# Record Number of Antimalarials in Development

BY BRUCE JANCIN
*Denver Bureau*

LISBON — More antimalarial drugs are in the developmental pipeline today than at any other time in history, Dr. Elizabeth A. Ashley reported at the 12th International Congress on Infectious Diseases.

Two main factors can explain this welcome state of affairs. One is the impressive productivity of Chinese scientists in the People's Republic in exploiting the potential of *Artemisia annua,* the plant also known as sweet wormwood or qing hao, from which artemisinin and related drugs are derived.

The other major factor has been the recent creation of public-private partnerships to aggressively support the drug development process, from compound identification through regulatory approval. In 2006 alone, the Medicines for Malaria Venture will take on 5-10 new drug discovery projects. Other major players include the Drugs for Neglected Diseases Initiative and World Health Organization–sponsored programs.

Universities, foundations, pharmaceutical companies, and other institutions have pitched in. For example, the Walter Reed Army Institute of Research is expediting development of intravenous artesunate for severe malaria. Food and Drug Administration approval could come next year, said Dr. Ashley of the University of Oxford Tropical Medicine Program and the Shoklo Malaria Research Unit, Mae Sot, Thailand.

But the first new drugs for uncomplicated falciparum malaria to reach the market will be novel combinations of old drugs. WHO malaria treatment guidelines issued earlier this year declare artemisinin-combination therapies (ACTs) the new standard of care because strains resistant to chloroquine and sulfadoxine/pyrimethamine have become so common. The emphasis now is on developing affordable fixed-dose ACTs in a single pill having at least two unrelated mechanisms of action to prevent artemisinin resistance and boost adherence.

Only one fixed-dose ACT is available internationally. Artemether-lumefantrine (Coartem) is registered in 75 nations. Novartis markets it at a subsidized cost of $2.50 per course for adults. That's still a lot of money in the poorest parts of the world, but "it's easy to imagine that once other fixed combinations come into the market, prices will fall," Dr. Ashley said.

**The emphasis now is on developing affordable fixed-dose artemisinin-combination therapies in a single pill.**

**DR. ASHLEY**

Among the new combinations of old drugs that are likely to earn broad international approval within the next year or so are artesunate-pyronaridine, dihydroartemisinin-piperaquine, chlorproguanil-dapsone-artesunate, artesunate-mefloquine, and artesunate-amodiaquine, she said at the congress, which was sponsored by the International Society for Infectious Diseases.

Some of these agents are undergoing redevelopment to meet international standards. Dihydroartemisinin-piperaquine, for example, has been used extensively in China and Vietnam since 1989 but isn't used elsewhere because China's Good Manufacturing Practice standards aren't internationally recognized.

That's also the case for parenteral artesunate. The older Chinese/Vietnamese version has to be mixed with a small vial of sodium bicarbonate shortly before administration. In contrast, the Walter Reed product designed for international approval comes premixed in an ampule.

"It's going to be a 10-cc volume, the only drawback of which will be for intramuscular injection in children in endemic countries. But this is certainly good news for returning travelers to the U.S. who otherwise would be faced with quinine," Dr. Ashley observed.

The physician noted that the landmark South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) recently showed in 1,461 randomized patients with severe falciparum malaria a compelling 35% reduction in the relative risk of death with artesunate (Lancet 2005;366:717-25).

Ten or more antimalarial drugs are poised for approval in 3-5 years. Many are novel agents, some acting on new targets. They include cysteine protease inhibitors to curb hemoglobin degradation, third-generation antifolates, synthetic peroxides, and farnesyltransferase inhibitors. Also in development are new synthetic artemisinin derivatives devoid of neurotoxicity in animals, unlike earlier derivatives.

In addition, tafenoquine is a long-acting 8-aminoquinoline now in clinical trials to replace 2 weeks of primaquine for nonfalciparum malaria. As with primaquine, it is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. ■



# Lipid Changes May Predict Severity of Hantavirus Infection

BY BRUCE JANCIN
*Denver Bureau*

LISBON — Clinically moderate to severe hantavirus infections are invariably characterized by a distinctive pattern of serum lipid changes, reported Dr. Jan Clement at the 12th International Congress on Infectious Diseases.

The size of the lipid perturbations correlates with the severity of the underlying hantavirus infection. And because the lipid changes precede by several days, the deterioration in renal function and worsening thrombocytopenia that mark a serious hantavirus infection, the extent of the lipid abnormalities can be used as an early warning system regarding the viral illness to come, according to Dr. Clement of the Rega Institute for Medical Research at the University of Leuven, Belgium.

This is the first report linking serum lipid changes to the subsequent severity of hantavirus infection, he noted. Although the work was restricted to Belgian hantavirus patients, Dr. Clement has studied numerous cases of the viral infection from disparate areas of the globe and believes the phenomenon occurs worldwide.

He reported on 58 Belgians with serologically confirmed hantavirus infection. Their associated serum lipid changes consisted of a marked reduction in total cholesterol and HDL accompanied by hypertriglyceridemia. Baseline serum lipid levels weren't available for many patients. However, the mean total cholesterol at the peak of the illness was 141 mg/dL, compared with 238 mg/dL after recovery. The perturbation in HDL was even more profound: a mean of 14 mg/dL during the early and peak phases of the illness, compared with 52 mg/dL after recovery. Triglyceride levels rose to a mean of 329 mg/dL during the hantavirus infection, even though some patients experienced anorexia and vomiting, before declining to 199 mg/dL upon recovery, Dr. Clement added at the congress, which was sponsored by the International Society for Infectious Diseases.

There were significant correlations between the extent of hypocholesterolemia and low HDL and the degree of thrombocytopenia and renal impairment. For example, the two patients who developed hantavirus-induced adult respiratory distress syndrome requiring mechanical ventilation had the lowest values of these lipids recorded in the entire study: an average nadir of 53 mg/dL for total cholesterol and 5 mg/dL for HDL. In 38 patients with moderately severe hantavirus infection, defined by a peak serum creatinine in excess of 1.5 mg/dL, the mean nadir total cholesterol was 129 mg/dL. In contrast, total cholesterol bottomed out at a mean of 162 mg/dL in patients with a milder infection (a peak creatinine below 1.5 mg/dL).

The mechanism by which serum lipid changes serve as a predictor of the clinical severity of hantavirus infection is thought to be that the lipid levels provide an indirect measure of proinflammatory cytokine bioactivity, said Dr. Clement. ■