

Food and Nutrition Implications of Antiretroviral Therapy in Resource Limited Settings

Tony Castleman, Eleonore Seumo-Fosso,
and Bruce Cogill

Interactions between antiretroviral therapy (ART) and food and nutrition can affect medication efficacy, nutritional status, and adherence to drug regimens. Drug-food interactions consist of the effects of food on medication efficacy, the effects of medication on nutrient utilization, the effects of medication side effects on food consumption, and unhealthy side effects caused by medication and certain foods. As ART interventions scale up in resource limited settings, addressing food and nutrition implications becomes a critical component of care and support programs and services. Service providers can help address these implications by working with people living with HIV/AIDS (PLWHA) and caregivers to identify the specific food and nutrition requirements of the medications being taken and to develop feasible food and drug plans to meet these requirements. Programs working with people taking ART may need to strengthen human capacity to address nutritional issues, establish linkages to food and nutrition programs, and incorporate information about drug-food interactions into communication materials, staff training and orientation, and supervision systems.

This technical note provides information and guidance about the food and nutrition implications of ART and how to manage the effects of these implications in resource limited settings. The purpose of the document is to assist program planners, groups developing guidance on care and support, service providers, and networks of people living with HIV/AIDS to understand and address ART interactions with food and nutrition. The information presented here can also help managers of programs that include ART components to incorporate food and nutrition counseling and other interventions as needed. While this document is not designed for direct use by community-level health workers, it can be used to support the development of communication materials such as counseling aids, as well as training materials.

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LIST OF ACRONYMS

AED	Academy for Educational Development
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral Drug
CBC	Co-Blister Combination
FANTA	Food and Nutrition Technical Assistance
FDC	Fixed Dose Combination
GI	Gastrointestinal
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
PLWHA	People/Person Living with HIV/AIDS
RTI	Reverse Transcriptase Inhibitor
USAID	United States Agency for International Development
WHO	World Health Organization

Access to antiretroviral drugs (ARVs) is increasing among PLWHA in developing countries as a result of local, national, and international efforts.¹ Issues related to ART in resource limited settings have become increasingly relevant to PLWHA, caregivers, service providers, and programmers. Interactions between ARVs and food and nutrition can significantly influence the success of ART by affecting drug efficacy, adherence to drug regimens, and the nutritional status of PLWHA. Managing the interactions between ART and food and nutrition is a critical factor in the extent to which the therapy is effective in slowing the progression of HIV/AIDS and improving the quality of life of PLWHA. In resource limited settings, many PLWHA lack access to sufficient quantities of nutritious foods, which poses additional challenges to the success of ART.

This technical note summarizes the types of ARVs commonly used; offers a framework for understanding drug-food interactions; describes key issues and steps for managing ARV-food interactions; identifies areas where knowledge gaps exist; and lays out the specific food and nutrition implications of ARVs commonly used in resource limited settings (see Table 3). This information aims to support program design and service provision.

General Nutritional Care and Support

While this document focuses on ART, it is important to note that individuals infected with HIV have special nutritional needs, such as increased energy requirements, irrespective of whether they use ART. Although access to ART in developing countries is expanding, the majority of PLWHA still do not have access to ART.² Maintaining adequate food consumption and nutrient intake levels and meeting the special nutritional needs the disease generates are critical for all PLWHA. Proper nutrition helps to strengthen the immune system, manage opportunistic infections, optimize response to medical treatment, and may contribute to slowing the progression of the disease.

It is recommended that asymptomatic PLWHA increase energy intake by 10% over the requirement for healthy, non-HIV-infected persons of the same age, sex, and physical activity level, and that symptomatic PLWHA increase energy intake by 20-30% over the requirement for healthy, non-HIV-infected persons of the same age, sex, and physical activity level. It is recommended that PLWHA meet the protein and micronutrient intake levels recommended for healthy, non-HIV-infected persons of the same age, sex, and physical activity level.³

Ensuring a diet with sufficient quantities of nutrient-rich foods is critical for all people, and nutrition is an integral component of care and support of PLWHA under any condition. ART can reduce viral loads and contribute to improved nutritional status, but also can create additional nutritional needs and dietary constraints.

Classes and Types of ARVs

Antiretroviral drugs have been shown to significantly reduce the rate of replication of HIV in the body of an HIV-infected person. ARVs do not completely destroy the virus and do not cure the disease, but they can greatly decrease the viral load and significantly slow the progression of the disease, thereby increasing life expectancy and improving the quality of life of PLWHA. ARVs are not required by all PLWHA at all stages of HIV; research is continuing on the subject, but most often ARVs are prescribed when the virus has begun to significantly damage the immune system.⁴

There are two classes of commonly used ARVs – reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) – and each acts at a different stage in the replication of HIV. A third class of ARV, fusion inhibitors, is seldom used at present in resource limited settings, and no fusion inhibitors are included in the list of ARVs published by the World Health Organization (WHO) for resource limited settings. This technical note focuses on reverse transcriptase inhibitors and protease inhibitors.

¹ For example, USAID has initiated projects that provide ARVs in Sub-Saharan Africa, and a key objective of the U.S. President's Emergency Plan for AIDS Relief is to treat 2 million HIV-infected people by 2008. The U.S. Centers for Disease Control and Prevention, the Global Fund for AIDS, Tuberculosis and Malaria, and others support efforts to expand access to ARVs in developing countries.

3

² It is estimated that in 2003, 6 million PLWHA in developing countries required ART, of whom only 400,000 received it. A third of those receiving ART in 2003 live in Brazil. Source: WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003, p. 5.

³ WHO. *Nutrient Requirements of People Living with HIV/AIDS: Report of a Technical Consultation*. Geneva, 2003.

⁴ WHO recommends that "in ARV treatment programs in resource-limited settings HIV infected adolescents and adults should start ART therapy when they have confirmed HIV infection and one of the following conditions: clinically advanced HIV disease: WHO Stage IV HIV disease irrespective of CD4 count [or] WHO Stage III HIV disease with consideration of using CD4 counts <350/mm³ to assist decision-making. WHO Stages I or II HIV disease with CD4 counts <200/mm³." Source: WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

Table 1: Classes and Types of ARVs

Class	Type	Examples of Drugs
Reverse Transcriptase Inhibitor	Non-nucleoside reverse transcriptase inhibitor (NNRTI)	efavirenz, nevirapine
	Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)	abacavir, didanosine lamivudine, stavudine tenofovir, zidovudine
Protease Inhibitor	Protease Inhibitor (PI)	indinavir, lopinavir, nelfinavir ritonavir, saquinavir

Adapted from WHO's *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

⁵ WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

When HIV infects a cell, the viral RNA converts to viral DNA and is copied into the host cell's DNA by an enzyme called reverse transcriptase. Then the viral DNA instructs the cell to make copies of HIV genetic material. The protease enzyme assembles this copied viral genetic material into new viruses, after which they are released from the cell to infect other cells.

The first class of ARV, reverse transcriptase inhibitors, operates early in the HIV life cycle to stop viral replication after HIV has infected a cell. Two types of these drugs exist: non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), also called nucleoside analogues. NNRTIs bind onto the reverse transcriptase enzyme and prevent the HIV RNA from converting into DNA, thereby preventing it from being copied into the cell's DNA. NRTIs incorporate into the viral DNA and prevent it from producing copies of the virus.

The second class of ARV, protease inhibitors (PIs), operates later in the life cycle of HIV. These drugs stop the protease enzyme from assembling the new HIV material to be released to infect other cells.

In most cases, one ARV alone cannot sufficiently stop replication of the virus. To optimize efficacy and reduce the chances of drug resistance, ART usually involves the administration of more than one ARV.

This is referred to as combination therapy or highly active antiretroviral therapy (HAART). Inclusion of two or more drugs in a single pill is referred to as a fixed dose combination (FDC), and inclusion of two or more pills containing different drugs in the same blister pack is referred to as a co-blister combination (CBC). WHO recommends four first-line HAART regimens for adults and adolescents in resource limited settings.⁵

Table 2: First-Line ARV Regimens Recommended by WHO for Resource Limited Settings

1. stavudine + lamivudine + nevirapine
2. zidovudine + lamivudine + nevirapine
3. stavudine + lamivudine + efavirenz
4. zidovudine + lamivudine + efavirenz

Source: WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

Other Medications

In addition to ARVs, PLWHA often take other drugs to treat opportunistic infections, such as tuberculosis, thrush, pneumonia, and intestinal infections, which occur as a result of weakened immune systems. PLWHA also take drugs to treat other common diseases, such as malaria. While this technical note focuses on ARVs, nutrition is a critical factor in the safety and efficacy of many other medications commonly taken by PLWHA. Many of the principles and processes described below for ARVs can be used to identify and manage the food and nutrition interactions of other drugs.⁶

ARV Interactions with Food and Nutrition

ARVs can interact with food and nutrition in a variety of ways, resulting in both positive and negative outcomes. Figure 1 depicts the four main types of interactions that can occur between drugs and food and nutrition. Because different ARVs interact with food and nutrition differently, it is critical to understand the specific nutritional interactions and implications of the par-

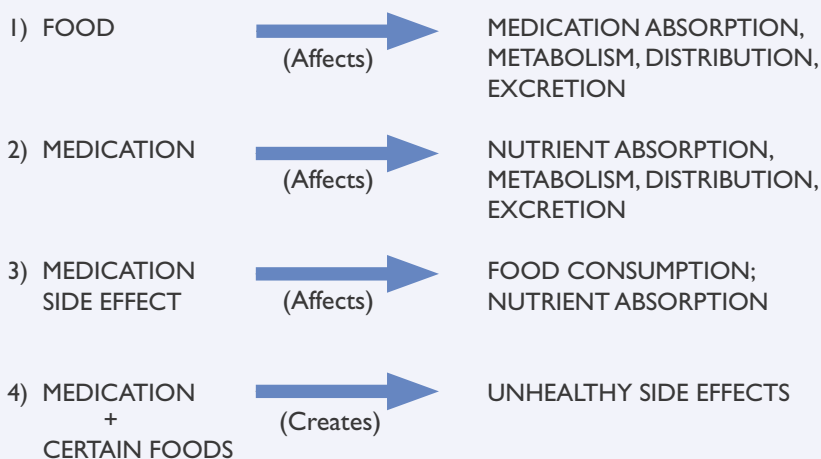
ticular drugs being taken. This understanding enables effective management of these interactions to maintain nutritional status and to improve drug efficacy, tolerance, safety, and adherence.

The examples of specific ARVs' food interactions given here are intended to illustrate the different types of drug-food interactions. When planning management of drug-food interactions, it is important to obtain complete and up-to-date information from drug product information, medical facilities, publications, or other sources. Table 3 provides information about food implications of the 13 ARVs included in WHO's ARV guidelines.⁷

1) Food can affect medication absorption, metabolism, distribution, excretion.

Certain foods affect the efficacy of certain ARVs by affecting their absorption, metabolism, distribution, or excretion. Food enhances the efficacy of some ARVs and inhibits the efficacy of others. For example, a high energy, high fat, high protein meal decreases absorption of the PI indinavir.⁸ A high fat meal increases the bioavailability of the NRTI tenofovir.⁹

Figure 1: Interactions between Medications and Food/Nutrition



⁶ Sources of information about specific food interactions of non-ARV drugs include the following:

U.S. Food and Drug Agency website: www.fda.gov

Fields-Gardner C., C. Thomson, and S. Rhodes.

A Clinicians Guide to Nutrition in HIV and AIDS. American Dietetic Association, 1997.

Pronsky, Z., S.A. Meyer, and C. Fields-Gardner. *HIV Medications Food Interactions*. Second Edition. Birchrunville, PA: 2001.

Zeman F. *Clinical Nutrition and Dietetics*. Second Edition. New York: Macmillan, 1991.

5

⁷ WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

⁸ Pronsky, Z., S.A. Meyer, and C. Fields-Gardner. *HIV Medications Food Interactions*. Second Edition. Birchrunville, PA: 2001, p. 81.

⁹ *ibid.* p. 126.

¹⁰ Currier, J. "Metabolic Complications of Anti-retroviral Therapy and HIV Infection" in *HIV/AIDS: Annual Update 2001*. iMedOptions, 2001. Medscape.

¹¹ *ibid.*

¹² Gelato, M. "Insulin and Carbohydrate Dysregulation." *Clinical Infectious Diseases*. 2003. 36: S91-5.

¹³ Pronsky, Meyer, Fields-Gardner, *op.cit.*, pp. 60, 138.

¹⁴ See Mondy, K., and P.Tebas. "Emerging Bone Problems in Patients Infected with Human Immunodeficiency Virus." *Clinical Infectious Diseases*. 2003. 36: S101-5, and

Tebas, P., W.G. Powderly, S. Claxton, D. Marin, W. Tantisiriwat, S.L. Teitelbaum, et al. "Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy." *AIDS* 2000. 14: F63-7.

If not properly managed, these interactions result in reduced effectiveness of the therapy. Consequently, some ARVs should be taken with food, others on an empty stomach, and others with or without specific types of foods.

2) Medications can affect nutrient absorption, metabolism, distribution, excretion.

Certain ARVs affect nutrient utilization by affecting nutrient absorption, metabolism, distribution, or excretion. For example, certain protease inhibitors, such as ritonavir and nelfinavir, can cause changes in the metabolism of lipids (fats), resulting in an elevation in blood cholesterol and triglyceride levels.¹⁰ Elevated blood cholesterol and triglyceride levels can increase the risk of coronary heart disease. Such interactions may call for nutritional responses, such as reduced consumption of saturated fats, if other food options are available. Lipodystrophy, characterized by changes in body fat distribution, has been associated with the use of some PIs and NRTIs.¹¹ The use of some protease inhibitors has been associated with changes in carbohydrate metabolism, leading to insulin resistance.¹² Insulin resistance is associated with increased risk of diabetes.

3) Medication side effects can negatively affect food consumption and nutrient absorption.

The side effects of some medications can lead to reduced food intake or reduced nutrient absorption that exacerbates the weight loss and nutritional problems experienced by PLWHA. ARV side effects, such as nausea, taste changes, and loss of appetite may reduce food consumption, while side effects such as diarrhea and vomiting may increase nutrient losses. For example, the NRTI zidovudine can cause anorexia, nausea, and vomiting, and side effects of the NRTI didanosine include diarrhea and vomiting, loss of appetite, and dryness of the mouth.¹³

Appropriate dietary changes can help PLWHA to manage certain ARV side effects and to reduce the impact these side effects have on their nutritional status. A simple example is that if zidovudine causes nausea, then taking it with a light meal, eating dry, salty foods, and drinking fluids between meals may help to prevent nausea. If consumption of didanosine causes diarrhea, drinking plenty of fluids and eating foods rich in energy and other nutrients – as is recommended for diarrhea generally – will help to reduce the impact of diarrhea on health and nutritional status.

ARVs can also have unhealthy side effects that are not related to food consumption or nutrient absorption but call for food and nutritional responses. For example, some studies have shown that certain ARVs increase the risk of osteopenia and osteoporosis, though further research is continuing on the subject. These conditions lead to poor bone health. Ensuring adequate vitamin D and calcium intake is a recommended nutritional response for patients with osteoporosis.¹⁴

While the majority of people who take ARVs experience some side effects during the treatment period, the prevalence, frequency, and severity of side effects vary among ARVs, among individuals, and among different side effects.¹⁵

4) Combination of medication and certain foods can produce unhealthy side effects.

Some ARVs can create dangerous side effects when combined with certain foods. For example, consuming drinks that contain alcohol while taking didanosine can cause pancreatitis, an inflammation of the pancreas that can be serious and even fatal.¹⁶ Service providers need to make PLWHA aware of the foods contraindicated with the drugs they are taking so these foods can be avoided.

Table 3: Food and nutrition implications of two classes of ARVs: Reverse Transcriptase Inhibitors and Protease Inhibitors ¹⁷

ARV Class: REVERSE TRANSCRIPTASE INHIBITORS			
ARV Type: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
Medication Generic Name (abbreviation)	Food Recommendations	Avoid	Possible Side Effects [Nutritional management of side effects is given in Table 4.]
efavirenz (EFZ)	Can be taken without regard to meals, except do <u>not</u> take with a high fat meal. (A high fat meal increases drug absorption.)	Alcohol.	Elevated blood cholesterol levels, elevated triglyceride levels, rash, dizziness, anorexia, nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence.
nevirapine (NVP)	Can be taken without regard to food.	St. John's wort.	Nausea, vomiting, rash, fever headache, skin reactions, fatigue, stomatitis, abdominal pain, drowsiness, paresthesia. High hepatotoxicity.

ARV Class: REVERSE TRANSCRIPTASE INHIBITORS			
ARV Type: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)			
Medication Generic Name (abbreviation)	Food Recommendations	Avoid	Possible Side Effects [Nutritional management of side effects is given in Table 4.]
abacavir (ABC)	Can be taken without regard to food.		Nausea, vomiting, fever, allergic reaction, anorexia, abdominal pain, diarrhea, anemia, rash, hypotension, pancreatitis, dyspnea, weakness, insomnia, cough, headache.
didanosine (ddl)	Take 30 minutes before or two hours after eating. Take with water only. (Taking with food reduces absorption.)	Alcohol. Do not take with juice. Do not take with antacids containing Aluminum or Magnesium.	Anorexia, diarrhea, nausea, vomiting, pain, headache, weakness, insomnia, rash, dry mouth, loss of taste, constipation, stomatitis, anemia, fever, dizziness, pancreatitis.
lamivudine (3TC)	Can be taken without regard to food.	Alcohol.	Nausea, vomiting, headache, dizziness, diarrhea, abdominal pain, nasal symptoms, cough, fatigue, pancreatitis, anemia, insomnia, muscle pain, rash.
stavudine (d4T)	Can be taken without regard to food.	Limit the consumption of alcohol.	Nausea, vomiting, diarrhea, peripheral neuropathy, chills and fever, anorexia, stomatitis, anemia, headaches, rash, bone marrow suppression, pancreatitis. May increase the risk of lipodystrophy.
tenofovir (TDF)	Take with a meal.		Abdominal pain, headache, fatigue, dizziness.
zidovudine (ZDV/AZT)	Better to take without food, but if it causes nausea or stomach problems, take with a low-fat meal. Do not take with a high-fat meal.	Alcohol.	Anorexia, anemia, nausea, vomiting, bone marrow suppression, headache, fatigue, constipation, dyspepsia, fever, dizziness, dyspnea, insomnia, muscle pain, rash.

NNRTI

NRTI

¹⁵ For information about the prevalence of ARV side effects, see:

Carr, A., and D. Cooper. "Adverse Effects of Antiretroviral Therapy." *The Lancet*. 2000. 356: 1423-30.

Fellay, J, et al. "Prevalence of Adverse Events Associated with Potent Antiretroviral Treatment: Swiss HIV Cohort Study." *The Lancet*. 2001. 358: 1322-27.

Pronsky, Meyer, Fields-Gardner, *op.cit.*

¹⁶ Pronsky, Meyer, Fields-Gardner, *op.cit.*, p.60.

¹⁷ The drugs included in this table are the 13 ARVs included in WHO's *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

Medication Generic Name (abbreviation)	Food Recommendations	Avoid	Possible Side Effects [Nutritional management of side effects is given in Table 4.]
indinavir (IDV)	Take on an empty stomach, one hour before or two hours after a meal. Or take with a light, non-fat meal. Take with water. Drink at least 1500 ml of fluids daily to prevent kidney stones.	Grapefruit. St John's wort.	Nausea, abdominal pain, headache, kidney stones, taste changes, vomiting, regurgitation, diarrhea, insomnia, ascites, weakness, dizziness. May increase the risk of lipodystrophy.
lopinavir (LPV)	Can be taken without regard to food.	St John's wort.	Abdominal pain, diarrhea, headache, weakness, nausea. May increase the risk of lipodystrophy. May increase the risk of diabetes.
nelfinavir (NFV)	Take with a meal or light snack. Taking with acidic food or drink will cause a bitter taste.	St John's wort.	Diarrhea, flatulence, nausea, abdominal pain, rash. May increase the risk of lipodystrophy.
ritonavir (RTV)	Take with a meal if possible.	St John's wort.	Nausea, vomiting, diarrhea, hepatitis, jaundice, weakness, anorexia, abdominal pain, fever, diabetes, headache, dizziness. May increase the risk of lipodystrophy.
saquinavir (SQV)	Take with a meal or light snack. Take within two hours of a high fat and high-calcium meal.	Garlic supplements. St John's wort.	Mouth ulceration, taste changes, nausea, vomiting, abdominal pain, diarrhea, constipation, flatulence, weakness, rash, headache, insomnia. May increase the risk of lipodystrophy.

Sources: Pronsky, Z., S.A. Meyer, and C. Fields-Gardner, *HIV Medications Food Interactions*, 2001.
 Nerad, J., M. Romeyn, E. Silverman, J. Allen-Reid, D. Dietrich, J. Merchant, V. Pelletier, D. Tinnerello, and M. Fenton, "General Nutrition Management in Patients Infected with Human Immunodeficiency Virus." *Clinical Infectious Diseases*. 2003:36.
 "Optimizing Anti-HIV Medications," *The Cutting Edge*, 2001. [www.tceconsult.org]
 WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

Table 4: Nutritional Management of Common ARV Side Effects

Side Effect	Recommended Nutritional Management
Anorexia	Eat small and frequent meals. Eat favorite foods. Select foods that are energy dense. Avoid strong smelling foods.
Change or Loss of Taste	Use flavor enhancers such as salt, spices, or lemon. Chew food well and move around in mouth to stimulate receptors.
Constipation	Eat foods high in fiber content. Drink plenty of liquids. Avoid processed or refined foods. Exercise regularly according to capacity.
Diarrhea	Drink plenty of fluids. Continue eating during and following illness. Prepare and drink rehydration solution regularly. Avoid fried foods.
Fever	Drink plenty of fluids. Eat energy and nutrient dense foods.
Flatulence	Avoid gas-forming foods, such as beans, cabbage, broccoli, and cauliflower.
High Blood Cholesterol	Eat a low fat diet and limit intake of foods rich in cholesterol and saturated fat. Eat fruits and vegetables daily. Exercise regularly according to capacity.
High Triglycerides	Limit sweets and excessive carbohydrate and saturated fat intake. Eat fruits, vegetables, and whole grains daily. Avoid alcohol and smoking. Exercise regularly according to capacity.
Nausea or Vomiting	Eat small quantities of food at frequent intervals. Drink after meals and limit intake of fluids with meals. Avoid having an empty stomach. Avoid lying down immediately after eating. Eat lightly salty and dry foods to calm the stomach. Rest between meals.

Sources: *HIV/AIDS: A Guide for Nutrition, Care and Support*. FANTA, Academy for Educational Development, 2001. Pronsky, Z., S.A. Meyer, and C. Fields-Gardner. *HIV Medications Food Interactions*. 2001. American Dietetic Association. *Manual of Clinical Dietetics*. Chicago, 2000.

Multiple Drug Considerations

Since different drugs have different food interactions, PLWHA taking more than one drug at the same time need to consider the interactions and requirements of each drug. For those taking multiple ARVs (combination therapy), sometimes one ARV needs to be taken with food and one without food, requiring the drugs to be taken at separate times. Drug and food timetables need to be set to meet these requirements.

In some cases, the food interactions of ARV combinations are different from those of the individual drugs. For example, as mentioned above, taking the PI indinavir with a high energy, high fat, high protein meal reduces its absorption; studies have shown a 77% reduction in absorption of indinavir when taken with such a meal. But when indinavir is taken in combination with the PI ritonavir, then food has no effect on the absorption of indinavir, and it may be taken with or without food.¹⁸

Variation of ARV-Food Interactions

- Some ARVs should be taken with food, others on an empty stomach, and still others are contraindicated with certain foods.
- Some ARVs reduce nutrient absorption or metabolism and may require foods rich in specific nutrients or may require nutritional supplementation.
- Certain ARVs cause side effects that affect food consumption, and some side effects can be managed by specific food responses.

Because of this variation, ARV-food management must be drug-specific.

¹⁸ Hsu, A., G.R. Granneman, M. Heath-Chiozzi, E. Ashbrenner, L. Manning, R. Brooks, P. Bryan, K. Erdman, and E. Sun. "Indinavir Can Be Taken with Regular Meals when Administered with Ritonavir." Abbot Laboratories. 12th World AIDS Conference, 1998.

All of the recommended combination ARV regimens have food and nutrition implications, though the specifics and the severity of ARV-food interactions vary among the different regimens. Management of the food and nutrition implications of a particular regimen requires consideration of the food and nutrition interactions of each drug in the regimen, as well as any interactions that may be different due to the drug combination (such as the indinavir/ritonavir example described previously). The box below gives an example of dietary recommendations for a combination ARV regimen.

In addition to combinations of ARVs, other drugs PLWHA take to treat opportunistic infections, malaria, and other diseases may also have food and nutrition interactions that need to be considered when managing

interactions between drugs and food and nutrition. The box below gives an example of dietary recommendations for a combination ARV regimen.

Furthermore, multiple medications taken at the same time can interact with each other, which may enhance or inhibit drug efficacy and may aggravate side effects. For example, didanosine can interact with antacids containing magnesium or aluminum, leading to increased side effects.¹⁹ Hence, it is important to account for all of the different drugs being taken – ARVs and others – when planning drug and food consumption.

The need to consider drug-drug interactions applies to traditional therapies as well as modern medications. Many PLWHA use traditional therapies to treat opportunistic

Illustrative Example of Managing Food and Nutrition Interactions of an ARV Combination Regimen

The combination of zidovudine, lamivudine, and abacavir is used as a HAART regimen. Recommendations to manage food and nutrition interactions for this regimen are:

- Take on an empty stomach if possible. If this is not possible because of gastrointestinal (GI) side effects, then take with low fat meals.
- Do not consume alcohol.

Side effects may include: nausea, vomiting, abdominal pain, diarrhea, anorexia, fever, bone marrow suppression, anemia, rash, and hyperlactacemia (potentially fatal). Dietary management of common side effects include:

- Nausea:* Take the medication with food.
- Vomiting:* Eat small quantity of food at frequent intervals.
- Diarrhea:* Drink plenty of fluids and continue eating.
- Anorexia:* Eat small, frequent meals.
- Fever:* Drink plenty of fluids and eat energy and nutrient dense foods.

Abacavir has been associated with fatal hypersensitivity reactions, so people who develop a rash, fever, respiratory symptoms or GI problems should stop taking the combination regimen and be checked for hypersensitivity. Continuation of the regimen with dietary management of side effects is only recommended if hypersensitivity has been ruled out.

Sources: WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 Revision. Geneva, December 2003.

Nerad, J., M. Romeyn, E. Silverman, J. Allen-Reid, D. Dietrich, J. Merchant, V. Pelletier, D. Tinnerello, and M. Fenton. "General Nutrition Management in Patients Infected with Human Immunodeficiency Virus." *Clinical Infectious Diseases*. 2003;36.

"Trizivir brand abacavir + zidovudine + lamivudine (ABC + AZT + 3TC)." AIDSmeds.com.

¹⁹ "Videx (didanosine)." Patient Information Leaflet. Bristol-Myers Squibb, January 27, 2003.

infections, and some traditional therapies can interact with certain ARVs. For example, studies have shown that the blood concentration of the PI saquinavir decreases by 50% in the presence of a garlic supplement, which is sometimes taken as a traditional therapy to boost the immune system.²⁰ Because many traditional therapies exist and the contents are often unknown, it can be difficult to understand the interactions between these therapies and drugs.

Adherence to Drug Regimens

In addition to direct effects on medication efficacy, nutrient absorption, and food-related side effects, food and nutrition interactions with ARVs can also affect PLWHA's adherence to drug regimens. Non-adherence to drug regimens involves failure to follow drug schedules, taking incorrect doses, failure to follow other drug directions, or stopping consumption of the drug altogether. Because ART usually involves a lengthy period of treatment and because side effects are common, the risk of non-adherence to ARV regimens is high.

Non-adherence can have serious negative implications at both the individual and collective levels. For an HIV-infected individual, interrupting ART or taking it incorrectly may lead to a substantial decline in health, increased frequency of opportunistic infections, and faster progression of the disease. Non-adherence may also lead to development of drug-resistant strains of HIV. The spread of drug-resistant strains of HIV to others creates a greater number of PLWHA who cannot be effectively treated for HIV.

Failure to effectively manage ARV-food interactions can result in non-adherence. For example, side effects that create significant discomfort or inhibit eating may lead PLWHA to interrupt or terminate their drug regimens. Even in developed countries, where PLWHA have greater access to nutritious foods than in developing countries, food and nutrition side effects

and dietary restrictions can be a significant obstacle to adherence to ARV regimens. Enabling proper management of ARV-food interactions is a critical component of ensuring adherence to ARV regimens.

Management of Interactions between ARVs and Food and Nutrition

Management of interactions between ARVs and food and nutrition involves developing and communicating information about the interactions, identifying and implementing appropriate food and nutrition responses, and addressing food security constraints.

1) Information

Nutritional implications for ARVs cannot be generalized. Given the different types of drug-food interactions and the variation among ARVs, it is critical to be drug-specific when managing ARV-food interactions. The specific food and nutrition requirements of the specific drugs people are taking need to be understood, based upon which appropriate responses can be planned. Confusion between the food interactions of different medications may lead to reduced efficacy of the medication or to aggravation of side effects.

Because information about drug-food interactions continues to evolve, it is important to remain up-to-date as new ARVs become available in a particular context or as new information emerges about existing ARVs. Three critical steps in this process are: 1) identifying sources of current information about ARV-food interactions; 2) adapting information into forms easily understood by PLWHA and caregivers; and 3) identifying existing communication channels and developing new channels as needed to ensure that this information reaches PLWHA and caregivers.

Websites that contain information about ARV-food interactions are listed at the end of this document. Other possible sources of information include drug product information, medical or nutrition journals, Ministry

²⁰ Piscitelli, S.C., A.H. Burstein, N. Welden, K.D. Gallicano, and J. Falloon. "The Effect of Garlic Supplements on the Pharmacokinetics of Saquinavir." *Clinical Infectious Diseases*. 2002. 34: 234-8.

of Health facilities and services, pharmaceutical services, HIV/AIDS or health resource centers, and books and publications. Communication channels depend on the specific context and programming environment but may include existing community-based or home-based counseling opportunities, programs and facilities that provide ARV services, and mass media campaigns.

2) Food and Nutrition Responses

Based on information about the specific food and nutrition interactions of the ARVs and other drugs that an individual is taking, an appropriate diet should be identified and a drug and meal timetable planned. This may involve:

- adjusting the timing of drug and food consumption to enable specific drugs to be taken with or without food as required;
- increasing or decreasing consumption of certain foods (or supplements) to compensate for drug effects on nutrient absorption;
- changing the pattern or content of meals to address drug side effects;
- avoiding certain foods contraindicated by a drug;
- other responses as required by the food and nutrition interactions of the specific drugs the PLWHA is taking and the individual PLWHA's needs and reactions.

It is necessary to develop and adhere to a drug and meal plan that meets the food and nutrition requirements of the drugs being used and that is feasible and sustainable for the individual PLWHA. Planning options and diets must account for the obstacles that constrain PLWHA and households from adopting recommended practices. Food insecurity, psychosocial issues, stigma, and intra-household decision-making processes are factors that can prevent PLWHA from following appropriate diets and suitable drug and meal timetables.

Service providers, counselors, and home-based care providers can work with PLWHA, household members, and com-

munities to help them understand and anticipate the implications of ARVs on food and nutrition, identify options, and manage the economic, social and other constraints. It is critical for providers to follow up with PLWHA, elicit feedback about what has been effective and feasible, and facilitate adjustments as needed. Food and nutrition needs and drug-food interactions can vary between individuals, and appropriate responses must be designed to address individual experiences. Opportunities for such support may exist through home-based care, programs and facilities that provide ARVs, health and nutrition counseling sessions, health care services, PLWHA networks, or other interventions working with PLWHA and HIV/AIDS-affected households.

Some side effects of ARVs are similar to symptoms of opportunistic infections, such as diarrhea. Therefore, while nutritional management of drug side effects is important, one must continue to be alert to recognize symptoms of opportunistic infections and to treat these infections appropriately. Nutritional management of a given symptom is generally the same, whether it is caused by a medication side effect or by an opportunistic infection, but additional treatment will be required if an underlying infection or condition exists.

The special nutritional needs that HIV and opportunistic infections generate, combined with the food consumption constraints that symptoms create, make proper nutritional intake challenging for many PLWHA irrespective of ART, especially in resource limited settings. ARVs can significantly improve the health of those taking them but can also create additional food and nutrition needs and constraints for PLWHA.

3) Food Security Constraints to Management of Food-Drug Interactions

People living with HIV/AIDS in resource limited settings may often be unable to follow optimal food and nutrition recommendations for ARVs due to lack of access to the foods required. For example, PLWHA may

Suggested Steps for Service Providers to Support Dietary Management of Interactions between ARVs and Food and Nutrition

- 1. Identify the specific food and nutrition interactions** of the specific drugs and drug combinations the individual PLWHA is taking and identify the dietary needs that stem from these interactions. It is important to ensure that the PLWHA and primary caregivers understand the dietary implications of these interactions.
- 2. Identify available, accessible foods** that meet the nutritional needs the drugs call for, and identify those foods that are contraindicated by the drugs.
- 3. Plan a diet and a drug and meal timetable** that address the drug-food interactions and that meet the PLWHA's overall nutritional needs. The plan should account for food security and other constraints faced by the household and the PLWHA. Involve the PLWHA and caregiver in this planning process.
- 4. Follow up** to elicit feedback and assess whether the PLWHA is facing any difficulties in following the planned diet and timetable (due to food access, taste, or other reasons), and whether there have been any changes – positive or negative – in symptoms, side effects, or drug adherence.
- 5. Adjust** the planned diet and timetable if necessary, based on changed conditions or in order to make the plan more feasible in terms of food access, acceptability, quality, taste, or timing.

not be able to increase intake of foods rich in energy or specific micronutrients. For many households and communities affected by HIV/AIDS, food insecurity is caused or exacerbated by the economic impact of the disease, such as loss of earnings, depletion of assets and savings in order to pay for health care, or reduced household labor. In some cases the cost of accessing ARVs may itself increase PLWHA's food insecurity and reduce household resilience, as income used to purchase drugs reduces funds available to purchase adequate amounts of nutritious food.

Food insecurity limits the capacity of PLWHA to comply with special food requirements for ART, which can result in reduced drug efficacy, compromised drug regimen adherence, aggravated side effects, or a negative nutritional impact. While lack of information about drug-food interactions is a constraint that must be addressed, merely providing information about optimal food and nutrition responses is often insufficient to enable proper drug-food management by PLWHA. It is necessary to understand the specific constraints PLWHA face in accessing food and to help identify alternate, feasible options based on these constraints.

When recommended foods are not available or accessible due to economic, seasonal or other factors, it is important to find locally available substitutes. In food insecure situations it may be necessary to adopt second-best or third-best options such as identifying affordable foods that lack sufficient quantities of certain nutrients but that still provide more than the existing diet. If the schedules of other household members do not allow optimal frequency of feeding, it may be possible to develop a schedule that still enables greater frequency than usual for the PLWHA and includes meals with the medication as needed.

The process of involving PLWHA in identifying feasible dietary options can itself

contribute to maintaining adherence to drug regimens by generating ownership and interest in the continuation of ART. Health care workers, nutrition counselors, program functionaries, and other service providers can facilitate this process by ensuring full involvement of PLWHA in identifying options to manage drug-food interactions and in planning drug and food timetables.

While it is important to identify ways for food insecure PLWHA to effectively continue ART, the underlying food insecurity faced by HIV/AIDS-affected households and communities must also be recognized and addressed. Referrals and linkages should be developed between programs working with ART and nutrition and programs strengthening the food security and coping strategies of HIV/AIDS-affected households and individuals. In some cases, specific interventions such as food aid, fortification or supplements may be beneficial. For more information on mitigating the food security impacts of HIV/AIDS, refer to Bonnard, 2002.²¹

Adjusting household food expenditure patterns and intra-household food allocation can help enable improved management of ARV-food interactions. For example, households may be able to reallocate their food expenditures to increase purchase of foods rich in the nutrients that a specific drug requires. When intra-household food allocation patterns prevent PLWHA from accessing the quantity, quality, or frequency of food needed to manage drug-food interactions, facilitating changes in food allocation may be needed. Home-based care settings offer opportunities to support these types of adjustments.

Given the challenges that food insecurity poses to successful ART, planners of ART programs need to consider the food security situation of beneficiaries and what additional inputs may be required to address food security constraints.

Actions for ARV Program Designers and Managers

Programs and services that provide ARVs need to incorporate interventions that address the drugs' food and nutrition implications. These issues can also be addressed in programs that do not themselves provide ARVs but that work with PLWHA who are taking them, such as home-based care or health and nutrition education programs.

Key actions programmers can take include:

- Ensure the **human capacity** exists to address food and nutrition implications of the drugs the program offers. Human capacity constraints can be significant, and strengthening capacity will often be required to enable effective incorporation of nutrition issues. This may involve hiring staff knowledgeable in nutrition issues and food-drug interactions and/or training key personnel in management of the interactions and in providing appropriate counseling.
- Orient **front-line workers** about the food and nutrition implications of drugs the program offers and about appropriate responses and support to be provided to program participants. Supervision of front-line workers can also include these issues.
- Establish **links and referral systems** to other programs and services that address food and nutrition issues, as needed. For example, these may include food aid programs, services that strengthen household coping mechanisms or increase access to food, or nutrition counseling services.
- Include key information about drug-food interactions in **behavior change messages and communication materials**. Make information available in a form that is easy to understand and culturally appropriate. Program design should allow service providers to reinforce and follow up these messages at different points of interaction with PLWHA.

Knowledge Gaps

Issues related to interactions between ARVs and food and nutrition in resource limited settings are relatively recent, and there are a number of areas where further information is required.

Most research conducted on ARVs has involved well-nourished, food secure population groups, and recommendations are based on findings from these groups. Some food and nutrition implications for individuals with pre-existing malnutrition may differ. This relates both to drug efficacy and to nutrient absorption and metabolism. The effects of pre-existing malnutrition on the absorption and metabolism of ARVs are not fully known. If malnutrition adversely affects the efficacy of certain ARVs, specific nutritional responses may exist to mitigate these effects. Conversely, the impact of ARVs on the nutritional status of chronically malnourished individuals is also not fully known.

Since some ARVs can affect lipid metabolism, use of these drugs may have implications for the breastmilk composition of lactating women who take these drugs. Further research is needed on this subject, which is particularly relevant to resource limited settings, where many HIV-infected women breastfeed.²²

Additional information is also required about the interactions between ARVs and various traditional therapies commonly used by PLWHA. Given that many PLWHA use traditional therapies, greater understanding of the interactions between these therapies and ARVs will help to prevent adverse interactions and promote optimal drug efficacy.

Further research is needed about these issues, especially as access to ARVs continues to scale up in resource limited areas. Until additional findings emerge, service providers and counselors should guide PLWHA based on existing information and recommendations about ARV-food interactions and based on basic health and nutritional principles.

Considerations for Guidance on ARV-Food Interactions

In areas and programs in which people have access to ART, accurate and user-friendly guidance should be provided on the food and nutrition interactions of available ARVs. In addition to stand-alone information, guidance can be integrated into national guidelines, program materials, training curricula for counselors and service providers, and other types of materials.

Consideration of the questions listed below may help in developing guidance appropriate for a specific context or program:

- What ARVs are used in this context and what are the specific food interactions for these medications? Consider the four types of drug-food interactions (see Figure 1), and provide details on those that apply to ARVs in use.
- What are the nutritional implications of these interactions? How can these be managed through food and nutrition responses? To what extent are other responses, such as medical management, called for? Guidance can offer specific food and nutrition recommendations to manage specific interactions, as well as general recommendations about how to address nutritional implications through development of diet plans and drug-food timetables.

²² WHO recommends, "When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life. To minimize HIV transmission risk, breastfeeding should be discontinued as soon as feasible, taking into account local circumstances, the individual woman's situation and the risks of replacement feeding (including infections other than HIV and malnutrition)." Source: WHO. *New Data on the Prevention of Mother-to-Child Transmission of HIV and their Policy Implications: Conclusions and Recommendations*. Geneva, 2001.

- What food and nutrition recommendations are likely to present difficulties to population groups in this context due to food insecurity, food habits, or other reasons? If possible, identify the specific food security constraints most likely to pose problems. How can these constraints be addressed? What are alternative recommendations for these situations? What processes can be used by households, service providers, or counselors to identify feasible alternatives for food insecure PLWHA?
- Where is information available about food and nutrition implications of ARVs – both to periodically update guidance and to enable PLWHA and caregivers to access up-to-date information?
- What mechanisms can be used to elicit feedback from PLWHA on the effectiveness and feasibility of approaches and options and to incorporate this feedback into recommendations and guidance?
- How can nutritional management of non-ARV drugs and traditional therapies commonly taken by PLWHA be effectively included within the same guidance information?
- What channels exist to effectively disseminate information on ARV-food interactions? Who are the key target groups the guidance aims to reach (e.g., PLWHA, caregivers, service providers, counselors, trainers, and HIV/AIDS, health/nutrition, or agricultural extension programs)?
- How can key points be most effectively communicated in guidance? For instance, tables such as Table 3 can be an effective method to display the food and nutrition interactions of specific medications.

Conclusion

The capacity to effectively manage the food and nutrition implications of ART is a critical factor in the success of antiretroviral therapy in resource limited settings. Failure to address drug-food interactions can reduce drug efficacy, lead to poor adherence to drug regimens, aggravate side effects, or undermine the nutritional status of PLWHA. Increased access to ART in developing countries must be accompanied by measures to identify and enable feasible dietary responses to the drugs' interactions with food and nutrition. Policies, strategies, and programs involving ART should include mechanisms that provide information and guidance on drug-food interactions and that enable appropriate management of these interactions, especially in food insecure contexts.

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Websites with Information about Interactions between ARVs and Food and Nutrition

AIDS Info

www.aidsinfo.nih.gov

AIDSMeds.Com

www.aidsmeds.com

American Medical Association

www.ama-assn.org

Association of Nutrition Services Agencies (ANSA)

www.aidsnutrition.org

Clinical Infectious Diseases

www.journals.uchicago.edu/CID/journal/contents/v36nS2.html

The Cutting Edge

www.tceconsult.org

U.S. Food and Drug Administration

www.fda.gov

Food Medication Interactions

www.foodmedinteractions.com

Immunodeficiency Clinic - University Health Network of Toronto General Hospital

www.tthhivclinic.com

International Association of Physicians in AIDS Care

www.iapac.org

Johns Hopkins AIDS Service

www.hopkins-aids.edu

Medline Plus (U.S. National Library of Medicine and National Institutes of Health)

www.nlm.nih.gov/medlineplus

Medscape

www.medscape.com

World Health Organization

www.who.org



Food and Nutrition
Technical Assistance Project
Academy for Educational
Development
1825 Connecticut Ave., NW
Washington, DC 20009-5721
Tel: 202-884-8000
Fax: 202-884-8432
E-mail: fanta@aed.org
<http://www.fantaproject.org>

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