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Editorial

Initial antiretroviral therapy: The dilemmas ahead

Terapia antirretroviral inicial: los dilemas a enfrentar

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The Food and Drug Administration approved zidovudine in 1987. Twenty-five years later, clinicians taking care of HIV-infected patients in the developed world have 26 antiretroviral drugs of six different classes at their disposal. This incredible pace of drug development has enormously benefited the prognosis of HIV-infected patients. Mathematical models estimate that the life expectancy for a 30-year-old homosexual infected with drug-sensitive virus who receive antiretroviral therapy (ART) is 75 years.¹

Of the 26 available antiretrovirals, six are preferred for treatment naïve patients. The Spanish,^{2,3} European⁴ and the United States Department of Health and Human Services (DHHS) guidelines⁵ recommend two nucleoside/nucleotide reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil fumarate) and the nonnucleoside reverse transcriptase inhibitor efavirenz, the ritonavir-boosted protease inhibitor atazanavir or darunavir, or the integrase strand-transfer inhibitor raltegravir. The consensus among guidelines regarding these four regimens is based on their excellent antiviral efficacy, good toxicity profile and improved convenience.

It could be thought that after 25 years of ART the field is so mature that no major changes are to be expected in the near future. Although it is true that the pipeline for new antiretrovirals is drying progressively, in the next five years we are still going to incorporate important additions to our antiretroviral armamentarium. These additions would (fortunately) increase the therapeutic dilemmas faced by HIV clinicians.

To prescribe or not to prescribe a single tablet regimen?

Of the preferred combinations currently only efavirenz, emtricitabine, and tenofovir disoproxil fumarate are coformulated in a single-tablet once-daily regimen. In the immediate future it is quite possible that three new single-tablet once-daily regimens would be available.

Rilpivirine, another non-nucleoside reverse transcriptase inhibitor, has been coformulated with emtricitabine, and tenofovir disoproxil fumarate in a single tablet once-daily regimen.

Coformulated rilpivirine/emtricitabine and tenofovir disoproxil fumarate is approved in Europe for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients with a viral load less or equal to 100,000 HIV-1 RNA copies/ml.⁶ This indication is based on the results of the ECHO and TRHIVE clinical trials^{7,8} in which pooled analyses showed the risk of virological failure with rilpivirine was highest in patients with a baseline viral load above 100,000 copies/ml. Rilpivirine needs to be taken with a meal, lacks the central nervous system adverse events characteristic of efavirenz and has a good interaction profile with the important exception of proton pump inhibitors that drastically decrease rilpivirine exposure. Both the DHHS⁵ and the British HIV Association Guidelines⁹ recommend coformulated rilpivirine/emtricitabine and tenofovir disoproxil fumarate as an alternative regimen in treatment naïve patients. However, due to its convenience and good tolerability there is a lot of interest in the use of the rilpivirine single tablet regimen as a switch regimen in patients who have already achieved virological suppression. This concept is being tested in clinical trials.¹⁰

The other single tablet regimen that would be soon available is the coformulation of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (also known as “QUAD”). In QUAD, cobicistat is used as a pharmacokinetic enhancer in the same way low dose ritonavir is used to potentiate protease inhibitors. Compared to ritonavir, cobicistat is a more specific inhibitor of CYP3A without antiretroviral activity. The full spectrum of cobicistat interactions is still not known. Cobicistat can increase serum creatinine and decrease estimated glomerular filtration rate by inhibiting tubular efflux of creatinine without directly affecting actual glomerular filtration rates.

Two clinical trials^{11,12} have clearly demonstrated that QUAD can be used in antiretroviral naïve patients. The efficacy of QUAD was almost identical to the efficacy of coformulated efavirenz, emtricitabine, and tenofovir disoproxil fumarate¹¹ or emtricitabine, tenofovir disoproxil fumarate plus boosted atazanavir.¹² Given these results it is quite likely that QUAD is going to be approved and supported by guidelines to be used in naïve patients.

In the two pivotal trials, QUAD has been used in patients with creatinine clearance above 70 mL/min. In both trials cobicistat produced small increases in serum creatinine that are probably not clinically significant but clinicians should be aware of the need for

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monitoring renal function in patients receiving cobicistat. Other limitations of the two pivotal trials are the lack of a substantial number of patients with baseline CD4 cell count lower than 200 cells/ μ L and that women were underrepresented.

Dolutegravir is another once-daily unboosted integrase strand-transfer inhibitor that is currently finalizing phase III trials. Results of a phase II trial of antiretroviral naïve patient compared with efavirenz have been favorable showing high activity and a good toxicity profile.¹³ Dolutegravir is also an inhibitor of tubular creatinine secretion and produces small non-progressive increases in serum creatinine. It is likely that dolutegravir would be combined with abacavir and lamivudine to form another single tablet once-daily regimen.¹⁴

To prescribe or not to prescribe generic antiretrovirals?

Apart from lamivudine in the next four years there would be generic forms of nevirapine, abacavir, efavirenz, ritonavir, tenofovir disoproxil fumarate, darunavir and lopinavir/ritonavir. Given the current economic crisis it is very likely that drug cost is going to be a critical determinant of antiretroviral choices. The Spanish GESIDA experts have already performed a pharmacoeconomic analysis of the preferred combinations for ART naïve patients.¹⁵ In this context, the availability of generic antiretrovirals can profoundly transform ART. There is no single-tablet regimen composed of generic antiretrovirals.

Although we do not have definitive evidence, it is quite plausible that single tablet regimens improve long-term adherence and reduce the risk of HIV resistance development.¹⁶ These long-term benefits are very difficult to prove in clinical trials that follow patients for a maximum of five years. Despite this lack of evidence, there is consensus among experts in considering that single-tablet regimens are ideal for a disease that needs to be treated lifelong. The GESIDA,^{2,3} BHIVA⁹ and the European⁴ guidelines already recommend when possible to use coformulated combinations.

To prescribe or not to prescribe less than three antiretrovirals?

Without exception, all antiretroviral guidelines recommend initial treatment of HIV-infected patients with three antiretrovirals. With the realization that boosted protease inhibitors have an extraordinary high genetic barrier to the development of resistance it has been possible to evaluate the use of ART with less than three drugs.

Clinicians and researchers still have interest for novel dual combinations that do not include nucleoside/nucleotide reverse transcriptase inhibitors. Although abacavir and tenofovir have an overall good toxicity profile, these nucleoside/nucleotide are not completely exempt of important adverse events. The abacavir hypersensitivity reaction can be virtually avoided by the use of HLA 5701 genotyping.¹⁷ However, there is still controversy regarding a possible increased risk of cardiovascular events in patients who have recently initiated an abacavir based regimen.¹⁸ The long-term effects of tenofovir on renal and tubular function and in bone metabolism are still a source of concern especially in a progressively aging HIV-infected population.¹⁹

During the past two years, a number of pilot clinical trials have explored the efficacy and safety of nucleoside/nucleotide-sparing combinations in ART naïve patients: lopinavir/ritonavir plus raltegravir,²⁰ darunavir/ritonavir plus raltegravir²¹ and atazanavir/ritonavir plus maraviroc (only in patients infected with CCR5-tropic HIV).²² In these studies, sample sizes were small and one of them was a single arm clinical trial.²¹ Preliminary results have varied between promising^{20,22} and disappointing.²¹

Consequently prudent clinicians would wait for the results of ongoing large randomized clinical trials^{23,24} before using these dual combinations in clinical practice. Another experimental strategy in active evaluation in clinical trials is the combination of a boosted protease inhibitor plus lamivudine.²⁵ Lamivudine is a nucleoside reverse transcriptase inhibitor with an extremely good toxicity profile. If proven efficacious this dual combination might have toxicity and pharmacoeconomic advantages.

In summary in the next five years clinicians taking care of HIV-infected patients would have to confront important therapeutic dilemmas. It is fortunate that the number of ART options would increase thanks to the advent of three new single tablet regimens and (perhaps) new nucleoside/nucleotide sparing combinations. However, in the current economic environment, especially in Spain, pharmaceutical industry, clinicians and payers would need to make important agreements on the fair economic impact of these wealth of choices.

Conflict of interest

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References

- Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, et al. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS*. 2012;26:335–43.
- Consensus document of Gesida and Spanish Secretariat for the National Plan on AIDS (SPNS) regarding combined antiretroviral treatment in adults infected by the human immunodeficiency virus (January 2012). *Enferm Infecc Microbiol Clin*. 2012;30:e1–89 [Epub 2012 May 23].
- 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). *Enferm Infecc Microbiol Clin*. 2012;30:315–24.
- European AIDS Clinical Society (EACS) guidelines. Version 6.1; November 2011. Available online at: <http://www.europeanaidsclinicalsociety.org/images/stories/EACSPdf/eacsguidelines-v6.english.pdf>
- Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents; March 27, 2012. <http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf> [accessed 10.06.12].
- Eviplera: EPAR—Product Information. Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002312/WC5000118802.pdf [accessed 10.06.12].
- Molina J-M, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al., on behalf of the ECHO study. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naïve adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active controlled trial. *Lancet*. 2011;378:238–46.
- Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, et al., on behalf of the THRIVE study group. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet*. 2011;378:229–37.
- BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy; 2012. Available online at: <http://www.bhiva.org/TreatmentofHIV1.2012.aspx> [accessed 18.07.12].
- Study to Evaluate Switching From Regimens Consisting of Ritonavir-boosted Protease Inhibitor (PI) and Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) to a Fixed Dose Tablet Containing Emtricitabine/Rilpivirine/Tenofovir DF. ClinicalTrials.gov Identifier: NCT01252940.
- Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379:2439–48.
- DeJesus E, Rockstroh JK, Henry K, Molina J-M, Gathe J, Ramanathan S, et al. Coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. 2012;379:2429–38.
- van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naïve adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. *Lancet Infect Dis*. 2012;12:111–8.

14. Evaluation of the Bioequivalence of a Combined Formulated Tablet. ClinicalTrials.gov Identifier: NCT01622790.
15. Blasco AJ, Arribas JR, Boix V, Clotet B, Domingo P, González-García J, et al. Análisis de costes y de coste/eficacia de las pautas preferentes de GESIDA/Plan Nacional sobre el Sida en 2012 para el tratamiento antirretroviral inicial en adultos infectados por el virus de la inmunodeficiencia humana (VIH). *Enferm Infecc Microbiol Clin.* 2012;30:283–93.
16. Llibre JM, Arribas JR, Domingo P, Gatell JM, Lozano F, Santos JR, et al. Clinical implications of fixed-dose coformulations of antiretrovirals on the outcome of HIV-1 therapy. *AIDS.* 2011;25:1683–90.
17. Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomazic J, et al. HLAB* 5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358:568–79.
18. Behrens GMN. Abacavir and myocardial infarctions: the benefit of doubt? *AIDS.* 2011;25:2043–5.
19. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS.* 2012;26:867–75.
20. Reynes J, Trinh R, Pulido F, Soto-Malave R, Gathe JC, Qaqish R, et al. Lopinavir/ritonavir (LPV/r) combined with raltegravir (RAL) or tenofovir/emtricitabine (TDF/FTC) in antiretroviral (ARV)-naïve subjects: 96-week results of the PROGRESS study. *AIDS Research and Human Retroviruses.* 2012, <http://dx.doi.org/10.1089/AID.2011.0275> [published online first].
21. Taiwo B, Zheng L, Gallien S, Matining RM, Kuritzkes DR, Wilson CC, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naïve HIV-1-infected patients (ACTG A5262). *AIDS.* 2011;25:2113–22.
22. Portsmouth S, Craig C, Mills A, Mildvan D, Podzamczar D, Fätkenheuer G, et al. 48-Week results of a dual-therapy regimen of once-daily maraviroc (MVC) 150 mg in combination with ritonavir-boosted atazanavir (ATV/r) compared to emtricitabine/tenofovir (FTC/TDF) + ATV/r in treatment-naïve (TN) patients infected with CCR5-tropic HIV. In: Program and abstracts of the 6th IAS conference on HIV pathogenesis, treatment and prevention. 2011 [Abstract TUAB0103].
23. Study of darunavir/r + tenofovir/emtricitabine vs. darunavir/r + raltegravir in HIV-infected antiretroviral naïve subjects (ANRS 143). ClinicalTrials.gov Identifier: NCT01066962.
24. Comparative trial of maraviroc versus emtricitabine/tenofovir both with darunavir/ritonavir in antiretroviral-naïve patients infected with Ccr5 tropic HIV 1 (MODERN). ClinicalTrials.gov Identifier: NCT01345630.
25. Study of lopinavir/ritonavir and lamivudine versus standard therapy in naïve HIV-1 infected subjects. (GARDEL). ClinicalTrials.gov Identifier: NCT01237444.