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ACTG AIDS CLINICAL TRIALS GROUP

Hepatotoxicity during Isoniazid Preventive Therapy and Antiretroviral Therapy in people living with HIV with Severe Immunosuppression

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BACKGROUND

- Tuberculosis (TB) is a leading cause of death and morbidity in people living with HIV (1).
- Combining IPT and ART has greater efficacy at preventing TB than when each is used alone (2).
- Combining IPT and ART has high rates of hepatotoxicity attributed to hepatic drug interactions and shared toxicities between the drugs (3).
- There are few studies of IPT use in severely immunosuppressed people with HIV even though they have highest mortality of TB
- We conducted an analysis to examine the baseline risk factors of hepatotoxicity during concurrent IPT and ART use in participants with advanced HIV disease.

METHODS

- The REMEMBER trial:
  - enrolled HIV positive people with CD4 cell counts <50cells/ul from settings with high burden of TB. Confirmed/suspected TB was an exclusion criteria
  - Had 2 intervention arms: Empiric TB treatment arm + ART and IPT + ART arm for 24 weeks. Participants were followed up to 96 weeks.
  - The aim was to assess whether empiric TB treatment reduced early mortality in people with advanced HIV disease living in high-burden settings compared with IPT.
  - The trial demonstrated similar mortality between the two arms and in a secondary analysis, lower TB incidence in the IPT arm (4).
- We conducted a secondary analysis restricted to the IPT and ART arm and up to 24 weeks of follow up; the period IPT and ART were used.
- Outcome variable:
  - Hepatotoxicity- grade 3 (5.1–10.0 x upper limit of normal (ULN)) or grade 4 (> 10.0 x ULN) AST or ALT per the DAIDS Toxicity Table or a diagnosis of hepatitis after initiating IPT and ART.
- Baseline predictor variables:
  - Age
  - Sex
  - CD4 cell count
  - Karnofsky Performance Score
  - BMI
  - HBsAg status
  - Elevated pretreatment AST/ALT (AST/ALT ≥1.25x ULN and <2.5xULN)
  - Anemia
  - alcohol use within 30 days of study entry

Statistical analysis

- Univariate logistic regression to examine as possible pretreatment risk factors
- Multivariate logistic regression with step-wise model selection to identify the best set of risk factors for hepatotoxicity.
- Time to hepatotoxicity was estimated by the Kaplan-Meier method.

RESULTS

- 426 participants were randomized to the IPT arm
  - 53% male, median age 35 (IQR 30–42 years), 77% from sub-Saharan Africa
  - The participants had very low CD4 cell counts (median CD4 count 19 cells/µL; IQR 9–33)
- 31/426 (7.3%) developed hepatotoxicity
  - Incidence highest in participants with elevated AST/ALT and HBsAg positive at baseline (45.5%)
  - Lowest in participants with normal AST/ALT and HBsAg negative at baseline
- Raised pretreatment AST/ALT (OR 3.6, 95% CI 1.7-7.7) and HBsAg sero-positivity at baseline (OR 4.7, 95% CI 1.7-12.9) were the statistically significant predictors of developing hepatotoxicity
- The mean time to hepatotoxicity was 23.0 weeks
- Participants with raised pretreatment AST/ALT and HBsAg sero-positivity and those with raised AST/ALT only had earlier onset of hepatotoxicity

Table 1 Baseline characteristics of participants started on IPT in the REMEMBER trial (N=426)

Characteristics	n (%) or median (IQR)*
Age (years)	35 (30–42)
Sex	
Male	226 (53%)
Female	200 (47%)
Race	
Black (African)	388 (91%)
Other	38 (9%)
Country	
Malawi	98 (23%)
South Africa	90 (21%)
Kenya	75 (18%)
Haiti	56 (13%)
Zimbabwe	27 (6%)
Uganda	24 (6%)
Peru	19 (4%)
Zambia	19 (4%)
India	12 (3%)
Brazil	6 (1%)
Pretreatment AST/ALT	
Normal	327 (77%)
Raised	99 (23%)
Hepatitis B surface antigen†	
Negative	384 (94%)
Positive	26 (6%)
CD4 cell count (cells/µL)	19.0 (9–33)
Hemoglobin (g/dL)	11.3 (10.2-12.6)
HIV-1 RNA log10 (cps/mL)	5·3 (4·9–5·7)
Hospital admission within the past 30 days	23 (5%)
Body-mass index <18·5	128 (30%)
Alcohol intake	
Never	214 (50%)
Takes alcohol	33 (8%)
No answer	179 (42%)

Figure 1. Occurrence of hepatotoxicity in the IPT arm in the REMEMBER trial by 24 weeks

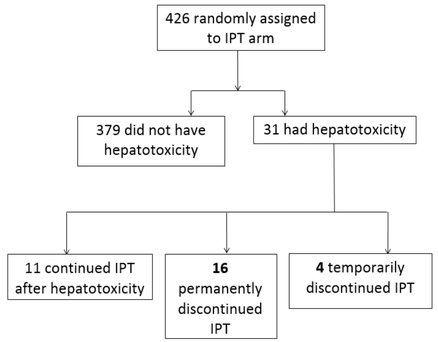
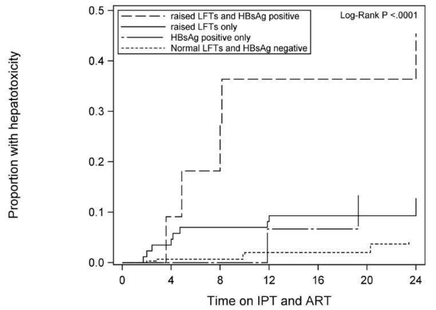


Figure 2. Time to hepatotoxicity during IPT and ART by pretreatment AST/ALT and HBsAg status

A.



raised LFTs and HBsAg positive	11	10	8	7	7	7	6
raised LFTs only	86	82	80	78	77	77	75
HBsAg positive only	15	15	15	14	14	13	13
Normal LFTs and HBsAg negative	298	295	295	292	291	289	286

Table 2 Univariate odds ratios for having hepatotoxicity in the IPT arm within 24 weeks of follow up in the REMEMBER trial (N=426)

	Hepatotoxicity Yes n=31	Hepatotoxicity No n=395	OR	95% CI	P-value
CD4 count (cells per µl)					
<25	16 (6%)	241(94%)	1		
25-50	15 (9%)	154 91%)	1.5	0.7-3.1	0.31
HIV-1 RNA (copies per mL) †					
<100,000	9 (7%)	122(93%)	1		
100,000-500,000	13 (7%)	178 93%)	1.0	0.4-2.4	0.98
≥500,000	9 (9%)	93(91%)	1.3	0.5-3.4	0.58
Body mass index (kg/m^2)					
≥18.5	26 (9%)	272(91%)	1		
<18.5	5 (4%)	123(96%)	0.4	0.2-1.1	0.09
Hospital admission within 30 days of study entry					
No	28 (7%)	375(93%)	1		
Yes	3 (13%)	20(87%)	2.0	0.6-7.2	0.28
Age (years)					
≤35	19 (9%)	203(91%)	1		
>35	12 (6%)	192(94%)	0.7	0.3-1.4	0.29
Sex					
Male	16 (7%)	21 (93%)	1		
Female	15 (8%)	185(93%)	1.1	0.5-2.2	0.87
Hepatitis B surface antigen*					
Negative	23 (6%)	361(94%)	1		
Positive	7 (27%)	19(73%)	5.8	2.2-15.2	<0.001
Anemia					
No anemia	7 (7%)	98(93%)	1		
Anemia	24 (8%)	297(93%)	1.1	0.5-2.7	0.80
Pretreatment AST/ALT					
Normal	15 (5%)	312(95%)	1		
Raised	16 (16%)	83(84%)	4.0	1.9-8.4	<0.001
Alcohol intake					
Never	17 (8%)	197(92%)	1		
Takes alcohol	4 (12%)	29(88%)	1.6	0.5-5.1	0.4
No answer	10 (6)	169(94%)	0.7	0.3-1.5	0.36

† 2 results were not obtained
*16 results were not obtained

Table 3A: Predictors of hepatotoxicity after multivariate logistic regression (N=410)*

Characteristics	Hepatotoxicity Yes (n=31)	Hepatotoxicity No (n=395)	Odds Ratio	95% CI	P-value
Hepatitis B surface antigen*					
Negative	23 (6%)	361 (94%)	1		
Positive	7 (27%)	19 (73%)	4.7	1.7-12.9	0.002
Pretreatment AST/ALT					
Normal	15 (5%)	312 (95%)	1		
Raised	16(16%)	83(84%)	3.6	1.7-7.7	0.001

Table 3B. Univariate logistic regression for the combined variable for raised pretreatment AST/ALT and HBsAg positive at baseline (N=410)*

None	12 (4%)	286 (96%)	1		
Raised AST/ALT only	11(13%)	75 (87%)	3.5	1.4-8.2	<0.001
HBsAg positive only	2 (13%)	13(87%)	3.7	0.7-18.1	0.11
Both	5 (45%)	6 (55%)	19.9	5.3-74.3	<0.001

*16 results were not obtained

CONCLUSION

There was a high incidence of hepatotoxicity in people with advanced HIV taking IPT and ART. Among those with raised AST and ALT or who test HBsAg positive at baseline, closer monitoring and/or initiation of alternative TB preventive regimens which are less hepatotoxic (i.e. 12-week rifapentine plus isoniazid or rifampicin plus isoniazid) may be warranted.

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