The Critical Need for Alternative Antiretroviral Formulations, and Obstacles to Their Development

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CASE STUDY

A 53-year-old black man with advanced human immunodeficiency virus (HIV) disease and hepatitis B coinfection was admitted to the hospital with severe ondynophagia. An upper gastrointestinal endoscopy revealed fungal esophagitis with a bronchial fistula. The patient could take nothing by mouth, so a stent and gastrostomy tube were placed and intravenous antifungal and antibiotic therapy was initiated. However, provision of antiretroviral therapy was more challenging. The patient had failed multiple antiretroviral regimens with development of resistance-associated mutations, but a regimen including tenofovir, etravirine, and raltegravir had potential activity for treating both HIV and hepatitis B infections. The patient's CD4 count was 73 cells/mm^3. Improvement in immunosuppression was key to his lasting recovery, but none of the agents selected were available in a parenteral formulation or a liquid preparation. Data on the safety and efficacy of dissolving or crushing these tablets was limited or lacking, and the best course of treatment for this individual was unclear.

SCOPE OF THE PROBLEM

This case illustrates one of many scenarios in which alternative antiretroviral formulations, for example, parenteral antiretroviral therapy, are urgently needed for patients who are unable to take currently available tablet or capsule formulations. Patients on chronic HIV therapy may be unable to swallow tablets or capsules because of a variety of gastrointestinal conditions or serious illnesses during which they are unconscious or otherwise unable to eat. Some HIV-infected patients without such conditions have difficulty swallowing tablets or capsules, particularly if the tablets or capsules are large. Patients must often take nothing by mouth during perioperative periods. Cancer chemotherapy, including autologous bone marrow transplantation for lymphoma, may cause mucositis severe enough to prevent oral ingestion of tablets or capsules [1]. Pregnant women with HIV disease who experience severe nausea and vomiting or hyperemesis may also have great difficulty swallowing pills. Of approved antiretroviral drugs, only zidovudine is available in an intravenous formulation, labeled exclusively for use during labor and delivery [2]. This problem is magnified in the management of HIV-infected children, for whom the list of antiretroviral agents with approved pediatric formulations is limited (see Table 1) and for whom dosage recommendations are often based on inadequate data [3].

For most patients with acute opportunistic infections and other serious AIDS-defining illnesses, current guidelines support initiation of antiretroviral therapy as soon as possible [4–6]. However, many such patients may be unable to take available oral formulations initially. This includes those with severe pneumonia requiring mechanical ventilation, gastrointestinal infections preventing oral ingestion and/or absorption, or central nervous system disorders causing a decreased level of consciousness. Currently available antiretroviral therapy is only successful if taken consistently every day; whenever possible,

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Table 1. Antiretroviral Agents Available in Liquid, Powder, or Parenteral Formulations

Drug	Formulation and strength	Comments
Nucleoside reverse transcriptase inhibitors		
Abacavir	Oral solution; 20 mg/mL	
Didanosine	Powder for oral solution; 10 mg/mL when reconstituted	Reconstituted oral solution must be mixed with antacid (Maximum Strength Mylanta); store in refrigerator; should be administered on an empty stomach.
Emtricitabine	Oral solution; 10 mg/mL	
Lamivudine	Oral solution; 10 mg/mL	Each 15-mL dose (150 mg) contains 3 grams of sucrose.
Stavudine	Dry powder for reconstitution to oral solution; 1 mg/mL	
Zidovudine	Oral syrup; 10 mg/mL Injection for intravenous administration; 10 mg/mL	Avoid rapid intravenous infusion (<1 hour) or bolus administration; recommended final concentration for infusion is 4 mg/mL.
Nonnucleoside reverse transcriptase inhibitors		
Nevirapine	Oral suspension; 10 mg/mL	May be administered with or without food; antacids do not affect absorption.
Protease inhibitors		
Fosamprenavir	Oral suspension; 50 mg/mL	May be given with or without ritonavir. Administration with a high-fat meal reduced plasma amprenavir AUC by 28%. If given with ritonavir, authors would recommend administration with food to improve tolerability.
Lopinavir/ritonavir	Oral solution; LPV, 80 mg/mL with RTV, 20 mg/mL	Contains 42.4% alcohol by volume; oral solution should be administered with food to enhance absorption.
Nelfinavir	Powder for oral suspension; 50 mg/g or 200 mg per level teaspoonful	Powder contains 11.2 mg phenyalanine per gram. Oral powder may be mixed with water. Nelfinavir should be administered with fatty food to enhance absorption.
Ritonavir	Oral solution; 80 mg/mL	Contains 43% alcohol by volume. Absorption of the oral solution is decreased 7% with food. The oral solution had poor palatability; administration with food helps to improve acceptance and tolerability.
Tipranavir	Oral solution; 100 mg/mL	Contains 116 IU vitamin E/mL; the reference daily intake of vitamin E is 30 IU for adults and approximately 10 IU for children. Tipranavir must be administered with ritonavir; the oral solutions of tipranavir and ritonavir should be administered with food to enhance absorption.
Fusion inhibitors		
Enfuvirtide	Lyophilized powder for subcutaneous injection; 90 mg/mL when reconstituted	Enfuvirtide has been given intravenously in anecdotal reports but is not approved for this route of administration.
Drugs with anti-HIV activity but not approved for antiretroviral use		
Interferon-α	Intravenous or subcutaneous administration possible	1 log drop in HIV viral load in short-term studies.
Foscarnet	Intravenous infusion only	0.5 log drop in HIV viral load in short-term studies, but significant toxicities associated with short-term use.

NOTE. HIV, human immunodeficiency virus; LPV, lopinavir; RTV, ritonavir.

therapy should be initiated with oral formulations that can be taken indefinitely [5, 6]. Interruption of therapy for an intercurrent illness may be difficult to avoid, but can result in serious negative consequences including rebound viremia. Loss of control of viral replication may lead to the development of viral resistance, worsening immunosuppression, and risk of disease progression. Complicating the issue further, the different half-lives of antiretroviral agents can result in persistence of some drugs but not others when combination therapy is stopped. For example, most nonnucleoside reverse transcriptase inhibitors (NNRTIs) have long plasma half-lives while most nucleoside reverse transcriptase inhibitors (NRTIs) do not. Interruption of therapy with a combination of these agents may result in persistence of NNRTIs alone in the plasma, which has been shown to promote the development of drug resistance [7]. The availability of parenteral formulations would be helpful in preventing this complication.

CURRENTLY AVAILABLE AGENTS

While alternative formulations of all currently licensed antiretroviral agents in the United States (US) would be

Table 2. DHHS Regimens and Liquid/Parenteral Dosage Forms

Regimen	Formulation
Preferred regimens	
EFV/TDF/FTC	No liquid or parenteral formulation of combination or all individual agents. Extemporaneously compounded liquid solution prepared from crushed Atripla tablet did not meet FDA bioequivalence definition for EFV and TDF (see text).
ATV/r + TDF/FTC	No liquid or parenteral formulations of individual agents.
DRV/r + TDF/FTC	No liquid or parenteral formulations of individual agents.
RAL + TDF/FTC	No liquid or parenteral formulations of individual agents.
LPV/r + ZDV/3TC (for pregnant women)	LPV/r: oral solution; LPV 80 mg/mL with RTV 20 mg/mL ZDV: oral syrup; 10 mg/mL 3TC: oral solution; 10 mg/mL Comment: This regimen should be administered with food.
Alternative regimens	
EFV + (ABC or ZDV)/3TC	No liquid or parenteral formulations of all individual agents.
NVP + ZDV/3TC	NVP: oral suspension; 10 mg/mL ZDV: oral syrup; 10 mg/mL 3TC: oral solution; 10 mg/mL Comment: This regimen may be given with or without food.
ATV/r + (ABC or ZDV)/3TC	No liquid or parenteral formulations of all individual agents.
FPV/r + [(ABC or ZDV)/3TC] or TDF/FTC	FPV: oral suspension; 50 mg/mL RTV: oral solution; 80 mg/mL ABC: oral solution; 20 mg/mL ZDV: oral syrup; 10 mg/mL 3TC: oral solution; 10 mg/mL Comment: If FPV is combined with RTV, the authors recommend administration with food to improve tolerability.
LPV/r + [(ABC or ZDV)/3TC] or TDF/FTC	LPV/r: oral solution; LPV 80 mg/mL with RTV 20 mg/mL ABC: oral solution; 20 mg/mL ZDV: oral syrup; 10 mg/mL 3TC: oral solution; 10 mg/mL Comment: This regimen should be administered with food.

NOTE. 3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; DHHS, Department of Health and Human Services; DRV/r, darunavir/ritonavir; EFV, efavirenz; FDA, Food and Drug Administration; FPV, fosamprenavir; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine

optimal to permit uninterrupted treatment of patients unable to take approved oral formulations, current choices are severely limited. Only 2 approved agents can be given parenterally: zidovudine, which is available in an intravenous preparation for the prepartum phase of prophylaxis for the prevention of perinatal transmission of HIV [8], and enfuvirtide, an expensive subcutaneously administered peptide with substantial local injection site reactions that limit its clinical utility [6]. Several approved antiretroviral drugs are available in liquid or suspension form for oral administration, and several other capsule or tablet formulations can be suspended or dissolved by the patient or pharmacy (Table 1). However, data on the bioequivalence of such liquids are very limited. For patients unable to swallow pills, administration of such liquids (eg, by nasogastric tube or other enteral feeding tubes) may not be appropriate in many settings. Table 2 presents regimens currently recommended as preferred or alternative by the US Department of Health and Human Services (DHHS) guidelines. These tables illustrate that no current DHHS preferred regimen for antiretroviral-naive persons can be administered with the commercially available liquid, powder, or parenteral formulations alone, with the exception of lopinavir/ritonavir plus zidovudine and lamivudine for pregnant woman in labor. This lack of flexibility in drug formulations raises frequent questions as to whether the available solid formulations may be crushed to facilitate administration. Little pharmacokinetic data and clinical experience exist to answer these questions for most drugs.

Pharmacokinetic data illustrate the potential hazards of using such liquids. The pharmacokinetics of a pharmacist-compounded liquid formulation of efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) from the crushed Atripla tablet were compared with the commercial fixed-dose combination tablet in healthy volunteers [9]. The resulting data indicate the liquid formulation does not meet the US Food and Drug Administration standard bioequivalence definition for efavirenz (EFV) and tenofovir (TDF). However, based on our current pharmacodynamic knowledge for EFV and TDF, the risks of using this formulation, especially for a short period of time in a person who was stabilized on the

EFV/TDF/FTC tablet with an undetectable viral load, seem low.

The pharmacokinetics of lopinavir/ritonavir (LPV/r) tablets (200/50 mg), administered as the whole tablet or crushed tablet, were determined in a randomized crossover evaluation in 12 children (6–17 years) who had been receiving LPV/r for >2 weeks [10]. Plasma concentrations were significantly reduced when given as the crushed tablet, suggesting that the LPV/r tablet formulation should not be crushed for administration in either children or adults. The manufacturer similarly recommends that the LPV/r tablet and the RTV tablet formulations not be crushed. The pharmacokinetics of LPV/r 800/200 mg once daily, given as the tablet or liquid formulation, have been investigated in 17 HIV-infected adults on stable therapy with plasma HIV RNA <75 copies/mL. The median (interquartile range) of the area under the curve at 24 hours (AUC_{24}) and concentration at 24 hours (C_{24}) for the tablet were 236 (178–276) mcg*h/mL and 3.7 (1.2–7.4) mcg/mL, respectively, and were 150 (110–185) mcg*h/mL and 1.1 (0.3–3.6) mcg/mL, respectively, for the liquid formulation [11]. These data suggest that the bioavailability of the tablet and liquid formulations is not equivalent. Confirmation of this finding is needed. Pending additional data, clinicians should exercise caution in using the liquid formulation in adults and probably only use twice-daily dosing of this formulation.

We have found no information on opened capsule, crushed tablet, or other extemporaneous compounding for administration of atazanavir, darunavir, or raltegravir. Etravirine and nelfinavir tablets can be dispersed in a glass of water for patients who are unable to swallow these tablets. This information is provided by the manufacturers of these agents; however, no comparative pharmacokinetic data for the whole tablet versus water dispersion are provided in the product information. The World Health Organization (WHO) guidelines for antiretroviral therapy in infants and children include information on crushing tablets or opening capsules for several antiretroviral agents [12]. Pharmacokinetic data to support these recommendations are not provided or referenced, and it appears these recommendations have largely arisen from clinical experience in pediatrics. These WHO guidelines state that the following tablet dosage forms may be crushed and the contents mixed with a small amount of water and immediately ingested: abacavir (ABC), lamivudine (3TC), nevirapine and zidovudine (ZDV); fixed-dose tablets containing ABC/3TC, ZDV/3TC, or ABC/3TC/ZDV may similarly be crushed. These guidelines also state the capsule formulations of FTC, EFV, and stavudine may be opened and the contents mixed with a small amount of water and immediately ingested. Some pharmacists have reported mixing crushed tablets with Ora-Sweet, a sugar-free compounding syrup.

ALTERNATIVE FORMULATIONS IN DEVELOPMENT

Parentally administered antiretroviral agents currently in development include monoclonal antibodies targeting cell entry of the virus and nanoformulations of approved and investigational antiretroviral drugs. In addition, technologies are being investigated to allow administration of antiretroviral agents transdermally via iontophoresis and various chemical and solvent techniques that enhance permeation [13]. These latter technologies are in the very early stages of development.

Monoclonal Antibodies

Ibalizumab, formerly TNX-355, is a humanized murine monoclonal antibody that binds CD4 at the interface between domains 1 and 2 [14–16]. It does not inhibit HIV binding to CD4 but interferes with cell entry of HIV through a yet to be fully articulated postbinding conformational effect. With intravenous administration, it has demonstrated in vivo anti-HIV activity in single-dose and small multiple-dose phase II monotherapy studies, with maximal plasma HIV RNA reductions of approximately 1 $\log_{10}$ copies/mL [15, 16]. Antiretroviral activity correlated with coating of the CD4 receptors on cells. These coating studies and the pharmacokinetics of the drug support weekly or every-other-week dosing. Larger, longer-term studies are under way. In addition, a subcutaneous formulation has been produced and is soon to undergo testing in human trials.

PRO 140 is an anti-CCR5 monoclonal antibody that blocks HIV cell entry by binding to the CCR5 coreceptor [17]. PRO 140 binds to CCR5 at a site that is distinct from that of maraviroc and other small-molecule CCR5 inhibitors and is synergistic in vitro with these other agents [17]. When administered intravenously as a single dose, PRO 140 lowers plasma HIV RNA levels by approximately 2 $\log_{10}$ copies/mL [18]. A brief multidose study of a subcutaneous preparation showed durable activity of comparable potency [19]. The subcutaneous form of the drug is moving forward in development. As with ibalizumab, pharmacokinetic analyses suggest PRO 140 could be administered subcutaneously weekly or biweekly.

Nanoformulations

Rilpivirine, a new nonnucleoside reverse transcriptase inhibitor has been formulated into a nanosuspension for parenteral use [20]. When administered either intramuscularly or subcutaneously to dogs and rats, antivirally active concentrations are maintained in the blood for 2–6 months [21]. Single doses in HIV-negative human volunteers also resulted in an estimated plasma half-life of about 5 weeks. Nanosuspensions of other antiretroviral drugs have been created and have demonstrated prolonged activity in animal models when loaded onto

monocyte-derived macrophages [22]. In addition to nanosuspensions, drugs can be attached to nanoparticles with the ability to distribute widely and persist in vivo. For example, in vitro work has shown that antiretroviral peptides can be loaded onto gold and other nanoparticles [23]. Nanotechnology has the potential to produce formulations capable of delivering long-acting activity by the parenteral route and could play a role in other nonconventional routes of delivery, such as transdermal.

ALTERNATIVE ANTIRETROVRIAL FORMULATIONS: IS THERE A WAY FORWARD?

Availability of effective, convenient, and affordable combination antiretroviral therapy has broadened the number of treated patients worldwide, estimated to exceed 6.5 million by the end of 2011 [24]. The most common concurrent conditions that make daily oral drug administration difficult or impossible include mucositis from treatment of concurrent malignancy, gastrointestinal or other surgery requiring that the patient take nothing by mouth for a period of time, and neurological conditions with a risk of aspiration, as well as HIV-related diseases like severe esophageal candidiasis or aphthous stomatitis. In addition, the rigor of lifelong daily intake of oral medications is challenging for many individuals and can result in "treatment fatigue."

Some of these conditions can be managed through judicious short-term use of enteral administration, for example, crushed or dissolved tablets given by nasogastric or enteral feeding tube. However, this is not advisable for a number of antiretroviral drugs and could result in the need to change the patient's regimen. As such, there are circumstances when parenteral administration of antiretroviral drugs may be the only option. Today's approved parenteral antiretroviral formulary is limited to 2 drugs—zidovudine and enfuvirtide—and 2 other antiviral drugs shown to have anti-HIV activity in short-term proof-of-concept studies, interferon-α, and foscarnet [25, 26]. The latter 2 drugs are too toxic to be considered for use in most clinical settings.

Why aren't there more parenteral antiretroviral agents? The answer is mainly an economic one. Development and approval of alternative antiretroviral formulations would require a large investment of time and capital and, if used in a small number of patients per year, would be unlikely to generate adequate return on investment for a legacy pharmaceutical company. What are the alternatives for meeting this growing need?

First, it may be possible to develop a parenteral formulation with multiple uses. The best example is sustained-release nanoformulated rilpivirine, which could have applications in long-term treatment and prevention scenarios that do not necessarily involve patients unable to take oral medications. Such formulations may also enhance adherence to therapy, a critical element for treatment success [27], making them more attractive for use in other settings.

Second would be involvement of generic drug manufacturers in producing parenteral versions of off-patent medications. The barrier for approval of such products is likely to be high, since traditional bioequivalence studies would not satisfy regulatory safety and efficacy concerns. It is nearly impossible to develop a parenteral formulation with a pharmacokinetic profile equivalent to that of an orally administered drug, and the costs involved in pursuing such a project would likely be prohibitive for a generic manufacturer.

Finally, there are alternative approval strategies that could be applied for development of a formulation that will be used in a small number of very ill patients. Orphan drug status would lower some regulatory hurdles for such a formulation, but a hefty investment would still be required to bring such a product to market.

It is unlikely that parenteral and other alternative formulations can be made available for all approved antiretrovirals, and pushing for such an outcome would be unwise. This is especially true since most of these formulations would only be used for a short time while awaiting the patient's return to oral medications.

It is imperative to develop consensus about which antiretrovirals can and should be made available as high-priority alternative formulations. One strategy might be to target a single NNRTI, a single protease inhibitor, and an additional NRTI (probably 3TC or FTC) to be paired with ZDV. Other drug classes could be pursued if the pathway to approval were efficient.

This clinical problem does not lend itself to solution under a traditional for-profit economic model. The possibility of developing such formulations as part of a not-for-profit effort, as has been recently pursued for some antiparasitics and topical microbicides, should be considered [28]. The tools to solve this problem are readily available, and the need for alternative formulations of approved antiretrovirals will only increase.

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