Management of oral antiretroviral administration in patients with swallowing disorders or with an enteral feeding tube

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Bonnes pratiques d'administration des formes solides d'antirétroviraux chez les patients présentant des troubles de déglutition ou ayant une sonde entérale

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Keywords: antiretroviral agents, deglutition, drug administration routes, drug monitoring, enteral nutrition

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Keywords: antiretroviral agents; drug administration routes; drug monitoring; enteral nutrition

Mots clés : antirétroviraux, nutrition entérale, surveillance pharmacologique, voies d'administration des médicaments

Abstract

HIV infection has evolved into a chronic disease with comorbidities since the combination antiretroviral therapy era. Complications still occur and patients may need to be admitted to an intensive care unit. Acute respiratory failure is the first cause of these admissions, questioning the administration of solid oral dosage formulations. This issue is also observed in geriatric units where the prevalence of dysphagia is high and underestimated. The problem of antiretroviral administration is critical: altered solid oral dosage formulations and/or administration via enteral feeding tubes are sometimes the only option. The aim is to help manage antiretroviral treatment in unconscious or intubated patients and those with swallowing disorders who are hospitalized in intensive care units or geriatric units. This review provides information on the main antiretroviral regimens and on practical and legal aspects of manipulating solid oral dosage formulations and administration via enteral feeding tubes. Alternatives to the solid formulation are available for most of the 27 oral antiretrovirals available, or manufacturers provide recommendations for patients who are unable to swallow. Manipulation of solid oral dosage formulations such as crushing tablets or opening capsules and administration via feeding tubes are frequently reported but should be the last option for safety and liability issues. Before any off-label administration of a drug, physicians should consider alternatives to the solid oral dosage formulation and check whether the drug can be altered. Therapeutic monitoring is important in this particular setting as the pharmacokinetic profile of drugs is difficult to predict.

Introduction

Since the combination antiretroviral therapy (cART) era, HIV infection has evolved into a chronic disease with comorbidities. The life expectancy of HIV-infected patients has increased, with reduced life-threatening complications related to the HIV infection. However complications still occur, and patients might need admission to an intensive care unit (ICU). Most ICU patients have trouble using oral medication or ingesting solid oral dosage formulations (SODFs). Indeed, more than 30% of HIV-infected ICU inpatients are now admitted for acute respiratory failure [1,2], representing the leading cause of admission to an ICU. Most ICU inpatients also have high plasma HIV-RNA level and low CD4 cell count [3,4]. Therefore, initiating antiretroviral (ARV) therapy at admission with the risk of immune reconstitution inflammatory syndrome could be difficult. In parallel, delayed management of the HIV infection in the ICU might increase the risk of life-threatening complications, in particular infections, with subsequent mortality and morbidity.

With the increase in aging HIV-infected patients, a higher number of them will be managed in geriatric units where the prevalence of dysphagia is high and underestimated. In France 30% to 40% of elderly people living in nursing homes have swallowing disorders [5]. Some disorders are temporary and may be reversible (oropharyngeal mycosis) while others often relating to neurodegenerative diseases, dementia, or muscular diseases are irreversible. Moreover, elderly patients often take many medications, which may increase the risk of dysphagia. Anticholinergic drugs such as tricyclic antidepressants, neuroleptics, antiemetics, and antidiarrheal drugs or Parkinson's treatment may reduce saliva production and induce dysphagia [6].

Besides ICU admission and geriatric patients, there is a third main reason for swallowing difficulties and the above physiological barriers. As ARV combination may be dispensed as large pills, patients may have trouble taking them which may impact compliance with treatment [7].

Hence, the problem of ARV therapy and of its administration can be critical. In these various cases, altering the SODF of ARV drugs and/or administration via an enteral feeding tube can sometimes be the only option because most ARV drugs are only available in SODF, such as tablets and/or capsules. However, the altered formulation of the drug raises several questions about its bioavailability, and plasma concentration may lead to modified effectiveness and/or adverse effects. The plasma drug concentration of a number of

drugs is affected by food and might be subject to drug-drug interactions. Misunderstanding or not taking into account all these features might put the effectiveness and safety of the HIV treatment at risk.

The objectives of the present review were to collect and provide information on the main ARV regimens, on practical and legal aspects of manipulating the SODF ARVs, and on their administration via enteral feeding tubes. This information may help clinicians to manage ARV therapy in unconscious patients or in patients with swallowing disorders in ICUs and geriatric units.

Literature review

We consulted the European AIDS Clinical Society guidelines [8], the French National Guidelines [9], and the website AIDSinfo.gov [10] to collect recommendations for ARV therapy in HIV-infected adults and in specific populations such as elderly patients or those admitted to ICUs. We also consulted the US Food and Drug Administration (FDA) [11] and the European Medicines Agency (EMA) [12] product labels. Information was gathered on the ARV drug formulation availability (nature, form, dosage, size, and shape), effects of food on oral absorption, and manipulation of the SODF (crushing tablets or opening capsules) of the drug formulation (solution or dispersion). The availability of a generic formulation was also collected. We also searched guidelines on the manipulation of SODF and administration of drugs through enteral feeding tubes drafted by scientific societies such as the European Society for Clinical Nutrition and Metabolism (ESPEN) [13], American Society for Parenteral and Enteral Nutrition (ASPEN) [14], British Association for Parenteral and Enteral Nutrition (BAPEN) [15], and French National Authority for Health (HAS) [16]. MEDLINE via PubMed was used to search regulatory aspects using the search terms “law”, “legal”, “manipulation”, “crushing”, and “splitting”. Additionally, MEDLINE via PubMed and Clinicaltrials.gov were used for any drugs without label recommendations. The terms “crush”, “chew”, “sprinkle”, “antiretroviral”, “tube”, “enteral”, “swallow”, “deglutition”, “solution”, and the generic name of the various ARV agents were included into the search. International conference abstracts were also reviewed using the same search terms.

Main ARV regimens

More than 20 SODF ARVs were commercialized in 2018 in North America and Europe, but among them 12 are currently used in northern countries, namely abacavir, emtricitabine, lamivudine, tenofovir, rilpivirine, efavirenz, atazanavir, darunavir, ritonavir dolutegravir, elvitegravir/cobicistat, and raltegravir. Guidelines [8,9,17] recommend a first-line regimen combining two nucleoside reverse transcriptase inhibitors (NRTIs) with a third agent such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI).

The choice of regimen is based on several factors such as the genetic barrier of drugs to resistance, effectiveness, tolerability profile, convenience, and pill burden. Patient's comorbidities, concomitant medications and their potential risk for drug interactions should also be considered. For instance, the INSTI-containing regimen is the first-line therapy because of its high potency and low risk of drug interactions. Despite their high genetic barrier to resistance, only two of the PIs (darunavir/ritonavir or cobicistat and atazanavir +/- ritonavir or cobicistat) are recommended because of the pill burden and the adverse effects of the other PIs [18].

ARV medications

The SODF size and shape, generic availability, oral powder or solution availability, alteration of SODF, and food considerations of the commonly used ARV drugs are summarized in Table I [12,19–26], Table II [12,27,28], and Table III [8,12,29–33].

Oral solutions

When patients have swallowing disorders, ARV oral solutions can be the best alternative. Among the 12 oral ARV drugs currently used, seven (i.e., NRTIs and PIs) are available as oral solution or powder, including three compounds (abacavir, lamivudine, and tenofovir disoproxil fumarate) for which crushing or sprinkle procedures are available in the product label. Among the four remaining compounds, only one (efavirenz) can be altered based on the label information, and no recommendations are available from the manufacturer or the FDA or EMA product label for rilpivirine, dolutegravir, and elvitegravir/cobicistat,

although their small tablet size (<10 mm of diameter) makes their deglutition easier. Three drugs (zidovudine, enfuvirtide, and foscarnet) are available as injectable solution, but their indications and use are restricted: zidovudine is only used during labor to prevent perinatal transmission; enfuvirtide and foscarnet are mostly used as salvage cART [34].

Alteration of SODF: legal aspects

Altering SODF remains a significant source of medication errors and harmful outcomes, and might have legal implications [35,36]. According to the French public health code, nurses can crush or split tablets only if there is a medical prescription detailing how to do it or if the drug label mentions it [37]. The administration of the altered drug is in practice not registered and not always checked with the physician [38–40]. Besides, as crushing or splitting tablets refers to an off-label use of the drug, the manufacturer is no longer liable if any harm is caused to the patient. Liability is therefore shared between the prescriber and the pharmacist. In addition when possible, patient consent is always required for the off-label use [41]. When dispensing the ARV drugs, the pharmacist should analyze the prescription, prepare the dose to administer, and provide information and advice for the proper use of the medicine [42]. The pharmacist can also refuse to dispense the treatment if the prescription does not seem safe for the patient [43].

Alteration of SODF: practical aspects

Crushing tablets or opening capsules is not ordinary considering the potential associated risks. The HAS and BAPEN published guidelines on the manipulation of the SODF [5,44]. For patients with swallowing disorders, caregivers should inform the prescriber to consider altering the SODF. To reduce the risks associated with SODF manipulation, they can contact the pharmacy to obtain the drug in a more suitable form such as liquid solution, powders or granules for suspension, or dispersible tablet, if available. Ideally, the pharmacist can prepare a properly labeled, patient-specific oral syringe or unit-dose liquid package. The practitioner might also change the ARV for another one of the same class available in a suitable form or with a different route of administration after checking that the switch is acceptable in terms of viral genotype,

pharmacokinetics, and tolerability. Only three injectable forms of ARV are available, but new injectable forms will be available with the recent development of long-acting nano-formulations. If a suitable form is not available, practitioners should check whether crushing the tablet or opening the capsule of each of the combined ARV is safe on the basis of updated online databases of crushable ARVs [8,45,46]. Specific drug formulations should not be crushed. For instance, crushing enteric coated tablets (e.g., didanosine) eliminates the coating that protects the drug against gastric acid, and crushing modified/slow-release tablets (e.g., nevirapine) will lead to the release of a massive dose of the drug, which might have toxic effects and reduce drug effectiveness [47]. These forms are only available for didanosine and nevirapine, but they are both available as oral solutions.

Depending on the compound's physicochemical properties (mainly liposolubility), various procedures for crushing tablets or sprinkling capsules and solubilization or dispersion are reported. For instance, indinavir, atazanavir, and rilpivirine solubility are decreased in poorly acidic solvent (e.g., in combination with proton pump inhibitors), whereas raltegravir should be solubilized in neutral pH.

To avoid drug incompatibility and cross contamination, drugs should be crushed one by one and the pill crusher device should ideally be cleaned after each use. Observational studies reported that nursing staff often skip these steps because they are time-consuming [39,40]. Stability of the various compounds after altering the solid formulation may vary. Administration should be immediate to prevent any variation in stability.

Administration by enteral feeding tube

Administration of oral drugs by enteral feeding tube is a frequent problem but guidelines have been published on drug administration by enteral feeding tube [48–50]. Considering the various types of enteral feeding tubes, several parameters should be considered when administering drugs.

The site of drug delivery is of utmost importance, especially when the tube is placed after the jejunum. Drug absorption might be reduced due to the abnormal drug absorption site because the pH difference between the stomach and the intestines affects the solubility of pH-dependent drugs. Tubes are

mainly made out of polyurethane and silicone rubber as they are well-tolerated and flexible. The tube diameter is measured in French units (1 French unit = 1/3 mm). The diameter of most tubes ranges from 8 to 16 French units. Small-bore tubes (5-12 French units) are more comfortable for patients although associated with a higher risk of obstruction. A diameter >14 French units might induce a wide opening of the cardia but is less prone to clogging than small-bore tubes. When drugs are administered as solutions, the tube size should be about 10 French units. If tablets or capsules are altered, the tube size should not be less than 12 French units. Enteral feeding tubes usually require regular, effective flushing with an appropriate solvent to prevent tube blockage.

Liquid formulations are the main alternative when patients cannot properly swallow tablets or capsules. Of note, the bioavailability of a drug such as emtricitabine can vary between the solid and liquid oral formulations. In addition, the commercial availability of oral solution or oral powder may differ in the various northern countries. For instance, the EMA granted marketing authorization for atazanavir oral powder, but this formulation is not available in all countries.

Liquid formulations may not always be the best administration option and several factors should be considered. For instance, the unpalatable taste of pediatric oral solution of PIs may reduce treatment compliance. Extreme hyperosmolar solution or the presence of excipients such as sweeteners or stabilizers may also increase the risk of gastrointestinal symptoms such as cramping and diarrhea. Most liquid ARV drugs are formulated for pediatric use, implying a larger volume for adults and therefore exposure to overdose of excipients. It is recommended not to exceed 10 to 20 g of sorbitol per day and 600 mOsm/L osmolality [48,51,52]. As viscous liquids might obstruct the feeding tube, dilution with an equal amount of sterile water is required. Irrespective of the container volume, liquid formulations should be well shaken just before administration. It is recommended to use an oral syringe to prevent parenteral administration of a non-adapted formulation [48,53].

In the absence of liquid oral or injectable drug formulations, SODFs are widely administered after appropriate crushing and suspension for patients receiving enteral nutrition. Liquid or semi-liquid formulations can be used. Tablets or capsules can be crushed or sprinkled in water (favorable because it is

an inert solvent), sugar syrup, fruit juice (acidic solvent), applesauce to maximize solubilization and absorption in the stomach or the intestines. The use of sorbitol syrup is also possible for patients with type 1 diabetes or glucose intolerance. However, some highly liposoluble ARVs such as efavirenz, rilpivirine, elvitegravir, and cobicistat are not soluble in water.

To prevent incompatibilities (resulting in tube clogging, adverse reactions, modification of absorption, etc.), formulations or compounds should not be mixed and separate intake such as bolus is preferred. Enteral feeding tubes should be flushed with at least 30 mL of water or with the same formulation before and after each individual drug administration if possible, to recover the full dose and to avoid drug interaction or tube clogging. If a container is used, an additional quantity (30 mL) should be used to recover all potential residues and the rinse must be administered immediately. Volumes should be adapted for fluid-restricted patients because it might worsen the patient's underlying disease. Air flushes can be replaced by water flushes. When drugs have to be taken in fasting conditions, tube feeding should be discontinued 30 minutes before administration and resumed at least one hour after administration.

Conclusion

Half of the 27 available oral ARV drugs are currently commonly used, and alternatives are available for patients unable to swallow, or manufacturers' recommendations on crushing drugs are available for most of them. Despite the increase in single-tablet regimen availability, separate prescription might be an option when alteration is not possible. Use of the injectable form is also possible for limited specific cases such as suspicion of brain reservoirs (foscarnet and zidovudine) or a time-limited intensification of treatment (enfuvirtide).

It is also recommended to maintain the antiretroviral therapy as discontinuation may result in viral rebound, immune decompensation, clinical progression but also in the emergence of resistance mutations [54–57]. Although pharmacokinetic data on SODF manipulation is available for some ARV drugs, little information is available on the pharmacokinetics of crushed tablets or sprinkle capsules versus the standard oral route [29,58–60]. Thus, therapeutic drug monitoring should be considered to monitor the absorption of

the various compounds (1-3 hours after the last drug intake), the toxicity profile, potential drug interaction, or interaction with the tube material [61], and the ARV treatment effectiveness (before the next intake).

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Table I. Antiretrovirals that can be crushed or dispersed

Tableau I. Antirétroviraux qui peuvent être écrasés ou dissous

Active substance/ Specialty name	Pharmaceutical formulation	Food consideration (label information)	Doses per day (mg)	Size (mm)	Shape	Scoring/ splitting tablets?	Oral solution or powder	Comments	References
Nucleoside reverse transcriptase inhibitors (NRTIs)									
abacavir **Ziagen®**	Film-coated tablet	No food restriction	300 BID 600 QD	18	Oval	Bi-scored	Solution 20 mg/mL	Product label: tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be taken immediately PK/PD data not available	[12]
lamivudine **Epivir®** **Zeffix®**	Film-coated tablet	No food restriction	150 BID 300 QD 100 QD	17	Diamond-shaped	150 mg: scored	Solution 10 mg/mL	Product label: tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be taken immediately PK/PD data not available	[12]
tenofovir disoproxil fumarate	Film-coated tablet	With food	300 QD	17	Almond-shaped	No	Powder 40 mg/g	Product label: tablets may be crushed and disintegrated in at least 100 ml of water, orange juice, or grape juice	[12]

Viread®				shape d			PK/PD data not available	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)								
efavirenz **Sustiva® or** **Stocrin®**	Film-coated tablet Capsule	Fasting conditions	600 QD	19 22	Oval Capsu le- shape d	No	Oral nano- formulation in trial	Tablets cannot be crushed Carefully open the capsule and mix its content with 5-10 mL of food, stir to disperse, and administer the mixture no more than 30 minutes after mixing. No additional food should be consumed for up to 2 hours after administration	[12, 19]
etravirine **Intelence®**	Tablet	With food	200 BID 400 QD		Oval	-	No	Tablets may be dispersed in at least 5 mL of water	[12]

Active substance/ Speciality name	Pharmaceutical formulation	Food consideration (label information)	Doses per day (mg)	Size (mm)	Shape	Scoring/ splitting tablets?	Oral solution or powder	Comments	References
Protease inhibitors (PIs)									
atazanavir **Reyataz®**	Hard capsule	With food	300 QD 400 QD	23	-	No	Powder 50 mg/1.5 mg	Capsules can be opened and mixed with applesauce (5 mL). Administration with food should be immediate.	[12, 20]
darunavir **Prezista®**	Film-coated tablets	With food	800 QD 600 BID	21	Oval	No	Solution 100 mg/mL	Three case reports showed that tablets may be crushed	[12, 21,22]
Integrase strand transfer inhibitors (INSTIs)									
dolutegravir **Tivicay®**	Film-coated tablet	No food restriction	50 QD 50 BID	9	Round	No	Powder 50 mg/10 g in trial	Tablets may be crushed and added to small amount of semi-solid food or liquid to be taken immediately in its entirety	[12, 23]

raltegravir **Isentress®**	Film-coated tablet Chewable tablet	No food restriction	400 BID 800 QD 1,200 QD	16	Oval	Chewable scored	Powder 100 mg/pack Solution 20 mg/mL	Tablets can be crushed and mixed with 300 mL of water	[12, 24]
Injectables									
enfuvirtide **Fuzeon®**	Injectable	SC route	90 BID	-	-	-	Powder 90 mg/mL	No bioavailability by the oral route	[12]
foscarnet **Foscavir®**	Injectable	IV route	-	-	-	-	Solution 6 g/250 mL	Induction regimen: 85 mg/kg BID used concomitantly with 1,500 mL of normal saline, calcium and phosphorus supplementation with thymidine analog (and avoiding TDF for renal safety)	[25]
zidovudine **Retrovir®**	Injectable Hard capsule Tablet	No food restriction	300 BID	16 10	- Oval	No	Solution 10 mg/mL	No data available	[26]

SC, subcutaneous; IV, intravenous; QD, once daily; BID, twice daily; PK/PD: pharmacokinetics/pharmacodynamics; TDF: tenofovir disoproxil fumarate

Table II. Antiretrovirals that cannot be crushed and alternatives to solid forms

Tableau II. Antirétroviraux qui ne peuvent être écrasés et alternatives aux formes solides

Active substance/ Specialty name	Pharmaceutical formulation	Food consideration (label information)	Doses per day (mg)	Size (mm)	Shape	Scoring/ splitting tablets?	Oral solution or powder	Alternative	I
Nucleoside reverse transcriptase inhibitors (NRTIs)									
emtricitabine **Emtriva®**	Hard capsule	No food restriction	200 QD	19	-	-	Solution 10 mg/mL	Switch to oral solution (the two forms are not bioequivalent)	[
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)									
nevirapine **Viramune®**	Tablet Prolonged-release tablet	No food restriction	200 BID 400 QD	- 19	Oval	Scored, not intended to be divided No	Solution 10 mg/mL	Switch to oral solution	[

rilpivirine **Edurant®**	Film-coated tablet	No food restriction	25 QD	6.4	Circular	No	Oral solution and injectable long-acting formulation in trial	Tablet size is small, oral solution is not available, one case report recommends increasing the daily dose to 50 mg	[2
Protease inhibitors (PIs)									
ritonavir **Norvir®**	Film-coated tablet	With food	100 QD 100 BID	22	Oval	No	Powder 100 mg/pack Solution 80 mg/mL	Switch to oral solution	[
cobicistat **Tybost®**	Film-coated tablet	With food	150 QD	10.3	Round	No	Not available	Switch to ritonavir oral solution	[
Integrase strand transfer inhibitor (INSTIs)									
elvitegravir **Vitekta®**	Film-coated tablet	No food restriction	150 QD	8.9	Pentagon-	-	Solution 5 mg/mL	Switch to another INSTI	[2

		shape d	in trial

QD, once daily; BID, twice daily

Table III. Characteristics of ARV combinations and alternatives to solid forms

Tableau III. Caractéristiques et alternatives aux formes solides des associations antirétrovirales

Active substances	Specialty name	Food consideration (label information)	Doses per day (mg)	Size (mm)	Shape	Components available separately?	Alteration of SODF	References
2-drug combination								
ABC/3TC	**Kivexa®**	With food	600/300 QD	-	Capsule-shaped	Yes	Use solution of individual compounds	[8,12]
FTC/TDF	**Truvada®**	With food	200/300 QD	19	Capsule-shaped	Yes	Dissolve in 10 mL of water, orange or grape juice	[8,12]
FTC/TAF	**Descovy®**	No food restriction	200/25/200/10 QD	12.5	Rectangular	Yes*	No data available	[8,12]
DTG/RPV	**Juluca®**	With food	50/25 QD	-	Oval, biconvex	Yes	No data available	[8,12]
3-drug combination								
EFV/FTC/TDF	**Atripla®**	No food restriction	300/200/600 QD	20	Oblong	Yes	Crushed tablets are not bioequivalent with intact tablets	[8,12,29]

RPV/FTC/TDF	**Eviplera®**	With food	300/200/25 QD	19	Capsule-shaped	Yes	Crushing tablets and dispersion into a liquid are not recommended. RPV is not soluble in water over a wide pH range.	[8,12]
ABC/3TC/DTG	**Triumeq®**	No food restriction	600/300/50 QD	22	Oval	Yes	Tablets may be crushed and added to a small amount of semi-solid food or liquid and should be immediately taken in their entirety.	[8,12,30]
RPV/FTC/TAF	**Odefsey®**	With food	25/200/25 QD	15	Capsule-shaped	Yes*	Tablets should be swallowed whole and should not be chewed, crushed, or split	[8,12]
4 drugs combination								

EVG/COBI/FTC/TDF	**Stribild®**	With food	300/200/150/150 QD	20	Capsule-shaped	Yes	Crushing tablets does not significantly modify the pharmacokinetic profile	[8,12,28,31,32]
EVG/COBI/FTC/TAF	**Genvoya®**	With food	10/200/150/150 QD	19	Capsule-shaped	Yes*	No data available	[8,12]
DRV/COBI/FTC/TAF	**Symtuza®**	With food	800/150/200/10 QD	-	Oval	Yes*	Splitting or crushing tablets does not significantly modify the pharmacokinetic profile	[8,12]

ABC, abacavir; EFV, efavirenz; 3TC, lamivudine; RPV, rilpivirine; FTC, emtricitabine; DRV, darunavir; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; EVG, elvitegravir; TAF, tenofovir alafenamide; COBI, cobicistat; QD, once daily; SODF, solid oral dosage formulation
*TAF only approved for HBV treatment at 25 mg once daily