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# Dietary practices, obesity and CD4 count among adults with HIV on antiretroviral therapy in Johannesburg, South Africa: a secondary cross-sectional analysis of the ADVANCE trial

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**Additional Declarations:** No competing interests reported.

# Abstract

**Background:** The substantial weight gain observed in the ADVANCE trial has raised important questions about the factors contributing to obesity among people receiving ART. While dietary practices may play a role, evidence from South African cohorts remains limited. The dietary assessments collected during the ADVANCE extension offered an opportunity to examine whether selected dietary behaviours were associated with obesity and CD4 count in a well-characterised cohort of adults receiving long-term ART.

**Methods:** We performed a secondary cross-sectional analysis of food-intake assessments from the ADVANCE extension. The supplied export contained 1393 diary records from 618 unique participants. To avoid treating repeated records as independent observations, one index record per participant was defined as the earliest available scheduled food-diary assessment and, within that visit, the earliest dated diary. Obesity was defined as body mass index (BMI) ≥30 kg/m². CD4 count <500 cells/μL was analysed as a pragmatic marker of lower current CD4 count, not as a diagnostic definition of immune suppression. Dietary frequencies were collapsed a priori into clinically interpretable categories. Separate logistic regression models were adjusted for age, sex, country of birth, employment, index visit and ART regimen, with Benjamini–Hochberg false-discovery-rate correction across exposure contrasts.

**Results:** Mean age was 33.7 years (SD 7.5), 56.1% were female, 27.7% had obesity and 40.8% had CD4 count <500 cells/μL. Nominal associations with obesity included reporting a special diet (adjusted odds ratio [aOR] 4.37, 95% CI 1.19–16.01; p=0.026), fruit intake 1–3 times/week versus <1/week (aOR 0.45, 95% CI 0.21–0.96; p=0.038), and EFV+TDF+FTC versus DTG+TAF+FTC (aOR 0.55, 95% CI 0.34–0.90; p=0.018). DTG+TDF+FTC versus DTG+TAF+FTC was nominally associated with CD4 count <500 cells/μL (aOR 1.56, 95% CI 1.03–2.35; p=0.035). None of the 18 exploratory contrasts for either outcome remained significant after false-discovery-rate correction (all q≥0.228 for obesity and q≥0.629 for CD4).

**Conclusions:**

Despite the high prevalence of obesity in this treated cohort, the dietary practices assessed were not independently associated with obesity or lower CD4 cell counts after adjustment for multiple comparisons.

The nominal special-diet and fruit findings should be interpreted cautiously because of sparse exposure, possible reverse causation and lack of a dose-response pattern. Prospective studies with quantitative dietary assessment, energy intake, physical activity and food-security measures are needed.

**Trial registration:** ClinicalTrials.gov NCT03122262; first posted 20 April 2017 (retrospectively registered relative to study start).


# Background

Expanded access to effective ART has substantially improved survival among people with HIV in South Africa, shifting a growing share of long-term morbidity toward non-communicable diseases [1]. Obesity

is now a major component of this burden. A systematic review and meta-analysis of South African studies estimated an overall obesity prevalence of 23.2% among people with HIV, with a higher burden among women [2].

ART regimen can also influence weight trajectories. In ADVANCE, participants were randomized to dolutegravir (DTG)+tenofovir alafenamide (TAF)+emtricitabine (FTC), DTG+tenofovir disoproxil fumarate (TDF) + FTC, or efavirenz (EFV) + TDF+FTC [3, 4]. The 192-week analysis confirmed greater mean weight gain in the DTG + TAF+FTC arm than in the other two arms, with particularly marked gain among women [5]. Observational and secondary analyses in South Africa further link DTG-associated weight gain with incident hypertension and related cardiometabolic concerns [6, 7].

Diet is an important, potentially modifiable determinant of body weight, yet detailed evidence among South African adults with HIV remains limited. In a Cape Town cohort, ART-experienced adults reported low dietary diversity and modest physical activity [8]. A more recent Cape Town study found suboptimal diet quality across BMI categories [9]. In the wider South African population, high consumption of ultra-processed foods and poor compliance with dietary recommendations have also been documented [10]. Mechanistic and epidemiological reviews support an association between ultra-processed food consumption and obesity, while emphasizing the importance of both nutrient profile and food processing [11, 12].

Nutrition is an important contributor to immune function in people living with HIV. Previous studies have shown that poor dietary intake and micronutrient deficiencies may adversely affect CD4 recovery and overall health outcomes, even in the ART era. Understanding dietary practices may therefore provide additional insight into factors associated with both obesity and immune status among adults receiving long-term ART.

The present study therefore aimed to describe dietary practices among adults with HIV participating in the ADVANCE extension and to examine their cross-sectional associations with obesity and with CD4 count < 500 cells/μL. Because a CD4 threshold of 500 cells/μL does not by itself define clinical immune suppression in a treated population, we interpret this outcome as a marker of lower current CD4 count and avoid causal or diagnostic language. Prior work in sub-Saharan Africa demonstrates that immune recovery despite virological suppression is heterogeneous and influenced by multiple clinical factors [13].

## Methods

# Study design, setting and parent trial

This was a secondary cross-sectional analysis nested within the ADVANCE trial and its extension. ADVANCE was an investigator-led, open-label, randomized phase 3 non-inferiority trial conducted in Johannesburg, South Africa. The parent trial compared DTG + TAF+FTC, DTG + TDF+FTC and EFV + TDF+FTC as first-line ART [3, 4]. Participants who continued into the extension were followed to week

192, with food-intake assessment/diary collection incorporated into extension visits. The final parent-trial safety and efficacy results have been reported [5].

## Analytic population and index food-diary record

The raw food-diary export supplied for this analysis contained 1393 records from 618 unique participants, spanning scheduled visits at weeks 120, 144, 168 and 192. Repeated records were present both across visits and, for some participants, within the same scheduled visit. Within-visit repeats most likely reflect duplicate diary entries logged on separate clinic-attendance days during an extended visit window, or minor data-entry corrections, rather than deliberately repeated dietary assessments designed to capture within-visit variability; the instrument was not intended for repeated same-visit sampling. To avoid pseudoreplication in a cross-sectional analysis, we retained one observation per participant: the earliest scheduled trial visit with an available food-intake assessment, and the chronologically earliest diary record within that visit. This yielded 618 unique participants. Index assessments occurred at week 120/144 for 362 participants (58.6%), week 168 for 222 (35.9%) and week 192 for 34 (5.5%). The index diary dates ranged from 1 June 2020 to 18 November 2021. Weeks 120 and 144 were combined for reporting because only one participant's index assessment fell at week 120; this single record was grouped with the week 144 stratum to avoid an uninformative single-participant category rather than because the two visits were considered clinically equivalent. All regression models adjusted for index visit as a categorical covariate, so any residual difference between the week 120 and week 144 assessments for this one participant is accounted for in the adjusted estimates.

No participant was classified by HIV serostatus using the plasma HIV-1 RNA result. All members of the ADVANCE cohort had documented HIV-1 infection; plasma HIV-1 RNA was an efficacy laboratory measure in the parent trial [3, 16]. This distinction was important because “Not detected” in the viral-load field denotes virological suppression, not absence of HIV infection.

## Dietary assessment and exposure definitions

The extension food-intake assessment was an interviewer-administered structured questionnaire completed by trial-site staff at scheduled clinic visits, captured in the trial's electronic case-report form, rather than a self-administered paper diary. The extension food-intake assessment recorded whether participants followed a special diet, used vitamin or mineral supplements, skipped meals almost every day, added salt during cooking, added salt/Aromat/sauces at the table and added sugar to tea or coffee. It also recorded frequency of fried food, takeaway/fast food, pap, fruit and vegetable consumption. These variables were self-reported and represent dietary practices rather than quantitative nutrient intake.

To reduce sparse cells and unstable estimates, frequency responses were collapsed a priori to < 1 time/week (including never, rarely and 2–3 times/month), 1–3 times/week, and ≥ 4 times/week

(including 4–6 times/week, daily and 2–3 times/day). Salt during cooking was grouped as always versus not always (sometimes, never or do not know). Meal skipping was grouped as any meal versus none. For pap, a blank frequency response accompanied by an unchecked pap-selection field was classified as < 1 time/week; one record that could not be classified was treated as missing.

## Outcomes and covariates

BMI was calculated as weight in kilograms divided by height in metres squared. BMI categories were underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²) and obesity (≥ 30.0 kg/m²). Height, weight and CD4 count were recorded as part of the same scheduled-visit record as the index food-diary assessment; because these measures were captured at the same clinic encounter rather than a separate visit, no additional date-matching window was required or applied. Obesity was the primary binary outcome. The secondary outcome was CD4 count < 500 cells/μL, used as a pragmatic marker of lower current CD4 count rather than a definition of clinical immune suppression. CD4 count was dichotomized at 500 cells/μL, rather than analysed only as a continuous variable, because this threshold gives a single, clinically interpretable comparison that is directly comparable across the 18 exposure contrasts and consistent with commonly used programmatic thresholds; it was not chosen because CD4 count is normally distributed above or below this cut-point. To assess whether dichotomization affected our conclusions, we additionally fitted a sensitivity analysis modelling CD4 count as a continuous outcome (linear regression) using the identical covariate adjustment; results are reported alongside the primary CD4 findings (Additional file 1: Table S1).

Covariates were age (modelled per 10-year increase), sex, country of birth (South Africa, Zimbabwe or other), employment (employed/self-employed versus not employed/schooling), index trial visit and randomized ART regimen. Descriptive analyses also included marital status and educational attainment. Pre-ART (parent-trial baseline) BMI and CD4 count, which are strong predictors of current BMI and CD4 count respectively, were not available in the supplied food-diary export and could therefore not be included as covariates in the obesity and CD4 models; this is noted as a limitation below.

# Statistical analysis

Continuous variables were summarized using mean and standard deviation (SD), and CD4 count was additionally summarized using median and interquartile range (IQR). Categorical variables were summarized as counts and percentages using non-missing observations as denominators. No a priori sample-size calculation was performed because the analytic sample comprised all unique participants represented in the supplied food-diary export.

For each dietary exposure, we fitted a separate logistic regression model for obesity and a separate model for CD4 count < 500 cells/μL. Models were adjusted a priori for age, sex, country of birth, employment, index visit and ART regimen. When ART regimen itself was the exposure, regimen was omitted from the adjustment set. Analyses used complete cases; model sample size was 614 for most

comparisons and 613 for pap frequency. We report adjusted odds ratios (aORs), 95% confidence intervals (CIs), nominal p values and Benjamini–Hochberg false-discovery-rate q values calculated across 18 exposure contrasts separately for each outcome [14]. Nominal $p < 0.05$ was treated as exploratory; $q < 0.05$ was the threshold for evidence robust to the planned multiplicity correction. No post-hoc variable selection was used. Two pre-specified sensitivity analyses are reported as additional files: CD4 count modelled as a continuous outcome by linear regression (Additional file 1: Table S1), and likelihood-ratio tests of exposure-by-sex interaction for both outcomes across all 18 contrasts, with joint Benjamini–Hochberg correction across the resulting 24 interaction tests (Additional file 2: Table S2; Additional file 3: Table S3).

The data audit and revised analyses were executed in Python 3.13.5 using pandas 2.2.3, stats models 0.14.6, SciPy 1.17.0 and NumPy 2.3.5. Reporting was guided by the STROBE recommendations for observational studies [15]; a completed STROBE checklist for cross-sectional studies, indicating where each item is reported in this manuscript, is provided as a supplementary reporting checklist.

# Use of generative AI-assisted technology

A large language model based assistant was used to support literature synthesis, review of the supplied analysis code, editing of text, as well as fact checking, during formatting and preparation of this manuscript. All AI-assisted outputs were reviewed, fact checked against source literature and edited by authors.

## Ethics approval

The ADVANCE study was conducted in accordance with the Declaration of Helsinki and was approved by the University of the Witwatersrand Human Research Ethics Committee (reference 160606B), the South African Health Products Regulatory Authority (reference 20160620) and relevant local authorities. Participants provided written informed consent for the parent study. This secondary analysis used existing study data.

## Results

# Participant characteristics

The analytic sample included 618 unique adults with HIV. Mean age was 33.7 years (SD 7.5; range 19–62 years) and 347 (56.1%) were female. Mean BMI was 26.8 kg/m² (SD 6.2); 174 participants (28.2%) were overweight and 171 (27.7%) had obesity. Most participants were single (71.0%), 57.3% were born in South Africa and 38.0% in Zimbabwe. Among 614 participants with employment data, 71.0% were employed or self-employed. The median CD4 count was 543 cells/μL (IQR 390–719), and 252 participants (40.8%) had CD4 count < 500 cells/μL (Table 1).

Table 1
Participant characteristics at the index food-diary assessment

| Characteristic | Frequency | Non-missing n |
|---|---|---|
| **Age, years, mean (SD)** | 33.7 (7.5) | 618 |
| **Age group** | | 618 |
| 18–29 | 189 (30.6%) | 618 |
| 30–39 | 301 (48.7%) | 618 |
| 40–49 | 109 (17.6%) | 618 |
| ≥50 | 19 (3.1%) | 618 |
| **Sex** | | 618 |
| Female | 347 (56.1%) | 618 |
| Male | 271 (43.9%) | 618 |
| **Body mass index, kg/m², mean (SD)** | 26.8 (6.2) | 618 |
| **Body mass index category** | | 618 |
| Underweight | 26 (4.2%) | 618 |
| Normal | 247 (40.0%) | 618 |
| Overweight | 174 (28.2%) | 618 |
| Obese | 171 (27.7%) | 618 |
| **Marital status** | | 618 |
| Single | 439 (71.0%) | 618 |
| Married | 116 (18.8%) | 618 |
| Other | 63 (10.2%) | 618 |
| **Country of birth** | | 618 |
| South Africa | 354 (57.3%) | 618 |
| Zimbabwe | 235 (38.0%) | 618 |
| Other | 29 (4.7%) | 618 |
| **Employment** | | 614 |
| Employed/self-employed | 436 (71.0%) | 614 |

Values are n (%) unless otherwise indicated. Percentages use non-missing values as denominators. BMI, body mass index; IQR, interquartile range; SD, standard deviation.

| Characteristic | Frequency | Non-missing n |
|---|---|---|
| Not employed/schooling | 178 (29.0%) | 614 |
| **Education** | | 616 |
| No schooling | 3 (0.5%) | 616 |
| Primary | 46 (7.5%) | 616 |
| Secondary | 526 (85.4%) | 616 |
| Tertiary | 41 (6.7%) | 616 |
| **ART regimen** | | 618 |
| DTG + TAF+FTC | 229 (37.1%) | 618 |
| DTG + TDF+FTC | 209 (33.8%) | 618 |
| EFV + TDF+FTC | 180 (29.1%) | 618 |
| **Index food-diary trial visit** | | 618 |
| Week 120/144 | 362 (58.6%) | 618 |
| Week 168 | 222 (35.9%) | 618 |
| Week 192 | 34 (5.5%) | 618 |
| **CD4 count, cells/μL, mean (SD)** | 578.5 (250.5) | 618 |
| **CD4 count, cells/μL, median (IQR)** | 543 (390–719) | 618 |
| **CD4 count < 500 cells/μL** | | 618 |
| No | 366 (59.2%) | 618 |
| Yes | 252 (40.8%) | 618 |

Values are n (%) unless otherwise indicated. Percentages use non-missing values as denominators. BMI, body mass index; IQR, interquartile range; SD, standard deviation.

*[Insert* Table 1 *here]*

# Dietary practices

Only 14 participants (2.3%) reported following a special diet, whereas 309 (50.0%) reported vitamin or mineral supplement use. Meal skipping almost every day was reported by 272 (44.0%). Salt was always added during cooking by 515 (83.3%), and 246 (39.8%) added salt, Aromat or sauce at the table. Most participants reported pap at least four times per week (406/617, 65.8%), fruit at least four times per week (375/618, 60.7%) and vegetables at least four times per week (420/618, 68.0%). Sugar was added to tea or coffee by 560 participants (90.6%) (Table 2).

Table 2
Dietary practices at the index food-diary assessment

| Dietary practice | Category | n (%) | Non-missing n |
|---|---|---|---|
| Special diet | No | 604 (97.7%) | 618 |
| | Yes | 14 (2.3%) | 618 |
| Vitamin/mineral supplement | No | 309 (50.0%) | 618 |
| | Yes | 309 (50.0%) | 618 |
| Meal skipping almost every day | None | 346 (56.0%) | 618 |
| | Any meal | 272 (44.0%) | 618 |
| Salt added during cooking | Always | 515 (83.3%) | 618 |
| | Not always | 103 (16.7%) | 618 |
| Salt/Aromat/sauce added at table | No | 372 (60.2%) | 618 |
| | Yes | 246 (39.8%) | 618 |
| Fried food frequency | < 1/week | 171 (27.7%) | 618 |
| | 1–3/week | 298 (48.2%) | 618 |
| | ≥ 4/week | 149 (24.1%) | 618 |
| Take-away/fast-food frequency | < 1/week | 408 (66.0%) | 618 |
| | 1–3/week | 151 (24.4%) | 618 |
| | ≥ 4/week | 59 (9.5%) | 618 |
| Pap frequency | < 1/week | 39 (6.3%) | 617 |
| | 1–3/week | 172 (27.9%) | 617 |
| | ≥ 4/week | 406 (65.8%) | 617 |
| Fruit frequency | < 1/week | 59 (9.5%) | 618 |
| | 1–3/week | 184 (29.8%) | 618 |
| | ≥ 4/week | 375 (60.7%) | 618 |
| Vegetable frequency | < 1/week | 32 (5.2%) | 618 |
| | 1–3/week | 166 (26.9%) | 618 |
| | ≥ 4/week | 420 (68.0%) | 618 |

Frequency categories were collapsed a priori to reduce sparse cells. “<1/week” includes never, rarely and 2–3 times/month; “≥4/week” includes 4–6 times/week, daily and 2–3 times/day. Pap frequency had one missing observation.

| Dietary practice | Category | n (%) | Non-missing n |
|---|---|---|---|
| Adds sugar to tea/coffee | No | 58 (9.4%) | 618 |
| | Yes | 560 (90.6%) | 618 |

Frequency categories were collapsed a priori to reduce sparse cells. “<1/week” includes never, rarely and 2–3 times/month; “≥4/week” includes 4–6 times/week, daily and 2–3 times/day. Pap frequency had one missing observation.

*[Insert* Table 2 *here]*

# Associations with obesity

In adjusted models, three contrasts had nominal $p < 0.05$. Participants reporting a special diet had higher odds of obesity than those not reporting a special diet (aOR 4.37, 95% CI 1.19–16.01; $p = 0.026$), but only 14 participants were in the exposed category, and the confidence interval was wide. Fruit consumption 1–3 times/week versus < 1 time/week was associated with lower odds of obesity (aOR 0.45, 95% CI 0.21–0.96; $p = 0.038$), whereas fruit consumption ≥ 4 times/week was not (aOR 0.90, 95% CI 0.46–1.76; $p = 0.749$), providing no evidence of a monotonic frequency-response relationship. Participants randomized to EFV + TDF+FTC had lower odds of obesity than those randomized to DTG + TAF+FTC (aOR 0.55, 95% CI 0.34–0.90; $p = 0.018$). None of these findings remained significant after false-discovery-rate correction; the smallest q value was 0.228 (Table 3).

Table 3
Adjusted associations with obesity

| Exposure | Comparison | Model n | aOR (95% CI) | p | BH q |
|---|---|---|---|---|---|
| Special diet | Yes vs No | 614 | 4.37 (1.19–16.01) | 0.026 | 0.228 |
| Vitamin/mineral supplement | Yes vs No | 614 | 1.00 (0.58–1.71) | 0.996 | 0.996 |
| Meal skipping almost every day | Any meal | 614 | 1.07 (0.71–1.60) | 0.751 | 0.845 |
| Salt added during cooking | Not always vs Always | 614 | 1.29 (0.77–2.16) | 0.327 | 0.655 |
| Salt/Aromat/sauce added at table | Yes vs No | 614 | 1.36 (0.90–2.05) | 0.140 | 0.421 |
| Fried food frequency | 1–3/week vs < 1/week | 614 | 1.20 (0.74–1.95) | 0.456 | 0.747 |
| | ≥ 4/week vs < 1/week | 614 | 0.82 (0.46–1.49) | 0.518 | 0.777 |
| Take-away/fast-food frequency | 1–3/week vs < 1/week | 614 | 1.12 (0.69–1.81) | 0.649 | 0.835 |
| | ≥ 4/week vs < 1/week | 614 | 0.91 (0.40–2.04) | 0.812 | 0.860 |
| Pap frequency | 1–3/week vs < 1/week | 613 | 0.81 (0.36–1.83) | 0.615 | 0.835 |
| | ≥ 4/week vs < 1/week | 613 | 0.49 (0.22–1.08) | 0.076 | 0.273 |
| Fruit frequency | 1–3/week vs < 1/week | 614 | 0.45 (0.21–0.96) | 0.038 | 0.228 |
| | ≥ 4/week vs < 1/week | 614 | 0.90 (0.46–1.76) | 0.749 | 0.845 |
| Vegetable frequency | 1–3/week vs < 1/week | 614 | 0.54 (0.20–1.44) | 0.215 | 0.484 |
| | ≥ 4/week vs < 1/week | 614 | 0.66 (0.26–1.66) | 0.373 | 0.671 |

Each exposure was fitted in a separate logistic regression model. Models were adjusted for age (per 10 years), sex, country of birth, employment, index visit and ART regimen; regimen models omitted ART regimen from the adjustment set. BH q values are Benjamini–Hochberg false-discovery-rate adjusted across the 18 displayed contrasts. No q value was < 0.05. aOR, adjusted odds ratio; CI, confidence interval.

| Exposure | Comparison | Model n | aOR (95% CI) | p | BH q |
|---|---|---|---|---|---|
| Adds sugar to tea/coffee | Yes vs No | 614 | 0.64 (0.33–1.25) | 0.190 | 0.484 |
| ART regimen | DTG + TDF+FTC vs DTG + TAF+FTC | 614 | 0.64 (0.40–1.02) | 0.059 | 0.266 |
| | EFV + TDF+FTC vs DTG + TAF+FTC | 614 | 0.55 (0.34–0.90) | 0.018 | 0.228 |

Each exposure was fitted in a separate logistic regression model. Models were adjusted for age (per 10 years), sex, country of birth, employment, index visit and ART regimen; regimen models omitted ART regimen from the adjustment set. BH q values are Benjamini–Hochberg false-discovery-rate adjusted across the 18 displayed contrasts. No q value was < 0.05. aOR, adjusted odds ratio; CI, confidence interval.

Other dietary practices, including supplement use, meal skipping, salt use, fried-food frequency, takeaway/fast-food frequency, pap frequency, vegetable frequency and adding sugar to tea or coffee, were not associated with obesity after adjustment for the prespecified covariates (Table 3).

*[Insert* Table 3 *here]*

# Associations with CD4 count below 500 cells/μL

No dietary-practice contrast had a nominal $p < 0.05$ in adjusted models of CD4 count < 500 cells/μL. DTG + TDF+FTC, compared with DTG + TAF+FTC, was nominally associated with higher odds of CD4 count < 500 cells/μL (aOR 1.56, 95% CI 1.03–2.35; $p = 0.035$), but this did not remain significant after false-discovery-rate correction ($q = 0.629$). EFV + TDF+FTC was not associated with the CD4 outcome (aOR 1.26, 95% CI 0.82–1.94; $p = 0.286$). Across all 18 contrasts, no q value was < 0.05 (Table 4). In a pre-specified sensitivity analysis modelling CD4 count as a continuous outcome (linear regression) with identical covariate adjustment, results were consistent with the dichotomized analysis: no dietary-practice or ART-regimen contrast reached FDR-corrected significance (smallest $q = 0.337$). DTG + TDF+FTC, compared with DTG + TAF+FTC, was associated with an estimated 52.8 cells/μL lower mean CD4 count (95% CI − 96.8 to − 8.8; nominal $p = 0.019$), mirroring the direction of the dichotomized finding (Additional file 1: Table S1).

Table 4
Adjusted associations with CD4 count below 500 cells/μL

| Exposure | Comparison | Model n | aOR (95% CI) | p | BH q |
|---|---|---|---|---|---|
| Special diet | Yes vs No | 614 | 0.77 (0.24–2.50) | 0.662 | 0.890 |
| Vitamin/mineral supplement | Yes vs No | 614 | 0.92 (0.57–1.48) | 0.721 | 0.890 |
| Meal skipping almost every day | Any meal | 614 | 0.87 (0.61–1.24) | 0.432 | 0.890 |
| Salt added during cooking | Not always vs Always | 614 | 1.03 (0.64–1.66) | 0.899 | 0.899 |
| Salt/Aromat/sauce added at table | Yes vs No | 614 | 0.96 (0.68–1.37) | 0.831 | 0.890 |
| Fried food frequency | 1–3/week vs < 1/week | 614 | 1.04 (0.68–1.59) | 0.841 | 0.890 |
| | ≥ 4/week vs < 1/week | 614 | 1.09 (0.66–1.79) | 0.748 | 0.890 |
| Take-away/fast-food frequency | 1–3/week vs < 1/week | 614 | 1.07 (0.70–1.62) | 0.763 | 0.890 |
| | ≥ 4/week vs < 1/week | 614 | 1.46 (0.80–2.70) | 0.220 | 0.890 |
| Pap frequency | 1–3/week vs < 1/week | 613 | 1.33 (0.59–3.01) | 0.491 | 0.890 |
| | ≥ 4/week vs < 1/week | 613 | 1.26 (0.58–2.76) | 0.561 | 0.890 |
| Fruit frequency | 1–3/week vs < 1/week | 614 | 1.27 (0.66–2.44) | 0.467 | 0.890 |

Each exposure was fitted in a separate logistic regression model. Models were adjusted for age (per 10 years), sex, country of birth, employment, index visit and ART regimen; regimen models omitted ART regimen from the adjustment set. BH q values are Benjamini–Hochberg false-discovery-rate adjusted across the 18 displayed contrasts. No q value was < 0.05. aOR, adjusted odds ratio; CI, confidence interval.

| Exposure | Comparison | Model n | aOR (95% CI) | p | BH q |
|---|---|---|---|---|---|
| | ≥ 4/week vs < 1/week | 614 | 1.55 (0.84–2.86) | 0.158 | 0.890 |
| Vegetable frequency | 1–3/week vs < 1/week | 614 | 0.67 (0.30–1.48) | 0.317 | 0.890 |
| | ≥ 4/week vs < 1/week | 614 | 0.84 (0.39–1.80) | 0.654 | 0.890 |
| Adds sugar to tea/coffee | Yes vs No | 614 | 1.10 (0.60–2.05) | 0.751 | 0.890 |
| ART regimen | DTG + TDF+FTC vs DTG + TAF+FTC | 614 | 1.56 (1.03–2.35) | 0.035 | 0.629 |
| | EFV + TDF+FTC vs DTG + TAF+FTC | 614 | 1.26 (0.82–1.94) | 0.286 | 0.890 |

Each exposure was fitted in a separate logistic regression model. Models were adjusted for age (per 10 years), sex, country of birth, employment, index visit and ART regimen; regimen models omitted ART regimen from the adjustment set. BH q values are Benjamini–Hochberg false-discovery-rate adjusted across the 18 displayed contrasts. No q value was < 0.05. aOR, adjusted odds ratio; CI, confidence interval.

*[Insert* Table 4 *here]*

# Discussion

In this secondary analysis of adults receiving long-term ART in the ADVANCE extension, obesity was common, affecting more than one quarter of participants, yet measured dietary practices showed no reproducible association with obesity after adjustment for multiple testing.

The central finding is therefore not that specific foods caused or prevented obesity, but that the available self-reported dietary-practice measures provided limited evidence of adjusted associations with either outcome after correction for multiple comparisons.

We also examined whether dietary associations with obesity or CD4 count differed between men and women by testing sex-by-exposure interaction terms for all 18 contrasts and both outcomes. Two nominal interactions were observed for obesity (vitamin/mineral supplement and pap frequency), but neither survived false-discovery-rate correction across the 24 interaction tests. We therefore found no robust evidence that the measured dietary practices were differentially associated with obesity or CD4

count in men versus women, although the study may have been underpowered to detect modest sex differences (Table S2 and Table S3).

The obesity prevalence of 27.7% in this cohort is broadly consistent with the substantial obesity burden reported among people with HIV in South Africa. Gizamba and colleagues estimated a pooled prevalence of 23.2% in a national systematic review [2], while the more recent Cape Town study by Oyetunji and colleagues reported 40% obesity in an older, predominantly female ART-treated sample [9]. Differences across studies likely reflect age, sex composition, treatment era, setting and selection into long-term care. Within ADVANCE, regimen-related weight gain is well established, with the largest mean gain reported in the DTG + TAF+FTC arm at 192 weeks [5]. The nominally lower odds of obesity in the EFV + TDF+FTC arm in our cross-sectional analysis are directionally compatible with the parent-trial weight findings, but the association did not survive multiplicity correction and should not be interpreted as a new causal regimen effect.

The strongest dietary signal was the association between reporting a special diet and obesity. This estimate was imprecise because only 14 participants reported a special diet, eight of whom had obesity. Reverse causation is plausible: participants who had already gained weight or developed a metabolic concern may have adopted a special diet in response. The food-intake instrument did not characterize the indication, composition, energy content or duration of a special diet, so the observed association cannot distinguish cause from response.

Fruit intake 1–3 times/week was nominally associated with lower odds of obesity compared with < 1 time/week, but there was no corresponding association for ≥ 4 times/week. The non-monotonic pattern, together with a false-discovery-rate q value of 0.228, argues against a simple protective interpretation. Similarly, broad categories for fried foods and takeaway foods may not capture portion size, cooking method, energy density or total dietary pattern. Studies in South African populations show that diet quality can be poor even when individual food-frequency indicators appear favorable, and that ultra-processed food intake is an important feature of the contemporary food environment [8–12].

We also found no robust association between the measured dietary practices and CD4 count < 500 cells/μL. Immune recovery during suppressive ART is influenced by baseline immune status, duration of treatment, age, co-infections, adherence and other clinical factors [13]. The food-intake assessment was not designed to quantify micronutrient status or total nutrient adequacy, and cross-sectional diet responses collected years after ART initiation cannot establish whether prior diet influenced immune recovery. The nominal regimen contrast for the CD4 outcome did not withstand multiple-testing correction and is best regarded as a chance compatible exploratory signal rather than evidence of differential immune recovery by regimen.

# Strengths and limitations

Strengths include use of a well-characterized randomized trial cohort with standardized anthropometry and laboratory CD4 testing, incorporation of dietary assessments during extended follow-up, explicit de-

duplication to ensure one analytic record per participant, a priori covariate adjustment and formal control of the false discovery rate.

The study also has important limitations. First, this was a cross-sectional secondary analysis; temporality and causality cannot be established, and reverse causation is especially plausible for special diets. Second, diet was self-reported and captured frequency and selected practices rather than portion size, total energy intake, nutrient intake or a validated overall diet-quality score. Third, physical activity, food insecurity, household income, medication adherence and other potentially important confounders were unavailable in the supplied analytic export. Fourth, some dietary categories were sparse and estimates were imprecise. Fifth, the original export contained repeated food diary records; selecting the earliest assessment per participant produces a clear cross-sectional estimand but does not use within person longitudinal information. Sixth, complete case models excluded four participants for most comparisons and five for pap. Seventh, pre-ART baseline BMI and CD4 count were not available in the supplied export and could not be adjusted for, despite being strong predictors of current BMI and CD4 count; residual confounding by baseline anthropometric and immunological status cannot be excluded. Eighth, exploratory sex-by-exposure interaction tests across all 18 contrasts for each outcome identified two nominal interactions for obesity (vitamin/mineral supplement, $p = 0.016$; pap frequency, $p = 0.047$), but neither survived false-discovery-rate correction across the 24 interaction tests (smallest $q = 0.386$), so we found no robust evidence that dietary associations differed between men and women; this analysis was likely underpowered to detect modest effect modification (Additional file 2: Table S2; Additional file 3: Table S3). Finally, the extension population represents participants retained in a clinical trial over prolonged ART follow up and may not be representative of all people with HIV in South Africa.

## Conclusions

The high prevalence of overweight and obesity observed in this cohort reinforces the need to address cardiometabolic health as a core component of long-term HIV care. Although no clear associations were identified between the measured dietary practices and obesity or CD4 count, the findings suggest that weight gain among adults receiving ART is likely driven by a complex interplay of factors that extends beyond individual dietary behaviours. Future studies should focus on comprehensive assessment of diet, physical activity and social determinants of health to better inform prevention strategies.

## Abbreviations

aOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; FDR, false discovery rate; FTC, emtricitabine; HREC, Human Research Ethics Committee; IQR, interquartile range; SAHPRA, South African Health Products Regulatory Authority; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

## Declarations

### Ethics approval and consent to participate

The ADVANCE trial was conducted in accordance with the Declaration of Helsinki and was approved by the University of the Witwatersrand Human Research Ethics Committee (reference 160606B), SAHPRA (reference 20160620) and relevant local authorities. Written informed consent was obtained from participants in the parent trial. This secondary analysis used existing study data.

### Consent for publication

Not applicable. The manuscript reports aggregate study results and contains no identifiable individual participant information.

## Competing interests

Siphamandla Bonga Gumede (SBG) reported receiving institutional grant funding from the National Institutes of Health (NIH) and NIH Small Research Projects. Depika Dwarka (DD), Godspower Akpomiemie (GA), Simiso Sokhela (SS), and Tarryn Collings (TC) declared no competing interests. Jen Manne-Goehler (JMG) is an Academic Editor on the PLOS Medicine editorial board, a consultant to the WHO Department of Noncommunicable Diseases and the Pan American Health Organization, and conducts research funded by the US National Institutes of Health. WD Francois Venter (WDFV) reported receiving personal fees from ViiV Healthcare, Gilead Sciences, Mylan/Viatris, MSD, Adcock Ingram, Aspen, Abbott, Roche, Sanofi, Boehringer Ingelheim, Thermo Fisher, and Virology Education, as well as institutional grant funding from Gilead, Novo Nordisk, the Bill & Melinda Gates Foundation, the South African Medical Research Council, the National Institutes of Health, Unitaid, the Foundation for Innovative New Diagnostics, and the Children's Investment Fund Foundation. Samanta T. Lalla-Edward (STL-E) reported receiving institutional grant funding from the National Institutes of Health, the Bill & Melinda Gates Foundation, the UK Research and Innovation Medical Research Council, and the South African Medical Research Council. No other competing interests were declared.

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## Author Contribution

SBG, DD, GP, SS, TC, JMG, WDFV, SL-E contributed to the study conception and design. SG and STL-E performed data analysis and interpretation of data for the work. SG wrote the manuscript draft. All authors [SBG, DD, GP, SS, TC, JMG, WDFV, STL-E] critically commented on the article and read and approved the final manuscript.


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# Data Availability

Access to the data used for this analysis is subject to the ADVANCE data sharing process and institutional and ethical approvals. Requests should be directed at the corresponding author.

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