

Does Food Insecurity Undermine Adherence to Antiretroviral Therapy? A Systematic Review

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Abstract A growing body of research has identified food insecurity as a barrier to antiretroviral therapy (ART) adherence. We systematically reviewed and summarized the quantitative literature on food insecurity or food assistance and ART adherence. We identified nineteen analyses from eighteen distinct studies examining food insecurity and ART adherence. Of the thirteen studies that presented an adjusted effect estimate for the relationship between food insecurity and ART adherence, nine found a statistically significant association between food insecurity and sub-optimal ART adherence. Four studies examined the association between food assistance and ART adherence, and three found that ART adherence was significantly better among food assistance recipients than non-recipients. Across diverse populations, food insecurity is an important barrier to ART adherence, and food assistance appears to be a promising intervention strategy to improve ART adherence among persons living with HIV. Additional research is needed to determine the effectiveness and cost-effectiveness of food assistance in improving ART adherence and other clinical outcomes among people living with HIV in the era of widespread and long-term treatment.

Keywords Food insecurity · Food assistance · Antiretroviral therapy · Adherence · Review

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Introduction

Adherence to antiretroviral therapy (ART) is a primary determinant of HIV clinical outcomes [1–4]. Poor ART adherence is associated with virologic failure [2], CD4 decline [3], progression to AIDS [1], and increased mortality [4]. In addition to the clinical benefits of high levels of ART adherence for people living with HIV (PLHIV), ART dramatically reduces the likelihood of HIV transmission, underscoring the value of adherence for secondary prevention [5]. Despite the importance of high ART adherence, a meta-analysis found that the proportion of patients achieving adequate levels of ART adherence (as defined within each study) was 77 % in sub-Saharan Africa and 55 % in North America [6]. As the push for expanded access to HIV treatment intensifies under the new WHO treatment recommendations [7], it is essential to identify constraints to ART adherence and strategies to overcome them.

In qualitative data from resource-constrained settings, PLHIV have indicated lack of sufficient food or food insecurity as a reason for ART non-adherence due to the aggravation of side effects, increased hunger from treatment, and the inability to prioritize treatment among competing subsistence needs [8–10]. Food security “exists when all people, at all times, have physical and economic access to sufficient, safe and nutritious food to meet their dietary needs and food preferences for an active and healthy life” and is determined by adequate food availability, access, and utilization [11]. Food insecurity can manifest as inadequate intake of calories, poor diet quality and insufficient intake of diverse foods and nutrients required for a healthy life, and adverse psychosocial effects such as anxiety about the ability to find food [12]. Food insecurity is associated with adverse clinical outcomes

among PLHIV, including incomplete HIV RNA suppression [13–16], CD4 decline over time [17], lower body mass index [18], opportunistic infections [19], increased hospitalizations [19], worse health-related quality of life [19], and HIV-related mortality [20]. Food insecurity likely produces these adverse clinical outcomes among PLHIV through various pathways, such as adversely affecting a patient's nutritional status or mental health, and hindering adherence to ART and retention in care [21]. The extent to which food insecurity affects the health of PLHIV by impacting ART adherence has been increasingly explored in quantitative studies, but limited awareness of the breadth of this literature has precluded conclusions about the strength of this evidence or the consistency of the findings. In addition, food supplementation and livelihood support interventions are increasingly common among food-insecure HIV-infected populations [22–24]. Across 336 HIV care and treatment sites in nine sub-Saharan African countries, treatment for severe malnutrition and food rations were available at 36 and 31 % of sites, respectively [25]. Early data have suggested that food assistance may improve retention in care [23, 26], but the effect of such support on adherence to ART is poorly understood. As policymakers increasingly recommend food assistance as an important component of HIV care and as more resources are directed towards nutritional support for PLHIV [7], it is critical to understand the extent to which food insecurity is a barrier to ART adherence and if food assistance programs are effective in improving adherence. Thus, the purpose of this paper is to systematically review and summarize the evidence regarding the association between (1) food insecurity and ART adherence and (2) food assistance and ART adherence in order to better inform programmatic efforts.

Methods

Study Inclusion Criteria

Studies were included in the review if they examined the association between food insecurity and ART adherence or food assistance and ART adherence and presented or permitted calculation of an overall measure of association (e.g. risk ratio). This included studies that examined any measure of restricted food access or use, with the exception of medication-related food restrictions or instructions, or that assessed the influence of food rations or other types of food aid, with the exception of studies of micronutrient supplements as these have been summarized in another review [27] and were not considered a form of food assistance. Clinic- and community-based studies examining the influence of food insecurity or food supplementation on ART

adherence were eligible for inclusion regardless of whether other outcomes (e.g. CD4 count) were of primary interest. Adherence was conceptualized as daily compliance with prescribed medications, which we defined as distinct from missed clinic visits, treatment interruption greater than 3 months, or loss-to-follow-up and attrition. All adherence measurements, including self-report, unannounced or announced pill counts, pharmacy records and electronic medication monitoring, were acceptable for inclusion as were all adherence thresholds (i.e. >95, <90, <85, <80 % of prescribed doses or inadequate adherence according to missed doses). Qualitative studies, reviews or editorials, research published in abstract form only or that did not undergo peer review, studies examining adherence to pre- or post-exposure prophylaxis or prophylaxis for the prevention of mother-to-child transmission, and any studies that did not report a measure of association between food insecurity or food assistance and adherence were excluded. Methods for the review and inclusion criteria were specified in advance, with the following additional inclusion criteria specified after the full text review: (1) definition of treatment interruption as non-adherence for at least 3 months and exclusion of papers examining treatment interruption as the outcome, (2) exclusion of two papers identified in the search that compared adherence in two groups of wasted HIV patients receiving different types of food supplements [28, 29]; and (3) exclusion of studies identified in the search that evaluated combination support programs for PLHIV that included a nutritional component but did not present or permit estimation of the individual effect of food assistance distinct from the other services in the program [30–33]. Although we did not limit inclusion to adult populations, no studies examined the association between food insecurity and ART adherence in pediatric populations, and only one study examined the association between food assistance and adherence in a pediatric population [34], but was excluded because it did not specify the type of food assistance or the criteria for receiving such support.

Search Strategy

The review was conducted in accordance with PRISMA guidelines. We systematically searched PubMed/MEDLINE, Web of Science, PsychInfo, Sociological Abstracts, and EconLit from inception to August 15, 2013. We purposefully designed a broad search strategy to identify studies assessing the association between food insecurity and ART adherence or food assistance and ART adherence. There were no language or study design restrictions. Our search combined terms from broad categories of antiretroviral therapy, adherence, and food security and supplementation (see “Appendix” for full PubMed search

strategy). When available, we utilized the databases' controlled vocabulary or index (e.g., medical subject headings (MeSH)) as well as free text terms. In addition to food-related search terms (e.g. "food," "hunger," "nutrition"), we included search terms to identify papers examining a variety of adherence risk factors (e.g. "poverty," "barrier," "risk factors") as we anticipated that, in some manuscripts, food insecurity may be assessed as a covariate but not as the main exposure of interest. In these cases, when included as a covariate, we hypothesized that food insecurity would be unlikely to appear as a key word or in the title or abstract. After excluding papers by title and abstract review, we conducted a manual, full-text search of each potentially relevant article by searching for key terms related to food insecurity and food assistance such as "food," "hunger," "nutrition," "meal" or foreign language equivalents for articles written in French and Portuguese. In addition, we reviewed the reference list of all included studies for manuscripts that may have not been identified by our initial search strategy.

Data Abstraction and Analysis

From each study, we abstracted the following: date of publication, setting and timeframe of the study, sample size, measure of adherence, measure of food insecurity or food assistance, and the measure of effect for the association between food insecurity or food assistance and adherence. In order to better understand the intersection of food insecurity and poverty, we also abstracted any reported measure(s) of socioeconomic status (SES) (e.g. income, occupation, education) and whether SES was assessed as a confounder or effect modifier. Quality and risk of bias in individual studies was assessed by abstraction of the following indicators: clear description of the setting and study population, data measurement sources, study design, and other indicators of internal validity such as participation rate and sampling method. For intervention studies of food assistance, we paid particular attention to study design in order to assess internal validity. However, quality was not an inclusion criterion consistent with recommendations for systematic reviews and meta-analysis [35]. For the studies of food insecurity and ART adherence, we summarized measures of association with a forest plot and assessed the risk of bias by visual assessment of a funnel plot using STATA version 12 [36]. Due to the small number of intervention studies and the distinct measures of association, we were unable to create forest and funnel plots for the intervention studies on food assistance and ART adherence. Due to the variety of ART adherence thresholds and food insecurity or food assistance indicators, as well as significant variability in study populations

and geographic locations, a meta-analysis to produce a pooled measure of effect was not conducted.

Results

Search Yield

The database search produced 1,883 papers, of which 960 were excluded based on title alone and 554 were excluded based on abstract review (Fig. 1). Of the 369 remaining papers, 17 full-length papers were unable to be retrieved electronically but did not indicate by title or abstract that they included food insecurity or food assistance in their analyses. Overall, 352 full-length articles were searched for key terms related to food insecurity and food assistance.

Food Insecurity and ART Adherence

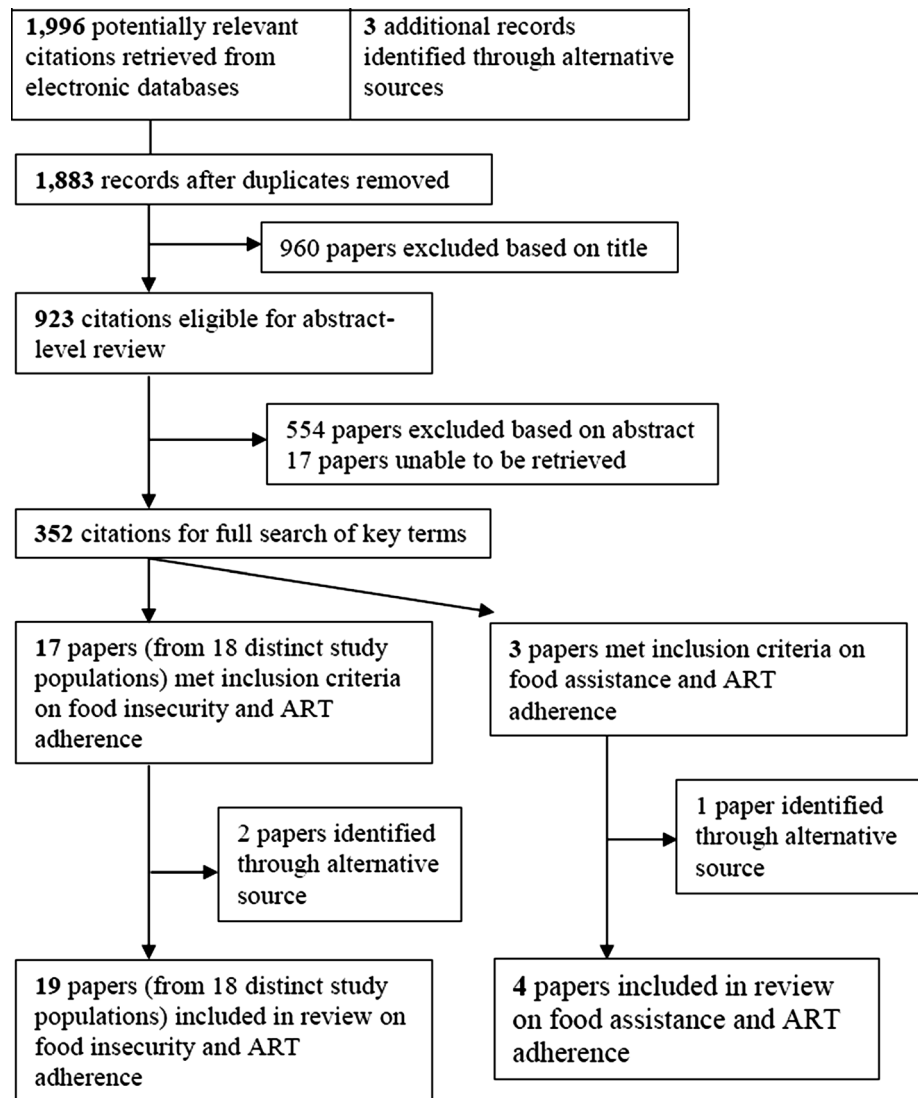
Seventeen papers, from sixteen distinct study populations, were identified as meeting the inclusion criteria for food insecurity and ART adherence through the electronic search. We were aware of two additional papers meeting inclusion criteria [37, 38] from a previous review on food insecurity and ART adherence [39] that were not identified through the database search. Two papers on food insecurity and ART adherence were from the same study [40, 41] presenting measures of association from overlapping samples of PLHIV, and both were included. Two additional papers were on sub-samples from a large survey population in Cameroon and both were included [42, 43]. In total, 19 papers from 18 distinct study populations met the inclusion criteria for food insecurity and ART adherence and are included in the review.

Food Assistance and ART Adherence

Of the 352 full-length articles searched for key terms, three papers met the inclusion criteria for food assistance and ART adherence. One additional paper not yet indexed in the included databases was identified through Google Scholar [44]. In total, four papers met the inclusion criteria for food assistance and ART adherence.

Characteristics of Food Insecurity Studies

The studies examining the association between food insecurity and ART adherence were carried out in diverse populations and geographic locations (Table 1). Twelve studies [13, 37, 38, 40–43, 45–49] were cross-sectional, five were prospective cohort studies [15, 16, 50–52], one was a retrospective cohort [53], and one was a case-control study [54]. One cross-sectional study [37] analyzed ART

Fig. 1 Systematic search results

adherence as the exposure and food insecurity as the outcome (the inverse of the pathway of interest); this study is included but cannot be directly compared to the other studies that examined food insecurity as the exposure of interest. Most studies used convenience or purposive samples; only five [13, 16, 38, 42, 43] used probability sampling and one [47] used administrative data. Of the eight studies that specified or allowed calculation of response rates, six [13, 15, 16, 42, 45, 50] had over 90 % participation.

Only three studies [13, 15, 16] used complete, validated food security scales to measure food insecurity whereas six studies [37, 40, 41, 46, 47, 53] used modified versions of validated food insecurity scales (i.e. the US Food Security Scale and the Radimer/Cornell Questionnaire) and two studies [50, 54] assessed food access with multiple questions that were not from validated scales (Table 2). The remaining eight studies [38, 42, 43, 45, 48, 49, 51, 52] used

single-question indicators of food access or number of meals consumed. Across the studies, food insecurity indicators had different recall periods (4 weeks/1 month, past year, or no time period specified) and used various terminology (e.g. “food insufficiency,” “hunger”) to refer to similar constructs. Measurement of ART adherence also varied; twelve studies used participant self-report, three [47, 50, 53] used pharmacy records, and four studies [13, 40, 41, 46] used unannounced pill counts to compute the ratio of pills counted relative to pills prescribed. The self-report assessments ranged from one to multiple questions or assessment by a visual analog scale and also had various recall periods.

Thirteen studies presenting the relationship between food insecurity and ART adherence adjusted for covariates, while six studies [13, 37, 43, 47, 49, 53] only presented an unadjusted measure of association. Studies adjusted for different sets of covariates, and most studies controlled for

Table 1 Characteristics of 18 observational studies (19 reports) examining the association between food insecurity and ART adherence and 4 observational studies examining the association between food assistance and ART adherence

Author/year	Type of study	Study size (N)	Location	Years	Sampling method	Response rate
<i>Food insecurity</i>						
Anema et al. [37]	Cross-sectional	457	British Columbia, Canada	2007–2008	Non-probability	Not specified
Anema et al. [47]	Cross-sectional	254	British Columbia, Canada	1998–2011	Administrative data	N/A
Berhe et al. [54]	Case-control	348	Ethiopia (urban and rural)	2012	Non-probability	Not specified
Birbeck et al. [50]	Prospective cohort	496	Zambia (rural)	2006–2008	Non-probability	>95 %
Boyer et al. [42]	Cross-sectional	2381	Cameroon (rural and urban)	2006–2007	Probability	96.6 %
Franke et al. [51]	Prospective cohort	134	Peru (urban)	2006–2009	Non-probability	Not specified
Gebo et al. [45]	Cross-sectional	196	Baltimore, MD	1999–2000	Non-probability	100 %
Kalichman et al. [40] ^a	Cross-sectional	344	Atlanta, GA	Jan 2008–Jun 2009	Non-probability	Not specified
Kalichman et al. [41] ^a	Cross-sectional	179	Atlanta, GA	Jan 2008–Jul 2009	Non-probability	Not specified
Kalichman and Grebler [46]	Cross-sectional	188	Atlanta, GA	Oct 2008–Aug 2009	Non-probability	Not specified
Kelly et al. [48]	Cross-sectional	374	Papua New Guinea (rural and urban)	2008	Non-probability	Not specified
Marcellin et al. [43]	Cross-sectional	533	Cameroon (urban)	2006	Probability	Not specified
Parashar et al. [53]	Retrospective cohort	212	British Columbia, Canada	2007–2010	Non-probability	Not specified
Peretti-Watel et al. [38]	Cross-sectional	1809	France	2003	Probability	59 %
Sasaki et al. [52]	Prospective cohort	157	Zambia (rural)	2010–2011	Non-probability	67 %
Van Dyk [49]	Cross-sectional	439	South Africa (rural and urban)	2008	Non-probability	Not specified
Weiser et al. [13]	Cross-sectional	104	San Francisco, CA	2006	Probability	100 %
Weiser et al. [15]	Prospective cohort	438	Uganda (rural)	2007–2010	Non-probability	100 % ^b
Weiser et al. [16]	Prospective cohort	284	San Francisco, CA	2007–2010	Probability	90 %
<i>Food assistance</i>						
Cantrell et al. [22]	Intervention cohort study	636 (Food group N = 442; Control N = 194)	Zambia	2004–2006	Enrolled all eligible participants	11 % withdrawn or lost at 12 months in food group; 7 % in control group ($p = 0.23$)
Posse et al. [44]	Retrospective intervention cohort study	357 (Food group N = 172; Control N = 185)	Mozambique	2007–2010	Probability	Not specified
Serrano et al. [57]	Intervention cohort study with a historical control group	180 (Food group N = 62; Control N = 118)	Niger	2005–2007	Non-probability	Not specified
Tirivayi et al. [56]	Retrospective intervention cohort study	291 (Food group N = 144; Control N = 147)	Zambia	2009–2010	Probability sample from 8 matched intervention and control clinics	109 patients (27 %) excluded due to insufficient laboratory or clinical data

^a These study samples overlap (per email communication with author, 02/15/2012). Kalichman and Grebler [46] is a distinct study^b Per communication with author, 11/24/2013

common confounders such as substance abuse, depression, and comorbidities. All thirteen studies that presented adjusted estimates considered confounding by SES in their analyses, with eight studies [15, 16, 38, 40, 41, 48, 50, 54] controlling for some measure of SES in their adjusted models (by inclusion of variables such as education, employment, income, household financial situation, and housing conditions). Five papers excluded a measure of SES from the final multivariable model either because it was determined not to be a confounder [42, 46, 51, 52] or because of collinearity with other variables in the model [45]. The funnel plot did not suggest that there was bias across studies of food insecurity and ART adherence, as most studies fell within or around the pseudo 95 % confidence intervals and were dispersed on both sides of the summary measure of association [55] (Fig. 2).

Association Between Food Insecurity and ART Adherence

Overall, of the thirteen studies that presented an adjusted effect estimate, ten found a statistically significant association between food insecurity and ART adherence (Table 2; Fig. 3). Nine of these studies found increased odds of ART non-adherence among food-insecure respondents. One study [52], conversely, found that food-insecure respondents were more likely to be adherent to ART in unadjusted and adjusted analyses. This association was based on reported food insufficiency in the 30 days prior to ART initiation. The investigators hypothesized that this positive association between food insufficiency at baseline and ART adherence at the end of the study period may be due to the possibility that participants reporting food insecurity at baseline were more likely to receive food assistance over the duration of the study from an external source, although the investigators were unable to validate this assumption. Finally, one study that did not find a statistically significant association between food insufficiency and ART adherence among the entire study population found that food insufficiency reduced the odds of perfect adherence (never missing a dose or having a late dose in the last week) compared to good adherence (having late doses but never missing a dose in the last week) when the analysis was restricted to adherent participants [48].

In order to take into account study design, we examined the results when stratified by type of study. Of the five prospective cohort studies, three found statistically significant increased odds of suboptimal ART adherence among persons reporting food insecurity [15, 16, 51], and one found a small and non-significant increased odds of suboptimal ART adherence among food-insecure persons [50]. One retrospective cohort study found reduced odds of ART

adherence among food-insecure, unstably-housed PLHIV in an unadjusted analysis but did not assess this relationship in multivariate analyses [53]. The single case-control study [54] found increased odds of suboptimal ART adherence among participants reporting that they were unable to get adequate or quality food or that they ate less than three meals a day.

Among the seven cross-sectional studies presenting adjusted measures of association, five found an association between food insecurity and ART non-adherence. The four cross-sectional studies that only presented unadjusted estimates found reduced odds of ART adherence among food-insecure respondents [13, 43, 47, 49]. Finally, one additional cross-sectional study examining the inverse pathway of interest found that respondents with self-reported adherence greater than at least 95 % of prescribed medications were less likely to be food-insecure in unadjusted analyses [37].

Characteristics of Food Assistance Studies

Four studies were identified that examined the effect of food assistance (i.e. food rations) on ART adherence (Table 1). All four studies were conducted in sub-Saharan Africa, and examined food supplementation programs compared to clinics or regions not receiving the programs. Food assistance consisted of monthly food rations (e.g. cereal, legume, soy, fortified vegetable oil) designed to meet either the individuals' or entire households' nutritional needs. Two studies in Zambia compared ART adherence among recipients of food aid compared to PLHIV who attended clinics not selected for food aid or that would not receive food aid until a later time (four intervention and four "control" clinics) [22, 56]. One study in Mozambique compared patients from Sofala Province selected to receive food assistance with patients not receiving food aid in the Zambezia region, where there was not a food assistance program at the time [44]. The study in Niger compared food aid recipients with a historical control group from the same clinic [57].

In order to assess how well comparison groups approximated the counterfactual, we examined the methods used to compare food recipients and non-recipients. Of the two studies comparing intervention and control clinics, one study assessed comparability of the food and control groups according to baseline characteristics [22] while the other study matched intervention clinics to control clinics on several criteria (active patient population, duration of operation, and historical patient survival) [56]. Two studies used propensity score matching to match food assistance recipients and non-recipients based on observed characteristics (gender, education, household size, etc.) and used difference in differences estimation to compare the change

Table 2 The unadjusted and adjusted associations between food insecurity or food assistance and ART adherence or non-adherence in studies included in the review

Author/year	Location (study population)	Exposure measurement	Outcome measurement	Unadjusted odds ratio	95 % CI	Adjusted OR	95 % CI	Assessed/adjusted for SES-related covariates?
<i>Food insecurity</i>								
Anema et al. [37]	British Columbia, Canada (Adult PLHIV)	ART adherence Self-reported adherence (yes vs. no), categorized as $\geq 95\%$ adherence and $< 95\%$ adherence within a one-month recall period	Food insecurity Modified eight-question version of the Radimer/Cornell questionnaire; categorized as food insecure if gave at least one positive answer (often/sometimes) to any question	0.41	(0.20–0.84)	N/A	N/A	N/A
Anema al. [47]	British Columbia, Canada (Adult HIV-positive injection drug users)	Food insecurity Abbreviated version of Radimer/Cornell scale; defined as food insecure if provided one positive answer to any of eight items measuring food insecurity	ART adherence Prescription refill compliance, defined as the number of days ART was dispensed over the number of days an individual was eligible for ART in past 12 months, at most recent date prior to survey ($\geq 95\%$ vs. $< 95\%$)	0.65	(0.37–1.12)	N/A	N/A	N/A
Berhe et al. [54]	Ethiopia (urban and rural) (Adult ART clinic patients)	Food insecurity Self-report questionnaire including items on ability to get enough and/or quality food; food consumption pattern of last 24 hours (greater or less than 3 meals); ability to afford balanced meals	Nonadherence to ART Self-report questionnaire and document review, defined as less than 95 % adherence due to missing doses completely or taking doses more than 2 hours outside of physician's recommendations	Unable to get enough or quality food: 2.6 Eating less than 3 meals: 8.8 Can't afford balanced meals: 2.7	(1.6–4.2) (3.5–22.2) (1.5–5.0)	2.1 10.9 2.0	(1.1–11.5) (1.3–81.4) (0.5–11.9)	Yes/Yes Education, average monthly income
Birbeck et al. [50]	Zambia (rural) (Adult ART clinic patients)	Food insecurity Four-question assessment of food access; categorized as food insecure if number of reported meals lower during "hunger" season compared to most of year	Nonadherence to ART Pharmacy records; lapses in drug acquisition resulting in greater than one week off ART categorized as "poor adherence"	1.68	(1.17–2.43)	1.08	(0.68–1.70)	Yes/Yes Years of education, wealth

Table 2 continued

Author/year	Location (study population)	Exposure measurement	Outcome measurement	Unadjusted odds ratio	95 % CI	Adjusted OR	95 % CI	Assessed/adjusted for SES-related covariates?
Boyer et al. [42]	Cameroon (rural and urban) (Adult HIV-positive hospital outpatients)	<2 meals/day Lack of access to regular meals (i.e. not being able to afford at least two meals a day)	Nonadherence to ART 14-question validated scale related to dose taking during the previous 4 days and the respect of the dosing time schedule during the previous 4 weeks; classified as “nonadherent” if had missed some doses during both the previous 4 days and 4 weeks	1.74	(1.39–2.17)	1.93	(1.44–2.57)	Yes/No Monthly household income, financial difficulties
Frankie et al. [51]	Peru (urban) (Adult PLHIV, some enrolled in a community-based ART adherence intervention)	Food insufficiency Single question assessment on frequency of inadequate food in household over previous month (never, sometimes, often or almost always)	ART interruption Respondents who interrupted treatment at least once for more than 2 consecutive days in the previous four weeks, compared to adherent respondents	1.35	(0.96–1.91)	N/A	N/A	N/A
Frankie et al. [51]	Peru (urban) (Adult PLHIV, some enrolled in a community-based ART adherence intervention)	Food insufficiency Single question assessment on frequency of inadequate food in household over previous month (never, sometimes, often or almost always)	Nonadherence to ART 30-day self-report tool adapted from the Adult AIDS Clinical Trials Groups (AACTG) tool; any month in which the patient reported taking <95 % of prescribed ART pills defined as suboptimal adherence	2.2	(1.3–3.8)	2.4	(1.4–4.1)	Yes/No Education level, employment, basic household services, passed a day without eating due to poverty
Gebo et al. [45]	Baltimore, MD (Adult HIV-positive urban hospital clinic attendees)	<2 meals/day Question(s) on ability to eat two or more meals a day	Nonadherence to ART Self-report questionnaire; adherence was defined as 90 % of doses taken and calculated as number of doses taken divided by number of doses prescribed over previous 2 week period	4.01	(1.44–11.14)	3.31	(1.11–9.92)	Yes/No Running out of money in past 90 days

Table 2 continued

Author/year	Location (study population)	Exposure measurement	Outcome measurement	Unadjusted odds ratio	95 % CI	Adjusted OR	95 % CI	Assessed/adjusted for SES-related covariates?
Kalichman, Cherry et al. [40]	Atlanta, GA (Adult PLHIV)	Food insufficiency	ART adherence	Not reported	Not reported	>80 % adherence: 0.3	>80 %: (0.1–0.8)	Yes/Yes
		Seven-item assessment adapted from the US Food Security Scale measuring food insecurity over the previous year.	Prospective unannounced telephone-based pill counts calculating the ratio of pills counted relative to pills prescribed per pharmacy records; adherence defined as 80 or 90 % of medications taken			>90 % adherence: 0.3	>90 %: (0.1–0.9)	Education, unemployment, income <\$1,000, unstable housing
Kalichman et al. [41]	Atlanta, GA (Adult PLHIV)	Hunger	ART adherence	Not reported	Not reported	1.01	(0.86–1.18)	Yes/Yes
		Four-item assessment adapted from the US Food Security Scale measuring food insecurity over the previous year	Prospective unannounced telephone-based pill counts calculating the ratio of pills counted relative to pills prescribed per pharmacy records; non-adherence defined as taking less than 85 % of medications					Education, employment
Kalichman & Grebler [46]	Atlanta, GA (Adult PLHIV with low literacy)	Poverty stressors	ART adherence	0.73	(0.62–0.86)	0.72	(0.59–0.89)	Yes/No
		Seven-item assessment adapted from the US Food Security Scale measuring food insecurity over the previous year, plus one question about housing access.	Prospective unannounced telephone-based pill counts calculating the ratio of pills counted relative to pills prescribed per pharmacy records; adherence defined as 85 % of medications taken in the month following baseline assessment					Income, employment, years education

Table 2 continued

Author/year	Location (study population)	Exposure measurement	Outcome measurement	Unadjusted odds ratio	95 % CI	Adjusted OR	95 % CI	Assessed/adjusted for SES-related covariates?
Kelly et al. [48]	Papua New Guinea (rural and urban) (PLHIV over 16 years of age)	Food insufficiency Question on having enough food to satisfy hunger asked only of participants reporting increased appetite; classified as having enough food or not having enough food	ART adherence Self-report questionnaire; classified as adherent (never missed a dose in the last week) or non-adherent (missed one or more doses in the last week) Adherent respondents were further classified into perfect adherence (never missed a dose or had a late dose in the last week) versus good adherence (having late doses but never missed a dose in the last week)	0.87 (N = 269, restricted to respondents reporting increased appetite)	(0.47–1.62)	1.49 (N = 367, included respondents reporting appetite unchanged or decreased)	(0.72–3.05)	Yes/Yes Employment type
Marcellin et al. [43]	Cameroon (urban) (Adult HIV-positive hospital outpatients)	<2 meals/day Self-reported consumption of at least two meals per day during previous 4 weeks	ART interruption Self-report of at least one treatment interruption longer than 2 days during the previous 4 weeks	1.75	0.98–3.14	N/A	N/A	N/A
Parashar et al. [53]	British Columbia, Canada (Adult unstably housed PLHIV)	Food insecurity Modified version of the Radimer/ Cornell questionnaire	ART adherence Percentage of prescription refill compliance, calculated as the number of days of antiretroviral medications dispensed, divided by the number of days of follow-up during the 12 months prior to interview date.	0.80	(0.38–1.66)	N/A	N/A	N/A
Peretti-Watel et al. [38]	France (Adult HIV-positive hospital outpatients)	Food privation Food privation in the household (i.e. whether or not a member of the household did not take any complete meal during a whole day due to lack of money during the prior four weeks)	Nonadherence to ART Four question assessment on dose-taking during the prior week; categorized as highly adherent versus non-adherent.	3.16 (men)* 1.69 (women)* 1.56 (men)** *heterosexual **homosexual	(1.71–5.88) (0.93–3.07) (0.86–2.83)	2.35 (men)* 1.30 (women)* N/A (men)**	(1.37–4.04) (0.72–2.35) N/A	Yes/Yes Yes/Yes N/A Financial situation of the household, housing conditions

Table 2 continued

Author/year	Location (study population)	Exposure measurement	Outcome measurement	Unadjusted odds ratio	95 % CI	Adjusted OR	95 % CI	Assessed/adjusted for SES-related covariates?
Sasaki et al. [52]	Zambia (HIV-positive clinic patients over 16 years of age newly registered for ART services)	Food insufficiency Single question assessment on frequency of inadequate food in household over previous month (never, sometimes, often or almost always)	ART adherence Self-report questionnaire item; full adherence defined as when a patient had never skipped prescribed drugs and had followed time restrictions during the 4 days prior to the interview	3.50 (N = 157)	(1.71–7.18)	5.00 (N = 96, explanation not provided for reduced sample size)	(1.81–13.76)	Yes/No Education, occupation
Van Dyk [49]	South Africa (Adult HIV-positive clinic or hospital patients)	Food insecurity 25-item scale on adherence barriers asked respondents to agree or disagree with the statement “I often do not have enough food to eat with those ARVs that must be taken with food”	ART adherence Self-reported adherence on a scale from 0 to 100 % in a typical month, classified as >90 % adherent, 70–90 % adherent, and <70 % adherent	0.45 (>90 adherence vs. ≤90 % adherence)	(0.29–0.70)	N/A	N/A	N/A
Weiser et al. [13]	San Francisco, CA (Homeless and marginally housed adult PLHIV)	Food insecurity Household Food Insecurity Access Scale, with scores ranging from 9 to 27; higher scores reflect more severe food insecurity	ART adherence Assessed by unannounced pill count and defined as less than 80 % adherence	0.39	(0.16–0.97)	N/A	N/A	N/A
Weiser, Palar et al. [15]	Uganda (rural) (Adult PLHIV)	Food insecurity Nine-item Household Food Insecurity Access Scale, classified as food secure versus food insecure	Nonadherence to ART Assessed quarterly by visual analog scale and defined as less than 90 % adherence over previous seven days	1.67	(1.23–2.26)	1.56	(1.10–2.20)	Yes/Yes Assessed only: education. Adjusted: employed, asset index.
Weiser, Yuan et al. [16]	San Francisco, CA (Homeless and marginally housed adult PLHIV)	Food insecurity Nine-item Household Food Insecurity Access Scale; individuals were categorized as food secure or food insecure (including mild, moderate, or severe food insecurity)	Nonadherence to ART Assessed by visual analog scale (VAS) and defined as less than 90 % adherence	1.60	(1.29–1.99)	1.48	(1.19–1.85)	Yes/Yes Assessed only: Education less than high school, income, uninsured. Adjusted: Living in shelter or on street.

Food assistance

Table 2 continued

Author/year	Location (study population)	Exposure measurement	Outcome measurement	Unadjusted odds ratio	95 % CI	Adjusted OR	95 % CI	Assessed/adjusted for SES-related covariates?
Cantrell et al. [22]	Zambia (Food-insecure PLHIV over 15 years of age enrolled in a home-based adherence support program)	Food assistance Monthly food rations provided by the World Food Program (WFP) to select clinics; program rolled out to control clinics 14 months later.	ART adherence Medication possession ratio (number of days late for pharmacy refills divided by the total days on therapy), adherence defined as $\geq 95\%$ MPR	Relative risk: 1.5	(1.2–1.8)	Relative risk: 1.5	(1.2–1.8)	No/No
Posse et al. [44]	Mozambique (Adult PLHIV)	Food assistance Monthly food rations provided by WFP for 3–9 months depending on nutritional improvement (soya, cowpeas, maize)	ART adherence Calculated gaps in medication coverage by comparing actual to scheduled pharmacy refill dates, dividing number of gaps by number of months (a higher score equates to lower adherence)	Mean difference in adherence score, before food assistance: 0.022 During: 0.045 Post: 0.07	<i>p</i> value: Before food assistance: 0.201 During: 0.029 Post: 0.001	Difference in differences with propensity score matching, during food assistance: 0.004 (6 months) –0.023 (12 months) After food assistance: 0.053 (6 months) 0.019 (12 months)	<i>p</i> value: During food assistance: 0.94 (6 months) 0.73 (12 months) After food assistance: 0.44 (6 months) 0.65 (12 months) N/A	Variables used to obtain the propensity score included education level
Serrano et al. [57]	Niger (ART treatment center patients with a CD4 cell count under 200/mm ³)	Food assistance Monthly food ration adequate to cover an entire family's nutritional needs (cereal, legume, fortified vegetable oil).	ART adherence Adherence was assessed by patient interviews, checking remaining tablets in ART boxes and clinical monitoring of adherence.	61/62 adherent in food group (98.4 %) vs. 82/106 (77.4 %) adherent in historical control group	<i>p</i> value: <0.005	N/A	N/A	N/A
Tirivayi et al. [56]	Zambia (Adult non-pregnant PLHIV)	Food assistance Monthly food rations provided by the World Food Program to select clinics (maize, vegetable oil, peas, corn and soy blend flour).	ART adherence Medication possession ratio (MPR), i.e. the total number of days the patient was late for pharmacy refills divided by the total days on ART during the study period.	Mean difference in MPR, without matching (intervention N = 133, control N = 147): 0.07 %	(–0.002, 1.4)	Mean difference in MPR with propensity score matching, i.e. average treatment effect on the treated (intervention N = 61, control N = 107): 9.5 %	(4.9, 14.0)	Variables used to obtain the propensity score included education, employment, asset and house ownership, and use of charcoal vs. electricity

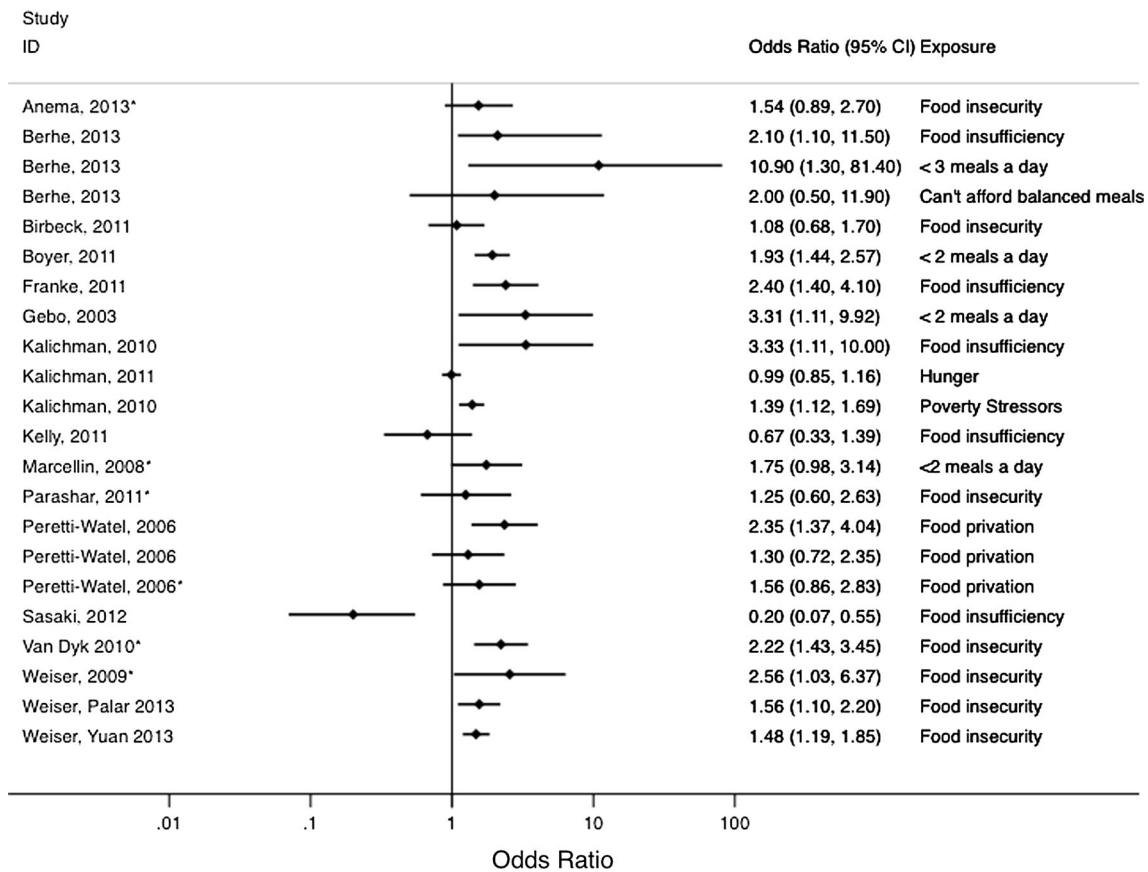


Fig. 2 Forest plot of measures of association between food insecurity and ART non-adherence. *Anema et al. [47], Marcellin et al. [43], Parashar et al. [53], Peretti-Watel et al. [38], Van Dyk [49], and Weiser et al. [13] presented unadjusted odds ratios. All other studies present adjusted odds ratios. Forest plot excludes Anema et al. [37] and includes multiple measures of association presented in the same study for Berhe et al. [54] and Peretti-Watel et al. [38] (see Table 2).

“Balanced meals” [54] was not defined. Poverty stressors [40] refers to a seven-item assessment adapted from the US Food Security Scale measuring food insecurity over the previous year, plus one question about housing access. Food privation [38] refers to whether or not a member of the household did not take any complete meal during a whole day due to lack of money during the prior 4 weeks

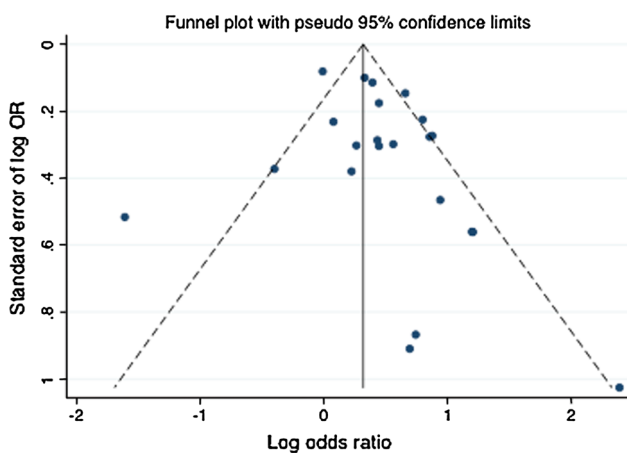


Fig. 3 Funnel plot of studies on food insecurity and ART non-adherence. Funnel plot excludes Anema et al. [37] and includes multiple measures of association presented in the same study for Berhe et al. [54] and Peretti-Watel et al. [38] (see Table 2)

in adherence over time for the food assistance recipients with the change in adherence over time for those who did not receive food aid by estimating the overall pre- and post-intervention difference between the two groups [44, 56].

Association Between Food Assistance and ART Adherence

In the Zambia study by Cantrell et al. which compared PLHIV in four clinics selected to receive food aid to PLHIV attending four clinics that did not receive food aid until a later time, patients in the food group were more likely to be adherent, defined as possessing their medication on at least 95 % of days during the first year of therapy, compared with those who did not receive food aid (RR = 1.5, 95 % CI (1.2–1.8) [22]. In another Zambia study, after propensity score matching of food recipients and non-recipients on socio-demographic characteristics, a greater proportion of food aid recipients had optimal

adherence compared to those who did not receive food aid after 6 months (98 vs. 89 %, $p < 0.01$) [56]. Likewise, in Niger, a greater proportion of PLHIV receiving food assistance were found to be adherent compared to a historical control group from the same clinic prior to the implementation of the food assistance program (98.4 vs. 77.4 %, $p < 0.005$) [57]. Finally, a retrospective study in Mozambique found no significant difference in ART adherence, measured as the number of times patients failed to collect their medication, among food assistance recipients and non-recipients residing in two separate provinces after 6 and 12 months [44].

Discussion

Over the past decade, the body of literature examining the relationship between food insecurity and ART adherence has expanded rapidly. Our review of this diverse literature found that food insecurity is an important barrier to ART adherence. Overall, the studies identified were conducted in very different geographic locations in both resource-rich and resource-poor countries, and both food insecurity and ART adherence were measured inconsistently across studies. However, there is a consistent negative association between food insecurity and ART adherence in all but three of the nineteen studies. In addition, three of four studies on food assistance found that food recipients were more adherent than non-recipients. These two lines of evidence buttress the growing body of qualitative evidence about the association between food insecurity, food assistance and adherence.

Nevertheless, weak study designs and inconsistent measurement limit our understanding of the causal relationship between food insecurity and ART adherence. Most of the studies to date are cross-sectional, precluding temporal or causal interpretation. However, four out of five longitudinal studies included in this review corroborated cross-sectional findings, suggesting that food insecurity may indeed lead to poor ART adherence. Furthermore, accurate measurement of both food insecurity and adherence is often inconsistent. All but seven of the food insecurity studies used self-reported ART adherence which may reflect only short-term or average adherence, or may overestimate adherence in comparison to more objective measurements such as pill counts, pharmacy data, or electronic medication monitoring [58–60]. Nine studies employed complete or modified validated food insecurity scales, while others used only single-question food insecurity indicators. Modified scales or single-question indicators may not adequately capture all aspects of food insecurity. Future research would benefit from more consistent indicators of food insecurity and distinct terms that

indicate which measure has been employed: for example, “food insecurity” may refer exclusively to the construct captured by validated scales (e.g. U.S. Household Food Security Survey or Household Food Insecurity Access Scale) measured minimally at baseline and endline, whereas “food access,” “food utilization,” and “food availability” could refer to specific dimensions of food insecurity captured by shorter scales or single questions. Future research should also use longitudinal study designs and objective measures of adherence such as electronic medication monitoring to better understand impacts of food insecurity on adherence. In addition, not all studies measured or adjusted for covariates that may be associated with both food insecurity and ART adherence, such as depression and substance abuse, which could lead to residual confounding. Although these study limitations preclude definitive causal conclusions, the consistency of the findings across studies employing diverse food insecurity and adherence measurements and adjusting for different sets of confounders bolsters confidence in the association between food insecurity and poor adherence.

The relationship between food insecurity and ART adherence is likely bidirectional [21, 39], complicating interpretation of the cross-sectional studies. Food insecurity may undermine adherence, and ART non-adherence may exacerbate food insecurity through worse health outcomes and limited ability to work. Indeed, antiretroviral therapy is a significant predictor of improved food security over time [61, 62]. In order to better elucidate the pathways through which food insecurity and ART adherence influence each other, future research would be strengthened by clearly documenting the time-ordering of food insecurity and adherence measures, explicitly assessing the relationships between food insecurity and SES measures to determine the overlap of these constructs [63], and considering alternative analytic methods such as the use of marginal structural models or targeted variable importance methods which can be used to rank factors according to their impact on health [64]. Additionally, adherence to ART is only one aspect of an HIV care continuum that includes HIV testing, successful linkage to care, ART initiation, and adherence to medications and maintenance of care [65, 66]. Although this review focused on ART adherence, other studies have found a relationship between food insecurity and retention in care [19, 23, 26]. Thus, future reviews should consider the possible effects of food insecurity across the entire spectrum of the HIV care continuum.

Studies examining the effect of food assistance on adherence to ART provide important additional evidence regarding the relationship between food security and ART adherence. Although our review only identified four studies quantitatively examining whether food assistance can

mitigate food insecurity and improve adherence, three of those studies found a positive association between food assistance and ART adherence. However, none of these intervention studies were randomized, which limits causal attribution. Randomized trials of food supplementation or other strategies to reduce food insecurity will provide valuable evidence for the benefits of improved food security on ART adherence and identify which types of support are best. Because ART must be continued for life, program evaluations that assess the long-term effectiveness of food assistance both for medication adherence as well as retention in care are critical to understanding strategies to mitigate the deleterious effects of food insecurity [67]. Although not included in our review, evidence indicating that food assistance increases adherence to clinic visits [23] suggests that food assistance may be used as an incentive to encourage patients to collect their medication [12, 68], and some argue that receipt of food support should be conditional upon both adherence to clinic visits and ART prescription refill compliance in order to optimize outcomes and increase sustainability. Though research on the role of conditional economic incentives in promoting ART adherence has been limited [68], additional studies are ongoing [69]. Food rations and livelihood support may be combined with other support services shown to improve adherence, such as treatment supporters, directly observed therapy, mobile-phone text messages, and diary cards [70], and such comprehensive treatment-support programs have been shown to increase ART adherence and retention [30, 31].

In conclusion, food security appears to influence ART adherence across different environments. In many of the studies reviewed here, food insecurity was associated with sub-optimal ART adherence even after controlling for SES and other factors known to influence adherence. Furthermore, food assistance was associated with improved adherence in three of the four intervention studies. The importance of food security for ART adherence is increasingly recognized by policymakers: for example, new WHO guidelines on the use of antiretroviral drugs identify nutritional support as a critical component of HIV care in food-insecure settings [7]. However, operations and feasibility assessments are required to determine the optimal policies about eligibility and targeting of food assistance or livelihood support and its duration: for example, food assistance may be targeted at alleviating malnutrition and severe illness among wasted PLHIV only, encouraging treatment adherence among patients initiating long-term antiretroviral therapy, or mitigating the more complex effects of food insecurity on HIV health outcomes among affected households and society as a whole [12]. These various scenarios have different implications for the resources required, types of food products needed, and dissemination strategies, and must be weighed against

alternate programs targeted to persons suffering from other illnesses with nutritional consequences and to healthy people struggling with food insecurity. Policy changes may also affect the implementation of food assistance or livelihood support programs: for example, as treatment eligibility criteria have been modified to encourage PLHIV to initiate ART at a CD4 count of 500 cells/mm³ or less [7], PLHIV starting treatment may be healthier and experience less severe food insecurity than in the past. Consequently, food and livelihood support programs may be more sustainable and less burdensome for the healthcare system in a setting of lower need. Furthermore, while several studies have examined the effect of food and nutrient supplementation on clinical outcomes such as viral load and CD4 count [71–73], much of this research was carried out before widespread and long-term use of ART. There is less understanding of the effects of food assistance on HIV virologic and immunologic outcomes and mortality among individuals on ART. Prospective studies examining the impact of food assistance that consider disease stage, duration of treatment, and adherence are needed to determine the extent to which food assistance improves clinical outcomes beyond ART alone. As the push for greater HIV treatment coverage intensifies, and with PLHIV remaining on ART for longer and longer durations of time, further examination of the impact of food insecurity on ART adherence is essential to understand ways to intervene to support PLHIV in maximizing treatment benefits and living longer and healthier lives.

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Appendix

Full PubMed Search strategy: (“Antiretroviral Therapy, Highly Active”[Mesh] OR “HIV Infections/drug therapy”[Mesh] OR “Anti-HIV Agents/therapeutic use”[Mesh] OR “Acquired Immunodeficiency Syndrome/drug therapy”[Mesh] OR antiretroviral OR HAART OR ART) AND (“Patient Compliance”[Mesh] OR “Medication adherence”[Mesh] OR adherence OR nonadherence OR non-adherence) AND (“Food Supply”[Mesh] OR food OR hunger OR “Socioeconomic factors”[Mesh] OR “risk factors” OR poverty OR barrier OR nutrition OR malnutrition).

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