Implementing Isoniazid Preventive Therapy in a TB-treatment experienced cohort on ART

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Abstract

SETTING—Urban clinical research site in Durban, South Africa

OBJECTIVE—To describe the outcomes associated with implementation of isoniazid preventive therapy (IPT) in a cohort of TB treatment experienced HIV infected patients on antiretroviral therapy (ART).

DESIGN—We conducted a secondary analysis of data collected between October 2009 and October 2013 from patients enrolled in a prospective cohort study conducted in Durban, South Africa.

RESULTS—There were 402 patients enrolled in the parent study. Of these 344 (85.6%) were eligible to receive IPT and of whom 212 (61.6%) initiated IPT. Among those that initiated IPT, 184 (86.8%) completed the six month course, 24 (11.3%) permanently discontinued IPT and of these, 3.8% discontinued due to side effects. More women (n=130; 61.3%) initiated IPT (p=0.001) than men. Overall median adherence to IPT was 97.6% (IQR: 94.2 – 99.4). There were 22 cases of incident TB in this cohort: 13 occurred prior to IPT and nine after IPT (incidence rate ratio 0.67; 95% CI 0.29–1.58; p=0.362).

CONCLUSIONS—IPT implementation amongst ART and TB treatment experienced patients was well tolerated with good completion rates and fewer TB cases diagnosed after IPT exposure.

Keywords

HIV; IPT; prophylaxis; latent tuberculosis

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Conflict of Interest

All authors report no conflict of interests.
INTRODUCTION

Tuberculosis (TB) has been the cause of 1.8 million deaths globally in 2015, of which 0.4 million were among HIV co-infected individuals.\(^1\) Over 35% of HIV related deaths are attributed to TB co-infection making TB the leading killer amongst HIV infected people.\(^2\) Isoniazid preventive therapy (IPT), a public health intervention for the prevention of TB, was recommended by the World Health Organisation (WHO)\(^3\) and adopted by the South African National Department of Health for use in Health Care Workers and people living with HIV.\(^4\) Despite the need, global uptake of IPT remains low\(^5\)–\(^9\). In 2015, only 9 out of the 30 high burden TB/HIV countries reported TB preventive therapy provision.\(^1\) Currently, IPT coverage is reported to be 38% in South Africa, similar to global trends.\(^1\)

The impact of IPT on mortality and morbidity in HIV infected patients has been investigated.\(^10\)–\(^12\) The TEMPRANO study demonstrated six months of IPT combined with early ART resulted in a 44% reduction in risk of severe HIV related illness and reduced all-cause mortality by 35%.\(^12\) IPT was shown to decrease mortality amongst tuberculin skin test (TST) positive individuals with CD4+ T-cell counts >200 cell/mm\(^3\) in Tanzania\(^11\) whilst in a study amongst South Africans on ART initiating IPT reported 49% reduction in mortality that remained significant even for those who had a past history of TB\(^10\). However, TST positive patients were shown to benefit the most by completing a 36 month IPT course, resulting in a 74% decreased active TB risk and 68% decrease in mortality when compared to 6 months of IPT.\(^13\)

There is limited data on IPT outcomes in ART experienced patients who were previously exposed to TB treatment. The purpose of our study was to report on clinical, programme related outcomes and challenges experienced with IPT implementation in a high TB/HIV burden amongst an ART and TB treatment experienced population and its effect on TB incidence.

METHODS

Study setting and design

The study was based in Durban, KwaZulu-Natal, SA, an area where it is estimated that 70% of TB patients are HIV co-infected.\(^14\)

Conducted between 2009 and 2013, the CAPRISA 005 TB Recurrence upon Treatment with HAART (TRuTH) study was a prospective cohort study assessing TB recurrence among patients initiated on ART. From 2011 onwards, IPT was offered to adult patients ≥18 years accessing HIV care in an urban clinical research clinic in accordance with national treatment guidelines.\(^15\) We present a secondary analysis of prospectively collected clinical and demographic data extracted from patient files and computerized pharmacy dispensing records for the period October 2009 to October 2013.

ART and Tuberculosis treatment procedures

At IPT initiation all patients were receiving ART according to current national treatment guidelines\(^16\). Adherence to ART was assessed using pill count data from returned unused
medication. Patients diagnosed with active TB received a TB re-treatment regimen aligned with the local standard of care. Patients agreeable to monthly IPT collection, with no signs and symptoms of active TB, and no clinical contraindications to isoniazid (INH) were deemed eligible and offered a six month IPT course. Patients were ineligible for IPT if they had a previous history of alcohol abuse, viremia, renal and/or hepatobiliary abnormalities. Routine TST was not required to screen for IPT eligibility.

IPT procedures and patient management

INH was prescribed as 300mg for those ≥60 kg, 250mg for 50–59.9 kg, and 200mg for those weighing 40–49.9 kg. A research nurse managed the patient monthly while on IPT, screened for TB symptoms and referred complicated cases and patients with presumptive TB to a clinician for assessment. If active TB was suspected, INH was stopped and the patient was referred immediately for investigation. Incident TB was diagnosed microbiologically through induced sputum smear microscopy and culture. Patients were screened for INH related side effects and those who showed symptoms of liver toxicity or where the clinician suspected liver toxicity, underwent liver function monitoring. INH related toxicity was graded using the Division of AIDS toxicity table for grading the severity of adverse events (Version 1.0 December 2004). Pyridoxine was co-administered for peripheral neuropathy prophylaxis.

The IPT adherence support programme (ASP) was counselor driven and aided by a multi-disciplinary inter-referral system between nurse, clinician and pharmacist to improve IPT course completion rates. The pharmacist confirmed eligibility for IPT monthly prior to dispensing INH, conducted pill counts, dispensed and counseled on appropriate INH use and storage. Data generated from the computerised dispensing system was used to provide feedback to the clinical team on duration of INH treatment, missed visits, course completion and interruptions.

Statistical analyses

Continuous data were summarised using means with standard deviation or medians with interquartile range. Categorical data were summarised using percentages. Wilcoxon signed rank sum test was used to compare selected laboratory measurements before and after IPT initiation.

TB incidence rates and follow-up duration before and after IPT initiation was calculated from TRuTH study enrolment to either date of TB diagnosis or one day before date of IPT initiation and from IPT initiation to either date of TB diagnosis or study termination date respectively. The mean monthly adherence to IPT was assessed across all visits by comparing the number of tablets returned at the current visit with the number of tablets dispensed at the last clinic visit compared to the number of tablets that should have been ingested between visits. The overall median adherence was then calculated using the monthly mean adherence at each visit.

Univariate and multivariate log-binomial regression models were used to identify predictors of IPT completion. To account for multiple measurements for each participant, generalised estimating equations (GEE) for a multivariate repeated measure logistic regression model
was used to identify predictors associated with high IPT adherence (≥80%) over time. Previous studies have used 80–90% adherence threshold to describe optimal adherence to IPT.\textsuperscript{17–19} Statistical analysis was performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina). All statistical tests were conducted at a 5% level of significance.

**Ethics**

Ethics approval was obtained for this analysis from the University of KwaZulu-Natal (UKZN) Biomedical Research and Ethics Committee [Reference numbers: BE373/14 (secondary analysis), BF051/09 (TRuTH Study)].

**RESULTS**

**Demographic and clinical data**

Among the 212 patients initiating IPT, 38.7% were male, had a median BMI of 26.5 (23.3 – 30.3), and 26.3% had more than one previous TB episode. Apart from significantly more females (n=130; 61.3%) than males initiating IPT (p=0.001) (Table 1), baseline characteristics were not statistically significantly different among IPT initiates and non-initiates. Approximately 77.4% of patients initiating IPT were on a tenofovir-containing first line ART regimen, had received a median of 4.1 years of ART, among whom 91% were virologically suppressed with a median CD4+ T-cell count of 571 (421 – 737) cells/mm\textsuperscript{3}.

**IPT uptake**

Overall, among 402 patients assessed for IPT initiation (Figure 1), 344 (85.6 %) were deemed eligible and 58 (14.4%) were not considered for IPT among whom 34 (8.4%) were ineligible and 24 (6%) were exited from the study prior to being offered IPT (lost-to-follow up, deceased, withdrew study participation, relocated). Reasons for IPT ineligibility were: previous or current drug resistant (DR) TB (n=7; 1.7%), current active or presumptive drug susceptible TB (n=9; 2.2%), other clinical contra-indications (n=10; 2.5%), and a combination of reasons mentioned above (n= 8; 2%). Among eligible patients, 212 (61.6 %) initiated IPT while 132 (38.4 %) refused IPT: 119/344 (34.6%) due to inability to adhere to monthly visits, 9 (2.6%) did not provide any specific reasons, 2 (0.6%) refused due to added pill burden, and 2 (0.6%) for fear of additive toxicity. IPT completion rates were 86.8% and median adherence to IPT assessed by pill count was 97.6% (95% CI: 94.2 – 99.4) (Figure 2). There were no statistically significant predictors of IPT course completion (Table 2).

**IPT outcomes**

Among IPT initiates, 167 (78.8%) completed the IPT course (Figure 1) with no interruption. Overall median duration of treatment was 174 days (IQR: 167.0 – 180.3). IPT interruption occurred in 45 patients: 24 (11.3%) were permanent IPT discontinuations, 17 (8%) were temporary interruptions (16 for suspected TB and one for an inter-current illness) for a median duration of 64 (52; 92) days, and four (1.9%) patients that transferred out prior to IPT completion. Reasons for permanent discontinuation included: INH toxicity (six grade two/three skin rash and two deranged liver function tests) n=8; suspected TB, n=7; patient requested withdrawal, n=3; confirmed TB, n=2, defaulted visits, n=2, alcohol abuse, n=1 and DR TB history that was previously missed, n=1.
Approximately 2.8% (6/212) of our participants experienced moderate to severe liver function test derangement, however only two needed IPT discontinuation. Participants’ median AST and ALT levels measured during IPT use were significantly higher (27 IU/L ALT; 32 IU/L AST) than levels measured before IPT (23 IU/L ALT; 29 IU/L AST) (p<0.001) (Figure 3). Additionally, the median AST and ALT levels dropped after IPT (23 IU/L; 29 IU/L) compared to during IPT (p<0.001) (Figure 3). There was no statistically significant difference of IPT effect on median AST (p=0.081) and ALT (p=0.51) levels before IPT and after IPT exposure.

**Impact of IPT on TB Incidence**

There were 22 cases of incident TB in this cohort: 13 occurred prior to IPT, nine after IPT (incidence rate ratio 0.67; 95% CI 0.29–1.58; p=0.362) (Table 3). Of the nine TB cases occurring in those exposed to IPT, two cases of drug susceptible TB were diagnosed five months into IPT, while six patients developed TB after completing the IPT course and one patient who had not completed IPT later developed TB. Incident TB was diagnosed a median of 279 (IQR: 141–336) days from 6 month IPT course completion.

**DISCUSSION AND CONCLUSION**

Our study showed high IPT uptake, adherence and completion rates with minimal interruption for IPT related adverse events among chronic stable HIV infected patients on ART who had all been treated for TB previously. Presumptive TB impacted IPT initiation and interruption rates. Among ineligible patients, suspected TB, confirmed TB and/or DR TB accounted for 27.6% of patients not being considered for IPT, while the majority of IPT interruptions (57.8%) were due to suspected TB. However, only two of the 26 interruptions were diagnosed with TB. Given the high TB burden in the study setting, the index of suspicion for incident TB by healthcare workers was understandably raised, resulting in frequent IPT treatment interruptions for TB investigation.

Prior to 2010, patients previously exposed to TB treatment were considered ineligible for IPT. Because of the small numbers and reduced follow-up, we found a non-significant decrease in TB incidence of 33% after 6-months of IPT among patients with previous TB on ART. We demonstrated that IPT works in this important group of individuals at high risk of both recurrent and drug resistant TB; however a one third reduction in incidence is not acceptable considering the high background TB transmission rates and the synergistic effect of ART in this population. Studies involving South African gold miners demonstrated that 6 months of IPT significantly reduced TB incidence by 55% in one study and 38% in the other,20,21 albeit in the absence of ART. Concomitantly administered IPT and ART in the THRio study demonstrated a 76% reduction in TB incidence after adjusting for age, past TB and immune status.22 Patients in our study had moderate immune dysfunction as IPT was started at a median CD4+ T-cell count of 571 cells/mm$^3$. Data from SSA has demonstrated that concurrent ART and IPT22,23,24 or initiating ART soon after completing IPT25 results in higher reductions in TB incidence compared to treating with either IPT or ART alone. The TEMPRANO study, conducted in patients with a CD4+ T-cell count > 500 cell/mm$^3$ also demonstrated 57% decrease in TB incidence among early ART and IPT initiators.
compared to those who didn’t use IPT. The gender disparity we found in this study where more females initiated IPT than men is congruent with previous reports.

Our findings suggest that six months of IPT is safe and well tolerated in patients with prior TB disease, while a statistically significant protective effect was not shown in this cohort. Current WHO guidance, supported by other research, recommends that IPT be provided for up to 36 months in a high TB burden setting. Interestingly, the TEMPRANO trial demonstrated that 6 months of IPT initiated with immediate ART significantly reduced the risk of severe HIV-related disease (44%) and all-cause mortality (35%). Overall, we were able to successfully integrate IPT visits with existing clinic ART visits resulting in a high IPT completion rates, further underscoring the efficiencies of IPT/ART programme integration, and reported benefit beyond reduction in TB incidence.

A meta-analyses shows highly variable IPT uptake in SSA ranging from 13–95%. In our study the requirements for monthly IPT follow up visits was the commonest reason for IPT refusal (34.6%), likely due to high unemployment and the associated costs with frequent clinic attendance. Strategies aimed at improving IPT uptake need to optimise IPT access, reduce clinic attendance, find innovative and convenient ways to enhance adherence to IPT and ART and monitor for TB infection.

The effect of IPT on liver toxicity and the return to normal liver function post IPT cessation was similar to findings amongst patients taking nine months of INH. There was also a similar prevalence of grade 2 and 3 liver toxicity events compared to the 6 month open label phase of the BOTUSA study.

Adherence to IPT has been described previously using IPT completion rates, medication adherence (pill count) or prescription refills. Our IPT completion and adherence rates were similar to reports from other African studies with findings ranging from of 78–98.9%. We attributed high IPT adherence to the well-resourced clinical research setting, structured adherence support programme and needing to come in for ART. There is strong evidence supporting combining ART use with IPT to significantly improve IPT adherence. While some studies reported predictors of IPT completion and adherence such as ART use and/or knowledge on IPT we did not measure all these variables in our study. However, although not statistically significant, women tended to have higher adherence. Others have reported that men demonstrate increased odds for loss-to-follow up and non-adherence to IPT than women.

There were several study limitations. The small sample size undermined our ability to show a statistically significant impact of IPT in patients with previous TB. Additionally, our model of IPT implementation may not be generalizable to the public sector healthcare setting given the resources directed to regularly timed TB symptom screening and laboratory and radiologic investigations aimed at evaluating incident TB in the parent study. This may have led to overly high rates of suspected TB and subsequent non-eligibility for IPT or IPT interruption.

IPT is an effective TB prevention intervention within ART programmes. We demonstrated a successful six month IPT roll-out in a TB endemic setting with good uptake of IPT, minimal
course interruptions or side effects reported and majority of the cohort having completed the IPT course amongst patients on ART with a past history of TB treatment exposure. More efficient point of care diagnostics for TB may play a role in reducing IPT course interruptions, and re-entry into the IPT programme. TB continues to undermine the success of ART programmes in sub-Saharan Africa, and our findings add to the body of evidence guiding operational IPT implementation.

Acknowledgments

BM and TG conceived the secondary analysis design and TG supervised the work. BM performed IPT data extraction and contributed substantially to final analysis. NYZ performed all TRuTH data analysis, conducted all tests and confirmed all final analyses. BM prepared the manuscript. TG, NYZ, SG, AN and KN edited the manuscript. We acknowledge the contribution of the TRuTH Study participants and the effort of the entire treatment team at CAPRISA eThekwini clinical site who worked on the parent study. We are grateful to Magashree Govender for extracting data from the computerised pharmacy dispensing records for the secondary analysis. CAPRISA is supported by the National Institute of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH) (grant no. AI51794). The TRUTH study was supported by the Howard Hughes Medical Institute, Grant Number 55007065, as well as the Centers for Disease Control and Prevention (CDC) Cooperative Agreement Number UY2G/PS001350-02. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of either the Howard Hughes Medical Institute or the Centers for Disease Control and Prevention (CDC). The research infrastructure to conduct this trial, including the data management, laboratory and pharmacy cores were established through the US National Institutes for Health’s Comprehensive International Program of Research on AIDS grant (CIPRA, grant # AI51794). KN and TG were supported by the Columbia University-South Africa Fogarty AIDS International Training and Research Program (AITRP, grant # D43 TW000231). Patient care was supported by the KwaZulu-Natal Department of Health and the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). The funding sources listed here did not have any role in the analysis or preparation of the data in this manuscript, nor was any payment received by these or other funding sources for this manuscript.

References


29. Gray EL, Goldberg HF. Baseline abnormal liver function tests are more important than age in the development of isoniazid-induced hepatotoxicity for patients receiving preventive therapy for latent tuberculosis infection. Internal medicine journal. 2016; 46(3):281–7. [PubMed: 26648478]


Figure 1.
IPT uptake and course outcomes
Figure 2.
Adherence to IPT by monthly pill count
Figure 3.
Liver function indicators in IPT users taken within a window 3 months prior to IPT initiation. Panel (A) is AST and panel (B) is ALT.
Table 1
Characteristics of patients on IPT compared to those not on IPT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initiated on IPT (N=212)</th>
<th>Not initiated on IPT (N=190)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>37 (31.5 – 44)</td>
<td>37 (32 – 42)</td>
<td>0.811</td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed race</td>
<td>1 (0.5)</td>
<td>2 (1.1)</td>
<td>0.605</td>
</tr>
<tr>
<td>Black</td>
<td>211 (99.5)</td>
<td>188 (98.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>82 (38.7)</td>
<td>104 (54.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>130 (61.3)</td>
<td>86 (45.3)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 count (cells/mm(^3)), median (IQR)</strong></td>
<td>470 (343 – 662)</td>
<td>426.5 (309 – 601)</td>
<td>0.069</td>
</tr>
<tr>
<td><strong>Viral load (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable</td>
<td>31 (14.6)</td>
<td>42 (22.1)</td>
<td>0.069</td>
</tr>
<tr>
<td>Undetectable</td>
<td>181 (85.4)</td>
<td>148 (77.9)</td>
<td></td>
</tr>
<tr>
<td><strong>ALT (IU/L), median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>19.5 (15 – 27)</td>
<td>20 (16 – 31)</td>
<td>0.153</td>
</tr>
<tr>
<td><strong>AST (IU/L), median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>27 (23 – 33)</td>
<td>28 (23 – 36)</td>
<td>0.441</td>
</tr>
<tr>
<td><strong>Haemoglobin (g/dL), mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>13.4 (1.6)</td>
<td>13.7 (1.6)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Previous episode of TB (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>139 (65.6)</td>
<td>140 (73.7)</td>
<td>0.084</td>
</tr>
<tr>
<td>&gt;1</td>
<td>73 (34.4)</td>
<td>50 (26.3)</td>
<td></td>
</tr>
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</table>

* 23 has missing data,
† 6 has missing data,
‡ 21 has missing data
Table 2

Predictors of IPT adherence and IPT completion

<table>
<thead>
<tr>
<th>Variable</th>
<th>IPT adherence</th>
<th></th>
<th></th>
<th>IPT completion</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR (95%CI)</td>
<td>p-value</td>
<td>aOR (95%CI)</td>
<td>p-value</td>
<td>aOR (95%CI)</td>
</tr>
<tr>
<td>Age (per 5 year increase)</td>
<td></td>
<td>0.94 (0.81–1.1)</td>
<td>0.441</td>
<td>0.98 (0.83–1.17)</td>
<td>0.843</td>
<td>0.99 (0.97–1.02)</td>
</tr>
<tr>
<td>Gender (ref=male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>1.65 (0.99–2.72)</td>
<td>0.050</td>
<td>1.47 (0.73–2.97)</td>
<td>0.286</td>
<td>1.05 (0.94–1.18)</td>
</tr>
<tr>
<td>CD4+ cell count (per 50 cells/mm$^3$ increase)*</td>
<td>1.06 (1.01–1.12)</td>
<td>0.043</td>
<td>1.03 (0.97–1.1)</td>
<td>0.273</td>
<td>0.99 (0.98–1.01)</td>
<td>0.411</td>
</tr>
<tr>
<td>Years on ART*</td>
<td>1.09 (0.83–1.44)</td>
<td>0.536</td>
<td>1.01 (0.75–1.36)</td>
<td>0.952</td>
<td>0.97 (0.91–1.02)</td>
<td>0.256</td>
</tr>
<tr>
<td>Haemoglobin (per g/dl increase)*</td>
<td>0.92 (0.79–1.07)</td>
<td>0.286</td>
<td>0.99 (0.84–1.17)</td>
<td>0.956</td>
<td>0.79 (0.59–1.05)</td>
<td>0.104</td>
</tr>
<tr>
<td>Previous episodes of TB (ref &gt;1)</td>
<td>1.09 (0.65–1.83)</td>
<td>0.744</td>
<td>1.03 (0.60–1.76)</td>
<td>0.912</td>
<td>0.89 (0.38–2.08)</td>
<td>0.784</td>
</tr>
</tbody>
</table>

* prior to IPT initiation

OR: odds ratio
RR: risk ratio
NE: no estimate
Table 3

TB incidence prior to and post IPT

<table>
<thead>
<tr>
<th></th>
<th>Before IPT initiation N = 212</th>
<th>After IPT initiation N = 212</th>
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</thead>
<tbody>
<tr>
<td>No. of TB cases</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Person-years</td>
<td>328.1</td>
<td>337.3</td>
</tr>
<tr>
<td>TB incidence rate</td>
<td>4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.1 – 6.8</td>
<td>1.2 – 5.1</td>
</tr>
<tr>
<td>IRR (95% CI); p-value</td>
<td>0.67 (0.29 – 1.58); p=0.362</td>
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