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Consensus document

Executive summary. Consensus document of GESIDA and SPNS (Spanish Secretariat for the National Plan on AIDS) regarding combined antiretroviral treatment in adults infected by the human immunodeficiency virus (January 2012)

Panel of Experts of GESIDA & Spanish Secretariat for the National Plan on AIDS[1,◊]

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ABSTRACT

In the present update of the guidelines, starting antiretroviral treatment is recommended in symptomatic patients, in pregnant women, in sero-discordant couples with high transmission risk, in patients co-infected with hepatitis B requiring treatment and in patients with HIV-related nephropathy. Guidelines on combined antiretroviral treatment (cART) are included in the event of concurrent HIV infection diagnosis with an AIDS-defining event. In asymptomatic naïve patients, cART will be based on CD4 lymphocyte count, plasma viral load (VL), patient age and patient comorbidity: (i) cART is recommended if CD4 count is lower than 350 cells/μL; (ii) cART is equally recommended if CD4 count is between 350 and 500 cells/μL and may only be deferred in the event of patient refusal with stable CD4 count and low VL; (iii) if CD4 count is higher than 500 cells/μL cART can be delayed, but it may be considered in patients with liver cirrhosis, chronic virus C hepatitis, high cardiovascular risk, VL >10^5 copies/mL, CD4 proportion lower than 14% and age over 55 years. cART in naïve patients requires a combination of three drugs and its aim is to achieve undetectable VL. Treatment adherence plays a basic role in sustaining good response. cART could and should be changed if virologic failure occurs in order to achieve undetectable VL again. Approaches to cART in HIV acute infection, in women and pregnancy and post exposure prophylaxis are also commented on.

Executive summary. Documento de consenso de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2012)

Palabras clave:
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RESUMEN

En la presente actualización se recomienda iniciar el tratamiento en los pacientes sintomáticos, en las embarazadas, en las parejas serodiscordantes con alto riesgo de transmisión, en la hepatitis B que requiera tratamiento y en la nefropatía relacionada con el VIH. En caso de diagnóstico simultáneo de infección VIH y evento definitorio de sida, se incluyen directrices sobre el inicio del tratamiento antirretroviral (TAR). En los pacientes asintomáticos el inicio de TAR se basará en la cifra de linfocitos CD4, la carga viral plasmática, la edad y las comorbilidades del paciente: 1) Si los linfocitos CD4 son inferiores a 350 células/μL se recomienda TAR; 2) Igualmente se recomienda si la cifra de linfocitos CD4 se encuentra entre 350 y 500 células/μL y sólo podría diferirse en caso de poca disposición del paciente cuando los CD4 se mantienen estables y la CVP es baja; 3) Si los linfocitos CD4 son superiores a 500 células/μL se puede diferir el tratamiento, pero puede considerarse en los pacientes con cirrosis hepática, hepatitis crónica por virus C, riesgo cardiovascular elevado, CVP >10^5 copias/mL, proporción de CD4 inferior a 14% y edad superior a 55 años. El TAR inicial requiere tres fármacos y el objetivo es conseguir CVP indetectable. La adherencia juega un papel fundamental en la duración de la respuesta. En caso de fracaso virológico se debe y puede conseguir de nuevo CVP indetectable. Se comentan los criterios de TAR en la infección aguda, en la mujer, el embarazo y la profilaxis postexposición.

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Introduction

Combined antiretroviral treatment (cART) is evolving so quickly that GESIDA and the Spanish National Plan on AIDS update their Treatment Guidelines annually. A Panel of experts has revised the advances published or reported to conferences in the last year and updated them. This is an executive summary of current guidelines.[1]

After more than 20 years of cART experience, a series of general principles have been defined on which this treatment is based. Decisions on treatment are taken taking into account the patient's clinical situation, CD4 lymphocyte count and plasma viral load. The goal of cART is to achieve VL <50 copies/mL or under the detection threshold. In order to achieve this goal we need three different drugs and a high level of patient adherence to treatment, this being essential to sustain good virologic response. By inhibiting viral replication it is possible to achieve a variable restoration of the immune system depending on previous damage level. Several negative aspects of cART have also been defined, such as adverse effects, frequent drug-drug interactions and the presence of resistant mutations when therapeutic drug levels are not achieved. By taking these principles into account and selecting available drugs, it is possible to design multiple treatment combinations. Clinicians should know patient characteristics in order to offer him/her the most suitable treatment and instruct on HIV transmission prevention measures.

How to monitor cART

A limited number of parameters are needed to monitor cART.

CD4 T-cell count. CD4 count is the main risk marker of opportunistic events and sets out when to start cART.

Recommendation:

1. CD4 count should be frequently monitored as it is the most important parameter in determining when to start cART **(A-I)**.

Plasma HIV RNA (viral load) testing. Viral load is a secondary determinant of starting cART and its fast and sustained suppression is a marker of cART effectiveness.

Recommendations:

1. Viral load should be measured jointly with CD4 T-cell count **(A-II)**.
2. Viral load is the most important indicator of response to antiretroviral therapy and is the main parameter to assess, change and define failures in cART **(B-I)**.
3. Viral load should be measured with a technique with a detection threshold of at least 50 copies/mL. It is convenient not to change the method **(A-I)**.
4. If a decision is to be taken after a plasma viral load testing result, this result should be confirmed before (with another test) **(A-II)**.

Drug-resistance testing. Viral genome mutations are the consequence of rapid HIV-1 turnover and the error prone reverse transcriptase. There is a relationship between the appearance of resistant mutations and virologic failure. Resistance mutations can be either primary or secondary to virologic failure.

Recommendations:

1. Genotypic resistance assay is recommended in clinical practice at diagnosis, when starting cART (if more than 1 year from previous determination), in pregnant women with detectable viral load, in virologic failure, and in post-exposition prophylaxis (to the source) **(B-II)**.
2. HIV subtype should be determined in immigrant patients or if there is quick clinical progression **(CIII)**.

Plasma drug levels. Plasma concentrations of antiretroviral drugs correlate with effectiveness or toxicity; therefore ascertaining drug levels may be useful to optimize drug doses.

Recommendation:

1. Measuring plasma drug levels of antiretroviral agents may be helpful in the management of specific clinical situations such as drug-drug interactions, in transplant recipients, severe underweight or obesity, and kidney or liver failure **(C-III)**.

*HLA B*5701 screening*. The presence of the HLA-B*5701 allele is related to a hypersensitivity reaction (HSR) to abacavir (ABC), a life threatening multiorgan clinical syndrome seen during the first 6 weeks of treatment.

Recommendations:

1. Screening for HLA-B*5701 should be performed at diagnosis or before starting an ABC-containing regimen **(A-I)**.
2. If HLA B*5701 is positive ABC should not be prescribed **(A-I**).
3. Negative tests do not rule out completely a future HSR in the future, so the patient should be informed about this possibility **(A-I)**.

HIV-1 co-receptor tropism assays. Tropism assay is useful when prescribing maraviroc.

Recommendations:

1. A tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered **(A-I)**.
2. Tropism assay is also recommended to patients on virologic failure when salvage therapy is to be been considered **(A-III)**.

Acute HIV infection

Acute HIV infection is symptomatic in more than half of the cases, but this is rarely recognized because symptoms are similar to a common viral infection.

It has been observed that progression to AIDS is faster in patients with certain characteristics such as symptom type, viral load, CD4 count and viral tropism. Taking these parameters into account we should choose whether or not to start cART. At the present time, starting cART during acute infection is controversial as the long-term potential benefit is not known.

Recommendations:

1. cART is recommended in acute HIV-infection if: (i) there is neurological involvement (meningitis, encephalitis, Guillain-Barré syndrome, etc.) or any other organ or system is affected (hepatitis, myocarditis, thrombocytopenia, etc.); (ii) the acute symptoms last for more than 7 days; (iii) an immunosuppression related event is diagnosed; or (iv) in case of severe immunosuppression (CD4 T-cell <350/μL) **(B-II)**.
2. Starting treatment should be considered when there is a high risk HIV-1 transmission **(A-II)**.
3. Drug-resistance testing and co-receptor tropism assay should be performed at diagnosis (of an acute or recent HIV infection), regardless of starting cART or not **(B-II)**.
4. If cART is to be started, the same drug-regimens recommended in chronic infection should be used. Raltegravir (RAL) and 2 nucleoside reverse transcriptase inhibitors (NRTI) (tenofovir/emtricitabine [TDF/FTC] of preference) would be of choice, due to the faster reduction in plasma viral load and higher concentration in genital secretions which may help in reducing HIV transmission **(B-III)**.
5. If drug-resistance testing result is not available, a boosted protease inhibitor (PI)-based regimen is preferred until this result is available **(A-II)**.