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The effect of TB treatment on health-related quality of life for people with advanced HIV

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Abstract

Introduction: We evaluated the impact of empirical tuberculosis (TB) therapy versus isoniazid preventive therapy (IPT) in addition to antiretroviral therapy (ART) among people living with HIV (PLHIV) on health-related quality of life (HRQoL), assessed changes over time, and examined associations between sociodemographic and clinical factors.

Methods: Participants >13 years were enrolled from outpatient clinics in 10 countries. HRQoL was assessed at weeks 0, 8, 24 and 96 with questions about daily activity, hospital or emergency room visits, and general health status. We used logistic regression to examine HRQoL by arm and association with sociodemographic and clinical factors.

Results: Among 850 participants (424 empiric arm, 426 IPT arm), HRQoL improved over time with no difference between arms. At baseline and week 24, participants with WHO stage 3 or 4 events, or who had grade 3 or 4 signs/ symptoms, were significantly more likely to report poor HRQoL using the composite of four HRQoL measures.

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Conclusions: HRQoL improved substantially in both arms during the study period. These findings show that ART, TB screening, and IPT can not only reduce mortality, but also can improve HRQoL in PLHIV with advanced disease.

Keywords

Health Related Quality of Life; tuberculosis; advanced HIV; IPT; antiretroviral therapy

INTRODUCTION

Tuberculosis (TB) remains a major global health concern, with an estimated 10 million TB cases in 2018[1]. TB is the leading infectious cause of mortality globally, having surpassed HIV/AIDS related deaths [2, 3]. Drug therapy for TB reduces morbidity and mortality, with global cure rates of 83% overall and 78% for HIV-associated TB [3]. Despite high cure rates, this prolonged multi-drug therapy can impact patients' health-related quality of life (HRQoL) due to adverse drug reactions [4], social stigma[5, 6], or anxiety and feelings of helplessness stimulated by the disease and its treatment processes[7]. Among persons with TB and HIV co-infection, there may be additional impact on HRQoL due to concurrent antiretroviral therapy (ART) and additive drug toxicity, and stigma and anxiety of two diseases. Therefore, measuring HRQoL is important for understanding the biological and psychological effect of TB disease and treatment in People Living with HIV (PLHIV)[5, 8].

HRQoL measurement can facilitate detection of groups at risk of psychological or behavioral challenges, which can affect treatment adherence and outcomes [6, 7, 9]. A better understanding of HRQoL in patients with TB/HIV could inform efforts to provide more patient-centered care as recommended by the WHO End TB Strategy [4]. A number of HRQoL instruments have been developed to measure patients' outcomes in clinical research and practice [6], and at least one has been validated among TB patients in sub-Saharan Africa [10, 11]. Although participants from controlled clinical trials may differ from those in clinical practice, measuring HRQoL in these studies is of importance. HRQoL was low among PLHIV before initiating first- [12] and second-line ART [13], and has varied with disease severity, demographic characteristics and country in two large clinical trials conducted in resource-limited settings. HRQoL has also improved after one year of second-line ART initiation [14] and may be used as predictor of low adherence and virological failure [15, 16].

In the AIDS Clinical Trial Group (ACTG) study A5274, we evaluated the impact of empirical TB therapy versus isoniazid preventive therapy (IPT), in addition to ART among PLHIV on HRQoL, assessed changes over time, and examined associations with sociodemographic and clinical factors.

Methods

Study Design

The ACTG 5274 study design has been reported previously [17]. Briefly, this was a randomized, open-label, phase IV strategy trial of participants aged >13 years with advanced HIV disease (CD4 cell count <50 cells/mm^3) initiating first-line ART and no probable or

confirmed TB disease and symptoms. Participants were enrolled from 18 outpatient research clinics in ten countries (Brazil, Haiti, India, Kenya, Malawi, Peru, South Africa, Uganda, Zambia and Zimbabwe) and followed up to week 96. Study sites adhered to local guidelines for ART initiation in each country. All participants with WHO stage 3 or 4 disease for those with CD4 cell counts < 350 cells/mm^3were initiated on ART. Active TB was excluded based on locally available diagnostics (e.g., symptom screen, smear, Xpert MTB/RIF). Anyone screened positive required further workup per local standard of care. The primary trial endpoint was survival at 24 weeks after randomization.

Participants who fulfilled all inclusion criteria were randomized 1:1 to either empirical TB therapy (Arm A) or isoniazid preventive therapy (IPT; Arm B); all participants received efavirenz-based ART. A full eligibility criterion is described in Supplementary Table S1. Participants randomized to Arm A received standard, weight-based, fixed-dose combination (FDC) TB treatment beginning either at the same time as ART initiation or within 7 days following ART initiation, based on the investigator's judgment. Rifampin/isoniazid/pyrazinamide/ethambutol (RHZE) FDC tablets were administered orally once daily for the intensive phase (8 weeks), followed by RH FDC tablets once daily for the continuation phase (16 weeks) as recommended by WHO. Participants in Arm B received 300 mg of isoniazid daily for 24 weeks, beginning within 7 days of ART. Weight-based dose adjustments were adhered to throughout the treatment period. Pyridoxine was provided to all participants throughout the treatment period.

Quality of life measures

A structured HRQoL questionnaire which was translated into local study site language was administered to all participants with HIV, beginning with a baseline assessment (week 0) inquiring about the 30 days prior to study entry. For post-entry visits, we collected HRQoL in each of the study visits. We also assessed HRQoL at the end of intensive phase of TB therapy (week 8), end of continuation phase of TB therapy (week 24), and end of follow-up (week 96).

Participants were queried on the number of 1) days stayed in bed, 2) days cut down on usual activities (such as job, housework, school, etc), 3) nights admitted to a hospital ward, and 4) visits to an emergency room (ER) with response options of: 0, 1–2, 3–5, 6–10, 11–16, or >16 days collected by quality of life questionnaire during study follow-up. We also queried about 5) if employed or not; 6) general health perception status using 5-point Likert scale (excellent, very good, good, fair or poor); and 7) rating of current health status using a visual analog scale (VAS; range: 0–100). For analysis, we created a composite variable that combined responses to days stayed in bed, cut down daily activities, nights stayed in hospital, or visits to Emergency Room into one outcome of whether a participant had at least one of the events for ≥ 1day. After reviewing frequency distributions for responses to individual and composite variables, and based on small cell sizes in responses ≥1 day, these variables were dichotomized as 0 vs. ≥1 day.

Sociodemographic and clinical measures

We collected basic demographic characteristics (sex, age, race, and region), socioeconomic factors (education level and socioeconomic status), HIV history (CD4+ cell count and WHO stage), and clinical history (signs and symptoms severity based on Division of AIDS toxicity table [18]. We categorized countries into three regions based on TB/HIV epidemiologic context: East & Central Africa (Kenya and Uganda), Southern Africa (South Africa, Malawi, Zimbabwe and Zambia), and Other (Haiti, Peru, India and Brazil).

We created a socioeconomic status (SES) index score using seven responses for education, household resources (electricity, drinking water, and cooking fuel), housing type, healthcare, and employment collected by structured sociodemographic questionnaire at study entry. Each measure was equally weighted with a score of 1 for “deprived” and 0 for “not deprived” based on comparable variables used in the United Nations Development Programme (UNDP) Multidimensional Poverty Index (MPI) [19]. The SES index score ranged between 0 and 7 by summing up the individual measures with a score of 0 or 1. A higher SES index score indicated the participant had more deprived standard of living. For education, we considered deprived if education level was equal or below completed primary (score of 1); for household, 3 measures were verified: electricity (No: deprived, score of 1), drinking water (surface water: deprived, score of 1; piped, well water or borehole: not deprived, score of 0) and cooking fuel (wood, coal, cow dung parties: deprived, score of 1; fuel, electricity: not deprived, score of 1). Total multi-dimensional poverty index (MPI) was based on education and household indicator with a score range of 0–4 (low to high deprivation).

We also calculated Socioeconomic status (SES) index using the MPI index, housing (home=not deprived; no permanent, correctional=deprived) + healthcare (government funding or private insurance=not deprived; self-pay=deprived) + work for pay (yes=not deprived; no=deprived). The SES index score ranged between 0 and 7. Higher SES index score indicates the participant had more deprived living.

Statistical Analysis

Complete case analysis was conducted. Categorical HRQoL outcome measures and explanatory variables were compared between the arms at weeks 0, 8, 24 and 96 using Chi square test (or Fisher’s exact test, where appropriate). For the continuous HRQoL outcome, the rating of current health status (VAS scale 0–100), we used Wilcoxon rank sum test to compare between arms. We used generalized estimating equation (GEE) models to examine change in HRQoL measures over time and differences by study arm. We have included the interaction between study arm and week in each GEE model. Bar charts and box plot were created to visually display the changes in HRQoL over time.

Additionally, logistic regression models were used to examine the associations of HRQoL measures dichotomized as 0 vs ≥1 day and baseline characteristics, sociodemographic or clinical factors (i.e., age, sex, race, education, SES index, WHO stage 3 or 4 event, grade 3 or 4 signs/symptoms) adjusted for study arm at weeks 0 and 24, cross-sectionally. In each individual logistic regression model, the HRQoL outcome was the dependent variable and

baseline characteristics, sociodemographic or clinical factors, and study arm were included as independent variables at each time point.

Differences in HRQoL measures between participants who prematurely discontinued the study and those who completed 96 weeks of study follow-up was assessed using Chi-square test.

Ethical Considerations

Ethical approval was obtained from each research site's local institutional review board. Written informed consent and assent was obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent).

Results

Baseline characteristics

There were 850 participants randomized: 424 in the empiric arm and 426 in the IPT arm. Four hundred fifty (53%) participants were male, 768 (90%) were black, and the median age was 36 (IQR: 30, 42) years (Supplementary Table S2). Majority of participants (78%) were from African countries. There were 253 (30%) participants who completed secondary school or higher and; 413 (50%) participants were unemployed. Median CD4 count was 18 cells/mm^3 (IQR: 9–32). Only 65 (8%) had a grade 3 or 4 sign/ symptom at baseline and 236 (28%) had a WHO stage 3 or 4 event. Overall, baseline characteristics of 850 enrolled participants were similar between arms.

Quality of life outcomes

There were 849 (99%), 845 (99%), 793 (93%) and 707 (83%) participants with HRQoL measures collected at weeks 0, 8, 24 and 96 visits, respectively. Overall, all HRQoL measures by treatment strategy improved over time in all domains with no difference between arms at each study visit (Figure 1). At baseline, 281 (33%) participants in the IPT arm reported staying in bed for ≥1 day because they did not feel well; this improved to 57 (7%) and 18 (3%) participants at weeks 24 and 96, respectively (**Panel 1a**). There were 340 (40%) participants on the IPT arm who reported cutting down on their usual activities (e.g., job, housework, school) at baseline, improving to 66 (8%) and 25 (4%) at weeks 24 and 96 (**Panel 1b**). Majority of participants in the IPT arm had not been admitted to a hospital ward (n=789, 93%) at baseline (**Panel 1c**) nor had an emergency room visit (n=750, 88%) at baseline (**Panel 1d**); this proportion decreased throughout the study. For the composite of four HRQoL measures (Days stayed in bed + Days cut down daily activities + Nights stayed in hospital ward + Visits to ER) the proportion of individuals scoring >=1 day/night/visit of each composite measure decreased by treatment strategy from 384 (45%) at baseline to 69 (9%) at week 24 and 28 (4%) at week 96 respectively (**Panel 1e**).

When asked to rate general health perception status, 470 (55%) participants in both IPT and empiric arms rated it as fair or poor at baseline; 65 (8%) and 19 (3%) reported their general health as fair or poor at weeks 24 and 96, respectively (**Pane 1f**). Using a visual analog

scale to rate current general health status from 0 (worst) to 100 (best), the median improved from 60 (IQR 50–70) for participants in IPT arm at baseline to 85 (IQR 70–90) and 90 (IQR 80–95) at weeks 24 and 96 **(Panel 1g)**.

At study entry, better HRQoL measures were reported among participants who prematurely discontinued the study compared to those who completed study follow-up. However, there was no significant difference in HRQoL reported at weeks 8, 24, and 96 between the two groups (data not presented, but available upon request).

Association between HRQoL measurements and treatment arms with sociodemographic and clinical characteristics

Supplementary Table S3 summarizes the odds ratio and 95% CI for the associations of HRQoL outcomes with study arm, and sociodemographic and clinical variables at weeks 0 and 24. At baseline, participants with WHO stage 3 or 4 event, or who had grade 3 or 4 signs/ symptoms, were significantly more likely to report poor HRQoL using the composite of four HRQoL measures. Participants with WHO stage 3 or 4 events and grade 3 or 4 signs/symptoms had a higher chance of ≥1 day in bed, decrease in activities, ≥1 night in hospital or ≥1 visit to ER [OR (95% CI): 2.31 (1.70, 3.14), p< 0.01 and 1.77 (1.07, 2.97), p=0.03]. At week 24, participants with WHO stage 3 or 4 event, or who had grade 3 or 4 signs/ symptoms at baseline, remained significantly more likely to report poor HRQoL using the composite measure. Participants with WHO stage 3 or 4 events and grade 3 or 4 signs/symptoms had a higher chance of ≥1 day in bed, decrease in activities, ≥1 night in hospital or ≥1 visit to ER [OR (95% CI): 6.59 (3.88, 11.14), p< 0.01 and 4.28 (2.28, 7.77), p< 0.01]. Additionally, at week 24, participants who reported <100% adherence to TB treatment had a higher chance of ≥1 day in bed, decrease in activities, ≥1 night in hospital or ≥1 visit to ER [OR (95% CI): 3.15 (1.18, 7.35), p= 0.01].

When asked to rate their general health perception, persons from “Other” regions (compared to Southern Africa), those who were unemployed, with no schooling (compared to completed secondary schooling or higher), had higher deprivation (SES index), or WHO stage 3 or 4 event were significantly more likely to rate their health as fair or poor at baseline. We observed the same HRQoL pattern at week 24, except for no schooling (no statistical significance) and grade 3 or 4 sign/ symptoms (significantly poorer HRQoL). Participants who reported <100% adherence to TB treatment were significantly more likely to rate their health as fair or poor [OR (95% CI): 3.34 (1.25, 7.82), p= 0.01] at week 24.There were no differences by treatment arm on any HRQoL measures cross-sectionally at any time point (Supplementary Table S3.1).

Discussion

The A5274 trial compared empiric TB treatment to isoniazid preventive therapy for reducing early mortality but found equal and low mortality (5%) in both groups [17]. In this study, we assessed the effect of these treatments on HRQoL. HRQoL was low at baseline in both groups, with nearly half reporting poor HRQoL by one or more measures; however, it became better over time. Despite differences in the TB treatment regimens assigned in this trial, HRQoL did not differ between study arms at any time points cross-sectionally. Factors

associated with poor HRQoL at baseline and at the end of treatment included lower SES, WHO stage 3 or 4 event, and grade 3 or 4 signs/symptoms.

Despite the evidence and policy guidance to start ART at any CD4 count, HIV programs globally continue to come across our study population of adults with advanced HIV disease. The median CD4 count in ART programs in low- and middle-income settings remains below 200 cells/mm^3 in approximately 40% of newly diagnosed PLHIV [20–24]. This group is at highest risk of developing and dying from TB. By focusing on individuals with advanced HIV disease, our study provides valuable evidence that ART, combined with TB screening and initiation of IPT or TB treatment results in markedly improved HRQoL in this group.

Several studies have demonstrated that the combination of IPT and ART at any CD4 count results in significant reductions in TB incidence and mortality [25–29]. Our study adds to this by showing that both empiric TB treatment and addition of IPT to ART resulted in improved HRQoL among individuals with highly advanced HIV disease (median CD4 count of 18 cells/mm^3). In addition, HRQoL was shown to improve after 1st line ART initiation in studies conducted in Africa [30–32].

Participants with poor sociodemographic or clinical status had lower HRQoL at baseline and after 6 months of treatment (week 24). This is consistent with other studies from diverse geographic settings that have shown employment and education was associated with better overall HRQoL among PLHIV [25, 33, 34]. Generally, education plays a critical role in understanding and communicating health-related information, eventually leading to a better perception of health that contributes to improved quality of life. Similarly, persons who are not employed may lack sufficient income, which can contribute to food insecurity and poor nutritional status, both of which can impact on HRQoL. A major strength is the multi-country nature of the trial which results in broader generalizability to other high TB and HIV settings that are scaling-up IPT and ART among PLHIV. These data are timely given multiple, large global initiatives underway to ensure all PLHIV receive life-saving treatment with IPT. Our study was limited by lack of data on factors such as depression or mental health disorders, pre-existing conditions other than TB, sexual behavior, recall bias and stigma that might be associated with HRQoL. The study conducted systematic TB screening prior to enrollment, therefore these results may differ in PLHIV who have TB symptoms or TB disease. The improvements in HRQoL could reflect factors other than the initiation of ART and TB treatment / prevention, such as changes in clinical care provided by participation in a clinical trial. We focused this analysis on 6-month outcomes as a large portion of participants were not able to be followed-up for the full study period due to funding constraints and sites closing (67% of 88 premature study discontinuations). An additional limitation is that questionnaire validity was not performed in this study. Lastly, the associations were adjusted only by study arm and the analysis was performed cross-sectionally.

Advanced HIV disease has a negative impact on the physical and general well-being of a person, significantly impacting their HRQoL. WHO recently introduced a package of care for persons with advanced HIV disease, which includes guidance for TB screening and provision of IPT [35]. Together with the primary trial results, these findings show that ART,

TB screening, and IPT can not only reduce mortality, but also can improve HRQoL in PLHIV with advanced disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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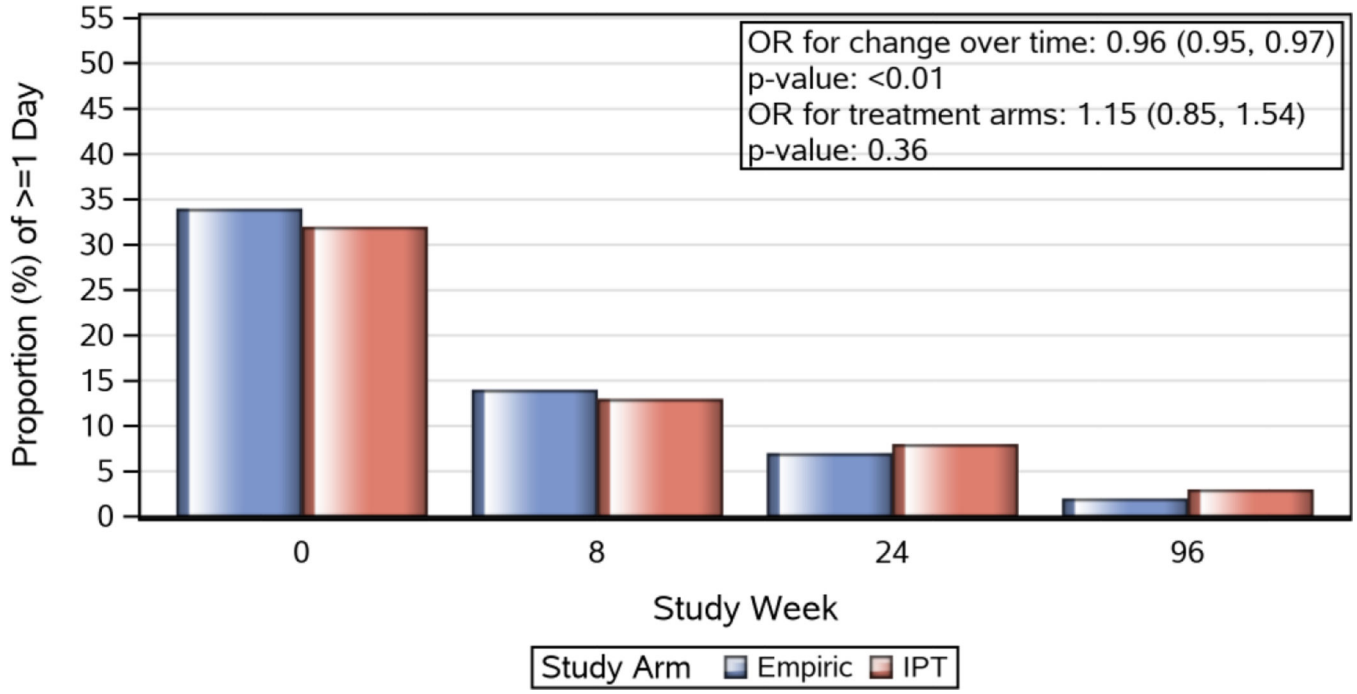

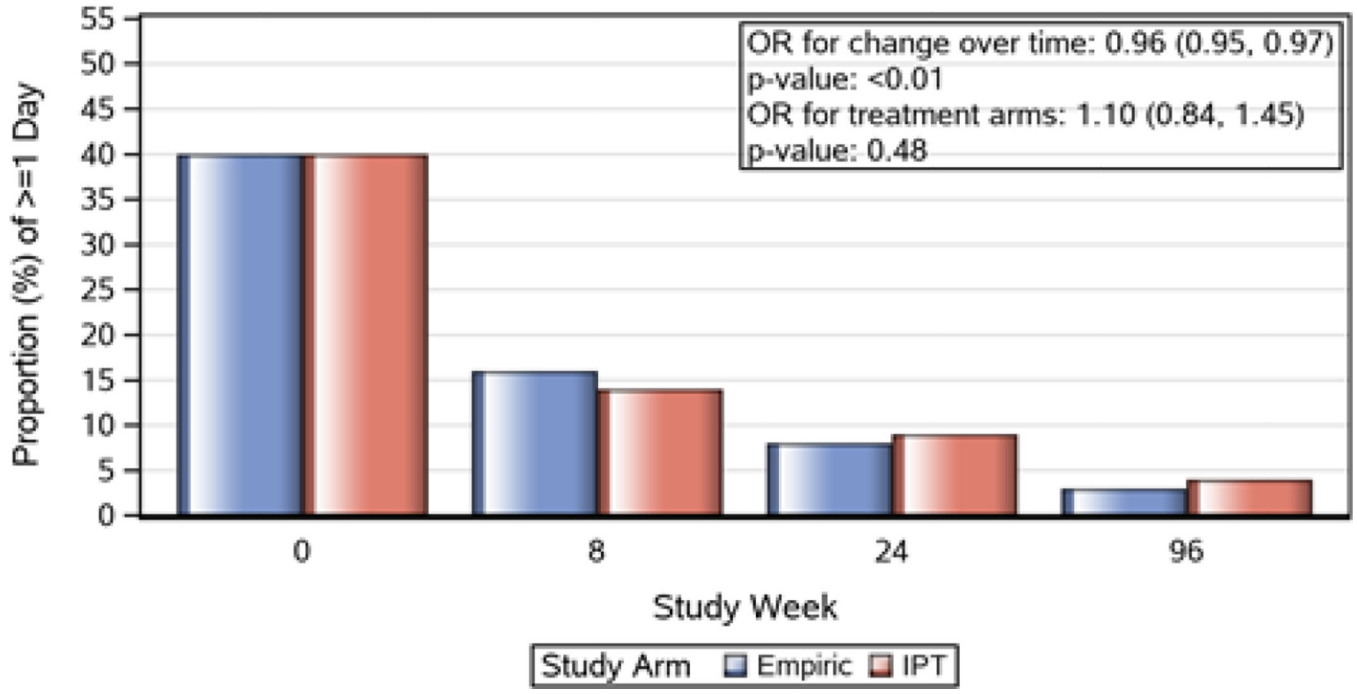

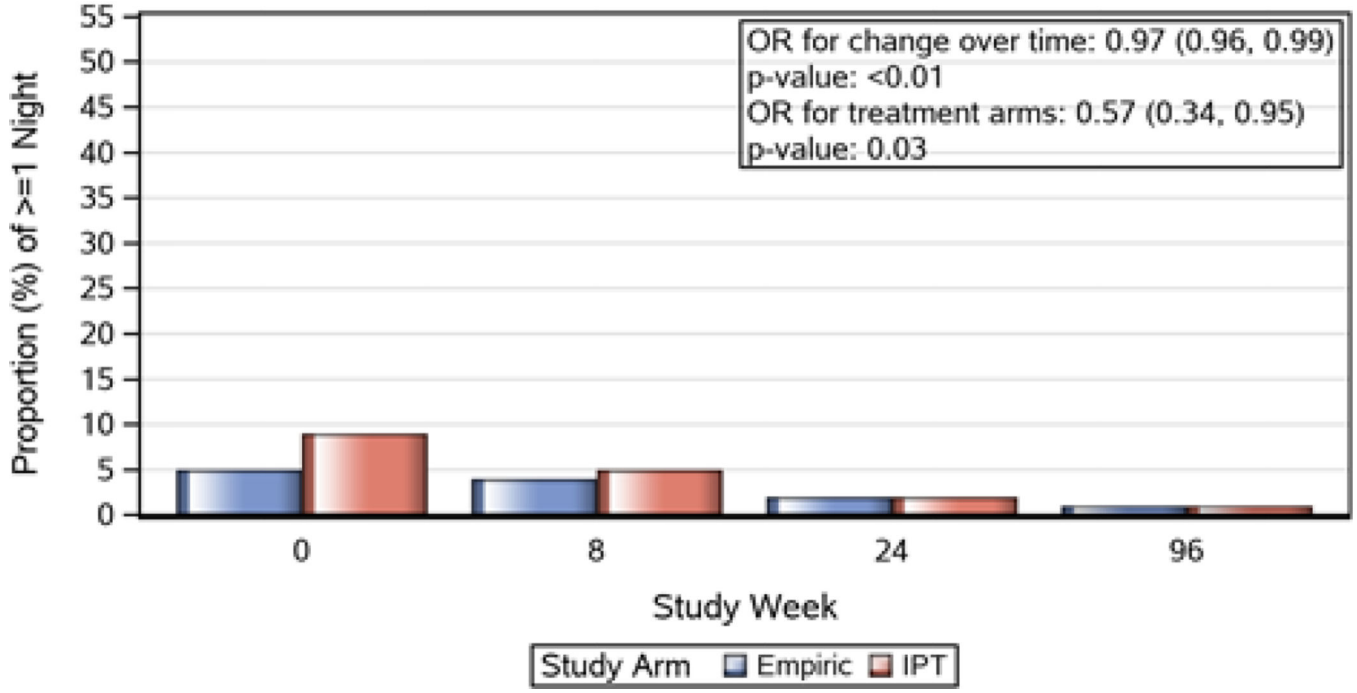

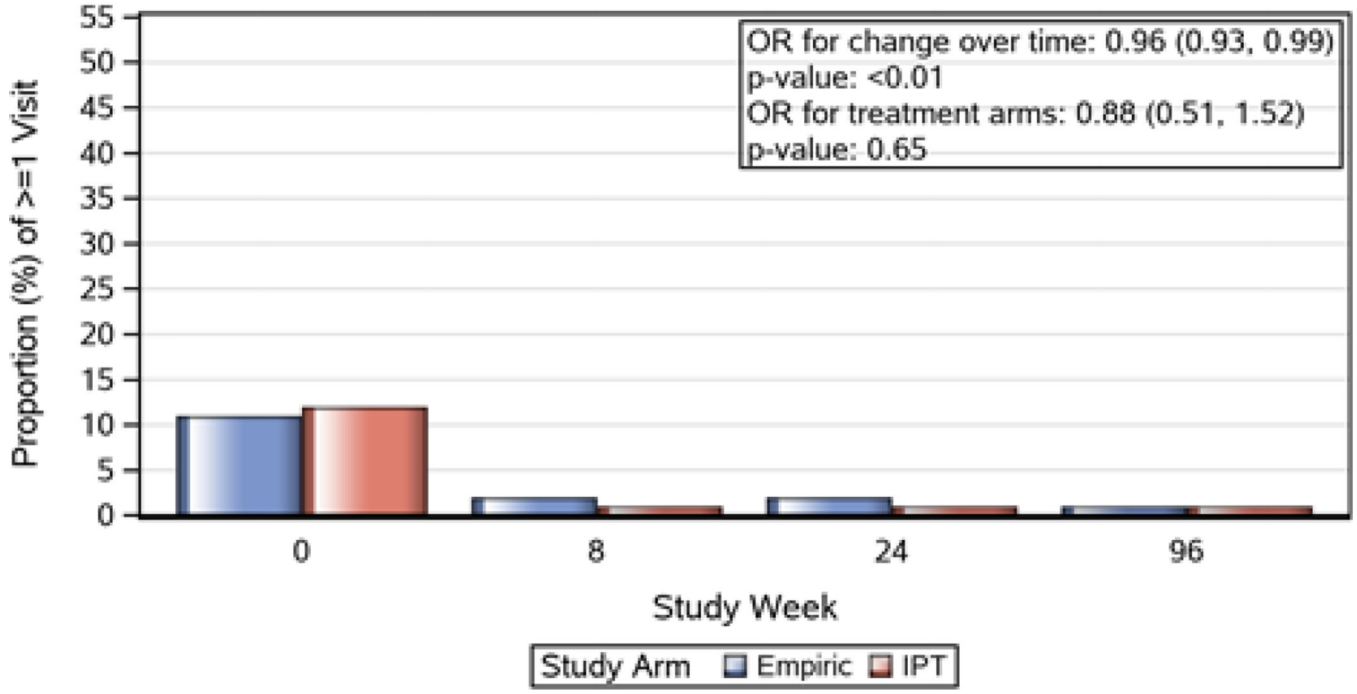

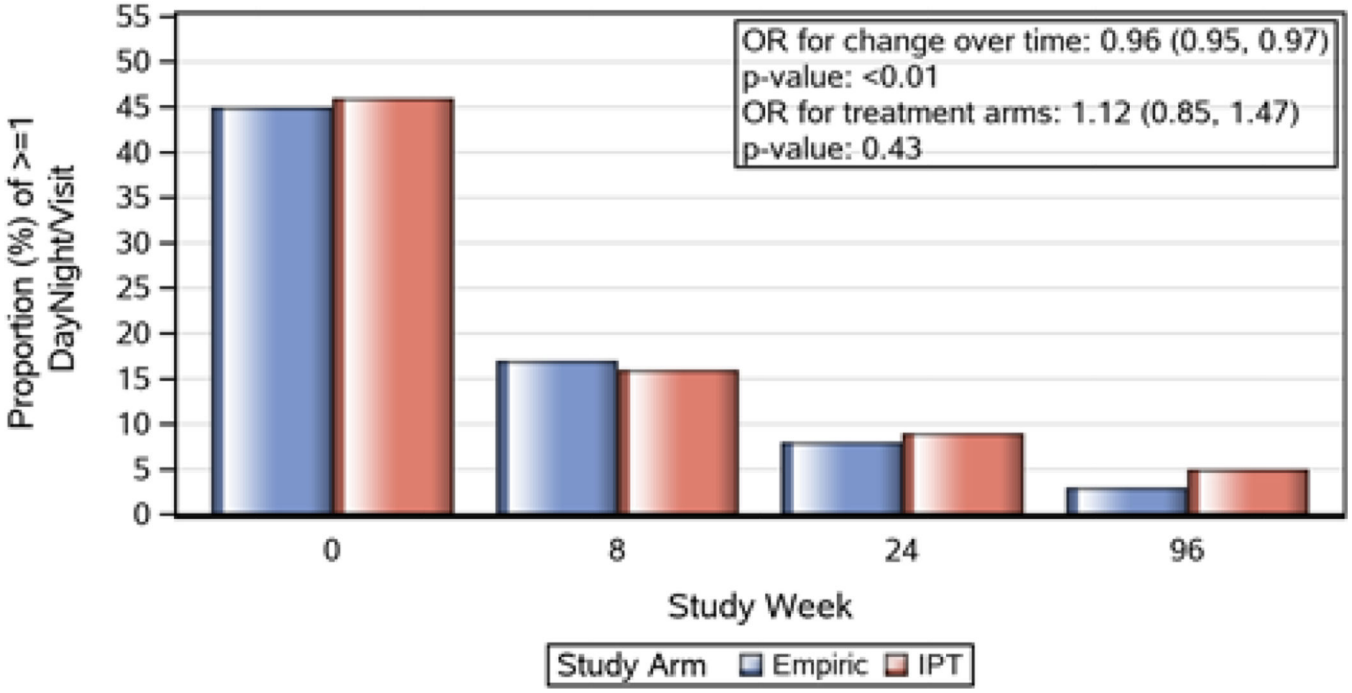

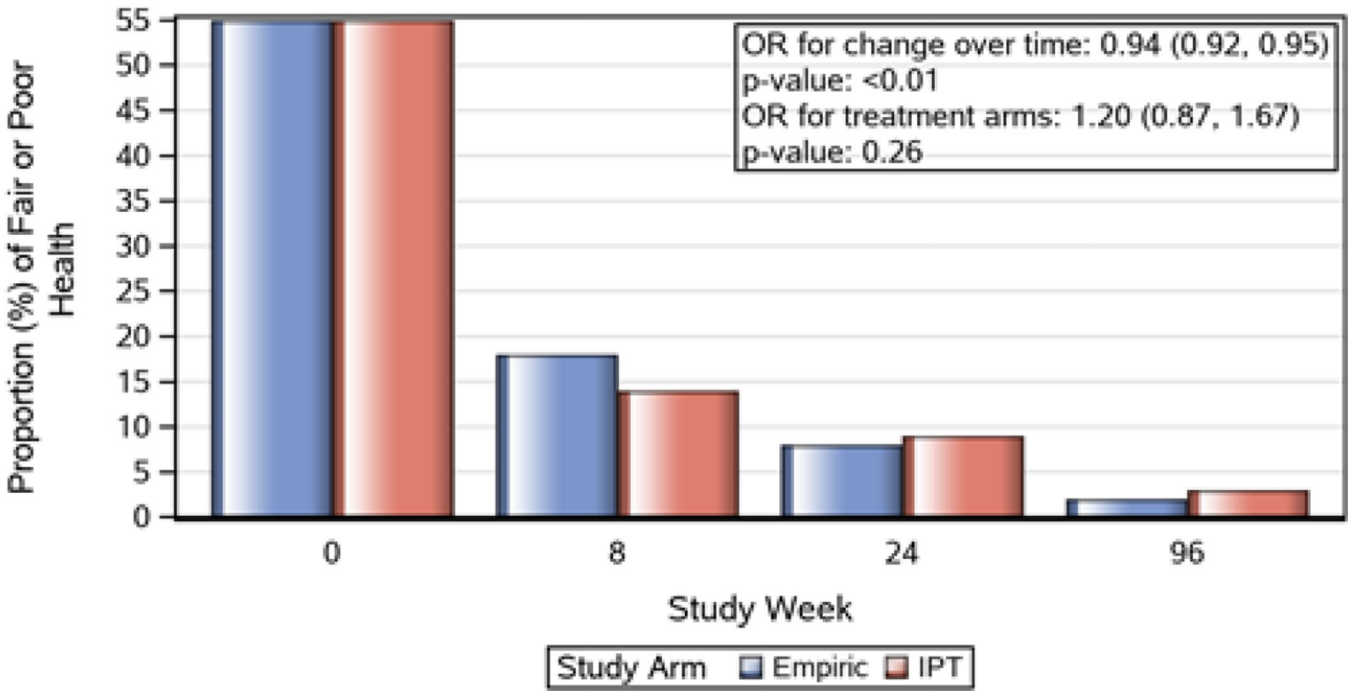

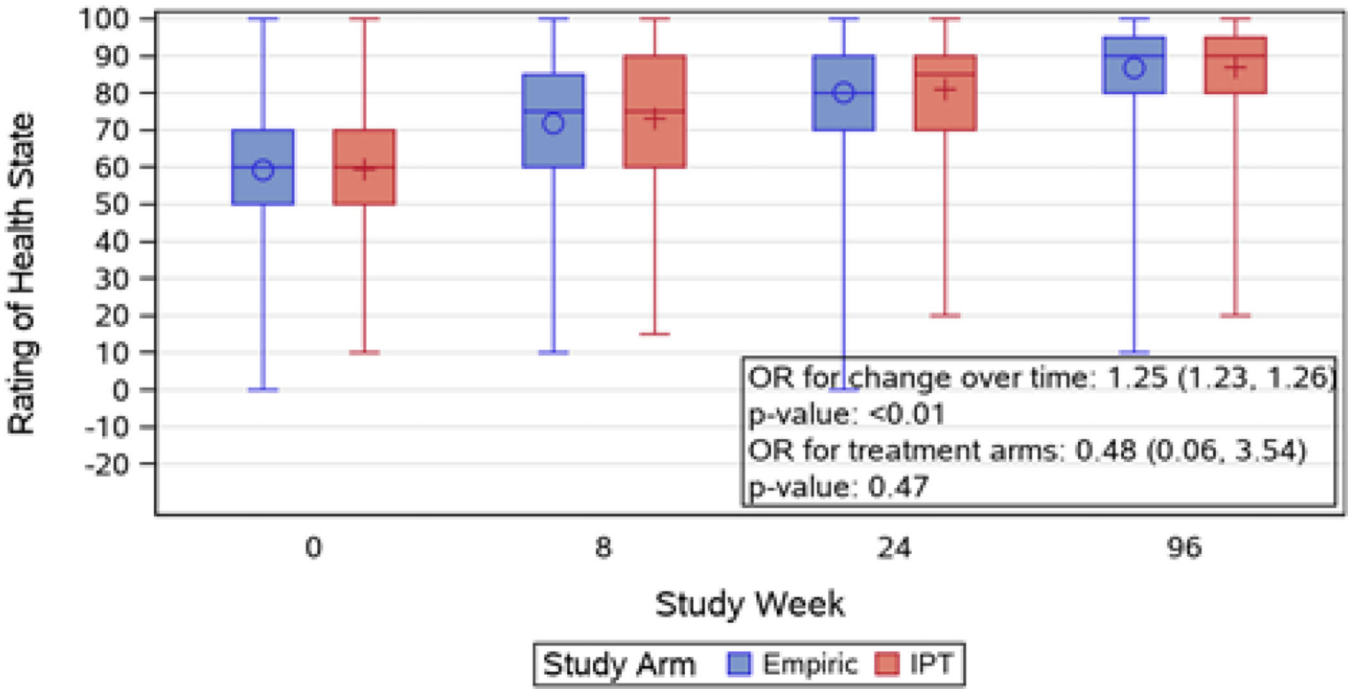

Figure 1. Health related quality of life measures by treatment strategy at weeks 0, 8, 24 and 96 (odds ratio and 95% confidence interval, based on generalized estimating equation [GEE] model)

Panel 1a. Proportion of participants reporting ≥1 day stayed in bed

Panel 1b. Proportion of participants reporting ≥1 day cut down on usual activities

Panel 1c. Proportion of participants reporting ≥1 night admitted in hospital ward

Panel 1d. Proportion of participants reporting ≥1 visit to an emergency room

Panel 1e. Proportion of participants reporting ≥1 day stayed in bed or cut down on daily activities or stayed in hospital or visit to an emergency room (Composite measure)

Panel 1f. Proportion of participants who described their health as fair or poor

Panel 1g. Participants' rating of current state of health, using visual analog scale (higher rate represents better health)The whiskers in the box plot represent the minimum and maximum values of the HRQoL outcome based on rating of current health status (scale 0–100).