Modern Highly Active Antiretroviral Therapy-A Very Well Tuned Compass for a Rapidly Evolving Field

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Highly active antiretroviral therapy (HAART) has forever changed the face of the HIV/AIDS pandemic. Since first introduced a decade ago, in 1996 at the International AIDS Society sponsored Vancouver AIDS Conference, HAART has shown a very rapid evolution[1]. This has driven the need for frequent revision of therapeutic guidelines[2]. As a result, one of the major challenges today represents the prompt and accurate dissemination of rapidly emerging information so that the fruits of current research efforts can have a real time impact at the bedside, where they are most needed. The new Spanish guidelines[3] put forward by GESIDA and the Spanish AIDS Plan for the Antiretroviral Treatment of Adults Infected with HIV represent a very welcome new development in this area. The Spanish guidelines represent a sound and comprehensive review of the state of the art in the field of antiretroviral medicine, which incorporates relevant new developments that have accrued in the recent past, many of which originated at the hands of Spanish investigators. It is also important to point out that this document represents the most comprehensive such initiative in the Spanish medical literature and, as such, it has tremendous implications for the continued fight against HIV/AIDS in Latin America.

Consistent with other international guidelines, the new Spanish guidelines appropriately encourage the use of simpler highly effective non-nucleoside reverse transcriptase-based HAART. When constructing a HAART backbone, tenofovir is recognized as having an edge over abacavir and this over zidovudine-based regimens. The backbone is to be completed with either lamivudine or emtricitabine, both widely accepted as excellent partners for any of the above. Having said that, it is clear that the field has moved towards the adoption of fixed dose combinations and once daily regimens have emerged as a key strategy to facilitate adherence. In this context, based on the available evidence, Truvada® (the one pill once daily fixed dose combination of tenofovir and emtricitabine) is generally preferred over Kivexa® (the one pill once daily fixed dose combination of abacavir and lamivudine), which in turn is generally preferred over Combivir® (the one pill twice daily fixed dose combination of zidovudine and lamivudine). The options in this regard will soon be widened with the entry of Atripla®, the first full NNRTI based HAART regimen available as a one pill once daily fixed dose combination of tenofovir, emtricitabine and efavirenz, recently approved in the USA by the Food and Drug Administration. When considering NNRTI based HAART it is important to acknowledge the small but significant problem of primary NNRTI resistance. As a result, it is strongly recommended that resistance testing be done as part of the baseline assessment of HIV-infected individuals prior to the initiation of NNRTI based HAART. Ritonavir-boosted protease inhibitor (PI) based HAART regimens have also been shown to be highly effective but because of pill burden and tolerability issues, these are generally regarded as an alternative option in first line therapy.

Consistent with other guidelines, the Spanish guidelines appropriately recognize that the strategy to be followed in second-line therapy is largely dictated by the circumstances leading to the failure of the prior regimen, and this is to be further informed by the results of sequential resistance testing, whenever possible. Perhaps the most significant new development in the treatment of experienced individuals pertains to the now established consensus reflected in the present guidelines that full suppression of viral replication to levels below the lowest limit of quantification of commercially available assays (< 50 copies/mL) should be the target for patients initiating salvage regimens, no different to the stated goal of initial therapy. This consensus is largely due to the entry of several agents which have proven to be highly active in experienced patients including the fusion inhibitor, enfuvirtide, as well as two second generation PIs tipranavir and darunavir, both to be used with ritonavir boosting. Several new entries are expected in the very near future in this area, which will further facilitate and simplify the treatment of highly experienced patients. In particular we are encouraged by the imminent availability through special access programs of TMC125, a new second-line NNRTI, and the first HIV integrase inhibitor (MK-0518).

Also of interest, a number of clinical trials have now been reported evaluating various strategies to simplify therapy among patients on older more complex regimens. Of note, while some controversy remains across the Atlantic regarding whether unboosted atazanavir is an adequate treatment option, the results of the SWAN[4] study suggest that atazanavir can play a significant role in the simplification of PI based HAART regimens. Similarly although still experimental, the reported success with PI based HAART simplification to ritonavir-boosted protease inhibitors alone, particularly with lopinavir/ritonavir, while not recommended as a standard of care within cur-

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rent guidelines, do provide a sense of confidence that these compounds not only carry significant antiviral potency but also quite a high genetic barrier, which makes it difficult for the virus to escape the antiviral drug pressure, over the short-term.

As expected, with the increased number of antiretrovirals now available, the potential for side effects has grown significantly. The same can be said about drug interactions whether they pertain to interactions between antiretroviral drugs or with other agents frequently used to deal with the frequent multiple co-morbidities that may affect HIV-infected individuals. All of this emphasizes the importance of concentrating HIV care in the hands of experienced physicians, a key independent contributor to securing optimal health outcomes.

Of interest, the current guidelines also make specific recommendations regarding post-exposure prophylaxis and the use of antiretroviral therapies to prevent mother-to-child transmission of HIV infection. As we enter the second decade of HAART, it becomes abundantly clear that we need to redouble our efforts to contain the spread of HIV. In this context, the contribution that HAART can make to the control of HIV spread has been often a neglected topic, probably because of the fear that this discussion may open the door for a relaxation of prevention practices, such as safer sex or harm reduction. It is now clear that the long-term sustainability of our HAART effort will ultimately depend on our ability to control the spread of HIV disease and, as such, the potential role of optimal and possibly expanded use of HAART as a means to enhance the control of HIV spread deserves to be explored further[5].

As we enter the second decade of HAART we have an opportunity to reflect on our collective achievements. It has recently been suggested that not less than 3 million years of life have been saved in the United States as a direct result of care of patients with AIDS[6]. While this represents a cause for celebration, multiple challenges have emerged as a result[7]. As we review the new Spanish guidelines, the lyrics popularized by Joan Manuel Serrat come to mind "Caminante no hay camino se hace camino al andar…" Let this be a tribute to the new Spanish guidelines, a most suitable and very well tuned compass in this most challenging voyage.

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