratories in both states have provided confirmatory serologic testing for ehrlichiosis since 1995. State laboratories tested serum specimens by indirect fluorescent antibody (IFA) assays to detect antibodies against *E. chaffeensis* and *E. equi*, and tested whole blood or serum using polymerase chain reaction (PCR) assays to detect *Ehrlichia* spp. DNA. A probable case was defined in New York as the presence of a single antibody titre ≥ 1:80 to either *Ehrlichia* sp., and in Connecticut as a titre ≥ 1:64 to *E. chaffeensis* or ≥ 1:80 to *E. equi*. A confirmed case was defined in both states as a fourfold or greater increase in antibody titre between acute-phase and convalescent-phase serum specimens, visualization of intracytoplasmic ehrlichiae (i.e. morulae) in peripheral blood leukocytes (plus, in New York, at least one antibody titre ≥ 1:80), or identification of DNA sequences of *E. chaffeensis* or the agent of HGE by PCR assay.

Connecticut: From 1995 through 1997, a total of 173 ehrlichiosis cases were reported in Connecticut; 131 (76%) were confirmed, and 42 (24%) were probable. Of the 173 confirmed and probable cases, 155 (90%) were HGE and nine (5%) were HME; nine (5%) persons had antibodies reactive with both *E. chaffeensis* and *E. equi*. Cases were identified by IFA (83), PCR (69), both assays (19), and visualization of morulae (two). Frequencies of

specific signs and symptoms were similar to frequencies identified in previous case series[1-3]. Information about fever (defined as ≥ 38.0° X) *ωασ κνοων φορ* 162 *πατιεντσ*; *οφ τηε* 138 (85%) *ωιτη φεϖερ*, *τηε μεδιαν τεμπερατυρε ωασ* 39.1° X. I*νφορματιον αβουτ λευκοπενια* (*δεφινεδ ασ α ωηιτε βλοοδ χελλ χουντ* [ΩBX] < 5.0×10^9/L) was known for 130 patients; of the 79 (61%) with leukopenia, the median WBC was 3.2×10^9/L. Information about thrombocytopenia (defined as a platelet count of < 150×10^9/L) was known for 130 patients; of the 92 (68%) patients with thrombocytopenia, the median platelet count was 87×10^9/L.

Ehrlichiosis cases occurred in all months except January; 133 (77%) of the 173 cases occurred during May-September. Illnesses occurred equally in males and females. The mean patient age was 53 years (range: 3 days to 90 years). The 19 (11%) patients who were hospitalized were substantially older (mean age: 61.9 years) than patients who were not hospitalized (mean age: 44.7 years). One patient died with cancer as the primary diagnosis at the time of death. Treatment information was available for 66 cases. Reported antibiotic therapy began at a median of 4.5 days from symptom onset; 59 of the 66 patients received docyxycline.

The statewide average annual reporting rate for 1995-1997 was 1.8 cases per 100,000 population (range: 1.1 in 1995 to 2.9 in 1997). In 1997, a total of 96 cases were reported, an increase from 40 in 1996 and 37 in 1995. Ehrlichiosis cases were reported in all eight Connecticut counties; the highest average annual reporting rates were in Middlesex and New London counties (9.3 and 4.8, respectively). Age-specific rates were higher among persons aged > 40 years; the highest rate (3.9) was among those aged 70 to 79 years.

New York: From 1994 through 1997, a total of 225 ehrlichiosis cases were reported in New York; 135 (60%) were confirmed, and 90 (40%) were probable. Of the 225 confirmed and probable cases, 197 (88%) were HGE, and 28 (12%) were HME. Cases were identified by IFA (138), PCR (57), and both assays (30); nine with a positive IFA titre also had visualization of morulae. Frequencies of specific signs and symptoms were similar to those reported for Connecticut patients. All 218 patients for whom fever information was available had fever (median temperature: 39.2° C). Information about leukopenia was known for 177 patients; of the 110 (62%) with leukopenia, the median WBC was 4.0×10^9/L. Information about thrombocytopenia was known for 171 patients; of the 122 (71%) with thrombocytopenia, the median platelet count was 114×10^9/L.

Ehrlichiosis cases occurred during all months; 182 (81%) of the 225 cases occurred during May-September. Most (123 [55%] of 225) cases occurred in males. The mean patient age was 50.1 years (range: 5 to 90 years). Ninety-three patients were hospitalized; one person with a probable case died from multiple organ failure. The statewide average annual reporting rate for 1994-1997 was 0.4 cases. In 1997, a total of 67 cases were reported, a decrease from 69 in 1996 but an increase from 51 in 1995 and 14 in 1994. Ehrlichiosis cases were reported in 19 of the 62 counties in New York. Most cases occurred in the lower Hudson River Valley and eastern Long Island; the highest yearly reported rates were in Westchester and Putnum counties (5.5 and 3.6, respectively). As in Connecticut, age-specifc rates were higher among persons aged > 40 years; the highest rates were among those aged 70 to 79 years.

MMWR Editorial Note: Since 1985, approximately 500 ehrlichiosis cases have been confirmed by the United States Centers for Disease Control and Prevention (CDC). The occurrence of these diseases reflects the seasonal activities and geographic distributions of the tick vectors. The preponderance of ehrlichiosis cases are observed between mid-spring and mid-summer. *E. chaffeensis* infections occur most frequently in southeastern and midwestern states with abundant lone star ticks (*Amblyomma americanum*). The blacklegged tick (*Ixodes scapularis*) is the principal vector of the HGE agent in the northeast and upper midwestern United States. This tick also transmits *Borrelia burgdorferi*, which causes Lyme disease, and most recognized HGE cases have originated from states with high rates of Lyme disease, particularly Connecticut, Minnesota, New York, and Wisconsin.

The findings in this report are subject to an important limitation. Surveillance case definitions developed for new or emerging infections such as ehrlichiosis are usually highly specific. Accordingly, case definitions used in the surveillance studies described in this report captured only those patients with recognized clinical findings; patients with less severe disease were excluded from confirmatory testing. The reported rates of disease therefore underestimate the true incidence of disease. When the clinical spectrum of ehrlichiosis is better defined and improved diagnostic tests for ehrlichial infections are available, the surveillance case definition can be expanded. Passive surveillance data for ehrlichial infections are sparse, collected from a few small geographic regions in a limited number of states where *Ehrlichia* spp. are endemic. Although ehrlichiosis is reportable in 21 states, few statewide summaries of ehrlichiosis cases are large enough for meaningful analysis. Surveillance for the ehrlichioses in Connecticut and New York is part of the CDC's Emerging Infections Program, and CDC's Tick-Borne Diseases Initiative is supporting active, population-based surveillance for these diseases in Connecticut, Missouri, and Wisconsin.

The findings in Connecticut and New York underscore the expanding recognition of these diseases and unresolved issues concerning the ehrlichioses. In these two states combined, < 30% of persons with ehrlichiosis required hospitalization. Previous patient series in which 55% to 60% of ehrlichiosis patients were hospitalized[1,2] possibly over-represented seriously ill patients. The decline in hospitalizations also might represent increasing physician awareness of these diseases and broader use of appropriate therapy. The finding that reported rates of ehrlichiosis increase with age is consistent with previous studies[1-3] and contrasts with age-specific incidences for Lyme disease and Rocky Mountain spotted fever, tick-borne diseases that frequently occur in children. Age-associated host factors may account for severity of disease; however, fatal ehrlichial infections have occurred in otherwise healthy young adults and children.

Serologic cross-reactivity between *E. chaffeensis* and *E. equi* is well recognized[3] and can hinder epidemiologic distinction between HME and HGE. There are 10 recognized species of *Ehrlichia*, and substantial serologic cross-reactivity exists among individual species within subgroups of this genus. Some "serologically confirmed" cases of HME and HGE may represent infections with the alternate agent or infections with other, antigenically-related ehrlichial species. Although IFA is the principal diagnostic tool for detecting ehrlichial infection, neither this assay nor PCR-based diagnostics are standardized. New techniques, including enzyme immunoassays using recombinant ehrlichial antigens and multiplex fluorescence-detection PCR, are under investigation. Doxycycline is the drug of choice for persons infected with ehrlichiosis. The optimal duration of therary has not been established, but current regimens recommend continuation of treatment for at least 3 days following defervescence, for a minimum total course of 5 to 7 days. Severe or complicated disease can require longer treatment courses. Because tetracyclines are contraindicated in pregnancy, rifampin has been used successfully in a limited number of pregnant women with documented HGE[4].

Limiting exposure to ticks reduces the likelihood of ehrlichial infection. In persons exposed to tick-infested habitats, prompt careful inspection for and removal of crawling or attached ticks remains an important method of preventing disease because *Ehrlichia*-infected ticks appear to require 24 to 48 hours of attachment to the host before the agent can be transmitted[5]. As with Lyme disease, peridomestic activities account for many of the tick exposures responsible for HGE in the northeastern United States[3], and strategies to reduce vector tick densities through area-wide application of acaricides and control of tick habitats (e.g. leaf litter and brush) have been effective in small-scale trials. New methods being developed include applying acaricides to rodents and deer and using baited tubes, boxes, and deer feeding stations in areas where these pathogens are endemic. Community-based integrated tick management strategies may be an effective public health response to reduce the incidence of tickborne infections.

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