Lack of weight gain during the first two months of treatment and HIV independently predict unsuccessful treatment outcomes in tuberculosis

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Brief summary: We evaluated the impact of HIV on weight gain and tuberculosis treatment outcomes. Findings suggest that persons living with HIV gained less weight and were more likely to have unsuccessful TB treatment outcomes (death, failure, relapse) than persons without HIV.

ABSTRACT

Background: Weight change may inform tuberculosis (TB) treatment response, but its predictive power may be confounded by HIV.

Methods: We prospectively followed adults with culture-confirmed, drug-susceptible, pulmonary TB receiving standard 4-drug therapy (isoniazid, rifampin, pyrazinamide, ethambutol) in Brazil and examined median weight change two months after treatment initiation by HIV status using quantile regression, and unsuccessful TB treatment outcome (treatment failure, TB recurrence, or death) by HIV and weight change status using Cox regression.

Results: Among 547 participants, 102 (19%) were HIV-positive, and 35 (6%) had an unsuccessful outcome. After adjusting for confounders, persons living with HIV (PLWH) gained a median 1.3 kg (95% confidence interval (CI): -2.8, 0.1) less than HIV-negative individuals during the first two months of TB treatment. PLWH were at increased risk of an unsuccessful outcome (adjusted HR=4.8, 95% CI: 2.1, 10.9). Weight change was independently associated with outcome, with risk of unsuccessful outcome decreasing 12% (95% CI: 0.81, 0.95) per 1 kg increase.

Conclusions: PLWH gained less weight during the first two months of TB treatment, and lack of weight gain and HIV independently predicted unsuccessful TB treatment outcomes. Weight, an easily-collected biomarker, may identify patients who would benefit from alternative treatment strategies.

Key words: Tuberculosis, HIV, body weight changes, treatment outcome, observational study

INTRODUCTION

Tuberculosis (TB) remains a major public health problem worldwide.[1–3] According to the World Health Organization (WHO), an estimated 10 million people developed TB and 1.3 million people died from TB in 2017, making it the deadliest infectious disease in the world.[1] Predictors and surrogate endpoints of unsuccessful treatment outcomes are needed to allow for possible interventions to improve outcomes.[4,5]

Malnutrition is one of the main risk factors for TB, a disease characterized by wasting,[6] and may negatively affect pharmacologic response to treatment.[7,8] This vicious cycle of malnutrition and TB is further complicated by HIV, which is a leading risk factor for TB and a predictor of TB-related death.[9] Persons living with HIV (PLWH) accounted for 9% of incident TB cases and 23% of TB deaths globally in 2017.[1] Further, the relationship between malnutrition and TB is most pronounced in PLWH.[9–11]

Because of the complex relationship between TB, HIV, and malnutrition, it is important to consider HIV when examining the association between weight change and TB treatment outcome. However, previous studies that examined weight change during TB treatment, from several geographic regions and among drug-susceptible and multi-drug resistant (MDR)-TB patients, rarely addressed TB-HIV co-infection.[12–18] One study concluded that weight gain was an unreliable predictor of overall treatment response,[12] whereas others found that inadequate weight gain (<5% initial body weight) after two months[13] or by the end of treatment[14] was associated with unsuccessful treatment outcomes among HIV-negative populations. Two additional studies suggest weight loss as a surrogate for TB treatment outcome included HIV-positive TB patients, but neither examined the effect of HIV on weight change during treatment.[15,16] Thus, we sought to examine the association between HIV and weight

change during the first two months of anti-TB treatment and characterize differences in weight change patterns between PLWH and HIV-negative persons. We also assessed associations between HIV, baseline weight, and early weight change with TB treatment outcomes, including TB treatment failure, TB recurrence, and death.

METHODS

Study design and participants. Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil is a prospective cohort study at five participating centers in Brazil: three in Rio de Janeiro (Instituto Nacional de Infectologia Evandro Chagas (INI), Clínica de Saúde Rinaldo Delmare (Rocinha), Secretaria de Saúde de Duque de Caxias (Caxias), one in Salvador (Instituto Brasileiro para Investigação da Tuberculose), and one in Manaus (Fundação Medicina Tropical Dr. Heitor Vieira Dourado). RePORT-Brazil enrolled participants ≥18 years-old who initiated treatment for culture-confirmed pulmonary TB[19]. Participants were excluded if they received anti-TB treatment for ≥7 days in the past, received >7 days of fluoroquinolone antibiotic therapy within the previous 30 days, were pregnant or breastfeeding women, or did not plan to remain in the region during the 24-month follow-up period. This analysis included drug-susceptible TB cases who were enrolled between June 2015 and May 1, 2018 and received ≥1 dose of intensive-phase standard TB therapy with follow-up through May 2019.

Data collection and definitions. Standard TB therapy was the combination of isoniazid, rifampin or rifabutin, pyrazinamide and ethambutol for two months, followed by isoniazid and rifampin for four months. Antimicrobial drug susceptibility testing was performed to assess drug resistance. At all study sites, participants are treated for TB according to guidelines by the Brazilian Ministry of Health; recommendations for treament length, directly observed therapy (DOT), and programmatic support are the same regardless of HIV.

Demographic, clinical, and diagnostic information was collected during 3 clinical visits (baseline, two months after initiating treatment, and at the end of treatment) and via telephone contact every 6 months thereafter until 24 months. A chest x-ray at baseline characterized the extent of lung disease and identified the presence or absence of lung cavitation. In accordance

with the Brazilian National TB program, all participants underwent HIV testing, unless they already had a positive test result. Participants with a positive HIV test result received CD4 count and HIV-1 RNA tests if none were available within the last 6 months.

Study outcomes and variables of interest. The primary outcome was change in weight, measured in kilograms (kg), between treatment initiation and two months of follow-up. Weight was measured using the same scale during all visits. The exposure of interest was HIV status, based on HIV testing results at baseline unless the participant was known to have HIV. Unsuccessful treatment outcomes, including TB treatment failure, TB recurrence, or death during follow-up, were defined according to WHO guidelines.[20] Treatment failure was defined as sputum-smear or culture positive for *Mycobacterium tuberculosis* at 5 months of treatment or later. TB recurrence was defined as a case considered cured at treatment completion but found to later have symptoms of active TB and a sputum smear or culture positive for *M. tuberculosis*.

We examined age, sex, race (white/other, black, mixed), household income (≤minimum wage, >minimum wage, or not reported/none), self-reported directly observed therapy (DOT; yes or no), tobacco use (current, former, never), alcohol use (current, former, never), current marijuana use, current cocaine use, baseline body mass index (BMI), baseline sputum smear result, lung cavitation on chest x-ray, glycated hemoglobin (HbA1c), and hemoglobin as potential risk factors and confounders. BMI was categorized by WHO criteria as underweight (<18.5 kg/m^2), normal weight (18.5-25 kg/m^2), or overweight (≥25 kg/m^2). HbA1c indicated diabetes status: normal (<5.7%), pre-diabetes (5.7%-6.5%), or diabetes (≥6.5%).[21] Hemoglobin indicated anemia severity: mild 11.00 to <13 g/dl (male) and 11.00 to <12 g/dl (female); moderate 8.00 to <11 (both sexes); severe <8 g/dl for both sexes.[22] Among PLWH, we also assessed CD4 count (<50 cells/mm^3 or ≥50 cell/mm^3), viral load (unsuppressed: ≥400

copies/mL or suppressed: <400 copies/mL), timing of antiretroviral therapy (ART), and ART regimen. Timing of ART was categorized into before TB treatment initiation, early (≤2 weeks after TB treatment initiation), or late (>2 weeks after TB treatment initiation). ART regimens were categorized as protease inhibitor (PI)-based, integrase inhibitor (INSTI)-based, or non-nucleotide reverse transcriptase (NNRTI)-based. CD4 cell count, and HIV-1 viral load were used as markers of severity of HIV infection. Baseline CD4 cell counts include the result closest to TB treatment initiation but within the range of 6 months before TB treatment initiation to 1 month after TB treatment initiation. Baseline HIV-1 viral loads include the result closest to TB treatment initiation but within the range of 6 months before TB treatment initiation to 1 week after TB treatment initiation.

Statistical analysis. Baseline characteristics of participants were summarized by HIV status and compared using Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. The primary analysis compared median weight change between PLWH and HIV-negative participants with bootstrapped quantile regression. We identified covariates for inclusion in multivariable models using a directed acyclic graph approach [23] (DAG; Figure 1). *A priori* identified confounders of the association between HIV and weight change included baseline weight, age, sex, study site, smear status, and hemoglobin. We also examined the association between severity of HIV infection (viral load and CD4 count) on weight change, by further categorizing PLWH according to HIV-related characteristics and comparing them to HIV-negative participants. There was a minimal amount of missingness for smear status (n=3, <1%) and hemoglobin (n=5, <1%), so missing values were singly imputed prior to multivariable modeling using the mode and median values, respectively.

In secondary analyses, we also examined the effect of HIV, baseline weight, and weight change on unsuccessful TB treatment outcomes (treatment failure, TB recurrence, or death). Using Cox proportional hazards regression, we examined hazard ratios (HR) for unsuccessful treatment outcome by baseline weight, weight change during the first two months of treatment, and HIV status. Follow-up times were calculated from TB treatment initiation until unsuccessful outcome or last contact. For each Cox model, we calculated crude and adjusted estimates, adjusting for a limited number of *a priori* considered confounders due to the low outcome rate. We also conducted mediation analysis to examine the total effect of HIV on unsuccessful treatment outcome, while evaluating the role of weight change as a potential mediator and distinguishing the direct effect of HIV on unsuccessful treatment outcome from the indirect effect mediated through weight change. Causal mediation analysis assumes a correctly specified causal model, no unmeasured confounding, and no uncontrolled confounding between exposure and mediator, between mediator and outcome, and between exposure and outcome. Mediation analysis was carried out using the *paramed* package in Stata, which used logistic regression to estimate parameters [24].

In sensitivity analysis, missing CD4 cell count (n=11) and HIV-1 RNA (n=32) viral loads were multiply imputed and compared to primary analysis. Additionally, because all but 8 PLWH were from INI and Manaus, we conducted sensitivity analyses for all analyses restricted to those sites.

All analyses used StataIC 15.0 (College Station, TX), and $p<0.05$ denoted statistical significance.

Ethical approval. The protocol, informed consent, and study documents were approved by the Institutional Review Boards at study sites and Vanderbilt University Medical Center. Participation was voluntary and written informed consent was obtained from all participants.

RESULTS

Among 598 participants enrolled in RePORT-Brazil during the study period, 547 (91%) also had weight measured at two months and were included in the study. Reasons for exclusion (n=51) include death (n=13) or loss to follow-up (n=28) before month 2, and missing weight measurement at month 2 (n=10). Excluded participants were more likely to be HIV-positive (30% vs. 19%, p=0.06), of mixed race (63% vs. 46%, p=0.02), or current or former smokers (current: 35% vs. 22%; former: 37% vs. 26%, p=<0.01) than those included. Additionally, none of the excluded participants were overweight, whereas 11% of those included were, but there was not a significant difference in median baseline BMI between the two groups (19.4 vs. 20.3, p=0.15)

Overall, participants had a median age of 37 (IQR: 37-49) years and 20% had HIV. Almost half of participants were either pre-diabetic or diabetic, 59% had some degree of anemia at baseline, and over half received DOT, based on self-report. PLWH were significantly more likely to be male than HIV-negative participants and had higher rates of anemia. As expected, PLWH had lower rates of sputum smear positivity and lung cavitation on chest x-ray compared to HIV-negative participants. There were additional differences in racial distribution, alcohol use, tobacco use, and hemoglobin between PLWH and HIV-negative individuals (Table 1). Median follow-up differed between PLWH and HIV-negative participants (12 months [IQR: 5.9, 17.8] vs.18 months [IQR: 12, 24], p<0.01).

Among the 102 PLWH, median CD4 count was 97 cells/mm^3 (IQR: 49-282) and 24 (26%) had baseline CD4 counts <50 cells/mm^3. Median viral load was 18,572 copies/mL (IQR: 566-162,035) and 57 (76%) PLWH were not virologically suppressed. Just over one-third of PLWH were on ART prior to anti-TB treatment initiation, 28 (28%) started within 2 weeks, 30 (29%) started between two weeks and two months, and 7 (7%) never started ART. Most PLWH received an INSTI-based (37%) or NNRTI-based (45%) ART regimen, and 10% were started on a PI-based regimen.

Primary analysis: weight change

During the first two months of anti-TB treatment, overall median weight change was a gain of 1.7 kg. There was a significant difference by HIV status, however. PLWH had median weight gain of 0.1 kg (IQR: -3.2, 2.6), whereas HIV-negative persons gained 2 kg (IQR: 0.4, 4). Among the 102 PLWH, 28% lost ≥5% of their baseline weight, 47% had stable weight (change between -5% and 5%), and 26% gained ≥5% of their baseline weight. Notably, among the 445 HIV-negative participants, only 3% had weight loss ≥5%, 60% had stable weight, and 36% had weight gain ≥5% (Table 2).

PLWH experienced less weight gain than HIV-negative persons, with an estimated -1.3 kg median difference (95% CI: -2.8, 0.1), adjusting for baseline weight, age, sex, site, smear status, and hemoglobin. The differences in weight change were even more pronounced among PLWH with low CD4 cell counts and unsuppressed viral load (Figure 2) but were relatively similar in regard to ART timing and ART regimen (data not shown). Aside from HIV, other factors associated with weight change included site, sex, self-reported DOT, BMI category, baseline smear status, and anemia. Neither smear nor culture results at month 2 were associated

with weight change among a subset of participants with available smear (n=423) or culture results (n=421).

Secondary analysis: unsuccessful TB treatment outcomes

The risk of unsuccessful outcome for anti-TB treatment was significantly associated with weight change during the first two months of treatment and with HIV status (Table 3). Overall, 35 people had an unsuccessful treatment outcome, corresponding to an incidence rate of 4.1 per 1,000 person-years (PY). The rates of death (n=13), failure (n=17), and recurrence (n=5) correspond to incidence of 1.5, 2.0, and 0.6 per 1,000 PY, respectively. People with an unsuccessful outcome lost a median of 0.4 kg (IQR: -3.4, 2), compared to a median gain of 1.9 kg (IQR: 0.1, 4) among people with a successful treatment outcome. Of the 188 people with weight gain >5%, only 6 (3%) had an unsuccessful treatment outcome, compared to 6% of people with stable weight change and 21% of people with weight loss >5%.

Only 4% of HIV-negative persons had an unsuccessful treatment outcome, compared to 18% risk among PLWH, corresponding to a hazard ratio of 4.79 (95% CI: 2.10, 10.91) after adjusting for sex and hemoglobin. Weight change was also associated with unsuccessful treatment outcome. For each one kg increase in weight, the risk of unsuccessful treatment outcome decreased by 12% (HR=0.88; 95% CI: 0.81, 0.95). Neither baseline weight nor weight at month 2 were predictive of treatment outcome (Table 3). We assessed the effect of both HIV and baseline weight on unsuccessful outcome in the full population (including the 51 participants without a month 2 visit who were excluded from the primary analysis) and found that the results were similar to those of the primary analysis (Table 3).

Mediation analysis

From the mediation analysis, the increased risk of unsuccessful TB treatment outcome among HIV-positive persons yielded an odds ratio of 4.96 (95% CI: 2.39, 10.27). The controlled direct effect of HIV on unsuccessful outcome was 3.6 (95% CI: 1.64, 7.82), which expressed how much the risk of the outcome would change on average if weight change were fixed at a uniform level for HIV+ and HIV- persons. The indirect effect was 1.38 (95% CI: 1.08, 1.78), which was the effect of HIV on unsuccessful treatment outcome for any level of weight change. This suggests that 35% of the effect of HIV on an unsuccessful outcome was mediated through weight change, suggesting 35% of the effect of the exposure would be reduced if the pathway through the mediator (weight change) were blocked.

Sensitivity analyses

In sensitivity analyses restricted to INI and Manaus, the impact of HIV on weight change remained similar, but the effect of HIV on unsuccessful outcome was slightly attenuated (Supplemental Table 1 and Supplemental Table 2). Imputing CD4 cell counts and HIV-1 RNA viral loads or using values from outside the recommended date window did not substantively alter the results (Supplemental Table 3).

DISCUSSION

In this prospective study of culture-positive, drug susceptible, pulmonary TB patients treated with standard anti-TB therapy, we found an association between HIV infection and weight change during the first two months of anti-TB treatment, including in site-restricted sensitivity analyses. In addition, PLWH and persons who did not gain adequate weight during the first two months of anti-TB treatment had increased risk of unsuccessful TB treatment outcomes. Conversely, few participants who gained ≥5% of their baseline weight after two months of anti-TB treatment had an unsuccessful treatment outcome, suggesting the benefit of adequate weight gain in early TB treatment. Results of mediation analysis highlighted the association between HIV and unsuccessful treatment outcomes, and comparison of direct and indirect effects indicated that over one-third of poor treatment outcome risk due to HIV was mediated by weight change. If the assumptions of causal mediation analysis are met (see Methods), these results suggest that it may be possible to prevent unsuccessful outcomes with an intervention to promote weight gain during TB treatment among PLWH. However, this finding must be carefully investigated in settings with multiple measures of weight prior to outcome in larger and more diverse populations, including intervention studies to promote weight gain.

Weight gain is an essential part of recovery during anti-TB treatment, especially among PLWH, who are more likely to have unsuccessful TB treatment outcomes.[25–28] However, to our knowledge, no previous studies have quantified differences in weight change during anti-TB treatment for drug-susceptible TB by HIV status and examined subsequent effects on treatment outcome. A prospective cohort study in Tanzania found no differences in fat mass and muscle mass changes during the first two months of anti-TB treatment by HIV status.[29] We found that PLWH on ART prior to anti-TB treatment initiation had minimal excess weight gain than

PLWH not on ART at baseline, and any association would likely be the result of them receiving antiretroviral treatment and having less severe consequences of the TB-HIV burden. Similar to the results of our analysis, a study in Ethiopia found that HIV-negative patients gained more weight than PLWH during TB treatment.[30] Although they did not examine overall treatment outcomes (death, failure, recurrence), they noted a strong inverse association between body weight gain and sputum conversion, which has been used previously as a predictor or surrogate for TB treatment outcome.[30] Of note, we did not find an association between weight change and smear or culture conversion at 2 months.

Other studies examining weight change during anti-TB treatment and impact on treatment outcome were conducted among HIV-negative persons or populations with low rates of HIV and, thus, were unable to assess differences in weight change during treatment by HIV status.[13,15,18,31,32] These studies mostly focused on baseline weight, baseline disease severity, DOT, age, and adherence as predictors of weight change, many of which were also predictors in our analysis, but not as strongly as HIV. Notably, two studies found that lack of "adequate" weight gain, defined as weight gain ≥5% baseline weight during the first two months of anti-TB treatment, was a predictor of unsuccessful outcome.[13,18] We confirmed this finding.

Correspondingly, our results may be explained by the finding that TB increases resting metabolic rate, a measure of the cost of sustained immune activation, by 14%, which rises to about 30% among persons with TB and HIV.[33,34] The impairment of net protein anabolism from increased energy expenditures to fight infection is increased in TB-HIV patients compared to patients with either TB or HIV alone.[11] Due to increased immune activation and resulting energy consumption, it may take longer for HIV-positive TB patients to sustain adequate weight

gain even after initiation of anti-TB therapy. Another study found that lack of 5% weight gain by the end of TB treatment was most predictive of a unsuccessful treatment outcome.[14] However, given their homogenous study population, they recommended future analyses examine weight changes among subsets of patients, including PLWH. As seen in our study, using end-of-treatment weight change as a proxy for unsuccessful treatment outcome would fail to capture deaths that occurred before that point.

Our study had limitations. First, 51 participants had insufficient follow-up to assess weight change at month two. Second, we examined weight change at two months of follow-up. It is possible weight change differences by HIV status vary as TB treatment duration increases, with gradual improvement in host immune function. However, the first two months of anti-TB treatment represent a critical time in the course of disease, and losses to follow-up and events thereafter may strongly influence conclusions about weight changes between baseline and end of treatment. In sensitivity analyses, we examined the impact of baseline weight on unsuccessful treatment outcome and found little effect, which further highlights the importance of weight change during the first two months of treatment. It is also difficult to discern key causative factors in our analysis: do unsuccessful TB outcomes occur because participants do not gain weight, or do participants not gain weight because they are not responding to therapy? Future studies of potential interventions to promote weight gain during the first two months of treatment could provide insights. Translational studies may be helpful in assessing immune function pertaining to *M. tuberculosis* and HIV in persons who do and do not gain weight during anti-TB therapy.

This study had several strengths, including its prospective design, active follow-up for recurrence, death, and treatment failure, and collection of data regarding TB and HIV clinical

characteristics. We were able to compare weight change and TB treatment outcomes by HIV status, and among PLWH, examined the impact of HIV severity on weight change and subsequent treatment outcomes. Lastly, we present results that should be generalizable to other low-resource countries with similar TB-HIV rates as Brazil, which is a high TB-HIV burden country.[1]

In conclusion, weight change in early TB treatment and HIV status have the potential to be effective, readily available, and inexpensive surrogate markers of unsuccessful TB treatment outcome and could trigger evaluation of interventions among patients at highest risk for these outcomes. More research is needed to identify the types of interventions that would best promote weight gain during TB treatment, especially among PLWH.

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FOOTNOTES

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Figures

Figure 1. Directed acyclic graph (DAG) for the primary[a] and secondary analyses[b].

[Attached separately as Figure1.tiff]

[a]***Primary analysis****: examine the association between HIV and weight change, while adjusting for potential confounders.*

[b]***Secondary analysis****: examine the independent effect of HIV and weight change on tuberculosis (TB) treatment outcome and use mediation analysis to examine the total, direct, and indirect effect of HIV and weight change on TB treatment outcome.*

Figure 2. Crude and adjusted[a] analysis of association between HIV-related characteristics and weight change during the first two months of TB treatment. Bootstrapped quantile regression

[Attached separately as Figure2.tiff]

[a]Adjusted models control for baseline weight, age, sex, site, smear status, and hemoglobin

Bold indicates statistical significance ($p<0.05$)

MD=median difference

Figure 1

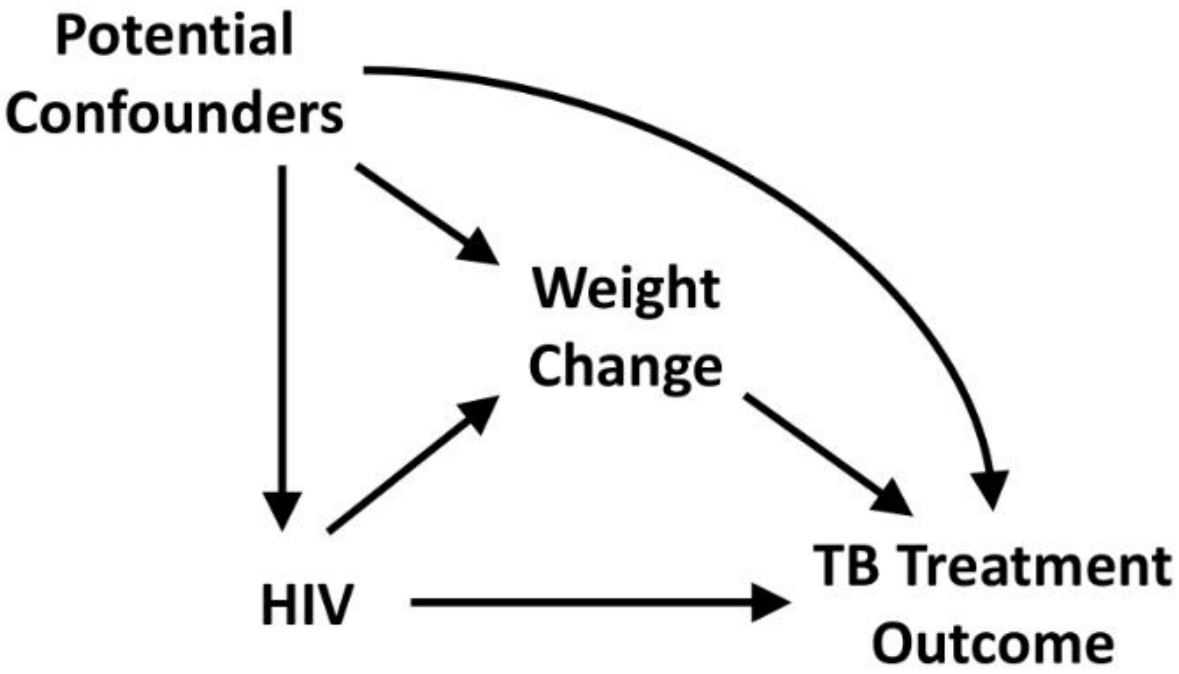

Figure 2

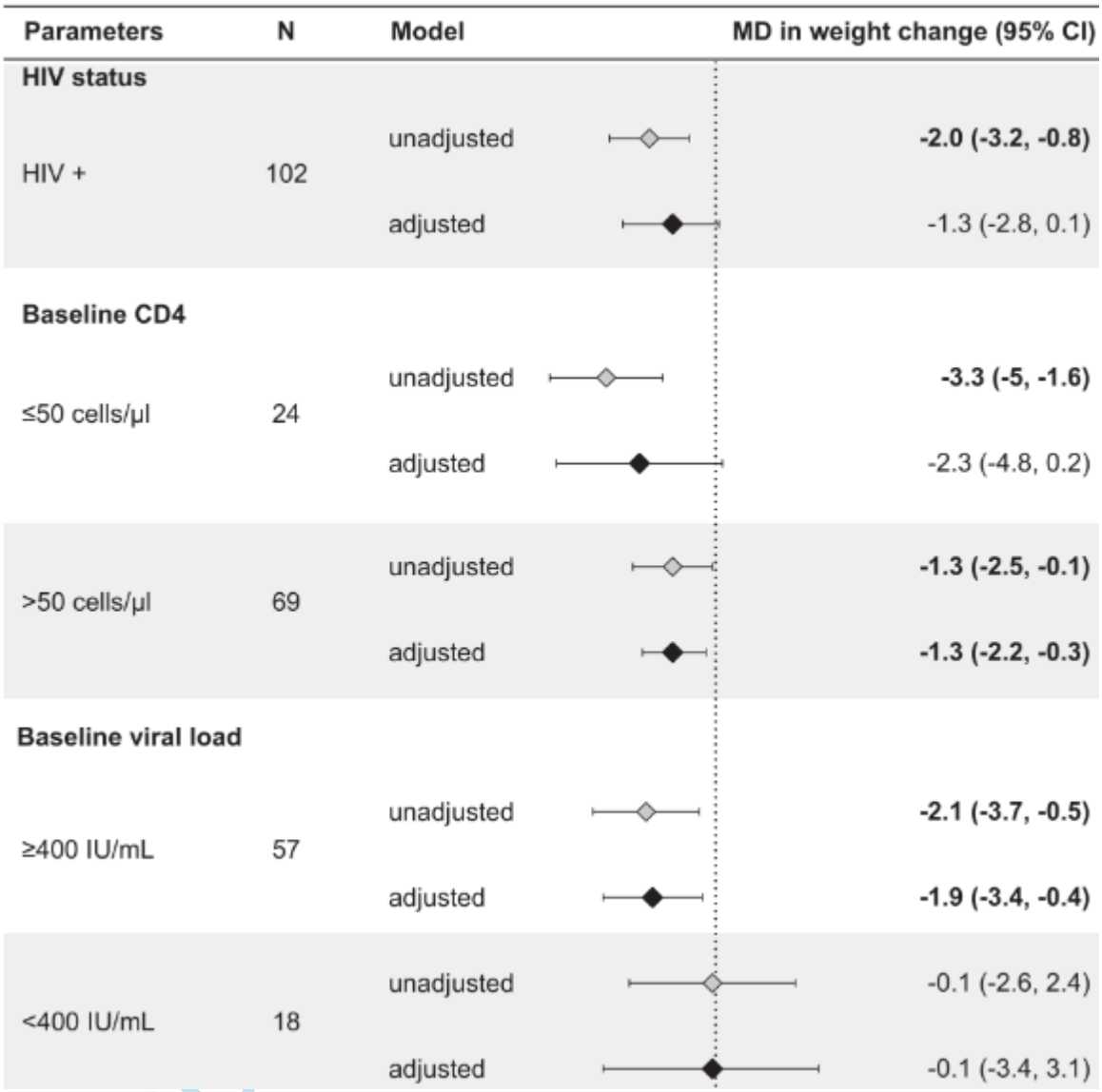

Table 1. Baseline clinical and demographic characteristics of the study population (HIV- vs. HIV+)

Characteristic	HIV- n=445 N (col %) or median [IQR]	HIV+ n=102 N (col %) or median [IQR]	p-value[a]
Age at enrollment (years)	37 [26-51]	37 [29-45]	0.60
Male sex	276 (62)	76 (75)	0.02
Site			<0.01
Manaus	38 (9)	69 (68)	
Caxias	111 (25)	4 (4)	
INI	63 (14)	27 (27)	
Rocinha	84 (19)	1 (1)	
Salvador	149 (34)	1 (1)	
Race			<0.01
White/Other	112 (25)	24 (24)	
Black	142 (32)	15 (15)	
Mixed	191 (43)	63 (62)	
Household Income			0.21
≤ Minimum wage	204 (46)	37 (36)	
> Minimum wage	154 (35)	42 (41)	
None/not reported	87 (20)	23 (23)	
Tobacco use			<0.01
Current	102 (23)	17 (17)	
Former	98 (22)	42 (41)	
Never	245 (55)	43 (42)	

Alcohol use			<0.01
Current	215 (48)	30 (29)	
Former	151 (34)	63 (62)	
Never	79 (18)	9 (9)	
Baseline BMI			
Continuous (kg/m^2)	20.3 [18.4-22.5]	20.5 [18.4-22.9]	0.61
Underweight (<18.5 kg/m^2)	121 (27)	29 (28)	0.55
Normal weight (18.5-25 kg/m^2)	278 (63)	59 (58)	
Overweight (≥25 kg/m^2)	46 (10)	14 (14)	
HbA1c (n=591)			
Continuous (%)	5.8 [5.4-6.3]	5.7 [5.2-6.2]	0.03
Normal (<5.7%)	217 (49)	52 (52)	0.24
Pre-diabetic (5.7%-6.5%)	126 (29)	34 (34)	
Diabetes (≥6.5%)	97 (22)	15 (15)	
Hemoglobin (n=593)			
Continuous (g/dL)	12.4 [11.3-13.5]	10.4 [8.7-11.8]	<0.01
No anemia (M: ≥13 g/dL; F: ≥12 g/dL)	214 (49)	15 (15)	<0.01
Mild anemia (M: 11-13 g/dL, F: 11-12 g/dL)	136 (31)	25 (25)	
Moderate anemia (8-11 g/dL)	83 (19)	46 (45)	
Severe anemia (<8 g/dL)	7 (2)	16 (16)	
Self-reported DOT (n=594)	224 (51)	63 (62)	0.05
Positive smear result (n=595)	375 (85)	66 (65)	<0.01
Lung cavitation (n=588)	272 (62)	28 (29)	<0.01

ART=anti-retroviral therapy; BMI=body mass index; DOT=Directly Observed Therapy; F=female; HbA1c=glycosylated hemoglobin; INI=Instituto Nacional de Infectologia Evandro Chagas

[a]Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables, comparing persons with and without 2 month follow-up visit

Table 2. Patterns of weight change from baseline to month 2 in the study population, by HIV status.

	HIV- N=445	HIV+ N=102	p-value[a]
	N (col %) or median [IQR]	N (col %) or median [IQR]	
Baseline weight	57 [50.2 -65]	55.1 [49.7-66]	0.72
Month 2 weight	59.5 [52-67.4]	56.1 [49-65.4]	0.02
Weight change			
Absolute (kg)	2 [0.4-4]	0.1 [-3.2-2.6]	<0.01
Percentage (%)	3.6 [0.7-7]	0.1 [-5.1-5.5]	<0.01
Weight change categories			<0.01
Weight loss ≥5%	15 (3)	28 (28)	
Stable weight	268 (60)	48 (47)	
Weight gain ≥5%	162 (36)	26 (26)	

[a]Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables

Table 3. Cox proportional hazards regression for predictors of unsuccessful treatment outcome (death, treatment failure, TB recurrence).

Factor	Total	Poor Outcome (%)	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Primary analysis population				
HIV status				
Positive	102	18 (18)	**6.14 (3.12, 12.10)**	**4.79 (2.10, 10.91)[a]**
Negative	445	17 (4)	Ref.	Ref.
Baseline weight (per 1 unit increase)	547	35 (6)	1.0 (0.99, 1.03)	0.99 (0.96, 1.02)[b]
M2 weight (per 1 unit increase)	547	35 (6)	0.97 (0.94, 1.01)	0.97 (0.94, 1.01)[b]
Weight change (per 1 unit increase)	547	35 (6)	**0.83 (0.77, 0.89)**	**0.88 (0.81, 0.95)[c]**
Percentage weight change (per 1 unit increase)	547	35 (6)	**0.89 (0.86, 0.93)**	**0.92 (0.88, 0.96)[c]**
Full population				
HIV status				
Positive	117	25 (21)	**5.63 (3.20, 9.90)**	**3.88 (1.81, 8.34)[a]**
Negative	481	24 (5)	Ref.	Ref.
Baseline weight (per 1 unit increase)	598	49 (8)	0.98 (0.96, 1.01)	0.98 (0.95, 1.01)[b]

Bold indicates statistical significance ($p<0.05$)

[a]Adjusted for sex and hemoglobin

[b]Adjusted for HIV and sex

[c]Adjusted for baseline weight, HIV, and sex