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FULL PAPER

Managing the long surviving HIV patient: a proposal for a multidimensional first-level diagnostic assessment

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SUMMARY

We propose a multidimensional first-level diagnostic assessment easy to use in routine clinical practice to allow infectious disease specialists to have a general and complete overview of persons living with HIV. Following the Delphi method, articles published from January 1, 2011 on controlled trials, clinical reports and observational studies dealing specifically with HIV and its co-morbidities were selected for review by the authors. Participants in the poll were selected among clinicians and infectious diseases specialists, working in 38 different dedicated HIV centres in Italy. The participants were given access to a website dedicated to the project and received a standardized information package containing a synopsis of the study and a description of the Delphi process and the selected literature. A total of 131 Items were divided into 10 first-level survey areas: anamnesis, objective examination, infectious diseases, osteoporosis diagnosis, metabolic pathologies diagnosis, cardiovascular diagnosis, nephrologic diagnosis, hepatological diagnosis, central nervous system diagnosis, evaluation of quality of life (QoL). This simple and concise first level tool identifies a few areas of multi-organ diagnostic assessment beyond the infectivity area. The identification of these areas will allow us to find shared and validated evaluation procedures with the intent to increase the likelihood of early recognition of patients at risk of comorbidity development, in order to facilitate more effective prevention, thereby reducing the overall impact on the quality of life of patients affected by this chronic illness.

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INTRODUCTION

HIV infection has become a chronic disease. The development of new therapies and the ever better quality of care have allowed a significant reduction in morbidity and mortality associated with the infection (Lohse *et al.*, 2007). The consequence of such success is the substantial increase in persons living with HIV (PLWHIV) who are now part of the working population and live normal lives. However, the presence of the virus not only often accelerates and makes other diseases more serious, but also exposes PLWHIV to a greater risk of comorbidities than age comparable HIV-negative subjects (Guaraldi *et al.*, 2011). As a consequence, therapeutic strategies for a chronic disease should take this new scenario into account. Indeed, pharmacological research should try to provide new drugs able to control or hopefully to eliminate the infection, but also more tolerable in the long term. Moreover, to reduce toxicities, the use and combination of drugs already available could differ from the past. The objective of old and new treatment strategies for PLWHIV should be a better quality of life. Indeed, a patient treated properly and as early as possible represents a resource not only for himself, but also for the community. In order to achieve this, the management of comorbidities should be as timely and as early as possible. The only way to obtain this is to facilitate and broaden the awareness of infectious disease specialists regarding a comprehensive approach to comorbidity management in PLWHIV. To this end, we propose a discussion among experts on the best strategies to prevent

Key words:
PLWHIV Management, Delphi method, Survey, Multidimensional first-level diagnostic assessment.

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and manage comorbidities and organ damage (liver, SNC, heart, bone and kidney). The aim of the project was to offer infectious disease specialists an appropriate algorithm for monitoring the health of these patients beyond the control of HIV viral load. The chosen tool, to support the discussion was a Delphi survey among Italian HIV specialists.

Objective

To propose a multidimensional first-level diagnostic assessment easy to use in routine clinical practice to allow infectious disease specialists to have a general and complete overview of PLWHIV.

MATERIALS AND METHODS

Study design

The Delphi method, originated in the 1960s, takes its name from the Delphic oracle's skills of interpretation and foresight (Njuangang *et al.*, 2017). It was developed at the RAND Corporation to obtain the most reliable consensus of opinion of a group of experts on a subject in a systematic manner (Matheson, 1982). It attempts to do this by a series of well-defined questionnaires based on surveys and feedback. This consensus statement was developed using the RAND/UCLA Appropriateness Method process (Bourrée *et al.*, 2008). This method is a formal group judgment process which systematically and quantitatively combines expert opinion and scientific (systematic literature review) evidence by asking panellists to rate, discuss, and then re-rate indicators. There is no intercommunication among the experts. It is the only systematic method of combining expert opinion and evidence. We performed a Delphi poll and subsequently submitted the obtained results to a restricted panel of 38 experts.

Delphi questionnaire preparation

Articles published from January 1, 2011 on controlled trials, clinical reports and observational studies dealing specifically with HIV and its co-morbidities were selected for review by the authors. All were identified by a MEDLINE systematic search up to and including *August 2015, using the MESH keywords "HIV", "comorbidity", "risk factors in HIV" and "complication"* (*Table 1*).

At this stage, the material obtained was used to set up the Delphi questionnaire. The identified diagnostic procedures (items of the questionnaire) were divided according to the area of competence (e.g. cardiology etc.) and for each item the following question was set up: "According to you, how relevant is this procedure for a *first-degree assessment (respectively second-degree assessment) of comorbidities in HIV patients?"* (*Table 2*).

Selection of expert panel size and composition

Participants in the poll were selected among clinicians and infectious diseases specialists working in 38 different dedicated HIV centres in Italy. 38 specialists finally agreed to take part in the poll. The participants were given access to a website dedicated to the project and received a standardized information package containing a synopsis of the study and a description of the Delphi process and the selected literature.

The survey

Between May 2016 and January 2017, the definitive list of diagnostic procedures in the questionnaire was submitted to 38 infectious diseases specialists throughout Italy. The steering committee planned to perform at least two Delphi rounds. The consensus process was conducted on line. Two reminders were sent at each round in case of non-response. This group responded using the Likert scale and the percentages were recorded. The experts assessed each procedure using a score ranging from 1 to 9 based on increasing appropriateness. The question posed to experts was: How important do you consider the information obtainable from diagnostics for items on the area displayed in *Table 2*, in the evaluation of the patient with HIV infection?

Table 1 - *Criteria for bibliographic research.*

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

Table 2 - *Items by clinical area.*

Area	*ITEMs first-degree assessment*	*ITEMs second-degree assessment*
Medical History	42	
Physical Examination	11	
Infectious disease diagnosis	14	18
Osteoarticular diagnostics	7	12
Metabolic diagnostics	7	5
Cardiovascular diagnostics	8	12
Nephrology Diagnostics	13	18
Hepatic diagnosis	14	18
CNS diagnostics	11	17
Psycho Diagnostics and Quality of Life	3	4
Management of risk factor	14	
Total	144	104

Data on Delphi results

In the first Delphi round, each member of the panel evaluated the clinical relevance of each of the diagnostic procedures on a 9-point scale. For each procedure, the experts were asked to answer the following question: "According to you, how relevant is this procedure for a first-degree assessment of comorbidities in HIV patients?". A 9-point scale with the anchors "not relevant at all" at 0 and "extremely relevant" at 9 was used to record the responses. Experts were also invited to suggest additional procedures, not included in the questionnaire, which they nonetheless deemed appropriate for HIV patients in a first stage screening procedure.

They were added at the subsequent round provided the medical specialist in the respective field did not consider them redundant because of already existing similar procedures.
In the second round, the experts considered the same diagnostic procedure, and were also informed of each procedure rating at the first round reporting. The experts were asked to rate each procedure again in light of the responses at the first round. 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 were defined as previously described (Brook, 1994; Fitch *et al.,* 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 panellists.
By this definition to define agreement we test the hypothesis that 80% of the hypothetical population of repeated ratings are within the same region (1-3, 4-6, 7-9) as the observed median. If we are unable to reject that hypothesis on a binomial test at the 0.33 level, we say that the indication is rated "with agreement".
Whereas to define disagreement we test the hypothesis that 90% of the hypothetical population of repeated ratings are within one of two extra wide regions (1-6 or 4-9).

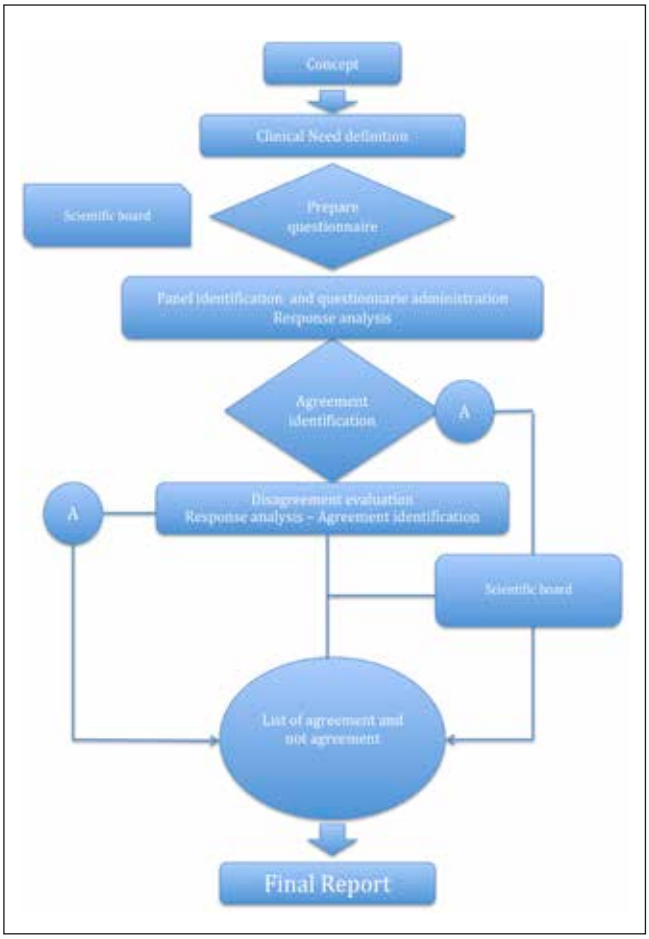

Figure 1 - *Delphi flow-chart.*

If we have to reject that hypothesis on a binomial test at the 0.10 level, we conclude that the indication is rated "with disagreement".
In conclusion we define:
1) Agreement -80% of panellists rating inside one of the 3-point region (1-3, 4-6, 7-9);
2) disagreement -90% of panellists ratings are within one of two extra wide regions (1-6 or 4-9).

This level of consensus was decided a priori. Different conditions of agreement and disagreement described above were rejected or modified. The collected assessments were evaluated for internal consistency and aggregated to obtain a composite judgment.
The results of the poll were discussed by the Steering Committee, according to criteria of clinical appropriateness and sustainability.

Statistical analysis

Calculations were performed using the Microsoft Office software package.

RESULTS

A total of 131 Items were divided into 10 first-level survey areas: anamnesis (42 items of which 21 in agreement), objective examination (12 items, 8 of which in agreement), infectious diseases (14 items, 9 of which in agreement), osteoporosis diagnosis (7 items, 5 of which in agreement), metabolic pathologies diagnosis (7 items, 6 of which in agreement) - cardiovascular diagnosis (8 items, 5 of which in agreement) nephrologic diagnosis (14 items, 9 of which in agreement), hepatological diagnosis (14 items, 13 of which in agreement), central nervous system diagnosis (11 items, 8 of which in agreement), evaluation of quality of life (QoL, 3 items, 1 of which in agreement) (*Table 3*).

DISCUSSION

There are many guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, but only a few analyze comorbidity management. In addition, recommendations are not similar and differences exist on several issues (Candel *et al.*, 2017). This does not simplify the clinician's work, because information is often different and sometimes recommendations are related to equipment not always available. Our study intentionally tested clinicians' agreement on first-line investigations for comorbidity screening in a real life situation.
Concerning patient's medical history, clinicians surprisingly identified some heterogeneous ITEMs to be assessed, excluding in this phase other ones. They essentially considered a mix of personal, biological, laboratory, pharmacological, habit, clinical and sexual data as fundamental: age, sex, therapies in progress and previous, CD4 + nadir, CD4 progress - stable or in progressive improvement, risk factors for HIV, presence of symptoms, other past illnesses and pathologies in progress, drug consumption and type of drugs, alcohol consumption, smoking, food disorders (i.e. bulimia and anorexia or diet, vegetarian or vegan or hyper-protein consumption), pregnancies, menopause, condom use, partner serology (in the presence of a fixed partner), HIV-RNA zenith. In the clinicians' shared opinion, these data constitute the essential anamnesis to be carried out in each patient; other common data are considered less powerful in this first phase.

Table 3 - *Results.*

ITEMs to be assessed	
Medical History	• Age • Sex • Therapies in progress • Previous Therapy • CD4 + nadir • CD4 Progress - Stable • CD4 Progress - In progressive Improvement • Risk factors for HIV • Presence of symptomatology • Other past illness • Pathologies in progress • Drug consumption • Type of drugs • Alcohol consumption • Smoke • Food Disorders (eg bulimia and anorexia or diet, vegetarian or vegan or hyperprotein information) • Pregnancies • Menopause • Condom use • Partner serology (in the presence of a fixed partner) • HIV-RNA zenith

General diagnostics	*ITEMs to be assessed*
Virological diagnostics	• HIV-RNA • Genotypic resistance testing
Immunological diagnostic	• Absolute CD4+ counts • CD4% • CD4+/CD8+ Ratio
Screening for co-infections	• Syphilis • HBV • HAV • HCV • TBC

Osteoarticular diagnostics	*ITEMs to be assessed*
Risk factors for osteoporosis	• Medical history
Estimate of risk of osteoporosis fractures	• FRAX
Exclusion of other caused of secondary osteoporosis	• *Level 1 Blood test:* ESR, full blood count, protein electrophoresis, serum calcium, phosphate, total alkaline phosphatase, creatinine, 24 h urinary calcium
Diagnosis of osteomalacia	• 25 hydroxy Vitamin D • PTH

Metabolic pathologies diagnosis, 7 items, 6 of which in agreement - Cardiovascular diagnosis, 8 items, 5 of which in agreement - Nephrologic diagnosis, 14 items, 9 of which in agreement.

Metabolic diagnostics	*ITEMs to be assessed*
Risk factors for dyslipidaemia	• Medical history
Measurements	• BMI • Waist circumference
Lipoartopy and lipohypertrophy	• PE
Hyperglycaemia /diabetes, dyslipidaemia	• Lipid profile (CT, TG, HDL, LDL) • Glycaemia

Cardiovascular diagnostics	*ITEMs to be assessed*
Risk factors for CVD	• Family medical history • Lipid profile (CT, LDL, HDL, TG) • Glycaemia • AP • Waist circumference
CVD risk estimate	• Framingham

Nephrology diagnostics	*ITEMs to be assessed*
Glomerular function	• Calculation of the eGFR with CKD-EPI
Glomerular function/ nephrolithiasis	• E.g. urine with sediment
Loss of protein	• Ratio of protein/CR in the urine
Exclusion of other causes of nephropathy	• BP measurement • Medications (including non-HIV)
Proximal tubule function	• Phosphatemia • Phosphaturia • Glycaemia • Glycosuria

Hepatological diagnosis, 14 items, 13 of which in agreement – Central nervous system diagnosis, 11 items, 8 of which in agreement – Evaluation of Quality of Life (QoL), 3 items, 1 of which in agreement.

Hepatic diagnostics	*ITEMs to be assessed*
Liver cytolysis, cholestasis	• ALT/AST ALP GGT • Bilirubin
Exclude other causes of liver disease	• History of viral infections • History of alcohol consumption • Presence of NASH
Exclude non-hepatic causes of hyper ALT/AST	• History of portal hypertension • Medication history • History of steatosis
Risk factors for liver disease	• Medical history
Phisycal examination	• Ascites • Hepatic encephalopathy
Viral hepatitis serology	• HBV serology • HCV serology

CNS diagnostics	*ITEMs to be assessed*
Exclusion of other neuropsychiatric disorders	• History of depression • History of anxiety disorders • History of other psychiatric disorders • Previous use of psychoactive and psychotropic substances • Current use psychoactive and psychotropic substances • Previous abuse of psychotropic drugs • Alcoholism

Psyco diagnostics and Quality of Live	*ITEMs to be assessed*
Measurement of adherence to therapy	Adherence was investigated with four separate questions, considering two different recall periods: last month and last week. For each period, patients were asked to report the proportion of doses taken and the proportion of doses taken with respect to the daily timing (±2 hours). In both cases a VAS scale was used collect data.

Moving to general diagnostics, from the clinicians' point of view only few ITEMs are really to be assessed during the first screening: two virologicaI (HIV-RNA plasma levels and genotypic resistance testing), three immunological (absolute CD4+ counts, CD4%, and CD4+/CD8+ Ratio), and screening for co-infections (syphilis, HBV, HAV, HCV, TB).
Concerning osteoarticular diagnostics, clinicians identified specific ITEMs to be assessed. First of all, medical history, searching for risk factors for osteoporosis, in particular sex, age, race, family history, body frame size, sex hormones, thyroid problems, overactive parathyroid and adrenal glands, low calcium intake, eating disorders, gastrointestinal surgery, steroids and other medications used to combat or prevent seizures, gastric reflux, cancer, transplant rejection, medical conditions (celiac disease, inflammatory bowel disease, kidney or liver disease, cancer, lupus, multiple myeloma, rheumatoid arthritis), sedentary lifestyle, excessive alcohol consumption, and tobacco use. These are very important issues to decide for an activation toward second level investigations.
Very relevant is to estimate the risk of osteoporosis fractures with FRAX. This tool is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck. The models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. Is computer-driven and gives the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).
Following SIOMMMS (Italian Society of Osteoporosis, Mineral Metabolism of bone diseases) guidelines, clinicians opted to include the 'exclusion of other causes of secondary osteoporosis' by implementation of erythrocyte sedimentation rate, full blood count, protein electrophoresis, serum calcium, phosphate, total alkaline phosphatase, creatinine, and 24 h urinary calcium. Diagnosis of osteomalacia, correctly done only by biopsy, is suggested by 25 hydroxy-vitamin D and PTH plasma levels.
Interestingly, clinicians excluded DXA scan in this phase: indeed, DXA measures BMD, but osteoporosis is not a loss of bone mass, rather a loss of bone resistance, so we can observe fracture even with normal BMD values. In addition, DXA is not accessible to all clinicians.
Concerning metabolic diagnostics, clinicians analyzed ITEMs to be assessed in this phase. Even in this case, first they selected medical history, in order to evaluate the risk factors for dyslipidaemia, and in the perspective of a potential second level of investigations.
Concerning measurements, only two calculations were selected: body mass index (BMI) and Waist circumference. Waist circumference is mandatory, in order to consider visceral adipose tissue weight as the real estimate of cardiovascular risks related to BMI. Physical examination was approved to define lipoatrophy and lipohypertrophy.
To evaluate hyperglycaemia/diabetes, and/or dyslipidaemia, lipid profile (CT, TG, HDL, LDL) and glycaemia are considered enough.
Concerning cardiovascular diagnostics, ITEMs to be assessed partially overlap with metabolic ITEMs. First of all, clinicians shared medical history, searching for risk factors for cardiovascular disease (CVD), in particular family medical history, lipid profile (CT, LDL, HDL, TG), glycaemia, blood pressure determination, and waist circumference measurement. For CVD risk estimate, Framingham's algorithm was selected. The Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual, developed starting from data obtained from the Framingham Heart Study, to estimate the 10-year risk of developing coronary heart disease. This tool has two limitations: it could predict only future coronary heart diseases, since it does not predict risk for stroke, transient ischemic attack (TIA), and heart failure, and could overestimate (or underestimate) risk in populations other than the US population.
Moving to nephrology diagnostics, from the clinicians' point of view the following ITEMs should be assessed during the first screening:
- the calculation of eGFR with CKD-EPI, in order to evaluate glomerular function;
- urine test with sediment to investigate glomerular function/nephrolithiasis;
- search for loss of protein, by means of the protein/creatinine ratio in the urine.

As before, it is mandatory to exclude other causes of nephropathy, through blood pressure measurement and a list of possible concomitant nephrotoxic medications (including non-HIV drugs). In addition to glomerular func-

Table 4 - *Assessment management.*

Assessment management	*ITEMs to be assessed*
Management of risk factors and comorbidities	It is advisable to monitor the risk of OSTEOPOROSIS in the patient with HIV six-monthly/annually (repeated first-level exams
	It is advisable to monitor the risk of METABOLIC DISORDERS in the patient with HIV six-monthly/annually (repeat first-level texts)
	It is advisable to monitor the risk of CARDIOVASCULAR disease the patient with HIV six-monthly/annually (repeat first-level texts)
	It is advisable to monitor the risk of NEPHROPATY the patient with HIV six-monthly/annually (repeat first-leveltexts)
	It is advisable to monitor the risk of LIVER DISEASE the patient with HIV six-monthly/annually (repeat first-level texts)
	It is advisable to monitor the risk of NEUROLOGICAL disorders the patient with HIV six-monthly/annually (repeat first-level exams)
	It is advisable to monitor the risk of PSYCHOLOGICAL CONDITION and QUALITY OF LIFE of the patient with HIV six-monthly/annually (repeat first-level exams)

tion, proximal tubule function also needs to be investigated: clinicians also selected phosphataemia, phosphaturia, glycaemia and glycosuria.
Concerning hepatic diagnostics, ITEMs to be assessed in the clinicians' opinion are essentially laboratory and clinical: first of all, medical history, searching for risk factors for liver disease. To investigate liver cytolysis and cholelithiasis, clinicians selected ALT, AST, ALP, GGT and bilirubin plasma levels. To exclude other causes of liver disease, they chose the history of viral infections and alcohol consumption, in addition to the presence of NASH, and physical examination, searching for the presence of ascites and/ hepatic encephalopathy to exclude non-hepatic causes of hyper ALT/AST. Finally, regarding laboratory tests, clinicians selected HBV and HCV serology.
Moving to CNS Diagnostics, ITEMs to be assessed by clinicians are those able to exclude other neuropsychiatric disorders: history of depression, history of anxiety disorders, history of other psychiatric disorders, previous use of psychoactive and psychotropic substances, current use of psychoactive and psychotropic substances, current abuse of psychiatric drugs, previous abuse of psychotropic drugs, alcoholism.
Finally, concerning psychodiagnostics and Quality of Life ITEMs, the only one to be assessed in this first screening phase is the measurement of adherence to therapy, to be conducted as follows: adherence is investigated with four separate questions, considering two different recall periods: last month and last week. For each period, patients are asked to report the proportion of doses taken and the proportion of doses taken with respect to the daily timing (±2 hours). In both cases a VAS scale should be used to collect data.
To add advice concerning optimal timing of follow-up, clinicians were asked for the assessment management of risk factors and comorbidities, regarding each specific ITEM (*Table 4*).

CONCLUSIONS

PLWHIV have changed, and it is time to find a new approach to better react to new challenges. Currently, few guidelines consider comorbidity issues, and sometimes with different diagnostic strategies. Our approach was based either on clinical practice or literature data. Our starting idea was that in order to find an agreement among clinicians is fundamental to a discuss and share a common approach to the same problems.
This simple and concise first-level tool identifies a few areas of multi-organ diagnostic assessment beyond the infectivity area, namely: osteoporosis, cardiovascular, metabolic, renal, hepatic, central nervous system and quality of life. The identification of these areas will allow us to find shared and validated evaluation procedures with the intent to increase the likelihood of early recognition of patients at risk of comorbidity development, in order to facilitate more effective prevention, thereby reducing the overall impact on the quality of life of patients affected by this chronic illness. Future steps will constitute specific technological support of a new practical tool for clinicians to effectively react to this fascinating new scenario.

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