J Clin Tuberc Other Mycobact Dis 16 (2019) 100107

Contents lists available at ScienceDirect

J Clin Tuberc Other Mycobact Dis

journal homepage: www.elsevier.com/locate/jctube

Plasma levels of CRP, neopterin and IP-10 in HIV-infected individuals with and without pulmonary tuberculosis

Fausto Ciccacci[a,*], Marco Floridia[b], Roberta Bernardini[c], Zita Sidumo[d], Remigio Josè Mugunhe[e], Mauro Andreotti[b], Alfeu Passanduca[d], Noorjehan Abdul Magid[d], Stefano Orlando[a], Maurizio Mattei[c,f], Marina Giuliano[b], Sandro Mancinelli[a], Maria Cristina Marazzi[g], Leonardo Palombi[a]

[a] Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[b] National Center for Global Health, Istituto Superiore di Sanità, Rome, Italy
[c] Centro Servizi Interdipartimentale – STA, University of Rome Tor Vergata, Rome, Italy
[d] DREAM Program, Community of S. Egidio, Maputo, Mozambique
[e] DREAM Program, Community of S. Egidio, Beira, Mozambique
[f] Department. of Biology, University of Rome Tor Vergata, Rome, Italy
[g] LUMSA University, Rome, Italy

ARTICLE INFO

Keywords:
Tuberculosis
Diagnosis
Biomarkers
Africa
Mozambique

ABSTRACT

Introduction: Tuberculosis (TB) is a major cause of morbidity and death worldwide, and disproportionally affects people with HIV. Many cases still remain undiagnosed, and rapid and effective screening strategies are needed to control the TB epidemics. Immunological biomarkers may contribute.

Methods: Plasma samples from healthy individuals (n: 12) and from HIV-infected individuals with (n: 21) and without pulmonary TB (n: 122) were tested for C-reactive protein (CRP), neopterin, and interferon-gamma-inducible protein-10 (IP-10). Increased levels of biomarkers and WHO 4-symptom-screening were compared with the presence of pulmonary TB. Survival status at 12 months was recorded. Associations with CD4 count, BMI, haemoglobin, disease severity, and mortality were analysed.

Results: The plasma levels of the biomarkers were significantly higher in TB-positive (*n*:21) compared to TB-negative (*n*:122) subjects. WHO symptoms, increased neopterin (>10 nmol/L) and CRP (>10 mg/L) showed similar sensitivity and different specificity, with increased CRP showing higher and increased neopterin lower specificity. The three markers were inversely correlated to haemoglobin and to CD4, and CRP levels inversely correlated to BMI. The markers were also significantly higher in individuals with subsequent mortality and in individuals with higher mycobacterial load in sputum according to Xpert results (IP-10 and CRP).

Conclusion: This study showed significant associations of the biomarkers analysed with TB infection and mortality, that could have potential clinical relevance. Biomarker levels may be included in operational research on TB screening and diagnosis.

1. Introduction

Tuberculosis (TB) is a major cause of morbidity and death worldwide, and disproportionally affects people with human immunodeficiency virus (HIV), with a severe impact on mortality and economic growth of highly affected countries [1–4]. Despite several improvements in diagnosis, mostly due to the introduction of rapid tests such as GeneXpert and urine LAM test, that quickly detect presence of nucleic acids or other bioproducts of Mycobacterium Tuberculosis in biological samples [5,6], many cases remain undiagnosed, and rapid and effective screening strategies are still needed to control more successfully the TB epidemics in countries with limited resources [7–9]. Active TB produces an increase in the blood levels of some markers of inflammation or immune response such as C-reactive protein (CRP), interferon gamma, neopterin, complement factor H, interferon gamma inducibile protein 10 (IP-10), transthyretin and others. Biomarkers have been studied as diagnostic tools in screening strategies in addition to molecular tests and symptom screening. Although some studies have

* Corresponding author.
E-mail address: fausto.ciccacci@gmail.com (F. Ciccacci).

https://doi.org/10.1016/j.jctube.2019.100107

Table 1
Population characteristics.

	All (*n*: 143)	Xpert-positive (*n*: 21)	Xpert-negative (*n*: 122)	*P* value[b]
Site (*n*,%)				
- Maputo	50	11 (22.0%)	39 (78.0%)	0.070
- Beira	93	10 (10.8%)	83 (89.2%)	
Gender (*n*,%):				
- Male	74	12 (16.2%)	62 (83.8%)	0.592
- Female	69	9 (13.0%)	60 (87.0%)	
WHO HIV Clinical stage (*n*,%):				
- I	70	2 (2.9%)	68 (97.1%)	
- II	41	4 (9.8%)	37 (90.2%)	<0.001
- III	31	15 (48.4%)	16 (51.6%)	
- IV	1	0 (0%)	1(100.0%)	
Age (years: median, IQR) (*n*: 143)	36 (29–43)	38 (31.5–44.5)	35.5 (29.0–43.0)	0.369
Time from HIV diagnosis (weeks: median, IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.474
Body mass index (Kg/m^2: median, IQR)[a]	21.0 (19.1–24.3)	18.8 (17.4–20.6)	21.3 (19.3–24.8)	<0.001
CD4 cell count, (cells/mm^3, median, IQR)	194 (122–326)	133 (93–200)	202 (142–354)	0.012
Haemoglobin (g/dl, median, IQR)	11.4 (10.1–13.1)	9.5 (8.9–11–3)	11.6 (10.4–13.2)	0.001
At least one WHO-4SS symptom (*n*,%)	60	18 (30.0%)	42 (70.0%)	<0.001
No WHO-4SS symptoms (*n*,%)	83	3(3.6%)	80 (96.4%)	

[a] *n*: 142.
[b] chi-square test for categorical variables; Mann–Whitney *U* test for quantitative variable.

evaluated individual markers and panels of serum proteins for the diagnosis of active TB [10–12], none has been included in recommended screening strategies yet. In order to further investigate this issue, we measured the blood levels of some markers of inflammation and immune activation in blood samples from a population of HIV-infected patients that were screened for TB using the WHO symptom screening and the GeneXpert molecular test on sputum within a multicenter study conducted in Mozambique [13].

2. Study population and methods

We used stored blood samples and clinical data from patients participating to a study of intensive TB case finding with symptom screening, conducted in Mozambique within the Disease Relief through Excellent and Advanced Means (DREAM) program of the Community of S. Egidio, an Italian faith-based non-governmental organization. The study, described elsewhere [13], enrolled patients between 2014 and 2016, following informed consent and according to the approval by the National Committee for Health Bioethics of the Mozambican Ministry of Health in 2014 (ref. 36/CNBS/2014). This laboratory substudy obtained an additional specific approval for use of collected samples by the National Committee for Health Bioethics of the Mozambican Ministry of Health in 2018 (IRB0002657, ref. 364/CNBS/18). The samples analyzed here represent residual plasma amounts that were stored at –80 °C at the laboratories of the DREAM health centers of Beira and Maputo following routine analyses for the clinical care of patients followed at the two above DREAM clinical sites. We included all available samples of Xepert-positive patients and a casual sample of Xpert-negative individuals. All the patients had a record of survival status at 12 months available. A small number of available plasma samples from healthy laboratory personnel with no declared risk of infection with HIV served as control group in comparative analysis of biomarkers. No additional information regarding the contol group was collected.

In accordance with WHO guidelines, active TB was defined by a positive result to a molecular TB assay on sputum (Xpert MTB/RIF Assay system, Cepheid, Sunnyvale, CA, USA) [5], and symptom screen positivity was defined by presence of any of four WHO symptoms (WHO-4SS: current cough, fever, night sweats, weight loss) in the previous 30 days [14]. Demographic and clinical information was collected during routine clinical visits at the DREAM health centers. The three host biomarkers evaluated in plasma samples were CRP, Neopterin, and IP-10. Biomarkers levels were measured according to manifacturer's instructions using the following commercial assays: Human CRP ELISA Kit (Arigo Biolaboratories Corporation, Hsinchu City, Taiwan); Neopterin ELISA (IBL-International GMBH, Hamburg, Germany); Quantikine ELISA Human CXCL10/IP-10 Immunoassay (R&D Systems Europe, Abingdon, UK).

Population characteristics were summarized as medians with interquartile ranges (IQR). The CRP threshold concentration defining a screen positive for TB was set at 10 mg/L, according to previous studies [12]. For neopterin, a cutoff level <10 nmol/L was used to define normal values, for consistency with previous studies [15]. For IP-10, in the absence of established threshold values for screening purposes, we performed exploratory analyses based on different thresholds. Point estimates and 95% CIs were calculated for the sensitivity, specificity, negative and positive predictive value (NPV, PPV) in reference to Xpert results. Differences in sensitivity and specificity were compared with McNemar's test of paired proportions. Qualitative variables were compared using the chi-square or the Fisher test, and quantitative variables using the Mann–Whitney *U* test. Correlations between quantitative variables (levels of biomarkers, CD4 cell count, BMI and haemoglobin) were assessed with the Spearman test. For all tests, p values below 0.05 were considered statistically significant. All analyses were performed using the SPSS software, version 22 (IBM Corp, 2013, Armonk, NY, USA).

3. Results

Stored samples were available for 143 patients enrolled in the intensive TB case finding study (21 with a Xpert-positive test result [14.7%] and 122 [85.3%] with two sequential negative Xpert tests) and for 12 controls. The general characteristics of the HIV-infected individuals evaluated for TB are shown in Table 1. The presence of a positive Xpert test on sputum was associated, as expected, with worse clinical and immunological conditions, and with presence of TB-related symptoms (Table 1). The comparative analysis of the levels of CRP, neopterin and IP-10 according to TB status, showed significantly higher levels of all the three biomarkers in Xpert-positive compared to Xpert-negative subjects. Both groups of HIV-infected subjects, with and without TB, had significantly higher levels of all biomarkers compared to control subjects (Table 2).

The potential diagnostic value (sensitivity, specificity, PPV and NPV) of hypothetical screening strategies for TB based on WHO symptoms or of increased levels of neopterin (>10 nmol/L) and CRP (>10 mg/L) is reported in Table 3. The three strategies showed minor and non-significant differences in sensitivity, but were significantly

Table 2
Levels of biomarkers in each group.

	Panel A: HIV-positive, Xpert-positive (*n*: 21)	Panel B: HIV-positive, Xpert-negative (*n*: 122)	Panel C: Controls (*n*: 12)	*P* value, A vs. B	*P* value, A vs. C	*P* value, B vs. C
IP-10 (pg/ml, median, IQR)	1268 (771–1701)	449 (262–735)	120 (107–147)	< 0.001	< 0.001	< 0.001
Neopterin (nmol/L, median, IQR)	50.4 (32.6–86.6)	15.0 (9.5–26.4)	6.5 (5.5–8.4)	< 0.001	< 0.001	< 0.001
CRP (mg/L, median, IQR)	15.7 (6.3–19.2)	1.1 (0.7–1.5)	0.6 (0.6–0.6)	< 0.001	< 0.001	< 0.001

All *p* values: Mann–Whitney *U* test.

different in terms of specificity, with CRP >10 mg/L significantly better than both neopterin >10 nmol/L and WHO-4SS, and with neopterin significantly worse than the other two markers. Negative predictive value was high (> 95%) for all the three strategies, while positive predictive value was much more variable, reflecting the observed differences in specificity (Table 3). We also explored the potential diagnostic value of IP-10 using different thresholds but no threshold showed adequate combinations of sensitivity and specificity (data not shown).

We then explored the correlations that linked each individual biomarker with the other two and with three general markers of health status in people with HIV, represented by CD4 cell count, body mass index and haemoglobin. The results of these correlations are reported in Table 4. Each biomarker showed significant positive correlations with the other two, with the best correlation found between neopterin and IP-10 (R: 0.769, $p < 0.001$). The levels of the three markers were also significantly and inversely correlated with CD4 cell count and haemoglobin, and, although less consistently, with BMI, indicating that biomarkers levels increased significantly with decreasing values of these health status indexes. The possible prognostic value in terms of subsequent mortality for the levels of the three biomarkers, CD4 cell count, age, haemoglobin and BMI is shown in Table 5. Baseline age, haemoglobin and BMI were substantially similar between individuals with and without mortality during follow up, while significant differences were found for CD4 cell count (lower levels associated with mortality) and for IP-10, neopterin and CRP (higher levels associated with mortality, Table 5). Among TB-positive individuals only, the levels of the three markers showed some differences (significant for IP-10 and CRP and close to statistical significance for neopterin) according to the mycobacterial load in sputum, as defined by the semiquantitative Xpert results, with consistently higher levels of the three markers in the presence of higher MTB load (Table 5).

4. Discussion

This study showed that levels of IP-10, neopterin and CRP were significantly associated with pulmonary TB and other clinical outcomes in HIV-infected individuals. In HIV-infected persons from a clinical study, the levels of all the three biomarkers were significantly higher in the presence of pulmonary TB, and were also much higher compared to healthy controls. Using commonly accepted thresholds for the definition of increased levels of neopterin (>10 nmol/l) and CRP (>10 mg/l), both markers performed relatively well in terms of sensitivity compared to the traditionally used WHO four-symptom screening panel for pulmonary TB, but had marked differences in specificity, that was particularly poor for neopterin (27.0%, significantly inferior to both symptom screening and CRP), and very good for CRP (95.1%, significantly superior to both symptom screening and neopterin). Overall, neither increased levels of neopterin nor increased levels of CRP appeared to perform substantially better than WHO-4SS in both sensitivity and specificity. Our data, however, confirming that CRP >10 mg/l has better specificity for pulmonary TB compared to symptom screening [12], suggest that this biomarker might deserve further consideration in screening strategies. A major problem, shown by this and other studies, is represented by the lack of clinical or laboratory indexes that may effectively obtain in screening strategies, alone or combined, 100% sensitivity [12,16].

Despite such limitations, biomarkers can still provide useful information, and in this study their levels were strongly linked not only with presence of TB, but also with other indexes of health status, disease severity and mortality. Together with significant positive correlations among the levels of the three biomarkers, we showed significant inverse correlations of all biomarkers with haemoglobin, and a significant inverse correlation between CRP levels and BMI. Even more importantly, the levels of all biomarkers were higher in HIV-infected patients than in controls, and significantly associated with degree of immune deterioration (CD4 cell counts). This should be taken into

Table 3
Diagnostic value of different indexes as predictors of pulmonary TB (positive Xpert test).

	Xpert-positive	Xpert-negative	*P* value[a]	Sensitivity	Specificity	PPV	NPV
WHO4SS: at least one symptom	18/21, 85.7%	42/122, 34.4%	<0.001	85.7[b,d]	65.6[d,f]	30.0	96.4
Neopterin, >10 nmol/L	20/21, 95.2%	89/122, 73.0%	0.027	95.2[c,d]	27.0[f,g]	18.3	97.1
CRP, >10 mg/L,	16/21, 76.2%	6/122, 4.9%	<0.001	76.2[b,c]	95.1[e,g]	72.7	95.9

[a] Chi-square test or Fisher test
PPV: positive predictive value; NPV: negative predictive value.
[b] WHO-4SS versus CRP >10 mg/L: *p* value for the comparison of sensitivity: 0.688, McNemar test.
[c] CRP>10 mg/L versus Neopterin >10 nmol/L: *p* value for the comparison of sensitivity: 0.127, McNemar test.
[d] WHO-4SS versus neopterin >10 nmol/L: *p* value for the comparison of sensitivity: 0.625, McNemar test.
[e] WHO-4SS versus CRP >10 mg/L: *p* value for the comparison of specificity: <0.001, McNemar test.
[f] WHO-4SS versus neopterin >10 nmol/L: *p* value for the comparison of specificity: <0.001, McNemar test.
[g] CRP>10 mg/L versus Neopterin >10 nmol/L: *p* value for the comparison of specificity: <0.001, McNemar test.

Table 4
Correlations.

	CRP (mg/L)	IP-10 (pg/ml)	CD4 (cells/mm^3)	Haemoglobin (g/dl)	BMI (kg/m^2)
Neopterin (nmol/L)	R: 0.342 *P* < 0.001	R: 0.769 *P* < 0.001	R: −0.340 *P* < 0.001	R: −0.262 *P* = 0.002	R: −0.155 *P* = 0.065
CRP (mg/L)		R: 0.298 *P* < 0.001	R: −0.253 *P* < 0.001	*R*= −0.288 *P* < 0.001	R: −0.285 *P* = 0.001
IP-10 (pg/ml)			R: −0.323 *P* < 0.001	R: −0.285 *P* = 0.001	R: −0.119 *P* = 0.157
CD4 (cells/mm^3)				R: 0.329 *P* < 0.001	R: 0.159 *P* = 0.058
Haemoglobin (g/dl)					R: 0.206 *P* = 0.014

R: Spearman's Rho. All *p* values: Spearman correlation test.

Table 5
Laboratory and clinical markers according to subsequent life status (alive or deceased, all subjects) and to MTB load (as provided by Xpert testing, Xpert-positive subjects only).

	All subjects (*n*: 143)	Alive (*n*: 130)	Deceased (*n*: 13)	*p* value	Low MTB load (*n*: 13)[a]	High MTB load (*n*: 8)[b]	*p* value
IP-10 (pg/ml, median, IQR)	505 (293–945)	502 (263–898)	726 (463–2221)	0.029	793 (609–1452)	1701 (1272–2623)	0.008
Neopterin (nmol/L, median, IQR)	16.7 (10.5–34.4)	16.6 (9.6–30.9)	34.4 (14.9–98.6)	0.011	46.6 (17.0–67.8)	65.3 (46.9–121.6)	0.089
CRP (mg/L, median, IQR)	1.15 (0.75–2.20)	1.14 (0.73–1.83)	1.44 (1.17–13.0)	0.032	11.7 (1.7–17.7)	17.2 (14.5–23.5)	0.043
CD4 count (cells/mm^3, median, IQR)	194 (122–326)	199 (137–354)	102 (70–195)	0.004	142 (94–176)	117 (58–281)	0.800
Age (years, median, IQR)	36 (29–43)	36 (30–43)	40 (27.5–52.5)	0.380	38.0 (31.5–41.0)	41.0 (30.2–48.5)	0.327
Haemoglobin (g/dl, median, IQR)	11.4 (10.1–13.1)	11.5 (10.1–13.2)	10.9 (9.6–12.7)	0.390	9.5 (7.9–12.2)	9.4 (9.0–11.3)	0.800
Body mass index (Kg/m^2, median, IQR)	21.0 (19.1–24.3)	21.1 (19.1–24.3)	20.8 (16.9–23.1)	0.279	19.6 (17.6–20.8)	18.0 (17.3–19.7)	0.355

[a] Low MTB load: Xpert level: low or very low.
[b] High MTB load: Xpert level: intermediate or high. All *p* values: Mann–Whitney *U* test.

account when considering biomarkers as diagnostic tools for TB in HIV-infected patients. It should be also noticed that levels of biomarkers were strongly associated with subsequent mortality, and (for IP-10 and CRP) with mycobacterial load in sputum. The association with mortality, already described by Bedell et al. for CRP [17], indicates a strong prognostic potential that should be further explored. The association with mycobacterial load in sputum, although limited to a small number of cases, and significant only for IP-10 and CRP, is consistent with the results of other studies [18,19], and indicates that even within the group of individuals with pulmonary TB, significant differences can be found in biomarker levels according to severity and, possibly, transmissibility of TB disease.

5. Conclusions

In summary, this study provided a comprehensive evaluation of three commonly used biomarkers of immune activation and inflammation in HIV-infected individuals with and without TB. Despite the limitation of a relatively small sample size, this study showed several significant associations of potential clinical and pathogenetic relevance. The observed findings may represent the basis for subsequent clinical and operational research, particularly in the identification of effective screening strategies for TB, that represent a strong and urgent health priority.

Acknowledgments

This work was possible thanks to the dedication of professor Massimo Amicosante who made a substantial contribution in designing this study. Professor Amicosante passed away in Sophia, Bulgaria on 1 October 2017 and didn't get to see the full results of the study.

Massimo was a respected scientist, devoted to understanding and designing experimental diagnostics for HIV, tuberculosis, berylliosis and cystic echinococcosis. He accompanied the earlier steps of this study with generosity and kindness.

This work is dedicated to his memory.

References

[1] UNAIDS. Fact sheet November 2016, Global HIV Statistics; 2016. Available at: http://www.unaids.org/en/resources/fact-sheet. Accessed April 4, 2017.
[2] WHO. Global Tuberculosis Report 2018; 2018. Available at: http://www.who.int/

tb/publications/global_report/en/. Accessed November 4, 2018.
[3] Ford N, Matteelli A, Shubber Z, et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis. J Int AIDS Soc 2016;19(1):20714. https://doi.org/10.7448/IAS.19.1.20714.
[4] Burki TK. The global cost of tuberculosis. Lancet Respir Med 2018;6:13https://doi.org/10.1016/S2213-2600(17)30468-X.
[5] Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2014;1:33–6. https://doi.org/10.1002/14651858.CD009593.pub3. CD009593
[6] Shah M, Hanrahan C, Wang ZY, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults. Cochrane Database Syst Rev 2016;5:32–4. https://doi.org/10.1002/14651858.CD011420.pub2. CD011420
[7] Wasserman S, Meintjes G. The diagnosis, management and prevention of HIV-associated tuberculosis. S Afr Med J 2014;104(12):886–93.
[8] Manosuthi W, Wiboonchutikul S, Sungkanuparph S. Integrated therapy for HIV and tuberculosis. AIDS Res Ther 2016;13(1):22. https://doi.org/10.1186/s12981-016-0106-y.
[9] Orlando S, Triulzi I, Ciccacci F, et al. Delayed diagnosis and treatment of tuberculosis in HIV+ patients in Mozambique: a cost-effectiveness analysis of screening protocols based on four symptom screening, smear microscopy, urine LAM test and Xpert MTB/RIF. PLoS One 2018;13(7):e0200523https://doi.org/10.1371/journal.pone.0200523. Published 2018 Jul 19.
[10] Wallis RS, Maeurer M, Mwaba P, et al. Tuberculosis-advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers. Lancet Infect Dis 2016;16(4):e34–46. https://doi.org/10.1016/S1473-3099(16)00070-0.
[11] Chegou NN, Sutherland JS, Malherbe S, et al. Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB. Thorax 2016;71(9):785–94. https://doi.org/10.1136/thoraxjnl-2015-207999.
[12] Yoon C, Semitala FC, Atuhumuza E, et al. Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study. Lancet Infect Dis 2017;17(12):1285–92. https://doi.org/10.1016/S1473-3099(17)30488-7.
[13] Floridia M, Ciccacci F, Andreotti M, et al. Tuberculosis case finding with combined rapid point-of-care assays (Xpert MTB/RIF and determine TB LAM) in HIV-positive individuals starting antiretroviral therapy in mozambique. Clin Infect Dis 2017;65(11):1878–83. https://doi.org/10.1093/cid/cix641.
[14] World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011. (WHO/HTM/TB/2011.11).
[15] Skogmar S, Schön T, Balcha TT, et al. Plasma levels of neopterin and C-reactive protein (CRP) in tuberculosis (TB) with and without HIV coinfection in relation to CD4 Cell Count. PLoS One 2015;10(12):e0144292https://doi.org/10.1371/journal.pone.0144292.
[16] Yoon C, Davis JL, Cattamanchi A. C-reactive protein and tuberculosis screening: a new trick for an old dog? Int J Tuberc Lung Dis 2013;17(12):1656. https://doi.org/10.5588/ijtld.13.0579.
[17] Bedell RA, van Lettow M, Meaney C, et al. Predictive value of C-reactive protein for tuberculosis, bloodstream infection or death among HIV-infected individuals with chronic, non-specific symptoms and negative sputum smear microscopy. Trop Med Int Health 2017;23(3):254–62. https://doi.org/10.1111/tmi.13025.
[18] Wergeland I, Pullar N, Assmus J, et al. IP-10 differentiates between active and latent tuberculosis irrespective of HIV status and declines during therapy. J Infect 2015;70(4):381–91. https://doi.org/10.1016/j.jinf.2014.12.019.
[19] García-Basteiro AL, Mambuque E, den Hertog A, et al. IP-10 kinetics in the first week of therapy are strongly associated with bacteriological confirmation of tuberculosis diagnosis in HIV-infected patients. Sci Rep 2017;7(1):14302. https://doi.org/10.1038/s41598-017-13785-3.