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Criteria for Non-Formulary Use of HMGs in Patients Receiving Protease Inhibitor Therapy

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To All Chiefs of Pharmacy (please distribute to medical providers):

Recently, there has been concern regarding the management of dyslipidemia in HIV-infected individuals receiving protease inhibitors in combination with our formulary hydroxymethylglutaryl-coenzyme A reductase inhibitors (HMG-CoA RI's) simvastatin or lovastatin. This concern arose as a result of a presentation made during the 7th Conference on Retroviruses and Opportunistic Infections in February, 2000 in which HIV seronegative volunteers were randomized to receive pravastatin 40 mg/d, simvastatin 40 mg/d or atorvastatin 40 mg/d on days 1-4 and 15-18. On days 5-18, volunteers received dual protease inhibitors (ritonavir 400 mg bid plus saquinavir 400 mg bid). Investigators noted a 31.6 fold increase in simvastatin and a 4.5 fold increase in atorvastatin median estimated area under the curve concentrations (AUC_{0-24}) when used in combination with ritonavir and saquinavir. Median estimated AUC_{0-24} decreased nonstatistically in those subjects receiving dual protease inhibitors with pravastatin. Authors concluded from this data that simvastatin and atorvastatin either be avoided or used in lower doses in patients receiving ritonavir plus saquinavir in order to avoid potential toxicity from these agents. In addition, reduced doses of pravastatin do not appear necessary in patients receiving ritonavir plus saquinavir[1].

All of the protease inhibitors (PIs) are inhibitors of the cytochrome P450 3A4 (CYP 3A4) isoenzyme system. Ritonavir is reported to be the most potent inhibitor of the PIs. Because of its potential for drug interactions, it had not been as widely used. However, its use is increasing due to the fact that it can inhibit the metabolism of other PIs (saquinavir, indinavir, amprenavir) resulting in higher PI concentrations and less frequent daily dosing when ritonavir is combined with another PI[2].

Although data, specifically addressing the combination of the protease inhibitors with the HMG CoA RIs, is lacking, it is known that simvastatin, lovastatin, atorvastatin, and cerivastatin are metabolized by CYP 3A4 to some degree. Fluvastatin is metabolized by CYP 2C9 and pravastatin is not metabolized by the CYP isoenzyme system. Therefore, potential exists for increased concentrations of simvastatin, lovastatin, atorvastatin, or cerivastatin when used in combination with the PIs, especially ritonavir. The increased concentration of HMG CoA RIs may result in an increased risk for myopathy and

rhabdomyolysis. The risk may be even greater in those HIV-infected patients receiving PIs plus other known inhibitors of CYP 3A4.

Two groups of experts have made recommendations regarding the use of HMG CoA RIs in HIV-infected individuals receiving PIs including the Adult AIDs Clinical Trials Research Group (AACTG) Cardiovascular Disease Focus Group and the Centers for Disease Control and Prevention/Department of Health and Human Services/Henry J Kaiser Foundation. Both groups have recommended avoidance of simvastatin and lovastatin in patients receiving PIs and suggest atorvastatin, fluvastatin, cerivastatin, and pravastatin be considered as alternatives that could be used with caution[3-4].

As a result of this potential patient safety issue, involving drug interactions with our formulary HMG CoA RIs (simvastatin and lovastatin), the VA Pharmacy Benefits Management Strategic Health Group and Medical Advisory Panel (VA PBM-SHG/MAP) recommend that VISNs make pravastatin available on a nonformulary basis for those patients receiving a protease inhibitor or delavirdine.

If a provider considers the medical benefit of prescribing simvastatin, lovastatin, cerivastatin or atorvastatin to a patient receiving a protease inhibitor or delavirdine to outweigh the potential risk, the patient must be advised to promptly report any unexplained muscle pain, tenderness or weakness. Patients experiencing muscle pain, tenderness or weakness, should be instructed to discontinue the HMG CoA RI immediately and providers should obtain a CPK level as soon as possible.

1. http://www.retroconference.org
2. Beyzarov EP. Two Guidelines Offer New Insights on Treatment of HIV. Drug Topics 2000;Feb:31-35.
3. http://www.hivatis.org
4. http://www.aactg.s-3.com/ann.htm

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