Beyond Italian guidelines in the management of HIV-positive patient

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Although AIDS/HIV infection and related deaths have significantly decreased in Italy in recent years, new problems have made it more challenging to manage the disease. To overcome the new hurdles, the Italian National Plan of Interventions against HIV and AIDS was recently issued by the National Health Authorities, and the Italian Guidelines (GL) for diagnosis, therapy and management of HIV-1 infection were subsequently drafted by the Italian Society of Infectious and Tropical Diseases (SIMIT). Although the GLs provide clear recommendations, they are open to personal interpretation depending on the experience and/or background of individual healthcare professionals. To minimize the interpretative variability, eight residential meetings were organized in Italy in 2019 to promote a multidisciplinary approach and discuss specific HIV-associated conditions, such as cardiovascular or neuro-psychological comorbidities, advanced stage of infection, and high CD4 cell counts. To undertake this educational program, the GLs were simplified into key steps by creating ad hoc decisional algorithms, and an innovative multimedia technology was used during the meetings to collect and summarize individual opinions up to the final statements. For HIV patients with cardiovascular diseases, “CV risk factor identification” and “change of patients’ lifestyle” were the most commonly shared approaches by all healthcare professionals, regardless of individual attitudes. Among HIV individuals with neurocognitive and psychological comorbidities, “more neurocognitive tests”, “better customization of antiretroviral therapy (ART)”, and “assessment of psychological symptoms” were the most frequently identified options to carry out. Advanced HIV infection and low CD4 cell count being a particularly serious condition burdened by high mortality, almost all specialists oriented their opinion toward a prompt and scrupulous clinical evaluation to be performed just before and immediately after the start of ART. Finally, the most pursued recommendations in patients with acute HIV infection and high CD4 cell count were the achievement of a “prompt diagnosis” and “start of well-shaped ART”, as the most appropriate means to keep the viral load as low as possible. Undoubtedly, despite negligible discrepancies in individual interpretation among specialists, this nationwide educational program was able to capture local differences, but to guarantee at the same time a constant alignment of individual specialists towards the Italian clinical practice GLs. Different priorities in the daily management of the four HIV-1 subpopulations highlighted during the meetings reflect the presence of different regional health policies nationwide, in turn generating different healthcare offers. This program offered state-of-the-art management of four widely represented subpopulations of HIV-1 patients.

**Keywords**: Italian guidelines, comorbidities, multidisciplinary approach, HIV subpopulations.

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**INTRODUCTION**

In Italy, the annual incidence of subjects with AIDS and new diagnoses of HIV infection has reached a plateau in the last decade, but due to the increasing effectiveness of antiretroviral therapy (ART) the number of people living with HIV is growing [1]. Over the years, the improved knowledge on infection and its progression phases, the escalation of increasingly effective drugs, the sharpening of therapeutic strategies and the implementation of both national and international surveillance systems has made it possible to accurately define the existence of subpopulations needing customized care and management. According to the most recent surveillance report of AIDS/HIV in Europe, the rates per 100,000 population of new HIV diagnoses in Italy slightly decreased in 2018 (4.7) compared to previous years 2017, 2016, 2015, 2014 (5.9, 6.1, 5.9, 6.3, respectively), thus mirroring the trend of EU/EEA [2]. AIDS-related deaths are also decreasing in Italy as well as in the EU/EEA, but the changing epidemiology, the persistent spread of the infection and the emergence of new problems make the management of the disease more challenging. With the aim of outlining the best possible path to achieve the urgent objectives indicated by international agencies (ECDC, UNAIDS, WHO), and making them feasible in Italy, the Italian National Plan of Interventions against HIV and AIDS (PNAIDS) 2017-2019 has been issued in 2016 [3]. To enable implementation of indications contained in PNAIDS 2017-2019, the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Ministry of Health had drafted the Italian Guidelines (GLs) on the use of Antiretroviral Therapy and the diagnostic-clinical management of subjects with HIV-1 infection [4]. Although this document provides important guiding elements for clinical activities, however the attitude and interpretation of recommendations by individual health professionals may differ across the country according to professional backgrounds and cultural attitudes. In the attempt to decrease the interpretative variability of the new GLs and to standardize the perspectives of the management approach of Italian specialists, during 2019 a series of residential meetings were held in Italy. Four different settings of HIV patients, already described in the Italian GLs, were presented and the multidisciplinary approach was strongly promoted, facilitating information exchange, comparison and mutual understanding of various issues among specialists, in the interest of patient care. Below the results of these interactive meetings are presented and discussed.

**MATERIALS AND METHODS**

From May to December 2019, eight residential meetings have been organized in main cities of Northern, Central and Southern Italy: Rome, Florence, Naples, Palermo, Pescara, Padua, Turin, and Milan. Almost 40-50 infectious disease specialists participated each meeting, and all were challenged to define their personal diagnostic, therapeutic and management approach in four different patient settings:

1) HIV patient on ART and with cardiovascular comorbidities;
2) HIV patient on ART and with neurological comorbidities;
3) patient with advanced HIV infection and low CD4 cells count;
4) patient with acute infection and high CD4 cells count.

The four clinical settings are well defined topics extensively addressed by the Italian GLs, where all clinical or health care related question have been framed and answered by PICO (Problem/Patient/Population, Intervention/Indicator, Comparison, Outcome) process [4]. The strength of the recommendations was expressed by the letters A, B, and C (Strongly recommended, Moderately recommended, Optional, respectively), whereas the level of evidence by the numbers I, II and III (Data obtained from at least one controlled and randomized study or meta-analysis of controlled studies; Data from non-randomized research or observational cohort studies; Recommendation based on case studies or expert consent, respectively).

Although GLs are clear and exhaustive, an effort is needed to accurately and quickly identify the critical decisions to be made in the management of the four HIV patient settings. For these reasons, and to encourage an effective discussion between attending specialists, a board of faculty members and co-authors of the Italian GLs reviewed each of the four clinical settings some time before the start of the educational program. Each setting was then simplified into an ad hoc decisional algorithm.
(Figures 1A-4A) on which to shape physicians’
daily clinical approach. The “algorithm meth-
method” has allowed each specialist to give his/her
own interpretation of the GLs based on individ-
ual healthcare background, but without deviating
from recommendations of the reference GLs.
In each meeting, formal presentations were held
to take stock of each clinical setting and to focus
attention on the items to be discussed. After-
wards, interactive workshops have been organ-
ized. Participants were divided into four groups,
each group led by a faculty member as facilitator.
Each attending specialist was provided with a tab-
let on which the ad hoc decisional algorithms were
played in the form of clinical “path”. Each algo-
rithm appeared progressively on the screen tab-
let, according to a “step-by-step” method, so as to
focus the attention on important decision-making
points to stimulate discussion. Specialists were
then invited to state their opinion about diagnos-
tic, therapeutic or clinical management choices
every time a decision point (step) appeared on
the screen tablet. Thanks to an innovative multi-
media technology (Practice & Solutions S.p.A.),
physicians were allowed to write their own per-
sonal opinions by means of virtual post-it notes
on the tablets, and attach the notes over related
decisional points on the screen. Then, individual
opinions were progressively collected by the mul-
timedia system by real time, automatically strat-
ified by type of opinion and classified into final
statements in the form of Take-Home-Messages
(THMs), thus summarizing the audience’s opin-
on over each setting of HIV patient.

**RESULTS**

**HIV patient on ART and with cardiovascular comorbidities**

In this setting, the specialists proposed differ-
ent approaches and, in each meeting, a differ-
ent priority of diagnostic, therapeutic and clini-
cal management attitudes emerged. However,
common approaches arose among the meetings,
even though they were expressed with different
strength. Overall, the common approaches, listed
in descending order, have been:

1) identification of risk factors for cardiovascular
diseases;

2) interventions to induce changes in the pa-
tient’s lifestyle;

3) screening of cardiovascular parameters;

4) identification of clinical pathways for preven-
tion, diagnosis and follow-up of cardiovascu-
lar risks and/or diseases;

5) identification and selection of appropriate algo-
rithms and scores for estimating the risk of cardio-
vascular events.

In addition, in some meetings minor approaches
were proposed by a limited number of specialists,
such as: cardio-CT scan, long-term monitoring
of antiretroviral (ART) therapy effects, primary
prevention of cardiovascular diseases, increased
used of lipid-lowering medications class, statins
(Figure 1B).

Although specialists from different Italian areas
have expressed common approaches, guided by
the published Italian GLs on HIV infection, these
approaches have been interpreted differently in
different areas. The “identification of risk factors
for cardiovascular diseases” was the universal ap-
proach shared in each meeting, with special atten-
tion to body mass index (BMI) (Naples), to other
comorbidities, such as hypertension, stroke, myo-
cardial infarction, diabetes (Pescara), to smoking
habit associated to modification of patient’s life-
style (Turin). The common proposal to promote
“interventions to induce changes in the patient’s
lifestyle” was customized with recommendation
of improving also the physical activity (Rome),
whereas the approach to “screen the cardiovascu-
lar parameters” was tailored to monitor the Inti-
ma-media thickness (IMT) (Florence), the arteri-
al blood pressure (Palermo, Pescara), to expand
the screening with instrumental and bio-humoral
tests (Padua), and stratify the screening accord-
ing to patient’s profile and monitor inflamma-

tory clinical markers to improve diagnosis (Turin).

Interestingly, specialists from the three cities pro-
posing the “identification of clinical pathways”
all agreed to plan the paths in cooperation with
cardiologists, in order to allow a multidiscipli-

dary patient’s management (Florence, Turin, Mi-
lan). No special issues emerged among support-
ers of “identification and selection of appropriate
algorithms and scores” (Rome, Naples).

**HIV patient on ART and with neurological comorbidities**

The most common approaches to management of
HIV patients with neurological and psychological
concomitant diseases have been:
1) implementation of neurocognitive tests;
2) selection of the most appropriate ART therapy customized to individual neurological conditions;
3) assessment of psychological symptoms;
4) identification of clinical pathways for specific patient’s management;
5) cooperation with neurologist. Minor approaches were to follow European flow-charts (Rome), implement the clinical use of algorithms (Rome) and consider the negative impact of neurological disease on the long-term prognosis of HIV patient (Pescara) (Figure 2B). In addition to the general recommendation of “implementing neurocognitive tests”, a group of specialists expressed a well-structured approach to the management of neurological comorbidities in HIV patients: the group suggested to use different neurocognitive tests according to patients’ conditions (i.e., not the same tests for all patients) and to promote an individual clinical evaluation in order to plan additional tests according to the patient’s needs (Rome). The therapeutical choice to “maximize the efficacy and minimize the neurological toxicity (appropriate ART)” was another medical need widely shared among the majority of specialists attending the meetings. Beyond the assessment of central nervous system (CNS) drug toxicity (Rome, Milan), other issues have been debated, such as the customization of therapy based on specific patient’s conditions and neglect Letendre therapy based on the CNS drugs Penetration and Effectiveness (CPE) score (Rome); the identification of cerebrospinal fluid (CSF) HIV RNA escape in symptomatic patients (Florence, Naples); the assessment of the ART safety profile (Pescara).
Large importance has also been recognized to the “psychiatric conditions in the HIV patient”. In some meetings it has been suggested to perform a combined psychiatric and medical evaluation for detecting possible underlying drug abuses (Palermo, Turin); or alternatively, to specifically assess depressive symptoms (Padua, Milan); to provide psychological support to HIV patients (Pescara); to schedule an annual subject’s follow-up associated to CSF analysis as constant monitoring for possible onset of HIV-associated dementia (HAD) (Padua).

Patient with advanced HIV infection and low CD4 cells count
The most popular approaches in this clinical setting were:

1) choose an early and highly effective ART (expressed with higher strength in some meetings);
2) diagnosis, prevention and treatment of opportunistic infections (OIs);
3) assessment of comorbidities;
4) evaluation of the AIDS disease stage;
5) promote multidisciplinary patient management.

Minor approaches were the “increase of public sensitivity about AIDS disease” (Turin) and the “identification of patient’s fragilities” (Turin) (Figure 3B).

“Early and effective ART” has been proposed differently across the meetings: early-therapy for AIDS associated to OIs prophylaxis and treatment (Rome); avoid the use of 2-drug regimen (2DR) (Rome); resort to high genetic barrier therapies (Naples); use of consolidated ART (Florence); achieve rapid reduction of viral load (Pescara). The statement “effective ART” has been
reported in Palermo, Pescara and Milan. Greater relevance to “early and accurate OIs diagnosis” arose in Rome, Naples, Pescara and Milan, while “prevention and treatment of OIs” has been reported in Florence and Palermo. Specialists in Palermo, Padua and Milan proposed to “assess comorbidities”, but in Florence it was suggested to “evaluate comorbidities in association to the viral genotype and patient’s cardiovascular risks”. In Naples to “customize ART according to risk factors and comorbidities”, and in Padua to perform “frequent comorbidities follow-up”. Among physicians suggesting to “assess the stage of AIDS disease”, it was proposed to “assess presence of immune reconstitution inflammatory syndrome (IRIS)” (Rome); to “identify AIDS-related conditions leading to delayed start of ART” (Pescara); or to “recognize the patient’s condition with slow and incomplete CD4 recovery” (Padua). The “multidisciplinary patient’s management” has been proposed in Florence and Turin.

**Patient with acute infection and high CD4 cells count**

In the management of HIV patient with acute infection, the most strongly recommended approaches were:

1) early ART;
2) early diagnosis associated to early ART;
3) relevance of initial diagnosis;
4) maintain viral load as low as possible.

Minor approaches have been: take into account a possible low patient’s compliance to treatment (Rome), the key role of counseling with infectious disease specialists (Rome), physicians’ emotion control in patient management (Na-
Among all specialists suggesting the “early ART”, different interpretations were observed in different areas. In Rome it was recommended the early combination antiretroviral therapy (c-ART), whereas in Turin it was proposed that, in case of acute HIV infection, ART should start within 1-3 days, while in case of non-acute infection ART could start within 15 days according to patient’s conditions (Turin). Many physicians have emphasized the “relevance of making an initial diagnosis”, but this approach was interpreted differently in different areas: launch of screening campaigns (Naples), greater consideration of rapid tests and suggestive patients’ symptoms (Turin), or higher concern of differences among patients due to gender and risk factors (Padua).

**DISCUSSION**

Italy has made great progress over the years in the management of HIV infection and AIDS, evaluating the ever-changing epidemiology, deepening scientific knowledge and optimizing its health resources. In addition to these progresses, the country has increasingly approached international goals such as the UNAIDS 90-90-90 treatment targets, despite the final target has nearly to be achieved [5]. Recently, important steps have been realized in Italy to improve the therapeutic standards of the intervention network for the treatment of HIV/AIDS in public facilities. The Italian National Plan of Interventions against HIV and AIDS (PNAIDS) has been issued in 2016 with the main purposes to reduce the number of new infections, facilitate access to the diagnostic tests,
increase the early diagnosis of AIDS presenters and promote the treatment maintenance of already diagnosed and treated patients [3]. A year later, the Italian Guidelines (GLs) on the use of Antiretroviral Therapy and the diagnostic-clinical management of people with HIV-1 infection have been issued [4]. This technical document aimed at providing a guidance for prescribing antiretroviral therapy and for the management of HIV patients by infectious disease specialists and other specialists involved in the multidisciplinary management, as well as providing a landmark for administrators and political decision-makers of public health services. However, it is inevitable that the implementation of guidelines recommendations can undergo to individual physician’s interpretation, who in turn may be biased by the daily working conditions, type of population visited in his/her center and/or local health policies. These and other poorly explored conditions may easily lead to regional discrepancies in the use of the national GLs. For these reasons, a nationwide educational program has been created to bring out and guide the healthcare professionals’ choices implemented on HIV patients in the real life, try to catch local differences, but to guarantee at the same time a constant alignment of individual specialists towards a nationally shared clinical practice GLs based on clinical evidence.

The four clinical setting explored in this program exemplify four subpopulations that represent a small portion of other well-defined subpopulations described in the Italian GLs, such as patients with lipodystrophy, liver disease, bone disease, kidney disease, chronic obstructive pulmonary disease, sexual and reproductive disturbances, tumors, infection with hepatitis viruses and tuberculosis. All subpopulations are representative of an aging population that faces new problems and pathologies, related to the long-term management of their disease, comorbidities that often have an even greater weight than the HIV infection itself. Cardiovascular diseases are among the leading causes of death from non-AIDS events in the HIV-infected population and the Italian GLs strongly steer specialists in the evaluation of patient’s clinical path. GLs highlight critical phases in the identification and management of patients with high CV risk, but the wide range of recommendations may be followed in different ways, by different specialists, and in different country areas.

In the present educational program, recommendations were outlined and simplified in key steps by means of ad hoc decisional algorithms. Therefore, it is not surprising that specialists have chosen to “identify CV risk factors” during the diagnostic workup and to “change patient’s lifestyle” during the management phase of HIV patients with cardiovascular comorbidities, as approaches that reached the highest number of shares, regardless regional attitudes. GLs offer a wide range of risk factors and treatment strategies to follow, and specialists moved within these borders giving preference to one risk factor or another during the identification process (i.e., body mass index, smoking habit, CV comorbidities, arterial blood pressure, intima-media thickness screening, appropriate algorithms, etc.) or preference to a treatment strategy or another during the intervention phase (i.e., change patient’s lifestyle). It is of note that many specialists recognized the professional cooperation with cardiologists as the key factor for a successful patient’s management due to the increasing complexity of cardiovascular comorbidities.

Neurocognitive disorders in HIV patients are attributable to HIV damage to the CNS and, in this case, they are defined as HIV-associated neurocognitive disorders (HAND). In other circumstances, neurocognitive disorder can preexist the HIV infection, attributable to other causes, and both situations can overlap. These disorders can be identified or confirmed, if clinically evident, through neurocognitive tests (alteration in at least two cognitive areas). However, neuropsychological tests do not allow to identify the nature of cognitive alterations, if caused by HIV or other conditions, such as depression, anxiety, psychiatric diseases, drug abuse, Alzheimer’s disease or other forms of dementia, and other neurological pathologies. For this reason, further laboratory and instrumental investigations may be necessary to confirm/exclude the presence of these conditions. Additionally, HIV-associated cognitive disorders, including HIV-associated dementia (HAD), can be associated with viral escape in the CSF. The symptomatic viral escape is generally associated with progressive encephalopathy with cognitive and motor disorders and, more rarely, with particularly severe evolving forms, whereas an asymptomatic viral escape can occur in about 10% of neuro-impaired HIV patients [4].
Adequate diagnosis of psychiatric disorders in HIV patients is a key step in the successful patient’s management, as symptoms are relevant per se and for their confounding effect in the diagnosis of HIV-related cognitive disorders, possibly interfering with the results of neurocognitive tests. In the management of patients with psychiatric disorders, possible interactions between antiretroviral drugs and psychiatric or neurological drugs must be considered, which may compromise the effectiveness of both therapies or increase their side effects.

Therefore, during the nationwide educational program, the analysis of subpopulation of HIV patients with neurological comorbidities focused the attention on three major approaches: implementation of neurocognitive tests; selection of the most appropriate ART therapy customized to individual neurological conditions; assessment of psychological symptoms. The three approaches mirrored the GLs recommendations, which suggest to submit patients to different levels of neurocognitive and psychiatric tests, and to favour a highly effective ART (drugs with proven neuro-penetration and/or neuro-efficacy in case of documented symptomatic/asymptomatic viral escape). Notably, a group of specialists in Rome strictly followed GLs recommendations for the management of HIV patients with neurocognitive disorders, suggesting to customize neurocognitive tests according to patients’ neuro-psychological profile and to plan additional tests according to the individual patient’s needs. As regards the many perspective of an effective ART, great importance has been given to the evaluation of drug neurotoxicity, as well as to the aforementioned pharmacokinetic ability to penetrate the CNS.

The advanced HIV infection and low CD4 cells count is a particularly serious condition, because frequently associated to OIs AIDS or non-AIDS related which, in turn can increase the mortality rate, in spite of an ongoing effective ART. Usually, this condition may be sustained by different clinical circumstances, as AIDS presenters with low CD4 cells count (<200 cells/μL); subjects with no or incomplete infection control due to several reasons (i.e., ART ineffectiveness, poor treatment adherence, drug toxicity, viral persistence, drug interactions, biological factors of the host); patients with absent or inadequate immune recovery paralleled by a good virological response (discordant response). Beyond the need to implement optimal preventive and therapeutic strategies for the major OIs, in patients with advanced HIV disease a careful clinical evaluation before and immediately after the start of ART is of paramount importance, due to the high mortality risk, the poor immunological recovery and the possible occurrence of new OIs [4].

The approaches proposed by specialists attending the meetings were compliant with GLs recommendations in this setting. The main option was the need to identify and implement a highly effective ART by combining three drugs (3DR), with a high genetic barrier and able to achieve a quick reduction of viral load. All these features were indicated as essential for minimizing the onset of new or recurrent OIs, as an effective ART represents the best strategy for the control and prevention of OIs and should therefore be started as early as possible. Secondly, great importance was given to diagnose, prevention and treatment of OIs associated to the assessment of comorbidities and accurate evaluation of AIDS stage. All these three conditions are closely related to each other as they all impact on the preparation of ART, OIs’ treatments and possible treatments’ changes after the start. For instance, IRIS onset can lead to c-ART suspension in case of severe IRIS or CNS involvement. As well as in the management of HIV patient with cardiovascular or neurological comorbidities, the multidisciplinary patient’s management” was advocated by some groups of specialists.

Acute HIV infection is the disease phase that occurs immediately after transmission, which is typically characterized by viremia as detected by the presence of HIV RNA or p24 antigen. The immediate start of ART without attending the results of genotypic and HLA-B*5701 tests, offers the opportunity to significantly reduce the reservoir of HIV in terms of HIV-DNA level. Indeed, the goal of ART during early HIV infection is to suppress plasma HIV RNA to undetectable levels and to prevent the transmission of HIV. Individuals who are treated during early infection may experience immunologic and virologic benefits. Early HIV infection is often associated with high viral load and increased infectiousness, and the use of ART to achieve and maintain a viral load <200 copies/mL is expected to substantially reduce the risk of HIV transmission. The urgency to start the ART as soon as possible in the case of acute infection was
one of the GLs recommendations mostly followed by attending specialists at the educational meetings. Remarkably, despite Italian GLs recommend to start the ART within the first 4 weeks from the possible infection, some group recommended the immediate start within 1-3 days. Concomitantly, an early diagnosis was endorsed by giving relevance to early symptoms and to rapid diagnostic tests. The promptness of therapeutic and diagnostic interventions also aimed at both making the subject aware of his/her condition as soon as possible and reducing the viral load as low as possible, simultaneously reducing the transmissibility of the infection.

This educational program depicts the state-of-art about implementation and interpretation of the recent guidelines issued by the Italian Society of Infectious and Tropical Disease (SIMIT) on the treatment and management of the HIV patient. During the nationwide meetings, no major deviations from the GLs were detected, although it is possible to assume that different priorities given to some intervention or dissimilar management choices by attending specialists may have been generated by different health policies conditioning the healthcare givers’ daily job. Public health in Italy is managed on regional base and this gives rise to health policies that are sometimes dissimilar between Regions, generating different offers of healthcare services for both health professionals and patients.

Therefore, alongside the pharmacological expenditure for therapies, there is the need to think about the costs of comorbidities, to implement the “total taking charge” of the HIV/AIDS patient, and the governance of chronic diseases, through a new management model of the disease that still absorbs significant economic resources.

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