



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

Carine San, M.P. Lê, S. Matheron, B. Mourvillier, M. Caseris, J.-F. Timsit, M. Wolff, Y. Yazdanpanah, D. Descamps, G. Peytavin

► To cite this version:

Carine San, M.P. Lê, S. Matheron, B. Mourvillier, M. Caseris, et al.. Management of oral antiretroviral administration in patients with swallowing disorders or with an enteral feeding tube. *Médecine et Maladies Infectieuses*, 2020, 50, pp.537 - 544. 10.1016/j.medmal.2019.10.010 . hal-03491589

HAL Id: hal-03491589

<https://hal.science/hal-03491589>

Submitted on 22 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

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

Minh Patrick LÊ^{1,2,§}, Carine SAN^{2,§}, Sophie MATHERON^{1,3}, Bruno MOURVILLIER^{1,4}, Marion
CASERIS⁵, Jean-François TIMSIT^{1,4}, Michel WOLFF^{1,4}, Yazdan YAZDANPANAH^{1,3}, Diane
DESCAMPS^{1,6}, Gilles PEYTAVIN^{1,2}

¹ IAME, INSERM UMR 1137, Université Paris Diderot Sorbonne Cité, Paris, France

²AP-HP, Hôpital Bichat-Claude Bernard, Laboratoire de Pharmacologie-Toxicologie, Paris,
France

³AP-HP, Hôpital Bichat-Claude Bernard, Service de Maladies Infectieuses et Tropicales, Paris,
France

⁴AP-HP, Hôpital Bichat-Claude Bernard, Réanimation Médicale et Infectieuse, Paris, France

⁵AP-HP, Hôpital Robert Debré, Service de Pédiatrie, Paris, France

⁶AP-HP, Hôpital Bichat-Claude Bernard, Laboratoire de Virologie, Paris, France

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

***Corresponding author:**

Dr Minh Patrick Lê, Laboratoire de Pharmacologie-Toxicologie, Hôpital Bichat-Claude Bernard,
75018 Paris, AP-HP, France.

Tel: +33 1 40 25 84 54; fax: +33 1 42 63 58 25;

E-mail: minh.le@aphp.fr

§: These authors equally contributed to this work

Acknowledgements

Minh P Lê and Carine San equally contributed as first author. We would like to thank Jonathan Amsellem for assisting with data collection. We also dedicate this work to the memory of our colleague Emmanuelle Papy.

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).

References

1. Barbier F, Roux A, Canet E, Martel-Samb P, Aegerter P, Wolff M, et al. Temporal trends in critical events complicating HIV infection: 1999-2010 multicentre cohort study in France. *Intensive Care Med*. 2014 Dec;40(12):1906–15.
2. Akgün KM, Huang L, Morris A, Justice AC, Pisani M, Crothers K. Critical Illness in HIV-Infected Patients in the Era of Combination Antiretroviral Therapy. *Proc Am Thorac Soc*. 2011 Jun 1;8(3):301–7.
3. Coquet I, Pavie J, Palmer P, Barbier F, Legriel S, Mayaux J, et al. Survival trends in critically ill HIV-infected patients in the highly active antiretroviral therapy era. *Crit Care*. 2010;14(3):R107.
4. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients With HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest*. 2009 Jan;135(1):11–7.
5. ANSM. Nutritional support strategy for protein-energy malnutrition in the elderly [Internet]. 2007. Available from: https://www.has-sante.fr/portail/upload/docs/application/pdf/malnutrition_elderly_guidelines.pdf
6. Puisieux F, D'Andrea C, Baconnier P, Bui-Dinh D, Castaings-Pelet S, Crestani B, et al. Swallowing disorders, pneumonia and respiratory tract infectious disease in the elderly. *Revue des maladies respiratoires*. 2011;28(8):e76–93.
7. Dorman RM, Sutton SH, Yee LM. HIV-Related Pill Aversion: A Novel Barrier to Adherence, poster abstract 469. Conference on Retroviruses and Opportunistic Infections; 2017 Feb 13; Seattle, WA.
8. European AIDS Clinical Society. Guidelines version 9.0, October 2017 [Internet]. Available from: http://www.eacsociety.org/files/guidelines_9.0-english.pdf. Last accessed July 1, 2018.
9. Morlat P (dir.). Initiation d'un premier traitement antirétroviral. In: *Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts, sous la direction du Pr Philippe Morlat et sous l'égide du CNS et de l'ANRS* [Internet]. 2017. Available from: https://cns.sante.fr/wp-content/uploads/2017/01/experts-vih_initiation.pdf. Last accessed July 1, 2018.
10. AIDSinfo. Information on HIV/AIDS Treatment, Prevention and Research [Internet]. 2018. Available from: <https://aidsinfo.nih.gov/>. Last accessed July 1, 2018.
11. FDA. Office of the Commissioner. U.S. Food and Drug Administration [Internet]. 2018. Available from: <http://www.fda.gov>. Last accessed July 1, 2018.
12. EMA. European public assessment reports [Internet]. 2017. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125. Last accessed July 1, 2018.

13. ESPEN [Internet]. 2018. Available from: <https://www.espen.org/>. Last accessed July 1, 2018.
14. ASPEN [Internet]. 2018. Available from: <https://www.nutritioncare.org/>. Last accessed July 1, 2018.
15. Malnutrition and Nutritional Care in the UK - BAPEN [Internet]. 2018. Available from: <https://www.bapen.org.uk/>. Last accessed July 1, 2018.
16. Haute Autorité de Santé - Portail HAS Professionnels [Internet]. 2018. Available from: <https://www.has-sante.fr/>. Last accessed July 1, 2018.
17. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2017.
18. Boesecke C, Cooper DA. Toxicity of HIV protease inhibitors: clinical considerations. *Curr Opin HIV AIDS*. 2008 Nov;3(6):653–9.
19. Kumar P, Lakshmi YS, Kondapi AK. An oral formulation of efavirenz-loaded lactoferrin nanoparticles with improved biodistribution and pharmacokinetic profile. *HIV Med*. 2017 Aug;18(7):452–62.
20. Prohaska ES, King AR. Administration of antiretroviral medication via enteral tubes. *Am J Health Syst Pharm*. 2012 Dec 15;69(24):2140–6.
21. Scholten S, Mauruschat S, Hindermann S, Ranneberg B. Administration of darunavir tablets in patients with difficulties in swallowing – two case reports. *J Int AIDS Soc*. 2010 Nov 8;13(Suppl 4):P114.
22. Kim CH, Muzevich KM, Fulco PP. Orogastric administration of crushed darunavir tablets for a critically ill patient. *Can J Hosp Pharm*. 2014 Jan;67(1):39–42.
23. Patel P, Song I, Borland J, Chen S, Peppercorn A, Wajima T, et al. Relative bioavailability of a paediatric granule formulation of the HIV integrase inhibitor dolutegravir in healthy adult subjects. *Antivir Ther (Lond)*. 2014;19(3):229–33.
24. Cattaneo D, Baldelli S, Cerea M, Landonio S, Meraviglia P, Simioni E, et al. Comparison of the in vivo pharmacokinetics and in vitro dissolution of raltegravir in HIV patients receiving the drug by swallowing or by chewing. *Antimicrob Agents Chemother*. 2012 Dec;56(12):6132–6.
25. ANSM. Foscavir: Résumé des caractéristiques du produit. 2017.
26. ANSM. Retrovir: Résumé des caractéristiques du produit. 2017.
27. Turley SL, Fulco PP. Enteral Administration of Twice-Daily Dolutegravir and Rilpivirine as a Part of a Triple-Therapy Regimen in a Critically Ill Patient with HIV. *J Int Assoc Provid AIDS Care*. 2017 Apr;16(2):117–9.

28. Custodio JM, Liu Y, Graham H, Hepner M, Wiser L, Quirk E, et al. Bioequivalence of Two Pediatric Formulations vs Adult Tablet Formulation of Elvitegravir, poster abstract 902. Conference on Retroviruses and Opportunistic Infections; 2014 Mar 3; Boston, MA.
29. King J, McCall M, Cannella A, Markiewicz MA, James A, Hood CB, et al. A randomized crossover study to determine relative bioequivalence of tenofovir, emtricitabine, and efavirenz (Atripla) fixed-dose combination tablet compared with a compounded oral liquid formulation derived from the tablet. *J Acquir Immune Defic Syndr*. 2011 Apr 15;56(5):e130-132.
30. Roskam-Kwint M, Bollen P, Colbers A, Duisenberg-van Essen M, Harbers V, van Crevel R. Crushing of dolutegravir combination tablets increases dolutegravir exposure, poster abstract 429. Conference on Retroviruses and Opportunistic Infections; 2017 Feb 14; Seattle, WA.
31. Jongbloed-de Hoon M, Colbers A, Velthoven-Graafland K, Duisenberg-van Essen M, Kruijsen M, Abbink E, et al. Pharmacokinetics of Crushed Elvitegravir Combination Tablet Given with or without Enteral Nutrition. *J Acquir Immune Defic Syndr*. 2017 Jan 3;
32. Fulco P, Ayala-Sims V. Sustained virological response after taking crushed elvitegravir-cobicistat-emtricitabine- tenofovir tablets. *American Journal of Health-System Pharmacy*. 2014 May 15;71(10):784–5.
33. Brown K, Thomas D, McKenney K. Relative Bioavailability of Darunavir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (D/C/F/TAF) Single-Tablet Regimen When Administered as a Whole, Split, or Crushed Tablet, Oral abstract PS8/3. 16th European AIDS Conference; 2017 Oct 25; Milan, Italy.
34. Canestri A, Ghosn J, Wirden M, Marguet F, Ktorza N, Boubezari I, et al. Foscarnet salvage therapy for patients with late-stage HIV disease and multiple drug resistance. *Antivir Ther (Lond)*. 2006;11(5):561–6.
35. Arnaud P. Le broyage des comprimés, l'ouverture des capsules, quelles responsabilités ? *Le Pharmacien Hospitalier et Clinicien*. 2015;50(3):309–11.
36. Devers G. La dispensation des médicaments. *Droit, Déontologie & Soins*. 2012;12(3):314–30.
37. France. French Public Health Code, Article R4311-7. French Public Health Code.
38. Barry Perdureau V, Moreau C, Friocourt P, Harnois C. Écrasement des médicaments en gériatrie : Mise au point et recommandations de bonnes pratiques. *LA REVUE DE GERIATRIE*. 2015 Oct 1;(8):463–70.
39. Caussin M, Mourier W, Philippe S, Capet C, Adam M, Reynero N, et al. Crushing drugs in geriatric units: an “handicraft” practice with frequent errors which imposed recommendations. *Rev Med Interne*. 2012 Oct;33(10):546–51.

40. Kelly J, Wright D, Wood J. Medication errors in patients with dysphagia. *Nurs Times*. 2012 May 22;108(21):12–4.
41. France. French Public Health Code, Article L5121-12-1. French Public Health Code.
42. France. French Public Health Code, Article R4235-48. French Public Health Code.
43. France. French Public Health Code, Article R4235-61. French Public Health Code.
44. BAPEN. Administering drugs via enteral feeding tubes: a practical guide [Internet]. 2004. Available from: http://www.bapen.org.uk/pdfs/d_and_e/de_pract_guide.pdf. Last accessed July 1, 2018.
45. Liverpool Drug Interactions Group. Antiretroviral dosage forms for swallowing difficulties [Internet]. 2017. Available from: https://liverpool-web-production.s3.amazonaws.com/printable_charts/pdfs/000/000/028/original/ARV_Swallowing_2017_Apr.pdf?1512034916. Last accessed July 1, 2018.
46. Foisy M, Hughes C, Lamb S, Tseng A. Oral antiretroviral administration: information on crushing and liquid drug formulations [Internet]. 2017. Available from: https://hivclinic.ca/main/drugs_extra_files/Crushing%20and%20Liquid%20ARV%20Formulations.pdf. Last accessed July 1, 2018.
47. Cooper CL, van Heeswijk RPG. Once-daily nevirapine dosing: a pharmacokinetics, efficacy and safety review. *HIV Med*. 2007 Jan;8(1):1–7.
48. Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, et al. Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr*. 2009 Apr;33(2):122–67.
49. Boullata JJ, Carrera AL, Harvey L, Escuro AA, Hudson L, Mays A, et al. ASPEN Safe Practices for Enteral Nutrition Therapy. *JPEN J Parenter Enteral Nutr*. 2017 Jan;41(1):15–103.
50. White R, Bradnam V. Handbook of drug administration via enteral feeding tubes. London: Pharmaceutical Press; 2007. 569 p.
51. Williams NT. Medication administration through enteral feeding tubes. *Am J Health Syst Pharm*. 2008 Dec 15;65(24):2347–57.
52. Neuville S, Lannoy D, Delatre C, Bouchoud L. Administration des médicaments oraux chez le patient bénéficiant d’une nutrition entérale. *Nutrition Clinique et Métabolisme*. 2013;27(4):255–62.
53. Institute for Safe Medication Practices. Oral syringes: A crucial and economical risk-reduction strategy that has not been fully utilized [Internet]. 2009. Available from: <https://www.ismp.org/newsletters/acutecare/articles/20091022.asp>. Last accessed July 1, 2018.

54. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006 Nov 30;355(22):2283–96.
55. DART Trial Team. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/microl. *AIDS*. 2008 Jan 11;22(2):237–47.
56. Holkmann Olsen C, Mocroft A, Kirk O, Vella S, Blaxhult A, Clumeck N, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. *HIV Med*. 2007 Mar;8(2):96–104.
57. Chilton D, Dervisevic S, Pillay D, Rider A, Copas A, Miller RF, et al. Determinants of HIV drug resistance mutations in plasma virus after treatment interruption. *AIDS*. 2005 Dec 2;19(18):2174–5.
58. Duggan JM, Akpanudo B, Shukla V, Gutterson G, Eitnien L, Sahloff EG. Alternative antiretroviral therapy formulations for patients unable to swallow solid oral dosage forms. *Am J Health Syst Pharm*. 2015 Sep 15;72(18):1555–65.
59. Sandkovsky U, Swindells S, Moore R, Acosta EP, Fletcher CV. Acceptable plasma concentrations of raltegravir and etravirine when administered by gastrostomy tube in a patient with advanced multidrug-resistant human immunodeficiency virus infection. *Pharmacotherapy*. 2012 Feb;32(2):142–7.
60. Huesgen E, DeSear KE, Egelund EF, Smith R, Max B, Janelle J. A HAART-Breaking Review of Alternative Antiretroviral Administration: Practical Considerations with Crushing and Enteral Tube Scenarios. *Pharmacotherapy*. 2016 Nov;36(11):1145–65.
61. Manassis A, Lascher S, Bukberg P, Darmody T, Yen V, Sadek S, et al. Quantifying amount of adsorption of levothyroxine by percutaneous endoscopic gastrostomy tubes. *JPEN J Parenter Enteral Nutr*. 2008 Apr;32(2):197–200.

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

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

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
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	No food	25 QD	6.4	Circular	No	Oral solution	
	tablet	restriction					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
Protease inhibitors (PIs)								
ritonavir Norvir®	Film-coated	With food	100 QD	22	Oval	No	Powder	
	tablet		100 BID				100 mg/pack Solution 80 mg/mL	Switch to oral solution
cobicistat Tybost®	Film-coated	With food	150 QD	10.3	Round	No	Not available	Switch to ritonavir oral solution
Integrase strand transfer inhibitor (INSTIs)								
elvitegravir Vitekta®	Film-coated	No food	150 QD	8.9	Pentagon-	-	Solution	
	tablet	restriction					5 mg/mL	Switch to another INSTI

shape 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		Doses per day (mg)	Size (mm)	Shape	Components		References
		consideration					available	Alteration of SODF	
		(label information)					separately?		
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]

[illegible]

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