Potent combined antiretroviral therapy (cART) dramatically changed the history of HIV/AIDS, and constitutes one of the major achievements of modern medicine. From the introduction of zidovudine in 1987 to contemporary cART, physicians and patients have been continuously on a challenging and demanding roller coaster through a constantly evolving field. The short initial excitement and hope accompanying zidovudine introduction soon was followed by the disappointing evidence of failure of ART monotherapy. Eight years passed until the impressive superiority of cART was clearly documented, first with dual nucleoside reverse transcriptase inhibitors (NRTI) and soon later with the addition of protease inhibitors (PI). Shortly thereafter the first non nucleoside reverse transcriptase inhibitor (NNRTI) was licensed and the way to modern cART was paved. Consequently, cART use expanded greatly and a dramatic decrease of HIV-associated opportunistic infections, AIDS incidence, and mortality associated with late presentation was observed in well-resourced countries.

Following these major breakthroughs, the introduction of new drugs and fine tuning of cART decreased further morbidity and mortality as well as drug-associated side effects and pill burden. The discovery of additional antiretrovirals, including new classes, significantly increased the number of potential drug combinations. Today we can choose from 23 antiretroviral drugs and 6 different drug classes, a fact simply unthinkable only two decades ago. Moreover, 5 fixed-dose drug combinations (FDC) marketed in Western countries are available. This increasing variety and complexity derived from cART, co-infections and co-morbidity lead to the need of periodically updated, evidence-based guidelines in this field.

Several important sets of HIV treatment guidelines exist, i.e. the US Department of Health and Human Services (DHHS) guidelines; the European AIDS Clinical Society (EACS) guidelines; the International AIDS Society-USA panel (IAS) guidelines; and the World Health Organization (WHO) guidelines. Renown national guidelines include the British HIV Association (BHIVA) and the Spanish guidelines put forward by the Grupo de Estudio de SIDA (GESIDA) and the Spanish Secretariat for the National Plan on AIDS (SPNS).

These guidelines share more similarities than differences. However, there are characteristics which make them useful for specific scenarios and needs. The WHO guidelines are designed to guide ART provision in resource-limited settings and for obvious reasons, differ in scope and approach from other guidelines mentioned above. Importantly, WHO guidelines take into account operational challenges associated with ART delivery and monitoring in the context of fragile health systems. In high-income countries, the IAS guidelines, provide a concise update on the most relevant aspects of cART (i.e. when to start, what to start, monitoring, when and what to change) which is also very valuable for non HIV experts, as they are regularly published in the Journal of the American Medical Association (JAMA). The DHHS guidelines are comprehensive and most detailed, and provide extensive and continuously updated references. They constitute a complete guide for cART use in naïve and experienced patients, special populations, co-infections, and on ART toxicity and interactions. The EACS distinctly provides additional comprehensive recommendations on the prevention and management of non-infectious co-morbidities. Also, the latter guidelines are translated into more than 10 languages and are presented in a practical pocket-size booklet with displayed procedures and algorithms, ideal to be used at the bedside of the patient. Hence, these regularly updated complementary guidelines should provide good and comprehensive guidance on HIV treatment in any given scenario.

Thus, the obvious question is “do we need national guidelines?”. In other words, are there any substantial differences among high income countries to justify this multiplicity of recommendations? Today, we do have close to a hundred guidelines on HIV treatment worldwide, as an expression of the adoption of international guidelines and evidence based medicine to the national level, including specific aspects of particular health systems.

The present edition of the GESIDA/SPNS guidelines, published in this issue of Enfermedades Infecciosas y Microbiología Clínica, constitute impressive proof of regularly updated knowledge. Since 1995, they are published annually and provide extensively documented recommendations, including almost 900 references.
from publications written in English, French or Spanish, as well as conferences communications. Remarkably, in order to rate the different cART regimens, the panel developed a strict scale, including parameters such as virologic efficacy, tolerability, long-term toxicity, emergence of resistances, co-morbidities, drug-drug interactions and convenience, giving a final score to each regimen ranging from 0 to 100. In addition, concurring with other guide-
lines, the strength of each recommendation is graded by adapting the Infectious Diseases Society of America (IDSA) criteria. Also, cART regimens that reached complete consensus among the panel members are differentiated from those which did not. Finally, all relevant studies are extensively summarized in a well structured manner to provide the reader with a clear and unbiased picture of the basis of recommendations. The authors certainly deserve credit for this extraordinary effort.

The present GESIDA/SPNS guidelines include several revisions compared to the 2011 edition. Concurring with the DHHS and the EACS guidelines, there is a completely new section on cART particularities for TB, chronic hepatitis, renal failure, and HIV-2 infection. Also, a new section on osteoporosis and bone fractures is included, derived from the better understanding of tenofovir toxicity. Importantly, in line with DHHS and IAS guidelines, GESIDA/SPNS recommends starting treatment in all patients with less than 500 CD4 cells/µL whereas the EACS guidelines are somewhat more conservative on this aspect. The authors of GESIDA/SPNS guidelines acknowledge the absence of evidence from randomized trials to support this specific guidance. However, they recommend earlier starting cART on the basis of 3 large cohort studies showing a decreased risk of progression to AIDS and death among patients starting treatment with CD4 cell counts above 350 cells/µL. Also, the authors refer to the results of the HPTN 052 study, which suggest a lower risk of progression and death among patients initiating treatment between 350 and 550 cells/µL vs. less than 250 cells/µL as well as a decreased risk of sexual transmission. Based on this evidence, the guidelines also strongly recommend offering cART to a seropositive individual in a serodiscordant couple in order to reduce sexual transmission of HIV to the seronegative partner.

What to start with - the panel has eliminated the notion of alternative regimes, considering that there are enough options available to treat any patient with the recommended regimes. Also, fixed dose combinations are recommended to maximize adherence. Concurring with EACS-, but in contrast with DHHS- and IAS-guidelines, tenofovir/emtricitabine and abacavir/lamivudine are equally recommended as NRTI backbone of initial regimens. However, caution is included, derived from the better understanding of tenofovir toxicity. Importantly, in line with DHHS and IAS guidelines, GESIDA/SPNS recommends starting treatment in all patients with less than 500 CD4 cells/µL whereas the EACS guidelines are somewhat more conservative on this aspect. The authors of GESIDA/SPNS guidelines acknowledge the absence of evidence from randomized trials to support this specific guidance. However, they recommend earlier starting cART on the basis of 3 large cohort studies showing a decreased risk of progression to AIDS and death among patients initiating treatment between 350 and 550 cells/µL vs. less than 250 cells/µL as well as a decreased risk of sexual transmission. Based on this evidence, the guidelines also strongly recommend offering cART to a seropositive individual in a serodiscordant couple in order to reduce sexual transmission of HIV to the seronegative partner.

Simplification - based on recent evidence, GESIDA considers a switch to monotherapy with lopinavir/ritonavir BID or darunavir/ritonavir QD in patients with undetectable HIV RNA for more than 6 months, excellent adherence, and signs or symptoms of NRTI toxicity. Concerns about NRTI long-term toxicity and costs may justify this strategy in well selected patients, but long-term follow-up data and more safety information regarding HIV replication in the central nervous system is needed to widely adopt this recommendation.

Noteworthy, the guidelines include a last section on the comparative monthly average wholesale prices of different ART regimens, an increasingly relevant factor when prescribing antiretrovirals in the context of the current global economic recession and health cuts in Spain.

In summary, and in response to the question aforementioned, yes, we do need national cART guidelines of this quality and level of detail. With no doubt, the present edition of the Spanish GESIDA/SPNS guidelines helps to ensure an ongoing discussion and adaptation for the best possible use of available drugs, and we encourage the authors to keep annually updating this extraordinary piece of work.

References