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Iron Status of a People Living with HIV in Sub-Saharan Africa Using a Multi-Criteria Approach Based on the Determination of Blood Ferritin, sTfR, CRP and sTfR-F Index

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Abstract

Background: The assessment of iron status using a single biomarker of iron metabolism is not enough sensitive and specific to reliably diagnose iron deficiency associated with multiple comorbidities. The objective of this study was to describe the iron status of people living with HIV in sub-Saharan Africa using a multi-criteria approach based on the determination of blood ferritin, sTfR, CRP and the calculation of sTfR-F index. **Methods**: This study was conducted using a retrospective panel of 933 sera/plasmas. We determined serum ferritin concentration, serum sTfR concentration, and C-reactive protein (CRP) by immunoturbidimetry for each subject. The sTfR-F index was determined by calculating the sTfR/log ferritin ratio. The statistical test used was Chi^2. **Results**: Regardless of the inflammatory syndrome, we determined 3.80%, 30.29%, and 42.70% iron deficiency based on the separate interpretation of ferritin concentration, sTfR, and sTfR-F calculation, respectively. We used those biomarkers in addition to CRP in an algorithm for the diagnosis of iron deficiency. Subjects without inflammatory syndrome, had iron deficiency of 2.89% (n = 26). Taking into account the presence of an inflammatory syndrome, the frequency obtained was n = 88 (9.78%). Overall, iron deficiency was diagnosed in 114 (12.67%) patients when we used the diagnostic algo-

rithm. **Conclusion**: The use of diagnostic algorithms combining several biomarkers of iron metabolism and taking into account the presence or absence of an inflammatory syndrome is a good approach to detect a large number of iron deficiencies in a population. Therefore, an assessment of the effectiveness of different diagnostic algorithms is necessary.

Keywords

Iron Deficiency, Iron Metabolism Biomarkers, HIV Infection, CRP

1. Introduction

Several markers of iron metabolism are used for the diagnosis of iron deficiency. These biomarkers can be selected according to the compartment of iron metabolism that is explored [1] [2] [3]. The iron storage level is assessed by determining the blood concentration of ferritin [4] [5] [6]. However, ferritin concentrations do not reflect real iron stores depletion during inflammation [3] [7]. The plasma soluble transferrin receptor (sTfR) concentration is related to the quantity of hematopoietic cells surface receptors. Therefore, sTfR blood concentration is helpful to explore erythropoietic iron with the advantage to not be influenced by an inflammatory syndrome [2] [6] [8] [9] [10]. A recent ratio of biomarkers (sTfR/log(Ferritin)) named sTfR-F index has been validated as a reliable appraisal tool of iron storage especially during an inflammatory syndrome [6] [9]. It is assumed to have a higher diagnostic performance than sTfR and ferritin [11] [12].

Several iron biomarkers are influenced by associated pathology, and induce misinterpretation [13]: the diagnosis of iron deficiency could be difficult in case of underlying inflammatory process [6] [13] [14]. In the absence of a non-invasive gold standard biomarker, diagnosis of iron deficiency is more accurate with the use of multi-criteria indicators [14]. Authors have proposed an approach of multi-criteria indicators (diagnosis algorithm) taking into account an eventual inflammatory syndrome. It uses the determination of blood ferritin, sTfR or the calculation of the sTfR-F index [2]. This approach could be relevant for the diagnosis of iron deficiency, especially in tropical environment with the highest frequency of iron deficiency and infectious diseases (HIV/AIDS, tuberculosis, ...) [15] [16]. The objective of this study was to describe the iron status of a black population of people living with HIV in sub-Saharan Africa using multi-criteria approach (ferritin, sTfR, sTfR-F index and CRP).

2. Materiel and Methodes

The present retrospective descriptive and analytical study took place at the Center for Diagnosis and Research on AIDS and other Infectious Diseases (CeDReS) in teaching hospital of Treichville, Abidjan, Ivory Coast from July to September

2016. It was conducted on a retrospective panel of 933 sera/plasma from the initial workup at month 0 (M0) of patients of the ANRS 12136 TEMPRANO trial cohort [17]. Subjects eligible for the trial were 18 years old and older, with positive serology for HIV1 or for HIV 1 & 2. All patients had a CD4+ count at inclusion less than 800 cells/mm^3 and did not meet any criteria for starting antiretroviral (ARV) therapy according to World Health Organization (WHO) guidelines at this moment [18]. All the subjects gave their informed written consent. All patients not respecting these eligibility criteria were excluded from the study.

The study was designed and conducted following the Declaration of Helsinki. It was reviewed and approved by the scientific committee of the medical biology chair of Pharmaceutical and Biological Sciences faculty (University Felix Houphouet-Boigny).

In purpose to determine the iron status, we used a multiple-criteria blood indicators approach according to Nathalie Mario and *et al.* [2] showed in **Figure 1**. For each subject, we determined C-reactive protein (CRP) before. And then, if there was no inflammatory process, we determined the serum ferritin concentration only to know iron status of the subject. If there was an inflammatory process, sTfR and/or sTfR-F-index was determined to know iron status of the subject. Serum ferritin concentration, serum sTfR concentration, and C-reactive protein (CRP) was determinated by immunoturbidimetry on the Cobas C311 (ROCHE Diagnostic). Other variables were obtained from the subject medical files in the TEMPRANO ANRS 12136 trial database. The sTfR-F index was determined by calculating the sTfR/log Ferritin ratio. The references values used are recorded in **Table 1**.

Statistical analyses were performed with SAS® 9.4 software. The comparisons were made using Chi^2. All comparison test and correlation were considered statistically significant for a p-value inferior to 0.05.

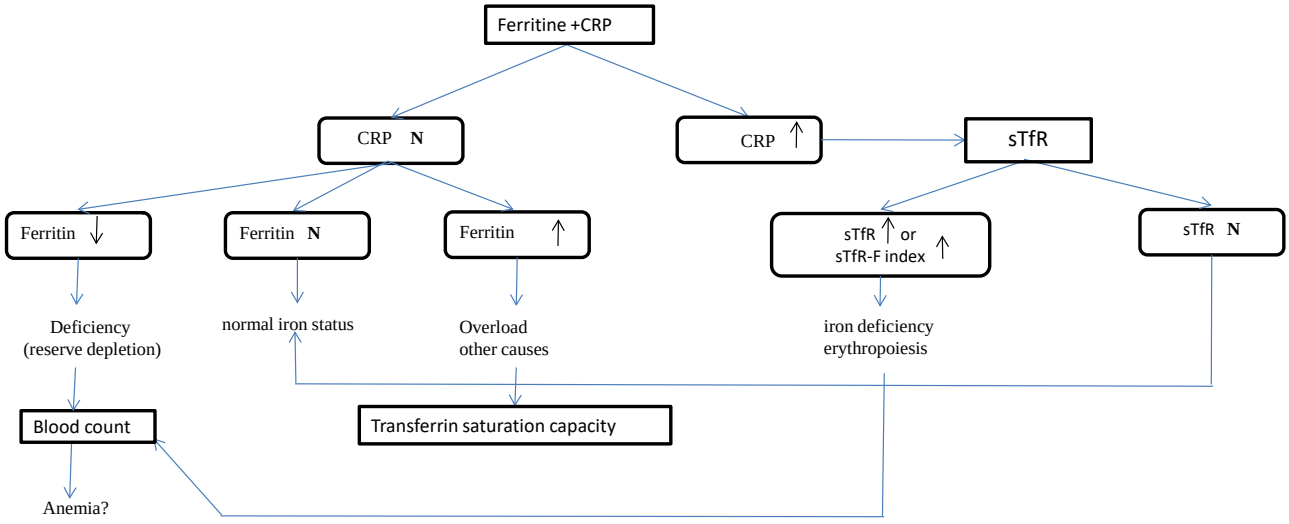

Figure 1. Algorithm for iron deficiency diagnosis. N: normal; ↓: decrease; ↑: increase; sTfR: soluble transferrin receptor; sTfR-F index: sTfR/log Ferritin ratio [2].

Table 1. References values.

Biomarkers	References values	References
CRP	<5 mg/l	[19]
ferritin	Male: 27 to 365 ng/ml Female: 13 to 148 ng/ml	[20]
sTfR	2.2 to 5 mg/l	[21]
sTfR-F index	>2	[22]

3. Results

This figure shows the individual interpretation of biomarkers regardless inflammatory syndrome or not (**Figure 2**).

The results after applying the diagnosis algorithm of iron deficiency, using multi-criteria indicators, taking into account inflammatory syndrome are shown in **Figure 3**. Overall, iron deficiency was diagnosed in 114 (12.7%) patients, of which 26 (2.9%) were based on the criterion "ferritin decrease without inflammatory" and 88 (9.9%) with the criterion "sTfR increase and/or sTfR-F index > 2" in presence of inflammation.

4. Discussion

In this study, we used the multicriteria approach of Nathalie Mario *et al.* for the diagnosis of iron deficiency. These authors designed a diagnostic algorithm based on ferritin, sTfR, sTfR-F index and CRP.

First, the iron status of each patient was described using the biomarkers ferritin, sTfR and sTfR-F index individually. We did not take into account the patient's inflammatory status. The percentage of iron deficiency, obtained with ferritin, was the lowest compared to the other biomarkers under study. The WHO recommends using low ferritin concentration as the primary measure of iron deficiency in the population. However, during an inflammatory process, the increase in ferritin concentration masks the depletion of iron stores in many patients. It has been advocated that for the diagnosis of iron deficiency, the threshold of ferritin values should be <30 (WHO) or <100 µg/l or more (other authors). Unfortunately, arbitrarily increasing blood ferritin thresholds may probably overestimate iron deficiency. In our study, the thresholds considered were inferior to 27 ng/ml for men and inferior to 13 ng/ml for women, respectively. Therefore, we determined 3.80% (n = 35) of iron deficiency. The low thresholds of blood ferritin concentration used in our study could explain this low percentage of iron deficiency. Namaste *et al.* found an estimated percentage of iron deficiency of 13.6% $CI_{95\%}$ = [10.7 - 16.4] [7]. The estimated percentage by these authors was significantly different from ours (p values less than 0.0001). The observed differences were probably due to the composition of the study populations. Ours was composed of mixed gender aged above 18 years. The authors' study was composed only of women of childbearing age and not pregnant, aged

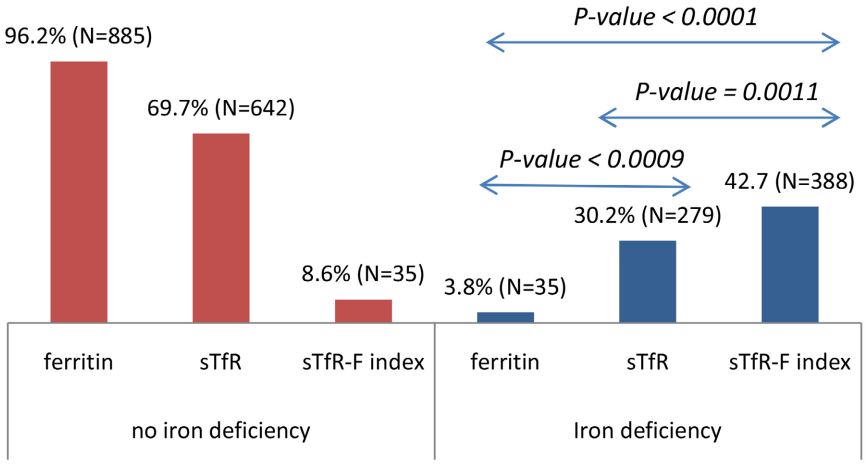

Figure 2. Iron status according separate interpretation of ferritin, sTfR, and sTfR-F index. In comparing, two by two, percentages of iron deficiency determinate individually by ferritin, sTfR, sTfR-F index, we see a significantly difference between; fernitin (3.8%, N = 35) and sTfR (30.29%, N = 279) (p-value= P = 0.0009), between ferritin (3.8%, N = 35) and sTfR-F index (42.70%, N = 388) (p-value < 0.0001), and between sTfR (30.29%, N = 279) and sTfR-F index (42.70%, N = 388) (p-value = 0.0011). sTfR: soluble transferrin receptor; sTfR-F index: sTfR/Log Ferritin.

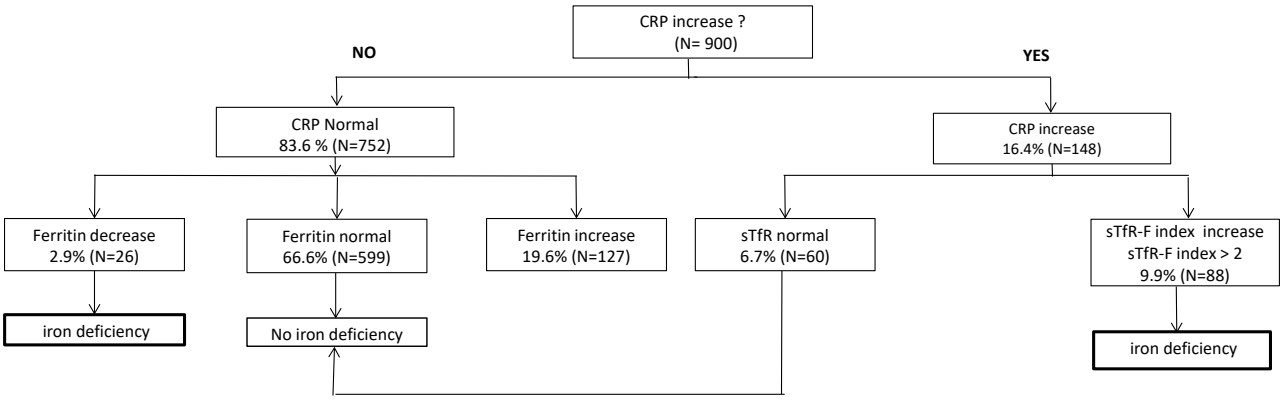

Figure 3. Iron deficiency diagnosis according to multi-criteria indicator.

15 to 49 years. [7]. Due to menstruation, this age group is subject to a higher prevalence of iron deficiency [23].

The sTfR and sTfR-F index have been accepted as alternatives to increase the sensitivity of iron deficiency diagnosis [3] [11] [12] [24] [25]. We observed an increase in the estimated percentage of iron deficiency, from 3.8% (n = 35) obtained with ferritin, to 30.3% (n = 279) and to 42.7% (n = 388) respectively with the sTfR and the sTfR-F index. These percentages were all statistically different. In their study of subjects with chronic inflammatory bowel disease, some authors made the same finding. The sTfR-F index in addition to the criterion of serum ferritin < 30 ng/mL, increased the rates of diagnosis of iron deficiency by 36% [22].

Unfortunately, an iron metabolism biomarker used alone is not specific and sensitive enough to reliably assess iron status, especially to correctly diagnose

iron deficiency in multiple comorbidities [26]. For accurate diagnosis of iron deficiency in diseases with multiple comorbidities, such as HIV, where inflammation remains high, some authors have proposed diagnostic algorithms [2] [4] [22] [27] [28] [29]. We used the algorithm proposed by Nathalie Mario *et al.* to describe the iron status of our population [2]. The percentage of iron deficiency was 9.78% with our subjects with increased CRP. Diagnosis of iron deficiency for this group of subjects was made for an increased sTfR concentration and/or sTfR-F index above 2. The low ferritin concentration was used as the only diagnostic biomarker in the absence of inflammatory syndrome. Our subjects without inflammatory syndrome were 752 (83.56%). Only 2.89% (n = 26) of these subjects had iron deficiency. This percentage was statistically different (p-value < 0.0001) from Namaste study [7]. After excluding subjects with inflammation, they found 15.3% (n = 660) iron deficiency based on a decreased ferritin as the only biomarker.

A high percentage of iron deficiency was found in our population with an inflammatory process compared to those without an inflammatory process (9.78% *vs* 2.89%). The difference between these two percentages was statistically significant (p-value < 0.0001).

The overall percentage of iron deficiency was 12.67% in our study population. This percentage obtained with the algorithm proposed by Nathalie Mario, was significantly different from those obtained with the biomarkers (ferritin, sTfR, sTfR-F index) considered separately (p-values < 0.0001). The overall percentage of iron deficiency was different from those reported by Abibol *et al.* [22]. They found 32.7% iron deficiency. The authors used in their algorithm, the ferritin threshold less than 30 ng/mL and the threshold sTfR-F index above 2, and when patients had a blood ferritin between 30 and 100 ng/mL, CRP was the decision maker (CRP > 2.5 mg/L).

Due to the specificity of our study population (black African subjects living with HIV in West Africa) the results of this study cannot be extrapolated to a Caucasian population. Neither does our study claim to establish an epidemiological profile of iron status, but rather a description of the iron status of our subjects regard to Mario's algorithm. Moreover, in the absence of bone marrow puncture to determine stainable iron in our patients, it is difficult for us to comment on the real state of the subjects' iron deficiency.

5. Conclusion

The use of diagnostic algorithms combining several biomarkers of iron metabolism is more sensitive to detect iron deficiencies in a context of inflammation. Our study showed an increase of iron deficiency frequency by using a diagnostic algorithm compared to solely using a decreased ferritin concentration, as recommended by the WHO. However, because of the diversity of biomarkers and algorithms, further studies should evaluate their sensitivity and specificity in different type of populations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Schaefer, R.M., Huch, R. and Krafft, A. (2007) Current Recommendations for the Treatment of Iron Deficiency Anemia. *Revue Médicale Suisse*, **3**, 874-880.

[2] Mario, N. and Pernet, P. (2007) Quels marqueurs pour le bilan martial? *Spectra Biologie*, No. 163, 6.

[3] Pfeiffer, C.M. and Looker, A.C. (2017) Laboratory Methodologies for Indicators of Iron Status: Strengths, Limitations, and Analytical Challenges. *The American Journal of Clinical Nutrition*, **106**, 1606S-1614S. https://doi.org/10.3945/ajcn.117.155887

[4] Al-Naseem, A., Sallam, A., Choudhury, S. and Thachil, J. (2021) Iron Deficiency without Anaemia: A Diagnosis That Matters. *Clinical Medicine* (*London*), **21**, 107-113. https://doi.org/10.7861/clinmed.2020-0582

[5] Camaschella, C. (2019) Iron Deficiency. *Blood*, **133**, 30-39. https://doi.org/10.1182/blood-2018-05-815944

[6] Pasricha, S.R., Tye-Din, J., Muckenthaler, M.U. and Swinkels, D.W. (2021) Iron Deficiency. *The Lancet*, **397**, 233-248. https://doi.org/10.1016/S0140-6736(20)32594-0

[7] Namaste, S.M., Rohner, F., Huang, J., *et al.* (2017) Adjusting Ferritin Concentrations for Inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. *The American Journal of Clinical Nutrition*, **106**, 359S-371S. https://doi.org/10.3945/ajcn.116.141762

[8] R'zik, S. and Beguin, Y. (2001) Serum Soluble Transferrin Receptor Concentration Is an Accurate Estimate of the Mass of Tissue Receptors. *Experimental Hematology*, **29**, 677-685. https://doi.org/10.1016/S0301-472X(01)00641-5

[9] Suega, K., Kandarini, Y. and Tubung, J. (2019) Role of Soluble Transferrin Receptor and Transferrin Receptor-Ferritin Index to Detect Iron Deficiency Anemia in Regular Hemodialysis Patients. *Open Access Macedonian Journal of Medical Sciences*, **7**, 97-102. https://doi.org/10.3889/oamjms.2019.012

[10] Stoltzfus, R.J. and Klemm, R. (2017) Research, Policy, and Programmatic Considerations from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. *The American Journal of Clinical Nutrition*, **106**, 428S-434S. https://doi.org/10.3945/ajcn.117.999

[11] Infusino, I., Braga, F., Dolci, A. and Panteghini, M. (2012) Soluble Transferrin Receptor (sTfR) and sTfR/log Ferritin Index for the Diagnosis of Iron-Deficiency Anemia A Meta-Analysis. *American Journal of Clinical Pathology*, **138**, 642-649. https://doi.org/10.1309/AJCP16NTXZLZFAIB

[12] Krawiec, P. and Pac-Kożuchowska, E. (2019) Soluble Transferrin Receptor and Soluble Transferrin Receptor/Log Ferritin Index in Diagnosis of Iron Deficiency Anemia in Pediatric Inflammatory Bowel Disease. *Digestive and Liver Disease*, **51**, 352-357. https://doi.org/10.1016/j.dld.2018.11.012

[13] Camaschella, C. (2017) New Insights into Iron Deficiency and Iron Deficiency Anemia. *Blood Reviews*, **31**, 225-233. https://doi.org/10.1016/j.blre.2017.02.004

[14] Cappellini, M.D., Comin-Colet, J., de Francisco, A., Dignass, A., Doehner, W., Lam, C.S., *et al.* (2017) Iron Deficiency across Chronic Inflammatory Conditions: International Expert Opinion on Definition, Diagnosis, and Management. *American Journal of Hematology*, **92**, 1068-1078. https://doi.org/10.1002/ajh.24820

[15] https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_fr.pdf

[16] OMS|Carences en micronutriments. WHO. World Health Organization.

[17] The TEMPRANO ANRS 12136 Study Group (2015) A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *The New England Journal of Medicine*, **373**, 808-822. https://doi.org/10.1056/NEJMoa1507198

[18] World Health Organization (2010) Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach—2010 Revision. World Health Organization, Geneva. https://apps.who.int/iris/handle/10665/44379

[19] Dati, F., Schumann, G., Thomas, L., Aguzzi, F., Baudner, S., Bienvenu, J., *et al.* (1996) Consensus of a Group of Professional Societies and Diagnostic Companies on Guidelines for Interim Reference Ranges for 14 Proteins in Serum Based on the Standardization against the IFCC/BCR/CAP Reference Material (CRM 470). International Federation of Clinical Chemistry. Community Bureau of Reference of the Commission of the European Communities. College of American Pathologists. *European Journal of Clinical Chemistry and Clinical Biochemistry*, **34**, 517-520.

[20] Lotz, J., Hafner, G. and Prellwit, W. (1997) Reference Study for Ferritin Assays. *Kurzmitteilung Clinical Laboratory*, **43**, 993-994.

[21] Lehmann, P., Lotz, J., Roeddiger, R., *et al.* (2000) Löslicher Transferrin-Rezeptor (sTfR) und Ferritin (F) als Diagnostische Marker der Anämien.

[22] Abitbol, V., Borderie, D., Polin, V., Maksimovic, F., Sarfati, G., Esch, A., *et al.* (2015) Diagnosis of Iron Deficiency in Inflammatory Bowel Disease by Transferrin Receptor-Ferritin Index. *Medicine* (*Baltimore*), **94**, e1011. https://doi.org/10.1097/MD.0000000000001011

[23] Kumar, A., Sharma, E., Marley, A., Samaan, M.A. and Brookes, M.J. (2022) Iron Deficiency Anaemia: Pathophysiology, Assessment, Practical Management. *BMJ Open Gastroenterology*, **9**, e000759. https://doi.org/10.1136/bmjgast-2021-000759

[24] Castel, R., Tax, M.G.H.M., Droogendijk, J., Leers, M.P.G., Beukers, R., *et al.* (2012) The Transferrin/Log(Ferritin) Ratio: A New Tool for the Diagnosis of Iron Deficiency Anemia. *Clinical Chemistry and Laboratory Medicine*, **50**, 1343-1349. https://www.degruyter.com/document/doi/10.1515/cclm-2011-0594/html

[25] Beguin, Y. (2003) Soluble Transferrin Receptor for the Evaluation of Erythropoiesis and Iron Status. *Clinica Chimica Acta*, **329**, 9-22. https://doi.org/10.1016/S0009-8981(03)00005-6

[26] Gupta, D., Choudhary, R., Sharma, M., Saluja, S. and Gupta, B. (2016) Role of Soluble Transferrin Receptor and Soluble Transferrin Receptor Index in Diagnosing Iron Deficiency Anemia in Patients with Chronic Kidney Disease. *Astrocyte*, **3**, 125-130. https://doi.org/10.4103/2349-0977.201006

[27] Maggi, P., Ricci, E., Messina, V., Salzillo, A., Simeone, F., Iodice, A., *et al.* (2021) Dangerous Liaisons? The Role of Inflammation and Comorbidities in HIV and SARS-CoV-2 Infection. *Expert Review of Clinical Immunology*, **17**, 201-208. https://doi.org/10.1080/1744666X.2021.1886080

[28] Hunt, P.W., Lee, S.A. and Siedner, M.J. (2016) Immunologic Biomarkers, Morbidity, and Mortality in Treated HIV Infection. *The Journal of Infectious Diseases*, **214**, S44-S50. https://doi.org/10.1093/infdis/jiw275

[29] Dignass, A.U., Gasche, C., Bettenworth, D., Birgegård, G., Danese, S., Gisbert, J.P., *et al.* (2015) European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases. *Journal of Crohn's and Colitis*, **9**, 211-222. https://doi.org/10.1093/ecco-jcc/jju009