Selling Sustiva

A “protease sparing” drug? Not so fast.

March 1, 1999 By Stephen LeBlanc

Even before efavirenz (brand name Sustiva) was approved last September, DuPont Pharma began promoting its antiretroviral as a “protease sparing” drug. The claim, later echoed by some AIDS physicians, was that this third drug in the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) works well with nucleoside analogs (nukes) alone, thus saving protease inhibitors for later.

Yet other AIDS docs and activists cite reasons to question this logic. First, in the only study finding efavirenz effective beyond a year, all efavirenz-takers also took a protease inhibitor. Second, no clinical data show that a “protease sparing” strategy is better in the long run. Finally, evidence suggests that HIV can quickly become resistant to every NNRTI (efavirenz, nevirapine [Vira-mune] and delavirdine [Rescriptor]) when used in a combo that doesn’t completely suppress viral load. Last fall, Project Inform and ACT UP/Golden Gate charged DuPont with promoting efavirenz as “protease sparing” primarily to justify its high, near-protease price.

I share these concerns. In 1996, I enrolled in the first efavirenz trial, which had no “protease sparing” arm. At the time, I was failing nukes and fast going downhill. A similarly situated friend and I researched options and concluded that our best chance for long-term viral suppression was a three-class combo including a protease inhibitor, a potent NNRTI and one or more nukes. I started Crixivan/ efavirenz/nukes, and he started Crixivan/delavirdine/nukes. We’ve both had excellent results, going in a few months from viral loads in the 100,000s to less than 20 copies and staying there for two-plus years. I worry that other PWAs may lose their chance to duplicate these results if they follow the advice of DuPont’s marketers.

“Physicians and patients should be very suspect of drug companies promoting ‘protease sparing’ combinations for marketing reasons, rather than because we have any data suggesting that this is the best strategy,” warns Marcus Conant, MD, a San Francisco–based expert in AIDS care.

DuPont argues, however, that its studies found efavirenz as effective as a protease inhibitor when used with nukes. One study indicates that at 36 weeks, efavirenz/AZT/3TC reduced viral load as much as or more than either efavirenz/Crixivan or Crixivan/AZT/ 3TC. This data won the drug FDA approval and convinced a federal panel to add an efavirenz/two nukes combo to the official treatment guidelines as a viable first-line anti-HIV therapy. “Recognition by an independent panel

of experts...clearly illustrates the benefit of Sustiva as a first-line therapy, and expands the current standard of care to include a convenient protease inhibitor sparing regimen as an option," declared Nicholas L. Teti, president of DuPont Pharma.

Robert Schooley, MD, professor of medicine at the University of Colorado and chair of the federal AIDS Clinical Trials Group (ACTG), grants that "protease sparing" efavirenz regimens may have some use in people experiencing protease inhibitor side effects, but he emphasizes, "There is no data showing that starting naïve [never-treated] patients on a protease sparing combination is better than using protease inhibitors with efavirenz in a three class/four drug combination."

And in the nuke-experienced, there is clear evidence *against* a "protease sparing" strategy. Preliminary 24-week results of ACTG 364, an ongoing study of 196 pretreated patients, show that a three-class combination trumped either of the two-class combos tested: 80 percent of patients on the efavirenz/nelfinavir (Viracept)/two nukes arm had undetectable viral loads (less than 500), compared to just 60 percent of patients only on efavirenz/nukes, and less than 50 percent of those on nelfinavir/nukes.

DuPont's efavirenz studies could have examined whether three-class therapy should be the new standard of care. If a new ACTG trial (384) looking at this duplicates the results of ACTG 364, many people might avoid drug failure by using a three-class NNRTI/ protease/nuke combo. (But beware: NNRTIs can alter blood levels—and thus effectiveness or side effects—of protease inhibitors; check with your doctor.) Indeed, efavirenz has moderate advantages over other NNRTIs—it requires only a single daily dose, remains in the blood longer and seems to cause a lower rate of *severe* side effects (although half of efavirenz-takers in studies reported neurological or psychiatric symptoms).

DuPont could have used these selling points to market efavirenz as a unique drug for *everyone* considering anti-HIV therapy. The first trial, designed before the present business team was in place, suggested this direction. Instead, efavirenz is being marketed to compete with protease inhibitors. In grabbing for the "protease sparing" brass ring, DuPont may have limited its own market, while shortchanging PWAs.

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