On antiretroviral guidelines and evidence based medicine

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Another year, another set of guidelines. What is the purpose of having multiple guidelines? Are they really different? Do we need a set of guidelines to treat HIV infection for each country of the world? All of us ask ourselves these kinds of questions every time we see this type of document. Obviously guidelines need to be updated as the science in the field progresses, and this document really fulfills that need. These guidelines are necessary, timely and reasonable, but I am supposed to editorialize about them. Kenneth Tynan, a caustic British theater critic once said that “A critic is a man who knows the way but can’t drive the car”. I feel a little like that, I know the problems of guidelines, but I do not know a very good alternative. I praise the authors for their courage writing them, and accept the criticism from people like me.

The main objectives of therapeutic guidelines are to improve the quality, the appropriateness of care, and the cost-effectiveness of medical interventions, and to serve as educational tools for health care providers with less experience. There are many other, less altruistic objectives of guidelines that are almost never stated in public: recognition of the authors as experts in the particular field, setting up the “standard of care” for legal purposes in malpractice lawsuits, (especially in countries like the US where this is a frequent phenomenon), and last but not least, guiding insurance companies and governments with regards to which services should or should not be compensated.

Hundreds of guidelines are published every year. There are web sites devoted to guidelines (http://www.guideline.gov); there are guidelines to make guidelines, and articles have been published about how well guidelines follow guidelines. Sometimes I feel we spend more time writing about how care should be done rather than providing care ourselves, and performing the studies necessary to improve it.

If guidelines are used properly they are incredible tools that improve the quality of the care of our patients. If they are used like “cookbooks”, replacing clinical judgment, they become dangerous, because they remove the responsibility of care away from the physician and the individual patient. Physicians should be clearly aware that guidelines apply to populations and not necessarily to individual patients, and that they are not the “Ten Commandments” written in stone.

Decisions about the care of individual patients can not be purely based in a set of guidelines, even if they are based in the “sacrosanct” principles of evidence based medicine (EBM). EBM has its own limitations and optimal care of the individual patient still relies in other forms of knowledge that are not obtained through large randomized trials. Is this knowledge wrong or inferior, as the A, B, C classification of the levels of evidence seems to suggest, or is it just different? I would favor the second interpretation.

I will put two examples that apply to these specific guidelines in order to convey my viewpoint. The first example refers to prophylaxis of maternal-fetal transmission of HIV infection. We have good evidence that demonstrates that AZT monotherapy decreases the risk of transmission from the mother to the baby (evidence level A –from a randomized placebo controlled trial-). However nobody would recommend the administration of AZT monotherapy in this situation and most of us, including the authors of these guidelines, would recommend the administration of potent antiretroviral therapy, which has only been evaluated as part of large prospective cohort studies (evidence level B). Have we forgotten the principles of EBM? Are we comparing across trials with different designs? Should we wait for a large randomized trial to change the standard of care? The answer is no. The hierarchy that EBM applies to clinical evidence does not apply to this particular case (and many others). In this case, evidence based in cohort studies is “stronger” than the evidence obtained from a large randomized trial. The hierarchical classification of medical knowledge sometimes just does not work.

The second example relates to the recommendations for the treatment of acute HIV infection. We lack the evidence of good clinical trials, and this and other guidelines do not support the use of antiretroviral therapy in this situation and instead recommend the politically correct “the patient should be enrolled in a clinical trial”. The problem is that sometimes there is no clinical trial around to enroll the patient and the patient and the doctor need to make a decision. Most HIV clinicians would evaluate that patient and if they felt there is a reasonable probability of success they would recommend treatment for a variable period of time. Again: are we all wrong? Where is EBM? Do we need a large randomized trial to recommend therapy in this situation? The answer is again probably no. There are
reasons that make many good clinicians think that treatment in this situation is a good option but they have not been evaluated in a large trial. There is some evidence from very small non-randomized trials that favors early therapy in this situation, and it makes sense from what we know about the pathogenesis of HIV disease. This kind of knowledge can not be captured in a set of guidelines and is part of the “discredited” clinical expertise.

My point is that we should embrace the principles of EBM, but understand its limitations. The same applies to therapeutic guidelines. Even David Sackett, the “guru” of EBM, has expanded the definition of EBM to include individual clinical expertise as an intrinsic part of it. He defines EBM as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research”.

Guidelines are a good working tool for diseases like diabetes or hypertension that are very prevalent and taken care of by a very diverse group of clinicians with variable degrees of expertise. They provide a “minimum of good care”, and probably improve outcomes at the population level. That is less clear at the individual level, when the care for the disease in question is highly specialized, or when new information comes continuously and the standards of care change rapidly.

The care of patients with HIV infection is concentrated in the hands of only a few doctors. In the USA there are approximately 2,000 doctors that write most of the prescriptions of the more than 250,000 patients under care. In Spain there are approximately 200 doctors (probably less) that take care of more than 100,000 HIV infected patients (approximately one quarter of them not yet under care). The standard of care of HIV changes so quickly that guidelines often lag behind what has already become accepted general practice.

The main news of the current guidelines is that they have become more conservative than ever before. They suggest delaying the initiation of antiretroviral therapy until the CD4 count falls below 350 cells/μl and minimizing the contribution of HIV RNA load into making such a decision. Those recommendations are not based in results of a large randomized trial (which will probably never be done) but rather on other types of knowledge with a lower hierarchy in the classification of EBM: these include the impossibility of eradication of the cellular reservoirs of HIV, the high frequency of complications associated with treatment, and the lack of a clear clinical benefit of early initiation of therapy.

The reader should be aware that “the pendulum” can swing back in the future, and that future guidelines might again be more aggressive.

These new guidelines also provide an update about resistance and resistance testing, (both genotypic and phenotypic), the use of therapeutic drug monitoring and interventions to prevent maternal fetal transmission of HIV. A quickly growing section of this document refers to the treatment of co-infections with hepatitis B and C viruses. Chronic hepatitis and its complications including cirrhosis and hepatocarcinoma have become a very common problem in this era of increased survival of HIV. The recommendations about the treatment of hepatitis C shows another limitation of therapeutic guidelines: their limited durability. New evidence from a large randomized trial demonstrates the superiority of pegylated interferon and ribavirin over regular interferon alpha in combination with ribavirin for the treatment of hepatitis C. The standard of care today for the treatment of chronic hepatitis C in HIV-infected individuals is a combination of pegylated interferon and ribavirin. These guidelines also include numerous tables that will help you find quickly the information you need.

Do I disagree with the content of these and other guidelines? Of course not. Guidelines represent the prevailing wisdom in the field. My prevailing ideas are not very different from the majority of physicians, especially now that everyone seems to be a little more conservative.

We all attend the same meetings, view the same presentations, read the same studies, and thus, it makes sense that we reach similar conclusions when we systematically evaluate the published and unpublished evidence.

There are areas, however where I clearly disagree. For example, I do not understand why we keep recommending single therapy with AZT for 4 weeks in a situation in which the risk of HIV acquisition is between 1 and 2% (the newborn baby of an HIV-infected mother), yet we recommend triple therapy in the case of a needle stick from an HIV-infected patient, where the risk is 0.3%.

Wouldn’t make more sense to recommend triple therapy during the first month of life?

One of the missing elements of these otherwise very reasonable guidelines is the target audience: who is going to be reading them? Are they directed to HIV physicians in Spain, Latin America, or all over the world? My assumption is that they are directed to the Spanish physician, and if correct, then for future editions they might consider including more detailed information about particular areas of HIV care that are specific for Spain. Spain has a decentralized National Health Service and all HIV care is provided in highly specialized units generally located in large hospitals. All antiretroviral drugs are “hospital based medications” and distributed directly from the hospital pharmacies. This practice dramatically decreases the cost for the government, who saves what would otherwise be the margin of the private pharmacy in other countries (in Spain the cost of prescription medicines is covered in most cases). This particular phenomenon requires a very close relationship between clinicians and hospital pharmacists and allows for a very good monitoring of adherence. It might be a model to imitate in some countries that are thinking in providing antiretroviral drugs to their citizens.

I would like to finish this editorial with a proposal for the future. The theme for the XIV International AIDS Conference that will take place in Barcelona in July 2002 is “Knowledge and Commitment for Action”. We need to integrate our knowledge with health care providers of the developing world to develop guidelines that are desperate services needed for the care of the patients in countries with limited resources. In the Caribbean and Latin America there are more than 2 million people infected with HIV, many of whom have no access to HIV medications or experienced health care providers. This is an area where therapeutic guidelines written in Spanish
will be very helpful. By working with humbleness and respect together with governments, health care providers, and non-governmental organizations and recognizing how much we just do not know, we can improve the care of the millions still infected with this devastating disease.

References