

Review

When Patients Cannot Take Pills: Antiretroviral Drug Formulations for Managing Adult HIV Infection

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Providing antiretroviral therapy for the HIV-infected population is a complex and challenging task. Treatment is often complicated by the shifting demographic of HIV-infected patients that now includes a large aging population in which patients often have multiple comorbidities. HIV clinicians are challenged with choosing the optimal combination of antiretrovirals based on potency, tolerability, bioavailability, and ease of administration. The issue of bioavailability is of paramount importance for those patients who can't swallow tablets, are unable to take anything by mouth before a procedure, or who need medication through a nasogastric tube or percutaneous endoscopic gastrostomy tube. A thorough search of several drug databases, a literature search of MEDLINE through Ovid, and a review of full prescribing information for each currently available antiretroviral drug, was performed to obtain insight into the bioavailability of antiretrovirals. Implications for the findings are discussed as they relate to adherence, resistance, alternative methods of administration, and the sometimes conflicting information on bioavailability that exists for various antiretroviral agents.

Introduction

Thirty years have passed since the global recognition of HIV as the cause of AIDS. Since that time, scientists have developed a number of medications with activity against the virus—the antiretroviral drugs—that exert their effects by inhibiting viral replication, thereby allowing for immune system recovery. Since 1996, scientists and practitioners have recognized the benefits of multidrug therapy in the treatment of HIV infection. Strategies for implementing triple-drug therapy were created in response to the treatment challenge presented by the rapidly evolving nature of HIV; the virus acquires mutations that cause decreased efficacy of antiretroviral drugs (ie, resistance), thereby leading to viral rebound and immune system destruction.

Because of the increased understanding of the appropriate use and combinations of antiretroviral drugs,

HIV infection has evolved from a disease associated with high mortality to a chronic disease for patients who have full access to well-managed care and who adhere to treatment. The demographic of HIV-infected patients also has shifted throughout the years; what was once a viral infection primarily associated with young men has become an epidemic that includes a large aging population. HIV care practitioners must now consider that the patient groups infected with the virus are living longer and receiving their diagnosis at later stages of the disease than patients affected in earlier years of the epidemic. For example, in the United States, the population of HIV-infected patients over age 50 years increased by almost 20% from 2001 to 2005.¹

This enhanced longevity of HIV-infected patients is largely the result of the development of potent antiretroviral regimens, before which coinfections and complications of HIV disease often resulted in negative or

fatal outcomes for patients. In the current treatment era, mortality has substantially decreased, and HIV-seropositive patients have an improved quality of life.²

With advanced age from declining mortality, however, comes a new subset of health care issues for patients. Current treatment involves not only the use of complex antiretroviral regimens for life but may also require periodic hospital stays or outpatient visits to manage comorbidities or complications of treatment, particularly diabetes and cardiovascular or cerebrovascular effects. HIV infection as an inflammatory disease is recognized to contribute to increased risks of myocardial infarction or stroke, as has been demonstrated in the SMART (Strategies for Management of Antiretroviral Therapy) trial³ and the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study.⁴

With this increased understanding, so too has understanding of the importance of sustained viral suppression in reducing these long-term risks associated with HIV infection and its treatment. In 2008, treatment guidelines from the IAS–USA⁵ began to reflect the field's paradigm shift toward treating HIV infection earlier in the course of the disease to prevent long-term sequelae, a trend that continued in the 2009 US Department of Health and Human Services (DHHS) guidelines,⁶ the 2010 IAS–USA guidelines,⁷ and the 2011 DHHS update.⁸ Although the benefits of early treatment are many, so is the importance of increased understanding of the bioavailability and alternative dosage forms of these

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drugs for patients across the treatment spectrum.

Current Challenges in Bioavailability of Antiretrovirals

Currently, more than 20 antiretroviral drugs have been approved by the US Food and Drug Administration (FDA) for treatment of HIV infection. The majority of these drugs are available solely in tablet form for ease of administration; however, this limited formulation availability creates problems for patients unable to take medications orally. Examples of such situations include patients undergoing inpatient or outpatient procedures that do not allow them to take drugs by mouth, patients with swallowing disorders, and those with gastrointestinal diseases for which they receive nutrition through an alternative route.

A study of HIV-infected patients between 2000 and 2002 revealed that 20% utilized hospital inpatient services.⁹ The impact of hospital stays on antiretroviral drug adherence and long-term viral suppression can be damaging if treatment is not managed properly during the inpatient period. In a study by Heelon and colleagues, most prescribing errors involving antiretroviral drugs included those in the following categories: incomplete regimens, incorrect dosages, incorrect schedules, medication-disease interactions, incorrect formulations, incorrect antiretroviral drugs, duplication of therapy, and prescription of drugs with drug-drug interactions.¹⁰ With appropriate monitoring of patients by HIV specialists, these prescribing errors can be reduced.

Because complications and subsequent mortality can be lessened with viral suppression and immune restoration, it is vital for HIV-infected patients to continue receiving their antiretroviral regimens without interruption whenever possible. For patients unable to take oral medications, many issues need to be addressed when analyzing the bioavailability of the various antiretroviral drugs. For several medications, conflicting information exists. Alternative administration of many

antiretroviral drugs may profoundly change the drugs' bioavailabilities, pharmacokinetics, and subsequent efficacies. To ensure that health care practitioners are best able to make antiretroviral treatment decisions when facing alternative drug administration issues, a literature search was conducted and information guide created.

Search Methods and Results

Full prescribing information from respective manufacturers of each currently available oral antiretroviral drug formulation was reviewed for any data indicating that the medication could be crushed, opened, or added to water or food. In addition, a search was performed on each drug using information in databases from Lexi-Comp,¹¹ Clinical Pharmacology,¹² and Facts & Comparisons.¹³ For any drug without a specific formulation recommendation, a MEDLINE search through Ovid was completed using the drug trade name, the generic name, and the search terms "crush," "sprinkle," "extemporaneous preparation," and "bioavailability." The manufacturers were contacted for information on alternative administration of each product. For any drug that still lacked information, it was assumed that the medication could not be crushed or opened because of a lack of evidence. The search results are compiled in Table 1.

Discussion

The medical management of persons living with HIV infection or AIDS can be challenging for health care practitioners who are not experienced with antiretroviral drugs.¹⁴ Given the growing complexity and longevity of this patient population, HIV care has become highly specialized. HIV-infected patients are about 25% more likely to experience a medication error while in the hospital than are patients admitted without HIV infection.¹⁵ These drug errors are most likely the result of incorrect dosing, incorrect regimens, incorrect formulations, or incorrect scheduling.

Although current treatment of HIV infection consists of combinations of drugs and lower pill burdens than in the past, the regimens are increasingly complex, and their design requires careful and frequent monitoring to prevent drug interactions and avoid unwanted adverse events and antiretroviral drug resistance. Although outcomes have improved, successful outcomes may be precluded by the emergence of drug resistance.¹⁶ Adherence rates of less than 95% can lead to antiretroviral drug resistance and ultimately, treatment failure.¹⁷ Prevention of HIV resistance requires strict adherence to treatment, without which long-term suppression of HIV cannot be maintained because of rapid replication and mutation of the virus.¹⁸

The challenge of maintaining dosage schedules of antiretroviral drugs under different patient conditions (eg, patients using nasogastric or percutaneous endoscopic gastrostomy tubes or those for whom oral foods and liquids are being withheld) is one of substantial clinical importance. Although this challenge often presents itself in an inpatient care setting, the aging HIV-infected population, whether inpatient or outpatient, should not be overlooked with respect to this issue. Aging HIV-infected patients may have many of the same issues associated with dysphagia and aphagia as do inpatient HIV-infected persons. Bioavailability data should be considered for any HIV-infected patients with comorbid conditions that affect normal function.

The bioavailability of antiretroviral drugs is complicated by interactions with certain foods, different chemical forms of the drugs, and the physiologic state of the patient. The literature and database search revealed that 79.3% (23/29 listed in Table 1) of antiretroviral medications cannot be crushed, sprinkled, or administered through a percutaneous endoscopic gastrostomy or nasogastric tube. Some regimens may thus need to be taken in a different formulation or ultimately changed to ensure that the patient receives the full benefit of treatment.

Currently, there is not sufficient evi-

Table 1. Current Antiretroviral Drug Formulations for the Management of Adult HIV Infection

Drug	Can Be Crushed or Sprinkled	Solution or Suspension Available	Food Considerations	Special Administration
Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)				
Delavirdine ^{19,a}	100-mg tablets: Yes 200-mg tablets: No (Do not readily disperse in water)	No	May be taken without regard to meals	100-mg tablets may be dispersed in water. To prepare dispersion, add 4 100-mg tablets to ≥ 3 ounces of water, let stand for a few minutes, then stir until a uniform dispersion occurs. Administer immediately, rinse glass, and have patient swallow each rinse completely to ensure entire dose is consumed.
Efavirenz ^{12,20}	Yes	No	Take on an empty stomach	Has a peppery taste; grape jelly has been used to disguise this.
Etravirine ²¹	Yes	No	Take after meals	Tablets may be dispersed in water; stir well and have patient drink mixture immediately. Rinse glass with water several times, and have patient swallow each rinse completely to ensure entire dose is consumed.
Nevirapine ²²	No information	50 mg/5 mL suspension	May be taken without regard to meals	
Rilpivirine ²³	No (25-mg tablets do not readily disperse in water)	No	Should be taken with food	Needs to be taken with a meal (> 533 calories). Protein drinks should not replace a meal when taking this medication.
Nucleoside Analogue Reverse Transcriptase Inhibitors (nRTIs)				
Abacavir ²⁴	No information	20 mg/mL solution (strawberry-banana flavored)	May be taken without regard to meals	
Didanosine ^{11-13,25}	No	Pediatric powder for solution, in 2g/bottle and 4g/bottle	Take on an empty stomach (30 minutes before or 2 hours after food)	
Emtricitabine ²⁶	No information	10 mg/mL solution (cotton candy flavored)	May be taken without regard to meals	
Lamivudine ²⁷	No information	10 mg/mL solution (strawberry-banana flavored)	May be taken without regard to meals	
Stavudine ^{13,28}	Yes	1 mg/mL powder for solution (fruit flavored)	May be taken without regard to meals	Capsules can be opened carefully and mixed into 30 mL of yogurt or applesauce.
Tenofovir ⁴⁷	No information	No	May be taken without regard to meals	No pharmacokinetics studies performed on crushed versus whole tablet. Tablet lacks enteric coating or sustained-release mechanism and will disintegrate in water, grape juice, or orange juice. Drug is moisture sensitive and must be consumed immediately after mixing. Rinse container and consume rinse.
Zidovudine ^{13,29}	No (Even unopened, the capsule can cause esophageal irritation and ulceration)	50 mg/5 mL syrup (strawberry flavored) and 10 mg/mL injection solution	May be taken without regard to meals	

^aDelavirdine is rarely prescribed and is not recommended for initial therapy for HIV infection

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Table 1. Current Antiretroviral Drug Formulations for the Management of Adult HIV Infection (continued)

Drug	Can Be Crushed or Sprinkled	Solution or Suspension Available	Food Considerations	Special Administration
Protease Inhibitors				
Atazanavir ^{12,30}	No	No	Absorption increases with food	
Darunavir ^{13,31}	No	No	Absorption increases with food	
Fosamprenavir ³²	No information	50 mg/mL solution (grape, bubblegum, or peppermint flavored)	Adult solution must be taken without food Pediatric solution must be taken with food	
Indinavir ³³	No information	No	Should be taken on an empty stomach, but with 48 ounces of water daily	
Lopinavir/ritonavir ^{11-13,34}	No	80 mg/mL or 20 mg/mL solutions	Solution should be taken with food	
Nelfinavir ³⁵	Yes	50 mg/g oral powder for suspension	Should be taken with food	May place whole or crushed tablets in small amount of water to disperse before ingestion, or mix crushed tablets in small amount of food. Once mixed, entire contents must be consumed within 6 hours to obtain the full dose. Entire contents should be consumed immediately after mixing. The drinking glass should be rinsed and each rinse swallowed completely to ensure entire dose is consumed. Acidic foods or juices (eg, orange juice, apple juice, or applesauce) are not recommended for mixing because the combination may have a bitter taste.
Ritonavir ^{12,36,37}	No	80 mg/mL solution (peppermint or caramel flavored)	Should be taken with food	
Saquinavir ³⁸	Yes	No	Take within 2 hours of a meal	Opening capsules is permissible for patients unable to swallow them. No clinical studies evaluate the safety or efficacy when administered as extemporaneous preparation. Capsules were the most palatable when contents were mixed with simple syrup or strawberry-flavored jelly or jam. Bioavailability as an extemporaneous preparation in simple syrup was similar to that of unopened capsules. When administered as extemporaneous preparation in jelly, jam, or baby formula, there was a 44%-60% increase in area under the curve and a 42%-48% increase in maximum plasma concentration over the unopened capsules.
Tipranavir ^{13,39}	No	100 mg/mL solution (butternut or butter-toffee flavored)	May be taken without regard to meals	

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Table 1. Current Antiretroviral Drug Formulations for the Management of Adult HIV Infection (continued)

Drug	Can Be Crushed or Sprinkled	Solution or Suspension Available	Food Considerations	Special Administration
Integrase Strand-Transfer Inhibitor				
Raltegravir ^{12,40}	No	No	May be taken without regard to meals	
NNRTI-nRTI Combinations				
Efavirenz/emtricitabine/tenofovir ⁴¹	No (Efavirenz is water insoluble; manufacturer recommends not crushing for this reason)	No	Should be taken on an empty stomach	
Rilpivirine/emtricitabine/tenofovir ⁴²	No information	No	Should be taken with food	Need to be taken with a meal (>533 calories). Protein drinks should not replace a meal when taking this medication.
nRTI Combinations				
Abacavir/lamivudine ⁴³	No information (Individual drugs available in solution)	No	May be taken without regard to meals	
Abacavir/lamivudine/zidovudine ⁴⁴	No information (Individual drugs available in solution)	No	May be taken without regard to meals	
Emtricitabine/tenofovir ⁴⁵	No information	No	May be taken without regard to meals	No pharmacokinetics studies performed on crushed versus whole tablet. Tablet lacks enteric coating or sustained-release mechanism and will disintegrate in water, grape juice, or orange juice. Drug is moisture sensitive and must be consumed immediately after mixing. Rinse container and consume rinse.
Lamivudine/zidovudine ⁴⁶	No information (Individual drugs available in solution)	No	May be taken without regard to meals	No pharmacokinetics studies performed on crushed versus whole tablet. Tablet lacks enteric coating or sustained-release mechanism and will disintegrate in water, grape juice, or orange juice. Drug is moisture sensitive and must be consumed immediately after mixing. Rinse container and consume rinse.
Fusion Inhibitor^b				
Maraviroc ⁴⁸	No information	No	May be taken without regard to meals	

^bEnfuvirtide was not included in this table because it is administered subcutaneously and thus has virtually no bioavailability issues.⁴⁹

dence to support crushing or sprinkling of many of the available antiretroviral drugs. Further research needs to be conducted to determine more specific bioavailability data. These studies also need to identify cohorts of older persons to provide information on antiretroviral drug bioavailability in the aging population.

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