Kinks in the Pipeline

Recently, Three HIV drugs got stuck in clinical trials. Why? Here's a look at the twists and turns of drug approval.

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Long before drugs land on pharmacy shelves, they face a marathon of trials in test tubes, animals and humans. The final three tests in people (Phases I, II and III) find the safest and most effective dose while checking for short-term side effects and proof that "the next big thing" actually works.

This past fall, three HIV drugs stumbled near the finish line. Two are entry inhibitors (EIs), a new class promising HIV control even for those resistant to older meds; the third is a new nuke that could work for those resistant to nukes. The setbacks, advocates agree, are a sign of heightened scrutiny by the FDA after 2004's Vioxx debacle. But could raising the bar harm people in need of new treatment options? (See "Studying Safety: Two Views," page 14.)

Kink #1: An EI turns out to be toxic

Closest to the end of the pipeline—in late Phase II trials with enrollment for Phase III underway—was aplaviroc, an EI made by GlaxoSmithKline (GSK). Trials halted in October, when a liver problem appeared in three study participants out of 276—two new to treatment and one a med veteran. Since this little liver complication is frequently lethal, GSK wasted no time pulling its pill from the pipeline—leaving only HIV treatment advocates' praise to show for the estimated ten-year $400 million effort.

It's a sad irony that safety issues sunk this EI: The new class has HIV treatment activists cheering because studies have showed its ability to control HIV with few or no side effects. EIs bar HIV from entering immune cells at specific stages or at certain points on cell surfaces (Fuzeon, the one EI that's been approved, blocks HIV from fusing with immune cells, the last step before entry). In this way, EIs are different from the older classes of HIV meds—nukes, non-nukes and protease inhibitors—which muck up both HIV's and your cells' inner workings at the same time.

Tom Gegeny, cochair of the AIDS Treatment Activists Coalition's (ATAC's) drug-development committee, says aplaviroc's problem doesn't necessarily spell trouble for all EIs: "Studies with the other EIs have not seen similar issues." GSK is currently analyzing aplaviroc's surprise toxicity. And Judith Millard, of the GSK EI research team, says, "We are still making aplaviroc available to those therapy-experienced patients who were gaining benefit at the time we stopped the studies." Such people will be monitored closely for liver function until alternative regimens can be found to

replace their aplaviroc combos.

Kink#2: An EI proves too weak
Strength, not safety, hobbled vicriviroc, Schering-Plough's EI. People new to meds fared worse on Combivir/vicriviroc than Combivir/Sustiva combos, with viral loads rising after 20 weeks. Schering stopped that study, but vicriviroc is still being tested in drug-resistant folks as a lower-dose add-on to their combos, boosted by Norvir (ritonavir). "It's premature to say vicriviroc isn't fulfilling dreams," says activist Tim Horn. "We're still waiting for data from studies in the treatment-experienced, who need it most."

While it's also premature to say why vicriviroc stopped controlling HIV, some advocates say Schering's once-a-day dosing for those new to meds was a marketing move that backfired. No way, counters Bob Consalvo, Schering's global communications head. "We know the science supports a once-daily schedule, as vicriviroc's drug levels remain sufficient over 24 hours," he says. "Once we understand why it lost viral suppression, we intend to continue testing this EI in the treatment-naive."

Meanwhile, Pfizer's experimental EI, maraviroc, currently in tests as both a once- and a twice-daily in 1,000 people worldwide, has emerged as the front-runner.

Kink #3: A nuke has power problems
Almost half the 20-plus drugs in the pipeline are new versions of older, tried-and-true meds. One, Reverset (dexelvucitabine), promises to revitalize the oldest HIV class, nukes, offering treatment-experienced people a once-a-day to clobber resistance to the nuke class. But when Incyte, the little lab behind Reverset, announced a Phase III trial, the FDA said, "Not so fast!" With Phase II showing only a lackluster viral-load drop, officials demanded a redo.

Reverset has safety issues, too: It can't be used with Videx (ddI), due to a heightened risk of pancreatitis, or cornerstone nukes Epivir (3TC) or Emtriva (FTC). "Incyte is not back to square one," Horn says. But positive people in need of a new nuke will have to wait an additional 18 months before Reverset is ready for the FDA's OK.

For now, activists, researchers and clinicians agree that these kinks are par for the course—and no cause for pipeline panic. While the fall's triple chiller raised many questions, one thing is clear: With entry inhibitors—and the way-out integrase and maturation inhibitors (which block other points in HIV's reproductive cycle)—in the works, these experts say we will someday see a brave new HIV treatment world, where the current meds (and their baggage of side effects) are a last resort.

But one veteran HIV doctor deems it foolish to put such stock in pipeline promises. Joseph Sonnabend, MD, rejects the notion that most people with HIV will inevitably have their current combos fail and that new med models provide the only answer. "We should address becoming less dependent on a continuing flow of new drugs," the AIDS maverick says, "by improving patient care in ways that prolong the durability of HIV regimens." His Rx for docs? Stop wasting meds by

switching combos whenever patients have detectable, but stable and safe, viral loads. And take responsibility for poor adherence by offering patients tolerable regimens and trusting relationships for frank talk about missed doses.

Sonnabend's 4-1-1: Don't think kink—love the meds you're with.

Studying Safety: Two Views

Since the FDA had to recall the painkiller Vioxx after neglecting data on its major heart attack and stroke risk, the feds have upped scrutiny of safety issues in clinical trials. Is this good or bad for HIV?

The Cost of Caution

Heightened security could slow fast-track HIV drug approval—and research and development. "Fewer new drugs will be licensed, when they might be sorely needed," says John Moore, MD, a pioneering entry inhibitor researcher. "And the more drugs that are rejected late in the pipeline, the less likely that new-drug programs will be initiated," Moore says. "It's understandable that the FDA raises the [safety] bar, but is it right? That's for the HIV community to decide."

Roll On, Reforms

Long-term survivor and treatment activist Nelson Vergel believes that the community can have it all: more, better, safer trials and meds. Increased safety scrutiny was a much-needed reform, he says, as was instituting trials for people with much resistance and few med options. "Now the FDA should enforce intercompany collaboration in combination studies of drugs," Vergel says, so med vets can get more than one new drug at a time. He hopes Tibotec's Phase III trial of its experimental non-nuke/protease combo (see "In and Out of the Pipeline," right) "may help shift the FDA toward a paradigm with more MEAT," or Multi-Experimental Agent Trials—the hot issue on activist agendas.

In and Out of the Pipeline

For the first time, a clinical trial is testing two experimental HIV drugs together. A combo of the non-nuke TMC125 and the protease inhibitor (PI) TMC114 is being put under the glass in a Phase III study, says Tibotec Pharmaceuticals, which makes both. The tests involve 18 countries and 600 people with HIV resistant to non-nukes and PIs.

And in October, Abbott Laboratories got FDA approval of a new tablet to replace the gel-cap version of their PI, Kaletra (lopinavir with a ritonavir [Norvir] booster). Benefits: fewer pills per day, no food requirements and no need for refrigeration. Studies suggest it may also cause fewer gastrointestinal side effects. Abbott is working on a new version of Norvir by itself, too.