Harvard docs pitch global AIDS drug program

Last month, more than 100 Harvard doctors, economists and public health specialists released a multi-year, multi-billion dollar plan to deliver AIDS drugs to the world's poor. The idea stems from the fact that a subset of the group has been quietly distributing antiretroviral therapy to a few dozen AIDS patients at a small hospital in central Haiti for years the group thinks the same approach could be used to save the lives of several million people with AIDS. "We believe that it is scientifically feasible and financially possible to do this," says Jeffery Sachs, director of Harvard's Center for International Development.

The plan runs counter to conventional public health wisdom. Until now, antiretroviral drug therapy has been too expensive and too complicated to consider in places like sub-Saharan Africa, which is home to the vast majority of the world's 36 million AIDS patients. But the Harvard doctors cite the Haiti program as well as others as proof that the drugs can be delivered in difficult settings. Moreover, they note that many of the makers of antiretroviral drugs have recently agreed to dramatic price reductions.

Although the effort gained widespread media attention, it prompted the Bill and Melinda Gates Foundation to issue a statement calling for "...a balanced approach: we must work together on prevention as well as treatment." And activist AIDS groups which have been fighting for lower prices for years are worried that the Harvard plan could undermine their efforts. According to Paul Davis of ACT UP Philadelphia, the large pharmaceutical companies only agreed to cut prices after some countries started using bootleg generic AIDS drugs. "What we are very concerned about is that Sachs *et al.* might negotiate a plan that excludes generic producers from the table," says Davis.

But Sachs argues that the issue is not prevention versus treatment, rather it is how to come up with the money. The group estimates that their approach would cost $6.3 billion annually, a sum they say wealthy countries should pay. And he personally believes that an ideal plan would allow major drug makers to maintain and enforce patents, as long as they could still deliver affordable drugs to the poor. See also page 521

Tinker Ready, Boston

Cash invigorates European AIDS study

The world's largest multinational cohort study of HIV-infected patients has received a funding boost from the European Commission (EC) in Brussels. A new four-year grant of 1.2 million EUROS ($1.8 million) from the commission will help EuroSIDA—a study originated in 1979 and headed by Jens D. Lundgren of Hvidovre University Hospital in Denmark—to continue assessing how anti-HIV therapies affect the course of chronic infection based on 8,500 patients in 20 countries.

Particular focus will be placed on the treatment of HIV in Eastern Europe, where AIDS is increasing through intravenous drug use. Although a number of Eastern European countries are already involved in the project, Lundgren says that additional countries, such as the Baltic States and hopefully the Ukraine, will be added over the next four years. Eventually the number of patients covered by the study is expected to increase to 12,000.

"This new money is valuable because it will allow us to initiate an extensive analysis of the plasma bank that we have built up from volunteers participating in the study," says Lundgren. He adds, "Such an analysis will provide us with important information about the role of resistance to antiretroviral therapies." In addition to funding from the EC's Biomed programs, EuroSIDA receives a similar level of support from the pharmaceutical companies GlaxoSmithKline, Roche and Boehringer Ingelheim.

Another goal is to assess the patterns of HIV-related diseases. The study has already shown that the pattern in patients receiving highly active antiretroviral therapy (HAART) is changing, with relatively more cases of non-Hodgkin lymphoma and an increase in the number of patients who are dying without having experienced a so-called 'AIDS-defining' disease. One possible explanation is the late-onset side effects from HAART, such as increased risk of cardiovascular disease. "The possible long-term side effects are something that the new money will allow us to study more closely," says Lundgren.

EuroSIDA's data on the effectiveness of HAART have already had implications for treatment guidelines. For example, the information that HAART induced reconstitution of the immune system—as indicated by a rise in blood $C4^+$ lymphocyte levels—enabled chemoprophylaxis of opportunistic infections to be safely discontinued and have contributed to the recent revision of treatment guidelines in the US (http://hivatis.org/trtgdlns.html).

David Dickson, London

First sepsis drug nears market

Based on promising clinical trial data, the US Food and Drug Administration (FDA) has agreed to fast-track Eli Lilly's sepsis treatment, Zovant. Instead of the usual 12 months that the FDA takes to evaluate a new drug application, Zovant will be reviewed in 6 months. If approved, it will become the first drug on the market for this life-threatening condition.

Sepsis—bacterial infection of the blood—kills between 30–50% of its victims or 225,000 people annually in the US alone. Although more than 20 medicines for treating the condition have entered clinical trials, only a handful have advanced to late-stage testing, and so far, none have worked convincingly. The reason might lie in the complex nature of the condition. Bacterial endotoxins and other inflammatory mediators released into the blood stream set off a cascade of events that results in inflammation, damage to the endothelium, coagulation and thrombosis. The resulting clots clog the microvasulature, causing multiple organ failure and death.

Efforts to design treatments for sepsis have targeted early events in the pathological process, such as endotoxin release. But in the last decade the focus has shifted to the interplay between inflammation, coagulation and fibrinolysis, and the role that the vascular endothelium plays in tying inflammation and coagulation pathways together.

Zovant is activated protein C (APC), a natural anti-coagulant which showed such a robust reduction in mortality in Phase III trials that an independent Data Safety and Monitoring Board halted the trial last June, prompting Lilly to petition the FDA for an urgent review. Basic research confirms a unique role for APC in hemostasis of the vasculature, where it acts as a feedback inhibitor of the coagulation cascade. In sepsis patients, protein C is depleted and the ability to produce endogenous APC is impaired, shifting the balance toward greater systemic inflammation, coagulation and cell death.

But the secret of APC's success may lie beyond its anti-thrombotic activity. Brian Grinnell and coworkers from Lilly's Division of Research Technologies have shown that APC has an im-