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Instituto Nacional de Infectologia
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FUNDAÇÃO OSWALDO CRUZ
INSTITUTO NACIONAL DE INFECTOLOGIA EVANDRO CHAGAS
DOUTORADO EM PESQUISA CLÍNICA EM DOENÇAS INFECCIOSAS

ADRIANA COSTA BACELO

EVOLUÇÃO NUTRICIONAL DE PACIENTES COM TUBERCULOSE EM TRATAMENTO MEDICAMENTOSO

Rio de Janeiro
2015

TESE DPCDI-INI A.C.BACELO 2015

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Tese apresentada ao programa de pós-graduação *Stricto Sensu* em pesquisa clínica em doenças infecciosas do Instituto Nacional de Infectologia Evandro Chagas para a obtenção do grau de doutor em doenças infecciosas, sob a orientação da Profª Drª Valéria Cavalcanti Rolla e Profª Drª Rejane Andréa Ramalho Nunes da Silva.

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Orientador:
Profª Drª Valéria Cavalcanti Rolla e Profª Drª Rejane Andréa Ramalho Nunes da Silva

Aprovado em: / /

BANCA EXAMINADORA

_____
Drª Valéria Cavalcanti Rolla
Instituto Nacional de Infectologia Evandro Chagas - FIOCRUZ

_____
Drª Rejane Andréa Ramalho Nunes da Silva
Instituto Josué de Castro - UFRJ

_____
Dr. Pedro Emmanuel Brasil
Instituto Nacional de Infectologia Evandro Chagas - FIOCRUZ

_____
Drª Claudia dos Santos Cople-Rodrigues
Instituto de Nutrição - UERJ

_____
Drª Patricia Dias de Brito
Instituto Nacional de Infectologia Evandro Chagas – FIOCRUZ

_____
Dra. Cecilia Lacroix
Instituto de Nutrição - UERJ

_____
Dr Itallo Collopy Junior
Instituto Federal do Rio de Janeiro - IFRJ

A Deus e à Nossa Senhora das Graças pela proteção e inspiração.

Ao meu marido Clévio Fonseca, aos meus pais Agostinho e Marnise Bacelo, e ao meu irmão Alexandre Bacelo por serem exemplo de dedicação aos estudos, e pela paciência, apoio e amor incondicionais.

Aos orientadores e revisores pela paciência e ensinamentos.

AGRADECIMENTOS

A Deus que abençoou cada passo e guiou cada descoberta. À virgem Santíssima, que como mãe esteve zelando por meus passos.

Ao meu marido Clévio Fonseca pelas discussões clínicas e pelas constantes provas de amor.

Aos meus pais Agostinho e Marnise Bacelo pelo incentivo constante e amor incondicionais.

Aos meus familiares pela paciência com minha ausência.

À minha orientadora Valéria Rolla, que foi além do papel de docente e com competência, e com senso ético, comprometimento e transparência se mostrou um exemplo a ser seguido no âmbito da pesquisa.

À minha orientadora Andréa Ramalho por ter me ensinado que a técnica, o comprometimento e a persistência precisam fazer parte da formação profissional.

Aos pesquisadores Pedro Emanuel Brasil e Claudia Cople pela incansável contribuição científica e pelos exemplos de humildade e competência ao longo de todos os seminários.

Às pesquisadoras Daniela Casagrande e Daniele Marano, que tiveram muitos dos encontros sociais comigo transmutados em discussões técnico científicas.

Às colegas do Serviço de Nutrição do Instituto Nacional de Infectologia Evandro Chagas pelo incentivo e apoio. Em especial, à pesquisadora Patrícia Brito, pela boa vontade, generosidade e competência técnico científica na revisão deste documento.

Aos amigos e parceiros de trabalho que aceitaram as minhas ausências e me motivaram a continuar.

À enfermeira Solange Alves da Cruz, à pesquisadora Georg Ingebourg, às equipes do laboratório de coleta de sangue e do laboratório de imunodiagnóstico do INI-FIOCRUZ que ajudaram na coleta de dados.

Às médicas do ambulatório, Flávia Marinho Sant´Anna e Carolina Arana Stanis Schmaltz, e aos nutricionistas Eliane Paiva, Ivan Maia e Erika Ennes que ajudaram na coleta de dados.

"*Mesmo quando tudo pede um pouco mais de calma. Até quando o corpo pede um pouco mais de alma. A vida não para...*
...Enquanto todo mundo espera a cura do mal
E a loucura finge que isso tudo é normal...
...Será que é tempo que lhe falta pra perceber? Será que temos esse tempo pra perder? E quem quer saber? "A vida é tão rara..."

Osvaldo Lenine Macedo Pimentel (Lenini) e Carlos Eduardo Carneiro de Albuquerque Falcão (Dudu Falcão)

Bacelo, C.A. **Evolução nutricional de pacientes com tuberculose em tratamento medicamentoso**. Rio de Janeiro, 2014. 121 f. Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz.

RESUMO

A Tuberculose (TB) e a má nutrição são problemas de saúde pública que acometem milhões de pessoas anualmente. O Ministério da Saúde do Brasil (MS) e a Organização Mundial de Saúde (OMS) recomendam a realização do aconselhamento dietético baseado na *Recommended Dietary Allowance* (RDA) para os pacientes em tratamento de TB com má nutrição leve ou moderada. **Objetivo:** avaliar a capacidade do aconselhamento dietético exclusivo preconizado pelo MS de suprir todas as demandas nutricionais causadas pela TB em pacientes infectados ou não pelo vírus da imunodeficiência humana (HIV). Assim como, identificar os fatores que interferem na adesão ao aconselhamento dietético. **Metodologia:** estudo longitudinal e observacional realizado com pacientes adultos em acompanhamento medicamentoso para TB, infectados ou não pelo HIV. Foram realizadas as avaliações antropométrica, bioquímica e dietética (Recordatório de 24 horas) e em seguida implementou-se o aconselhamento dietético. A percepção de adesão dietética foi avaliada por autorreferência nas diferentes consultas durante os 180 dias de estudo. Foi considerada má nutrição quando pelo menos um dos resultados da avaliação nutricional estava fora dos valores de referência, sendo classificada de acordo com os parâmetros considerados, em: global (todos os parâmetros), calórica (Índice de Massa Corporal - IMC, dobra cutânea triciptal – DCT, e circunferência do braço - CB), proteica (circunferência muscular do braço - CMB, albumina e transferrina), ou específica (marcadores séricos de ferro, selênio, zinco, retinol e ∂-tocoferol). Os dados foram analisados no programa R-project® versão 3.0.2. Os resultados foram divididos em tempo inicial e seguimento. As diferenças foram consideradas significantes quando o valor de p foi ≤ 0.05. **Resultados**: 68 pacientes foram incluídos, com idade média de 41.1 (±13.4) anos, predomínio do sexo masculino, de baixa escolaridade e baixa renda, com forma clínica pulmonar. Todos os pacientes apresentavam algum tipo de má nutrição, entretanto aqueles com HIV (22 pacientes) tinham maior comprometimento de proteínas totais, hemoglobina e hematócrito. Apesar de apenas 25% dos pacientes estarem desnutridos pelo IMC; 66.1% estavam com anemia; 95.6% estavam com má nutrição proteica, 70.6% tinham má nutrição calórica, e 82.4% má nutrição específica. Trinta e quatro pacientes completaram o protocolo do estudo (180 dias). O consumo médio de energia, proteína e zinco durante o tratamento estiveram próximo ao mínimo recomendado pela RDA, enquanto que para os outros nutrientes o consumo médio esteve geralmente abaixo do valor recomendado pela RDA. A adesão ao aconselhamento dietético foi baixa, entretanto, não houve diferença estatística entre infectados ou não pelo HIV. Apenas uma pequena parcela da população (< 80% para calorias e < 40% para os demais nutrientes, em todos os momentos) ingeriu pelo menos uma vez a RDA conforme aconselhado. Os transtornos gastrointestinais foram os motivos mais prevalentes de não adesão dietética. **Conclusão:** a má nutrição não foi revertida ao longo do tratamento da TB, independente da infecção ou não por HIV. O uso isolado do IMC não foi um marcador sensível para identificar má nutrição. A adesão ao aconselhamento foi prejudicada principalmente pela presençade transtornos gastrointestinais e anorexia.

Palavras-chave: tuberculose, má nutrição, micronutriente, HIV, estado nutricional, aconselhamento dietético, adesão autorreferida

Bacelo, C.A. **Nutritional Status during tuberculosis treatment**. Rio de Janeiro, 2014. 121 f. Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz.

ABSTRACT

Tuberculosis (TB) and malnutrition are public health problems that affect millions of people annually. The Brazilian Ministry of Health (MS) and the World Health Organization (WHO) recommend dietary counseling for Patients with mild or moderate malnutrition due to the tuberculosis treatment (TB). **Objective:** to assess the ability of unique dietary counseling recommended by the Ministry of Health in order to supply all the nutritional demands caused by TB in patients infected by Human Immunodeficiency Virus (HIV) or not. As well as the factors that can affect adherence to dietary counseling. **Methods:** prospective observational study conducted in adults treated for TB, infected and not infected by HIV. These subjects were assessed through body composition, serum biomarkers and dietary (24-hour recall), then we offered dietary counselling with subsequent verification of its execution, using the self-reported adherence in 180 days of study. Malnutrition was when at least one of the nutritional assessment results was outside the normal range. And was classified according to the parameters considered in: global (all parameters), caloric (Body Mass Index - BMI, triceps skinfold - TSF, and arm circumference - MUAC), protein (mid-arm muscle circumference - MAMC, albumin and transferrin), or specific (serum iron markers, selenium, zinc, retinol and ∂-tocopherol). Data was analysed using the program R-project version 3.0.2 and considered as a significant difference $p \leq 0.05$. **Results:** 68 patients were included at the average age of 41.1 (± 13.4) years, were predominantly male and of low education status, low income and presented pulmonary clinical form. All patients had some kind of malnutrition. However, those with HIV (22 patients) had greater impairment of total proteins, hemoglobin and hematocrit. Although only 25% of patients were malnourished by BMI, 66.1% had anemia, 95.6% had protein malnutrition, 70.6% had energy malnutrition and 82.4% some degree or type of micronutrient disability. Thirty-four patients completed the study protocol (180 days). The average of energy, zinc and protein consumption, during treatment, were close to the RDA recommended minimum, while for the other nutrients average consumption was generally lower than the recommended RDA. Adherence to a dietary counselling was low. However, there was no significant difference among groups. Only a small portion of the population (<80% of calories and <40% for all other nutrients, at all times) ingested at least once in the RDA counseling. Gastrointestinal disorders were the most prevalent reasons for a self-reported not adherence. The time of treatment, HIV infection and age appear to be capable to influence calorie intake. **Conclusion**: dietary counseling alone did not reverse malnutrition during TB treatment, in patients with or without HIV. BMI isolated was not a sensitive marker to identify malnutrition, being necessary to include biomarkers, hematology and body composition. Dietary counseling was impaired by gastrointestinal disorders and loss of appetite.

Keywords: tuberculosis, malnutrition, micronutrients, HIV, nutritional state, dietary consultation, self-reported adherence.

LISTA DE ABREVIATURAS

TB	Tuberculose
HIV	Vírus da imunodeficiência humana
AIDS	Síndrome da imunodeficiência aguda
CD4	Linfócitos T tipo CD4.
CD8	Linfócitos T tipo CD8
Th1/Th2	Citocinas ou células T auxiliares tipo 1 e tipo 2
IL-1	Interleucina-1
IL-2	Interleucina-2
IL-4	Interleucina-4
IL-5	Interleucina-5
IL-10	Interleucina-10
TNF-α	Fator de necrose tumoral-alfa
IMC	Índice de massa corporal
CMB	Circunferência muscular do braço
DCT	Dobra cutânea triciptal
CB	Circunferência braquial
TCLE	Termo de consentimento livre e eslarecido
CV	Carga viral
ART	Terapia antiretroviral

LISTA DE SIGLAS

ASPEN	American Society for Parenteral and Enteral Nutrition
MS	Ministério da Saúde do Brasil
OMS	World Health Organization
FDA	Food and Drug Administration
RDA	Recommended Dietary Allowance
SISVAN	Sistema de Vigilância Alimentar Nutricional
FAO	Food and Agriculture Organization of the United Nations

SUMÁRIO

1. INTRODUÇÃO

Os pacientes infectados pelo vírus da imunodeficiência humana (HIV) possuem risco aumentado de infecção primária, reativação e novos episódios de tuberculose (TB) por re-infecção exógena (van Rie et al. 1999; Havlir e Barnes 1999; Ministério da Saúde do Brasil 2011), tornando tanto a TB como a infecção pelo HIV alvo de preocupação da saúde pública mundial (Ministério da Saúde 2014).

A elevação de citocinas inflamatórias associada à queda da liberação do hormônio orexígeno grelina já foram identificadas na TB (Chang et al. 2013; Zheng et al. 2013) associada ou não ao HIV (Islam et al., 2013; Schwenk et al., 2004; Motswagole et al., 2013; Hsu et al., 2005), e podem promover ou agravar a má nutrição e outras alterações nutricionais (Tulchinsky e Varavikova, 2014), principalmente na população brasileira, que habitualmente consome alimentos ricos em calorias vazias e pobres em micronutrientes (Instituto Brasileiro de Geografia e Estatística 2010a).

Desta forma, é importante que se discuta o tratamento nutricional de pacientes com TB (Sinclair et al. 2011), mas são escassos os trabalhos brasileiros que abordam o estado nutricional do paciente com TB e HIV (Baruzzi et al. 2001; Klautau e Kuschnaroff 2005; Orellana et al. 2006; Cantalice Filho 2009; Piva et al. 2013), bem como a capacidade de adesão do paciente ao aconselhamento dietético durante o tratamento para TB (Sinclair et al. 2011; Pee et al. 2014).

Portanto, a identificação das alterações nutricionais relacionadas à TB, associada ou não ao HIV, e da capacidade de adesão ao aconselhamento dietético conforme preconizado pelo Ministério da Saúde (Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006; Ministério da Saúde do Brasil 2011; Ministério da Saúde do Brasil 2013), devem ser objetos de investigação com a finalidade de subsidiar o estabelecimento/revisão do protocolo terapêutico nutricional dirigido ao paciente com TB e HIV.

2. JUSTIFICATIVA

Em 2013, o Brasil diagnosticou 71.123 casos novos de tuberculose (incidência de 35,4/100.000 habitantes), com uma taxa de infecção por HIV associada de 9,8% (Brasil 2014). O Ministério da Saúde do Brasil (Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006; Ministério da Saúde do Brasil 2011; Ministério da Saúde do Brasil 2013) e a Organização Mundial de Saúde (OMS) (WHO 2013) reconhecem a existência da má nutrição calórica, proteica e de déficits de micronutrientes associados à TB e à infecção pelo HIV. Esse reconhecimento é seguido da recomendação de que seja realizado o aconselhamento do consumo de uma alimentação saudável que atenda a Recommended Dietary Allowance (RDA) (Billon, 2005; Maras et al., 2004; Govender, Kindness e Jonnalagadda, 2009) para os casos de má nutrição leve ou moderada (IMC entre 16 e 18,5Kg/m2) (World Health Organization. 2008), e a suplementação alimentar nos casos graves, sem que haja descrição de como esta deva ser efetuada (Billon, 2005; Maras et al., 2004; Govender, Kindness e Jonnalagadda, 2009).

A RDA determina a quantidade de nutrientes que deve ser ingerida para a manutenção da saúde nos diferentes ciclos da vida, não considerando a variabilidade entre os indivíduos dentro de cada grupo, nem a existência de diferentes doenças que impactam no estado nutricional (National Academy Press 1989). Enquanto a American Society for Parenteral and Enteral Nutrition (ASPEN) (ASPEN 2009) aponta que, independente da doença de base, o aconselhamento dietético só deve ser implementado quando a capacidade de ingestão alimentar adequada tiver sido restaurada. Sugerindo que a suplementação oral ou terapia nutricional enteral ou parenteral deve ser considerada quando exista o baixo consumo alimentar ou o aumento da demanda nutricional relacionada ao quadro clínico de uma doença.

Soma-se a isso, a não existência de critérios bem definidos de classificação ou de quantificação para o monitoramento da qualidade da adesão dietética (Desroches et al., 2011), e que há poucos trabalhos

brasileiros conduzidos com pacientes TB tratados nutricionalmente (Baruzzi et al., 2001; Klautau e Kuschnaroff, 2005; Orellana et al., 2006; Cantalice Filho, 2009; Piva et al., 2013).

Portanto, a discussão do estado nutricional antes, durante e ao final do tratamento da TB nos pacientes tratados no Brasil é importante, principalmente pelo fato do sistema de saúde brasileiro fornecer as medicações para TB e HIV gratuitamente, indicando uma condição diferenciada e dificultando a extrapolação de investigações conduzidas em outros países (Armijos et al., 2010; Gaikwad et al., 2013; Motswagole et al., 2013; Kawai et al., 2013; Islam et al., 2013) para os pacientes tratados no Brasil.

3. OBJETIVO

3.1 Objetivo geral

Avaliar a capacidade do aconselhamento dietético exclusivo preconizado pelo Ministério da Saúde de suprir todas as demandas nutricionais causadas pela tuberculose em pacientes infectados ou não pelo HIV.

3.2. Objetivos específicos

a) Descrever o estado nutricional de pacientes com tuberculose, infectados ou não pelo HIV, que receberam aconselhamento dietético exclusivo durante o tratamento.
b) Identificar o grau de adesão ao aconselhamento dietético e os fatores que interferiram nesta adesão.

4. DESENVOLVIMENTO

4.1. Tuberculose e HIV

A TB é um importante problema de saúde pública, e tem como principal forma de transmissão a inalação de partículas contendo bacilos expelidos pela tosse, fala ou espirro de doentes com TB ativa de vias respiratória (Ministério da Saúde do Brasil 2011). Os sinais clínicos da disseminação da TB são bastante variados e sofrem influência de uma série de fatores como: idade, resistência imunológica, estado nutricional, presença de co-morbidades, virulência do bacilo, local da infecção.

O HIV é um vírus linfotrópico humano capaz de infectar particularmente as células CD4 T *helper* por sua alta afinidade. Independente do número de células infectadas a disfunção imunológica é inevitável, pois a replicação do vírus ocorre com mais eficiência na ativação das células CD4 (Stebbing, Gazzard, e Douek, 2004). Este processo resulta na vulnerabilidade para grande variedade de doenças graves, como pneumonia, tuberculose, meningite, sarcoma de Kaposi e outros tipos de câncer (Fagundes et al., 2010). A manifestação clínica da TB num paciente soropositivo para o HIV depende da sua condição imunológica (Ministério da Saúde do Brasil 2011).

Em indivíduos infectados por HIV as manifestações clínicas da TB podem ser muito mais graves do que em indivíduos HIV negativo (Klautau e Kuschnaroff, 2005). Os indivíduos infectados por HIV sem intervenção terapêutica têm cerca de 10% de chance ao ano de desenvolver a TB (van Rie et al. 1999; Havlir e Barnes 1999; Jamal e Moherdaui 2007; Ministério da Saúde do Brasil 2011). Perspectiva alarmante no contexto brasileiro, onde anualmente são notificados aproximadamente 70 mil casos novos de TB e ocorrem 4,6 mil mortes em decorrência da TB (Ministério da Saúde 2014).

4.2. Tuberculose e estado nutricional

As alterações nutricionais são outro importante problema de saúde pública em muitos países e quando a deficiência de micronutrientes está presente é capaz de agravar a evolução clínica de pacientes com doenças infecciosas (Tulchinsky e Varavikova, 2014). A má nutrição em pacientes com TB associada ou não com HIV é comum, e cursa usualmente com o baixo consumo alimentar, a má absorção e o aumento da demanda calórica (Islam et al., 2013; Schwenk et al., 2004; Motswagole et al., 2013; Hsu et al., 2005).

A má nutrição prejudica diversos aspectos da defesa do hospedeiro, principalmente a imunidade mediada por células, havendo declínio na produção de citocinas, como interferon-γ e interleucina-2 (IL-2), interleucina-1 (IL-1) e o fator de necrose tumoral (TNF-a), assim como induz alterações hormonais tireoidianas, sendo comumente relacionada tanto com a coexistência da TB, quanto com a sua maior morbimortalidade (Dai, Phalen, e McMurray, 1998).

Portanto, o bom estado nutricional é fundamental para a longevidade dos pacientes com TB, principalmente os portadores de HIV, e para a eficácia das drogas relacionadas ao tratamento (WHO 2013).

Nutrientes como a proteína tem amplo reconhecimento de sua importância no manejo clínico. As proteínas séricas são marcadores importantes do estado nutricional bioquímico uma vez que avaliam a má nutrição proteica, com destaque para a albumina que é o marcador mais frequentemente utilizado pelo seu importante poder na evolução de eventos clínicos, pela sua abundância como circulante do plasma e dos líquidos extracelulares e pela sua função no transporte de drogas, sendo, portanto, importante parâmetro de má nutrição de fase não aguda devido à sua longa meia vida (18 a 20 dias) (Santos et al., 2004; Celano et al., 2007).

Infecções como a TB necessitam do emprego de marcadores nutricionais agudos como a transferrina sérica (meia vida de 7 a 8 dias) que traduz o déficit proteico logo quando este se inicia. Pode estar aumentada em situações como a carência de ferro, as hepatites agudas, os quadros de anemia, as infecções e as hepatopatias crônicas, além das neoplasias,

tornando ainda mais importante o monitoramento de micronutrientes (Celano et al., 2007; Peres e Koury 2011).

4.2.1. Desnutrição em tuberculose

Ao longo da história, a TB é sinônimo de consumo orgânico relacionado à alteração energético metabólica e ao baixo consumo alimentar resultantes do aumento de citocinas inflamatórias. Estas alterações reduzem a concentração de leptina plasmática, levando a uma modificação da composição corporal caracterizada por diminuição das massas muscular e adiposa. Essa modificação da composição corporal é denominada pela FAO (State of Food and Agriculture 2013: Food Systems for Better Nutrition. 2013) como má nutrição por redução de massa corporal ou desnutrição e exige especial atenção na avaliação e no diagnóstico do estado nutricional (Islam et al. 2013; Schwenk et al. 2004), principalmente em pacientes com doenças infecciosas.

Nas pessoas com TB e com HIV a desnutrição agrava o risco de progressão das doenças e é considerada um preditor de mortalidade (WHO 2013). A OMS (WHO 2013) e o MS (Ministério da Saúde do Brasil 2011) preconizam o uso do Indice de Massa Corporal (IMC) ou do percentual de perda de peso para monitorar o grau de magreza e de risco clinico nutricional. Muitos dos estudos sobre o estado nutricional de pacientes que receberam aconselhamento dietético ou suplementação nutricional durante o tratamento da TB utilizam o IMC como marcador de recuperação ou não do estado nutricional (Sinclair et al. 2011).

Mas o SISVAN (Ministério da Saúde do Brasil 2004) propõe o uso de outras medidas antropométricas para melhor entendimento das alterações de massa corporal. As medidas de circunferências e dobras, como a circunferência do braço (CB) e a dobra cutânea triciptal (DCT), já são reconhecidas como medidas de avaliação nutricional importantes na prática clínica (JW et al. 2014) pela sua capacidade preditiva e facilidade de verificação de composição corporal (Qureshi et al. 1998; Tsiaousi e Hatzitolios 2012; Landi, Liperoti, e Onder 2013).

4.2.2. Má nutrição de micronutrientes em tuberculose e HIV

A má nutrição no paciente com TB e HIV pode ocorrer devido à anorexia, diminuição da absorção de micronutrientes ou aumento da necessidade, decorrente do catabolismo aumentado (Karyadi et al., 2000), elevando o risco de deficiência de vitaminas e de minerais, principalmente ∂-tocoferol, retinol, piridoxina, folato e zinco (Van Lettow et al. 2004), que pode ainda ser agravada pelo excesso de radicais livres provenientes tanto da progressão da TB, como o da síndrome da imunodeficiência adiquirida (AIDS) (Valle, Hernández e Ávila, 2013).

Os organismos se protegem do estresse oxidativo por mecanismos químicos e enzimáticos. Químicos quando os agentes antioxidantes como o ∂-tocoferol, o retinol, o selênio, o ácido ascórbico e a glutationa reduzida, diminuem a ação tóxica das espécies reativas de oxigênio, como o peróxido de hidrogênio (H_2o_2), o superóxido (0_2^-) e os lipoperóxidos produzidas intra e extra celularmente. Enzimático quando os organismos expostos a espécies reativas de oxigênio sintetizam as proteínas antioxidantes (enzimas), como superóxido dismutase, catalase e glutationa peroxidase (Pereira 1996; Speisky C. e Jiménez T. 2000; Ramalho, Saunders, e Accioly 2005).

O ∂-tocoferol é importante na redução do processo citotóxico das reações em cadeia de radicais livres, comuns em pacientes infectados por HIV (Deresz et al., 2007; Magalhães, 2013; Valle, Hernández e Ávila, 2013). A demanda do ∂-tocoferol é aumentada na ativação da capacidade antioxidante dos macrófagos, uma vez que seu conteúdo em macrófagos e em monócitos é aproximadamente 10 vezes maior do que em plaquetas e hemácias (B. Pereira 1996), estando diretamente envolvido na prevenção da peroxidação da membrana celular (Ramirez-Bribiesca et al. 2005).

O ∂-tocoferol e o selênio têm funções biológicas relacionadas. O selênio (Se) é um componente essencial na formação da glutationa peroxidase, enzima envolvida na detoxicação do peróxido de hidrogênio e na hidroperoxidação lipídica (Ramirez-Bribiesca et al. 2005). Sendo considerado forte marcador de prognóstico na infecção por HIV (Feitosa, 2012).

A deficiência combinada de selênio com as de ácido ascórbico e ∂-tocoferol podem causar danos ao músculo esquelético e quando combinado com a deficiência proteica acarreta implicações orgânicas significantes (Bertinato et al. 2007).

A deficiência de vitamina A (retinol e carotenoides) também é comumente encontrada em pacientes infectados por HIV, independente da presença de imunodeficiência, gravidade ou da existência de infecção oportunista e da presença de sintomas da deficiência (Silveira et al. 1999). Os carotenoides possuem habilidade de neutralizar os radicais peroxil e o oxigênio singleto*,* através da transferência de energia excitável, do oxigênio singleto para o carotenoide, com subseqüente dissipação de energia na forma de calor (com regeneração do carotenoide) ou através de reação química, do carotenoide com o oxigênio singleto, ocasionando a destruição irreversível do antioxidante (Palace et al. 1999).

A piridoxina participa da cadeia respiratória das células e ajuda no metabolismo das proteínas e dos aminoácidos. Com especial importância no tratamento da TB, para evitar os efeitos adversos do uso da isoniaziada, que pode provocar deficiência de niacina devido à competição do uso do piridoxal fosfato, importante cofator da aminotransferase na via metabólica de conversão do triptofano à niacina (de Maria e Moreira 2011; Mv, Vg, e As 2011; Rosa 2014).

A ação antioxidante do folato decorre da sua importância, como substrato para a síntese de metionina, que catalisa a remetilação da homocisteína, considerado um biomarcador de estresse oxidativo, produzido como consequência da conversão de metionina a cisteína, e que quando em excesso aumenta a produção de espécies reativas do metabolismo do oxigênio (Ondani, Carvalho, e Galvão 2011; Rebuglio Vellosa et al. 2013).

O zinco está envolvido na atividade de trezentas enzimas, em todas as principais vias metabólicas, tendo papel crítico na síntese de proteínas e do metabolismo de carboidratos, na manutenção do paladar e olfato, podendo seu *déficit* resultar na recusa alimentar por hiposmia e hipogeusia; além de ter papel essencial na função imunológica e no transporte da vitamina A aos tecidos alvo (Peres e Koury, 2011).

O zinco apesar de estar em baixas concentrações nos órgãos, participa diretamente da manutenção do crescimento e do desenvolvimento normais, do funcionamento adequado do sistema imunológico, da defesa antioxidante, da função neurosensorial e, também, da transcrição e tradução de polinucleotídios (Salgueiro et al. 2000). Sua deficiência resulta na diminuição da função do timo em até 80% e na inibição da replicação viral de infectados por HIV, que impõe maior demanda deste mineral (B. Pereira 1996; Tanchou et al. 1998; Luisi et al. 2014).

O ferro também merece especial atenção em infectados por HIV. Na fase aguda da AIDS a anemia e a diminuição da hemoglobina e do ferro circulantes decorrem da queda imunológica do hospedeiro por menor produção de hemácias e pelo sequestro do ferro no fígado, nos músculos e em células do sistema fagocítico-mononuclear (Bobbio-Pallavicini et al. 1989).

Sabe-se que usualmente a ferritina encontra-se aumentada em pacientes infectados por HIV, como resultado da capacidade de agregar os átomos de ferro, apartando-os para o compartimento de armazenamento do ferro, diminuindo a disponibilidade de ferro livre para bactérias e outros microorganismos, otimizando os sistemas bacteriostáticos e bactericidas do soro, linfa e exsudatos (Bobbio-Pallavicini et al. 1989). O *M. tuberculosis* e outras bactérias podem utilizar o ferro heme para garantir seu crescimento, não sendo esperado identificar deficiência de ferro sérico, por serem capazes de bloquear a entrada do ferro na célula, permitindo sua disponibilidade no meio sérico (Thomas et al. 2011; Jones e Niederweis 2011).

Os achados aqui mencionados reforçam a hipótese de que para combater o aumento do estresse oxidativo associado à presença concomitante de TB e HIV é preciso manter o bom estado nutricional desses pacientes (WHO 2013).

4.2.3. Manejo da má nutrição em tuberculose

O Ministério da Saúde do Brasil (Ministério da Saúde 2013; Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente

Transmissíveis/AIDS (Brazil) 2006) e a Organização Mundial de Saúde (OMS) (WHO 2013) recomendam que seja feito o aconselhamento do consumo de uma alimentação saudável que atenda a Recommended Dietary Allowance (RDA) para os pacientes com má nutrição leve ou moderada (IMC entre 16 e 18,5Kg/m^2), e a prescrição da suplementação alimentar nos casos graves (Billon 2005; Maras et al. 2004; Govender, Kindness, e Jonnalagadda 2009).

Contudo, a RDA estabelecida pela *Food and Nutrition Board of the National Academy of Sciences*, determina a quantidade de nutrientes que deve ser ingerida para a manutenção da saúde nos diferentes ciclos da vida (National Academy Press 1989). Ela não leva em consideração a variabilidade entre os indivíduos dentro de cada grupo, nem que as diferentes doenças impactam no estado nutricional gerando diversos graus e tipos de deficiência nutricional (National Academy Press 1989), o que leva provavelmente a necessidades nutricionais especiais.

Uma questão relevante na prática clínica é a adesão dos pacientes à proposta de mudança do comportamento alimentar temporária ou definitiva, assunto pouco discutido na literatura científica, não existindo critérios bem definidos de classificação ou de quantificação, principalmente quanto às técnicas para o monitoramento da qualidade de adesão no âmbito da alimentação (Desroches et al. 2011). Apesar de não haver estudos brasileiros sobre a má adesão dietética (Scabim, Eluf-Neto, e Tess 2012), sabe-se apenas, que o abandono do acompanhamento nutricional é elevado, podendo variar de 20 a 60% (Westman et al. 2002; Scabim, Eluf-Neto, e Tess 2012).

Desta forma, a ASPEN propõe que a nutrição enteral ou parenteral deve ser implementada quando a má nutrição estiver instalada ou a capacidade de se alimentar de forma adequada estiver prejudicada por adoecimento, sugerindo que a prescrição dietética por via oral por dieta individualizada ou através de aconselhamento padronizado ou individualizado, somente seja implementada quando a capacidade de alimentação estiver restabelecida (ASPEN - American Society for Parenteral and Enteral Nutrition 2011; ASPEN - American Society for Parenteral and Enteral Nutrition 2009).

5. MÉTODOS

5.1 Desenho do estudo

Estudo observacional com seguimento prospectivo, realizado em pacientes que receberam diagnóstico de TB no período de julho de 2008 a setembro de 2013.

5.2 Critérios de elegibilidade e de inelegibilidade

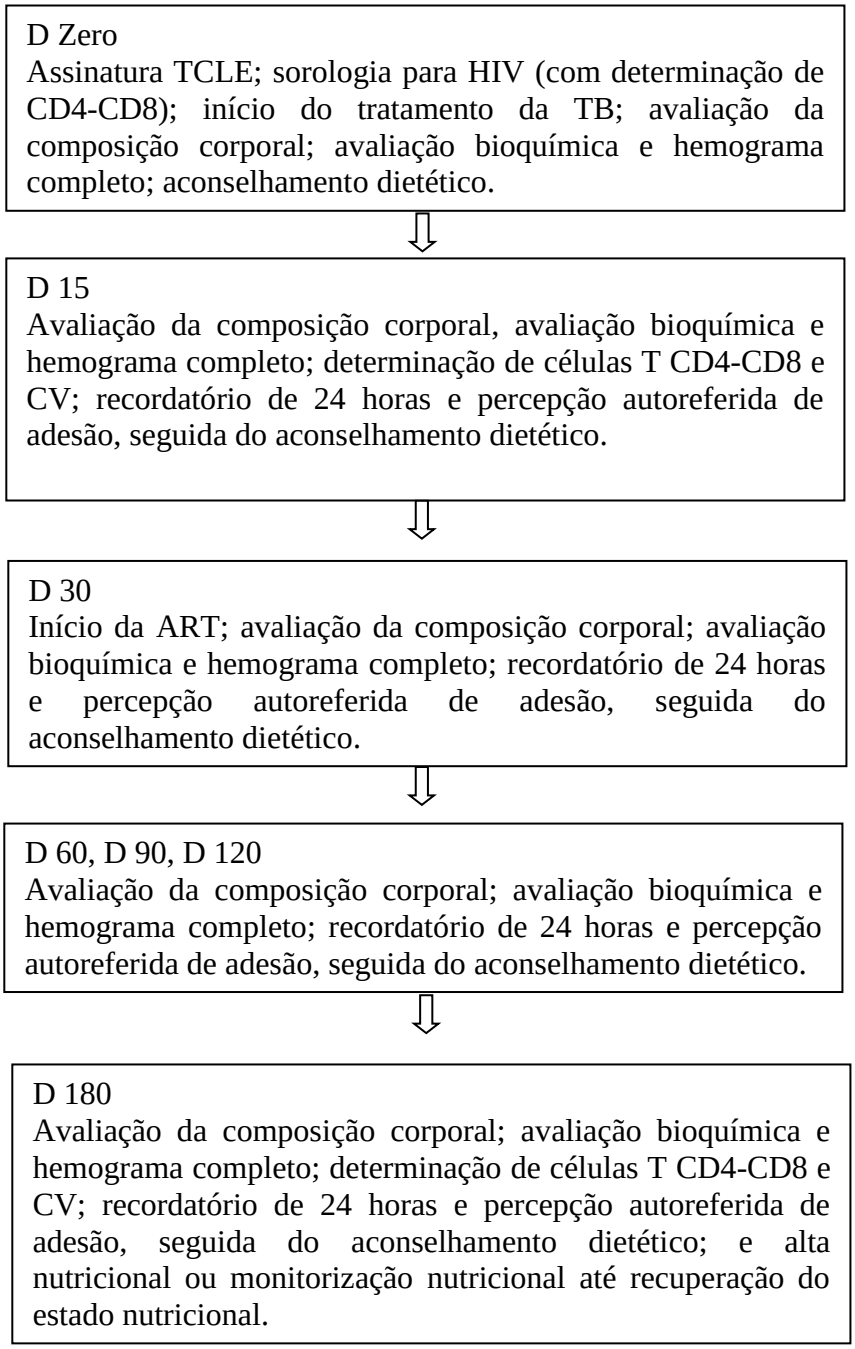
Foram elegíveis os pacientes infectados ou não por HIV, desde que virgens de tratamento antirretroviral, com TB e idade entre 18 a 65 anos, de ambos os sexos, que concordaram em participar do estudo, bem como em não utilizar nenhum suplemento nutricional sem consentimento do investigador durante todo o período do estudo.

Foram inelegíveis os indivíduos com diagnóstico nutricional de má nutrição grave (por necessitarem de suplementação), aqueles que utilizaram algum tipo de suplementação nutricional nos seis meses que precederam o estudo, aqueles com doenças hipermetabólicas ou disabsortivas, e as gestantes e nutrizes.

Somente a suplementação de piridoxina (vitamina B6) foi permitida, respeitando-se o protocolo do MS (Ministério da Saúde do Brasil 2011) que a recomenda a todos os pacientes que fazem uso de isoniazida.

5.3 Etapas do estudo

As etapas do estudo seguiram o monitoramento do tratamento da TB, conforme figura 1.



D= dia; TCLE = termo de consentimento livre e esclarecido; HIV= vírus da imunodeficiência humana; ART = terapia antiretroviral; Avaliação bioquimica = albumina, capacidade de fixação de ferro, ferro, selênio, zinco, retinol e tocopherol; CD4= linfócito TCD4; CD8= linfócito TCD8; CV = carga viral; aconselhamento dietético = o documento proposto pelo Ministério da saúde brasileiro foi entregue e lido com o paciente ("CGAN - Coordenação-Geral de Alimentação e Nutrição" 2014).

Figura 1. Etapas do estudo

5.4 Diagnóstico Clínico e Nutricional

O diagnóstico de TB foi estabelecido pelos sinais e sintomas clínicos da doença, pelo exame radiológico compatível e pela identificação do *Mycobacterium tuberculosis* em cultura. Quando o *Mycobacteium tuberculosis* não foi isolado foram considerados casos de TB aqueles que tiveram prova terapêutica positiva, seguindo as recomendações de diagnóstico e tratamento do MS de 2011 (Ministério da Saúde do Brasil 2011). Da mesma forma, o diagnóstico e o tratamento da infecção pelo HIV também seguiu as recomendações do MS (Ministério da Saúde do Brasil 2008; Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006; “Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em adultos (Brazil) 2013” 2014).

Os pacientes foram submetidos à avaliação da composição corporal e ao aconselhamento dietético no diagnóstico e durante os seis meses do tratamento da TB. Em todas as consultas o aconselhamento dietético foi reforçado após a realização do recordatório de 24 horas e do questionamento de adesão autorreferida.

A avaliação do estado nutricional (anexo II e III) englobou parâmetros antropométricos e bioquímicos. As medidas antropométricas foram mensuradas e seguiram os pontos de corte estabelecidos no SISVAN (Ministério da Saúde do Brasil 2004). Foram verificados: peso, estatura, circunferência braquial (CB), dobra cutânea triciptal (DCT) e circunferência muscular do braço (CMB). As medidas de peso e estatura foram anotadas para determinação do índice de massa corporal (IMC), e de acordo com o proposto por Lohman (Lohmann, Roche, e Martorell 1988) (quadro 1), como utilizado pelo Ministério da Saúde (Ministério da Saúde do Brasil 2011) e Organização Mundial da Saúde (WHO 2013) para identificação do impacto do estado nutricional na evolução clinica do paciente e sugestão terapêutica nutricional (aconselhamento ou suplementação) em pacientes com TB e em infectados por HIV.

Quadro 1 – Parametros Antropométricos utilizados na avaliação nutricional dos pacientes durante o tratamento da TB.

Indicador	Valor de referência	Método	Referência bibliográfica
IMC	18.5-24.9Kg/m^2	Obtido apartir dos valores de peso em quilos e da estatura em metros. Peso (Kg) ÷ estatura $(m)^2$	Ministério da Saúde do Brasil 2004 Lohmann, Roche, e Martorell 1988
CB	28.5-29.3cm	Contornar o braço com a fita antropométrica no ponto médio da parte superior do braço de forma que a fita fique aderida à pele, mas não pressione os tecidos moles	
DCT	11.4-18.2mm	Medida do ponto médio posterior superior do braço não dominante. Com os dedos, polegar e indicador da mão esquerda pinçar a dobra de pele e tecido adiposo, suspendendo-o levemente. Ajustar o paquímetro horizontalmente a cerca de 1 cm, manter por três segundos e repetir a operação por 03 vezes.	
CMB	21.0-27.8cm	Obtido a partir das medidas CB e DCT. CMB = CB – (DCT x π)	

A albumina, proteína total (PTN), capacidade de fixação de ferro (CLFe), ferro, selênio, zinco, retinol, ∂-tocoferol, hemoglobina, hematócrito, leucócitos e linfócitos foram os componentes da avaliação bioquímica (quadro 2), pelo já reconhecido papel do estado corporal de proteína e de micronutrientes nas funções imunológicas (Mocchegiani et al. 2014).

Quadro 2 – Biomarcadores utilizados na avaliação nutricional dos pacientes durante o tratamento da TB.

Indicador	Valor de referência	Método	Referência bibliográfica
Hemoglobina	11 - 18g/dl	Microscopia óptica automatizada	“baracioli_lmsv_dr_sjrp.pdf” 2013; Ministério da Saúde do Brasil 2014a
Hematócrito	34 - 54%	Microscopia óptica automatizada	NAOUM e Naoum 2008
Albumina	3.4 - 5.0g/dl	Cromatrografia líquida	Blackburn e Thornton 1979; Helio Vannucchi et al. 1996
PTN	6.4 - 8.2g/dl	Cromatrografia líquida	Mahan et al. 2005
Globulina	2.5 - 4.0g/dl	Cromatrografia líquida	Mahan et al. 2005
CLFE	250 - 450mg/dl	Cromatrografia líquida	Dale, Burritt, e Zinsmeister 2002
Retinol	> 0.7 mcg/dl	Cromatografia líquida de alto desempenho	Ministério da Saúde do Brasil 2000; Ministério da Saúde do Brasil 2014a
Tocoferol	> 0.5 mg/l	Cromatografia líquida de alto desempenho	Hélio Vannucchi et al. 1994
Zinco	> 70mg/dl	Espectometria de absorção atômica	Sarni et al. 2010
Selenio	70 – 90mcg/l	Espectometria de absorção atômica	Catania, Barros, e Ferreira 2009
Ferro	50 –170mcg/dl.	Cromatografia líquida de alto desempenho	Dale, Burritt, e Zinsmeister 2002

As amostras de soro foram congeladas (-20 °C a -10 °C) para análise de vitaminas A e E e zinco; e o plasma foi refrigerado entre 2 a 8 °C para análise de selênio. Todos os tubos foram transportados para o laboratório para análise com um máximo de sete dias de amazenamento. As demais análises foram feitas imediatamente após a coleta de sangue.

Considerou-se como nutridos, os indivíduos com todos os resultados de composição corporal e da avaliação bioquímica e hematológica dentro do padrão de normalidade; e como mal nutridos, aqueles com pelo menos um

destes resultados fora dos valores de referência (State of Food and Agriculture 2013: Food Systems for Better Nutrition. 2013).

Os pacientes foram classificados nas seguintes formas de má nutrição: (a) global, considerando todos os parâmetros avaliados; (b) calórica utilizando apenas os parâmetros IMC, DCT e CB; (c) proteica utilizando apenas o parâmetro somático CMB, e os parâmetros viscerais: proteína sérica, albumina, transferrina e capacidade de fixação de ferro; (d) específica através dos marcadores séricos de ferro, selênio, zinco, retinol e ∂-tocoferol.

A avaliação da adesão ao aconselhamento dietético foi realizada pelo método autorreferido, por ser muito utilizado tanto em pesquisa clínica, quanto na atenção cotidiana na área da saúde (Polejack e Seidl 2010). O registro auto-referido foi uma adaptação das propostas de Polejack (Polejack e Seidl 2010), Marques (MARQUES et al. 2010), Dig (Dig 2010) e Vargas (da Silva VargasI et al. 2011). Esta foi registrada em todas as consultas, através das categorias "*sim, segui*", usada quando o paciente referia seguir completamente o que orientado; "*segui muito satisfatoriamente*" usado quando paciente referia ter seguido quase todas as orientações, mas ter tido dificuldade em poucos aspectos; "*segui pouco satisfatoriamente*" quando o paciente referia ter tentado seguir, mas admitia não ter seguido a maior parte do orientado, e "*não segui*" usado quando o paciente referia não ter seguido nada do que foi orientado. Sendo feito, o registro da percepção do indivíduo sobre o quanto seguiu do que foi orientado e os fatores que influenciaram negativamente a qualidade da adesão. Considerou-se como boa adesão ao aconselhamento dietético os indivíduos com relato de "*sim segui*" e "*segui muito satisfatoriamente*" e má adesão o relato de "*não segui*" ou "*segui pouco satisfatoriamente*".

A avaliação do consumo calórico e de macro e micronutrientes foi realizada pelo recordatório de 24 horas. O inquérito dietético recordatório de 24 horas foi aplicado em todas as consultas, sendo anotados, em medidas caseiras, todos os alimentos e líquidos consumidos nas 24 horas anteriores a consulta, e foram analisados no software Dietwin Profissional Plus®. Os resultados dos recordatórios de 24 horas foram comparados a *Recommended Dietary Allowance* (RDA) para determinar se a ingestão dos pacientes atingiu ou não a recomendação preconizada.

Os desfechos do estudo foram a recuperação ou não de todos os tipos de má nutrição ao final dos 180 dias de tratamento da TB, a ingestão ou não da recomendação proposta pela *Recommended Dietary Allowance* (RDA) ao longo dos 180 dias de tratamento da TB, e a quantidade de calorias totais consumidas, isoladamente, ao longo do tratamento de TB.

5.5 Aspectos éticos

Este estudo foi conduzido de acordo com os padrões éticos para pesquisa em seres humanos da Declaração de Helsinki, tendo aprovação pelo Comitê de Ética em Pesquisa do Instituto de Pesquisa Clínica Evandro Chagas sob o número CAAE 0008.0.009.000-08 em abril de 2008. Todos os pacientes que aceitaram participar do estudo assinaram um termo de consentimento livre e esclarecido (TCLE) (anexo I).

5.6 Plano de Análise

Os dados foram analisados usando o programa R-project® versão 3.0.2. Os resultados foram expressos dividindo os dados em tempo inicial e seguimento tanto para o grupo de infectados por HIV, quanto para os não infectados. Para o tempo inicial as frações e as contagens de pacientes em cada categoria estabelecida ou indicador utilizado foram apresentadas para informações categóricas, e para as variáveis contínuas a média e desvio padrão ou mediana e o intervalo interquartil foram estimados se a variável apresentasse distribuição normal ou não respectivamente. Nos tempos seguintes as mesmas informações foram estratificadas considerando o momento da visita ao longo do tratamento. Os gráficos foram mostrados como trajetórias não ajustadas individuais para cada variável, e como fração de sujeitos com ou sem as condições de interesse em cada tempo. As diferenças foram consideradas significantes se o valor de p foi ≤ 0.05.

Para modelagem de consumo calórico, modelos marginais foram utilizados. Tomando-se como desfecho a representação binária do consumo de uma RDA (sim ou não), modelou-se com uma função “glm” (generalized linaer models) para dados longitudinais da família binomial considerando-se intervalos de tempos irregulares dentro de cada paciente. Estratégia de

análise semelhante adotou-se para o desfecho consumo total de calorias (Kcal) estimado pelo recordatório, no entanto, a família adotada para o “glm” foi a gaussiana. Para ambas estratégias, a estrutura de correlação que melhor se adequou aos dados foi a substituível (ou “*exchangeable*”). Os seguintes preditores definidos com antecedência foram testados com algumas interações: tempo, infecção pelo HIV, adesão, renda, escolaridade, forma clínica da TB. Removeu-se as variáveis com p valor < 0.05 no teste Wald. Os erros padrão foram todos estimados de forma robusta.

6. ARTIGOS

Os resultados obtidos neste estudo serão apresentados no formato de artigos em fase de publicação.

Nesta seção, esses resultados estão ordenados da seguinte forma:

6.1. ARTIGO 1: apresenta e discute o estado nutricional dos pacientes infectados e não infectados por HIV, em tratamento para tuberculose, submetidos ao aconselhamento dietético conforme RDA, com base nos resultados da análise de composição corporal e bioquímica nutricionais.

Título: "*Nutritional supplementation is a necessary complement to dietary counseling among tuberculosis and tuberculosis-HIV patients*."

Submetido à *PLOS ONE* em 03 de julho de 2014, com recebimento confirmado em 10 de julho de 2014, tendo sido aceito com solicitação de alterações em 06 de agosto de 2014. O prazo para resposta com as últimas correções foi até 21 de dezembro de 2014 (anexo IV).

6.2. ARTIGO 2: apresenta e discute a capacidade de adesão ao aconselhamento dietético dos pacientes infectados e não infectados por HIV, em tratamento para tuberculose.

Título: "*Dietary counseling adherence during tuberculosis treatment: a longitudinal study*."

Foi submetido em 06 janeiro de 2015 a *BioMed Research International* aguardando posicionamento da revista (anexo V).

6.1 Artigo 1

Full Title: **Nutritional supplementation is a necessary complement to dietary counseling among tuberculosis and tuberculosis-HIV patients.**

Short Title: **Malnutrition in tuberculosis patients.**

Adriana Costa Bacelo[2*], Andrea Ramalho[3], Pedro Emmanuel Brasil[4], Cláudia dos Santos Cople-Rodrigues[5], IngebourgGeorg[6], Eliane Paiva[7], Sheila Argolo[8], Valeria Rolla[1]

1 – Clinical Research Laboratory on Mycobacteria –National Institute of Infectious Diseases Evandro Chagas - Fiocruz – Rio de Janeiro/RJ – Brazil;
2 – Nutrition Service –National Institute of Infectious Diseases Evandro Chagas – Fiocruz – Rio de Janeiro/RJ - Brazil;
3 – Josué de Castro Institute- UFRJ – Rio de Janeiro/RJ –Brazil;
4 – Clinical Reasearch Laboratory on Chagas Disease –National Institute of Infectious Diseases Evandro Chagas – Fiocruz – Rio de Janeiro/RJ – Brazil
5 – Institute of Nutrition- UERJ – Rio de Janeiro/RJ –Brazil;
6 – Diagnostics Activities Coordinating – Immunodiagnostic Section–National Institute of Infectious Diseases Evandro Chagas– Fiocruz – Rio de Janeiro/RJ –Brazil;
7 – Department of Nutrition– UNISUAM – Rio de Janeiro/RJ –Brazil;
8 – Sergio Franco Laboratory – Caxias/RJ –Brazil.

* Corresponding author:
Email: **adriana.bacelo@ini.fiocruz.br**

Abstract

The Brazilian Ministry of Health and the World Health Organization recommend dietary counseling for patients with malnutrition during tuberculosis treatment. Patients under tuberculosis therapy were followed-up to evaluate the effectiveness of dietary counseling. **Methods:** an observational follow-up study over a 180 day period of tuberculosis therapy in adults was conducted. Subjects were assessed for body composition (using BMI, TSF and MUAC parameters), serum biomarkers and offered dietary counseling. The data obtained at each visit (D15, D30, D60, D90, D120, D150, and D180) were analyzed, showing trajectories over time and central tendencies each time. **Results:** at baseline, mean age was 41.1 (±13.4) years; they were predominantly male, with income lower than a local minimum wage and at least six years of schooling. Patients showed predominantly pulmonary tuberculosis. All patients suffered from malnutrition. At baseline, the overall energy malnutrition prevalence was 70.6%. At the end, energy malnutrition was reduced to 57.1% (42.9% of HIV- and 71.4% of the HIV+). Micronutrients malnutrition was evident in 71.4% of the HIV- patients and 85.7% of HIV+ patients at the end of tuberculosis therapy. Using BMI (≤18.5 kg/m^{2}cutoff) as an index of malnutrition, it was detected in 23.9% of the HIV- and 27.3% of the HIV+ patients at baseline with no evident improvement over time; using TSF (≤11.4mm as cutoff) or MUAC (≤28.5cm as cutoff), malnutrition was detected in 70.1% and 85.3% of all patients, respectively. In this study, anemia at baseline was observed in both groups (63.2%), however it was significantly more pronounced in the HIV+. **Conclusion:** dietary counseling was not enough to recover from malnutrition. BMI was not sensitive for assessing changes in nutritional status. HIV+ patient recovered better from anemia than the non-infected patients. Triceps skin fold, mid–upper-arm circumference and serum biomarkers were more sensitive to detect and follow-up on nutritional status.

Keywords: malnutrition, micronutrients, tuberculosis, HIV, nutritional status, dietary counseling.

Introduction

Tuberculosis and the human immunodeficiency virus (HIV) are historically associated with malnutrition, reduced appetite, low dietary intake, malabsorption and increased caloric demand (Schwenk et al. 2004; Hsu et al. 2005; Islam et al. 2013; Motswagole et al. 2013).

The Brazilian Ministry of Health (BMH) (Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006) and the World Health Organization (WHO) (WHO 2013) recognize the existence of caloric malnutrition, protein malnutrition and micronutrient deficits associated with tuberculosis and HIV infection. This is followed by the recommendation that patients with mild or moderate malnutrition should eat a healthy diet that meets the Recommended Dietary Allowance (RDA) (Maras et al. 2004; Govender, Kindness, e Jonnalagadda 2009). On the other hand, patients with severe malnutrition should have food supplementation. However, neither WHO nor BMH currently recommend any specific nutritional supplementation for severe malnutrition in these settings.

Studies conducted with patients being treated for tuberculosis, who followed dietary advice exclusively or received supplemental food donation (Martins, Morris, e Kelly 2009; Khan et al. 2012; Gaikwad et al. 2013), showed early BMI improvement. Additional parameters with evidence of improvement with this intervention were: total caloric intake, sanitary requirements for food preparation, serum protein and clinical response. This intervention also determined earlier improvement on acid fast bacilli detectionon sputum smears and reduced bronchial secretion (Martins, Morris, e Kelly 2009).

There is an extensive discussion on the nutritional status of patients with tuberculosis, including the occurrence of anemia, reduced food consumption and adherence to treatment when food is donated (Sinclair et al. 2011), however not much has been studied on nutritional supplementation among Brazilians (Baruzzi et al. 2001; Klautau e Kuschnaroff 2005; Orellana et al. 2006; Cantalice Filho 2009; Piva et al. 2013). The discussion of nutritional status before, during and after tuberculosis treatment in patients treated in Brazil is particularly intriguing, as the Brazilian Health Care System provides free access to tuberculosis and HIV treatments. This is a unique situation, and it is not expected that findings from studies conducted in other countries (Armijos et al. 2010; Gaikwad et al. 2013; Motswagole

et al. 2013; Kawai et al. 2013; Islam et al. 2013) could be extrapolated to Brazilian patients.

This study aims to describe the nutritional status of patients with tuberculosis, including those infected with HIV, who received dietary counseling exclusively during tuberculosis treatment in Rio de Janeiro and to evaluate if this strategy is enough to recover their nutritional impairment observed at the beginning of tuberculosis treatment.

Methods

Study design

This is an observational prospective follow-up study that was conducted in patients who received tuberculosis diagnosis from July 2008 to September 2013.

Eligibility and ineligibility criteria

Patients were eligible if they had tuberculosis, and they were between 18 and 65 years old and agreed to participate in the study. Patients were urged to refrain from using nutritional supplements during the entire study period. Exclusion criteria were: those who had hyper metabolism, digestive diseases or who used any nutritional supplementation up to six months before tuberculosis treatment. Only the supplementation of pyridoxine (vitamin B6) was allowed, in conformity with the protocol of the Brazilian Ministry of Health (Ministério da Saúde do Brasil 2011), which recommends vitamin B6 concomitant with isoniazid for all patients being treated for tuberculosis. Individuals were discontinued from the study if they presented severe malnutrition at any point, as in such cases a supplementation was provided.

Clinical diagnosis and nutrition

The diagnosis of tuberculosis was established by assessing clinical signs and symptoms, compatible radiological findings and the identification of *Mycobacterium tuberculosis* in culture. In cases where the *Mycobacterium tuberculosis* was not isolated, the diagnosis of tuberculosis was made using therapeutic response (Ministério da Saúde do Brasil 2011). The strategies for both tuberculosis and HIV infection diagnosis and treatment followed the Brazilian Ministry of Health recommendations (Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006; Ministério da Saúde do Brasil e

Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006; Ministério da Saúde do Brasil 2008).

Patients underwent nutritional evaluation and received dietary counseling after tuberculosis diagnosis and during their tuberculosis treatment. The steps and procedures usedin this study are presented in Figure S1.

Anthropometric and biochemical biomarkers, including the analysis of serum micronutrients, were used to assess nutritional status. Anthropometric evaluation was conducted using the body mass index (BMI – 18.5-24.9Kg/m^2), mid–upper-arm circumference (MUAC – 28.5-29.3cm), triceps skin fold (TSF – 11.4-18.2mm) and mid-arm muscle circumference (MAMC – 21.0-27.8cm), according to Lohman (Lohmann, Roche, e Martorell 1988) (Table S3).

Serum biomarkers were assessed, including analysis of blood count, using automated optical microscopy with reference value of 11-18 for hemoglobin and 34-54 for hematocrit. Chromatic measurement with a reference value of 3.4-5.0 for albumin; 6.4-8.2 for total protein; 2.5-4.0 for globulin; 250-450 for iron fixation capacity. High performance liquid chromatography with a reference value of >0.7 for retinol and >0.5 for tocopherol. Atomic absorption with reference value of >70 for zinc, 70-90 for selenium and 50-170 for iron (Table S3).

Serum samples were frozen (-20°C to -10°C) for analysis of vitamins A, E and zinc; and plasma was refrigerated from 2 to 8°C for selenium analysis. All tubes were transported to the laboratory for analysis with a maximum of 7 days of storage. The analyses for the remaining biomarkers were done immediately after blood collection.

The study endpoint was the recovery from malnutrition. Individuals were considered to be without malnutrition, at any time, if all the biomarkers (anthropometric, hematological, biochemical and micronutrients) were within the reference values, as established by FAO (*State of Food and Agriculture 2013: Food Systems for Better Nutrition.* 2013). And they were considered to be without malnutrition, at any time, if at least one of the biomarkers was outside the reference values, as established by FAO (*State of Food and Agriculture 2013: Food Systems for Better Nutrition.* 2013).

Patients were classified within the following malnutrition statuses, at every moment: (a) global, using BMI, TSF, MUAC, serum protein, albumin, transferrin and iron fixation; (b) energy, using the parameters BMI and TSF; (c) protein, using the somatic parameter MAMC, and visceral parameters serum protein, albumin,

transferrin and iron fixation; (d) micronutrients, using serum biomarkers (iron, selenium, zinc, retinol and tocopherol).

Dietary counseling

The dietary counseling proposed by BMH ("CGAN - Coordenação-Geral de Alimentação e Nutrição" 2014) was delivered at every single visit, to every participant. At each visit, participants had time to ask questions, clear any doubts about his/her diet and to correct some identified misconceptions.

Ethical Aspects

This study was conducted in accordance with the ethical standards outlined for research in humans in the Declaration of Helsinki, and approved by the Research Ethics Committee of the Evandro Chagas National Institute of Infectious Diseases, under identification number CAE 0008.0.009.000-08. All patients who agreed to participate in the study signed an informed consent form.

Analysis Plan

The data were analyzed using the R-project software,version 3.0.2. The results were obtained by dividing the data into a baseline time point and follow-up. For baseline, the fractions and number of patients in each category were shown for categorical variables. For the continuous variables, either the mean and standard deviation, if the variable follows the normal distributionor median and interquartile range, were estimated. At follow-up, the same information was shown but stratified bytime. The graphs show bootstrap correlation adjusted trajectories for each variable, or the fraction of subjects with malnutrition at each time. Hypothesis tests was considered statistically significant when $p \leq 0.05$.

Results

Sixty-eight patients were included in the study. Exclusions and its reasons were: 5 patients needed nutritional supplementation, 3 patients died and 24 patients were lost to follow-up. Thirty four patients remained until the end of the study (Figure S2).

At baseline the mean (standard deviation) age was 41.1 (±13.4) years old and there was a predominance of males, with income less than a local minimum wage, average of six years of education, and pulmonary clinical form of tuberculosis (Table S1). In addition, a minority of patients were drinkers and smokers. Twenty-two of the volunteers were not infected with HIV (Table S1).

At the beginning of the study, all of the patients exhibited malnutrition (Table S2). In both HIV-infected and non-infected patients, micronutrient malnutrition, reduced visceral and somatic protein levels and energy malnutrition were found. However, total protein levels, hemoglobin and hematocrit had a more intense impairment among those infected with HIV (Table S2).

It is noteworthy that BMI measurements were less sensitive than TSF to detect energy malnutrition. BMI detected a quarter of patients with energy malnutrition at baseline and TSF detected more than two-thirds at baseline (Table S2).

A pattern of progressive increase over time was not observed for BMI, retinol and selenium. However, there was an apparent linear increase over time of the following parameters: weight, hemoglobin, hematocrit, iron fixation, transferrin, iron and tocopherol (Table S3 and Figure S3). The iron-related metabolism biomarkers showed a very slight trend of increase over time, however this increase was not enough to reach the normal limits for most of the volunteers for all biomarkers but total iron (Figure S3). The remaining values appeared unstable and no linear trends could be established (Table S3).

The average transferrin and retinol levels were below the reference range and remained low until the end of the follow-up. In addition, patients exhibited a reduced ability to fix iron, and had low hematocrit and albumin levels (Table S3). The remaining parameters assessed were found to be below the reference range at the beginning of the study and remained so to the end of the study, or the baseline mean values were within the normal reference range and remained stable through the study period (Table S3).

The nutritional status did not show any apparent trend over time, except for the energy nutritional status. The energy nutritional status had an apparent increment after the second month of follow-up. However, a visually perceptible linear trend was not evident (Figure S4). Energy malnutrition is observed more often among individuals infected with HIV to the end of the treatment course. These changes are not observed in other parameters used to assess nutritional status (Table S4).

Discussion

The main results of this study were: (a) all tuberculosis patients had malnutrition at baseline and, despite of the BMH and WHO recommendation of dietary counseling, none of the patients recovered nutritional status; (b) the nutritional impairment was

more intense in patients infected with HIV than in non-infected, regarding total protein and parameters related to iron metabolism; and (c) the BMI was not a sensitive marker to detect malnutrition.

Studies conducted in other countries showed impairment of nutritional status only in HIV-infected patients (Villamor et al. 2005; Swaminathan et al. 2008). In the present study, there is evidence of malnutrition in both groups. These results may have been influenced by the use of anthropometric parameters other than BMI and the use of serum biomarkers to define malnutrition. This is an important issue, because the different concepts of malnutrition will lead to different abilities to detect it, probably leading to underestimation of its prevalence depending on the concept/method used. Therefore, a number of patients may miss the opportunity to receive appropriate diet counselling and nutritional supplementation, where malnutrition is underestimated.

The choice of malnutrition concept that uses different nutritional parameters, besides the anthropometric, is a consequence of the fact theses additional parameters are considered important in the clinical progression of organic changes (*State of Food and Agriculture 2013: Food Systems for Better Nutrition.* 2013). The concept that incorporates biochemicals biomarkers comes from an awareness that several diseases can affect the nutritional status in a variety of ways. The different forms may include isolated changes or a combined deficiency of macro- or micro-nutrients that are not always perceptible in anthropometric or semiological assessments. The risks of complications or morbid events associated with these diseases or nutritional status are different for each malnutrition type (*State of Food and Agriculture 2013: Food Systems for Better Nutrition.* 2013).

Regardless of the possibility that malnutrition had occurred prior to tuberculosis or HIV infection, there are several factors that may have influenced the food choices of patients, or their access to more nutritionally complete foods, including: food taboos and beliefs (Instituto Brasileiro de Geografia e Estatística 2010b), stigma associated with HIV and tuberculosis (Makanjuola, Taddese, e Booth 2014), presence or absence of family support (King et al. 2010; NICUS 2014; Braveman, Egerter, e Williams 2011; Thiam S et al. 2007), education (Braveman, Egerter, e Williams 2011; Gupta et al. 2011; Thiam S et al. 2007); and the high cost of foods or low income (Cardoso, Moriguchi, e Schneider 2010; Instituto Brasileiro de Geografia e Estatística 2010a; Instituto Brasileiro de Geografia e Estatística e Coordenação de Trabalho e Rendimento 2010). The group studied here had an average of six years of

education, income less than a local minimum wage, and was aware of the stigma associated with the disease(s). Therefore, the combination of these factors may have negatively influenced their nutritional status, regardless of whether they have received dietary advice.

Therefore, energy malnutrition, and specially protein, iron and retinol deficiencies, could be the result of social issues, which were intensified by illness, and they remained after tuberculosis treatment was over. Since we did not have information on the nutritional status of the patients prior to tuberculosis and HIV infection, we are unable to confirm that the nutritional deficiencies were due to the illness or to their social condition prior to treatment. This assumption can be supported by published reports, which indicate that the Brazilian population has moderate prevalence of malnutrition even without consumptive associated diseases (Ramalho, Flores, e Saunders 2002). Consequently, it would be expected that a fraction of the treated patients would have some nutritional parameters improved, but their global nutritional status would not completely improve.

Surprisingly, vitamin A deficiency was identified in all of the volunteers throughout the treatment period, regardless of their HIV status. Studies conducted outside of Brazil showed a persistent vitamin A deficiency only in HIV-infected patients (Visser et al. 2011; Baeten et al. 2006). It is also known that hypovitaminosis affects 13 to 56% of the residents of Rio de Janeiro (Ramalho, Flores, e Saunders 2002).

A retinol deficiency in 71.4% of tuberculosis patients not infected with HIV at the end of treatment was unexpected, suggesting a persistent vitamin A deficiency on Brazilians, regardless of HIV infection.

On the other hand, it was expected that serum zinc and selenium levels in the patients with this degree of malnutrition would be below the reference range (Amin, Bhat, e Gulleria 2012; Ghone 2013), but this phenomenon was not observed. It is possible that the protein malnutrition found in both groups has limited the availability of both micronutrients for their antioxidant function, since selenium availability depends on protein levels to act as a cofactor for glutathione peroxidase (Guo, Hsia, e Chen 2013; Mehdi et al. 2013). Zinc is used as catalyst and structural cofactor for about 3000 zinc-binding proteins (Maret 2011), which are involved in the antioxidant process (Wessels et al. 2013), thus it suffers from the low protein concentration in a similar way as selenium does.

We expected to find anemia in TB-HIV patients because both diseases are involved in different mechanisms that lead to anemia the disease itself, antiretroviral therapy or blocked iron entry into the cell caused by *Mycobacterium tuberculosis* (Thomas et al. 2011). Anemia was observed in both groups, but more intense in the HIV infected group.

As serum iron values did not change during tuberculosis treatment, the anemia and the impairment on the iron-related metabolism observation were possible because, besides total iron, other iron related biomarkers were measured. In clinical practice, iron supplementation is neither used nor recommended in any guidelines, perhaps because iron deficiency and iron-related metabolism alterations are not so easily identified.

BMI is an anthropometric parameter, for the monitoring of nutritional status. It has been used in clinical practice and at research settings to describe the nutritional status of study volunteers and was adopted by the Brazilian Ministry of Health (Ministério da Saúde do Brasil 2011; Ministério da Saúde do Brasil e Programa Nacional de Doenças Sexualmente Transmissíveis/AIDS (Brazil) 2006) and the World Health Organization (WHO 2013) as an anthropometric index. Possibly, these entities utilize BMI for monitoring nutritional status due to its ease of use. Anthropometry is a technique that requires only easy-to-transport equipment, it is universal, and its application is inexpensive and non-invasive (Ministério da Saúde do Brasil 2004). However, the criterion established by the FDA in 2013 (*State of Food and Agriculture 2013: Food Systems for Better Nutrition.* 2013) allows the inclusion of results nutrition-related biomarkers, including measurements of serum protein, iron and vitamins, body compartments and serum analysis of micronutrients. The results presented here in show that BMI is not sensitive enough to detect malnutrition. If patient evaluations were based on BMI alone, 60% to 70% of subjects included would be considered as nourished.

The lack of sensitivity of BMI for the monitoring of nutritional status has already been described by other authors (Oliveira et al. 2010; Al Moamary, Alorainy, e AL-Hajjaj 2014) who highlighted the possibility of an erroneous perception of recovered nutritional status. The specific deficits of protein and micronutrients cannot be identified using BMI. Following this premise, the measure of MUAC has been suggested as alternative anthropometric parameter for malnutrition diagnosis (Chakraborty, Bose, e Koziel 2011). It was possible to verify in this study that the

average MUAC remained below the normal limit in both groups in the whole observation period, and that although the TSF oscillated irregularly throughout the tuberculosis treatment, after the sixth month it remained below the normal limits, mainly in HIV-infected patients.

TSF is an anthropometric measure whichis extremely sensitive to energy malnutrition (Freedman et al. 2013; Freedman, Horlick, e Berenson 2013). There is evidence about TSF improvement during the tuberculosis treatment of patients not infected with HIV submitted to dietary supplementation (Freedman et al. 2013; Freedman, Horlick, e Berenson 2013). However, the tuberculosis patients in this study indicated once more the importance of a careful and early analysis of additional parameters associated with anthropometry.

Limitations:

The main limitations of the study were the sample size and subject retention, both for the nutritional follow-up and for tuberculosis treatment. This absence of data, due to loss in follow-up, raises an uncertainty about the conclusions, as many outcomes are unknown. However, the prevalence of malnutrition observed at the end of follow-up was high, and selective loss in follow-up would be a problem only if this loss in follow-up is some how related to full recovery of nutritional status. It is unlikely that this has happened as it would be necessary to observe a pattern in which preferably the subjects with the less impaired nutritional status are lost during follow-up. However, this pattern was not observed. Some patients were discontinued because of severe malnutrition, to receive dietary supplement and others died. Also, this information could be interpreted as an absence of recovery of their nutritional status increasing the amount of patients with unfavorable outcomes. At the end, the lack of compliance with the follow-up could also be interpreted a lack of effectiveness of the current recommendation. Another point is the lack of interventions to make patients feel "treated", and the lack of financial support to allow them to choose the food they would like to eat.

Conclusions:

The nutritional status of patients remained below the desired levels until the end of tuberculosis treatment. Patients infected with HIV had worse condition throughout tuberculosis treatment, indicated by parameters related to protein and iron biomarkers. BMI alone was not a sensitive marker to detect malnutrition. The diagnosis of nutritional status of these patients should be performed with the additional parameters such as MUAC, TSF, albumin, iron fixation capacity, iron, selenium, zinc, retinol, tocopherol, hemoglobin and hematocrit.

Acknowledgements

We thank nurse Solange Alves da Cruz, responsible for the blood collection sector, doctors Flavia Marinho Sant´Anna and Carolina Arana Stanis Schmaltz, and nutritionists Ivan Rocha Maia and Erika Ennes who assisted with data collection. We appreciate the support of the INI Nutrition Service in the development of this study.

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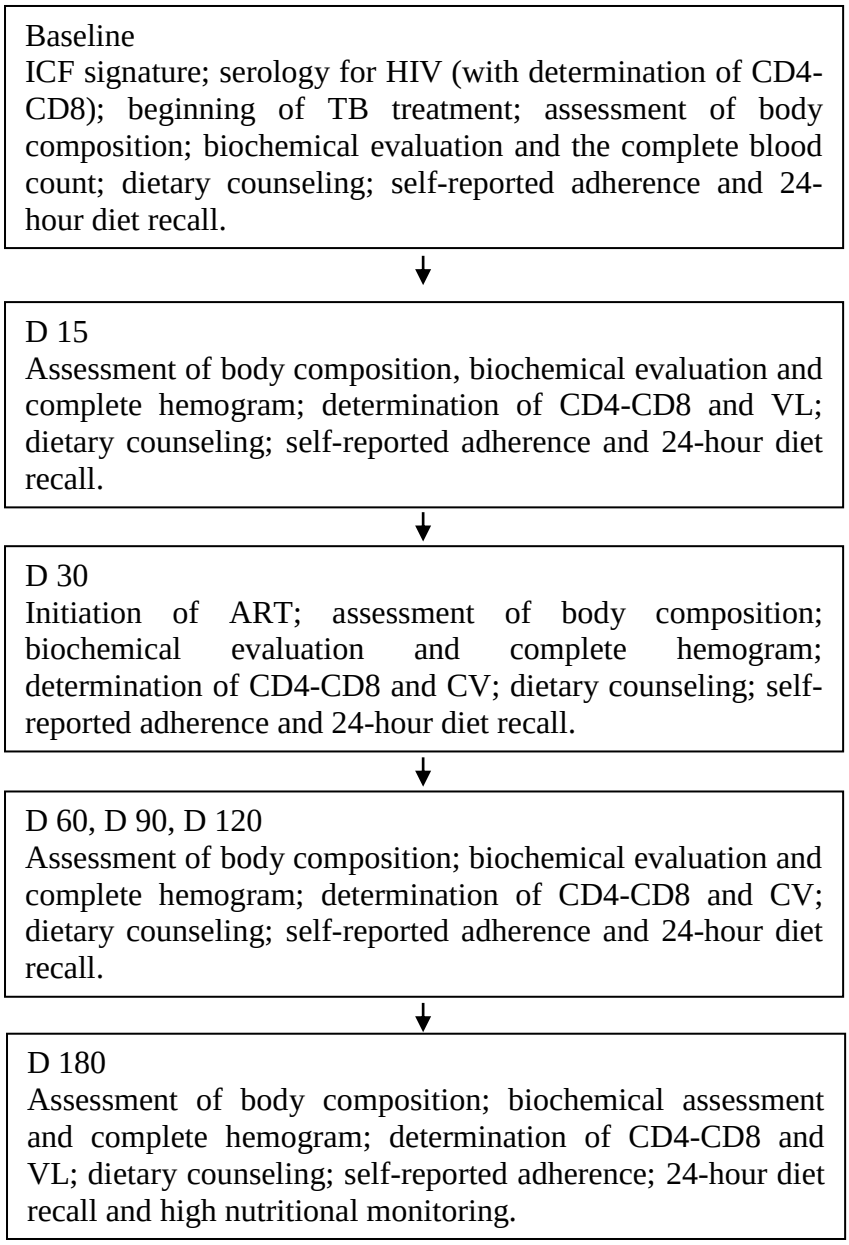

D = day of visits; ICF = informed consent form; HIV = human immununodeficiency virus; ART = antiretroviral therapy; Biochemical assessment = albumin, iron fixation capacity, iron, selenium, zinc, retinol and tocopherol; CD4 = lymphocyte TCD4; CD8 = lymphocyte TCD8; VL = viral load; dietary counselling = was delivered and read with patients the document proposed by the ministry of health ("CGAN - Coordenação-Geral de Alimentação e Nutrição" 2014).

Figure 1 – Flow Chart of the Study

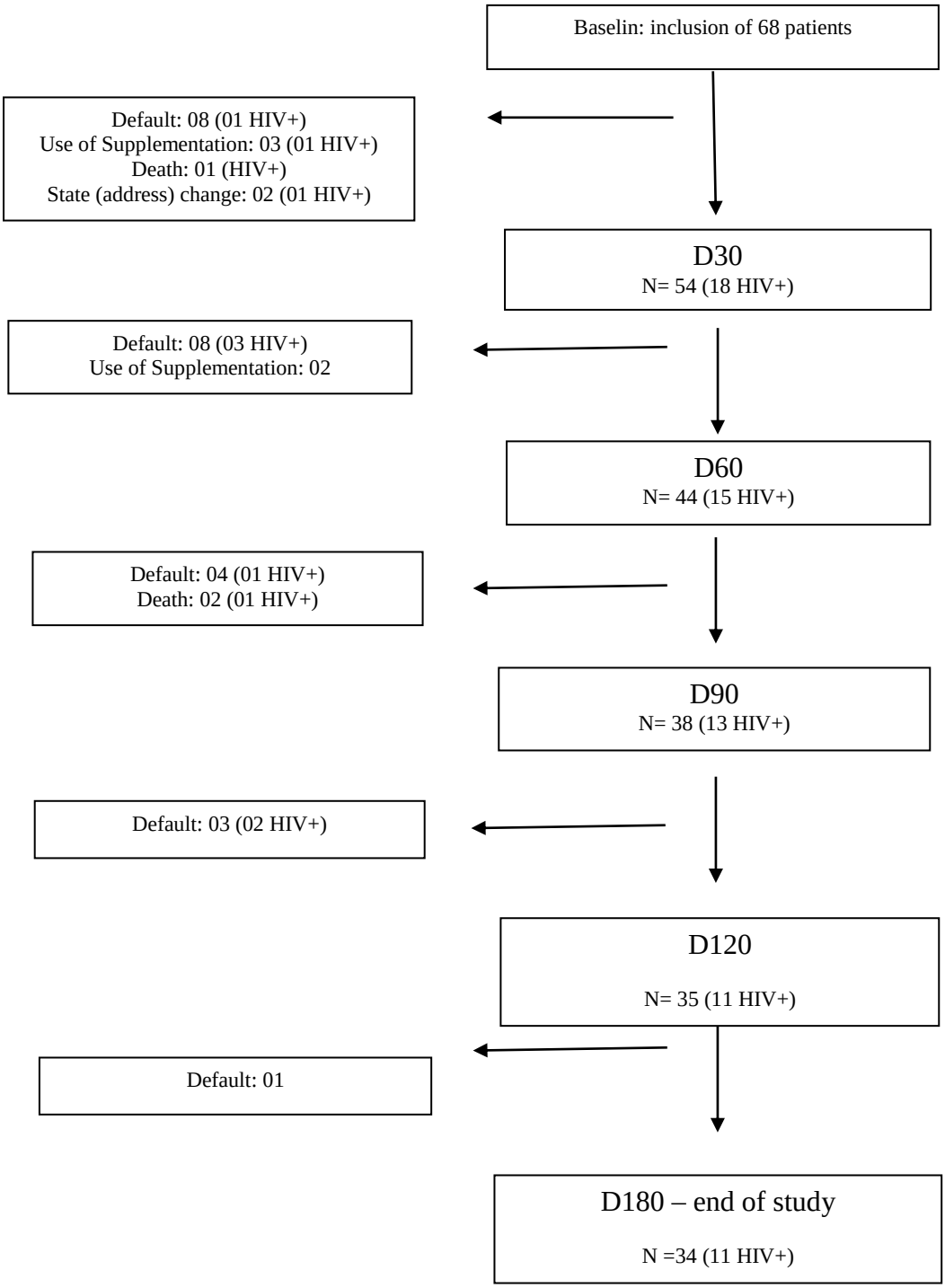

Figure 2. Causes of discontinuation throughout the TB treatment course

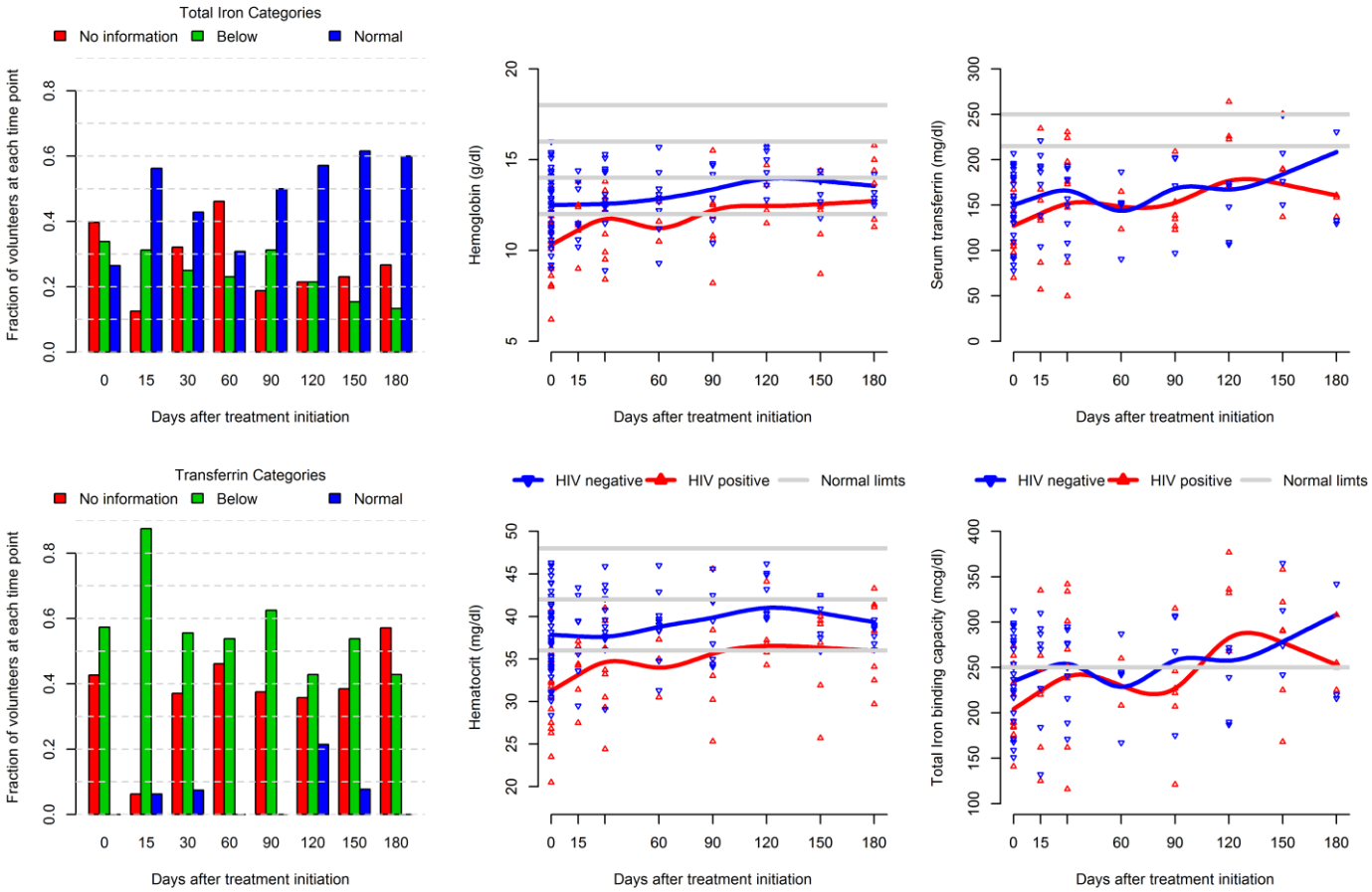

Figure S3. Body condition of iron related biomarkers in HIV-infected and non-infected patients during the tuberculosis treatment.

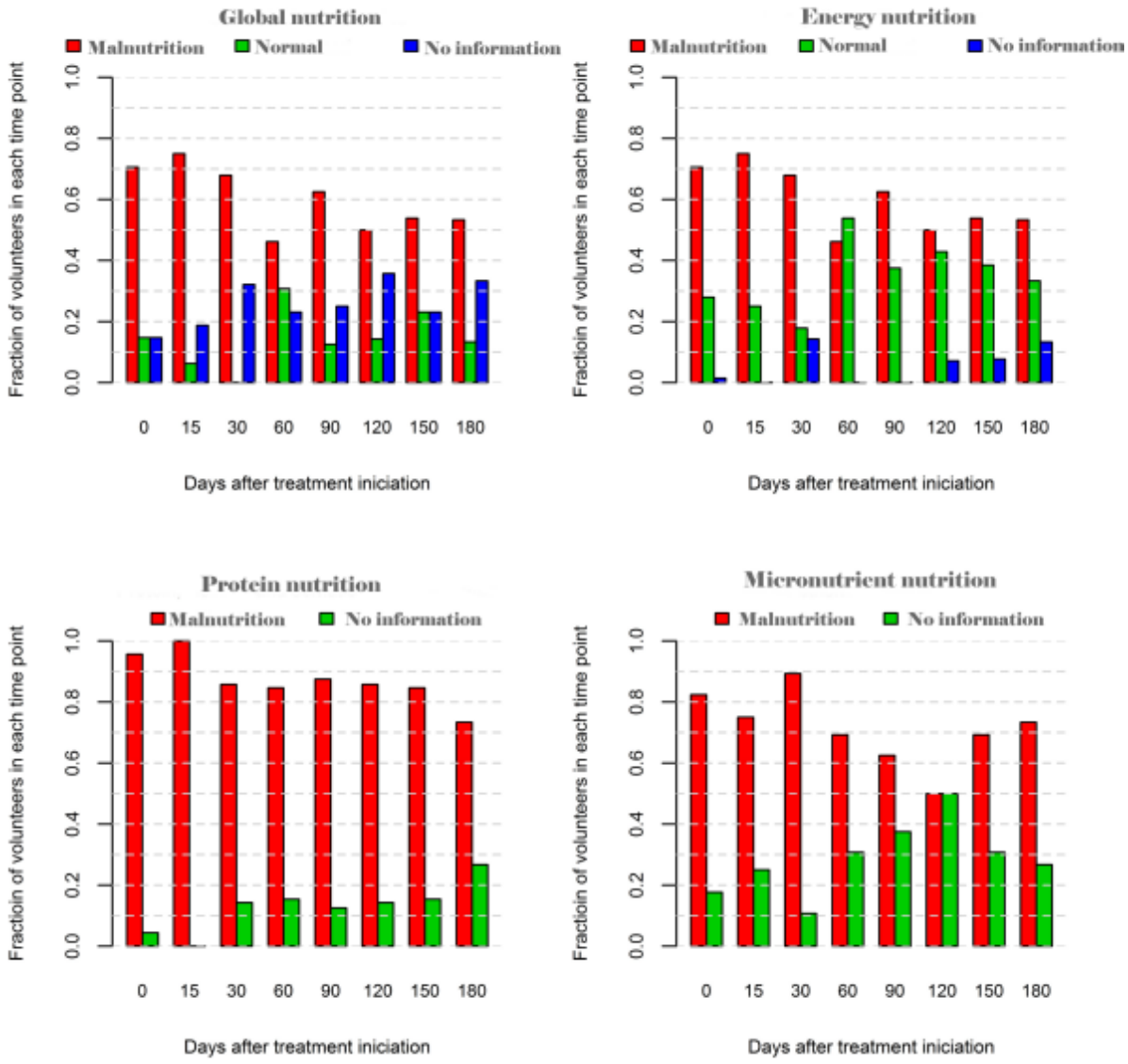

Figure S4 - Tuberculosis patients fraction of different types of malnutrition at each follow-up visit.

Table S1. Socio-demographic and clinical characteristics of individuals with tuberculosis, who are either HIV-infected or non-infected at the beginning of the follow-up.

	HIV +	HIV -	Total	Hypothesis testing	P value
Total	46	22	68		
Sex [1]				Chisq. (1 df) = 1.04	0.308
Male	26 (56.5)	16 (72.7)	42 (61.8)		
Female	20 (43.5)	6 (27.3)	26 (38.2)		
Age				t-test (66 df) = 0.62	0.535
Mean (SD)	40.4 (15.1)	42.6 (9.1)	41.1 (13.4)		
Age groups [1, 2]				Fisher's exact test	0.043
16-24	7 (15.2)	1 (4.5)	8 (11.8)		
25-34	15 (32.6)	3 (13.6)	18 (26.5)		
35-44	6 (13.0)	9 (40.9)	15 (22.1)		
45-54	8 (17.4)	7 (31.8)	15 (22.1)		
55-64	8 (17.4)	2 (9.1)	10 (14.7)		
65-71	2 (4.3)	0 (0.0)	2 (2.9)		
Education				Ranksum test	0.961
Median (IQR)	6 (4.0 – 1.0)	5 (4.0 – 9.0)	6 (4.0 - 10.8)		
Monthly income[3]				Ranksum test	0.666
Median (IQR)	800 (550.0 – 1244.0)	800 (620.5 – 1560.0)	800 (585.0 -1370.0)		
Smoker [1]				Chisq. (2 df) = 1.8	0.407
No	25 (54.3)	14 (63.6)	39 (57.4)		
Yes	8 (17.4)	5 (22.7)	13 (19.1)		
Ex-smoker	13 (28.3)	3 (13.6)	16 (23.5)		
Alcoholism [1]				Chisq. (2 df) = 2.02	0.365
No	23 (50.0)	12 (54.5)	35 (51.5)		
Yes	13 (28.3)	3 (13.6)	16 (23.5)		
Ex-alcoholic	10 (21.7)	7 (31.8)	17 (25.0)		
Clinical form of tuberculosis[1]				Fisher's exact test	0.218
Pulmonary	15 (71.4)	5 (38.5)	20 (58.8)		
Extra pulmonary	4 (19.0)	5 (38.5)	9 (26.5)		
Disseminated	2 (9.5)	3 (23.1)	5 (14.7)		

[1]= n (%); [2] = years; [3] = Real (R$); IQR= interquartile range.

Table S2. Biochemical and hematological assessment of HIV-infected and non-infected patients at the beginning of the follow-up.

	HIV -	HIV +	Total	Hypothesis testing	P valor
Total	46	22	68		
Arm circumference				Ranksum test	0.506
Median (IQR)	25 (23.0– 27.0)	24 (23.0– 26.0)	25 (23.0– 27.0)		
MUAC classification [1]				Fisher's exact test	1.000
No information available	1 (2.2)	0 (0.0)	1 (1.5)		
Below average	39 (84.8)	19 (86.4)	58 (85.3)		
Normal	6 (13,0)	3 (13.6)	9 (13.2)		
Triceps				Ranksum test	0.444
Median (IQR)	10 (6.0– 16.0)	10 (6.2 – 11.0)	10 (6.0– 15.0)		
TSF classification [1]				Fisher's exact test	0.296
Below average	29 (64.4)	18 (81.8)	47 (70.1)		
Normal	5 (11.1)	2 (9.1)	7 (10.4)		
Above	11 (24.4)	2 (9.1)	13 (19.4)		
Body mass index				Ranksum test	0.322
Median (IQR)	20.6 (18.5 - 22.9)	19.7 (18 - 21.1)	20.5 (18.5 - 22.4)		
BMI classification[1]				Chisq. (2 df) = 0.51	0.776
Below average	11 (23.9)	6 (27.3)	17 (25.0)		
Normal	28 (60.9)	14 (63.6)	42 (61.8)		
Above	7 (15.2)	2 (9.1)	9 (13.2)		
Energetic nutrition[1]				Fisher's exact test	0.422
Malnutrition	30 (65.2)	18 (81.8)	48 (70.6)		
Normal	15 (32.6)	4 (18.2)	19 (27.9)		
No information available	1 (2.2)	0 (0.0)	1 (1.5)		
Mid-arm muscle circumference				Ranksum test	0.758
Median(IQR)	21.1 (19.8 - 23.4)	21.4 (20.2 - 23.2)	21.2 (19.9 - 23.2)		
MAMC classification[1]				Fisher's exact test	0.713
Below average	29 (63.0)	15 (68.2)	44 (64.7)		
Normal	16 (34.8)	6 (27.3)	22 (32.4)		
Above	1 (2.2)	1 (4.5)	2 (2.9)		
Albumin				t-test (56 df) = 1.77	0.082
Mean (SD)	3.3 (0.7)	2.9 (0.7)	3.1 (0.7)		
Albumin classification[1]				Chisq. (2 df) = 0.64	0.727
No information available	7 (15.2)	3 (13.6)	10 (14.7)		
Below average	27 (58.7)	15 (68.2)	42 (61.8)		
Normal	12 (26.1)	4 (18.2)	16 (23.5)		
Serum iron				Ranksum test	0.933
Median (IQR)	41.5 (26.0– 82.0)	48 (31.0– 64.0)	44 (27.0– 72.0)		
Total iron classification[1]				Chisq. (2 df) = 0.06	0.971
No information available	18 (39.1)	9 (40.9)	27 (39.7)		
Below average	16 (34.8)	7 (31.8)	23 (33.8)		
Normal	12 (26.1)	6 (27.3)	18 (26.5)		
Transferrin				t-test (37 df) = 1.90	0.066
Mean (SD)	148.5 (40.2)	124.5 (33.2)	139.9 (39.2)		

Transferrin classification[1]				Chisq. (1 df) = 0.21	0.644
No information available	21 (45.7)	8 (36.4)	29 (42.6)		
Below average	25 (54.3)	14 (63.6)	39 (57.4)		
Total iron binding capacity				t-test (37 df) = 1.90	0.065
Mean(SD)	239.5 (50.4)	209.4 (41.4)	228.7 (49.0)		
TIBC classification[1]				Chisq. (2 df) = 1.47	0.479
No information available	21 (45.7)	8 (36.4)	29 (42.6)		
Below average	14 (30.4)	10 (45.5)	24 (35.3)		
Normal	11 (23.9)	4 (18.2)	15 (22.1)		
Hemoglobin				t-test (60 df) = 4.42	< 0.001
Mean(SD)	12.5 (1.8)	10.3 (1.8)	11.8 (2.0)		
Anemia [1]				Fisher's exact test	0.005
No information available	3 (6.5)	3 (13.6)	6 (8.8)		
Severe anemia	0 (0.0)	2 (9.1)	2 (2.9)		
Anemia	27 (58.7)	16 (72.7)	43 (63.2)		
Normal	16 (34.8)	1 (4.5)	17 (25.0)		
Hematocrit				t-test (57 df) = 4.92	< 0.001
Mean (SD)	37.8 (4.7)	31.1 (5.1)	35.7 (5.7)		
Hematocrit classification [1]				Chisq. (2 df) = 7.03	0.030
No information available	13 (28.3)	4 (18.2)	17 (25.0)		
Below average	24 (52.2)	18 (81.8)	42 (61.8)		
Normal	9 (19.6)	0 (0.0)	9 (13.2)		
Visceral and somatic protein nutrition [1]				Fisher's exact test	1.000
Malnutrition	44 (95.7)	21 (95.5)	65 (95.6)		
No information available	2 (4.3)	1 (4.5)	3 (4.4)		
Serum zinc				t-test (52 df) = 1.30	0.200
Mean (SD)	77.8 (20.8)	85.6 (19.4)	80.3 (20.5)		
Zinc classification[1]				Chisq. (2 df) = 2.80	0.247
No information available	9 (19.6)	5 (22.7)	14 (20.6)		
Below average	15 (32.6)	3 (13.6)	18 (26.5)		
Normal	22 (47.8)	14 (63.6)	36 (52.9)		
Serum selenium				Ranksum test	0.428
Median (IQR)	62.5 (47.2 - 74.8)	68 (53.1 - 76.7)	64 (47.7 - 76.1)		
Selenium classification [1]				Fisher's exact test	0.910
No information available	12 (26.1)	7 (31.8)	19 (27.9)		
Below average	21 (45.7)	9 (40.9)	30 (44.1)		
Normal	8 (17.4)	3 (13.6)	11 (16.2)		
Above	5 (10.9)	3 (13.6)	8 (11.8)		
Serum vitamin A				t-test (46 df) = 0.96	0.340
Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)		
Retinol classification [1]				Fisher's exact test	0.593
No information available	14 (30.4)	6 (27.3)	20 (29.4)		
Below average	29 (63.0)	16 (72.7)	45 (66.2)		
Normal	3 (6.5)	0 (0.0)	3 (4.4)		
Serum vitamin E				t-test (46 df) = 1.15	0.255

Mean (SD)	8.9 (4.5)	7.3 (4.3)	8.4 (4.4)		
Tocopherol classification [1]				Fisher's exact test	0.346
No information available	14 (30.4)	6 (27.3)	20 (29.4)		
Below average	3 (6.5)	4 (18.2)	7 (10.3)		
Normal	29 (63.0)	12 (54.5)	41 (60.3)		
Micronutrient malnutrition[1]				Fisher's exact test	1.000
Malnutrition	38 (82.6)	18 (81.8)	56 (82.4)		
No information available	8 (17.4)	4 (18.2)	12 (17.6)		
Total protein				Ranksum test	0.021
Median (IQR)	7.7 (7.2 - 8.1)	8.5 (8.1 - 9.5)	8 (7.3 - 8.5)		
Total protein classification[1]				Chisq. (2 df) = 9.03	0.011
No information available	26 (56.5)	9 (40.9)	35 (51.5)		
Normal	14 (30.4)	3 (13.6)	17 (25.0)		
Above average	6 (13.0)	10 (45.5)	16 (23.5)		
Global nutrition[1]				Fisher's exact test	0.241
Malnutrition	30 (65.2)	18 (81.8)	48 (70.6)		
Nutrition	7 (15.2)	3 (13.6)	10 (14.7)		
No information available	9 (19.6)	1 (4.5)	10 (14.7)		
Nutritional status[1]				Fisher's exact test	1.000
Malnutrition	45 (97.8)	22 (100.0)	67 (98.5)		
No information available	1 (2.2)	0 (0.0)	1 (1.5)		

[1]= n (%); anemia = hemoglobin < 12g/dl; severe anemia = hemoglobin< 8g/dl; energy malnutrition = verified by BMI, MUAC and TSF; micronutrient malnutrition = verified by retinol, tocopherol, zinc, selenium and iron; protein malnutrition =verified by MAMC, albumin, TIBC; global malnutrition =verified by all the available nutritional parameters.

Table S3.Measurements of body composition and biomarkers of all patients throughout tuberculosis treatment.

	Time course of tuberculosis treatment (days)								
	RV	D0	D15	D30	D60	D90	D120	D150	D180
Current weight[1, 2]	-	58.2 (±11.8)	60.1 (±14.1)	59.5 (±12.2)	60.4 (±11.7)	61.2 (±14.9)	66.6 (±13.9)	61.8 (±9.8)	62.0 (±10.1)
BMI[1, 3]	18.5–24.9	21.0 (±3.9)	21.1 (±4.1)	21.1 (±3.4)	22.0 (±3.4)	21.7 (±4.3)	23.0 (±4.1)	22.5 (±3.3)	21.8 (±2.8)
MUAC[1, 4]	28.5–29.3	25.4 (±3.8)	26.2 (±4.1)	26.3 (±3.6)	26.9 (±3.4)	26.4 (±5.0)	27.2 (±2.8)	27.2 (±2.7)	27.5 (±2.9)
TSF[1, 5]	11.4–18.2	11.9 (±7.5)	13.5 (±11.9)	12.3 (±8.4)	19.5 (±11.4)	15.8 (±9.8)	13.2 (±7.3)	13.3 (±6.6)	12.9 (±5.1)
MAMC[1, 4]	21.0 –27.8	21.4 (±4.0)	21.6 (±3.1)	22.1 (±3.1)	21.1 (±3.8)	21.8 (±4.1)	23.1 (±2.3)	23.2 (±2.2)	23.7 (±2.8)
Hemoglobin[1, 6]	11.0 –18.0	11.8 (±2.0)	12.1 (±1.6)	12.3 (±1.9)	12.5 (±1.6)	12.4 (±1.9)	13.9 (±1.4)	12.6 (±1.6)	13.4 (±1.3)
Hematocrit[1, 7]	34.0 –54.0	35.7 (±5.7)	35.8 (±4.4)	36.7 (±5.3)	37.9 (±4.3)	37.1 (±5.5)	40.6 (±3.7)	37.8 (±4.6)	38.0 (±3.5)
Globulin [1, 6]	2.5–4.0	5.2 (±1.5)	4.5 (±1.5)	4.6 (±1.6)	3.8 (±0.6)	5.1 (±1.9)	4.5 (±1.4)	5.3 (±1.2)	4.4 (±1.0)
Albumin [1, 6]	3.4–5.0	3.1 (±0.7)	3.2 (±0.7)	3.3 (±0.6)	3.5 (±0.6)	3.4 (±0.6)	3.7 (±0.3)	3.5 (±0.6)	3.7 (±0.5)
TIBC[1, 8]	250.0 –450.0	228.7 (±49.0)	237.1 (±63.5)	252.0 (±61.8)	236.0 (±38.5)	239.4 (±62.6)	274.3 (±64.9)	284.8 (±60.7)	253.0 (±47.8)
Transferrin [1, 9]	250.0 –300.0	139.9 (±39.2)	158.9 (±50.1)	159.6 (±49.6)	145.8 (±30.8)	155.8 (±38.8)	177.1 (±53.0)	193.7 (±41.2)	152.5 (±40.0)
Retinol [1, 8]	>0.7	0.4 (±0.2)	0.3 (±0.1)	0.4 (±0.2)	0.3 (±0.2)	0.4 (±0.1)	0.5 (±0.2)	0.4 (±0.2)	0.5 (±0.2)
Tocopherol[1, 10]	>5.0	8.4 (±4.4)	9.0 (±3.5)	9.3 (±2.8)	10.6 (±4.4)	9.1 (±2.0)	9.6 (±1.9)	9.5 (±2.1)	9.6 (±5.2)
Zinc [1, 9]	> 70.0	80.3 (±20.5)	71.8 (±12.5)	102.8 (±121.1)	75.6 (±20.0)	89.3 (±27.2)	94.9 (±22.1)	218.3 (±389.4)	85.3 (±24.3)
Selenium[1, 11]	70.0 –90.0	73.8 (±50.1)	66.0 (±19.8)	76.7 (±38.4)	90.3 (±56.3)	49.8 (±18.5)	79.6 (±40.5)	60.8 (±22.4)	65.9 (±27.4)
Iron[1, 8]	50.0 –170.0	53.1 (±36.0)	60.5 (±33.8)	61.3 (±33.4)	65.0 (±30.2)	66.2 (±30.9)	71.9 (±23.6)	76.1 (±23.7)	76.2 (±29.0)

1 = mean (SD); 2 = kilogram (Kg); 3 = kilogram per square meter (Kg/m^2); 4 = centimeters (cm); 5 = millimeters (mm); 6 = grams per deciliter (g/dl); 7 = percentage (%); 8 = micrograms per deciliter (mcg/dl); 9 = milligrams per deciliter (mg/dl); 10 = milligrams per liter (mg/l); 11 = micrograms per liter (mcg/l);BMI =body mass index; MUAC =mid–upper-arm circumference; MAMC= mid arm muscle circumference; TSF =triceps skin fold thickness; TIBIC = iron fixation capacity; RV= reference values.

Table S4. Nutritional status of HIV-infected and non-infected patients at the end of tuberculosis treatment

Nutritional diagnosis	HIV- (%)	HIV+ (%)	Total
Energy malnutrition[1]	3 (42.9)	5 (71.4)	8 (57.1)
Protein malnutrition [1]	5 (71.4)	5 (71.4)	10 (71.4)
Micronutrient malnutrition [1]	5 (71.4)	6 (85.7)	11 (78.6)
Global malnutrition[1]	3 (42.9)	5 (71.4)	8 (57.1)
Nutritional status - malnutrition[1]	5 (71.4)	7 (100.0)	12 (85.7)
Selenium deficiency [1]	3 (42.9)	2 (28.6)	5 (35.7)
Zinc deficiency [1]	1 (14.3)	1 (14.3)	2 (14.3)
Tocopherol deficiency [1]	1 (14.3)	0 (0.0)	1 (7.1)
Retinol deficiency[1]	5 (71.4)	5 (71.4)	10 (71.4)
Iron deficiency [1]	2 (28.6)	0 (0.0)	2 (14.3)
Anemia [1]	2 (28.6)	3(42.9)	5 (35.7)

1= n (%); poor energy nutrition = verified by BMI, MUAC and TSF; specified malnutrition = checked for retinol, tocopherol, zinc, selenium and iron; protein malnutrition = verified by MAMC, albumin, TIBIC, transferrin; global malnutrition = checked using all available nutritional status parameters.

6.2 Artigo 2

Dietary counseling adherence during tuberculosis treatment: a longitudinal study

Adriana Costa Bacelo[2], Pedro Emmanuel Alvarenga Americano do Brasil[3], Cláudia dos Santos Cople-Rodrigues[4], Georg Ingebourg[5], Eliane Paiva[6], Sheila Argolo[7,] Andrea Ramalho[8], Valeria Rolla[1]

Affiliation

1. Clinical Research Laboratory on Mycobacteria – National Institute of Infectious Diseases Evandro Chagas – Oswaldo Cruz Foundation
2. Nutrition Service – National Institute of Infectious Diseases Evandro Chagas – Oswaldo Cruz Foundation
3. Clinical Research Laboratory on Chagas Disease – National Institute of Infectious Diseases Evandro Chagas – Oswaldo Cruz Foundation
4. Nutrition Institute – Rio de Janeiro State University
5. Diagnostics Activities Coordination – Immunodiagnostic Section – National Institute of Infectious Diseases Evandro Chagas – Oswaldo Cruz Foundation
6. Department of Nutrition – Augusto Motta University Center
7. Sergio Franco Laboratory
8. Josué de Castro Institute – Rio de Janeiro Federal University

Electronic Address

1. valeria.rolla@ini.fiocruz.br
2. adriana.bacelo@ini.fiocruz.br
3. pedro.brasil@ini.fiocruz.br
4. claudiacople@gmail.com
5. ingebourg.georg@ini.fiocruz.br
6. elianepaivanutricao@gmail.com
7. sheila.argolo@dasa.com.br
8. aramalho.rj@gmail.com

Address

1. Av. Brasil 4365, Rio de Janeiro/RJ – Brazil, ZIP code 21040-900
2. Av. Brasil 4365, Rio de Janeiro/RJ – Brazil, ZIP code 21040-900
3. Av. Brasil 4365, Rio de Janeiro/RJ – Brazil, ZIP code 21040-900
4. Rua São Francisco Xavier 524, Rio de Janeiro/RJ, ZIP code 20550-900
5. Av. Brasil 4365, Rio de Janeiro/RJ – Brazil, ZIP code 21040-900
6. Av. Paris 72. Rio de Janeiro/RJ, Brazil, ZIP code 21041-020
7. Av. Carlos Chagas Filho, 373, CCS Bloco J, 2º andar, Rio de Janeiro/RJ – Brazil, ZIP code 21941-901
8. Rua Conde de Porto Alegre, 119, Duque de Caxias/RJ – Brazil, ZIP code 25085-007

Mail to:
Adriana Bacelo
Nutrition Service
National Institute of Infectious Diseases Evandro Chagas-Fiocruz
Av. Brasil 4365 - Manguinhos
Rio de Janeiro - CEP 21040-900
Email: adriana.bacelo@ini.fiocruz.br

Abstract

Introduction: the benefit of dietary counseling during tuberculosis treatment depends on patients' adherence to achieve nutritional recovery. The World Health Organization (WHO) recommends the use of dietary counseling to overcome malnutrition. **Objective:** to identify the adherence to dietary counseling along the six months of tuberculosis therapy. **Methods:** prospective observational study conducted in adult's, with and without HIV, treatment for tuberculosis. Self-reported adherence and 24-hour diet recall were checked at each visit, and diet counseling according to WHO strategy was offered. The endpoint was the adherence to the recommended dietary allowance (RDA) and total calories consumed during tuberculosis treatment. Data were mainly analyzed with marginal models to estimate adjusted trajectories. **Results:** 68 patients were included in our study. The maximum probability of total calories consumption of at least one RDA was 80%. The determinants of adherence were the presence of appetite and nausea/vomiting. For patients with troubles of appetite and nausea/vomiting, the probability of total calories consumption of at least one RDA is less than 20% at any time. **Conclusion:** dietary counseling is highly susceptible to non-adherence regardless of HIV infection. Self-reported adherence was ineffective. Gastrointestinal adverse events are highly prevalent and contribute to non-adherence to dietary counseling.

Key words: tuberculosis, HIV, nutritional status, dietary counseling, adherence, compliance.

Introduction:

The Food and Nutrition Board of the National Academy of Sciences established the RDA to determine the quantity and quality of nutrients necessary to maintain health in different life cycles [4]. It appreciates the variability between individuals; however, it disregards the special or individual nutritional needs. Furthermore, it does not address how different diseases impact a patient´s nutritional status, potentially generating various degrees and types of nutritional deficiency [4].

The World Health Organization (WHO) (WHO 2013) and the Brazilian Ministry of Health (BMH) [2, 3] recommends dietary supplementation only in severe cases of malnutrition. The recommendation for patients with mild to moderate malnutrition is to offer counseling (RDA) [1, 2, 4].

Among the options, the dietary counseling is a simple and cheap strategy to change the eating behavior, but its full benefit will only be achieved if the individual adheres to counseling (Desroches et al. 2011). Unfortunately, the current recommendations do not make any comment on effectivity of dietary counseling or adherence [1, 2].

Adherence is the extent to which a person's behavior agreed with recommendations from a health care provider towards: a) use of medication; b) following recommendations related to diet or; c) lifestyle changes. The patient's correct understanding of prescription and recommendations, as well as the patient's agreement with the recommended therapy is crucial to improve interventions effectiveness in public health programs [6].

One way to improve effectiveness of interventions is to understand the reasons which lead to non-adherence. Determinants of non-adherence may be related to patient's individual issues, including habits, beliefs and behaviors.

The association between tuberculosis and malnutrition is widely recognized, and the nutritional status has been previously identified as predictor of failure in tuberculosis therapy [7]. Non-adherence has been previously reported as a prevalent and persistent problem both for tuberculosis treatment [8, 9], and nutritional care [5]. Nutritional counseling in developing countries should receive the proper attention in order to understand if adherence to costly food in these scenarios is a possible strategy to overcome malnutrition.

The objective of this study is to identify the degree of adherence to dietary counseling and predictors of adherence among patients undergoing tuberculosis treatment, whether or not they were infected with HIV.

Methods

Study design

This is an observational prospective follow-up study.

Criteria establishing eligibility and ineligibility

Patients were eligible if they had tuberculosis diagnosed during the period of July 2008 to September 2013, and aged from 18 to 65 years old. All patients included in the study agreed to refrain from the use of nutritional supplements throughout the entire study.

Exclusion criteria were severe malnutrition (because supplementation was necessary), the use of nutritional supplementation during the six months preceding the study, patients with hypermetabolism, digestive diseases, pregnancy or those who were breast feeding. Only the supplementation of pyridoxine (vitamin B6) was allowed to prevent peripheral neuropathy, conforming with the Brazilian Ministry of Health [2].

Tuberculosis diagnosis

The tuberculosis diagnosis was established by assessing clinical signs and disease symptoms, by compatible radiological findings and by the identification of *Mycobacterium tuberculosis* in culture. In cases where the *Mycobacterium tuberculosis* was not isolated, the diagnosis was made using therapeutic response with clinical improvement. All tuberculosis diagnosis and treatment procedures followed the recommendations of the Brazilian Ministry of Health [2, 3, 11, 12].

Dietary counseling and self-reported adherence

The dietary counseling was delivered and read out to patients according to what was established by the Brazilian Ministry of Health [13] in the six nutritional visits performed 1 month apart. Self-reported adherence and 24-hour diet recall were taken at each visit by competent nutritionist before dietary counseling. After this, all patients had the opportunity to make questions and clarify their doubts at each visit. The steps and procedures of the study are shown in figure 1.

Nutritional assessment and adherence to dietary counseling were evaluated using a self-reporting strategy at all visits. The answers were recorded using the following categories: "yes follow", used when the patient followed what was advised, "followed satisfactorily", used when the patient followed most of the advises, and experienced little difficulty, "did not follow satisfactorily" when the patient did not follow most of the advises, and "did not follow", when the patient did not adhere to what was advised. We considered individuals who reported "yes followed" and

"followed satisfactorily" as patients with good adherence. We considered individuals who reported "did not follow satisfactorily" and "did not follow" as patients with poor adherence. Patients were also asked about reasons for their lack of adherence.

Outcome

Evaluation of caloric intake, macronutrients and micronutrients was performed via a 24-hour recall used to collect dietary data [14, 15]. Data from the 24-hour recall were applied to all food and liquid consumed within the preceding 24-hour period, and were analyzed with the professional Dietwin plus® software. The results of 24-hour recalls were compared to RDA, to determine whether or not patient intake reached the minimum recommended nutrients quantities.

The endpoint of this study was weather patients were able to consume at least the amount of total energy intake (1580 to 1870 Kcal/day) proposed by RDA at each visit over the 180 days of tuberculosis treatment, as well as the amount of total energy consumed.

Data Analysis plan

The data were analyzed using the R-project® software version 3.0.2. Data were analyzed following a plan of sample description of the baseline and the follow-up and analysis of the follow-up data. For the baseline period, the fractions and the number of patients in each category were shown. For the continuous variables, the mean and the standard deviation (if data were from normal distribution) or median and the inter-quartile range (if data were not from normal distribution) were estimated. At follow-up, the same information shown in baseline was stratified by the visits of the tuberculosis treatment period.

As for calories consumption, marginal models were used. The binary result of RDA consumption (yes or no) was modeled with a "GLM" function (Generalized Linear Model) for longitudinal data with binomial family distribution, considering irregular time intervals of outcomes observed in each patient. A similar analysis strategy was adopted for the total calories consumption outcome although with Gaussian family distribution. For both strategies, the "exchangeable" correlation structure suited best to the data. The following predictors defined in advance were tested: time, gastrointestinal symptoms, appetite, HIV infection, self-reported adherence, income, education, and clinical form of tuberculosis. Wald test was used to retain variables from the full model. All standard errors were estimated through a robust process.

Ethical aspects

This study was conducted in accordance with the ethical standards outlined for research in humans in the Declaration of Helsinki, and it approved by the Research Ethics Committee of the National Institute of Infectious Diseases Evandro Chagas, under the identification number CAE 0008.0.009.000-08. All patients who agreed to participate in the study signed an informed consent form.

Results

Sixty-eight patients were included in the study; and 34 patients remained until the end of the study. All exclusions and reasons are shown in figure 2. The mean age was 41.1 (± 13.4) years old and male was the predominant gender, with few years of school, low income and pulmonary form of tuberculosis (table 1). In addition, the minority of patients were drinkers and smokers. Twenty-two volunteers (32.4 %) were infected with HIV.

The average consumption of total energy, protein, and zinc during treatment was close to the minimum value recommended by RDA, while the average intake of other nutrients was usually lower than the values suggest by the RDA (table 2). Retinol intake was irregular over time and always below the recommended average, and the selenium intake was extremely low at any time.

The adherence to dietary counseling was low. More than half of the patients reported bad adherence up to D30. Adherence had a small improvement after day 60, and there was no noticeable difference between HIV infected and non HIV infected (figure 3).

The analysis of the reported reasons why the counseling was not followed (partially or completely) showed that patients presented a high prevalence of tuberculosis, or tuberculosis and AIDS gastrointestinal disorders or treatment. Up to 35.7% of individuals complained about nausea and vomiting, 15.4% of individuals complained about diarrhea and 38.5% of individuals complained about hyporexia or anorexia (table 3). Complaints that compromised the proper food intake included decreased appetite, nausea or vomiting (table 4). Despite the limited number of observations, there was an apparent decrease of gastrointestinal disorders over time (table 4). Financial restrictions and the feeding habits were also frequent causes of nutritional counseling non-adherence, either in HIV-infected and not infected patients.

The non consumption of food throughout the treatment becomes more evident with the observation of low proportion of individuals who ingested at least one RDA. About 60% of patients succeeded to consume the one RDA recommended for total energy intake. Approximately 20% consumed the expected amount of protein and micronutrients according to RDA recommendation (figure 4). There is no increase in the number of patients with proper RDA consumption during the follow-up. In fact, this is more clearly perceptible with the micronutrients data (figure 4).

The probability of people consuming at least one RDA is 80% in calories, if appetite is preserved and there is no nausea or vomiting. However, the probability to consume at least one RDA if changes in appetite and nausea or vomiting are present is less than 20% at any time (figure 5). According to the model strategy, the predictors were appetite (hyporexia or anorexia) and gastrointestinal symptoms (nausea or vomiting) (table 5).

In a linear regression model, the same predictors of at least one RDA for total energy consumption were identified. Additionally, time had a subtle positive effect on total energy intake, detectable at the end of tuberculosis therapy. Patients were consuming, at the end of treatment, approximately 370 kcal more than at the beginning of treatment (table 6).

Patients whose appetite was preserved consumed on average 435 Kcal more at any time, and patients with nausea or vomiting consumed, on average, 324 kcal less at any time. Therefore, patients without nausea, vomiting or compromised appetite consumed around 2000Kcal, and patients with nausea, vomiting and compromised appetite consumed around 1200Kcal (figure 6).

Discussion

In this study, the main findings were: (a) the majority of patients treated for tuberculosis failed to follow the dietary counseling; (b) there is little evidence of adherence improvement during tuberculosis treatment; (c) the predictors of non-adherence to dietary counseling were primarily related to gastrointestinal disorders, which include nausea, vomiting, hyporexia and anorexia; (d) the self-reported adherence was not a good method for monitoring dietary consumption.

The majority of patients treated for tuberculosis failed to follow the dietary counseling. This failure could be attributable to type of disease [16], lack of family support [17], adverse financial/educational conditions [18–21], taboos or beliefs related to food [22], ingrained eating habits, emotional and psychological conditions, and disorders related to problems or health treatment [16], which can influence food consumption. In Brazil, the high cost of nutritionally complete food was previously related to low consumption of micronutrients and high consumption of carbohydrate and fat [21]. However, these elements are usually related to inability to adhere to the minimum recommended dietary intake to be considered nutritionally healthy, and could be present even before tuberculosis diagnosis, as a personal habit.

Besides, the concept of health food consumption is debatable depending on the context. The RDA recommended daily consumption of protein to prevent deficiencies is less than the standard consumption in many countries [23]. Based on body weight of logical proportions, some authors recommended a wide range of protein consumption for a healthy diet of an adult. In some cases this recommended consumption could be up to 70g/day of protein above the consumption of protein recommended by the RDA [24, 25].

There was no information about feeding habits before the tuberculosis diagnosis; nevertheless, the inability of health food intake may frequently be intensified during the tuberculosis treatment. This circumstance turns the adherence to healthy diet a process with particular elements. Possibly, the disease itself and its treatment may play a direct or indirect role.

The tuberculosis treatment includes hepatotoxic medicines that can compromise appetite. Appetite impairment interferes with food intake capacity and the adherence of dietary counseling [26]. The nutritional counseling, like other forms of counseling (such as the use of condoms to prevent HIV transmission and other behavioral changes), does not have the same impact as therapeutic interventions. People in general don't feel treated if they don't take pills or powders [27, 28].

There is evidence that the repetitive exposure to the same information or recommendation followed by discussion or conversation would increase the chance of a better understanding about nutrition. The understanding about a disease or a strategy could affect behavior changes [29]. However, the evidence here presented through the adjusted analysis showed a little improvement in total calories intake at the last visit. Also, it is likely that the improvement on tuberculosis signs and symptoms could lead to a decrease in gastrointestinal complaints resulting in clinical improvement and increased capacity of healthy food consumption. If this is true, than it seems that the time spent for tuberculosis treatment was not enough to observe the desired change in food consumption.

The American Society for Parenteral and Enteral Nutrition (ASPEN) states that in the presence of low dietary intake or increased nutritional needs, an increase risk of malnutrition is expected [30]. This risk could be reduced using oral supplementation of nutrients as one of the options. This society also suggests that dietary counseling have to be implemented only when suitable dietary intake capacity has been restored

[30, 31]. What happens in Tb-HIV patients after TB therapy, but not at the beginning.

WHO and BMH recommend dietary counseling with focused on meeting the RDA. As a public health recommendation, dietary counseling is particularly attractive because it stimulates the intake of healthy food, it is easy to implement in different health facilities, it can be performed by any health professional, and it is freely available [13]. However, this study has shown that nausea, vomiting, hyporexia and anorexia interfere with the capacity to follow dietary counseling.

The elevation of inflammatory cytokines and ghrelin [36, 37], common in the acute phase of infectious diseases, was reported as the main cause of reduced appetite. The occurrence of nausea and vomiting was also linked to the use of antiretrovirals [38], and to the impairment of overall food intake. Changes in appetite were also linked to HIV infection, the influence of dietary counseling adherence and morbidity and mortality [39].

Drug-induced hepatoxicity is a well-known complication of tuberculosis treatment. It has been estimated from 5% to 35% [40, 41], and may manifest as elevation in liver transaminases or bilirubin [42], nausea and vomiting [41]. These findings are similar to the evidence here presented, which shows that gastrointestinal symptoms are more frequently reported by the patients as causes of non-adherence to dietary counseling at the first quarter of tuberculosis treatment.

Both tuberculosis and HIV infection are diseases known to affect nutritional status [33–35]. One could expect that the food consumption of patients with both tuberculosis and HIV infection would be lower than the food consumption of patients with tuberculosis only. This rationale is reasonable as patients with both HIV and tuberculosis are more susceptible to complications and adverse effects of medications, including gastrointestinal involvement [40]. However, the evidence here presented shows that HIV infection is not a predictor of non-adherence to dietary counseling.

There are those who argue that the dietary prescriptions should be individualized [43, 44]. The aim of this strategy is to offer different doses of drugs to patients according to their pharmacogenetics characteristics. The objective is to reduce toxicity and improve the outcomes [45]. The lower prevalence of adverse reactions would improve the adherence of nutritional counseling associated with gastrointestinal signs [46]. Several individualized dietary strategies contribute to reduce symptoms, such as

poor appetite, nausea or vomiting. The use of food in low temperature [47] and the appropriate choice of food nature already demonstrated to be beneficial for reducing nausea/vomiting [47]. These supplements are a well-known way to offer high quality food adequate for individuals during the treatment period. Nutritional counseling is different because it depends on multiple patient factors to be effective that nutritional staff have little governance [48].

Health professional uses self-reported dietary adherence to know the patient perception about their food consumption. This seems to be an indicator of what patients would like to do rather than what they actually did. It was discussed before that patients had difficulties to understand that a "healthy" diet is not just about eating more in quantity. They are also sometimes afraid to disappoint health care professionals when they do not follow the recommendations [49]. The evidence here presented suggests that the self-reported dietary adherence overestimated food intake when compared with food intake identified by 24-hour recall. This is an expected trend in literature [50, 51] that point out that self-reported dietary adherence is not reliable.

Limitations

The main limitations of the study were the sample size and retention, both for the nutritional follow-up and for tuberculosis treatment, and the patient-dependent type of data used for the main outcome. Lack of data due to failure in following-up turns the conclusions more susceptible to errors. There are several discussions regarding lack of adherence during tuberculosis treatment [9], however, as far as we are concerned, there is no longitudinal data on adherence to dietary counseling during tuberculosis treatment. On the other hand, the dropout and adherence rates observed are similar to other nutritional studies [52, 5]. One may distinguish the adherence as attending to nutritionist appointment or follow the nutritional counseling. It is likely that if the patient does not attend nutritionist appointment this patient does not follow the counseling. If this is true, lack of adherence with the follow-up could also be interpreted as lack of adherence to the dietary counseling itself. Therefore, dietary adherence could be even more impaired than inferred.

In malnourished patients, interventions that modify indicators of nutritional status may have an important impact on the mortality of patients. And the energy intake, which was analyzed, is a major dietary factor potentially influencing nutritional status [53].

The 24-hour recall method to estimate nutrients intake relies on patient's memory and report of his/her intake. It is not known if this period of 24-hour could represent the whole food consumption occurred in the previous 30 days (the period between visits). The nutrients intake estimated from a single interview using the 24-hour recall method can range from 4 to 400% when compared with other methods, such as food dietary registry and food frequency registry. However, this type of error can be mitigated with repetitive interview with the 24-hour recall methods over a certain period, and with a higher expertise of interviewer with this method [54]. Alternative methods to estimate nutrients intake could be food dietary registry or food frequency registry. Nevertheless, they are operationally more complicated, may suffer from the same disadvantage of relying on patient's memory, require a reasonable reading and writing capacity, or need to be previously validated with the population of interest. Despite of the 24-hour recall method limitations, it has been widely used in researches and it is accepted for this purpose [14, 15].

Conclusion

The self-reported adherence was not a good mechanism for checking caloric intake in this population, and gastrointestinal symptoms – hyporexia, anorexia, nausea and vomits – were the predictors of low adherence to dietary recommendations. Research aiming at testing strategies to reduce gastrointestinal symptoms may bring benefits in nutritional status recovery.

Acknowledgements

We thank nurse Solange Alves da Cruz, responsible for the blood collection unit, doctors Flavia Marinho Sant´Anna and Carolina Arana Stanis Schmaltz, and the nutritionists Ivan Rocha Maia and Erika Ennes who helped us with data collection. We appreciate the support of the INI Nutrition Service in the development of this study.

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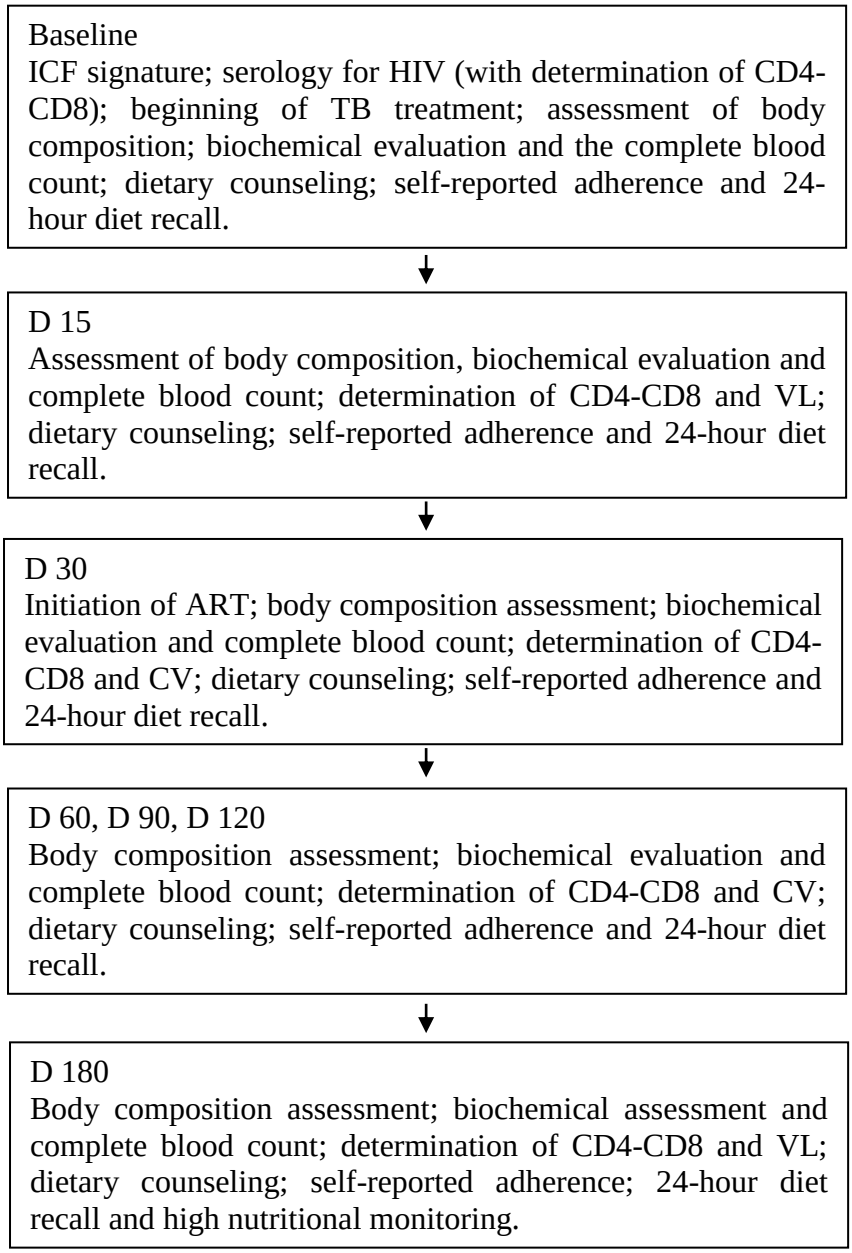

D = day of visits; ICF = informed consent form; HIV = human immunodeficiency virus; ART = antiretroviral therapy; Biochemical assessment = albumin, iron fixation capacity, iron, selenium, zinc, retinol and tocopherol; CD4 = lymphocyte TCD4; CD8 = lymphocyte TCD8; VL = viral load; dietary counselling = was delivered and read with patients the document proposed by the ministry of health ("CGAN - Coordenação-Geral de Alimentação e Nutrição" 2014).

Figure 1 – Flow Chart of Study

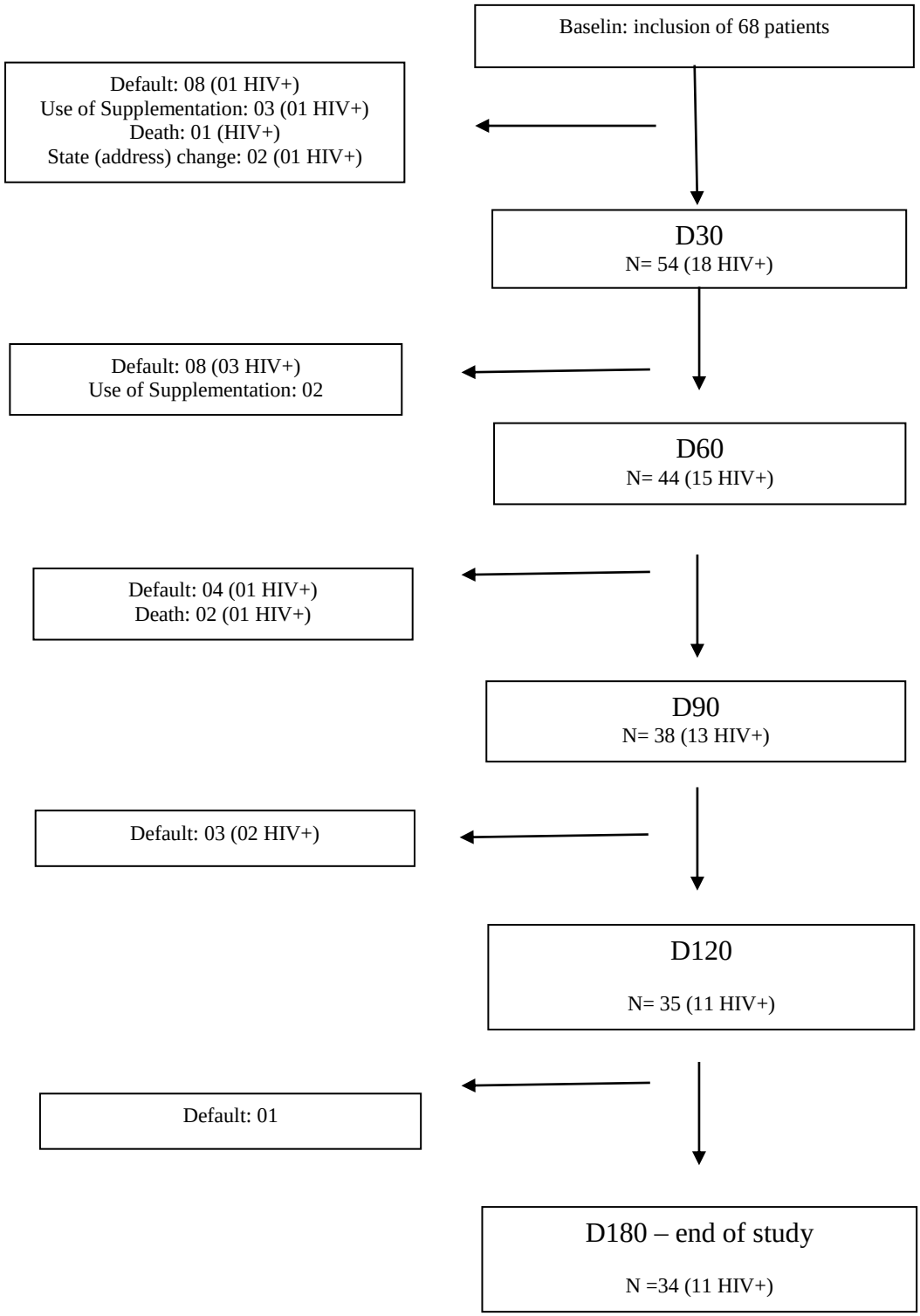

Figure 2. Causes of discontinuation throughout the TB treatment course

Table 1 Baseline socio-demographic and clinical characteristics of tuberculosis individuals HIV-infected or non-infected.

	HIV +	HIV -	Total	Hypothesis testing	P value
Total	46	22	68		
Sex [1]				Chisq. (1 df) = 1.04	0.308
Male	26 (56.5)	16 (72.7)	42 (61.8)		
Female	20 (43.5)	6 (27.3)	26 (38.2)		
Age				t-test (66 df) = 0.62	0.535
Mean (SD)	40.4 (15.1)	42.6 (9.1)	41.1 (13.4)		
Education				Ranksum test	0.961
Median (IQR)	6 (4.0 – 11.0)	5 (4.0 – 9.0)	6 (4.0 - 10.8)		
Monthly income [3]				Ranksum test	0.666
Median (IQR)	350 (240 - 540)	350 (270 - 680)	350 (255 - 600)		
Clinical form of tuberculosis [1]				Fisher's exact test	0.218
Pulmonary	15 (71.4)	5 (38.5)	20 (58.8)		
Extra pulmonary	4 (19.0)	5 (38.5)	9 (26.5)		
Disseminated	2 (9.5)	3 (23.1)	5 (14.7)		
Gastrointestinal disorder [1]				Fisher's exact test	0.051
Preserved appetite	24 (52.2)	7 (31.8)	31 (45.6)		
Polyphagia	4 (8.7)	1 (4.5)	5 (7.4)		
Anorexia	4 (8.7)	8 (36.4)	12 (17.6)		
Hyporexia	14 (30.4)	6 (27.3)	20 (29.4)		
Nausea / vomiting	14 (30.4)	7 (31.8)	21 (31.9)	Chisq. (1 df) = 0.00	1.000
Diarrhea	4 (8.7)	5 (22.7)	9 (13.2)		

[1]= n (%); [2] = years; [3] = United States Dollars (USD). IQR = interquartile range.

Table 2 Food consumption and intake of energy, protein and micronutrients of tuberculosis patients at diagnosis and during treatment visits.

24h recall	RDA	D15	D30	D60	D90	D120	D150	D180
N. of meals/day [1]	5 – 6	4.5 (3.2 – 5.0)	4.0 (4.0 – 5.0)	4.0 (4.0 - 5.2)	5.0 (4.0 – 5.0)	4.0 (4.0 – 5.0)	4.0 (4.0 – 6.0)	4.0 (4.0 – 5.0)
Total energy [1, 2]	1580.0 – 1870.0	1770.0 (1330.8 - 2156.8)	1948.5 (1466.0 - 2601.2)	1779.0 (1498.8 - 2044.8)	1812.0 (1457.0 - 2900.5)	1824.0 (1601.2 - 2274.5)	2085.5 (1506.0 - 2765.5)	1992.0 (1507.5 – 2109.0)
Protein [1, 3]	46 – 56	73.9 (46.4 - 95.1)	83.5 (70.1 - 107.4)	84.5 (67.5 - 89.8)	73.5 (45.1 - 85.2)	92.7 (60.8 - 102.1)	96.5 (78.6 - 120.4)	87.7 (67.4 - 92.1)
Retinol [1, 4]	700 – 900	295.4 (91.4 - 429.8)	617.8 (258.6 - 1111.8)	330.4 (182.2 - 554.2)	382.6 (215.0 - 993.7)	380.7 (276.4 - 436.5)	452.5 (155.3 - 998.1)	257.6 (167.2 - 346.3)
Tocopherol [1, 5]	15	9.2 (5.5 - 12.7)	10.6 (4.7 – 18.0)	7.6 (4.0 - 11.7)	9.1 (5.6 - 12.1)	11.0 (5.1 - 16.4)	10.8 (7.8 - 14.7)	7.5 (4.4 - 10.4)
Zinc [6, 5]	9 – 14	8.8 (4.3)	13.3 (8.6)	9.1 (5.0)	9.5 (5.6)	13.3 (6.1)	13.6 (6.4)	9.7 (2.8)
Selenium [1, 4]	0.7	0.1 (0.0 - 0.2)	0.0 (0.0 - 0.4)	0.0 (0.0 - 0.1)	0.1 (0.0 - 0.3)	0.0 (0.0 - 0.2)	0.1 (0.0 - 0.2)	0.0 (0.0 – 0.0)

RDA = 1x in the Recommended dietary allowance; Total energy = total energy intake; 1 = median (IQR); 2 = Kcal; 3 = grams; 4 = micrograms; 5 = milligrams; 6 = mean (SD).

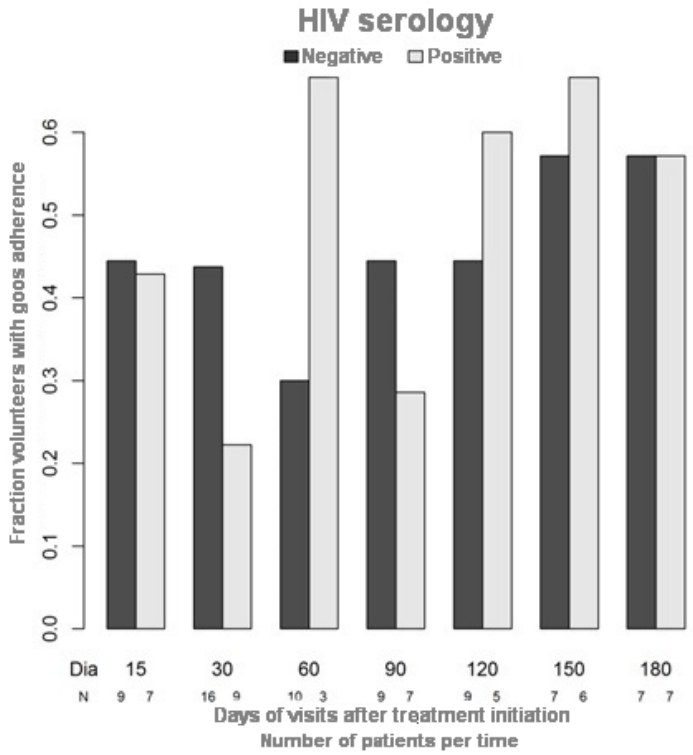

Figure 3. Perception of self-reported adherence to proper dietary counseling of patients being treated for tuberculosis, infected or not with HIV.

Table 3 Reported gastrointestinal disorders of tuberculosis patients at diagnosis and during treatment visits.

Gastrointestinal disorders	Baseline	D15	D30	D60	D90	D120	D150	D180
Preserved appetite [1,2]	31 (45.6)	9 (56.2)	20 (71.4)	4 (30.8)	9 (56.2)	14 (100.0)	10 (76.9)	13 (92.9)
Polyphagia [2]	5 (7.4)	3 (18.8)	3 (10.7)	1 (7.7)	3 (18.8)	0 (0.0)	1 (7.7)	1 (7.1)
Anorexia [1.2]	12 (17.6)	1 (6.2)	1 (3.6)	3 (23.1)	1 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hyporexia [1,2]	20 (29.4)	3 (18.8)	4 (14.3)	5 (38.5)	3 (18.8)	0 (0.0)	2 (15.4)	0 (0.0)
Nausea / vomiting[1.2]	21 (30.9)	1 (6.2)	10 (35.7)	4 (30.8)	4 (25.0)	3 (21.4)	4 (30.8)	1 (7.1)
Diarrhea [1,2]	9 (13.2)	0 (0.0)	3 (10.7)	2 (15.4)	2 (12.5)	0 (0.0)	1 (7.7)	0 (0.0)

1 = number of subjects; 2 = percentage (%).

Table 4 - Complains reported by HIV infected and non-infected patients that impacted adherence to dietary recommendation during tuberculosis treatment.

Visits	D-15	D-30	D-60	D-90	D-120	D-150	D-180	Total of complains
HIV+								
Gastrointestinal disorders [1]	3 (60)	5.0 (71.4)	1 (50.0)	3 (60.0)	-	1 (50.0)	2 (50.0)	15 (55.5)
Feeding habit [1]	-	-	-	-	1 (50.0)	1 (50.0)	2 (50.0)	4.0 (14.8)
Financial restrictions [1]	2 (40.0)	2 (28.6)	1 (50.0)	2 (40.0)	1 (50.0)	-	-	8 (29.6)
Complains subtotal	5	7	2	5	2	2	4	27
HIV-								
Gastrointestinal disorders [1]	5 (100.0)	6 (85.7)	3 (75.0)	3 (60.0)	1 (50.0)	-	-	18 (66,6)
Feeding habit [1]	-	1 (14.3)	1 (25.0)	1 (20.0)	1 (50.0)	-	3 (100.0)	7 (25.9)
Financial restriction [1]	-	-	-	1 (20.0)	-	1 (100.0)	-	2 (7.4)
Complains subtotal	5	7	4	5	2	1	3	27
Total of complains	**10**	**14**	**6**	**10**	**4**	**3**	**7**	**54**

[1] number of events (%).

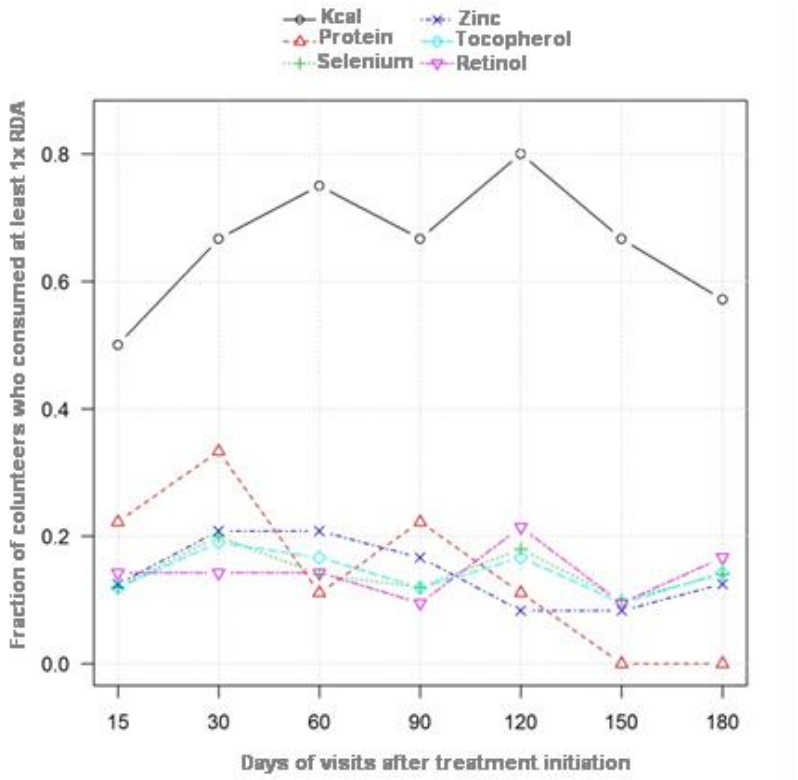

Figure 4. Proportion of individuals able to ingest at least 1x RDA, as verified by the 24-hour recall along tuberculosis treatment.

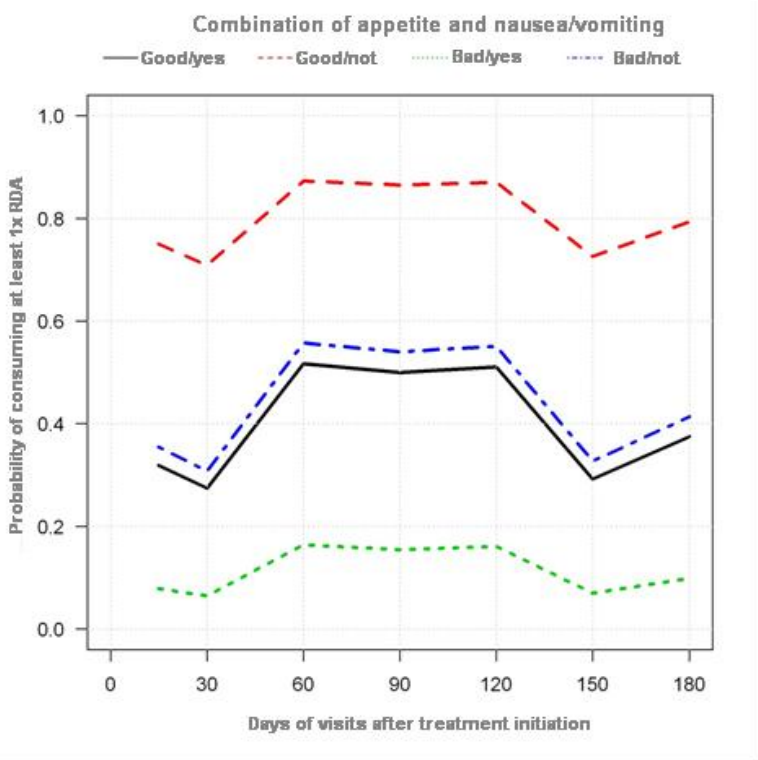

Figure 5. Predicting the probability of ingesting at least 1x the RDA in calories during tuberculosis treatment for individuals undergoing dietary counseling, according to the occurrence of preserved appetite or presence of nausea and vomiting.

Table 5. Longitudinal marginal model (logistic) for intake capacity of at least once of the Recommended Dietary Accomplishment during tuberculosis treatment.

Predictors	Estimate	Std.err	Wald	Pr (>|W|)	OR	Lower OR	Upper OR
Intercept	-0.5985	0.5902	1.0283	0.3105	0.5496	0.1729	1.7477
D30	-0.2099	0.5072	0.1712	0.6790	0.8107	0.3000	2.1907
D60	0.8285	0.8674	0.9125	0.3395	2.2900	0.4183	12.5355
D90	0.7606	0.6452	1.3898	0.2384	2.1395	0.6041	7.5766
D120	0.8034	0.9042	0.7895	0.3742	2.2332	0.3795	13.1407
D150	-0.1233	0.9319	0.0175	0.8947	0.8840	0.1423	5.4919
D180	0.2496	0.6747	0.1369	0.7114	1.2836	0.3421	4.8166
Preserved appetite	1.6965	0.5599	9.1798	0.0024	5.4547	1.8203	16.3452
Nausea / vomiting	-1.8583	0.4328	18.4367	0.0000	0.1559	0.0668	0.3642

Std. err = standard error; OR = odds ratio

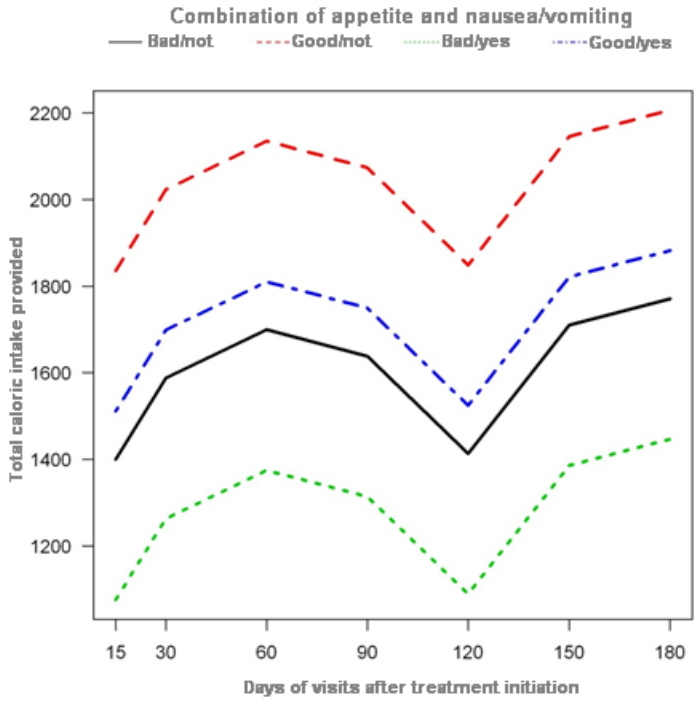

Figure 6. Forecast of Kcal intake during tuberculosis treatment for individuals undergoing dietary counseling, according to the occurrence of nausea and vomiting.

Table 6. Longitudinal marginal model (Gaussian) for total energy intake (Kcal) during tuberculosis treatment.

Predictors	Estimate	Std.err	Wald	Pr(>|W|)
Intercept	1400.1379	172.8116	65.6441	0.0000
D30	187.4700	146.9128	1.6283	0.2019
D60	299.0291	201.7728	2.1964	0.1383
D90	238.2486	167.3790	2.0261	0.1546
D120	13.4774	206.5822	0.0043	0.9480
D150	310.0042	197.8785	2.4544	0.1172
D180	370.4008	150.8481	6.0293	0.0141
Preserved appetite	435.4660	141.1930	9.5122	0.0020
Nausea / vomiting	-324.3217	123.0044	6.9520	0.0084

Std. err = standard error; OR = odds ratio

7. CONCLUSÃO

Conclui-se que o aconselhamento dietético não foi suficiente para reverter a má nutrição, que foi prevalente nos pacientes HIV + em todas as etapas do tratamento da tuberculose, com maior impacto sobre o estado corporal proteico e de ferro, e que a adesão ao aconselhamento dietético foi baixa, tendo na ocorrência de náuseas, vômitos e anorexia/hiporexia seus principais fatores limitadores.

8. RECOMENDAÇÕES E DESDOBRAMENTOS

O profissional de saúde não deve utilizar o IMC como indicador único para o monitoramento do estado nutricional desta população, bem como não deve se basear no autorrelato sobre adesão dietética, sendo mais importante verificar a ingestão real de cada sujeito pela anamnese dietética, assim como dos fatores limitadores da adesão.

Depois do tratamento da TB os pacientes que deram continuidade ao acompanhamento nutricional recuperaram o estado nutricional. Apontando que seria interessante promover futuras investigações para saber: a) quanto tempo leva para que os pacientes restabeleçam o estado nutricional depois de finalizado o tratamento da TB; b) quais diferentes intervenções promoveriam recuperação do estado nutricional do paciente de forma mais precoce; e c) devem ser testadas propostas de terapia nutricional para esta população visando reduzir hiporexia, náuseas e vômitos; e padronizar os parâmetros de monitoramento da ingestão alimentar e de adesão às mudanças de comportamento alimentar; e a evolução antropométrica a serem implementados como mandatórios além do IMC.

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10. ANEXOS

10.1. Anexo I - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

AVALIAÇÃO DO ESTADO NUTRICIONAL DE PACIENTES COM TUBERCULOSE EM ACOMPANHAMENTO MEDIMENTOSO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Pesquisadores envolvidos:
Adriana Costa Bacelo
Eliane Paiva
Ivan Maia
Flavia Marinho SantAnna
Carolina Arana Stanis Schmaitz
Rejane Andréa Ramalho
Valeria Cavalcanti Rolla

A tuberculose é uma doença muito debilitante, sendo importante cuidados alimentares. A alimentação habitual da população brasileira vem sendo modificada nos meios urbanos, pela queda da renda financeira, pela correria da rotina diária, e isso tem significado menor ingestão de minerais e vitaminas. Para tanto, temos como objetivo de é avaliar se a orientação dietética é capaz de suprir todas as demandas de micronutrientes causadas pela tuberculose.

Serão realizados dois tipos de exames, um de análise do sangue e outro de análise das medidas corporais, a cada dois meses. Este estudo espera ajudar a equipe de médicos e nutricionistas a melhorar a qualidade do atendimento. A não concordância em participar do estudo não irá ocasionar qualquer prejuízo, ou alterar seu tratamento. Se decidir participar terá o direito de abandonar a pesquisa quando for de seu desejo, sem que isso implique em qualquer desconforto.

Eu, _____

(paciente ou responsável) fui informada dos objetivos da pesquisa acima de maneira clara e detalhada. Sei que em qualquer momento poderei solicitar novas informações e modificar minha decisão. Os pesquisadores envolvidos

me certificaram de que todos os dados desta pesquisa referentes a mim serão confidenciais, e que terei liberdade de retirar meu consentimento de participação na pesquisa, face estas informações.

Em caso de novas perguntas sobre os meus direitos como participante deste estudo, posso chamar os pesquisadores no telefone 21 3865-9595.

Declaro que recebi cópia do presente Termo de Consentimento.

_____ _____

Assinatura do Paciente Data

_____

Nome em letra de forma

_____ _____

Assinatura do Pesquisador Data

_____

Nome em letra de forma

_____ _____

Assinatura da Testemunha Data

_____

Nome em letra de forma

10.2. ANEXO II - FICHA DE AVALIAÇÃO NUTRICIONAL – 1º Atendimento

FICHA DE AVALIAÇÃO NUTRICIONAL – 1º Atendimento

Data da avaliação:_____

Patologia(s) associada(s):_____

NOME: _____ REGISTRO: _____
PROFISSÃO: _____ NASCIMENTO: _____
SEXO:_____
IDADE:_____ anos
ESCOLARIDADE:_____
RENDA MENSAL: _____

1. MEDIDAS ANTROPOMÉTRICAS:

1.1. Peso Atual: _____Kg
1.2. Peso Usual:_____Kg
1.3. Altura: _____cm (H^2: _____)
1.4. Peso Ideal: _____ Kg (+ 10% :_____ Kg ; menos 10%:_____Kg)
1.5. Percentual de ☐ Perda ☐ Ganho de Peso: ___% em ___ ☐ dias ☐ meses
1.6. Circunferência Braquial (CB):_____cm
1.7. Dobra Cutânea Triciptal (DCT):_____
1.8. Circunferência Muscular do Braço (CMB):_____cm
1.9. Índices de Massa Corporal (IMC):_____Kg/m^2 (Engstrom - SISVAN - 2002)
1.10. Circunferência abdominal: _____ cm

2. BIOIMPEDÂNCIA:

2.1. %Gordura_____
2.2. % Massa magra_____
2.3. % Agua corporal _____-_____

3. TABAGISMO E ETILISMO:

Tabagismo: ☐ Sim ☐ Não ☐ Ex-tabagista há _____ (tempo)
Se “sim”, quantos cigarros por dia? _____

Etilismo: ☐ Sim ☐ Não ☐ Ex-etilista há _____ (tempo)
Se “sim”, qual o tipo de bebida? _____

Freqüência de consumo: ☐ diariamente ☐ 1 a 2 vezes por semana ☐ 3 a 5 vezes por semana ☐ raramente

4. HISTÓRIA DIETÉTICA:

4.1. Uso de suplementos vitamínicos e/ou minerálicos: ☐ Sim ☐ Não
Se “sim”, especificar _____

4.2. Alergia(s) alimentar (es): ☐ Sim ☐ Não
Se “sim”, especificar
_____

4.3. Consumo de alimentos entre as refeições: ☐ Sim ☐ Não
Se “sim”, especificar tipo:
_____

4.4. Refeições realizadas: ☐ desjejum ☐ colação ☐ almoço ☐ merenda ☐ jantar ☐ ceia

4.5. Frequência de consumo:
D = diariamente; R = raramente; N = nunca; 1 = 1 a 2 vezes/semana; 2 = 3 a 5 vezes/semana

5. EXAMES LABORATORIAIS:

5.1. Albumina: _____mg/dl
Transferrina: _____mg
Hemoglobina: _____g/dl
Linfócito: _____mg/dl
Selênio: _____mg/dl
Zinco: _____mg/dl
Globulina_____mg/dl
Ferro sérico: _____mg/dl
Capacidade Total de ligação de Ferro: _____mcg/dl
Vitamina C_____
Vitamina E: _____
Vitamina A: _____

6. EXAME CLÍNICO/FÍSICO:

a) Apetite: ☐ normal ☐ aumentado ☐ anorexia ☐ hiporexia ☐ comer compulsivo

b) Presença de edema: ☐ sim ☐ não
se “sim”: ☐ + / 4+ ☐ ++ / 4 + ☐ +++ / 4 + ☐ ++++ / 4 + ☐ Ascite ☐ Anasarca

c) Hidratação: ☐ Normal ☐ Hipohidratação

d) Salivação: ☐ Normal ☐ Xerostomia ☐ Sialorréia

e) Odinofagia: ☐ sim ☐ não

f) Disfagia: ☐ sim ☐ não

g) Ulcerações orais/ orofaringeanas: ☐ sim ☐ não
h) Náuseas / Vômitos: ☐ sim ☐ não

i) Dispepsia: ☐ Sim ☐ Não

j) Epigastralgia: ☐ Sim ☐ Não

k) Diarréia: ☐ sim ☐ não
Se “sim” o Nº de evacuações / 24 h é: _____ Consistência das fezes: _____

l) Obstipação: ☐ sim ☐ não
Se “sim” a freqüência de evacuação é de:_____vez (es) a cada _____ dias

m) Arcada Dentária: ☐ Própria ☐ Prótese ☐ Ambos ☐ Inexistente
Se “própria”, estado de conservação: ☐ Bom ☐ Regular ☐ Péssimo

10.3. Anexo III - FICHA ACOMPANHAMENTO NUTRICIONAL

FICHA ACOMPANHAMENTO NUTRICIONAL – Tempo: _____Data: _____

NOME: _____ REGISTRO: _____

1. MEDIDAS ANTROPOMÉTRICAS:

1.1. Peso Atual: _____Kg
1.2. Circunferência Braquial (CB): _____cm
1.3. Dobra Cutânea Triciptal (DCT): _____
1.4. Circunferência Muscular do Braço (CMB):_____cm
1.5. Índice de Massa Corporal (IMC): _____Kg/m^2 (Engstrom - SISVAN - 2002)
1.6. Circunferência abdominal: _____cm

2. BIOIMPEDÂNCIA:

2.1. %Gordura_____
2.2. % Massa magra_____
2.3. % Água corporal _____

3. EXAMES LABORATORIAIS:

Albumina:_____ mg/dl
Transferrina:_____ MG
Hemoglobina:_____ g/dl
Linfócito:_____mg/dl
Selênio:_____mg/dl
Zinco:_____mg/dl
Globulina:_____mg/dl
Ferro sérico:_____mg/dl
Capacidade Total de ligação de Ferro:_____mcg/dl
Vitamina C_____
Vitamina E:_____
Vitamina A:_____

6. Exame clínico/físico:

a) Apetite: ☐ normal ☐ aumentado ☐ anorexia ☐ hiporexia ☐ comer compulsivo

b) Presença de edema: ☐ sim ☐ não
Se “sim”: ☐ + / 4+ ☐ ++ / 4 + ☐ +++ / 4 + ☐ ++++ / 4 + ☐ Ascite ☐ Anasarca

c) Hidratação: ☐ Normal ☐ Hipohidratação

d) Salivação: ☐ Normal ☐ Xerostomia ☐ Sialorréia

e) Odinofagia: ☐ sim ☐ não

f) Disfagia: ☐ sim ☐ não

g) Ulcerações orais/ orofaringeanas: ☐ sim ☐ não

h) Náuseas / Vômitos: ☐ sim ☐ não

i) Dispepsia: ☐ Sim ☐ Não

j) Epigastralgia: ☐ Sim ☐ Não

k) Diarréia: ☐ sim ☐ não
Se “sim” o Nº de evacuações / 24 h é: _____ Consistência das fezes: _____

l) Obstipação: ☐ sim ☐ não
Se “sim” a freqüência de evacuação é de:_____vez (es) a cada _____ dias

Observações:
_____
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10.4. Anexo IV – SUBMISSÃO PLOS ONE

Os documentos a seguir são as páginas originais do:

10.4.1 Email de confirmação de recebimento da primeira submissão à PLOS ONE.

10.4.2 Ùltimo email de aceite com as solicitações dos revisores PLOS ONE.

---------- Forwarded message ----------
From: **PLOS ONE** <no-reply@editorialmanager.com>
Date: 2014-07-08 11:22 GMT-03:00
Subject: Submission Confirmation for Malnutrition of micronutrients occurs in tuberculosis patients with and without HIV infection due to the dietary counseling: a longitudinal study. - [EMID:8fe019b165e112ff]
To: Adriana Costa Bacelo <adribacelo@gmail.com>

PONE-D-14-30496
Malnutrition of micronutrients occurs in tuberculosis patients with and without HIV infection due to the dietary counseling: a longitudinal study.
PLOS ONE

Dear Mrs Bacelo,

Thank you for submitting your manuscript entitled "Malnutrition of micronutrients occurs in tuberculosis patients with and without HIV infection due to the dietary counseling: a longitudinal study." to PLOS ONE. Your assigned manuscript number is PONE-D-14-30496.

We will now begin processing your manuscript and may contact you if we require any further information. You will receive an update once your manuscript passes our in-house technical check; you can also check the status of your manuscript by logging into your account at http://pone.edmgr.com/.

Please visit EveryONE (http://blogs.plos.org/everyone), the PLOS ONE community blog for our published authors and readers, to find out what the journal is thinking, changing and doing.

If you have any inquiries or other comments regarding this manuscript, please contact plosone@plos.org.

Thank you for your support of PLOS ONE.

Kind regards,
PLOS ONE

---------- Forwarded message ----------
From: **PLOS ONE** <em@editorialmanager.com>
Date: 2014-12-19 7:29 GMT-02:00
Subject: PLOS ONE: Your submission PONE-D-14-30496R2 - [EMID:1654f7923971b56d]
To: Adriana Costa Bacelo <adribacelo@gmail.com>

PONE-D-14-30496R2
Nutritional supplementation is a necessary complement to dietary counseling among tuberculosis and tuberculosis-HIV patients to overcome malnutrition.
Mrs Adriana Costa Bacelo

Dear Mrs Bacelo,

Thank you for submitting your manuscript entitled "Nutritional supplementation is a necessary complement to dietary counseling among tuberculosis and tuberculosis-HIV patients to overcome malnutrition." to PLOS ONE. Your manuscript files have been checked in house but before we can proceed, we need you to address the following issues:

Please rename your figure and supporting information files so that they comply with PLOS file naming conventions. For figures please use the format "Fig#.file type" and for supporting information files please use the format "S#_Type.file type." For example, "Fig1.tif" or "S2_Dataset.xls".

Additionally, please ensure that your manuscript meets PLOS ONE's style requirements. The PLOS ONE formatting templates can be found at http://www.plosone.org/attachments/PLOS_ONE_Formatting_Sample_1_2014.pdf or http://www.plosone.org/attachments/PLOS_ONE_Formatting_Sample_2_2014.pdf

1. Please amend the title either on the online submission form or in your manuscript so that they are identical.

Your manuscript has been returned to your account. Please log on to PLOS Editorial Manager at http://pone.edmgr.com/ to access your manuscript.

Your manuscript can be found in the "Submissions Sent Back to Author" link under the New Submissions menu. After you have made the changes requested above, please be sure to view and approve the revised PDF after rebuilding the PDF to complete the resubmission process.

Please note that these changes have been requested to comply with

submission guidelines and your manuscript will *not* be sent to review until you have fully adhered to our requests. Once your paper has been seen by an Editor we may return it to you for further information or amendments.

Thank you for submitting your work to PLOS ONE.

Kind regards,

Laura Rendall
PLOS ONE

10.5. Anexo V – SUBMISSÃO Biomed Research International

O documento a seguir é a página original do:

10.5.1 Email de confirmação de recebimento da submissão à Biomed Research International.

---------- Forwarded message ----------
From: **BioMed Research International** <saly.sami@hindawi.com>
Date: 2015-01-06 20:34 GMT-02:00
Subject: 160384: Acknowledging Receipt
To: adribacelo@gmail.com
Cc: saly.sami@hindawi.com, pedro.brasil@ini.fiocruz.br, claudiacople@gmail.com, ingebourg.georg@ini.fiocruz.br, elianepaivanutricao@gmail.com, sheila.argolo@dasa.com.br, aramalho.rj@gmail.com, valeria.rolla@ini.fiocruz.br

Dear Dr. Bacelo,

The Research Article titled "Dietary counseling adherence during tuberculosis treatment: a longitudinal study," by adriana Costa Bacelo, Pedro Emmanuel Alvarenga Americano do Brasil, Claudia dos Santos Cople-Rodrigues, Georg Ingebourg, Eliane Paiva, Sheila Argolo, Andréa Ramalho and Valéria Rolla has been received and assigned the number 160384.

All authors will receive a copy of all the correspondences regarding this manuscript.

Thank you for submitting your work to BioMed Research International.

Best regards,

Saly Sami
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http://www.hindawi.com