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Report

"Review of recent scientific publications to support a decision on a change in the aeromedical certification of applicants for a commercial pilot license living with HIV"

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1 Executive summary

This report gives an overview of the work performed, results and recommendations of a literature review which was conducted to determine whether HIV seropositivity should per se preclude pilots from being issued with a medical certificate.

A steering committee composed of EASA staff and two external medical experts assembled a list of questions to be addressed based on a systematic literature review.

The literature review revealed that until now no specific research is available on the impact of HIV infection and its treatment on commercial pilots. There are, however, valuable findings from general HIV research on e.g. the impact of HIV infection and its treatment on mood disorders, cognitive performance and cardiovascular disease.

More specific research would be necessary to conclude whether there is a need to review EASA's acceptable means of compliance on the subject.

2 Background

In light of the progress that has been made with managing Human Immunodeficiency Virus (HIV) infection, a European Union Member State was challenged by an interest group on why it was possible for a pilot who becomes HIV -positive to obtain a Class 1 medical certificate with an operational multi-pilot limitation (OML) whilst an applicant who is yet to obtain a licence cannot. This is based on the European Union Regulations that only permit the endorsement of a medical certificate with an OML for a holder of a commercial pilot's licence (CPL), an airline transport pilot's licence (ATPL) or a multi-pilot's licence (MPL).
Thereby, HIV-positive applicants are excluded from training for a commercial pilot licence. Furthermore, the same Member State enquired about the conditions under which a fit assessment of applicants living with HIV could be considered without a multi-pilot limitation.
In order to support a decision on a potential change in the aeromedical certification of applicants for a commercial pilot license, EASA invited a renowned medical expert to support EASA with:

- the development of the scope and technical specifications for a tender to review recent scientific publications to determine the conditions under which the fit assessment of applicants for a Class 1 medical certificate living with HIV without an OML would be possible;
- the assessment of research organisations in order to identify providers with capability to perform such review; and
- the chairmanship of a steering committee (SC) that should give advice to EASA with regard to the selection of the research organisation and the assessment of the draft report on the subject.

The SC was composed of EASA staff members and two external experts, including the chairperson.

3 Medical background

Since the 1980s, when the Human Immunodeficiency Virus (HIV) was first recognized, there has been significant progress made in the management of infection and outcomes for quality of life and life expectancy. The advent of High Active Anti-Retroviral Therapy (HAART) has transformed the prognosis for someone living with HIV such that much of the emphasis now is on managing life-long chronic infection rather than acute illness. Even so, HIV infection per se affects every organ system in complex ways. In the initial infection (sero-conversion illness), there is massive systemic lympho-reticular infection by HIV and loss of CD4+ T cells. Associations of opportunistic infections and tumors with immunosuppression are well defined. There are now several classes of effective anti-HIV drugs, which target different phases of the HIV life cycle in human cells. They are used in combination to prevent drug resistance and are effective in >70% of patients bringing down blood viral loads to undetectable levels (e. g. <50 virus particles/ml blood). Despite the blood viral load becoming zero, there is no sterilization, there is always low-level, difficult –to-detect, latent infection in mononuclear cells, which will emerge when ART is stopped. That means, the majority of persons infected with HIV now, who have access to and comply with Anti-Retroviral Therapy ART, will: (a) never suffer a classic HIV-related disease; and (b) live nearly as long as the non-infected general population. In untreated HIV infection, people are in states of enhanced immunological activation with raised inflammatory markers in blood fluids. This also applies to those treated with ART with undetectable viral load and good CD4 counts. This has led to the concept of chronic immune activation, affecting body organs and function.

The flying task requires satisfactory musculoskeletal function, hearing, eye sight and intact cognition in the domains of language and communication, attention and concentration, executive functioning (judging, reasoning, planning, decision-making and behavioural control), memory (visual, verbal, motor and learning/recall), sensory and motor functioning (visuospatial processing, gross and manual fine-motor skills).Decisions on fitness for aeromedical certification are generally based on current functional ability and having an acceptable risk of an aeromedically relevant incapacitation due to a known medical condition.

Incapacitation may be sudden or slow in onset, overt or subtle, complete or partial and permanent (e.g. for the rest of a flight) or temporary. A risk model, the „one percent rule“, was proposed in the 1980s and is based on sudden incapacitation from cardiovascular disease. The model is based on a target all cause fatal accident rate, the failure rate of aircraft systems where the pilot is one of those systems, multi-pilot operations and the ability of the second pilot to take control during a critical phase of flight. In accordance with this model, Class 1 certification with a multi-pilot limitation is acceptable when the risk of incapacitation from the condition being assessed is less than 1% per annum. It is commonly assumed that unrestricted certification may be possible with a magnitude of risk lower i.e. 0.1% per annum or where the risk is the same as for a peer who does not have the condition in question. Whilst there are a number of potential flaws with this model and with extrapolating it to the risks associated with HIV infection, it can serve as a guide for acceptable incapacitation rates.

Applying this to HIV and fitness to fly, the assessment by a medical assessor at a national aviation authority will usually consider:

- functional ability and the absence of symptoms or signs including neurological, neurocognitive, psychiatric and cardiological, as well as an absence of side-effects from medication.
- Incapacitation risk from primary HIV infection and secondary conditions (including changes in cognitive function) and having suboptimal therapy or developing side-effects from medication.

4 Literature review project

The objective of the project was to determine whether HIV seropositivity should per se preclude pilots from being issued with a medical certificate. Following an analysis of the applicable Implementing Rules and acceptable means of compliance, and aeromedical best practices, the SC assembled a list of questions to be addressed based on a systematic literature search considering:

- studies between 2008 and June 2018,
- peer-reviewed research abstracts from major HIV conferences and
- guidelines of national and international societies and associations in the field

The list of questions covered ten subjects:

1. Testing and early management of infection
2. Monitoring
3. Anti-retroviral therapy
4. Co-infection
5. Mental Health related matters
6. Neurocognitive issues
7. Living with chronic infection
8. Life Expectancy
9. Additional issues (recovery and Pre-exposure Prophylaxis)
10. Fitness to fly

EASA invited nine renowned experts in the field of infectious diseases to submit project proposals for this literature project. EASA received only one offer from a consortium led by Prof. Cristina Mussini, Head of Department of Infectious Diseases and Tropical Medicine at the University Hospital in Modena, Italy.
The SC reviewed the offer. The SC and the consortium had three Webex meetings in 2019 and one Webex meeting in 2020 to monitor the progress and discuss the report. The final draft report was accepted by the SC in January 2020. The final draft was proofread by the EASA Better Regulation team in order to improve the linguistic quality which had been considered to be poor by the SC.

5 Results and recommendations

The results are summarised below.

5.1 Testing and early management of infection

HIV screening with assays that can detect recent HIV infection is recommended. Following a positive HIV diagnosis, a newly diagnosed individual should be immediately referred to an appropriate specialist HIV treatment centre for further management and care. Treatment may be started immediately. Certain tests should, however, be carried out e.g. to exclude active viral hepatitis and HIV-1 drug resistance.

HIV viraemia should be determined every 3–4 months until combination Anti-Retroviral Treatment (cART) is commenced, if there is a delay in starting therapy in cART-naive patients.

Age- and risk-appropriate screening for STIs at various anatomical sites, anal or cervical dysplasia, tuberculosis, general health, and medication toxicity is recommended.

5.2 Monitoring

Patients taking cART should have regular clinical and laboratory evaluations, including age- and risk-appropriate screening. HIV viraemia is the most important indicator of therapeutic efficacy; therefore, it should be measured at regular intervals, especially in patients starting cART.

CD4 T-cell measurements are recommended every 6 months until above 250/µl for at least 1 year with concomitant viral suppression.

The percentage value of CD4 T-cells and the CD4–CD8 ratio should be evaluated together with the absolute CD4 number in order to obtain a better estimate of the functionality of the immune system, especially in patients at risk of poor recovery of CD4.

For patients with low-level viraemia, the measurement of the residual HIV viral load (VL) with systems capable of detecting quantities of viruses from 50 copies/µl down to 1 copy/µl of HIV RNA is particularly interesting. Residual viraemia can be considered a useful parameter in virologically suppressed patients to predict negative developments of other diseases. For patient of all ages and both genders, monitoring of CD4 T-cell count and VL according to the guidelines should be performed every 4 to 6 months in order to detect virological failure as early as possible. Maintaining viral suppression is the goal of antiretroviral therapy and adherence to treatment is essential in order to achieve it. Remission or resolution of HIV infection is not achievable at the moment. HIV infection may, however, be defined as stable when the patient has more than 200/mm3 CD4 T-cell count on effective cART (HIV RNA <50 copies/µl) for more than 6 months.

5.3 Anti-retroviral therapy

All people living with HIV (PLWH) infection should start antiretroviral therapy as soon as possible. Laboratory assessments are recommended before treatment. Monitoring during treatment is recommended to assess response, adverse effects, and adherence. PLWH who do not want to take antiretrovirals should be monitored every 2 months since they could be rapid progressors. HIV elite controllers with undetectable VL and CD4 T-cell counts above 500 cells/µL should be monitored for CD4 and plasma VL every 4–6 months. Nonetheless, considering the higher cardiovascular risk in the absence of treatment compared to individuals on cART, HIV elite controllers should start antiretroviral treatment, even if more research is needed in the field.

Measurement of the HIV VL is recommended before cART initiation, while treatment may be started before results are available. Once the HIV RNA level is below 50 copies/µl, monitoring is recommended every 3 months until the virus is suppressed for at least 1 year. After 1 year of viral suppression, monitoring can be reduced to every 6 months if the patient maintains consistent medication adherence. Measurement of CD4

T-cell counts is recommended every 6 months until cell counts are >250/µl for at least 1 year with concomitant viral suppression. Measurement of the VL at 4 to 6 weeks after starting a new cART regimen is recommended. If the VL has not declined, adherence and toxicity should be discussed with the patient. If adherence appears to be sufficient, a genotype assay is recommended. For patients with persistent viraemia between 50 and 200 copies/µl, the cART regimen should be continued, with assessment of medication adherence and evaluation again within 4 weeks. HIV-positive persons should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity of the new regimen. ART may cause a number of side effects, including diarrhoea, nausea, central nervous system (CNS) adverse events (e.g. sleep disturbances, abnormal dreams, dizziness, headache and psychiatric side effects) and fatigue.

PLWH with depressive symptoms should avoid taking integrase inhibitors. Patients on treatment with integrase inhibitors should be monitored for the onset of insomnia and depression at each clinical visit. Patients with severe depressive symptoms should be evaluated to assess whether symptoms may be due to Rilpivirine (RPV) and whether the risks when continuing the same regimen outweigh the benefits. Efavirenz (EFV) should be avoided since it is not recommended and increases the risk of suicide. Moreover, EFV should be avoided in patients taking medication known to increase the risk of Torsades de pointes[1], or in patients at higher risk of Torsades de pointes.

It is difficult to assess the average time on cART after which common side effects are unlikely to occur. For example, hypersensitivity reaction (HSR) due to abacavir could occur in 4 weeks. For EFV, side effects such as abnormal dreams and dizziness are generally acute, but there are neuropsychiatric side effects due to a cumulative (in terms of years) exposure. Concerning integrase inhibitors as dolutegravir or bictegravir, neuropsychiatric side effects occur within 6 months from treatment start, but the follow-up of the patients could not, at present, exclude any long-term side effects. Therefore, it would be important to investigate the onset of neuropsychiatric side effects at each visit for people receiving dolutegravir or bictegravir. If the patient reports that the therapy is well tolerated, this could be enough to exclude potential easily recognisable side effects such as diarrhoea or nausea. Nevertheless, some neuropsychiatric side effects such as suicidal ideation should be investigated.

5.4 Co-infection

Concerning the impact on health condition and general performance status of people with hepatitis B or C co-infections, there are differences related to the stage of the disease. Concerning fibrosis in hepatitis B (HBV), the progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in persons with HBV/HIV co-infection than in persons with chronic HBV mono-infection.

Concerning hepatitis C (HCV), patients, with or without liver fibrosis, commonly experience fatigue, depression, anxiety, cognitive impairment, painful muscle and joint symptoms, irritability, nausea, abdominal discomfort, and right upper quadrant pain. Although these symptoms may not be life threatening, they cause substantial impairment in patients' health-related quality of life, work productivity, and everyday functionality.

Concerning treatment recommendations, individuals with HIV/HBV co-infection should be treated with antiretroviral regimens containing tenofovir (either diproxil fumarate or alafenamide) plus lamivudine or emtricitabine. Individuals with advanced liver fibrosis due to HCV or HBV co-infection should be monitored for liver decompensation (hepatic encephalopathy, flapping tremor, hepatic carcinoma) every 4 months. Individuals with HIV/HCV co-infection should be treated with direct antiviral agents (DAAs). Attention should

[1] Torsades de Pointes is a type of polymorphic ventricular tachycardia characterized by a gradual change in amplitude and twisting of the QRS complexes around an isoelectric line on the electrocardiogram.

be paid to the side effects of medication used for HIV-associated hepatitis B and C infection. Patients with hepatitis B should be monitored with the same frequency as HIV mono-infected patients, but they should be evaluated to assess the severity of HBV infection.
Patients with hepatitis B should be screened also for hepatitis C. Patients with chronic HBV should also be tested for immunity to hepatitis A (HAV) virus infection and, if non-immune, receive the HAV vaccination.
People living with HIV (PLWH) should be screened for latent tuberculosis (TB) at baseline and every 2 years by using Quantiferon Gold[2].
Liver enzyme elevation and neuropathy should be monitored in people who are treated for HIV-associated TB. Persons treated with drugs known to determine QT prolongation (bedaquiline, dalamanid moxifloxacin) should be accurately and frequently monitored during treatment for the risk of sudden death.

5.5 Mental Health related matters

In PLWH, the rate of mental health disorders is higher than in the general population. This difference has been observed in different groups of PLWH, such as youths with perinatal or behaviourally acquired HIV, adult men who have sex with men of colour, racial and ethnic minority women, people who inject drugs (PWID), and older adults. Therefore, HIV-infected people should be monitored at each visit for mood disorders including depression, post-traumatic stress disorder, and suicidal ideation. PLWH should be routinely screened for mental health problems using clinical questions and symptoms survey according to the European AIDS Clinical Society (EACS) guidelines. The frequency of the screening should be every year for patients with stable disease (HIV RNA<50 copies/µl and CD4 T-cell count >200 cells/mm3), and every 6 months for those with unstable disease or at particularly high risk according to the EACS guidelines. Mood disorders can also be a side effect of antiretroviral therapy (ART). In particular, EFV has been significantly associated with an increased risk of depression and suicidality. It should not be used in patients with psychiatric disorders or at risk of psychiatric disorders. Much less consistent association with mood disorders has been reported with rilpivirine. Depression and suicidality have been infrequently reported with integrase strand transfer inhibitor (INSTI) (mainly dolutegravir or raltegravir) use, primarily in patients with pre-existing psychiatric conditions.
Even in the recent ART era, an HIV-positive patient remains at higher risk of suicide than the general population. Among PLWH, a significantly independent increased risk remains for those with psychiatric treatment and those with depression. For PLWH with depression, a periodic psychiatric evaluation for suicide risk and questionnaire evaluation for suicide risk severity (as the Columbia University C-SSRS Questionnaire) should be mandatory. HIV-infected people who have been found to have characteristics associated to higher risk of suicidal ideation (SI) during their routine screening for mood disorders should increase the frequency of screening (every 6 months). This more frequent screening should be recommended especially for PLWH receiving EFV-based cART.
Concerning substance use disorders (SUD), the most commonly used substances by people living with HIV and AIDS (PLWHA) are tobacco and alcohol. The rate of different (injecting and non-injecting) substance use is higher in HIV-infected people compared to the general population. This should be addressed, even though data on specific groups of professional workers and on direct effects of substance abuse on depression is lacking.

5.6 Neurocognitive issues

The introduction of cART for HIV has successfully changed the clinical picture of PLWH, leading to a dramatic decrease of HIV-related morbidity and mortality. Nonetheless, even in the era of ART, HIV-associated

[2] QuantiFERON-TB Gold (QFT) is a simple blood test that aids in the detection of Mycobacterium tuberculosis, the bacteria which causes tuberculosis (TB).

neurocognitive disorders (HAND) still occur in PLWH. On the other hand, considering the relevance of predictive stratification factors, it is conceivable that the risk of developing HAND could be negligible for an individual of a younger age, not using substances, with stable HIV infection under therapy, low cardiovascular disease (CVD) risk, high educational level, and no mental health problems. Therefore, all HIV-infected people should be regularly (every 12 months) assessed for HAND with the aid of a screening tool. Any suspicion of neurocognitive impairment (NCI) should be confirmed by a complete neuropsychological assessment (NPA) through a standardised method. The monitoring for cognitive impairment, mood disorders, and behavioural aspects should be performed in an optimal environment, respecting the methodological aspects reported in the related guidelines, and not necessarily in a functional environment. It is necessary to include in the neuropsychological test battery cognitive domains such as executive functions, speed of information processing, attention/working memory, and motor skills. An instrumental activities of daily life (IADL) test with self- or other-reported scale is necessary in order to assess the level of functional impairment. The NPA should include tests in the following ability domains (if possible, with at least two test measures per domain): fluency; executive functions; speed of information processing; attention/working memory; verbal and visual learning/memory; motor skills.

As example of a comprehensive battery test, the following test (and related domains) should be included:

a) Digit Span forward and backward and Corsi's Block-Tapping Test (attention and working memory);
b) Trail Making Test-A and WAIS-R Digit Symbol (speed of information processing);
c) Trail Making Test-B, Stroop color and word (interference), phonemic verbal fluency (FAS) and Wisconsin Card sorting test (executive functions);
d) Rey Auditory Verbal Learning Test (RAVLT) with immediate and delayed recall (verbal episodic memory);
e) Grooved Pegboard Test with dominant/non-dominant hand (fine motor abilities).

Testing should be integrated with:

a) instrumental activities of daily life (IADL) test with self- or other-reported scale; and
b) Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI), with self-reported inventory, for controlling for mood disorder incidents, contributing or confounding co-morbidities.

5.7 At an initial aeromedical assessment after HIV diagnosis, a complete NPA by a large battery test exploring eight domains with at least two tests for each domain is recommended. The neuropsychological complete battery test should then be performed every 12 months.

The prevalence of HIV-infected people aged 50 years or older is also increasing rapidly. HIV-infected individuals may be more vulnerable to age-related conditions. That means, that this population often exhibits a higher number of co-morbidities and other age-related conditions at a younger age compared to the general population. As a result, non-AIDS-related mortality has eclipsed AIDS-related mortality as the major cause of death in HIV-infected persons with access to cART. From 2003 to 2013, the US Medicaid Database reported an increasing prevalence of cardiovascular diseases (CVD) (3 to 7 %), renal impairment (5 to 11 %), osteoporosis (4 to 6 %), and diabetes mellitus (DM) (9 to 19 %). PLWH are increasingly at risk of developing CVD, which may present differently (e.g. at a younger age) and with different underlying risk factors than in the general uninfected population. Therefore, individuals with HIV infection should start screening for co-morbidities at a younger age, i.e. when they are 40 years old and undergo cardiological monitoring with an assessment of the 10-year CV risk by using the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) score. In addition, the presence of cardiovascular (CV) risk factors — that is, high blood pressure, smoking, diabetes, and overweight — should be evaluated at least once a year and antiretroviral drugs, such as abacavir and darunavir, associated to a higher cardiovascular risk should be avoided. Metabolic disorders are also frequent among PLWH. The most important metabolic disorder is diabetes. Therefore, serum glucose

should be tested every 6 to 12 months, or more frequently if diabetes exists, and total cholesterol, HDL-cholesterol and triglycerides should be monitored once a year, or every 6 months if there is a higher risk.
Concerning health-related quality of life (HRQoL) of PLWH, only one study evaluating HRQoL in HIV infection in comparison with other chronic conditions has been performed in a sample of people with HIV and on cART for at least 6 months, by using the Medical Outcomes Study Short Form 36-item Health Survey. The authors added data from studies on diabetes mellitus (DM) type 1 and 2, and rheumatoid arthritis. HRQoL in the HIV group was comparable with that of people affected by DM type 1 and 2, but lower than in rheumatoid arthritis patients. Conversely, looking at the mental health domain, a poorer mental HRQoL was found in HIV-infected people compared to the other groups. In people with HIV, a history of AIDS, longer duration of cART and severe co-morbidities were associated with poor HRQoL.
The HRQoL should be regularly (every 12 months) assessed by validated questionnaires.

5.8 Life Expectancy

Not only the nadir of CD4 T-cell count but also the lifestyle of individuals influences the life expectancy of PLWH. That means, co-morbidities, social determinants and the adequacy of the viro-immunological control need also to be carefully assessed. The early start of cART strongly determines a longer life expectancy in any case. Consequently, a universal early cART start approach should be strictly recommended to increase the clinical benefit of the treatment.

5.9 Additional issues (recovery and Pre-exposure Prophylaxis)

It should be noted that people with a diagnosis of AIDS whose CD4 T-cell count increases above 200 cells/µl, as a result of ART, should not be considered to 'still have AIDS'. PLWH with a CD4 T-cell count nadir <200 cells/µl should, however, not discontinue treatment due the higher risk of developing AIDS events.
Concerning the use of pre-exposure prophylaxis (PrEP) regimens for HIV-negative partners and post-exposure prophylaxis (PEP) to prevent HIV infection, clinical trials, observational studies and studies of diagnostic accuracy showed that PrEP was associated with an increased risk of renal and mild reversible gastrointestinal adverse events (ADEs). Due to the frequent use of recreational drugs that are difficult to be detected by commercial tests, PrEP users should also be carefully interviewed for drug use.

5.10 Effects of flying on HIV infection

There is no evidence to support that even long-haul flights could have an influence on the CD4 T-cell count of PLWH.

5.11 Summary

In summary, the virological control (HIV RNA <50 copies/µl) as well as the preserved immune function (CD4 T-cell count >200/mm3) represent key aspects of a well-controlled HIV infection. They represent, however, just two of the aspects that should be monitored in order to reduce the risk of sudden or subtle incapacitation. PLWH are at higher cardiovascular disease (CVD) risk than the general population, even when on a suppressive cART and with well-preserved immune function. Therefore, the other aspects to be routinely monitored are represented by cardiovascular disease (CVD) assessment (ASCVD score and Framingham score) in order to prevent CVDs. This should involve a specialist, particularly if the CVD risk is high. The evaluation and management of CVD prevention should be based in any case on current guidelines and should aim to manage traditional CVD risk factors in all HIV-infected people regardless of their viro-immunological condition. Therefore, individuals should

- be helped to stop smoking;
- manage their lipids when LDL is above the risk threshold for the general;
- actively manage high blood pressure;
- be helped to reduce their weight if overweight;

A neurocognitive assessment by standardised tools should be routinely performed in order to identify early risk of incapacitation. If ANI is detected, a PLWH should be monitored for the risk of clinical progression to a mild neurocognitive impairment (MND) every 6 months by a standard neuropsychological test battery.
Plasma HIV RNA, CD4 T-cell counts along with CBC, and biochemical tests for liver and kidney function represent the analysis by which the infection should be routinely monitored.
Finally, it should be recognised that PLWH, even the early and successfully treated ones, are at higher risk of co-morbidities compared to the general population.

6 Recommendations

6.1 Recommendation 1

In general, HIV screening is recommended. All persons with HIV infection should be immediately referred to an appropriate specialist HIV treatment centre and start antiretroviral therapy as soon as possible. This also applies to HIV elite controllers. HIV viraemia, CD4 T-cell count, CD4-CD8 ratio should be monitored at regular intervals.

6.2 Recommendation 2

PLWH should be closely monitored for side effects of ART. PLWH with depressive symptoms should avoid taking integrase inhibitors. Those on treatment with integrase inhibitors should be monitored for the onset of insomnia and depression.

6.3 Recommendation 3

PLWH should be routinely screened for mental health problems using clinical questions and symptoms survey according to the EACS guidelines. Special attention should be given to certain HIV treatments which might cause depression.

6.4 Recommendation 4

PLWH should be regularly assessed for HAND. Any suspicion of neurocognitive impairment (NCI) should be confirmed by a complete neuropsychological assessment (NPA) through a standardised method.

6.5 Recommendation 5

Managing traditional CVD risk factors in all PLWH, regardless of their viro¬immunological condition, should be a priority.

6.6 Recommendation 6

PLWH who use PrEP should undergo every 3 months testing for creatinine, phosphataemia, serology for HIV, serologies for HBV in case of non-vaccination or non-response to vaccination, HCV Ab, serology for syphilis, chlamydia and gonorrhoea on rectal and pharyngeal swabs and urine by polymerase chain reaction (PCR). They should also be carefully interviewed on the use of recreational drugs which are difficult to detect with commercial tests.

7 Follow-on research

Until now, there has been no specific research on aircrew members who are living with HIV. It is thus difficult to make specific statements on this professional group. Focussed research is recommended to fine tune recommendations regarding the monitoring of PLWH for the purpose of assessing their fitness to fly.

8 Conclusions

The literature review did not reveal any risk that is not mitigated by the implementing rules and acceptable means of compliance. Furthermore, the current regulatory system allows issuing a Class-1 medical certificate to PLWH when certain conditions are met. More research would be necessary to justify any change to the acceptable means of compliance. A future research project would need to focus more closely on the specific circumstances of medically certified pilots so as to assess the impact of HIV-positive status, and of the side effects of combined antiretroviral treatment, on their fitness to fly and their general health and well-being.

Appendix A: Literature review ‘pilots living with HIV’

Appendix B: List of acronyms

REVIEW OF RECENT SCIENTIFIC PUBLIATIONS TO SUPPORT A DECISION ON A CHANGE IN THE AEROMEDICAL CERTIFICATION OF APPLICANTS FOR COMMERCIAL PILOT LICENSE LIVING WITH HIV

Cristina Mussini, Andrea Antinori, Carlo Federico Perno
October 2020

INTRODUCTION

Rationale and approach

Antiretroviral therapy (ART) has deeply changed the clinical course of the human immunodeficiency virus (HIV) infection. The life expectancy of persons living with HIV, assuming that the antiretroviral treatment is successful, approaches that of HIV-negative subjects. The ability to lower plasma viraemia to undetectable levels prevents the transmission of the infection through sexual intercourse or through vertical transmission during pregnancy. In light of the progress that has been made in managing HIV, a European Union Member State was challenged by an interest group on why it was possible for a pilot who becomes HIV-positive to obtain a Class 1 medical certificate with an operational multi-pilot limitation (OML) whilst an applicant who is yet to obtain a licence cannot, as European Union regulations only permit the endorsement of a medical certificate with an OML for a holder of commercial pilot licence (CPL), an airline transport pilot licence (ATPL) or a multi-pilot licence (MPL). Thereby, HIV-positive applicants are excluded from training for a commercial pilot licence. In our opinion, there should now be no obstacle for considering persons living with HIV in a similar way to any person living with other chronic inflammatory diseases such as lupus erythematosus, rheumatoid arthritis or diabetes (1, 2). Our strategy was to undertake a literature review in order to answer to a series of proposed questions.

Identification and analysis of documents for reviewing evidence

In order to answer the questions, we:

a) used the most recent guidelines:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/282.
2. EACS Guidelines, version 10.0, November 2019. Available at https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf.

b) used the most recent literature where the topic was not included in the guidelines above.

Analysis of evidence from scientific literature was performed by using a modification of the GRADE system in order to evaluate the strength of evidence. Informal questions were formulated on the basis of the PICO (population, intervention, comparator and outcome) framework. The analysis of the evidence was based on the review of: guidance documents (guidelines and consensus documents), summary documents (systematic review or meta-analysis), primary literature and grey literature. The documents were obtained by consulting the PUBMED, EMBASE and COCHRANE LIBRARY databases, selecting documents, published in English, up to 30 September 2019. The websites of international organisations (WHO, ECDC) and national organisations (NIH, NIAID, CDC, BHIVA, etc.) were also consulted.

Based on the documents found, the working group have commented on the strength of the recommendations and level of evidence. Recommendations are based upon scientific evidence and

expert opinion. Each recommended statement includes a letter (A, B, or C) that represents the strength of the recommendation and a Roman numeral (I, II, or III) that represents the quality of the evidence that supports the recommendation.

The rating scheme for the recommendations was as follows:

Strength of the recommendation:

A = Strong recommendation for the statement;

B = Moderate (conditional) recommendation for the statement;

C = Optional recommendation for the statement.

Quality of evidence for the recommendation:

I = One or more randomised trials with clinical outcomes and/or validated laboratory end points (high quality);

II = One or more well-designed, non-randomised trials or observational cohort studies with long-term clinical outcomes (moderate quality);

III = Expert opinion (low quality).

1. HIV testing and early management of the infection

1.1. Numerous HIV tests exist. Which of these tests are/is considered as gold standard in Europe?

Evidence from the literature

Primary HIV infection extends approximately 2 to 4 weeks from initial infection. This is the period from the point of virus entry to the appearance of HIV-specific antibodies that can be detected by an HIV antibody test (it is represented by an evolving anti-HIV antibody reactivity, from negative or indeterminate to positive). During primary infection, HIV is highly infectious because the virus is multiplying rapidly. The rapid increase in HIV viral load (VL) can be detected before HIV antibodies are present.

Primary HIV infection presents symptomatically in 23 to 92 % of newly infected individuals. Signs and symptoms that occur during seroconversion are often referred to as acute retroviral syndrome (ARS).

The diagnosis of chronic HIV-1 infection is based on the detection of specific antibodies (screening test), confirmed by a test based on western- or immuno-blotting (confirmation test), according to the methods set out in official policies for HIV testing in different European countries (example in Italy: Rep. N. 134/CSR del 27 luglio 2011 [11A11001]; G.U. Serie Generale n. 191 del 18 agosto 2011). Where a national accreditation scheme is not available, testing should be undertaken only using approved (e.g. CE, FDA) tests under the auspices of a strict quality assurance programme; quality assurance results should be made available for inspection where required.

Venous blood is the preferred specimen for HIV testing. Samples other than venous blood, such as fingerpick blood or oral fluid, may be used for HIV testing in specific circumstances and subject to rigorous training and quality assurance (1).

Laboratories should conduct initial testing for HIV with a fourth-generation antigen/antibody immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to test for established HIV-1 and HIV-2 infection and for acute HIV-1 infection respectively (Table 1). This formulation allows the detection of the presence of infection even in cases where antibodies are not yet formed (primary infection) or in advanced stages in which profound immunosuppression is accompanied by the possible loss of antibodies (2). Assays available in Europe have excellent sensitivities (99.78–100 %) and specificities (99.5–99.93 %) (3), and as such no further testing is required for specimens that are non-reactive on the initial immunoassay.

Table 1 — Food and Drug Administration (FDA) approved HIV screening tests for laboratory use only (Table modified as from Ref. 4)

Test Name	Target analyte	Approved specimen types and volume	Assay format
Abbott Architect HIV Ag/Ab Combo Assay (fully automated CLIA moderate assay)	HIV-1 p24 antigen and antibodies to HIV-1/2	Plasma/serum 150 µl	Chemiluminescent microparticle immunoassay (CMIA)
ADVIA Centaur HIV Ag/Ab Combo (CHIV) (fully automated CLIA moderate assay)	Antibodies to HIV p24 Ag, HIV-1 including group O, and/or HIV-2	Serum/Plasma	Chemiluminescent microparticle immunoassay (CMIA)
BioPlex® 2200 HIV Ag-Ab	Simultaneously detects and reports: HIV Ag-Ab overall result with HIV-1 p24 Ag HIV-1 Ab (groups M & O) HIV-2 Ab	Plasma (K2 EDTA, K3 EDTA), lithium heparin, sodium heparin, serum	Multiplex flow immunoassay
Bio-Rad GS HIV Combo Ag/Ab EIA (manual or semi-automated CLIA high complexity assay)	HIV-1 p24 antigen and antibodies to HIV-1/2	Plasma/serum 75 µl	Enzyme immunoassay micro-well format (EIA)
Ortho VITROS HIV Combo Test on the VITROS 3600 Immunodiagnostic System	HIV-1 p24 antigen and antibodies to HIV-1/2	Plasma/serum 80 µl	Immunometric 2-stage reaction
Roche Elecsys HIV combi PT on the cobas e 602	HIV-1 p24 antigen and antibodies to HIV-1/2	Plasma/serum 39 µl	Electro-chemiluminescence Immunoassay (ECLIA)

However, if there is a possibility of very early infection leading to a non-reactive initial antigen/antibody immunoassay, such as when recent HIV exposure is suspected or reported, then an HIV-1 nucleic acid test (NAT) should be conducted, or a further venous blood sample requested.

Confirmatory algorithms may vary. Generally, they include at least one additional antibody or antibody/antigen serology test that employs a different platform from the initial screening test. This may be replaced by testing a plasma sample for HIV-1 RNA, provided the VL is >1 000 copies/µl. In patients with a lower or undetectable VL, a second serum sample should be collected to repeat serological testing. Confirmatory tests, as well as nucleic acid detection, permit the distinction between HIV-1 and HIV-2 infection.

At least four commercial methods are available for the determination of HIV-1 viraemia by employing real-time amplification with analytical sensitivity of up to 20–40 copies/µl (4–7). These systems have a higher reliability than the previous systems based on non-real-time methods (sensitivity limit around 50 copies/µl).

The methods based on amplification in real-time are not generally significantly different in terms of sensitivity and reproducibility, and show an inter-method concordance with a correlation coefficient in an almost optimal range (0.90–0.97) (4). However, this concordance may decrease in the presence of viral strains belonging to different subtypes, and for low viraemia levels, in particular below

200 copies/µl (4). In this regard, some recent works have shown non-B strain differences in viraemia values even greater than 1 $\log_{10}$ between the different real-time polymerase chain reaction (PCR) methods; these differences may be even more common in the case of recombinant forms (CRFs), such as CRF02 AG (6, 7).

Recommendation

HIV screening should be performed with assays that can detect recent HIV infection, either an instrument-based combination p24-antigen/HIV-antibody fourth-generation assay, or a combination of a stand-alone antibody assay and nucleic acid testing (NAT) through real time.

Strength of the recommendation

AII

References

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1.2. What are the elements of a clinical assessment that should be assessed in a person that is newly diagnosed as HIV-positive?

Evidence from the literature

Following a positive HIV diagnosis, a newly diagnosed individual should be immediately referred to an appropriate specialist HIV treatment centre for further management and care (1).

Before starting combination antiretroviral treatment (cART), recommended laboratory monitoring includes:

1. HIV RNA level;
2. CD4 T-cell count;
3. reverse transcriptase and protease genotype;
4. general health (testing for kidney/liver function, lipid levels, complete blood cell count, glucose level, and pregnancy status);
5. co-infections (hepatitis A, B, and C, tuberculosis, and sexually transmitted infections (STIs)).

Unless there is pre-existing kidney or liver damage or a high likelihood of transmitted drug resistance, the results of these tests should not necessarily delay the start of cART (1–5).

Pre-therapy viraemia plays an important role in achieving virological suppression. In the presence of particularly high pre-therapy viraemia values, the achievement of virological suppression (<50 copies/µl) may take a longer time (sometimes more than the expected 24 weeks), and/or is less frequent (6). Some drugs or antiretroviral regimens are associated with a lower virological response in patients with a high pre-therapy VL (7), therefore the frequency of viraemia measurement at the beginning of the therapeutic path represents a fundamental element for a correct therapeutic planning (1). Lastly, all available HIV screening tests can have false-positive results, so additional testing with an HIV VL is recommended before cART initiation, although treatment may be started before results are available.

Genotypic resistance testing (GRT) is universally indicated as an indispensable diagnostic tool for a correct therapeutic approach aimed at prolonged maintenance of virological suppression and of immune and clinical homeostasis (1). Both genotypic and phenotypic resistance tests are available, though genotypic tests are universally used for this purpose (see below). The standard tests provide information on resistance to protease inhibitors (PIs) and to those of reverse transcriptase (RT), nucleoside (NRTI) and non-nucleoside analogues (NNRTI). Tests are also available for the evaluation of resistance to integrase inhibitors (INSTI) and fusion inhibitors (FIs), as well as tests for the determination of co-receptor tropism (R5, X4, Dual/Mixed) of HIV-1.

The genotypic test is preferred to the phenotypic one due to its lower cost, faster results, and greater sensitivity in identifying the quasi-species composed of resistant and sensitive viruses (8).

Performing a GRT close to the time of diagnosis makes it possible to appreciate in real time the transmission trend of resistance mutations (8). The presence of transmitted resistance is associated with greater progression of the disease. Furthermore, it is associated with a lower virological response if patients are treated with a non-fully active regimen (8, 9). Therefore, its assessment is necessary for a correct therapeutic approach aimed at achieving prolonged virological suppression and immune and clinical homeostasis.

The use of GRTs for viral protease and RT is recommended in all cART-naive patients (1). Integrase genotyping generally is not currently required and is not considered fully cost-effective at this time (1, 10). However, the high prevalence of polymorphisms potentially associated with INSTI resistance observed in the integrase of newly diagnosed patients (11) indicates the usefulness of carrying out an integrase GRT even in naive patients, in order to monitor the possible emergence of transmitted INSTI resistance (1).

The GRT has a particular clinical utility only if correctly interpreted. To this end, specific diagnostic algorithms exist, which require an integration with clinical data, including current and past therapies, as well as with VL and CD4 T-cell count.

Despite the genetic variability among the different HIV-1 subtypes (up to 12 % of the nucleotide sequence), to date there is no clinical data that clearly indicates a particular diagnostic and therapeutic caution towards strains other than subtype B (12).

It should be stressed that after positive HIV diagnosis, it is important to offer not only continuous monitoring of viral and immunological parameters for HIV infection, but also regular, comprehensive and easily accessible monitoring of other STIs and repeated sexual risk reduction counselling in a context of sympathetic, non-judgemental sexual history taking (13).

Recommendation

HIV screening with assays that can detect recent HIV infection is recommended, either in the form of an instrument-based antigen/antibody combination assay or as a combination of a stand-alone antibody assay and nucleic acid testing (NAT).

Strength of the recommendation

AII

Recommendation

Following a positive HIV diagnosis, a newly diagnosed individual should be immediately referred to an appropriate specialist HIV treatment centre for further management and care.

Strength of the recommendation

AI

Recommendation

Additional testing of the HIV VL is recommended before cART initiation, although treatment may be started before results are available.

Strength of the recommendation

AI

Recommendation

Samples for HIV-1 RNA level; CD4 T-cell count; HIV genotypic resistance testing for NRTI, NNRTI, and PI; laboratory tests to exclude active viral hepatitis; and chemistries should be drawn before beginning cART, but treatment may be started before results are available.

Strength of the recommendation

AI

Recommendation

In cART-naive patients where there is a delay in starting therapy, HIV viraemia should be determined regularly every 3–4 months until cART is commenced.

Strength of the recommendation

AII

Recommendation

HIV genotypic resistance testing should be performed to assess transmitted NRTI and NNRTI resistance. INSTI genotypic resistance testing at baseline is not currently recommended unless there is suspected exposure to a partner with INSTI resistance.

Strength of the recommendation

BIII

Recommendation

C-C chemokine receptor type 5 (CCR5) tropism testing is recommended each time when considering maraviroc, and HLA-B*5701 testing (only needed once) before use of abacavir.

Strength of the recommendation

AI

Recommendation

Age- and risk-appropriate screening for STIs at various anatomical sites, anal or cervical dysplasia, tuberculosis, general health, and medication toxicity is recommended.

Strength of the recommendation

AIII

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2. Monitoring

2.1. What parameters should be routinely monitored in someone living with HIV?

Evidence from the literature

Patients taking cART should have regular clinical and laboratory evaluations, including age- and risk-appropriate screening. From a virological and immunological standpoint, the following laboratory parameters should be routinely monitored:

1. **HIV viraemia:** The production of viral particles represents, even today, the driving force in disease progression, even in patients receiving cART, or in those who show an immunity situation not yet compromised (CD4 >350 cells/mm^3) (1, 2). The damage caused by the continuous viral replication is also aggravated by the risk of the emergence of resistant viral strains. All these considerations support both the need for continuous and careful monitoring of HIV-infected patients undergoing treatment, and the importance of maintaining the VL as low as possible during the entire treatment.

2. **CD4 T-cell count:** Once viral suppression occurs with cART, CD4 T-cell counts usually increase (3). The clinical impact of the frequent monitoring of CD4 T-cell in patients with a conserved immune system and persistent virological suppression has recently been questioned

by numerous large observational cohort studies (4–7). A retrospective study in 1 820 cART-receiving patients with undetectable viraemia showed that patients with CD4 >300 cells/µl are >99 % more likely to maintain >200 cells/µl over time (8). The usefulness of their frequent monitoring is therefore questioned, even in patients with inadequate immuno-reconstitution, for which there is no agreement about the usefulness of modifying the cART and/or associating adjuvant therapies. Finally, recent cost-effectiveness studies have shown that their monitoring appears to be less advantageous economically than virological monitoring (9, 10).

3. **CD4 T-cell percentage:** Co-morbidities and concomitant therapies can lead to variations in the total number of white blood cells, and consequently in the number of CD4 T-cells, without however changing the overall percentage, which must therefore be considered a useful parameter in assessing the actual immunological status of the patient.
4. **CD4–CD8 ratio:** Recently, the CD4–CD8 ratio has also taken on an increasing clinical significance as an indicator of the degree of functionality of the immune system. In fact, even in the case of effective cART, the CD4–CD8 ratio rarely normalises. An increasingly high number of literature data has clearly shown a strong association between CD4 T-cells, CD8 T-cells, immune activation, disease progression and mortality/morbidity during antiretroviral therapy with suppressed viraemia (11–13).

Recommendation

HIV viraemia is the most important indicator of therapeutic efficacy; therefore, it should be measured at regular intervals, especially in patients starting cART.

Strength of the recommendation

AI

Recommendation

CD4 T-cell measurements are recommended every 6 months until above 250/µl for at least 1 year with concomitant viral suppression.

Strength of the recommendation

BIII

Recommendation

Afterward, CD4 T-cell counts need not be measured unless cART fails (defined below) or the patient has an immunosuppressive condition or treatment, such as steroid treatments or chemotherapy.

Strength of the recommendation

AIII

Recommendation

The percentage value of CD4 T-cells and the CD4–CD8 ratio should be evaluated together with the absolute CD4 number in order to obtain a better estimate of the functionality of the immune system, especially in patients at risk of poor recovery of CD4.

Strength of the recommendation

AII

References

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2.2. How should HIV-positive patients with low-level HIV viraemia be monitored?

Evidence from the literature

The measurement of the residual HIV viral load (VL) with systems capable of detecting quantities of viruses from 50 copies/µl down to 1 copy/µl of HIV RNA is particularly interesting. In this regard, there is several relevant data that supports the hypothesis of a potential clinical relevance of the amount of residual viraemia (1–6). Several studies have shown a direct correlation between the amount of residual viraemia and the subsequent risk of virological failure (3–5). Indeed, in a retrospective study, Gianotti et al. analysed data of 194 patients receiving antiretroviral therapy with <50 HIV RNA copies/µl in plasma, history of virological failure, clade B HIV, HIV DNA and HIV RNA measured on the same day. Virological rebound (VR) occurred in 29 out of 194 (15 %) subjects during follow-up; VL at failure was 167 (81–1 932) HIV RNA copies/µl. Patients with residual viraemia (RV) had higher probability of VR than those with undetectable viraemia (UV) ($p = 0.006$), whereas higher HIV DNA loads were not associated with a higher probability of VR ($p = 0.714$) (5).

RV can therefore be considered a useful parameter in virologically suppressed patients. From a pathogenetic point of view, RV could contribute to persistent immune activation and inflammation, thus favouring the progression of the disease in patients treated with cART. Boyd et al., in a cross-sectional study, reported that median adjusted pro-inflammatory markers tended to be higher in patients with detectable (D-) than undetectable (UD-) viraemia (C-reactive protein: 3.11 versus 2.43 mg/l; interleukin (IL)-18: 213.8 versus 89.7 pg/ml; resistin: 6.48 versus 6.25 ng/ml; IL-6: 1.33 versus 0.79 pg/ml; D-Dimer: 147.4 versus 139.3 ng/ml, respectively) as was insulinemia (7.3 versus 6.0 mU/l), although no significant differences were observed (6). Likewise, patients with D-viraemia exhibited higher adjusted median levels of anti-inflammatory markers than with UD-viraemia (HMW/total adiponectin: 1.06/3.61 versus 0.92/2.54 mg/ml; IL-27: 1 325 versus 1 111 pg/ml; IL-10: 0.94 versus 0.65 pg/ml, respectively), with only differences in IL10 being significant ($p = 0.03$). In addition, no significant difference in chemokines were observed between groups, yet monokine induced by gamma interferon (Mig) was roughly 1.5 times higher and fractalkine 2 times higher in patients with D- versus UD-viraemia (6). The authors concluded that the generally higher inflammatory levels observed in patients with detectable versus undetectable HIV viraemia indicates that the degree of systemic inflammation may be slightly attenuated, compared to inflammation at higher HIV levels.

However, it should be noted that to date the quantitative assessment of residual viraemia, although clinically relevant, is carried out with ultrasensitive tests which are not yet standardised. In addition, there is no indication from clinical trials or international guidelines to intensify the regimen with additional antiretrovirals in case of persistence of low-level viraemia (7, 8). Concerning values of low-level viraemia between 50 and 200 copies/µl, previous studies have assessed the prognostic value of vireamia copy-years after cART initiation to predict mortality or clinical progression. Viraemia copy-years predicted all-cause mortality independent of traditional, cross-sectional VL measures and time-updated CD4 T-cell count in cART-treated patients (9), suggesting that cumulative HIV replication causes harm independent of its effect on the degree of immunodeficiency, and should be avoided.

Recommendation

Optimal care for patients with persistent viraemia between 50 and 200 copies/µl is not clearly defined yet. The cART regimen should be continued, with assessment of medication adherence. Switches can be considered in specific cases (VL increase, limited adherence to low-genetic barrier regimens, persistent low-level viraemia, etc.).

Strength of the recommendation

BIII

Recommendation

Residual viraemia can be considered a useful parameter in virologically suppressed patients to predict negative developments of other diseases.

Strength of the recommendation

BIII

References

1. Swenson LC, Cobb B, Geretti AM, et al., International Viral Load Assay Collaboration. Comparative performances of HIV-1 RNA load assays at low viral load levels: results of an international collaboration. J Clin Microbiol. 2014;52:517–23.
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treatment-naive HIV-infected patients initiating antiretroviral therapy. Clin Infect Dis. 2011;53:927–35.

2.3. Are there age-dependent differences in monitoring HIV-positive patients?

Evidence from the literature

Monitoring of CD4 T-cell count and VL according to the guidelines should be performed every 4 to 6 months in order to detect virological failure as early as possible (1). This is the indication for all subjects and there are no recommendations about age-dependent differences. Nevertheless, maintaining viral suppression is the goal of antiretroviral therapy and adherence to treatment is essential in order to achieve it. Indeed, a meta-analysis by Shubber et al. (2) showed that the most frequently reported individual barriers included forgetting, being away from home, and a change to daily routine. Depression was reported as a barrier to adherence by more than 15 % of the patients across all age categories, while alcohol/substance abuse as commonly reported by adults (12.9 %) and adolescents (28.8 %). Among adults, feeling sick was a more commonly cited barrier to adherence than feeling well. Health-service-related barriers, including distance to clinic and stock-outs, were also frequently reported.

Finally, in a paper of Ettenhofer M. L. et al., mean adherence rates were higher among older (> or = 50 years) than younger (<50 years) HIV-positive adults. However, neurocognitive impairment was associated with poorer medication adherence among older participants only. When cognitive subdomains were examined individually, executive functioning, motor functioning, and processing speed were most strongly related to adherence in >50 age group. CD4 T-cell count and drug use were also more strongly associated with adherence among older adults compared to the younger ones (3). There is evidence that treatment with raltegravir could determine a better lipid profile, i.e. lower triglycerides, but also lower platelet count (4). Virological failure after switching to raltegravir 1 200 mg/day in a 70-year-old man (5) has also been described.

Recommendation

There should not be difference in the monitoring of CD4 T-cell count and VL on the basis only of age in adult subjects.

Strength of the recommendation

AI

References

1. Caniglia EC, Cain LE, Sabin CA, et al., HIV-CAUSAL Collaboration; Comparison of dynamic monitoring strategies based on CD4 T-cell counts in virally suppressed, HIV-positive individuals on combination antiretroviral therapy in high-income countries: a prospective, observational study. Lancet HIV. 2017;4:e251–e259.
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2.4. Are there gender-specific differences in the monitoring of HIV-positive patients?

Evidence from the literature

Cross-sectional and longitudinal studies in acute (1–5) and chronic (6, 7) HIV infection showed that women have lower plasma VLs and higher CD4 T-cell counts than men. It has been shown that HIV VLs in untreated females are up to 40 % lower than those in males; however, despite harbouring lower VLs for a given level of viraemia, women had a 1.6-fold higher risk of progressing to AIDS (8), ultimately resulting in similar times to AIDS between infected women and men.

Concerning response to antiretroviral treatment, most randomised clinical trials enrolled a low percentage of females, but in the two trials conducted only in women, the rate of virological success was similar to that obtained in men; in particular, in the WAVES trial, at week 48 the virological success in elvitegravir arm was 87 %, while in ATV/r was 81 % (9); in the ARIA trial, at week 48 the virological success in dolutegravir arm was 82 %, while in atazanavir/ritonavir was 71 % (10). Concerning real-world data, a recent study conducted on a cohort of 1 989 women identified three trajectories with low (28.6 %), intermediate (39.4 %), and high (32.0 %) probability of detectable viraemia during antiretroviral treatment. Factors associated with a high probability of detectable viraemia between 2015 and 2017 were: younger age, African American or Hispanic race/ethnicity, depression symptoms, drug use, and unstable housing; nevertheless, 71.2 % of the women achieved sustained viral suppression, including 35.2 % of those in the group with a high probability of viraemia (11).

Recommendation

Men and women should be monitored for HIV with the same frequency of CD4 T-cell count and plasma viraemia monitoring.

Strength of the recommendation

AI

References

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2.5. How is remission, resolution and/or stability of the HIV disease defined?

Evidence from the literature

Remission or resolution of the HIV infection is not achievable at the moment, but the ‘stability’ of the HIV infection may be defined as having more than 200 CD4 T-cell count on effective cART, and HIV RNA <50 copies/µl for more than 6 months. This assessment is based on several considerations:

cART has reduced HIV-related morbidity and mortality at all stages of HIV infection (1–4), and has reduced HIV transmission (5–8). Maximal and durable suppression of plasma viraemia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 T-cell count, and confers substantial clinical benefits, all of which are important treatment goals (9).

Before the availability of cART, starting in the late 1980s, the use of chemoprophylaxis, immunisation, and better strategies for managing opportunistic infections improved the quality of life and prolonged the survival of persons with HIV (10–11). The introduction of highly effective cART in the mid-1990s has had the most profound influence on reducing opportunistic infection (OI)-

related morbidity and mortality in persons with HIV (12–17), and guidelines for stopping chemoprophylaxis for opportunistic infections have been developed based on the fact that immunological and virological criteria reached in people on cART determine a significantly reduced risk of developing opportunistic infection render the continuation of chemoprophylaxis useless. These criteria are to be on effective cART (HIV RNA <50 copies/µl) >6 months with CD4 T-cell count >200/mm^3.

Recommendation

The HIV infection may be defined as stable when the patient has more than 200/mm^3 CD4 T-cell count on effective cART (HIV RNA <50 copies/µl) for more than 6 months.

Strength of the recommendation

AII

References

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3. Antiretroviral therapy

3.1. Are there circumstances where someone living with HIV has a better prognosis (e.g. for not developing adverse effects of their infection) if they are not on ART?

Evidence from the literature

The START trial was a large, multi-national, randomised, controlled clinical trial designed to evaluate the role of early cART in asymptomatic patients with HIV in reducing a composite clinical end point of AIDS-defining illnesses, serious non-AIDS events, or death (1). In this study, cART-naive adults (aged >18 years) with CD4 T-cell count >500 cells/mm^3 were randomised to initiate cART soon after randomisation (immediate-initiation arm) or to wait to initiate cART until their CD4 T-cell counts declined to <350 cells/mm^3 or until they developed a clinical indication for therapy (deferred-initiation arm). The study enrolled 4 685 participants, with a mean follow-up of 3 years. When the randomised arms of the study were closed, the primary end point of serious AIDS or non-AIDS events was reported in 42 participants (1.8 %, or 0.60 events/100 person-years) in the immediate cART arm and 96 participants (4.1 %, or 1.38 events/100 person-years) in the deferred cART arm (hazard ratio (HR) 0.43, favouring early cART (95 % confidence interval (CI), 0.30–0.62, $P < .001$)). The most common clinical events reported were tuberculosis and AIDS and non-AIDS malignancies. The majority (59 %) of the clinical events in the deferred cART arm occurred in participants whose CD4 T-cell counts were still above 500 cells/mm^3, evidence for a benefit of immediate cART even before CD4 T-cell count declines below this threshold. Furthermore, the benefit of immediate cART was evident across all participant subgroups examined, including men and women, older and younger participants, individuals with high and low plasma HIV RNA levels, and participants living in high-income and low-/middle-income countries. Although START was not sufficiently powered to examine the benefit of immediate cART for each category of clinical events, the benefit of immediate cART appeared to be particularly strong for AIDS events (HR 0.28 (95 % CI, 0.15–0.50, $P < .001$)), tuberculosis (HR 0.29 (95 % CI, 0.12–0.73, $P = .008$)), and malignancies, especially those AIDS

related as Kaposi's sarcoma and lymphomas (HR 0.36 (95 % CI, 0.19 to 0.66; $P = .001$)). Importantly, immediate cART also significantly reduced the rate of pooled serious non-AIDS events (HR 0.61 (95 % CI, 0.38–0.97, $P = 0.04$)). Finally, immediate cART also decreased the risk of severe bacterial infections (2).

The TEMPRANO ANRS 12136 study was a randomised controlled trial conducted in Cote d'Ivoire (3). Using a two-by-two factorial design, participants with HIV who had CD4 T-cell counts <800 cells/mm^3 were randomised to either immediate cART or deferred cART (based on national guidelines' criteria for starting treatment); half of the participants in each group received isoniazid for the prevention of tuberculosis for 6 months and half did not. The primary study end point was a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases. More than 2 000 participants enrolled in the trial, with a median follow-up of 30 months. Among the 849 participants who had baseline CD4 T-cell counts >500 cells/mm^3, 68 primary outcome events were reported in 61 patients. The risk of primary events was lower with immediate cART than with deferred cART, with a hazard ratio of 0.56 in favour of early cART (CI, 0.33–0.94). On the basis of these results, the study team concluded that early cART is beneficial in reducing the rate of these clinical events.

Concerning side effects due to antiretroviral therapy, in the START trial there was an advantage of immediate treatment on glomerular filtration rate, quality of life and pulmonary capacity (4–6). On the other hand, immediate treatment had a negative influence on bone mineral density (7).

Recommendation

All subjects with HIV infection should start antiretroviral therapy as soon as possible.

Strength of the recommendation

AI

References

1. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al., Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373:795–807.

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3.2. For an asymptomatic person living with HIV who does not want to be on ART, what clinical assessment and investigations should be conducted and with what frequency?

Evidence from the literature

The START trial has clearly demonstrated the advantage of antiretroviral therapy also in asymptomatic subjects (1). The CASCADE collaboration showed that in more recent years (after 2000 compared to the early 1980s) there has been a change in the surrogate markers of infection. Indeed, they studied CD4 T-cell counts and VL at seroconversion in 15 875 individuals seroconverting from 1979 to 2008. Estimated CD4 T-cell counts at seroconversion for a typical individual declined from about 770 cells/µl (95 % CI, 750–800) in the early 1980s to a plateau of about 570 cells/µl (555–585) after 2002. The CD4 T-cell rate of loss increased up to 2002. The estimated set-point plasma VL increased from 4.05 $\log_{10}$ copies/µl (95 % CI, 3.98–4.12) in 1980 to 4.50 $\log_{10}$ copies/µl (4.45–4.54) in 2002 with a tendency to return to lower loads thereafter (2).

A small subset of individuals with HIV elite controllers maintain plasma HIV-1 RNA levels below the level of quantification for years without antiretroviral treatment (3, 4). There is limited data on the role of antiretroviral therapy in these individuals; nevertheless, elite controllers with normal CD4 T-cell counts also show evidence of abnormally high immune activation and surrogate markers of atherosclerosis, which may contribute to an increased risk of non-AIDS-related diseases (5). One observational study suggests that HIV elite controllers are hospitalised more often for cardiovascular and respiratory diseases than patients from the general population and cART-treated patients (6). It is unclear whether this potential immunologic benefit of cART in HIV elite controllers outweighs potential ART toxicity and results in clinical benefit. Unfortunately, randomised controlled trials to address this question are unlikely, given the very low prevalence of HIV elite controllers. At the opposite site of HIV elite controllers are rapid progressors. Out of 4 876 individuals, 2.8, 7.3 and 24.9 % experienced a decline in CD4 T-cell count to <100, <200, and<350 cells/mm^3 respectively within 1 year of seroconversion. Mean (95 % CI) AIDS-free survival at 10-year follow-up was 2.9 (2.3 to 3.6), 5.5 (5.0 to 6.1), 6.7 (6.5 to 7.0), 7.4 (7.2 to 7.6), and 8.1 (7.9 to 8.3), for those with minimum counts <100, 100–200, 200–350, 350–500, and >500 cells/mm^3 respectively. Using counts of
>500 cells/mm^3 as reference, the hazard ratios (95% CI) of AIDS/death were 15.0 (11.9 to 18.9), 3.6 (2.9 to 4.5), 2.1 (1.8 to 2.4), and 1.5 (1.3 to 1.7) respectively. The hazard ratio increased to 37.5 (26.5 to 53.1) when a minimum CD4 T-cell count of 100 was confirmed within 1 year of seroconversion (7).

Recommendation

Subjects with HIV infection who do not want to take antiretrovirals should be monitored every

2 months since they could be rapid progressors.

Strength of the recommendation

AII

Recommendation

HIV elite controllers with undetectable VL and CD4 T-cell counts above 500 cells/μL should be monitored for CD4 and plasma VL every 4–6 months.

Strength of the recommendation

BII

Recommendation

Considering the higher cardiovascular risk in the absence of treatment compared to individuals on cART, HIV elite controllers should start antiretroviral treatment, even if more research is needed in the field.

Strength of the recommendation

BII

References

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3.3. How should an individual be monitored when the antiretroviral therapy is initiated, modified or discontinued?

Laboratory assessments are recommended before treatment, and monitoring during treatment is

recommended to assess response, adverse effects, and adherence.

The Panel on Antiretroviral Guidelines for Adults and Adolescents of the U.S. Department of Health and Human Services (HHS), the European AIDS Clinical Society (EACS), and the International AIDS Society-USA (IAS-USA) panel recommend genotype drug resistance testing for people newly diagnosed with HIV prior to cART initiation (1–3). Resistance testing should be used to guide selection of a cART regimen.

Two surrogate markers are routinely used to monitor patients with HIV: CD4 T-cell count to assess immune function and plasma HIV RNA to assess the level of HIV viraemia. HIV RNA allows to predict the risk of clinical progression of the infection (prognostic marker) and evaluate the extent of the therapeutic response (9). Within 6 weeks of starting cART, adherence and tolerability of therapy should be assessed, along with HIV RNA level. HIV RNA suppression may take up to 24 weeks, or faster with INSTI-based regimens (1). Of note: when monitoring intervals are extended and therapy fails, resistance has more time to emerge.

Recommendations for laboratory monitoring are summarised in **Table 2** (Table modified as from Ref. 1):

Table 2

Test	At HIV Diagnosis	During ART	At Virologic Failure
HIV-RNA level	**X**	Within the first 6 weeks of starting ART or a new ART regimen, then every 3 months until <50 copies/mL for 1 year, then every 6 months	**X**
CD4 cell count	**X**	Every 6 months until >250/µL for 1 year then stop as long as virus is suppressed	**X**
HIV RT genotype	**X**		**X**
HIV integrase genotype			If failing ART regimen included an InSTI
Viral tropism			Each time before the start of ART that includes maraviroc
HLA-B 5701	X (before initiating abacavir; just one)	X (if considering abacavir and not determined previously)	
Safety testing	**X**	**X**	**X**
Co-infection (STIs, tuberculosis, hepatitis, Pap test)	**X**	**X**	
Health maintenance	**X**	**X**	

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer inhibitor; Pap, Papanicolaou; RT-pro, reverse transcriptase and protease; STI, sexually transmitted infection.

Once viral suppression occurs with cART, CD4 T-cell count usually increases (5). CD4 measurements are recommended every 6 months until above 250/µl for at least 1 year with concomitant viral suppression (6). Afterwards, CD4 T-cell count needs not be measured, unless cART fails (defined below), or the patient has an immunosuppressive condition or treatment, such as steroid treatment or chemotherapy (7).

HIV RNA testing is used to detect whether cART fails. Virologic failure is defined as HIV RNA level

above 200 copies/µl on at least two consecutive measurements. Once virologic failure is diagnosed, an HIV genotype should be obtained while the patient is taking the failing regimen.

If HIV genotyping is unsuccessful (not infrequent if HIV RNA level is <1 000 copies/µl), a proviral DNA analysis using deep sequencing methods may be used (8).

Optimal care for patients with persistent viraemia between 50 and 200 copies/µl is not well defined yet. There is no indication to intensify the regimen with additional antiretrovirals, unless specific conditions may occur, judged by the clinician.

The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of co-morbid conditions, and improve quality of life. When selecting a new regimen, the possibility of new drug–drug interactions with antiretroviral and concomitant medication, as well as the lag time for hepatic enzyme induction or blockade following discontinuation of the offending drug have to be carefully reviewed. If the switch implies discontinuing Tenofovir Disoproxil Fumarate (TDF) and not starting Tenofovir Alafenamide (TAF), the Hepatitis B Virus (HBV) status should be checked (avoid discontinuation of TDF in persons with chronic HBV and assess HBV vaccination status) (2).

Recommendation

Measurement of the HIV VL is recommended before cART initiation, while treatment may be started before results are available.

Strength of the recommendation

AI

Recommendation

Once the HIV RNA level is below 50 copies/µl, monitoring is recommended every 3 months until the virus is suppressed for at least 1 year. After 1 year of viral suppression, monitoring can be reduced to every 6 months if the patient maintains consistent medication adherence.

Strength of the recommendation

AIII

Recommendation

Measurement of CD4 T-cell counts is recommended every 6 months until cell counts are >250/µl for at least 1 year with concomitant viral suppression.

Strength of the recommendation

BIII

Recommendation

Measurement of the VL at 4 to 6 weeks after starting a new cART regimen is recommended.

Strength of the recommendation

AIII

Recommendation

If the VL has not declined, adherence and toxicity should be discussed with the patient. If adherence appears to be sufficient, a genotype assay is recommended.

Strength of the recommendation

AIII

Recommendation

HIV genotype to assess transmitted NRTI and NNRTI resistance should be performed; INSTI genotyping at baseline is not recommended unless exposure to a partner with INSTI resistance is suspected.

Strength of the recommendation

BIII

Recommendation

For virologic failure of INSTI containing cART, integrase resistance testing is recommended.

Strength of the recommendation

AIII

Recommendation

Once a new regimen is started, the HIV RNA level should be checked 4 to 6 weeks after initiation, following the same schedule as for the monitoring of the initial therapy.

Strength of the recommendation

AIII

Recommendation

Tropism testing is recommended at the time of virologic failure of a C-C chemokine receptor type 5 (CCR5) inhibitor.

Strength of the recommendation

AI

Recommendation

For patients with persistent viraemia between 50 and 200 copies/µl, the cART regimen should be continued, with assessment of medication adherence and evaluation again within 4 weeks.

Strength of the recommendation

BIII

Recommendation

HIV-positive persons should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity of the new regimen.
For individuals with active HBV infection (detectable HBsAg), a careful monitoring of HBV infection and liver function is recommended after discontinuation of TDF/emtricitabine.

Strength of the recommendation

AII

References

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3.4. Does the pattern of monitoring depend upon the type of the ART regimen?

Evidence from the literature

Abacavir is a nucleoside reverse-transcriptase inhibitor with activity against HIV (available for once-daily use in combination with other antiretroviral agents) that has shown efficacy, few drug interactions, and a favourable long-term toxicity profile. The most important adverse effect of abacavir that limits its use in therapy and mandates a high degree of clinical vigilance is an immunologically mediated hypersensitivity reaction (HSR) affecting 5 to 8 % of the patients during the first 6 weeks of treatment (1). Symptoms of HSR to abacavir include combinations of fever, rash,

constitutional symptoms, gastrointestinal tract symptoms, and respiratory symptoms that become more severe with continued dosing. Immediate and permanent discontinuation of abacavir is mandated, resulting in a rapid reversal of the symptoms. Subsequent rechallenge with abacavir is contraindicated, since it can result in a more severe, rapid, and potentially life-threatening reaction (2, 3). In 2002, an association between a diagnosis of HSR to abacavir and carriage of the major histocompatibility complex class I allele HLA-B*5701 was reported independently by two research groups (7, 8) and was subsequently corroborated by several independent studies (4, 5).

PREDICT 1 study has shown that the prevalence of HLA-B*5701 was 5.6 % (109 out of 1 956 patients enrolled). Screening for HLA-B*5701 eliminated immunologically confirmed HSR (0 % in the prospective-screening group versus 2.7 % in the control group, P <0.001), with a negative predictive value of 100 % and a positive predictive value of 47.9 %. HRS was clinically diagnosed in 93 patients, with a significantly lower incidence in the prospective-screening group (3.4 %) than in the control group (7.8 %) (P <0.001)(6).

Concerning maraviroc, C-C chemokine receptor type 5 (CCR5) is an attractive therapeutic target, since people with the delta32 deletion in both copies of the CCR5 gene lack CCR5 on the cell surface and are relatively resistant to HIV infection, whereas people who are heterozygous for the deletion have reduced expression of CCR5 on the cell surface and have delayed declines in the CD4 T-cell count and slower progression of the HIV disease (7–11).This data supports the rationale for testing CCR5 antagonists in people infected with R5 HIV-1. Finally, in the next question, toxicities are described that are related to single drugs. Actually, even if the frequency of the monitoring could be the same, more attention should be paid to the results of the exams known to be modified by the single drug.

Recommendation

HLA-B*5701 testing should be performed before initiation of abacavir.

Strength of the recommendation

AI

Recommendation

A viral tropism assay should be performed before initiation of a CCR5 antagonist or at the time of virologic failure that occurs while a patient is receiving a CCR5 antagonist.

Strength of the recommendation

AII

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3.5. What are the side effects of ART?
Based on the guidelines of the U.S. Department of Health and Human Services (HHS)

3.5.1. Protease inhibitors

3.5.1.1. Darunavir/ritonavir or darunavir/cobicistat

Patients taking DRV/r may develop skin rash, which is usually mild-to-moderate in severity and self-limited. Treatment discontinuation is necessary on rare occasions when severe rash with fever or elevated transaminases occur. ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. Bone mineral density (BMD) decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm (1). The likelihood of developing metabolic syndrome was equivalent between the three arms, although a larger increase in waist circumference was observed at 96 weeks in participants assigned to the RAL arm than in those assigned to the DRV/r arm ($P \leq 0.02$) (2). An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease (3).

3.5.1.2. Atazanavir/ritonavir or atazanavir/cobicistat

The main adverse effect is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations (4). Nephrolithiasis (5), nephrotoxicity (6), and cholelithiasis (7) have also been reported in patients who received ATV. Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhoea.

3.5.2. Non-nucleoside transcriptase inhibitors

3.5.2.1. Rilpivirine

In the ECHO, THRIVE, and STaR trials, fewer instances of central nervous system (CNS) adverse events (e.g. abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidaemia were reported in the RPV arms than in the EFV arms, and fewer patients in the RPV arms discontinued therapy due to adverse events (8–9). However, up to 9 % of the clinical trial participants experienced depressive disorders, including approximately 1 % of the participants who had suicidal thoughts or who attempted to commit suicide.

3.5.2.2. Efavirenz (EFV)

EFV can cause CNS side effects (e.g. abnormal dreams, dizziness, headache, and depression) that resolve over a period of days to weeks in most patients (8, 9). However, subtler, long-term neuropsychiatric side effects can occur. EFV use has also been associated with suicidality; however, various large studies have provided different results. An analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e. reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (LPV/r, ATV, ATV/r, or ABC-based regimens) (10). Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behaviour among participants in the immediate ART group who took EFV than among ART-naive controls; the risk increased for those with previous psychiatric diagnoses (11). This association, however, was not found in analyses of three large observational cohorts (12, 13), or in a retrospective cohort study that used U.S. administrative pharmacy data (14). A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried an increased risk of suicidal ideation or depression compared to NVP (15). EFV may cause elevation in LDL cholesterol and triglycerides (8, 9). QTc interval prolongation has been observed with EFV use (16, 17). Consider an alternative therapy to EFV in patients taking medication known to increase the risk of Torsades de pointes, or in patients at higher risk of Torsades de pointes.

3.5.2.3. Doravirine

In the DRIVE-AHEAD trial, a greater proportion of participants in the efavirenz arm discontinued their assigned antiretroviral regimen due to adverse events than in the doravirine arm (6.3 % versus 2.7 %). Neuropsychiatric side effects were more common in the EFV arm (18). The doravirine group had no change in LDL cholesterol and non-HDL cholesterol among the participants, whereas both LDL and non-HDL cholesterol increased with efavirenz or darunavir use (18, 19).

3.5.3. Integrase inhibitors

3.5.3.1. Raltegravir

Raltegravir use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported (20). Rare cases of severe skin reactions and systemic hypersensitivity reactions (HSRs) in patients who received raltegravir have been reported during post-marketing surveillance (20). Neuropsychiatric adverse events (e.g. insomnia, headache, depression, and suicidal ideation) have been reported in people receiving integrase inhibitors (21, 22).

3.5.3.2. Elvitegravir/cobicistat

The most common adverse events reported with EVG/c/TDF/FTC were diarrhoea, nausea, upper respiratory infection, and headache (23, 24). The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhoea, headache, and fatigue (25). Neuropsychiatric adverse events have been reported in people receiving INSTIs (25).

3.5.3.3. Dolutegravir

Dolutegravir is generally well tolerated. The most commonly reported adverse reactions of moderate-

to-severe intensity were insomnia and headache. Case series of neuropsychiatric adverse events (sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG have been reported (26). Two observational cohort studies reported a higher frequency of neuropsychiatric adverse events leading to treatment discontinuation in patients receiving DTG than in patients receiving other INSTIs (27, 28). However, analyses of data from large randomised controlled trials as well as a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and other ARV regimens (29), with neuropsychiatric events rarely leading to DTG discontinuation. Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs, not just DTG.

3.5.3.4. Bictegravir

Bictegravir is generally well tolerated. In clinical trials, the most commonly reported adverse reactions of all grades with an incidence ≥5 % included diarrhoea, nausea, and headache. However, randomised trials conducted in naive patients showed no difference in neuropsychiatric adverse events compared to dolutegravir. In particular, both dolutegravir and bictegravir were associated to insomnia 4 % in bictegravir versus 6 % in dolutegravir in the trial in which dolutegravir was combined with abacavir/lamivudine (31) and 5 % versus 4 % in the other trial where dolutegravir was combined with tenofovir alafenamide/emtricitabine (32).

A recent study using data from the Multicenter AIDS Cohort Study, a population-based prospective study of men who have sex with men (MSM) HIV-positive and HIV-negative, assessed every 6 months over 12 years of follow-up. Self-reported sleep disturbance (N2 weeks) and depressive symptoms (Clinical Epidemiologic Scale for Depression (CES-D)). Adjusted mixed effects logistic regression analyses tested whether sleep disturbance predicted depression (CES-D ≥16) at the immediate subsequent visit, and so on over 12 years, in non-depressed HIV-positives (N = 1 054; 9 556 person-visits) and non-depressed HIV-negatives (N = 1 217; 12 680 person-visits). In the HIV-positive MSM, sleep disturbance was associated with a significant increase in depression 6 months later (OR = 1.6; 95 % CI, 1.30, 1.96), which was significantly greater (P b .05) than in HIV-negative MSM (OR = 1.16; 95 % CI, 0.94, 1.44). HIV status and sleep disturbance interacted (P b .001), such that incidence of depression and normalised cumulative rate of depression were greater in HIV-positives with sleep disturbance than in HIV-positive without sleep disturbance and HIV-negative groups (all P's b 0.001) (33).

3.5.4. Nucleoside reverse transcriptase inhibitors

3.5.4.1. Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) and Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC)

New onset or worsening renal impairment has been associated with TDF use (34, 35). Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in females) and pre-existing renal impairment (36, 37). Concomitant use of a PK-enhanced regimen (with a PI or EVG/c) can increase TDF concentrations; studies have suggested that there is a greater risk of renal dysfunction when TDF is used in these regimens. As previously noted, adverse effects on renal biomarkers such as proteinuria, especially tubular proteinuria, were more frequent with TDF than with tenofovir alafenamide (35, 38–41). Adverse renal outcomes are more likely when TDF/FTC is

co-administered with PK boosters (RTV or COBI). A meta-analysis of randomised trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC with PK boosting (42). While initiation of all NRTI-containing regimens has been associated with a decrease in bone mineral density (BMD), the loss of BMD is greater with TDF-containing regimens (43, 44). Moreover, cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF (45). Adverse bone outcomes are more likely when TDF/FTC is co-administered with PK boosters (RTV or COBI). A meta-analysis of randomised trials found that fractures and discontinuation due to bone adverse events occur more frequently among patients who take TDF/FTC with PK boosting (42).

3.5.4.2. Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

In randomised controlled trials that compared TAF and TDF in treatment-naive or virologically suppressed patients, TAF had more favourable effects on renal biomarkers, in particular proteinuria, especially tubular proteinuria, and bone density than TDF (46–48). Concerning lipids, in randomised controlled trials in ART-naive patients, as well as in switch studies, LDL and HDL cholesterol and triglycerides levels were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol-to-HDL ratios did not differ among patients receiving TAF and TDF (48, 49).

3.5.4.3. Abacavir/lamivudine

Clinically suspected hypersensitivity reactions (HSRs) were observed in 5 to 8 % of the individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele; approximately 50 % of HLA-B*5701-positive patients will have an ABC-related HSR if given this drug (50, 51).

An association between ABC use and myocardial infarction (MI) was first reported in the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. This large, multinational, observational study group found that recent (i.e. within 6 months) or current use of ABC was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors. The most recent article showed that current ABC use was associated with a 98 % increase in MI rate (RR 1.98 (1.72–2.29)) (52, 54). Several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association (55–60). Others, including an FDA meta-analysis of 26 randomised clinical trials that evaluated ABC, have not (61–64). An analysis of data from NA-ACCORD found that the use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors (65).

Recommendation

Subjects with depressive symptoms should avoid taking integrase inhibitors.

Strength of the recommendation

BII

Recommendation

Patients on treatment with integrase inhibitors should be monitored for the onset of insomnia and depression at each clinical visit.

Strength of the recommendation

AI

Recommendation

Patients with severe depressive symptoms should be evaluated to assess whether symptoms may be due to RPV and whether the risks when continuing the same regimen outweigh the benefits.

Strength of the recommendation

AI

Recommendation

Efavirenz should be avoided since it is not recommended and increases the risk of suicide.

Strength of the recommendation

AII

Recommendation

Moreover, EFV in patients taking medication known to increase the risk of Torsades de pointes, or in patients at higher risk of Torsades de pointes, efavirenz should be avoided.

Strength of the recommendation

AI

Recommendation

HLA-B*5701 testing should be done if the use of ABC is being considered. In a patient who tests positive for HLA-B*5701, ABC should not be given and ABC hypersensitivity should be noted on the allergy list. Patients who are HLA-B*5701-negative are far less likely to experience HSR, but they should be counselled about the symptoms of the reaction. Patients who discontinue ABC because of a suspected HSR should never be re-challenged, regardless of their HLA-B*5701 status.

Strength of the recommendation

AI

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3.6. What period of time needs to elapse to be certain that common side effects and those likely to impair performance (physical or cognitive) are unlikely to occur?

It is difficult to assess the average time on cART after which common side effects are unlikely to occur. For example, hypersensitivity reaction (HSR) due to abacavir could occur in 4 weeks. For efavirenz, side effects such as abnormal dreams and dizziness are generally acute, but there are neuropsychiatric side effects due to a cumulative (in terms of years) exposure. Concerning integrase

inhibitors as dolutegravir or bictegravir, neuropsychiatric side effects occur within 6 months from treatment start, but the follow-up of the patients could not, at present, exclude any long-term side effects.

Recommendation

For subjects receiving dolutegravir or bictegravir it would be important to investigate the onset of neuropsychiatric side effects at each visit.

Strength of the recommendation

BI

Recommendation

If the patient reports that the therapy is well tolerated, this could be enough to exclude potential easily recognisable side effects such as diarrhoea or nausea. Nevertheless, some neuropsychiatric side effects such as suicidal ideation should be investigated.

Strength of the recommendation

CI

3.7. How should HIV patients established on cART and with suppressed VL be monitored?

Patients on cART should have regular clinical and laboratory evaluations, including age- and risk-appropriate screening. VL is the single greatest determinant of the risk of HIV transmission. Viral suppression is an indicator of treatment success and reduced potential for transmission (1). Clinical trials exploring switching strategies have defined suppression as an HIV VL <50 copies/µl for at least 6 months (2–3).

Once viral suppression occurs with cART, CD4 T-cell counts usually increase. The absolute number of CD4 T-cells is currently the most validated prognostic immunological marker, as it is the strongest predictor of clinical progression (AIDS and non-AIDS events) (4).

Current guidelines of the U.S. Department of Health and Human Services (HHS) recommend CD4 T-cell count monitoring every 6–12 months in clinically stable patients with suppressed VL (5). In the US, for people living with HIV/AIDS who are virologically suppressed and with high CD4 T-cell counts on cART, the frequency of CD4 T-cell count monitoring can be reduced without any additional risk to the patient in terms of clinical (AIDS and non-AIDS events) and immunological progression (decline of CD4 T-cell counts) (6). A retrospective study has shown that among patients infected with HIV, those with HIV-1 RNA <200 copies/µl and CD4 T-cell counts ≥300 cells/µl had a 97.1 % probability of maintaining durable CD4 T-cell count ≥200 cells/µl for ≥4 years, supporting less frequent CD4 T-cell count monitoring during VL (7).

Afterwards, CD4 T-cell counts need not be measured with great frequency unless cART fails or the patient has an immunosuppressive condition or undergoes treatment, such as steroid treatments or chemotherapy (2).

The combined use of CD4 and CD4–CD8 ratio as an outcome measure offers a new perspective for measuring immune recovery following antiretroviral therapy (8). A recent study by Serrano-Villar et al. has shown that during treated HIV infection, expansion of CD8 T-cells (reflected as a low

CD4–CD8 ratio) identifies a subgroup of individuals with a number of immunological abnormalities and a poor prognosis. Moreover, an early cART initiation might contribute to more rapid and robust CD4–CD8 ratio normalisation compared to later initiation. Hence, the CD4–CD8 ratio might help to further discriminate the risk of disease progression of successfully treated HIV-infected individuals, and a successful response to cART may require both normalisation of the peripheral CD4 T-cell count and the ratio of CD4-to-CD8 cell counts (9).

Recommendation

Once HIV RNA level is <50 copies/µl, monitoring is recommended every 3 months until the virus is suppressed for at least 1 year. After 1 year of viral suppression, monitoring can be reduced to every 6 months if the patient maintains consistent medication adherence.

Strength of the recommendation

AIII

Recommendation

CD4 T-cell measurements are recommended every 6 months until >250 cells/µl for at least 1 year with concomitant viral suppression.

Strength of the recommendation

BIII

Recommendation

In patients treated with cART and HIV RNA <50 copies/µl and steady CD4 T-cell count >500 cells/µl, monitoring frequency of CD4 T-cell counts may be delayed and measured with ≥6-month intervals.

Strength of the recommendation

BII (6–8)

Recommendation

In patients treated with cART and HIV RNA <50 copies/µl and steady CD4 T-cell count between 300 and 500 cells/µl, monitoring frequency of CD4 T-cell counts may be delayed and measured with 4–6-month intervals.

Strength of the recommendation

BII (6–8)

Recommendation

CD4 T-cell counts need to be measured infrequently (once a year, or less than a year) unless cART fails or the patient has an immunosuppressive condition or undergoes treatment, such as steroid treatments or chemotherapy.

Strength of the recommendation

AIII

Recommendation

The percentage value of CD4 T-cells and the CD4–CD8 ratio should be evaluated in conjunction with the CD4 T-cell absolute count in order to obtain a better estimate of the immune system function, especially in patients with a risk of poor CD4 T-cell count recovery (low CD4 nadir (<200 cells/mm^3) co-infections).

Strength of the recommendation

AII

References

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3.8. Are there favourable, less favourable and unfavourable ART regimens (e.g. monotherapy)?

Evidence from the literature

All protease inhibitor, lopinavir/ritonavir, darunavir/ritonavir and atazanavir/ritonavir monotherapies were inferior to combination antiretroviral therapy (1–4). Indeed, in trials, the reintroduction of nucleosides after a viraemic blip obtained resuppression of HIV plasma viraemia in most cases;

nevertheless, a recent real-life study, the PIVOT study, has clearly shown that monotherapy is inferior to triple therapy (5). Integrase strand transfer inhibitor monotherapy, in particular with dolutegravir, in experienced patients (already treated with cART) has resulted in virologic rebound and INSTI resistance (6, 7).

Recommendation

Monotherapy either with protease inhibitors or integrase inhibitors should not be considered a treatment option.

Strength of the recommendation

AI

References

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4. Co-infection

4.1. What is the impact of HBV or HCV co-infection on health condition and general performance status of HIV-infected people?

The impact on health condition and general performance status in subjects with hepatitis B or C co-infections differs on the basis of the stage of the disease. Concerning fibrosis in hepatitis B, the progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in persons with HBV/HIV co-infection than in persons with chronic HBV mono-infection (1). Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T lymphocyte cell responses following initiation of antiretroviral therapy (2, 3). A recent study has shown that in a cohort of 139 HIV/HBV co-infected subjects with virological response to antiretroviral treatment for HIV, over a third (37 %) had significant fibrosis (Ishak stage ≥2) and 24 % had advanced fibrosis (Ishak stage ≥3) (4). An analysis conducted among US inpatients has shown that HBV/HIV co-infection is a risk factor for in-hospital mortality, particularly in liver-related admissions, compared to HBV mono-infection. Overall, healthcare utilisation from HBV/HIV co-infection is also higher than for either infection alone and higher than the national average for all hospitalisations, thus emphasising the healthcare burden from these illnesses (5).

Concerning hepatitis C, patients, with or without liver fibrosis, commonly experience fatigue, depression, anxiety, cognitive impairment, painful muscle and joint symptoms, irritability, nausea, abdominal discomfort, and right upper quadrant pain (6–9). Although these symptoms may not be life threatening, they cause substantial impairment in patients' health-related quality of life, work productivity, and everyday functionality (10). Subjects who responded to treatment with interferon and ribavirin showed an improvement in patient-related outcomes (10), but new drugs have completely changed the landscape (11–13). Indeed, in those untreated, the natural history of the disease is that approximately one third of the subjects untreated progress to cirrhosis, at a median time of <20 years (13, 14). The rate of progression increases with older age, alcoholism, male sex, and HIV infection (15–17). A meta-analysis found that patients with HCV/HIV co-infection had a 3-fold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV mono-infection (16). Concerning extra-hepatic manifestations, cryoglobulinaemic vasculitis is one of the most important one and it responds to direct antiviral agents (DAAs) but it could relapse (18). Central nervous system impairment is present either in HCV mono-infected or HIV/HCV co-infected HCV mono-infected and HIV/HCV co-infected. Indeed, individuals display neuropsychological deficits indicative of impaired cognition (17, 19, 20). Magnetic resonance spectroscopy studies report alterations in cerebral metabolites among HCV-infected individuals correlated with neurocognitive impairment, including suppression of the neuronal marker, N-acetyl aspartate (21). Finally, HIV/HCV co-infected subjects have a higher cardiovascular risk than HIV mono-infected subjects (22).

Recommendation

Individuals with HIV/HBV co-infection should be treated with antiretroviral regimens containing tenofovir (either diproxil fumarate or alafenamide) plus lamivudine or emtricitabine.

Strength of the recommendation

AI

Recommendation

Individuals with advanced liver fibrosis due to HCV or HBV co-infection should be monitored for liver decompensation (hepatic encephalopathy, flapping tremor, hepatic carcinoma) every 4 months.

Strength of the recommendation

BI

Recommendation

Individuals with HIV/HCV co-infection should be treated with DAAs.

Strength of the recommendation

AI

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4.2. Which are the side effects of medication used for HIV-associated hepatitis B and C infection?

Evidence from the literature

Concerning hepatitis C, a recent study conducted in the French ANRS CO13 HEPAVIH cohort in 323 HIV-positive subjects treated for HCV with different DAAs and antiretrovirals for HIV, the most common adverse effects were fatigue and digestive disorders (1). This good tolerability has been described also in patients with cirrhosis, for example, in 137 subjects who were retreated with DAAs after having failed a first regimen (2).

Concerning hepatitis B, tenofovir (either diproxil fumarate or alafenamide) and lamivudine have all HIV antiviral activity and should be used in HIV/HBV co-infected patients (3). A recent study comparing efficacy and tolerability of tenofovir diproxil fumarate and alafenamide in persons mono-infected with hepatitis B has shown that the most common adverse events overall were upper respiratory tract infection, nasopharyngitis, and headache. 22 (4 %) patients receiving tenofovir

alafenamide and 12 (4 %) patients receiving tenofovirdisoproxil fumarate experienced serious adverse events, none of which was deemed by the researcher to be related to the study treatment. 187 (32 %) out of 581 patients in the tenofovir alafenamide group and 96 (33 %) out of 292 patients in the tenofovir disoproxil fumarate group had grade 3 or 4 laboratory abnormalities, the most common of which were elevations in ALT and AST (4). A study conducted on HIV/HBV co-infected patients showed that kidney function and especially eGFR decline under TDF therapy appears mainly associated with older age, non-African origin, higher baseline eGFR, and longer TDF administration but not with the type of viral infection (5). Concerning the bone, initiation of all NRTI-containing regimens has been associated with a decrease in bone mineral density (BMD), but the loss of BMD is greater with TDF-containing regimens (6, 7). BMD generally stabilises following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF (see above). Moreover, cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF (8). Finally, in case of intolerability to tenofovir, patients should be treated with entecavir remembering that when entecavir is used to treat HBV in patients with HBV/HIV co-infection who are not on ART, the drug may select for the M184V mutation since it has a low anti-HIV activity (9).

Recommendation

Since persons who are HIV/HBV co-infected have to be treated with tenofovir either diproxil fumarate or alafenamide, they should be monitored in case of tenofovir diproxil fumarate for kidney function every 4–6 months and for osteoporosis with DEXA every 2 years.

Strength of the recommendation

AI

References

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4.3. Which are the side effects of medication used for HIV-associated tuberculosis?

Evidence from the literature

Concerning drug-susceptible tuberculosis (TB), a study was conducted in France in a prospective cohort study between January 2003 and August 2004 to examine the impact of HIV infection and other factors on the risk and spectrum of adverse events related to anti-TB therapy. Out of 105 patients treated for TB, 30 were HIV infected. The overall incidence of adverse events was 122.5 ±18.5/100 patient-years (py) and the incidence of severe adverse events was 45.2 ±11.3/100 py. Age 50 years and HIV infection were independently associated with a higher risk of adverse events. Hepatitis and neuropathy were the most frequent adverse events (1). These effects are the same as in the general population as rush with rifampin or blurred vision with ethambutol (2).

Concerning drugs used for drug-resistant (MDR or XDR) TB, the new drugs delamanid and bedaquiline are presently classified in group D2 (3), and their use is recommended in adults for a maximum of 6 months, at the recommended doses, added to an OBR (optimised background regimen), under adequate clinical monitoring (particularly for the QT interval, e.g. measurement of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle), and in the presence of pharmacovigilance and informed consent (4, 5). A study conducted between 1 January and 31 August 2016 included 28 patients, out of which 11 (39 %) were HIV-positive. 24 patients (86 %) had isolates resistant to fluoroquinolones; 14 patients (50 %) had extensively drug-resistant TB. No patient had an increase of more than 500 ms in their QTcF interval. 4 patients (14 %) had 6 instances of QTcF increase of more than 60 ms from baseline but none permanently discontinued the drugs. 16 serious adverse events were reported in 7 patients. Out of 23 individuals with positive baseline cultures, 17 (74 %) converted to negative by month 6 of the treatment (6).

Moxifloxacin could be used either for sensitive or resistant TB, and should be used with caution in patients on antiarrhythmic drugs and other drugs with known effects on QT prolongation, notably bedaquiline, also used in the treatment of TB (7).

Concerning linezolid that could be used in MDR or XDR TB, 23 studies conducted in 14 countries and involving 507 patients were analysed in a meta-analysis. The incidence of neuropathy and other adverse events leading to permanent discontinuation of linezolid also showed no significance upon dose comparisons (8).

Recommendation

Liver enzyme elevation and neuropathy should be monitored in subjects with HIV infection who are receiving treatment for TB.

Strength of the recommendation

AI

Recommendation

Persons treated with drugs known to determine QT prolongation (bedaquiline, dalamanid moxifloxacin) should be accurately and frequently monitored during treatment for the risk of sudden death.

Strength of the recommendation

AI

References

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4.4. How should HIV-positive patients with hepatitis B or C, or tuberculosis, be monitored?

Evidence from the literature

Concerning hepatitis B, the progression of chronic HBV to cirrhosis, end-stage liver disease, or hepatocellular carcinoma is more rapid in persons with HBV/HIV co-infection than in persons with chronic HBV mono-infection (1). Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 T-cell responses following initiation of antiretroviral therapy (2, 3). Tenofovir alafenamide, tenofovir diproxil fumarate, lamivudine and emtricitabine are active on both infections and two of them (TDF or TAF + 3TC or FTC) should be included in the antiretroviral regimen (4). The TEMPRANO study, conducted in Africa, showed that subjects co-infected with HIV and hepatitis B showed an increased risk of death despite early antiretroviral initiation (5). Moreover, antiretroviral drug toxicities or several liver-associated complications attributed to flares in HBV activity after initiation or discontinuation of dually active ARV drugs can affect the treatment of HIV in patients with HBV/HIV co-infection (6–8). Finally, some ARV agents can increase transaminase levels. The rate and magnitude of these increases are higher with HBV/HIV co-infection than with HIV mono-infection (8–11). Concerning hepatitis C, a meta-analysis found that patients with HCV/HIV co-infection had a 3-fold greater risk of progression to cirrhosis or decompensated liver disease than patients with HCV mono-infection (12). The risk of progression is even greater in patients with HCV/HIV co-infection who have low CD4 T lymphocyte (CD4) cell counts. Although antiretroviral therapy (ART) appears to slow the rate of HCV disease progression in patients with HCV/HIV co-infection, several studies have demonstrated that the rate continues to exceed that observed in patients without HIV infection (13, 14). Recently, the advent of treatment which could eradicate the infection in more than 90 % of the subjects has completely changed the natural history of this infection even in HIV-positive subjects (15). Nevertheless, drug-induced liver injury following the initiation of ART is more common in patients with HCV/HIV co-infection than in those with HIV mono-infection. Individuals with HCV/HIV co-infection who have advanced liver disease (e.g. cirrhosis, end-stage liver disease) are at greatest risk of liver toxicity (16). Eradicating HCV infection with treatment may decrease the likelihood of ARV-associated liver toxicity (17). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored 4 to 8 weeks after initiation of ART and at least every 6 to 12 months thereafter, and if clinically indicated. Mild to moderate fluctuations in ALT and/or AST are typical in individuals with chronic HCV infection. In the absence of signs and/or symptoms of liver disease or increases in bilirubin, these fluctuations do not warrant interruption of ART. Patients with significant ALT and/or AST elevation should be carefully evaluated for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g. acute hepatitis A virus (HAV) or HBV infection, hepatobiliary disease, or alcoholic hepatitis). Reinfection with HCV is a problem especially in men who have sex with men (MSM). A recent study by Berenguer et al. has shown that reinfections were detected in 17 out of 2 359 HIV/HCV co-infected patients (0.72 %) overall, in 12 out of 177 (6.78 %) MSM, and in 5 out of 1 459 (0.34 %) people who inject drugs (18).

Concerning tuberculosis (TB), the treatment of latent infection is recommended by the WHO guidelines and shorter regimens are now available and efficacious (19). A recent study conducted in Taiwan has shown that retesting for latent TB in the course of HIV infection monitoring may not be

necessary (20). Active TB, either pulmonary or extra-pulmonary, requires hospitalisation.

4.4.1. Hepatitis B

Recommendation

Tenofovir alafenamide, tenofovir diproxil fumarate, lamivudine and emtricitabine are active on both infections and two of them (TDF or TAF + 3TC or FTC) should be included in the antiretroviral regimen.

Strength of the recommendation

AI

Recommendations

Patients with hepatitis B should be monitored with the same frequency as HIV mono-infected patients, but they should be evaluated to assess the severity of HBV infection.

Patients with hepatitis B should be screened also for hepatitis C. Patients with chronic HBV should also be tested for immunity to hepatitis A virus infection and, if non-immune, receive the HAV vaccination.

Before ART is initiated, all persons who test positive for hepatitis B surface antigen (HBsAg) should be tested for HBV DNA by using a quantitative assay to determine the level of HBV replication and the test should be repeated every 3 to 6 months to ensure effective HBV suppression.

Strength of the recommendations

AIII

4.4.2. Hepatitis C

Recommendations

Subjects with HCV co-infection should be monitored for HIV RNA and CD4 T-cell count, as HIV mono-infected subjects are.

In patients who have to start treatment for hepatitis C, antiretroviral treatment (ART) should be evaluated for drug–drug interaction and eventually modified. In case of antiretroviral modification, subjects who have suppressed plasma HIV RNA, HIV RNA should be measured within 4 to 8 weeks after changing HIV therapy to confirm the effectiveness of the new regimen. After HCV treatment is completed, the modified regimen should be continued for at least 2 weeks before reinitiating the original regimen. Continued use of the modified regimen is necessary because of the prolonged half-life of some HCV drugs and the potential risk of drug–drug interactions if a prior HIV regimen is resumed soon after HCV treatment is completed.

Cirrhotic patients should be evaluated for signs of liver decompensation according to the Child-Turcotte-Pugh classification system. All patients with Child-Pugh class B or C disease should be evaluated by an expert in advanced liver disease and for consideration of liver transplantation (21).

Subjects with HIV infection, especially MSM, with a previously treated HCV, should be tested once a year for HCV reinfection.

Strength of the recommendations

AII

4.4.3. Tuberculosis

Recommendation

Individuals should be screened for latent tuberculosis (TB) at baseline and every 2 years by using Quantiferon Gold.

Strength of the recommendation

BII

Recommendations

Subjects who had an active TB in the past that was successfully treated should be monitored as HIV mono-infected subjects are.

In subjects with latent TB infection or previously active infection, TB should be excluded in case of symptoms especially if cART was discontinued or there is a virological failure.

Strength of the recommendations

BIII

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5. Mental-health-related matters

5.1. Are people living with HIV at higher risk of mood disorders than those who are HIV-negative?

Evidence from the literature

In people living with HIV (PLWH) the rate of mental health disorders is higher than in the general population, and this difference has been observed in different groups of PLWH, such as youth with perinatal or behaviourally acquired HIV, adult MSM of colour, racial and ethnic minority women, people who inject drugs (PWID), and older adults (1–7). In a US multisite study with over 2 800 PLWH, 36 % had major depression and 15.8 % had generalised anxiety disorder (1), compared to only 6.7 and 2.1 % respectively in the general population (8).

Significant increases in health care services have been reported in patients with mental health disorders. In Ontario, a study using available electronic medical records indicated that 41 % of PLWH had a mental health condition compared to 22 % among non-HIV-infected adults (3). A study by Blank et al. conducted HIV tests with over 1 000 people who were seeking mental healthcare at university-based psychiatric inpatient units, intensive case-management programmes, and community mental health centres and they found that 4.8 % had confirmed positive HIV tests — much higher than the HIV prevalence rate in the general US population (9). In a study performed in Australia on 557 HIV-infected and 1 325 HIV-uninfected homosexual/bisexual men, 300 hospitalisations for anxiety and mood disorders were registered in 15.3 % of HIV-infected participants and 181 hospitalisations in 5.4 % of HIV-uninfected participants (10). In another study on 3 482 adults, HIV-positive participants with current depression-only (adjusted HR (95 % CI): 1.2 (1.1–1.4)), recreational drug use-only (1.3 (1.1–1.6)), or co-occurring depression and recreational drug use (1.4 (1.2–1.7)) were associated with elevated hazard of emergency department (ED) encounters compared to participants without these conditions (11). Studies on the risk of mental health disorders in European PLWH in the recent years were poor. Nevertheless, a recent Swiss HIV Cohort Study on suicide mortality documented that suicide rates have decreased substantially among PLWH in the last three decades but have remained about three times higher than in the general population since the introduction of cART (12).

Data from across the globe also indicates elevated rates of mental health disorders among PLWH compared to the general population. In South Africa, 26–38 % of PLWH are estimated to have a mental disorder compared to 13 % in the general population (13). Although major depression is one of the most commonly observed mental health disorders in PLWH, rates of post-traumatic stress disorder are also much higher among PLWH than in the general population, ranging from 10 to 74 % (14–16) compared to only 8 % in the US general population (17). Whether major depressive disorders impact on neurocognitive functions in HIV-positive persons is still to be defined because the results of the studies are inconsistent. A recent study showed that a history of alcohol and/or substance abuse was significantly more frequent in those with treated and unstable chronic major depressive disorders, but it was not associated with neuropsychological performance (18).

However, the increased risk of mental health disorders estimated in the body of evidence published may be influenced by the year of publication as well as income setting, employment status, age, and presence of other chronic conditions in the control group. This makes it difficult to estimate the current risk of mental health disorders (and specifically depression) in European, high-income, high-scholarly, younger-aged, employed PLWH.

Recommendation

HIV-infected people should be monitored at each visit for mood disorders including depression, post-traumatic stress disorder, and suicidal ideation.

Strength of the recommendation

BII

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5.2. Should people living with HIV be routinely screened for mental health problems?

According to what has been stated in Section 5.1 above, people living with HIV should be screened for mental health problems on the basis of what is reported in the guidelines, both from the European AIDS Society (1) and the U.S. Department of Health and Human Services (HHS) (2), and following the modalities reported in Table 3.

Recommendations

People living with HIV should be routinely screened for mental health problems using clinical questions and symptoms survey according to the EACS guidelines (see Table 3 below).

The frequency of the screening should be every year for patients with stable disease (HIV RNA <50 copies/µl and CD4 T-cell count >200 cells/mm^3), and every 6 months for those with unstable disease or at particularly high risk (see Table 3 below from the EACS guidelines).

Strength of the recommendations

AII

References

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Table 3 — Depression: Screening and diagnosis

Significance

- Higher prevalence of depression reported in HIV-positive persons (20–40 % versus 7 % in general population).
- Significant disability and poorer HIV treatment outcomes associated with depression.

Screening and diagnosis		
Whom to screen?	How to screen?	How to diagnose?
Screening of all HIV-positive persons recommended in view of the high prevalence of depression Populations at particularly high risk: • Positive history of depression in family • Depressive episode in personal history • Older age • Adolescence • Person with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity • Use of EFV • Use of neurotropic and recreational drugs • As part of the investigation of neurocognitive impairment	• Screen every 1–2 years • Two main questions: 1. Have you often felt depressed, sad or without hope in the last few months? 2. Have you lost interest in activities that you usually enjoy? • Specific symptoms in men: — Stressed , burn out, angry outbursts, coping through work or alcohol • Rule out organic cause (such as hypothyroidism, hypogonadism, Addison's disease, non-HIV drugs, vitamin B12 deficiency)	Symptoms — evaluate regularly: A. At least 2 weeks of depressed mood OR B. Loss of interest OR C. Diminished sense of pleasure PLUS 4 out of 7 of the following: 1. Weight chance of ≥5 % in 1 month or a persistent change of appetite 2. Insomnia or hypersomnia on most days 3. Change in speed of thought and movement 4. Fatigue 5. Feelings of guilt and worthlessness 6. Diminished concentration and decisiveness 7. Suicidal ideation or suicide attempt

5.3. Can mood disorders in HIV-positive people be a side effect of ART?

Evidence from the literature

There is a large and consistent base of evidence supporting EFV as the cause of central nervous system (CNS) side effects (e.g. abnormal dreams, dizziness, headache, and depression) that resolve over a period of days to weeks in most patients (1). However, long-term neuropsychiatric side effects can occur in patients receiving EFV. The neuropsychiatric symptoms and adverse side effects that have been associated to EFV exposure were somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Bedtime dosing may reduce the

symptoms. Risk factors include presence of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food (2).

Moreover, EFV use has also been associated with suicidality, even though some large studies have provided different results. As main observation, an analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e. reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (LPV/r, ATV, ATV/r, or ABC-based regimens) (3, 4). Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behaviour among participants in the immediate ART group who took EFV than among ART-naive controls; the risk increased for those with previous psychiatric diagnoses (5). However, this association was not found in analyses of three large observational cohorts after accounting for measured channelling bias (6–8) or in a retrospective cohort study that used U.S. administrative pharmacy claims data (9). A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried an increased risk of suicidal ideation or depression compared to NVP (10).

Rilpivirine has been associated with fewer neurological and psychiatric adverse effects (ADEs) than efavirenz over 48 weeks in treatment-naive, HIV-1-infected adults. In both groups, patients with prior neuropsychiatric history tended to report more neuropsychiatric ADEs but rates remained lower for rilpivirine than for efavirenz (11). However, despite the fact that the occurrence of neuropsychiatric ADEs was significantly lower in RPV than EFV, a slight risk of depression and suicidality has been reported in patients receiving rilpivirine.

Concerning other ARV drug classes different from NNRTIs, case series of neuropsychiatric ADEs (sleep disturbance, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported (12–14). Two observational cohort studies reported a higher frequency of neuropsychiatric ADEs leading to treatment discontinuation in patients taking DTG than in patients receiving other INSTIs (15, 16). However, analyses of data from large randomised controlled trials as well as a healthcare database demonstrated similar rates of neuropsychiatric ADEs between DTG-based regimens and other ARV regimens (17) with neuropsychiatric events rarely leading to DTG discontinuation. Moreover, DTG has been associated to a lower frequency of neuropsychiatric ADEs than EFV in a large double-blind placebo-controlled randomised trial (18), and no differences in terms of neuropsychiatric events between DTG and bictegravir (BIC) have been reporter in two comparative randomised studies (19–20). Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs (21), not just with DTG. In conclusion, depression and suicidality have been infrequently reported with INSTI use, primarily in patients with pre-existing psychiatric conditions. Further studies will be needed to clarify the true incidence and implications of these neuropsychiatric events. A pathophysiologic mechanism for these neuropsychiatric ADEs has not been defined.

Recommendation

Efavirenz has been significantly associated with an increased risk of depression and suicidality, and it should not be used in patients with psychiatric disorders or at risk of psychiatric disorders. Much less consistent association with mood disorders has been reported with rilpivirine. Depression and suicidality have been infrequently reported with INSTI (mainly DTG or RAL) use, primarily in patients with pre-existing psychiatric conditions.

Strength of the recommendation

AI

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5.4. Is an HIV-positive patient diagnosed with depression at higher risk of suicide than the general population diagnosed with depression?

Evidence from the literature

Historically, at the beginning of the AIDS epidemic, it had been observed that the rate of suicide among HIV-positive people was higher than in the comparable general population. In 1985, in New York City, there were 668 suicides in residents, yielding a rate of 9.29 per 100 000 person-years, and in men aged 20–59 years without a known diagnosis of AIDS, the rate was estimated at 18.75 per 100 000 person-years. There were 12 suicides in 3 828 men aged 20–59 years who lived 1 763.25 person-years with a diagnosis of AIDS. This yields a suicide rate of 680.56 per 100 000 person-years. Thus, the relative risk of suicide in men with AIDS aged 20–59 years was 36.30 times (95 % confidence limits, 20.45 to 64.42) that of men aged 20–59 years without an AIDS diagnosis, and 66.15 times (95 % confidence limits, 37.38 to 117.06) that of the general population. According to this data, AIDS diagnosis represented a significant risk factor for suicide (1). In a large survey conducted in the US population from 1987 to 1989 (2), a total of 165 suicides among persons living with AIDS occurred in 45 states and the District of Columbia. In all cases except one, males were involved. Among males, the rate was 165 per 100 000 person-years of observation, 7.4-fold higher than among demographically comparable men in the general population. However, in the same study the suicide risk for persons living with AIDS was increasing to significantly decrease from 1987 to 1989. In a study on the prevalence of HIV infection among the suicide victims in New York City from 1991 to 1993, the crude proportion of all suicide victims who were HIV-seropositive was 0.088, and the demographically adjusted proportion was 0.049. Over 90 % of all HIV-positive suicide victims were aged 25 to 54 years, and almost 90 % of them were men. Interestingly, more than two thirds of the HIV-seropositive suicide victims had no HIV-related pathology or AIDS-indicator conditions at autopsy. The demographically adjusted proportion of suicide victims who were HIV-positive (approximately 0.038 to 0.059), contrasted with the HIV seroprevalence estimates for the New York City general population (approximately 0.014 to 0.032), the absence of HIV-related

pathology among suicide victims, and the likelihood that many HIV-positive individuals had other risk factors for suicide, such as substance abuse, suggests that HIV seropositive status is associated in the worst-case scenario with a modest elevation in suicide risk (3).

In more recent years, after the large impact antiretroviral therapy had on the HIV population, the rate of suicide in the HIV population seemed to decline. In a large study performed on more than 15 000 HIV-infected patients who were followed up during the years 1988–2008 in the Swiss HIV Cohort Study, it was found that in HIV-infected patients suicide rates declined substantially after the introduction of highly active antiretroviral therapy (HAART), in both men and women, with a somewhat steeper decline in men (4). The Swiss HIV Cohort Study was one of the first HIV cohort studies worldwide and included about 40 % of all patients with HIV and about 70 % of patients with AIDS in the country, and these results were therefore likely to be representative for Switzerland and may also apply to other high-income settings. The association of increasing suicide rates with declining CD4 T-cell counts supports the hypothesis that HAART-related improvements in disease status may be responsible for the reduction in suicide rates over time. However, the comparisons with the general population showed that despite this decline, suicide rates remained well above those observed in the general population, with a standardised mortality ratio in recent years of 3.5 in HIV-infected men and 5.7 in HIV-infected women. More recently, an update of the risk of suicide mortality was made by the panel of the Swiss HIV Cohort Study, analysing even the recent years of combined ART (2009–2017). This updated analysis documented that suicide rates have decreased substantially among PLWH in the last three decades but have remained about three times higher than in the general population since the introduction of cART (5). In the same studies, the factors associated to increased suicide mortality in PLWH were: male gender, Swiss nationality, CDC group C, injection drug use (IDU) or MSM as transmission modality, and history of psychiatric treatment. Among HIV-infected people, those with a history of psychiatric treatment were at higher risk of suicide mortality, with an adjusted hazard ratio of 2.42 (95 % CI 1.32–4.43). No association was found with age (5). However, specific studies comparing the suicide risk in depressed PLWH and depressed general population are lacking. The increased risk observed for PLWH, as in the Swiss HIV Cohort Study (5), is related to comparison to unscreened general population.

A role of the CD4 T-cell count status on the suicide risk was confirmed by a nested case-control study in Australia, in which a CD4 T-cell count ≥500 cells/µl remained a significant predictor of reduced risk (OR 0.15, 95 % CI: 0.03–0.70) in a multivariate model adjusted for employment status, accommodation status, and HIV-positive date (6). More recently, a cross-sectional study developed to evaluate suicide risk and associated factors in HIV/AIDS patients at a regional reference centre for the treatment of HIV/AIDS in southern Brazil, assessed 211 patients in regard to suicide risk, clinical and sociodemographic characteristics, drug use, depression, and anxiety (7). Suicide risk was assessed with the Mini International Neuropsychiatric Interview, Module C. Suicide risk was high in this population, with 34.1 % at risk of suicide among the total sample. Variables independently associated with suicide risk were: female gender, age up to 47 years, unemployment, features indicative of anxiety or depression, and abuse of or addiction to psychoactive substances. In a study performed in Canada (8), HIV-positive homosexual and bisexual men experiencing significant levels of stigma were at higher risk of suicide. In 673 HIV-positive men, 22 % reported suicidal ideation (SI) and 5 % suicide attempt (SA). After adjusting for sociodemographic factors, both SI and SA were associated with each of the four measures of HIV stigma: being excluded socially for being HIV-positive, being rejected as a sexual partner, verbally abused, and physically abused. In a cross-

sectional survey performed in France in 2011–2012 on 2 973 participants with available self-reported data on suicide risk, a suicide risk was reported by 6.3 % of PLWH in the study sample (9). After adjustment for HIV immunological status and HCV co-infection, women and MSM had a higher suicide risk than the rest of the sample. However, in another observational study performed in France, HIV-related factors were not associated with a higher risk of suicide mortality (10). 70 cases and 279 controls were included in the study, and by multivariable analysis, the factors significantly associated with death from suicide were: not having children and several psychological co-morbidities such as active or substituted drug consumption, alcohol intake >20 g/day or history of alcohol abuse, history of depressive disorder and/or of attempted suicide, and psychotropic drug intake.

Recommendation

Even in the recent ART era, an HIV-positive patient remains at higher risk of suicide than the general population. Among PLWH, a significantly independent increased risk remains for those with psychiatric treatment and those with depression. For PLWH with depression, a periodic psychiatric evaluation for suicide risk and questionnaire evaluation for suicide risk severity (as the Columbia University C-SSRS Questionnaire) should be mandatory.

Strength of the recommendation

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5.5. Should people living with HIV be routinely screened for elevated risk of suicidal ideation and suicidal behaviour/self-harm?

Evidence from the literature

Based on the considerations available in the specific section on the risk of suicidal ideation (SI) in HIV-infected people compared to that in the general population, and considering that some antiretrovirals (in particular efavirenz and, to a lesser extent, even INSTI and rilpivirine) could be variably associated with higher risk of suicidality (see specific section on antiretroviral-associated risk of mood disorders), particular attention should be given to people taking these drugs, in particular if they have a history of psychiatric disorders. Specific guidelines, besides those regarding the frequency of screening for mood disorders, are not available (1–2); nevertheless, it could be assumed that an accurate screening for mood disorders, for assessing the HIV stigma, for previous drug abuse or addiction history should be performed routinely to support the early identification of people at risk of SI (3).

Recommendation

HIV-infected people who have been found to have characteristics associated to higher risk of SI during their routine screening for mood disorders should increase the frequency of screening (every 6 months). In particular, this more frequent screening should be recommended for PLWH receiving efavirenz-based cART.

Strength of the recommendation

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5.6. Is the rate of substance use disorders higher in HIV-positive patients than in the general population, and if so, does this remain the case in a group of professional workers, e.g. doctors, airline pilots, lawyers, etc.?

Worldwide, 84 to 190 million individuals inject psychoactive drugs (1). About 13 % of the people who inject drugs (PWID) are believed to be living with HIV, which amounts to roughly 17 million individuals (2). UNAIDS has estimated that 30 % of new HIV infections outside the more generalised HIV epidemic in sub-Saharan Africa are attributable to the use of injection drugs (2). Countries that

have been identified as being particularly affected by the HIV epidemic among PWID include China, Malaysia, Russia, Ukraine and Vietnam (3), and these countries account for half (47 %) of all PWID estimated to be living with HIV in low- and middle-income countries (4). Although prevalence estimates of HIV infections among PWID in China, Ukraine and Vietnam indicate notable improvements from the early 2000s to 2012 (5), the HIV epidemic is expanding in some regions of Eastern Europe and Central Asia, in the Middle East, and in North Africa, and this expansion is attributed in part to the use of injection drugs (5–6). Indeed, in 2014, 51 % of new HIV infections in Eastern Europe and Central Asia and 28 % of those in the Middle East and North Africa were estimated to be among PWID, highlighting their continued relevance as a key population in the global fight against HIV (7–8). Besides people who inject drugs, in the recent years much attention has been paid to people with generally speaking substance use disorders (SUDs). It has been estimated that 1.2 million Americans are living with HIV (9) and experience higher prevalence of SUDs than the general population (10, 11). Indeed, the Substance Abuse and Mental Health Services Administration reported that between 2005 and 2010, in HIV/AIDS civilian, non-institutionalised US population aged 12 years or older, nearly one third of those individuals who were diagnosed with HIV used illicit drugs or engaged in binge drinking in the past 30 days (12). During the same period, approximately 24 % of the people living with HIV/AIDS (PLWHA) in the USA met the criteria for SUDs (12). More recent studies have found higher prevalence of SUDs among PLWHA; for example, a recent multi-regional US cohort study found a 48 % SUD prevalence rate in an aggregated sample of 10 652 PLWHA (13). This prevalence was estimated in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) database, characterised by 83 % males, 70 % younger than 50 years old, 49 % non-Hispanic white, 75 % homosexuals, 79 % with MSM history, and 16 % with injection drug use (IDU) history as HIV transmission risk (13).

Several studies have examined substance use and SUD prevalence rates among PLWHA. The most commonly used substances by PLWHA are tobacco (11, 14, 15) and alcohol (1, 12–15). Prevalence rates for marijuana use range from 18 to 31 % (11, 12, 14), from 7.9 to 11 % for stimulant use (14, 16), and approximately 20 % are polydrug users (13). 7 % report non-prescription opioid use (13–14) and IDU. Not only are substance use rates higher among PLWHA than in the general population (11), but the reported proportion of PLWHA with SUDs is far greater than in individuals living with other chronic diseases (17–18). Anecdotal evidence suggests that MSM are increasingly combining sex and illicit drugs (an activity referred to as ‘chemsex’), in particular Gamma-hydroxybutyrate/Gamma-butyrolactone (GHB/GBL), ketamine, crystal meth, or mephedrone. Use of such drugs has been associated with mental health and sexual health harms (19–20). Substance/drug use during sexual activity (‘chemsex’) is being increasingly reported in sexual health clinics by gay, bisexual and other men who have sex with men (GBMSM). It has been reported that this type of non-injection substance use interplays with mental, physical and sexual health (21). To the best of our knowledge, there is no data on the prevalence of drug abuse in specific groups of professional workers. Nevertheless, even though it could be assumed that the presence of life stressors could be interconnected with and have a potential indirect relationship to HIV-related stigma, data on life stressors, depression, and drug abuse is conflicting, and in some studies both HIV-related stigma and stressful life events were directly related to depression, but there were no significant effects involving substance use (22).

Recommendation

The rate of different (injecting and non-injecting) substance use is higher in HIV-infected people compared to the general population, and this condition should be addressed, even though data on specific groups of professional workers and on direct effects of substance abuse on depression is lacking.

Strength of the recommendation

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6. Neurocognitive issues

6.1. What is the relevance of HIV-associated neurocognitive disorders (HAND) to cognitive performance?

Evidence from the literature

The introduction of combination antiretroviral therapy (cART) for the human immunodeficiency virus (HIV) has successfully changed the clinical picture of people living with HIV (PLWH), leading to a dramatic decrease of HIV-related morbidity and mortality. The incidence rate of HIV-associated dementia (HAD) has markedly reduced since 1997, even though patients with low CD4 T-cell counts, previous AIDS diagnosis, longer duration of HIV infection, and older age at seroconversion remain at increased risk (1). Despite these cART benefits mainly on severe HAND cases, more recent observations suggest that neurocognitive impairment (NCI) could have remained a relevant area of concern in HIV-infected individuals. In the CHARTER study, in a total of 1 555 HIV-infected adults recruited from six university clinical centres in the US, a prevalence of 52 % of NCI was still observed, with higher rates in groups with greater co-morbidity burden (2). The prevalence estimates for specific HAND diagnoses (excluding severely confounded cases) were 33 % for asymptomatic neurocognitive impairment (ANI), 12 % for mild neurocognitive disorder (MND), and 2 % for HAD. According to this data, milder forms of cognitive impairment remained relatively common, even among those receiving cART who had minimal co-morbidities. Among the participants with minimal co-morbidities, history of low nadir CD4 T-cell counts was a strong predictor of impairment, and the lowest impairment rate on cART occurred in the subset with suppressed plasma viral loads (VLs) and nadir CD4 ≥200 cells/mm^3. However, despite this data, a persistent high frequency of HAND in HIV-infected population treated with cART has been reported. On the other hand, several studies from 2013 to 2017, mainly performed in Europe, suggested a declining prevalence of HAND and that the prevalence proved to be lower than previously reported in the US (3–6). Moreover, recently published longitudinal studies have shown that HAND do not seem a progressive neurologic syndrome as it was in the pre-ART era (7, 8). In fact, in a cross-sectional study among 200 HIV-infected and 50 matched HIV-uninfected persons, characterised by an early diagnosed and managed HIV infection, NCI was diagnosed in 19 % (95 % CI 14–25 %), and the prevalence of NCI among HIV-infected individuals was similar to HIV-uninfected individuals (3). According to this observation, HIV-infected persons, diagnosed and managed early during the course of the HIV infection, have a low prevalence of NCI, comparable to that of matched HIV-uninfected individuals. In the Multicenter AIDS Cohort Study (MACS), a prospective study on homosexuals, the frequency of HAND for the HIV-positive individuals seen in 2007–2008 was 33 %, and for the HIV-positive individuals seen at all times during the 2007–2008, 2009–2010, and 2011–2012 periods were 25, 25 and 31 % respectively (7). Moreover, the overall frequency of HAND increased from 2009–2010 to 2011–2012. In a multi-centre, cross-sectional study of 448 HIV-positive patients attending five outpatient clinics in Europe to determine the prevalence of and the factors associated with NCI, 156 (35 %) of the participants had NCI (4). Very close to these results, in a large, single-centre cross-sectional study in Italy (5), an overall prevalence of HAND was observed. As explanation of this variable prevalence, it is likely that the characteristics of the population enrolled in the different studies may have contributed to these different estimates. This would be especially true for the proportion of enrolled patients on ART, prevalence of MSM, high educational level, and the proportion of enrolled patients with an optimal viro-immunological control. However, in all more recent survey analyses of HAND prevalence and characteristics, mild neurocognitive impairment (ANI or MND) resulted to be highly

prevalent compared to a more severe impairment as that observed in HAD (2–8). Despite this well-documented prevalence of mild cognitive disorders among cognitive impairments (in particular of the asymptomatic neurocognitive impairment (ANI) for which no evident interference with daily life has been recorded), a recent observation suggests an increased risk for patients affected by ANI to develop a symptomatic MND or HAD (9). Also, changes to the clinical phenotype of NCI in HIV-infected people have been observed (10). Moreover, despite the well-assessed role of early ART (independently of CD4 T-cell count at treatment initiation) in improving survival and reducing incidence of AIDS and non-AIDS morbidities (as demonstrated in the START trial), the specific advantage of early ART on NCI incidence and risk reduction was not conclusively assessed (11). This confirmed that even early ART was not able to completely normalise the increased risk of HAND in a well-treated population, possibly due to the multifactorial risk model of HAND pathogenesis in HIV-infected persons, as it is largely demonstrated by most observational studies on predictive factors associated to NCI. Concerning predictors of NCI in HIV-infected population, several factors have been associated with HAND in observational study models (12–21). Older age (12), substance use (13, 14), lack of virological control by ART (15), a lower CD4 T-cell count at nadir or at last determination (2, 15–17), traditional cardiovascular risk factors (especially diabetes) (18, 19), depression (20), lower level of education (21, 22), and even some ARV drugs (23), were all associated to an increased risk of developing HAND.

Conclusions

Even with consistent variability due to population characteristics, HAND remain elevated in PLWH, even in the recent era of ART. Considering the relevance of predictive stratification factors, it is conceivable that the risk of developing HAND could be negligible for an individual of a younger age, not using substances, with stable HIV infection under therapy, low cardiovascular disease (CVD) risk, high educational level, and no mental health problems.

Despite the fact that milder forms of HAND are prevalent in the last years, even ANI may increase the risk of symptomatic decline with functional impairment.

Even in the more recent years, ART-treated patients of older age, without virological control, with low CD4 T-cell count at nadir or current, high CVD risk factors, depression, substance use, low educational level, and exposure to certain ARV drugs, may all be considered as being at higher risk of developing HAND.

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6.2. Should people living with HIV be regularly assessed and monitored for HIV-associated neurocognitive disorders (HAND)?

Evidence from the literature

Several clinical algorithms have been developed for the diagnosis and management of neurocognitive disorders in HIV-infected individuals. Due to the largely multifactorial pathogenesis of HAND, in which viral-, host-, environment- and drug-related factors are involved, it is difficult in clinical practice to have a screening of HAND to identify selected individuals with specific predictors of neurocognitive impairment (NCI). Also, due to the still elevated prevalence of HAND in HIV-infected population treated with ART, all HIV-infected individuals should be screened for neurocognitive disorders, preferably by a simple, accurate, rapid and reproducible tool (1). A preliminary psychiatric evaluation for controlling depression as potential confounder is appropriate (1). Several screening tools and clinical algorithms have been proposed in the last years (2–12), even if accuracy (sensitivity, specificity, positive and negative predictive value) remains one of the main problems of the screening tools. Once a suspected NCI has been detected by a screening tool, a complete, large-battery-based neuropsychological assessment (NPA) should be performed. The NPA should ideally determine the presence and severity of NCI, the presence and severity of functional decline, and the degree to which NCI or functional decline are likely to have been influenced by co-morbid conditions or confounds (13). Moreover, the NPA should use criteria to recognise the following three conditions: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). In 2007, the National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke updated the research nosology for HAND, called Frascati's criteria (13). These criteria are valid both for research and clinical purposes. In the updated nosology, ANI is defined as an acquired impairment of the cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 standard deviation (SD) below the mean for age–education appropriate norms on standardised neuropsychological tests. In ANI, the cognitive impairment does not interfere with the everyday functioning, does not meet the criteria for delirium or dementia, and there is no evidence of another pre-existing cause for impairment (13). The HIV-1-associated MND is defined as an acquired impairment of the cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age–education appropriate norms on standardised

neuropsychological tests. Typically, this would correspond to a Memorial Sloan Kettering (MSK) severity stage of 0.5 to 1.0 SD (14). Characteristically, the cognitive impairment in MND produces at least a mild interference with the daily functioning, such as self-report of reduced mental acuity, inefficiency in work, homemaking or social functioning, or observation by knowledgeable others that the individual has undergone at least a mild decline in mental acuity with resultant inefficiency in work, homemaking or social functioning. Similarly to ANI, also for MND, the cognitive impairment does not meet the criteria for delirium or dementia, and there is no evidence of another pre-existing cause for mild impairment. HAD present a marked acquired impairment of the cognitive functioning, involving at least two ability domains, typically in multiple domains. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains of at least 2.0 SD or greater than the demographically corrected means. Typically, this would correspond to an MSK severity stage of 2.0 SD or greater. This cognitive impairment produces marked interference with the day-to-day functioning (work, home life, social activities) (15–16). The pattern of cognitive impairment in HAD does not meet the criteria for delirium or, if delirium is present, the criteria for dementia need to have been met during a prior examination when delirium was not present. Moreover, there is no evidence of another pre-existing cause for dementia (e.g. other central nervous system (CNS) infection, CNS neoplasm, cerebrovascular disease, pre-existing neurologic disease, or severe substance abuse compatible with CNS disorder) (13). Recently, other neurocognitive assessment methods have been suggested in order to better define HAND, especially milder forms as ANI (17–20), but none of the new proposed methodologies represents now a standard method that is really alternative to the NIH Frascati's criteria.

Recommendation

All HIV-infected people should be regularly (every 12 months) assessed for HAND with the aid of a screening tool. Any suspicion of neurocognitive impairment (NCI) should be confirmed by a complete neuropsychological assessment (NPA) through a standardised method.

Strength of the recommendation

AII

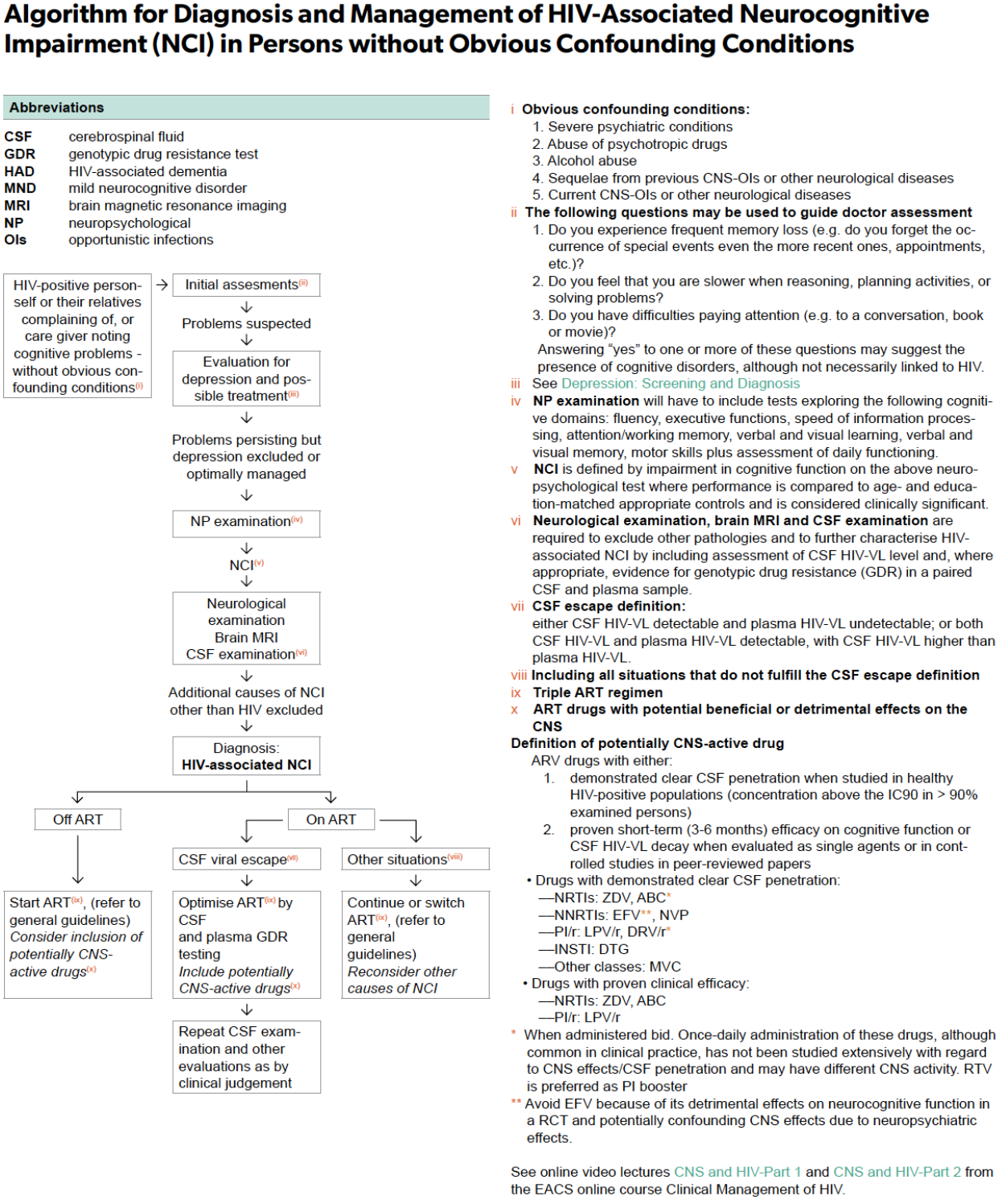

Figure 1 — Algorithm for the diagnosis and management of HIV-associated neurocognitive disorders from EACS Guidelines, version 10.0., Ref. 1)

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6.3. Should monitoring take place in a laboratory-based environment (battery of standardised cognitive function tests) or in a functional situation such as a high-fidelity flight simulator (or a combination of these, e.g. in alternate years)?

Evidence from the literature

There is neither specific literature nor guidelines on the comparison of the effectiveness of cognitive and behavioural monitoring in laboratory- or clinical-based environment and functional environments such as a flight simulator or similar. Nevertheless, any assessment should respect all methodological requirements: it should be performed in a comfortable environment both for patients and for evaluators, it should be performed with well-standardised tools, and it should be performed by trained personnel (1–2). Concerning the preferred domains that should be tested, attention is a very important cognitive domain as it is considered the cardinal cognitive function in the neurocognitive framework. Attentional deficit does not only concern aspects of this domain but can involve executive functions, with which it also shares part of the brain localisation, and processing speed. The impairment of attention and executive functions can inhibit the ability to focus on one or more target stimuli when there are distractors or concurrent information. This impairment interferes with planning and decision-making skills as well as correcting errors and finding a solution (problem solving). Finally, difficulties in executive functions can interfere with the ability to perform multiple actions simultaneously; decreasing the speed of information processing is often an indication of attentional deficit. The increase in reaction times can be decisive in a context where selective and continuous attention is required.

Recommendation

The monitoring for cognitive impairment, mood disorders, and behavioural aspects should be performed in an optimal environment, respecting the methodological aspects reported in the related guidelines, and not necessarily in a functional environment. It is necessary to include in the neuropsychological test battery cognitive domains such as executive functions, speed of information processing, attention/working memory, and motor skills. An instrumental activities of daily life (IADL) test with self- or other-reported scale is necessary in order to assess the level of functional impairment.

Strength of the recommendation

BIII

References

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6.4. What domains should be assessed and what battery of tests should be employed?

Evidence from the literature

According to the NIH updated research nosology for HIV-associated neurocognitive disorders (HAND), testing should cover multiple ability domains (1). Test results on at least two of these domains must be abnormal in order for the patient to be classified overall as having a neuropsychological (NP) impairment. Impairment on individual tests would require a performance that is more than one SD below the mean of a demographically comparable HIV seronegative group, or greater than one SD below the normative mean using published norms that are demographically adjusted (for age, education, gender, and/or ethnicity, as appropriate for the test). The importance of addressing appropriate norms was described above. The examination should include tests of the following ability domains (if possible, with at least two test measures per domain): fluency; executive functions; speed of information processing; attention/working memory; verbal and visual learning/memory; motor skills (Table 4). Neurocognitive impairment (NCI) requires that at least one of the tested ability deficits be primarily cognitive in nature (i.e. impairment that is limited solely to motor and sensory-perceptual functions would not qualify). Classification of moderate or greater overall NP impairment (a criterion for HAD) requires the performance on two ability domains to be greater than 2.0 SD below the normative mean; alternatively, the patient could score greater than 2.5 SD below normative expectations (an operational definition for moderate-to-severe impairment) for one domain and greater than 1.0 SD below expectations for another. This approach in the neuropsychological assessment (NPA) should take into account also the possible changing of cognitive phenotype (2–7), and perturbations in specific neural networks.

Table 4

Examples of neuropsychological (NP) tests that may be used to document impairments in ability domains	
Fluency Controlled oral Word Association Test (FAS) Thurstone Word Fluency Test Category Fluency Action Fluency Design Fluency Tests	**Verbal and Visual Learning** **Verbal** California Verbal Learning Test (Original and Revised; Total Learning) Rey Auditory Verbal Learning Test (Total Learning) Story Memory Test (Learning Component) Hopkin Verbal Learning Test WMS-III Logical Memory I WMS-III Paired Associates I
Executive Functions Stroop Color and Word Test	**Visual** WMS-III Visual Reproduction-I

Trailmaking Test — Part B Color Trails — II Wisconsin Card Sorting Test Halstead Category Test Odd Man Out Test 8 Tower Tests Delis-Kaplan Executive Function System	WMS-III Family Pictures-I Brief Visuospatial Memory Test — Revised (Total Learning) Figure Memory Test (Learning Component) Rey-Osterreith Complex Figure Test (immediate recall)
Speed of Information Processing WAIS-III Digit Symbol Subtest WAIS-III Symbol Search Subtest Symbol Digit Modalities Tests Trailmaking Test — I Color Trails — I Digital Vigilance Test Stroop Color Naming Reaction Time Tests, e.g. California Computerized Assessment Battery	**Verbal and Visual Memory** Delayed recall scores of the 12 learning/memory tests listed above, with interpretation also guided by results on any normed, forgetting/savings scores and delayed recognition scores
Attention/Working Memory WAIS-III Digit Span Subtest WAIS-III Letter-Number Sequencing Subtest WMS-III Spatial Subtest Paced Auditory Serial Addition Test Digit Vigilance Test (error component)	**Motor Skills** Grooved Pegboard Test Purdue Pegboard Test Arendt Central Motor Test Battery Finger Tapping Test Timed Gait

Recommendation

The neuropsychological assessment (NPA) should include tests in the following ability domains (if possible, with at least two test measures per domain): fluency; executive functions; speed of information processing; attention/working memory; verbal and visual learning/memory; motor skills.

As example of a comprehensive battery test, the following test (and related domains) should be included:

a) Digit Span forward and backward and Corsi's Block-Tapping Test (attention and working memory);

b) Trail Making Test-A and WAIS-R Digit Symbol (speed of information processing);

c) Trail Making Test-B, Stroop color and word (interference), phonemic verbal fluency (FAS) and Wisconsin Card sorting test (executive functions);

d) Rey Auditory Verbal Learning Test (RAVLT) with immediate and delayed recall (verbal episodic memory);

e) Grooved Pegboard Test with dominant/non-dominant hand (fine motor abilities).

Testing should be integrated with:

a) instrumental activities of daily life (IADL) test with self- or other-reported scale; and

b) Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI), with self-reported inventory, for controlling for mood disorder incidents, contributing or confounding co-morbidities.

Strength of the recommendation

AIII

References

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6.5. What assessment of cognition should be made at an initial aeromedical assessment after HIV diagnosis?

Evidence from the literature

It has been reported that in order to better assist in the management of HIV-associated neurocognitive disorders (HAND), it is important to develop and evaluate screening tools. Before their widespread use for clinical treatment decision making, these screening tools need to be shown to have adequate sensitivity and specificity with HAND, they need to be brief enough to be used in clinics or health centres, and trained individuals with minimum equipment should be able to administer them. A systematic review of the related literature on screening tools for HAND was performed in order to assess whether brief screening tools can accurately detect neurocognitive impairment (NCI) and whether they are able to differentiate among the various forms of HAND in the adult population of people living with HIV (PLWH) (1). Six electronic databases were researched to identify relevant studies published until May 2012 on the evaluation of brief screening tools (<20 min) for NCI in PLWH. Meta-analyses were completed on screening tools for which sufficient data was available. 51 studies met the inclusion criteria; the meta-analysis focused on 31 studies that compared brief screening tools with reference tests. Within these 31 studies, 39 tools were evaluated and 67 % used a comprehensive neuropsychological battery as a reference. The majority of these studies evaluated HIV-associated dementia (HAD). Meta-analyses demonstrated that the HIV Dementia Scale (HDS) has poor pooled sensitivity (0.48) and the International HIV Dementia Scale (IHDS) has moderate pooled sensitivity (0.62) in detecting a range of NCIs. Five newer screening tools had relatively good sensitivities (>0.70); however, none of the tools differentiated among the HAND conditions well enough to qualify for broader use. There were significant methodological shortcomings noted in most

studies. According to this data, HDS and IHDS perform well as regards screening for HAD but poorly for milder HAND conditions. Further tools may need to be developed for milder HAND conditions. This suggests that for high-risk critical conditions, in which neurocognitive assessment has a specific value, brief screening tools could not be appropriate due to the moderate sensitivity they have. A complete assessment by neuropsychological battery test according to Frascati's criteria (2) is necessary.

Recommendation

At an initial aeromedical assessment after HIV diagnosis, a complete neuropsychological assessment (NPA) by a large battery test exploring eight domains with at least two tests for each domain is recommended.

Strength of the recommendation

AIII

References

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6.6. In what circumstances should testing be repeated?

Evidence from the literature

With the chronicity of HIV infection and the risk of HAND developing or progressing despite viral control, it may be pertinent to repeat HAND screening more than just once (1). Despite this, there is limited data on the longitudinal use of such screening tools, particularly with regard to the effects of repeated cognitive tasks during the serial assessment of the performance results. Due to the presence of a 'practice effect' (2), the value of periodical monitoring of neuropsychological assessment (NPA) needs to be further elucidated (3). In addition, currently no guidelines exist on the time frame between testing intervals, or recommendation of the magnitude of the baseline impairment that warrants follow-up testing. HAND monitoring by a complete NPA should be defined according to specific monitoring of HIV co-morbidities (1 year) (4). Considering the increased risk of a deteriorating NCI related to a diagnosis of asymptomatic neurocognitive impairment (ANI), a patient with an ANI diagnosis should be monitored more frequently (every 6 months) (5).

Recommendation

The neuropsychological complete battery test should be performed every 12 months in all patients. More frequent monitoring (every 6 months) should be considered for patients with asymptomatic neurocognitive disorders (ANI).

Strength of the recommendation

BIII

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7. Living with chronic HIV infection

7.1. What is the effect of ageing and of age-related conditions, such as cardiovascular and bone health, on HIV-infected people?

Evidence from the literature

The prevalence of HIV-infected people aged 50 years or older is also increasing rapidly. According to data from the Dutch ATHENA cohort, the proportion of adults aged 50 and older will increase from 28 % in 2010 to 73 % in 2030 (1). In addition, HIV-infected individuals may be more vulnerable to age-related conditions (2, 3). This population often exhibits a higher number of co-morbidities and other age-related conditions at a younger age compared to the general population (3–8).

With the ageing of the HIV-infected population, non-communicable diseases or HIV-associated non-AIDS conditions have been increasing steadily (2–8, 9). From 2003 to 2013, the US Medicaid Database reported an increasing prevalence of cardiovascular diseases (CVD) (3 to 7 %), renal impairment (5 to 11 %), osteoporosis (4 to 6 %), and diabetes mellitus (DM) (9 to 19 %) (10). As a result, non-AIDS-related mortality has eclipsed AIDS-related mortality as the major cause of death in HIV-infected persons with access to cART (11-13). In addition, there is growing evidence that the prevalence of these co-morbidities and other age-related conditions (functional or neurocognitive/mental problems) is higher in the HIV-infected population than in the uninfected peers (14). The increased prevalence of CVD in this group reflects the complex interaction among age-related factors in this population: the high prevalence of typical cardiovascular risk factors (tobacco use, dyslipidaemia, diabetes, recreational drug use, etc.), the inflammatory status, and the effects of HIV replication and ART (15, 16). The HIV infection itself, as well as the impact of HIV on gut permeability, resulting in bacterial translocation, may lead to the development of accelerated atherosclerosis and decreased high-density lipoprotein (HDL) levels (17). Additionally, pro-

inflammatory populations of T-cells and activated monocytes may lead to functional or structural vascular changes linked with the development of coronary plaques (18).

Chronic kidney disease (CKD) is also more common in patients with chronic HIV infection than in the general population (19). CKD accounts for significant morbidity and mortality rates in 30 % of the HIV-infected individuals (20). Other common risk factors include ageing, hyperlipidaemia, diabetes, exposure to some antiretroviral drugs, and hepatitis B and C. Concomitant bone disease is also an emerging co-morbidity. The prevalence of osteopenia and osteoporosis is increased in HIV-infected persons (up to 60 % and 10–15 % respectively), although the mechanism and consequences of these changes are not fully understood (21). There is consistent evidence that neurocognitive ability is commonly impaired in HIV-infected patients; about half of all antiretroviral-treated patients present cognitive impairment. Advanced age increases susceptibility to HAND in HIV-infected individuals, leading to alteration of the presentation of HAND and an increase in the proportion of older HIV-infected adults with HAD. Although more severe neuropsychological impairment affects older HIV-infected persons more frequently than younger HIV-infected individuals, many middle-aged HIV-infected individuals are also experiencing cognitive decline similar to that observed in much older non-HIV-infected adults (22). A major and more common problem in these patients is the management of polypharmacy, compared to the general non-infected population of the same age (23). There is a debate as to whether HIV-infected subjects are ageing faster, with a clinical onset of multi-morbidities 10 years earlier than what is observed in the general population (24), or it is just a higher incidence of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer, but occurring at similar age (25). Finally, a study by Guaraldi et al., comparing patients who are ageing with HIV infection to those who acquired HIV at an older age and to the general population showed that HIV-positives had a higher rate of age-associated chronic conditions and multi-morbidities than HIV-negatives of the same age; moreover, that people with longer-duration HIV infection show higher probability of developing multi-morbidity than people who seroconverted at an older age (26).

Recommendation

Individuals with HIV infection should start screening for co-morbidities at a younger age, i.e. when they are 40 years old.

Strength of the recommendation

BII

References

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7.2. Does the HIV infection independently increase the risk of cardiovascular diseases and has acute myocardial infarction or sudden death been reported in HIV-positive patients?

Evidence from the literature

People living with HIV (PLWH) are increasingly at risk of developing cardiovascular diseases, which may present differently (e.g. at a younger age) and with different underlying risk factors than in the general uninfected population (1–3). Compared to uninfected people, PLWH are also at higher risk of developing myocardial infarction, arrhythmias, pulmonary hypertension, and subclinical myocardial dysfunction (systolic and diastolic), even after adjustment for traditional cardiovascular (CV) risk factors (4–12). Clinically overt heart failure (HF) also appears to be common among PLWH, though data is limited. Seminal analyses of a large cohort of US veterans used administrative codes to find significantly higher rates of HF among veterans with HIV compared to uninfected veterans (13–14). A recent study conducted by Feinstein et al. showed that the hazard ratio for HF (adjusted hazard ratio for PLWH versus uninfected controls: 2.10; 95 % CI, 1.38–3.21) was substantially higher than the results from recent studies that used administrative data to ascertain HF and they found that higher HIV viraemia and lower CD4 T-cell counts were associated with significantly elevated hazards of adjudicated HF (15). There were 374 (16 %) PLWH with HF. Among PLWH, 92 % were on cART and 63 % had a VL <200 copies/µl. Groups were similar with respect to age, sex, race/ethnicity, and CV risk factors. In the study, during the follow-up, PLWH had increased 30-day HF readmission (49 % versus 32 %) and CV risk factors (26 % versus 13.5 %), and all-cause mortality rates (38 % versus 22 %). Among PLWH, cocaine use, HIV-specific parameters (CD4 T-cell counts, VL), and coronary artery disease were predictors of 30-day HF readmission. Specifically, among PLWH, those with detectable VL had higher 30-day HF readmission and CV mortality, whereas PLWH with undetectable VL had a similar 30-day HF readmission rate and CV mortality to uninfected controls with HF. Similar outcomes were observed across strata of left ventricular ejection fraction and by CD4 (16).

In contrast to the evidence linking HIV infection to myocardial infarction, HF, and stroke, there are fewer studies on atrial fibrillation, sudden cardiac death, and peripheral artery disease (17). However, one study reported that PLWH have a 4-fold greater rate of sudden cardiac death compared to

expected rates in the general population (9). Low CD4 T-cell counts (<200 cells/mm^3) are associated with elevated incidence (11) and prevalence (19) of atrial fibrillation among PLWH, but it is unclear whether PLWH without detectable HIV viraemia or immune compromise have elevated atrial fibrillation risks. Similarly, several studies have shown that PLWH have an excess risk of peripheral artery disease compared to uninfected individuals (20, 21). HIV-related pulmonary arterial hypertension has been well described since the 1990s and is considered to be in group 1 of the World Health Organization classification of pulmonary hypertension (22, 27). The prevalence of HIV-associated pulmonary arterial hypertension is considerably higher than pulmonary arterial hypertension in the general population (28), and ART has not changed this epidemiology (29). Elevated pulmonary artery systolic pressure has also been reported in HIV-infected individuals (30). Finally, a retrospective Spanish study has found an association between HIV infection and deep venous thrombosis (DVT). The estimated incidence (events per 100 000 patient-years) in four calendar periods (1997–1999, 2000–2003, 2004–2007, and 2008–2013) of DVT-related hospitalisations had a significant upward trend in all HIV-infected patients (P <0.001), with significant differences between 1997–1999 and 2008–2013 (49.5 versus 88.1 (P <0.001)) (31). Finally, early start of ART does not favourably impact on CV risk. Actually, among the HIV-positive persons with preserved immunity, immediate ART led to increases in total cholesterol and low-density lipoprotein cholesterol but also concurrent increases in high-density lipoprotein cholesterol and decreased use of blood pressure medication. These opposing effects suggest that, in the short term, the net effect of early ART on traditional CVD risk factors may be clinically insignificant (32).

Recommendation

Individuals with HIV infection should undergo cardiological monitoring (electrocardiograph (ECG), echocardiography, etc.) twice a year with an assessment of the CV risk at 10 years by using the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) score.

Strength of the recommendation

AII

References

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7.3. Should HIV-positive patients have their cardiac risk profile assessed at baseline and routinely at follow-up?

Evidence from the literature

Considering all the evidence above, cardiac risk profile assessment is very important, but for each individual there is the problem of how to assess it (1). Clinical history is very important and includes early family history of myocardial infarction or stroke (men, age <55 years; women, age <65 years), persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L), chronic kidney disease (CKD), pre-eclampsia or premature menopause, subclinical atherosclerosis on imaging (including coronary artery calcium (CAC), and high levels of selected biomarkers associated with elevated atherosclerotic cardiovascular disease (ASCVD) risk independently of traditional risk factors (Lp(a) (lipoprotein(a)), hsCRP, and apoB (apolipoprotein B)) (2). At present, there is insufficient data to recommend routine measurement of subclinical atherosclerosis on imaging or inflammatory biomarkers because the additive value of these measurements for CVD risk stratification in HIV is unclear. Nevertheless, if already measured, atherosclerosis on imaging and elevated levels of Lp(a), hsCRP, or apoB suggest higher ASCVD risk and may warrant more aggressive strategies for ASCVD prevention. Indeed, a recent study confirmed not only a higher CV risk in the HIV-positive population, but also how

algorithms used in the general population underestimate the CV risk. Indeed, among 1 280 HIV-positive men followed for a median of 4.4 years, there were 80 (6.3 %) ASCVD events; the 5-year incidence rate was 16.7 per 1 000 person-years. Discrimination was moderate to poor as indicated by low c-statistic (0.68 for Framingham CHD, 0.65 for ACC/AHA, and 0.67 for Framingham ASCVD). Observed CVD risk exceeded the predicted risk for each of the functions in most deciles of predicted risk (1). The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study has elaborated (starting with 32 663 HIV-positive persons) a model to predict CV end points. The full D:A:D CVD prediction model included age, gender, systolic blood pressure, smoking status, family history of CVD, diabetes, total cholesterol, high-density lipoprotein, CD4 lymphocyte count, cumulative exposure to protease- and nucleoside reverse transcriptase-inhibitors, and current use of abacavir. A reduced model omitted antiretroviral therapies (ARTs). Statistically, the D:A:D models significantly predicted CVD risk more accurately than the recalibrated Framingham model (Harrell's c-statistic of 0.791, 0.783 and 0.766 for the D:A:D full, D:A:D reduced, and Framingham models respectively; $p < 0.001$). The D:A:D models also more accurately predicted the 5-year CVD risk for key prognostic subgroups (3).

In the national ATHENA cohort (AIDS Therapy Evaluation in The Netherlands), an individual-based model of CVD in HIV-infected people was constructed. Data on 8 791 patients on combination antiretroviral therapy (cART) was used. The model follows patients as they age, develop CVD (by incorporating a CVD risk equation), and start CV medication. Four prevention interventions were evaluated:

(a) increasing the rate of earlier HIV diagnosis and treatment;

(b) avoiding use of cART with increased CVD risk;

(c) smoking cessation; and

(d) intensified monitoring and drug treatment of hypertension and dyslipidaemia, quantifying annual number of averted CVDs and costs.

For the intensified monitoring and treatment of hypertension and dyslipidaemia at 50 % successful implementation, all patients with hypertension and dyslipidaemia were prescribed treatment, but only 50 % reached target blood pressure and cholesterol levels, while the rest reached blood pressure and cholesterol levels currently observed in ATHENA among patients on antihypertensive and lipid-lowering medication for ≥6 months (i.e. some patients do not reach target levels and some do).

The model predicts that annual CVD incidence and costs will increase by 55 and 36 % between 2015 and 2030. Traditional prevention interventions (i.e. smoking cessation and intensified monitoring and treatment of hypertension and dyslipidaemia) will avert the largest number of annual CVD cases (13.1 and 20.0 %) compared with HIV-related interventions — that is, earlier HIV diagnosis and treatment and avoiding cART with increased CVD risk (0.8 and 3.7 % respectively) — as well as reduce cumulative CVD-related costs (4).

Very recently, B-type natriuretic peptide (BNP) has been suggested to improve risk prediction of CV events and mortality. A study conducted in Germany aimed to evaluate the value of BNP to predict the composite primary end point of CV events and mortality alongside traditional and HIV-specific risk factors in HIV-infected population. At baseline, median BNP was 10.3 (IQR 5.4–18.9) pg/ml. The composite end point occurred in 158 (19.6 %) patients. Subjects with high BNP levels showed significantly increased frequencies of CV events and death (22 % for BNP ≤5 pg/ml,

30 % for BNP >5 up to ≤20 pg/ml, 38 % for BNP >20 up to ≤35 pg/ml, 59 % for BNP >35 up to ≤100 pg/ml, and 86 % for BNP >100 pg/ml, p-value <0.01). In the fully adjusted model that included traditional CV risks as well as HIV-specific factors, after a $\log_2$ transformation, doubling of BNP was significantly associated with increased risk for the composite end point (HR: 1.16 (95 % CI, 1.01–1.33); p = 0.031). Comparing BNP of <5 pg/ml to BNP >100 pg/ml, HR in the fully adjusted model was 3.25 (95 % CI, 1.50–7.08; p < 0.001) (5).

Recommendation

The presence of cardiovascular (CV) risk factors — that is, high blood pressure, smoking, diabetes, and overweight — should be evaluated at least once a year.

Strength of the recommendation

AII

Recommendation

Antiretroviral drugs, such as abacavir and darunavir, associated to a higher cardiovascular risk should be avoided.

Strength of the recommendation

AII

References

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7.4. What is the health-related quality of life (HRQoL) of people with HIV who have virological control and are immunologically stable compared to the general population?

Evidence from the literature

The HRQoL of people with HIV is generally considered lower than that of the general population, but very few data are available on the comparison between HIV and other chronic conditions (1). HIV-specific conditions, such as the communicable character of the disease and the social stigma attached to it (2–4), may determine a lower HRQoL compared to other conditions. Several studies have found that HIV-related symptoms, medication side effects, impaired immunological status, co-morbidities and low socio-economic status may be associated with a greater risk of lower HRQoL in HIV-infected people (5). However, considering that many studies have been performed before the use of cART, results from older studies may not be fully applicable today. For example, since an important progress has been made in developing more tolerable cARTs, HRQoL as regards side effects (such as diarrhoea, lipodystrophy and fatigue (1)) may currently play a less important role in the lives of people with HIV.

The only study evaluating HRQoL in HIV infection in comparison with other chronic conditions has been performed in the Netherlands, in a nationwide sample of people with HIV and on cART for at least 6 months, by using the Medical Outcomes Study Short Form 36-item Health Survey (6). The authors added data from studies on diabetes mellitus (DM) type 1 and 2, and rheumatoid arthritis. HRQoL in the HIV group was comparable with that of people affected by DM type 1 and 2, but lower than in rheumatoid arthritis patients. Conversely, looking at the mental health domain, a poorer mental HRQoL was found in HIV-infected people compared to the other groups. In people with HIV, a history of AIDS, longer duration of cART and severe co-morbidities were associated with poor HRQoL.

Recommendation

Even though data on HRQoL in HIV infection in comparison with other chronic conditions is scarce, people with HIV may have a poorer mental health HRQoL and should be regularly (every 12 months) assessed by validated questionnaires.

Strength of the recommendation

BII

References

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7.5. How should HIV-positive patients with metabolic disorders be monitored?

Evidence from the literature

Metabolic disorders are frequent among people living with HIV (PLWH). A study by Calza et al. recruited 586 patients: 98 naive to combination antiretroviral therapy (cART) and 488 undergoing the first antiretroviral treatment (ART). The prevalence of metabolic syndrome (MS), according to the NCEP-ATP III criteria, was significantly higher among the treated patients than among the naive ones (20.9 % versus 7.1 %; p = 0.014). The most frequently reported components of MS among the treated patients were high triglycerides (44.3 %), low high-density lipoprotein cholesterol (41.1 %), and hypertension (19.7 %). On multivariate analysis, the long duration of the HIV infection, low nadir of CD4 lymphocytes, high body mass index (BMI), current use of one protease inhibitor, and long duration of cART were significantly associated with a higher risk of MS, while current use of one integrase inhibitor was significantly associated with a lower risk of MS (1). Indeed, an important role is played by ART (2), but also demographic characteristics (3). The European Society of Cardiology has set the following levels of LDL cholesterol (4).

Table 5

RECOMMENDATIONS	CLASS	LEVEL
In patients at VERY HIGH CV risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50 % if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL) or a reduction of at least 50 % if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk, an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

The most important metabolic disorder is diabetes. A meta-analysis included 44 studies. The pooled incidence rates of overt diabetes and prediabetes were 13.7 per 1 000 person-years of follow-up (95 % CI = 13, 20; I = 98.1 %) among 396 496 person-years and 125 per 1 000 person-years (95 % CI = 0, 123; I = 99.4) among 1 532 person-years respectively. The major risk factors for diabetes and prediabetes were ageing, family history of diabetes, Black or Hispanic origin, overweight/obesity, central obesity, lipodystrophy/lipoatrophy, dyslipidaemia, metabolic syndrome (MS), increased baseline fasting glycaemia, and certain ART regimens (5). The D:A:D study aimed to develop a model to predict the short-term (6-month) risk of diabetes mellitus (DM) in HIV-positive populations

and to compare the existing models developed for the general population. Conventional risk factors identified in the general population as well as key HIV-related factors were assessed using the Poisson-regression model. Expected probabilities of DM events were also determined based on the Framingham Offspring Study DM equation. The D:A:D and the Framingham equations were then assessed using an internal–external validation process; area under the receiver operating characteristic (AUROC) curve and predicted DM events were determined. Out of 33 308 patients, 16 632 (50 %) were included, with 376 cases of new onset of DM during 89 469 person-years. Factors predictive of DM included higher glucose, body mass index (BMI) and triglyceride levels, and older age. Among the HIV-related factors, recent CD4 T-cell counts of <200 cells/µl and lipodystrophy were predictive of new onset of DM. The mean performance of the D:A:D and the Framingham equations yielded AUROC of 0.894 (95 % CI: 0.849, 0.940) and 0.877 (95 % CI: 0.823, 0.932) respectively. The Framingham equation over-predicted DM events compared to D:A:D for lower glucose and lower triglycerides, and for BMI levels below 25 kg/m (6).

Recommendation

Blood pressure checking once a year, or more frequently in case of borderline/high values.

Strength of the recommendation

AII

Recommendation

Total cholesterol, HDL-cholesterol and triglycerides should be monitored once a year, or every 6 months if higher risk.

Strength of the recommendation

AII

Recommendation

Serum glucose should be tested every 6 to 12 months, or more frequently if diabetes exists.

Strength of the recommendation

AII

References

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8. Life expectancy

8.1. What is the estimated life expectancy of people with recently acquired HIV infection?

Evidence from the literature

The life expectancy of people with recently acquired HIV infection is not easy to be determined, since very few studies have directly addressed progression and survival times in HIV-infected people with well-estimated seroconversion dates. One study reported data from seroconverter cohorts from 25 countries across four geographic regions: Africa, North America, Europe, and South-East/East (SE/E) Asia (1). In 16 373 eligible individuals with a median follow-up of 4.1 years (interquartile range 1.7–7.1), and mean age at seroconversion of 31.1 years (SD 8.8), the median survival for men aged 20 years at seroconversion was 13.0 (12.4–13.4), 11.6 (10.9–12.3), and 8.3 years (7.9–8.9) in Europe/North America, Africa, and SE/E Asia respectively. Mortality rates increase with age and vary by region. This data highlights how mortality rates exhibit regional- and age-specific differences, with decreased survival rates in African and SE/E Asian cohorts compared with Europe/North America and in older age groups. In high-income countries, among patients with HIV infection, the estimated life expectancy at age 20 has increased from 36.1 additional years during 1996–1999 (2) to 53.1 additional years during 2008–2011 (3) due to progressive improvements in antiretroviral therapy (ART) regimens and earlier diagnosis and treatment. Despite these improvements, a significant gap remains compared with the uninfected population for which life expectancy at 20 years in 2011 was estimated at an additional 59.5 years (3). A recent study was conducted in Switzerland in 16 532 HIV-positive patients and in a general population of 927 583 people: life expectancy at age 20 of HIV-positive individuals increased from 11.8 years in the monotherapy era to 54.9 years in the most recent combination antiretroviral therapy (cART) era. Differences in life expectancy across educational levels emerged with cART. In the most recent cART era, life expectancy at age 20 was 52.7 years with compulsory education, compared to 60.0 years with higher education. Estimates for the general population were 61.5 and 65.6 years respectively. Males (26 % higher risk than females), smoking (91 % higher risk than never smokers), injection drug use (IDU) (300 % higher risk than non-intravenous drug users), and low CD4 T-cell counts at enrolment (>350 cells/uL have a 71 % protection compared to <200 cells/uL) and having had AIDS (18 % higher risk) were also independently associated with mortality (4).

Recommendation

In order to evaluate the life expectancy of individuals living with HIV, the nadir of CD4 T-cell count and the lifestyle, including smoking and injection drug use (IDU), should also be evaluated.

Strength of the recommendation

BI

References

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8.2. What is the life expectancy of someone living with HIV who achieves and maintains viral suppression with antiretroviral therapy (ART)?

Evidence from the literature

Life expectancy is a key indicator used to assess mortality trends, and is also a surrogate for the overall health status of a population. In the absence of effective treatments, the HIV epidemic initially had a dramatic effect, reversing decades of progress on key development indicators including life expectancy. At the height of the HIV epidemic in sub-Saharan Africa, between 1990 and 2000, life expectancy deteriorated to 49.5 years. In 2006, it was reported that, in many countries, HIV and AIDS had decreased life expectancy by approximately 20 years (1, 2). Since the increasingly widespread use of cART, the prognosis of HIV-positive people who have access to antiretrovirals has substantially improved, resulting in reduced mortality rates and improved life expectancy (3, 4). Data coming from a meta-analysis on 8 cohort studies (5) estimating life expectancy of HIV-positive people initiating cART aged ≥14 years indicates an overall life expectancy in high-income countries of an additional 43.3 years in people starting cART at age 20 and 32.2 years in people starting cART at age 35, without any differences according to gender, and 28.3 and 25.6 additional years respectively in low-/middle-income countries, with higher life expectancy for women. The role of viro-immunological control of the HIV infection on life expectancy and on HIV progression is pivotal. In a recent study performed within the EuroSIDA consortium, in which participants were followed up after 1 January 2001 and grouped according to current HIV progression risk as 'high risk' (CD4 T-cell count ≤350/µl, VL ≥10 000 copies/µl), 'low risk' (CD4 T-cell count ≥500 cells/µl, VL <50 copies/µl), and 'intermediate risk' (other combinations), in 16 839 persons with 136 688 person-years of follow-up, those (aged 30 years or younger) at high risk had a 6-fold increased incidence of non-AIDS events compared with those at low risk, and a 2-to-3-fold increase (if older than 30 years) (6). A study conducted in the UK on subjects aged older than 20 years who started ART during 2000–2010 (excluding intravenous drug use (IDU)) in specialist HIV clinics contributing to the UK CHIC Study were followed up for mortality until 2012. Out of 21 388 patients who started ART, 961 (4.5 %) died during 110 697 person-years. At start of ART, the expected age at death of 35-year-old men with CD4 T-cell count less than 200, 200–349, or at least 350 cells/mm^3, was 71 (68–73), 78 (74–82) and 77 (72–81) years respectively, compared with 78 years for men in the general UK population. 35-year-old men who increased their CD4 T-cell count in the first year of ART from less than 200 to 200–349 or at least 350 cells/mm^3 and achieved viral suppression, gained 7 and 10 years respectively. After 5 years on ART, the expected age at death of 35-year-old men varied from 54 (48–61) (CD4 T-cell count <200 cells/µl and no viral suppression) to 80 (76–83) years (CD4 T-cell count ≥350 cells/µl and viral suppression). The conclusions of the authors were that successfully treated HIV-positive individuals have a normal life expectancy. Patients who started ART with a low CD4 T-cell count significantly improve their life expectancy if they have a good CD4 T-cell count response and undetectable VL (7). Nevertheless, a study conducted in the Kaiser Permanente California during 1996–2011, using a bridged life tables to estimate the expected years of life remaining ('life expectancy') at age 20 showed that even with early treatment and access to healthcare, an 8-year gap in life expectancy remains for HIV-infected individuals compared to HIV-uninfected individuals, but differed among groups. In 2008–2011, life expectancy at age 20 for HIV-infected individuals ranged from a low of 45.8 years for people of Black origin and 46.0 years for those with a history of IDU to a high of 52.2 years for people of Hispanic origin. HIV-infected individuals who initiated ART with CD4 ≥500 cells/µl had a life expectancy at age 20 of 54.5 years

in 2008–2011, narrowing the gap relative to HIV-uninfected individuals to 7.9 years (5.1–10.6 years). For these HIV-infected individuals, the gap narrowed further in subgroups with no history of hepatitis B or C infection, smoking, and drug/alcohol abuse (8). Since HIV-infected patients are getting older, it is important to estimate the health-adjusted life expectancy (HALE) of the adults living with HIV compared to that of the general population. In the COAST study (9) including all known people living with HIV (PLWH) and a 10 % random sample of the general population of British Columbia, from 1996 to 2012 at exactly 20 years of age, HALE was about 31 years (SD 0·16) among men living with HIV and 27 years (0·16) among women living with HIV. In the HIV-negative population, HALE was around 58 years (SD 0·02) for men and 63 years (0·02) for women.

Recommendation

The life expectancy of HIV-infected individuals should not be studied and assessed by considering only the HIV infection.

Co-morbidities, social determinants and inadequate viro-immunological control should be carefully evaluated since they could have a negative impact on the survival of HIV-infected individuals.

All efforts to manage and control these prognostic factors should be made.

Strength of the recommendation

AII

References

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8.3. Is life expectancy adversely affected by the time from infection until antiretroviral therapy (ART) start, and if so, is it possible to quantify the risk with increasing time to start ART?

Evidence from the literature

Life expectancy has increased in subjects who started ART in more recent years, but for those who started with a low CD4 count, mortality rates are still higher. A study conducted among 18 European and North American HIV-1 cohorts in 88 504 patients showed that 2 106 died during the first year of ART and 2 302 died during the second or third year of ART. All-cause mortality was lower in the first year after cART initiation in patients who started ART in 2008–2010 than in those who started cART in 2000–2003 (adjusted HR 0.71, 95 % CI 0.61–0.83). All-cause mortality in the second and third year after ART initiation was also lower in patients who started ART in 2008–2010 than in those who started ART in 2000–2003; this decrease was not fully explained by VL and CD4 T-cell count at first year (1). The fact that starting treatment late is associated with higher morbidity and mortality rates has been demonstrated by the START trial, a large, multi-national, randomised controlled clinical trial designed to evaluate the role of early ART in asymptomatic patients with HIV in reducing a composite clinical end point of AIDS-defining illnesses, serious non-AIDS events, or death (2). In this study, ART-naive adults (aged >18 years) with CD4 T-cell counts >500 cells/mm^3 were randomised to initiate ART soon after randomisation (immediate-initiation arm) or to wait to initiate ART until their CD4 T-cell counts declined to <350 cells/mm^3 or until they developed a clinical indication for therapy (deferred-initiation arm). The study enrolled 4 685 participants, with a mean follow-up period of 3 years. When the randomised arms of the study were closed, the primary end point of serious AIDS or non-AIDS events was reported in 42 participants in the immediate ART arm and in 96 participants in the deferred ART arm ($P < .001$). The most common clinical events reported were tuberculosis (TB) as well as AIDS and non-AIDS malignancies. The majority (59 %) of the clinical events in the deferred ART arm occurred in participants whose CD4 T-cell counts were still >500 cells/mm^3, evidence for the benefit of immediate ART even before the CD4 T-cell count declines below this threshold. Furthermore, the benefit of immediate ART was evident across all participant subgroups examined, including men and women, older and younger participants, individuals with high and low plasma HIV RNA levels, and participants living in high-income and low-/middle-income countries. Although START was not sufficiently powered to examine the benefit of immediate ART for each category of clinical events, the benefit of immediate ART appeared to be particularly strong for AIDS events and malignancies especially those AIDS related such as Kaposi's sarcoma and lymphomas. Importantly, immediate ART also significantly reduced the rate of pooled serious non-AIDS events. Finally, immediate ART also decreased the risk of severe bacterial infections (3). Starting cART at high level of CD4 T-cell count was associated to maintaining high level of adherence to the treatment and high virological response over time, as demonstrated by the HPTN 071 (PopART) trial (4). Another study was conducted to investigate the influence of the timing

of ART initiation relative to the HIV-1 infection on the normalisation of CD4 T-cell counts, AIDS risk, and immunological function. The median CD4 T-cell count in HIV-1-uninfected populations was approximately 900 cells/μl. Among 1 119 HIV-1-infected participants, CD4 T-cell count normalisation was achieved in 38.4 versus 28.3 % of those initiating ART within 12 months versus after 12 months from the estimated date of seroconversion (P = .001). Incrementally higher CD4 T-cell count recovery (<500, 500–899, and ≥900 cells/μl) was associated with stepwise decreases in AIDS risk and reversion of markers of immune activation, dysfunction, and responsiveness to levels approximating those found in HIV-1-uninfected persons. The conclusions were that deferral of ART beyond 12 months of the estimated date of seroconversion diminishes the likelihood of restoring immunologic health in HIV-1-infected individuals (5).

No clinical study has evaluated your question numerically; nevertheless, a very complicated theoretical mathematical model has been published which could be applied in order to understand in each patient the life expectancy with different timings of ART start (6).

Recommendation

The early start of combination antiretroviral therapy (cART) strongly determines a longer life expectancy. Consequently, a universal early cART start approach should be strictly recommended to increase the clinical benefit of the treatment.

Strength of recommendation

AI

References

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9. Additional issues

9.1. If a person has an AIDS-defining illness and subsequently makes a complete recovery with a CD4 T-cell count >200 cells/µl, are they considered to 'still have AIDS'?

Evidence from the literature

The study by Mussini C et al. has clearly shown that in subjects who already had a diagnosis of AIDS with a Pneumocystis carinii (now Jirovecii) pneumonia (PCP), it was possible to discontinue secondary prophylaxis when CD4 T-cell count increased >200 cells/µl (1). The same results were obtained concerning primary PCP by a few randomised trials (2, 3). Importantly, COHERE collaboration has shown in more than 23 000 patients that even if CD4 T-cell count does not reach a level >200 cells/µl, if the patients maintain an undetectable VL, i.e. <500 copies/µl, it is possible to discontinue primary PCP prophylaxis since the events were very low, irrespective of prophylaxis (4). Moreover, other studies have demonstrated that it is possible to discontinue all other primary or secondary prophylaxes for toxoplasmosis, mycobacterium avium or cytomegalovirus when CD4 T-cell count increases >100 cells/µl (5–8).

The possibility of discontinuing prophylaxis means that the immune system after ART is able to control opportunistic infections.

Recommendation

Subjects with a diagnosis of AIDS whose CD4 T-cell count increases above 200 cells/µl, as a result of ART, should not be considered to 'still have AIDS'.

Strength of the recommendation

AI

References

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9.2. Is the risk of future AIDS-defining conditions greater for someone who makes a complete recovery with a CD4 T-cell count >200 cells/µl than someone living with HIV and a CD4 T-cell count >200 cells/µl who has not had an AIDS-defining condition (if all other parameters are the same)?

Evidence from the literature

Only one study conducted in COHERE collaboration studied the issue on 75 336 patients contributing to 104 265 suppression episodes and suppressed while on cART for a median 2.7 years. The mortality rate was 4.8 per 1 000 years of viral suppression. A higher CD4 T-cell count has always been associated with a reduced risk of a new AIDS event or of death. A higher CD4 T-cell count has become even more beneficial over time for patients with CD4 T-cell counts <200 cells/µl (1). Moreover, nadir CD4 T-cell count has been shown to influence the decrease of CD4 T-cell count after treatment interruption. Indeed, a lower nadir CD4 T-cell count was associated with a steeper decline in CD4 after treatment interruption (2, 3). Concerning non-AIDS events, a recent study by Petit et al. has shown in a large, multi-centre cohort collaboration with standardised assignment of causes of death, the risk of death due to non-AIDS-defining events (NADEs) overall was over two times higher for patients with any AIDS-defining event after ART initiation compared to patients without any AIDS-defining events (ADE) following ART initiation (4).

Recommendation

Subjects with a CD4 T-cell count nadir <200 cells/µl should not discontinue treatment due the higher risk of developing AIDS events.

Strength of the recommendation

BI

References

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9.3. Where pre-exposure prophylaxis (PrEP) regimens for HIV-negative partners and post-exposure prophylaxis (PEP) to prevent HIV infection are advised, what is the impact on general health condition and performance status?

Evidence from the literature

A recent meta-analysis included 14 randomised clinical trials (18 837 subjects), 8 observational studies (3 884 subjects), and 7 studies of diagnostic accuracy (32 279 subjects). PrEP was associated with an increased risk of renal and gastrointestinal adverse events (ADEs); most ADEs were mild and reversible (1). The IPREX study showed a small but statistically significant decrease in bone mineral density (BMD) by week 24 that inversely correlated with tenofovir concentrations, with more stable BMD thereafter (2).

In the open cohort of the IPERGAY study, the proportion of participants reporting condomless sex at their last receptive anal intercourse significantly increased from 77 % at baseline to 86 % at 18 months' follow-up (p for trend = 0.0004). The incidence of a first bacterial sexually transmitted infection (STI) during this open-label phase was high, but did not change significantly compared with the randomised phase (3). Regarding the performance status, the problem is not related to antiretroviral drugs but to the use of other substances, which is frequent practice among PrEP users. For example, among 361 participants in the IPERGAY study, 30 % reported chemsex practice at least once during follow-up (4). An analysis conducted in the UK on 2 248 men who have sex with men (MSM) showed that 51 % used recreational drugs in the previous 3 months; 27 % used nitrites, 21 % used cannabis, 21 % used erectile dysfunction drugs, 20 % used cocaine, 13 % used ketamine, 12 % used 3,4-methylenedioxy-N-methylamphetamine (MDMA), 10 % used gamma-hydroxybutyrate or gamma-butyrolactone, 8 % used methamphetamine, and 7 % used mephedrone. In the 1 138 individuals who used drugs, 47 % used three or more drugs and 21 % used five or more (5). The best way to investigate the use of drugs for chemsex was to ask the individuals since most of the drugs are difficult to be detected by commercial tests (6). Concerning the safety of the PrEP use, a systematic

review identified that 13 randomised trials of PrEP was performed, using either TDF/FTC or TDF versus placebo or no treatment: VOICE, PROUD, IPERGAY, FEM-PrEP, TDF-2, iPrEX, IAVI Kenya, IAVI Uganda, PrEPare, PARTNERS, US Safety study, Bangkok TDF study, W African TDF study. The number of participants with grade 3–4 ADEs or serious adverse events (SAEs) was compared between treatment and control in the meta-analysis. Further analyses of specific renal and bone markers were also undertaken, with fractures as a marker of bone effects and creatinine elevations as a surrogate marker for renal impairment. Analyses were stratified by study duration (</>1 year of follow-up).

The 13 randomised trials included 15 678 participants in relevant treatment and control arms. The number of participants with grade 3–4 ADEs was 17.4 % on treatment versus 16.8 % on control. The number of participants with SAEs was 9.4 % on treatment versus 10.1 % on no treatment. The number of participants with creatinine elevations was 8/7 843 on treatment versus 4/7 835 on control. The number of participants with bone fractures was 217/5 789 on treatment versus 189/5 795 on control (difference = 0 %, 95 % CI 0–1 %). There was no difference in the outcome between studies with <1 versus >1 year of randomised treatment (6).

Recommendation

Due to the frequent use of drugs that are difficult to be detected by commercial tests, PrEP users should be carefully interviewed for drug use.

Strength of the recommendation

AII

Recommendation

Creatinine, phosphataemia, HIV test, serologies for HBV in case of non-vaccination or non-response to vaccination, HCV Ab, syphilis serology, chlamydia and gonorrhoea on rectal and pharyngeal swabs and urine by polymerase chain reaction (PCR) test every 3 months is recommended for all PrEP users.

Strength of the recommendation

AI

References

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10. Fitness to fly

10.1. Changes in the cellular proliferation rate of lymphocytes after long-haul flights have been reported for healthy individuals. Do they present a possible risk for patients with HIV infection?

Evidence from the literature

Very few experimental data or clinical studies exist on immunological changes, including those regarding possible alterations of CD4 T-cells counts, after short- or long-haul flights, either in healthy donors or in patients with HIV infection. Indeed, almost all studies concerning the effects of flight on the immune system have focused on astronauts, during and after missions of different time length in the low Earth orbit (at 200–400 km altitude above the Earth's surface). In these specifically selected individuals a number of changes have been described that affect almost all branches of the immune response, with a generalised decrease in cellular responses and activation of inflammatory pathways (reviewed in 1). Due to the completely different working environment, type of activity and level of stress, not to mention the different immunological pressure that microorganisms present in the cabin of a spaceship can exert, the results and conclusions derived from studies on astronauts are not applicable to aircraft pilots, nor to any other type of aircrew (e.g. cabin crew).

Cabin and flight crew members who fly 600–1 000 hours per year are exposed to an annual dose of cosmic radiation, primarily composed of charged particles and neutrons (2), of about 0.2–6 mSv (3). Thus, studies on persons working in aircraft (mainly crews) have mainly focused on the incidence of pathologies other than those affecting the immune system, i.e. tumours like breast cancer in women and melanoma in both genders, and found no evidence of increased mortality due to these diseases (4). Interestingly, a 37-year survey suggested a low all-cause mortality rate among flying personnel in Sweden, likely due to the frequent medical controls and visits these workers have to attend. However, the same study reported a higher-than-expected mortality rate for alcoholism and AIDS in only male cabin crews (5), mostly occurring in the pre-cART era.

Almost 20 years ago, it has been reported that changes in cellular proliferation and tolerance against chromate, both considered biomarkers of the cell capacity to repair damages that occur when chromate is used at extremely high doses, can occur after long-haul flights (6). In this study, cells from 22 healthy subjects and 18 HIV-infected patients in stage 2 and 3 were analysed at different time points after a long-haul flight. It was found that in the first 24 hours, tolerance against chromate significantly decreased in all groups, but returned to normal after 48 hours. Maximal proliferation rate dropped significantly in the second day after arrival compared to 1-week control values. Again, no differences were found among the groups, and the changes were attributed to the effects of cortisol and catecholamine on cellular immune response, and is in full agreement with thousands of reports that describe the negative, immunosuppressive effects of the psychological stress.

Recommendation

Persons with HIV infection could perform long-haul flights since there is no evidence of the influence of such flights on CD4 T-cell count.

Strength of the recommendation

CIII

References

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10.2. HIV infection and the conditions secondary to the infection, including those associated with ageing, can be the underlying cause of subtle (e.g. neurocognitive impairment (NCI), incapacitation secondary to AIDS-defining illness) or sudden (e.g. sudden death) incapacitation. The risk of incapacitation is key to the aeromedical assessment. For any given individual, is it possible to predict the likelihood of developing complications from primary HIV infection or the occurrence of a secondary condition in the next 12 months?

Evidence from the literature

The most relevant clinical aspects associated with higher subtle or sudden risk of incapacitation are represented by cardiovascular (CV) events (sudden incapacitation) and neurocognitive impairment (NCI) (subtle incapacitation).

With access to highly active antiretroviral therapy (HAART), the proportion of heart failure secondary to infective myocarditis is diminishing. Studies performed after the introduction of cART report that the HIV infection remains a risk factor for heart failure. In the Veterans Aging Cohort Study (VACS), excess rates and risk of heart failure among people living with HIV/AIDS (PLWHA) compared to uninfected people in age decades from <40 up to <70 years have been reported (1). Recent cross-sectional data suggests a 66 % greater prevalence of heart failure diagnoses among PLWHA compared to uninfected people using data from a hospital database (2). Other cross-sectional studies have shown over 2-fold increased odds of adjudicated heart failure among those with peak HIV viraemia ≥100 000 copies/μl and nadir CD4 <200 cells/mm^3 (3). Traditional risk factors for heart failure (e.g. older age, black race, overweight, hypertension, smoking, and prior myocardial infarction) identified in the general population also increase the risk among PLWHA. Additional risk factors that are particularly relevant among PLWHA include HIV viral replication, immunosuppression, liver fibrosis and depression (4–5). Pulmonary artery hypertension related to HIV infection is prevalent (more than idiopathic pulmonary artery hypertension) and may be another important driver of heart failure risk among PLWHA (6–7). Additionally, it remains unclear how disparities in cardiovascular disease (CVD) care contribute to increased heart failure risk, e.g. PLWHA are less likely to receive appropriate invasive management after myocardial infarction, a heart failure risk factor, compared to people without HIV (8–9). These disparities in treatment could be further exacerbated given recent reports on the restricted access of PLWHA to advanced heart failure care like heart transplantation (10). As the spectrum of cardiovascular diseases (CVDs) continues to change in the HAART era, peripheral artery disease (PAD) surfaces as an important understudied co-morbidity. Lower extremity PAD follows coronary artery disease and stroke as the third leading cause of atherosclerotic cardiovascular disease in the general population (11). PAD is common with ageing and occurs when there is partial or complete blockage of one or more peripheral arteries most often in the lower extremities (12). This leads to insufficient perfusion of the peripheral arteries which is often asymptomatic but may lead to pain and increasing disability (13). Many of the same conditions and behaviours that co-occur with PAD are drivers of atherosclerosis and are present with higher prevalence in HIV-infected populations, e.g. smoking, dyslipidaemia, diabetes, hypertension, and chronic kidney disease (12–13). There is a much better representation of longitudinal cohort studies for stroke than for PAD. Several of these cohort studies have described an approximately 30 % increased risk of ischemic stroke among PLWHA compared to uninfected people. A recent systematic review and meta-analysis of the risk of CVD by the HIV status reported

similar unadjusted incidence rates of ischemic stroke by the HIV status (14). Incidence rates in the USA were higher than those in Europe for both populations. In adjusted models, stroke risk was consistently elevated in PLWHA compared to uninfected people (pooled risk ratio 1.27 (1.15, 1.39)). There is some evidence suggesting a reduction in the excess risk of ischemic stroke associated with HIV among PLWHA with preserved immune function and suppressed viraemia (15–18). Regarding the relationship between HIV and myocardial infarction, a study within the Kaiser Permanente health system reported decreasing rate ratios (by HIV status) for myocardial infarction from 1996 until 2011. This suggests that the excess risk of myocardial infarction associated with the HIV infection diminished over time, likely a reflection of improved HIV care and growing literature during that time regarding the association of the HIV status with the risk of cardiovascular disease (CVD) (19). In a study within the VACS cohort, it has been reported that despite a greater relative risk of myocardial infarction associated with the HIV infection, PLWHA experience myocardial infarctions at approximately the same age as people without HIV (20). In the VACS cohort, a study grouping HIV-infected and HIV-uninfected people by CVD risk factor control and assessing myocardial infarction risk (21), reported a 2-fold increased risk of myocardial infarction among those with HIV compared to HIV-uninfected people. However, absolute rates of myocardial infarction were much lower among those with optimal cardiovascular health compared to those with at least one major risk factor, suggesting that the control of traditional CVD risk factors is critical to reducing absolute risk in HIV-infected individuals.

Recently, there has been interest in the recurrence of morbidity and mortality after myocardial infarction. Data from the Data Collection on Adverse Drug Events (D:A:D) study indicates that the proportion of PLWH dying from a CVD cause after their initial myocardial infarction decreased from 73 % in 1999–2002 to 41 % in 2011–2014 (22). Anyway, in most studies it seems to be suggested that maintaining immune function may improve cardiovascular outcomes in HIV-infected populations, even though some other studies report that well-controlled HIV infection was still associated with increased risk of death 1 year after myocardial infarction incidents adjusting for age, sex, year of myocardial infarction, smoking, hypertension, and diabetes (23). In conclusion, while the exact mechanisms driving excess myocardial infarction risk among PLWHA are being elucidated, there is sufficient evidence that intervening on traditional CVD risk factors while suppressing HIV viraemia and maintaining CD4 T-cell count levels with cART is a key prevention strategy.

Regarding neurocognitive impairment (NCI), it is well recognised that an HIV patient with asymptomatic neurocognitive impairment (ANI) may have a clinical progression of their neurocognition, with a progression to symptomatic HAND (24). A total of 347 human participants from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort were neurocognitively normal (NCN) (n 5 226) or had ANI (n 5 121) at baseline. Neurocognitive assessments were conducted approximately every 6 months, with median (interquartile range) follow-up of 45.2 (28.7–63.7) months. Symptomatic decline was based on self-report (SR) or objective, performance-based (PB) problems in everyday functioning. Proportional hazards modelling was used to generate risk ratios for progression to symptomatic HAND after adjusting for baseline and time-dependent covariates, including CD4 T-lymphocyte count, virologic suppression, cART, and mood. The presence of ANI had a shorter time to symptomatic HAND than the NCN after adjusting for baseline predictors: adjusted risk ratios for symptomatic HAND were 2.0 for either SR or PB. This would be considered as a subtle incapacitation condition or risk factor for developing a neurocognitive disorder.

Recommendation

Individuals with HIV infection are at higher cardiovascular disease (CVD) risk than the general population, even when on a suppressive cART and with well-preserved immune function. It should be a priority to manage traditional CVD risk factors in all HIV-infected people regardless of viro-immunologic condition. In particular, at every visit, individuals who declare some risk factors:

1. should be helped in stop smoking;
2. when LDL above the risk threshold for the general population (always changing), statins should be prescribed;
3. high blood pressure should be treated;
4. if overweight, a diet should be prescribed;
5. if ANI diagnosis, they should be monitored for the risk of clinical progression from ANI to a mild neurocognitive impairment (MND) every 6 months by a standard neuropsychological test battery.

Strength of the recommendation

AII

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If so, then:

10.3. What features of the HIV infection would be key to such an assessment?

Evidence from the literature

As we have previously reported, the virological control (HIV RNA >50 copies/µl) as well as the preserved immune function (CD4 T-cell count >200/mm^3 represent key aspects of a well-controlled HIV infection (1–2), but they represent just two of the aspects that should be monitored in order to reduce the risk of sudden or subtle risk of incapacitation. The other aspects to be routinely monitored are represented by cardiovascular disease (CVD) assessment (ASCVD score and Framingham score) (3) in order to prevent CVDs. The prevention of CVDs should take into consideration several aspects of the clinical condition of the patients and should involve a specialist, particularly if the CVD risk is high. Anyway, the evaluation and management of CVD prevention is based on current guidelines (4). Regarding the neurocognitive assessment, it has been reported in the specific questions and paragraphs.

Recommendation

Plasma HIV RNA, CD4 T-cell counts besides the CBC, and biochemical tests for liver and kidney function represent the analysis by which the infection should be routinely monitored. Nevertheless, an accurate assessment of the CVD risk and neurocognitive assessment by standardised tools should be routinely performed in order to identify early risk of incapacitation.

Strength of the recommendation

AII

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10.4. Can these be grouped/given numerical values so as to describe a lower-risk group?

We have understood what is requested, but our answer is unfortunately 'no' since there is no validated score.

10.5. Another approach to this: Can a person living with HIV be assessed with confidence as being free of all aeromedically significant complications of the HIV infection (including side effects from therapy), and with complete viral suppression will that person's risk of developing complications in the next 12 months be the same as that of a peer who is HIV-negative (assuming all other factors are equal)?

In this document, we have described how subjects living with HIV — even the early and successfully treated ones — are at higher risk of co-morbidities compared to the general population; thus, the answer to your question is clearly 'no'.

Risks

The present analysis entails some theoretical risks, since the specific literature (i.e. that concerning any specific work) is limited, and thus we will be forced to make extrapolations from other conditions. Moreover, we are physicians, so we will need to understand correctly with EASA what is required according to international rules as regards the licensing of flight crews with HIV. However, considering that in the consortium there are three main internationally renowned experts in the field (see our CVs) not only on HIV treatment (the leader), but also on the transmission (the virologist Carlo Federico Perno) and on the relationships between HIV and the central nervous system (Andrea Antinori), we think that we could give clear and practical indications according to the questions raised by EASA.

Work plan

1. The three experts will research Pubmed and all other databases on the specific topics in order to answer the specific questions (1 month).
2. Analysis of the literature by using the GRADE system in order to evaluate the strength of evidence. We will formulate the proposed questions on the basis of PICO (population, intervention, comparator, outcome) (1 month).
3. Draft the answers and recommendations including web and face-to-face meetings (15 days).
4. Interaction with EASA in order to understand whether the answers are consistent with the questions (7 days).
5. Final recommendations (7 days).

We estimate that the time required for this review will be 3 months: 15 days for the Medline and Pre-Medline, Embase and the Cochrane library. All study types between January 2008 and June 2018 will be included as abstracts presented at international conferences. Thus, a total of 45 days for reading the whole literature and 30 days to write the final document, including the recommendations to be submitted to EASA, will be needed.

The project leader, Professor Cristina Mussini, will be responsible for contacting EASA during the time of the project.

3TC=lamivudine
ABC=abacavir
ACTG= AIDS Clinical Trial Group
ADE= adverse events
AIDS= Acquired Immune Deficiency Syndrome
ALT= alanine aminotransferase
ANI=asymptomatic neurocognitive impairment
ARS= Acute Retroviral Syndrome
ARV= antiretroviral
ASCVD= atherosclerotic cardiovascular disease
AST= aspartate aminotransferase
ATV/r=atazanavir/cobicistat
ATV/r=atazanavir/ritonavir
BAI=Beck Anxiety inventory
BDI-II=Beck Depression Inventory-II
BIC=bictegravir
BMD= bone mineral density
BNP= B-type natriuretic peptide
CAC= coronary artery calcium
cART= combination antiretroviral treatment
CCR5= C-C Chemokine Receptor type 5
CD4= Cluster of Differentiation 4
CD8= Cluster of Differentiation 8
CE= European Conformity
CKD= Chronic kidney disease
CMIA= Chemiluminescent Microparticle Immunoassay
CNS=central nervous system
CRFs= Circulating Recombinant Forms
CSF=cerebrospinal fluid
CVD= cardiovascular disease
D:A:D= The Data Collection on Adverse events of Anti-HIV Drugs
DAAs= direct antiviral agents
DHHS= Department of Health and Human Services
DM= diabetes mellitus
DOR= doravirine
DRV/c=darunavir/cobicistat
DRV/r=darunavir/ritonavir
DTG=dolutegravir
DVT= deep venous thrombosis
EACS= European AIDS Clinical Society
ECLIA= Electro-Chemiluminescence Immunoassay
EFV=efavirenz
EIA= Enzyme Immunoassay
EVG/c/TAF/FTC= elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine
EVG/c=elvitegravir/cobicistat
FAS=Phonemic verbal fluency
FDA= Food and Drug Administration
FTC=emtricitabine

GBL=Gamma-butyrolactone
GHB=Gamma-hydroxybutyrate
GRT= Genotypic Resistance Testing
HAART= highly active antiretroviral therapy
HAD=HIV-associated dementia
HAND=HIV-associated neurocognitive disorders
HBsAg= Hepatitis B Surface Antigen
HBV= hepatitis B virus
HCV= hepatitis C virus
HDL= high-density lipoprotein
HDS=HIV dementia scale
HF= heart failure
HIV= Human Immunodeficiency Virus
HLA= Human Leukocyte Antigen
HRQOL=Health-related Quality of Life
hsCRP= high sensitivity C-reactive protein
IADL=Instrumental activities of daily life
IAS= International AIDS Society
IF= Fusion Inhibitor
IHDS=International HIV dementia scale
IL= Interleukin
INSTI=integrase strand transfer inhibitor
LDL= low-density lipoprotein
Lp= lipoprotein
LPV/r=lopinavir/ritonavir
MDR= multidrug resistant
MI= myocardial infarction
MS= metabolic syndrome
MSM=men who have sex with men
NAT= Nucleic Acid Test
NCEP= National Cholesterol Education Program
NCI=neurocognitive impairment
NMD=mild neurocognitive disorders
NNRTI=non-nucleoside reverse transcriptase inhibitor
NPA=neuropsychological assessment
NRTI=nucleoside reverse transcriptase inhibitor
NVP=nevirapine
PAD= peripheral artery disease
PCR= polymerase chain reaction
PI=protease inhibitor
PLWH=people living with HIV
PLWHA=people living with HIV and AIDS
PrEP= pre-exposure prophylaxis
PWID=people who inject drugs
RAL=raltegravir
RAVLT=Rey Auditory Verbal Learning Test
RNA= RiboNucleic Acid
RPV=rilpivirine

RT= Reverse Transcriptase
RV= Residual Viremia
SA= suicide attempt
SD= standard deviation
SI= suicidal ideation
STIs= Sexually-Transmitted Infections
SUD=substance use disorders
TAF=tenofovir alafenamide
TB= tuberculosis
TDF=tenofovir disoproxil
UV= Undetectable Viremia
VACS= veterans aging cohort study
VL= Viral Load
VR= Virological Rebound
WAIS-III=Wechsler Adult Intelligence Scale-Third Edition
WMS-III= Wechsler Memory Scale-Third Edition
XDR= extremely drug resistant