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Research Article

INFLAMMATION AND MICRONUTRIENT BIO-MARKERS PREDICT CLINICAL HIV TREATMENT FAILURE AND INCIDENT ACTIVE TB IN HIV-INFECTED ADULTS – A CASE-CONTROL STUDY

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Abstract:

Multiple individual biomarkers of micronutrient and irritation and status, frequently associated with each other, are linked with difficult dealing results in HIV “human immunodeficiency virus” diseased adults. The aim of this research was to analyze EFA exploratory factor analysis on different micronutrient and inflammation biomarkers to recognize bio-marker factors and regulate their link with HIV CTF (clinical treatment failure) and TB (incident active tuberculosis).

This trial is web-based multi-country randomized of ART (antiretroviral therapy efficacy) PEARLS among adults which HIV infected. A nested case-control study has been nested with (n=290: 166 controls and 124 cases) to analyze fundamental components which are based on 23 baseline EFA (pre-ART) inflammation and micronutrient biomarkers’ status. The EFA grouping biomarker’s outputs were utilized in Cox comparative hazards models to analyze the link with CTF (according to primary analysis where cases were specifically incident by World Health Organization stage three and four or by death through ART 96 weeks) or active incident of TB (considered as secondary analysis).

According to primary assessment, which is established in the EFA eigenvalues > 1 values, three components were obtained: 1) Carotenoids, 2) inflammation and 3) other nutrients. In the models of multivariable-adjustment, there was a boost in CTF hazard (adjusted ratio of hazard (aHR) 1.47, with the confidence interval of 95%, 1.17-1.84) every unit inflammation factor score increase. On the other hand in a secondary analysis of TB case-control, greater the scores of elevated carotenoids and low interleukin-18 component was protective against TB (aHR .48, confidence interval 95% .26-.87).

These components analyzed through EFA were linked with adverse results in the individuals of HIV infection. Frameworks focused on limiting the adverse HIV results by therapeutic involvements which put underlying factor targeting such as inflammation rather than affected individual observed biomarker focusing can be more reflective and may authorize further analysis.

Keywords: Tuberculosis, HIV, Antiretroviral Therapy, Inflammation, Exploratory factor analysis

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1.0 INTRODUCTION:

Antiretroviral therapy (ART)-naïve has been used to analyzed single biomarkers HIV infected adults patients in different studies and outputs represent that particular biomarker of micronutrient and inflammation concentrations are linked with severe results. Various inflammation markers, also including CRP, C-reactive protein soluble (CD14) (sCD14), and multiple cytokines (which are IL-6 “interleukin-6 and IL-18”), are linked with highly boosted morbidity and mortality. Morbidity comprises amplified CTF (Clinical Treatment Failure), Risk of Incident active TB, and similarly in longer-term results like cardiovascular disease. Several studies have represented that different micronutrients levels like as selenium, Vitamin D and Iron can also concern different outcomes of HIV (Arildsen et al., 2012).

Therefore, several of inflammation markers are linked with each other like as in those cases where they can be triggered by identical stimuli or monitoring pathway. Accordingly, the nutritional biomarkers can also be linked with each other, just for instance, if diverse micronutrients are component of similar food. Moreover, specific evidence is there that micronutrient and inflammation significance may directly impact each other. For instance, several studies represent that zinc and selenium circulating levels are declined in the time period of acute phase response. As a result, different studies on the link of the biomarkers with results can further benefit from associating the affiliation between these biomarkers (Carmody, 2014).

2.0 METHODS:

2.1 Study design and population

PEARLS has been conducted from June 2005 to June 2010 and there were 1571 HIV ART-naïve infected adults patients from different backgrounds to associated the ART regimens efficacy of three different natures: a) atazanavir plus didanosine and emtricitabine; b) efavirenz with lamivudine and c) efavirenz plus emtricitabine-tenofovir DF single dose daily. There is failure resulted as the primary efficacy of this treatment. PEARLS participants who basically meet up the criteria of inclusion (with age higher than 18 years and CDR+ T Cell calculation less than three hundred cells/mm₃) were registered from different countries (data gathered through PubMed Database). Acute illness individuals and pregnant women or adverse anemia patients were excluded from this research (Funderburg, 2014).

Specifically for this research, a specific case-control analysis (n=290; with 124 cases and including 166 control cases) inside PEARLS to analyze the line of pre-ART initiation baseline biomarkers of micronutrients and inflammation with CTF. Basically, CTF was described generally as an incident by the World Health Organization as the stage three and stage four event (with incident active TB) or post ART initiation 96 weeks death. Accordingly, all cases from this study with accessible values of biomarker were designated; controls were designated on the random subsampling basis of parent regiment stratified by the secondary control case approach (Jeremiah et al., 2012).

2.2 Data Gathering and Laboratory Assessment

With outcome analysis, clinical history was gathered at standard and at post ART initiation of 2, 4 and 8 weeks. Accordingly, after 8 weeks, the clinical history was gathered on every month through three months and every eight weeks after that by 96 weeks. Serum and plasma specimens were gathered at baseline and some other related time points which were stored at -80 °C. The variable exposure (which is 23 markers of micronutrient and inflammation status) was calculated from serum and plasma samples gather at pre-ART initiation baseline. Accordingly, inflammation markers analyzed in this research were interferon - γ (IFN- γ), (IFN- γ , IL-6, IP inducible Protein- 10, Inducible protein – 18, TNF- α , Tumor necrosis factor, and sCD14, CRP and IgM (EndoCAB immunoglobulin). Single-plex ELISAs were utilized to measure CRP plasma, sCD14 (both through research and development systems), (eBiosciences) IL-18 and (Cell Sciences, Endo-CAB IgM (Jones, 2015).

2.3 Statistical Analysis

Twenty-three micronutrient and immune biomarkers were utilized to perform EFA, and the major factor approach was used, which is the basic default component assessment method through STATA software. According to the factor method of principal, the factor loading generally measured while using squared different links. While in this research it is also considerate the variance proportion explanation and the final factor number which extracted through scree plot basis and eigenvalues (Jeremiah et al., 2012).

For the sake of simple interpretation, the factors basically preserved as orthogonal and were swapped

through the method of varimax, through which there is an improvement of inter as interpretability orthogonal factors specifically by revolving the observed axes variable and it will load highly on factors. The factors loading are focused importantly, and loading is related to the coefficient's regression which explains the unmeasured variable link and measured biomarker. The general features between biomarkers of high loading for every factor were utilized for the naming and interpreting of the factors.

3.0 RESULTS:

Study population characteristics of CFT case differed generally by the features of following baseline: Body Mass Index ($p=0.001$), country ($p=0.001$), prior TB diagnosis ($p=0.01$), hypoalbuminemia, CD4 T cell count and anemia ($p <0.001$ for all). From case-

control CFT, EFA assessment, there are three fundamental components which were extracted and based on the link among the experimental biomarkers (eigenvalues > 1). Accordingly, in an EFA, the factor names are provided by authors after very carefully analyzing what is general between scrutinized biomarkers which have larger loadings (correlation equal) on every characteristic. In this analysis factor, one (carotenoids) had larger factor loading (which is > 0.30) of carotenoids comprising β -cryptoxanthin, β -carotene, α -carotene, zeaxanthin, and lutein. Accordingly, in this analysis, the second factor (other nutrients) had a large loading of selenium, vitamin E, vitamin B₆, α -tocopherol, α -carotene, lycopene, and β -cryptoxanthin. And finally as per the factor three, (inflammation) had also large loadings of CRP (C - reactive protein), CD14 soluble (sCD14), IL-18,

interleukin, and (ferritin) as it is a marker of iron stores as an acute protein phase as mentioned in Table 1 (Shivakoti

Table 1 Characteristics of population by CTF cases and control status

Characteristic	All n=290	CTF n= 124 (43%)	Controls n=166 (57%)	p value ^a
Gender				
Male	160 (55)	71 (44)	89 (54)	0.55
Female	130 (45)	53 (41)	77 (59)	
Age (years)	35.0 (29.0–42.0)	35.5 (29.5–42.0)	35.0 (29.0–42.0)	0.81
Country				
Brazil	44 (15)	16 (36)	28 (64)	0.001
Haiti	34 (12)	11 (32)	23 (68)	
India	23 (8)	18 (78)	5 (22)	
Malawi	38 (13)	22 (58)	16 (42)	
Peru	19 (7)	4 (21)	15 (79)	
South Africa	38 (13)	20 (53)	18 (47)	
Thailand	23 (8)	6 (26)	17 (74)	
USA	44 (15)	17 (39)	27 (61)	
Zimbabwe	27 (9)	10 (37)	17 (63)	
Body mass index (kg/m²)				
< 18.5	29 (10)	18 (62)	11 (38)	0.001
18–25	192 (66)	89 (46)	103 (54)	
≥ 25	69 (24)	17 (25)	52 (79)	
Prior TB diagnosis				
Yes	59 (20)	34 (58)	25 (42)	0.01
No	231 (80)	90 (39)	141 (61)	
Treatment arm				
A	100 (35)	58 (56)	45 (44)	0.72
B	108 (37)	54 (42)	39 (58)	
C	82 (28)	67 (29)	27 (71)	
CD4 count (cells/mm³)				
< 100	103 (36)	50 (69)	22 (31)	< 0.001
100–200	93 (32)	45 (49)	46 (51)	
> 200	94 (34)	43 (41)	63 (59)	
Log viral load (copies/mL)				
< 4	21 (7)	6 (29)	15 (71)	0.18
4–5	98 (34)	38 (39)	60 (61)	
> 5	171 (59)	80 (47)	91 (53)	
Hypoalbuminemia				
Yes (≤ 3.5 g/dL)	77 (19)	51 (41)	26 (16)	< 0.001
No (> 3.5 g/dL)	215 (81)	73 (59)	140 (84)	
Anemia				
Yes	168 (58)	87 (54)	81 (49)	< 0.001
No	121 (42)	36 (50)	85 (50)	

et al., 2018).

(Source: Shivakoti et al., 2018)

In factor analysis it is common, different biomarkers such as vitamin D may not have large loadings in any mentioned three extracted factors. Carotenoids high scores and other factors of nutrients linked with declined vulnerabilities of CTF in models of univariable but not in specifically in model of multivariable which regulated for age, country, body mass index, sex, baseline status of TB, CD4 count, anemia, treatment arm, hypoalbuminemia and viral load, as mentioned in Table 2.

Table 2 Association of each factor with clinical treatment failure

	Univariable analysis HR (95% CI)	Multivariable analysis HR (95% CI)
Factor 1 (Carotenoids)	0.71 (0.56-0.90)	0.77 (0.57-1.05)
Factor 2 (Other nutrients)	0.79 (0.63-0.87)	0.83 (0.57-1.32)
Factor 3 (Inflammation)	1.53 (1.32-1.77)	1.47 (1.17-1.84)

(Source: Shivakoti *et al.*, 2018)

Due to the fact that there are various results that are primarily ranging according to the severity, discriminating the idea that the diagnosis stays the same when inferring on a smaller group of CTF which merely hallmarks complex diagnosis. A discrimination between the case-control population of the results showing severity, which comprised of cases and control was done which included CD4 count, BMI ($p = 0.003$), anemia (all $p < 0.001$), Hypoalbuminaemia, prior TB ($p = 0.02$) and country ($p = 0.01$) (data not manifested). However, EFA with the range (eigenvalues > 1) was set in order to analyze the severity level which had three main factors rooted in it. As a result, it was seen that the previously acknowledged results (Table S2) and factors of CTF were sharing the same profile with the newer outcomes of the analysis (Shivakoti *et al.*, 2018).

According to factor one (carotenoids) and factor two (other nutrients) had a large loading of the identical regarding same indicators, while inflammation (as our third factor) had an additional indicator with large IP-10 loading. On the contrary, greater scores of factor three (inflammation) had elevated hazards of adverse results in uni-variable but excluded from multivariable models (aHR, 1.60; with confidence interval 95%, 1.24-2.06), as mentioned in below Table 3.

Table 3 Association of each factor with severe outcomes

	Univariable analysis HR (95% CI)	Multivariable analysis HR (95% CI)
Factor 1 (Carotenoids)	0.71 (0.52-0.95)	0.86 (0.58-1.26)
Factor 2 (Other nutrients)	0.75 (0.57-0.98)	0.78 (0.49-1.26)
Factor 3 (Inflammation)	0.97 (0.61-1.53)	1.60 (1.24-2.06)

DISCUSSION:

In this research, regarding HIV infected patients originating ART, fundamental factors were extracted (three factors as mentioned above) from different biomarkers of immunological and nutritional baseline status and with the connection of these three factors with severe HIV results (CTF and “incident active” TB) was analyzed. Larger inflammation factor scores were linked with elevated CTF hazards (Tripathi *et al.*, 2017).

Significantly, larger notches of high carotenoids and IL-18 with low factor were also linked with declined incident active TB hazards. Our outputs, with the usage of analytical methods, which correlated account such as EFA between different biomarkers, help findings from different researches on the link of micronutrients and inflammation with HIV results, while advising that it may be worthy for concentrate on probable interventions that may address the original factor rather than any specific biomarker (Shivakoti *et al.*, 2018).

Exclusively, which extracted in TB assessment was differ with CFT assessment. Factor 1 included large carotenoids and lesser IL-18, and the factor of inflammation had a large loading of TNF- α , IFN- γ , IP-10 and IL-6. A specific reason for factor’s profile being variant between TB case-control and CTF is that the results are dissimilar (as in TB accounts regarding 31% of the CTF cases; 100% in case-control of TB). The association between IL-18 and carotenoids captivating and some research demonstrated that β -carotene metabolism can affect the level of IL-18. The depths of this research comprise the analysis of experience before the result, the analysis of different results and coping with collinearity about different correlated EFA biomarkers (Shivakoti *et al.*, 2018).

CONCLUSION:

In conclusion, research results propose that nutritional and immunological grouping underlying particular factors are linked with highly adverse events. Similarly, an approach also concentrated on targeting interventions of the original factor rather compared with any single experiential variable authorized investigation. Additionally, this research’s outputs concentrate on inflammatory biomarkers group which further approve the basic inflammation role in highly adverse HIV results, while also proposing the carotenoid probably protect against TB.

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