



Nanotechnology for Antiretroviral Drug Delivery

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As people with HIV live longer and require ongoing antiretroviral therapy for years or decades, the ease and tolerability of treatment assumes added importance.

Recent therapeutic advances that have contributed to increased convenience and improved adherence include ritonavir (Norvir) “boosting,” once-daily dosing, and fixed-dose coformulations that combine multiple drugs in a single pill.

Novel injectable formulations may further reduce the frequency of drug administration. Researchers have explored various high-tech strategies, taking advantage of the burgeoning field of nanotechnology. “Nano” approaches involve manipulation of structures on a nanometer (one billionth of a meter) scale—that is, at the level of individual atoms and molecules. One nanometer is approximately 100,000 times thinner than a sheet of paper.

Nanoformulations offer the potential for drugs with improved bioavailability that require smaller doses and last longer in the body. In addition, since they are not given orally, injectable drugs may avoid some types of side effects such as gastrointestinal symptoms and liver toxicity.

In the field of hepatitis C, for example, the development of pegylated interferon alfa (Pegasys and PegIntron), which is administered once weekly (as opposed to three times weekly with the older conventional interferon), has led to improvements in effectiveness, tolerability, and adherence.

Pegylation involves the attachment of polyethylene glycol molecules to a recombinant version of the natural immune cytokine interferon. Researchers are now studying interferon fused to the blood protein albumin, which may allow administration once every two to four weeks.

Nanotechnology was also used to produce a more bioavailable oral suspension of megestrol acetate (Megace ES), which in 2005 was approved as a treatment for lack of appetite and wasting in people with AIDS.

Antiretroviral Nanoparticles

Researchers have also explored injectable nanoformulations of several approved and investigational antiretroviral agents.

As described at the 2008 Conference on Retroviruses

and Opportunistic Infections, Chris Destache from Creighton University and colleagues produced nanoparticles containing ritonavir, lopinavir (combined with ritonavir in the Kaletra pill), and efavirenz (Sustiva), and tested the release of these drugs from the particles over 14 days in a laboratory study.

The nanoparticles were constructed by adding 10 mg of each drug to a biodegradable chemical compound in methylene chloride, a solvent widely used in the food industry (for example, in producing flavored extracts and decaffeinated coffee). The antiretroviral nanoparticles were then placed in a saline solution and centrifuged, and drug levels were analyzed.

The “loading efficiency,” or proportion of drug achieved in the nanoformulation, was 18.2% for ritonavir, 30.5% for lopinavir, and 46.4% for efavirenz. All three agents were released *in vitro* over 14 days. In cell cultures, the drug-carrying nanoparticles could be seen in microglia cells (from central nervous system tissue) under an electron microscope. In a previous study, the same researchers found that indinavir (Crixivan) nanoparticles taken up by the immune system’s macrophage cells crossed the blood-brain barrier and migrated to areas of inflammatory damage in the brains of mice with HIV-related encephalitis.

These findings are particularly exciting, given that many current antiretroviral drugs are unable to cross the blood-brain barrier and therefore cannot target HIV in the central nervous system.

Based on these findings, the researchers concluded that “nanoparticles could be a delivery system for multiple antiretroviral agents in the future.”

Good as Gold

In another study presented at the same conference and published in the May 13, 2008, issue of the *Journal of the American Chemical Society*, Mary Catherine Bowman from the University of North Carolina at Chapel Hill and colleagues explored the use of gold nanoparticles as a “scaffold” for an antiretroviral drug.

As proof of principle, they tested whether they could restore the anti-HIV activity of an inactivated form of the investigational CCR5 antagonist TAK-779 by attaching it to 2-nanometer gold particles. This class of drugs works by blocking one of the two coreceptors (CCR5 and CXCR4) that HIV uses to enter cells. Gold particles were used to replace an aluminum salt molecule in the original formulation of TAK-779 that proved toxic in the body.

When the altered agent was attached to the gold nanoparticles, it inhibited replication of CCR5-tropic HIV in cultured peripheral blood mononuclear cells as well as the original active form of TAK-779. Control gold nanoparticles that lacked the drug did not do so, however, indicating that the gold particles themselves were not responsible for the observed antiviral activity.

The researchers suggested that nanotechnology might be used to target intracellular protein interactions necessary for the HIV lifecycle with inhibitors that otherwise would not be able to reach intracellular spaces, protected areas such as the central nervous system, and types of cells that are inaccessible using existing small-molecule therapies.

Depot Rilpivirine

The antiretroviral nanoformulation furthest along in development is the experimental non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (formerly TMC278).

Oral rilpivirine—which has better bioavailability and a longer half-life than other drugs in its class—is in advanced clinical development (see “Open Clinical Trials,” page 51) and has demonstrated potent anti-HIV activity in treatment-naïve individuals. At 96 weeks, 73% of patients taking a combination HAART regimen containing once-daily oral rilpivirine at doses of 25, 75, or 150 mg maintained viral suppression below 50 copies/mL, compared with 71% of those taking efavirenz.

A depot nanoformulation of rilpivirine is further back in the pipeline, but has also demonstrated promising activity in early animal and human studies. “Depot” refers to formulations that are injected into the body and release their active agent slowly over time.

In a poster presentation at the XVII International AIDS Conference this summer in Mexico City, Rene Verloes and colleagues from Tibotec/Johnson & Johnson Research and Development in Belgium reported results from a study of a long-lasting injectable nanosuspension of rilpivirine consisting of tiny crystals of the drug with an average diameter of 200 nanometers in a liquid base, produced using the NanoCrystal technology developed by Elan Corporation.

The researchers analyzed the pharmacokinetics (how the body processes the drug) and tolerability of the rilpivirine nanoformulation in 51 HIV negative volunteers. Participants received a single subcutaneous (SC) abdominal or intramuscular (IM) gluteal (buttocks) injection of rilpivirine at doses of 200, 400, or 600 mg, or else placebo. Nine additional volunteers received a single 400-mg IM injection in the deltoid (shoulder) muscle.

As intended, rilpivirine was released slowly from the injection site, reaching a maximum plasma concentration after approximately three days. Blood levels then decreased biphasically, falling to about 20 ng/mL at week 8 and to less than 10 ng/mL by weeks 12 to 26. Maximum plasma concentrations (C_{max}) and areas under the time-concentration curve (AUC) were similar after 400 mg SC abdominal, IM deltoid, and IM gluteal injections (C_{max} of 70, 80, and 99 ng/mL, respectively). C_{max} refers to the highest level a drug reaches in the body after dosing, while AUC reflects the total concentration of a drug over time between doses.

Injection site reactions consisting of redness, bruising, pain, and in some cases induration (hard swelling) were more common with rilpivirine than with placebo injections, but no serious grade 3 or 4 adverse events were observed. IM injections were better tolerated than SC abdominal injections, and among IM injections, participants reported more pain at the deltoid compared with the gluteal site.

Based on these findings, the study investigators concluded that “TMC278 [rilpivirine] long-acting depot formulation administered in single doses provided prolonged exposure to TMC278 for several months and was well tolerated.”

Injectable Drugs: Benefits and Barriers

A majority of people tend to prefer oral medications over the discomfort and preparation hassles of injectable agents. For example, although it is highly effective and has proved to be

a life-saving salvage drug in heavily treatment-experienced patients with highly resistant virus, the sole approved HIV fusion inhibitor, enfuvirtide (T-20; Fuzeon), has not met market expectations, in large part because it must be injected twice daily and frequently causes injection site reactions.

Trimeris has tested a next-generation fusion inhibitor, TRI-1144, that can be administered less frequently—probably once daily—and causes fewer side effects. However, the company has announced that it does not plan to move forward with further development of the drug.

Nevertheless, the prospect of being able to administer an injectable drug less frequently—say, once per month instead of having to take pills every day—may overcome this barrier for many patients.

According to Verloes and colleagues, “injectable long-acting formulations may provide a new paradigm in anti-retroviral use and may facilitate long-term compliance.”

In particular, they suggested that nanosuspension formulations of agents such as rilpivirine might be used as once-monthly maintenance therapy after patients have achieved undetectable viral load with more intensive combination regimens.

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Selected Sources

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Recycle Your Medications!

The following U.S. organizations collect antiretroviral medications and/or medical supplies for donation abroad. Each organization follows its own set of rules; the majority request that all drugs be delivered in their original prescription bottles (all patient and doctor names will be removed before distribution).

AID for AIDS – New York, NY

212-337-8043

www.aid4aids.org

AIDS Medical Relief for Cuba – New York, NY

212-594-7741

babaluaye@aol.com

Being ALIVE – West Hollywood, CA

323-874-4322

www.beingalivela.org

International AIDS Empowerment – El Paso, TX

888-767-8474

www.internationalaids.org

United Trauma Relief (UTR) – Cambridge, MA

617-225-8365

630-369-2474

utr@mit.edu