Full paper

SLAM Project – Second-Level Diagnostic Assessment: Multidisciplinary approach to HIV Patients

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Running title: SLAM Project: a multidisciplinary approach to HIV infection

SUMMARY

The aim of the study is to propose a multidimensional second-level diagnostic assessment to allow follow-up in the event physicians observe the presence of risk factors and/or active co-morbidities in HIV-infected patients. To develop our proposal, we chose the Delphi method that has been used for about 30 years in the healthcare field. The CISAI Group (Coordinamento Italiano per lo Studio dell'Allergia in Infezione da HIV) conducted this study. The first phase of the study provided identification of the questionnaire for second-level diagnostic assessment of HIV-infected patients.

From March to July 2018 the questionnaire was submitted to 48 experts from 10 Italian HIV-dedicated sites. The questionnaire consisted of 102 items divided into 7 survey areas. The results can be summarized as follows: infectious disease diagnostics, 18 items reached

agreement in 9 cases; osteoporosis diagnostics 12 items with 3 agreements; metabolic and cardiovascular diagnostics 13 items with 4 agreements; nephrology diagnostics 19 items with 8 agreements; hepatology diagnostics 12 items with 9 agreements; CNS diagnostics: 18 items with 7 agreements; psychological diagnostics and quality of life assessment (QoL) 10 items with no agreement.

If these considerations are confirmed in required discussions and in-depth analyses, they will be able to produce an important indication in the drafting of national guidelines.

Key words: HIV infection, Delphi Method, Multidimensional second-level diagnostic assessment

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INTRODUCTION

Due to the introduction of high-efficacy therapy with reduced adverse events, HIV infection can now be considered a chronic disease. It is quite clear that this involves a radical change in the approach to treatment and to the follow-up offered to patients. The evaluation of treatment effectiveness is obviously still fundamental, but immediately after that, the physician should focus on monitoring co-morbidities. As known, the increase of the interest, both in research and clinical practice with regard to co-morbidities, is a consequence of two different problems. First, successful treatments allow HIV-infected patients to grow older, facing the onset of age-related diseases; then, it has been demonstrated that HIV, through the activation of inflammatory mechanisms, increases the risk of co-morbidities and anticipates their onset, as compared to age-comparable HIV-negative subjects.

In light of this recently acquired information, a debate has started among infectious disease specialists on the best strategies to apply, in order to manage co-morbidities and prevent organ damage.

There are a few well-established instruments to address these issues. The Delphi method, in particular, has already been used in the infectious diseases area, in a survey carried out among specialists treating HIV-infected subjects. The Delphi method is typical of social studies. It originated in the 1960s and has been used for about 30 years in the healthcare field and in clinical research as well (Njuangang et al., 2017). According to this methodology, a selected number of experts are asked to anonymously express their opinion on a given topic, in order to conduct a wide survey and an extensive comparison of experiences. This consensus statement was developed using the RAND/UCLA Appropriateness Method process (Bourrée et al., 2008). Indeed, this method allows comparison of opinions of selected national experts and scientific evidence available in the literature. There is no intercommunication among the experts, and opinions are individual and anonymous. The quantification of aggregated opinions is systematically given back to participants, always combined and in an anonymous way. In this way, the quality of judgement is free of any hierarchical bias and effectively represents the combination of each participant's opinions.

The Delphi method is useful when an organized exchange of opinions between experts is needed: several studies (Boulkedid et al., 2018; Nguyen-Lu et al., 2015; Cummins et al., 2018) have shown that it is the most effective way of exploring a problem and assessing all possible solutions. The Delphi method is a decision-making method and does not provide

further knowledge. It combines common knowledge in order to better address situations where several alternative choices are possible.

The first experiences using the Delphi method were in the cardiovascular field (Normand et al., 1998); recently it has been proposed in the fields of Dermatology (Lapadula et al., 2016) and Rheumatology (Todoerti et al., 2018). As for the Infectious Diseases area, the only experience was that recently described by Borderi et al. (2018).

This study defined a selection of tests to carry out as a first-level diagnostic assessment, as part of a strategy of evaluation of co-morbidities. Starting from these results, we continued to work along these lines, suggesting additional discussion on ways to further investigate co-morbidities, when actual risk factors or abnormalities in first-level tests have emerged. Our survey originated from this need.

The CISAI Group conducted this study. A Scientific Committee was set up, composed of four Italian experts in HIV related diseases clinical studies.

The aim of our study was to propose a multidimensional second-level diagnostic assessment to complete the Borderi et al. study on first-level assessments (2018). In that paper, panelists were asked to choose which items (among medical history, physical examination and diagnostic assessment) they deemed necessary to correctly address an HIV-infected patient at baseline.

In this second phase, we aimed at enabling the necessary follow-up, in the presence of risk factors and/or active co-morbidities in HIV-infected patients.

In a second phase of our project, we aimed at assessing the availability of diagnostic tests at centers participating in our survey. We also aimed at evaluating the tendency of HIV-specialists to involve other specialists in the management of their patients, specifying when a multidisciplinary approach of co-morbidities is needed.

MATERIALS AND METHODS

Study Design

To develop our proposal for an assessment, we chose the Delphi method to define a second-level diagnostic assessment of HIV-infected subjects to evaluate risk factors and co-morbidities. Therefore, we performed a Delphi poll and subsequently submitted the obtained results to a restricted panel of 48 experts from 10 different dedicated HIV centers in Italy.

Identification of the questionnaire

The first phase of the study provided the identification of the questionnaire for the second-level diagnostic assessment of HIV-infected patients. In the study by Borderi et al. (2018),

the drafting process of a very detailed questionnaire made up of both first and second-level items was described and the bibliography used as reference was indicated.

Our Delphi process examined only those items related to a second-level diagnostic assessment and considered the same the bibliographic results and first-level diagnostic algorithm obtained from the previous study's results (Table 1) as a starting point. In order to identify the questionnaire to submit to specialists, we started from the second-level items that had already been identified by the panel that dealt with the first-level study, but that had not yet been evaluated.

These items were reviewed and partially edited by the CISAI Group's Scientific Committee according to the most recent literature regarding comorbidities (Ballocca et al 2017; Bigna et al. 2017; Chazot et al. 2017; Brown et al. 2017; Swanepoel et al. 2018; Rockstroh 2017).

Selection of the national panel of experts

Panelists were selected according to their competence and experience. Participation in the study was proposed to 50 physicians from 10 Italian HIV-dedicated sites; 48 specialists agreed to participate. Therefore, the panel is representative of our national reality and expresses many years of experience in the field. Only 10% of the specialists who collaborated in this second working phase had previously participated in the first-level questionnaire.

Levels of aggregation of the consensus were assessed on each of the items selected during the first phase. Every participant had access to the project's web platform, and received all the necessary information regarding the project itself, such as a selection of bibliography, a synopsis of the study and the description of the Delphi method. The procedure involved two administrations of the questionnaire.

The survey

From March to July 2018, the questionnaire was submitted to the 48 experts who had agreed to participate in the study. The process took place online and provided, in case of non-response, at least two reminders via e-mail and as many by telephone. At the end of the project, all 48 experts had responded to first round of questions and 45 of them (94%) to the second one. Panelists were asked about what they considered useful for a second-level diagnostic assessment of HIV-positive patients. In evaluating each item individually each panelist referred to both his own experience or clinical judgement and to the scientific evidence in the literature.

The questionnaire consisted of 102 items divided into 7 survey areas: infectious diseases, osteo-articular, metabolic and cardiovascular, nephrology, hepatology, Central Nervous System (CNS), psychological diagnostics and quality of life assessment.

In the first round of the Delphi poll, panelists answered the following question for each item: "According to your experience as an infectious disease specialist, and to data available today on HIV-infected patients for whom a second-level diagnostic investigation is necessary, how relevant do you deem the following procedures for a 360-degree evaluation, that also takes into consideration risk factors and co-morbidities? – Please take a look into the project materials, in particular to the first-level tests, before offering your opinion on second-level diagnostic assessments".

The answers were distributed on a 1-9 Likert Scale, where 1=definitely not useful and 9=certainly useful. Intermediate values corresponded to different modulations of judgement: non-utility (2,3), doubtful utility (4-6) and utility (7-9).

The concept of consensus within a group was defined as homogeneity or consistency of opinion among the experts. The criteria of agreement and disagreement among experts was defined as previously described by Brook (1994) and Fitch (2001). In an attempt to anticipate the problem of how to deal with panels composed of more or fewer than nine members, the RAND/UCLA appropriateness method translated the definitions into a "somewhat statistical form," framed as tests of hypotheses on the distribution of ratings in a hypothetical population of repeated ratings by similarly selected panelists. By this definition, to define agreement we tested the hypothesis that 80% of the hypothetical population of repeated ratings were within the same region (1-3, 4-6, 7-9) as the observed median. If we were unable to reject that hypothesis on a binomial test at the 0.33 level, the indication was rated "with agreement." To define disagreement, we tested the hypothesis that 90% of the hypothetical population of repeated ratings were within one of two extra-wide regions (1-6 or 4-9). If the hypothesis was rejected on a binomial test at the 0.10 level, we concluded that the indication was rated "with disagreement."

In conclusion we defined:

1) Agreement -80% of panelists ratings inside one of the 3-point regions (1-3, 4-6, 7-9);

2) Disagreement -90% of panelists ratings within one of two extra-wide regions (1-6 or 4-9).

This level of consensus was decided "a priori." The assessments were evaluated for internal consistency and aggregated to obtain a composite judgment.

The results of the poll were discussed by the Scientific Committee, according to criteria of clinical appropriateness and sustainability.

Statistical analysis calculations were performed using the Microsoft Office software package. A database containing all answers from the panelists was created using an MS Excel sheet. Subsequently, aggregation for each answer (from 1 to 9) and aggregation intervals in percentage were calculated. Lastly, an assessment of agreement and/or disagreement was conducted.

In the second round, the panelists were informed of each procedure rating at the first-round reporting and asked to rate each procedure again. The evaluations of agreement and disagreement were repeated as previously described.

RESULTS

We analyzed the results related to the 102 items, summarized as follows:

- Infectious disease diagnostics: 18 items reached agreement in 9 cases
- Osteoporosis diagnostics: 12 items with 3 agreements
- Metabolic and cardiovascular diagnostics: 13 items with 4 agreements
- Nephrology diagnostics: 19 items with 8 agreements
- Hepatology diagnostics: 12 items with 9 agreements
- CNS diagnostics: 18 items with 7 agreements (6 in the first round and 1 in the second)
- QoL evaluation: 10 items with no agreement

There were no significant differences between the first and the second round; only one item went from disagreement to agreement. Therefore, we decided not to proceed with a third round of evaluation. The overall results of the consensus path are shown in Table 2-8.

DISCUSSION

In this study, the participating physicians agreed on less than 50% of items, with marked differences among survey areas. Hence, a discussion by diagnostic areas seems opportune.

Second-level infectious disease diagnostics

Co-infection screenings were highly favored, as well as screening for neoplasms. This probably reflects an increasing awareness, especially towards neoplastic diseases, whose incidence is rising in recent years. On the contrary, Chest X-ray and CT scan did not reach the agreement; equally HIV-DNA, TDM for patients on ARV treatment, coreceptor tropism assay and extensive evaluation of lymphocytes subsets were not validated.

Second-level osteo-articular diagnostics

Only 3 out of 12 proposed items obtained agreement; these were lumbar spine and femoral neck DXA and MRI scans to order in case of suspected osteonecrosis. Infectious diseases

specialists have got to know and fully understand these diagnostic test (DXA in particular) in the last few years. The Calcaneal QUS did not reach agreement, neither as a preliminary test to select patients as candidates for DXA scans, nor as an estimate of fracture risk. This could reflect the fact that data available on this test is scanty and inconclusive. Second-level tests and hormonal assays in women have not been approved.

Second-level cardiovascular diagnostics

Only four tests (out of 13), considered standard second-level assessment in clinical practice, reached agreement. A further step should be to evaluate whether disagreement or missing opinions regard tests not widely available, or needing a specialist's prescription. It is likely that the assessment of agreement and disagreement consistently reflected what can be done in clinical practice and what has immediate impact on patients' care.

Second-level nephrology diagnostics

GFR calculation, kidney ultrasound and proteinuria assays reached agreement. Second-level immunological tests and a series of tests to evaluate kidney function, such as urinary cystatin C and retinol binding protein, did not reach consensus, since they were probably more useful for research, rather than for clinical practice.

Second-level hepatic diagnostics

In this case, physicians agreed on most of the proposed items. This clearly reflected the overlapping of infectious disease specialist and referring specialist.

Second-level CNS diagnostics

Second-level tests, that infectious disease specialists usually order and interpret, such as CSF testing, CT scans, and MRI scans, reached agreement in the first round, whereas the Neurological Exam reached agreement in the second round. On the contrary, exams that are not considered second-level diagnostic assessments, but for which the infectious disease specialist has no interpretative competence and whose results do not immediately impact the clinical practice, did not reach agreement.

Second-level Psychological diagnostics and Quality of Life evaluation

In this case, none of the items reached agreement in the first round, and this result was confirmed in the second round as well. These results emerged despite the fact that, as for the CNS diagnostic items, there is a considerable debate in the scientific community on the need to "objectively" evaluate the psychological aspect and the quality of life of HIV-infected patients. As for CNS items, these results might be due to the fact that these assessments

involve complex tests, sometimes very demanding and time-consuming for both physicians and patients, and difficult to interpret outside a highly specialized field.

Considering the priorities indicated by panelists filling out the questionnaire, a substantial adherence to the Italian guidelines emerges. Most of the assessments evaluated with "dispersed opinions" are indeed rated with a level B of evidence in the guidelines, therefore as assessment to take into consideration but not strongly recommended. It is likely that the dispersion of opinions is related to the features of each panelist's Infectious Diseases site of origin, rather than being related to the availability of the assessment or the type of activity done at the site (assistance or clinical research as well).

Either way, the evaluations of agreement and disagreement in general seem to consistently reflect what is needed to address patients' issues in a strictly operational way and to guide further investigations or possible solutions.

It is likely that whilst evidently taking into account the issue of comorbidities, the Infectious Diseases specialist feels the need for a practical, multi-disciplinary approach to comorbidities - at least in clinical practice -, therefore providing a better appropriateness of prescription.

Limits of the study

As previously mentioned in the introduction, the Delphi method has recently been used in the Cardiovascular, Rheumatology and Dermatology areas (Lapadula et al., 2016 – Todoerti et al., 2018). In the Infectious Diseases field the only experience – quoted several times – was Borderi et al (2018). In that paper the authors investigated the first-level diagnostic assessment of HIV-infected patients, whereas our work aimed to define the clinical approach to patients for whom one or more risk factors for comorbidities were identified during a first-level assessment.

For these reasons we are not able to discuss a comparison between our data and other experiences'.

Conclusions

Surely physicians who participated in our study carefully considered the monitoring of co-morbidities in HIV-patients' follow-up. The general attitude seemed to favor evaluations and examinations with direct impact on clinical practice, useful to classify patient's issues and to orientate further investigation or possible solutions.

As anticipated, a further step will be evaluating which tests were actually available at participating centers, and if physicians thought that prescription was to be done by

themselves or by the referring specialist. This further assessment should provide better interpretative criteria for our findings.

Considering that aging HIV patients are likely to develop one or more co-morbidities, HIV specialists will be more and more in need of a multidisciplinary approach to ensure the appropriateness of prescription and the best management of patients' concomitant pathologies.

If our considerations are confirmed as part of necessary discussions and in-depth analysis, they will be able to produce an important indication in the drafting of national guidelines.

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Table 1 Criteria for bibliografic research (From Borderi et al. 2018)

Area	*Article*	*From*	*To*
CV	88	2011	2015
DIA	21	2009	2015
OST	21	2011	2015
CKD	74	2011	2015
CNS	73	2011	2015
HD	37	2011	2015

CV: Cardiovascular: DIA: General Diagnostic; OST: Osteo-articolar ;CKD: Chronic Kidney Diseases; CNS: Central Nervous System; HD: Hepatic Diseases

Table 2. General diagnostics results

General diagnostics	**Item***
Immunologic diagnostics	***HLA-B5701****
	Extensive analysis of lymphocyte subsets
Screening for co-infections	***HAV****
	Quantiferon*
	HPV*
	HZV
	HSV
	EBV
Screening for cancer	***Mammography****
	PAP-Test*
	Anoscopy with PAP-Test (MSM)*
	Total and free PSA*
	Alpha-fetoprotein*
	Chest X-ray
	Chest CT Scan
Virologic diagnostics	HIV-DNA
	Coreceptorial tropism test
Drug test	TDM (for patients on HAART therapy)

HAV: Hepatitis A Virus; HPV: Human Papilloma Virus; HZV: Herpes Zoster Virus; EBV: Epstein Barr Virus; TDM: ; HAART: Highly Active Anti-Retroviral Therapy. * **Bold lettering** indicate items showing agreement among survey participants.

Table 3. Osteo-articolar results

Osteo-articolar diagnostics	**Item***
BMD assessment	***Lumbar DXA Scan****
	Femoral neck DXA Scan*
Osteonecrosis diagnosis	***MRI Scan****
Estimate of fracture risk	DeFRA
	Calcaneal QUS
Exclusion of other causes of secondary osteoporosis	Second-level blood tests
Estimated fall risk	Estimated fall risk through an algorithm
Calcium intake	Dietary calcium intake
Menopause, hormonal changes	Hormonal assay
Search for osteoporosis/vertebral fracture	Type of pain
Search for vertebral fracture	Morphometric X-ray according to Gennant
Screening for DXA	Calcaneal QUS

BMD: bone mineral density; DXA: Dual X-ray Absorptiometry; QUS: quantitative ultrasound; * **Bold lettering** indicate items showing agreement among survey participants.

Table 4: Cardiovascular results

Cardiovascular diagnostics	**Item***
Risk factors for CVD	***HbA1c****
CVD risk estimate	***ASCVD Risk Score****
	ECG*
	IMT*
Vascular damage assessment	Insulinemia
	IL-6
	hsPCR
	Fibrinogen
	D-dimer
	Homocystein
	Flow-mediated Dilation Test
	Ankle-brachial pressure index
	CAC Score

CVD:Cardiovacular Diseases ; HbA1c: Hemoglobin A1c ; ASCVD Risk Score: Atherosclerotic Cardiovascular Disease Risk Score ; ECG:Electrocardiogram; IMT:Intima-media thickness ; CAC Score: Coronary Artery Calcium Score ; * **Bold lettering** indicate items showing agreement among survey participants.

Table 5: Nephrology results

Nephrology diagnostics	**Item***
Glomerular function	***eGFR Calculation with MDRD Equation****
	eGFR Calculation with Cockcroft-Gault Equation*
	Micro-albuminuria*
	Kidney Ultrasound*
Loss of protein	***24-hour urine collection****
	Protein/Cr urine ratio*
	Albumin/Cr urine ratio*
Nephrolithiasis	***Kidney Ultrasound****
Exclusion of other causes of nephropathy	IgG
	Complement
	ANA
	ASMA
	Urine protein electrophoresis
Proximal tubule function	Urinary C Cystatin
	TmPO4/GFR
	Retinol Binding Protein
	Beta 2 microglobulin
	Aminoaciduria
IR risk estimate	Renal artery resistive index

eGFR: Glomerular Filtration Rate ; MDRD: Modification of Diet in Renal Disease ; Cr Urine ratio: Creatinine Urine Ratio ; IgG:Immunoglobulin G ; ANA: Antinuclear Antibody; ASMA: Anti-Smooth Muscle Antibodies; TmPO4/GFR: renal Tubular reabsorption of Phosphate to Glomerular Filtration Rate; * **Bold lettering** indicate items showing agreement among survey participants.

Table 6: Liver diagnostics results

Liver diagnostics	**Item***
Fibrosis assessment	***Fibroscan****
Cirrhosis assessment	***MELD****
	EGD for varices assessment*
Screening for HCC	***Alpha-fetoprotein****
Follow-up on HBV and HCV treatment	***HBV-DNA****
	HCV-RNA*
	HBV drug resistance*
	HCV genotype*
	HDV*
Exclusion of non-hepatic causes oh hyper-ALT/AST	History of hemochromatosis, celiac disease, myopathy

MELD:Model for End-Stage Liver Disease; EGD: EsophagoGastroDuodenoscopy; HBV:Hepatitis B Virus; HCV: Hepatitis C Virus; HDV:Hepatitis D Virus; * **Bold lettering** indicate items showing agreement among survey participants.

Table 7: CNS results

CNS diagnostics	Item*
Exclusion of other neurological diseases	***CT Scan****
	MRI Scan*
	Cerebrospinal Fluid (CSF) Testing*
	Neurologic physical examination*
	Assessment of other neurological disease*
Assessment of viral escape in asymptomatic patients	***CSF HIV-RNA****
	CSF cell count*
	CSF drug resistance*
	Vascular dementia
	Alzheimer's disease
	Other neurodegenerative diseases
	Outcomes of CNS cancer
	Cranial trauma
Screening for HIV-related cognitive disorder	IHDS
	MODA
Assessment of HIV-related cognitive disorder	MoCA
	CogState
Drug test	HAART drugs CSF assay

CNS: Central Nervous System; CT Scan:Computed Tomography Scan, ; MRI Scan: Magnetic Resonance Imaging Scan; IHDS: International HIV Dementia Scale; MODA: Milan Overall Dementia Assessment; MoCA: Montreal Cognitive Assessment ; HAART:Highly Active Anti-Retroviral Therapy ; * **Bold lettering** indicate items showing agreement among survey participants.

Table 8: PSI-QoL results

PSI-QoL diagnostics	**Item***
Quality of Life Evaluation	ISS-QOL
	MOS-HIV
	EQ-5D
	WHOQOL-HIV-Bref
	FAHI
	SF36/12
Screening for depressive symptoms	CESD
	CES-D10
	Patient Health Questionnaire Depression Scale (PHQ9)
	Generalized Anxiety Disorder (GAD)
	CES-D10

PSI-QoL: Prolapse Symptom Inventory and Quality-of-Life Questionnaire : ISS-QOL:ISS Quality of Life Questionnaire ; MOS-HIV: HIV Medical Outcomes Survey ; EQ-5D: Euro Quality of Life-5D ; WHOQOL-HIV-Bref: WHO Quality of Life brief for HIV patients ; FAHI: Functional Assessment of HIV Infection ; SF36/12: The Short Form 36 and 12 Composite Scores; CESD and CES-D10: Center for the Epidemiological Studies of Depression Short Form ; * **Bold lettering** indicates items showing agreement among survey participants.