ADVANCES IN HIV/AIDS TREATMENT

PLENARY PRESENTATION, JULY, 11, 2000

Mauro Schechter, MD PhD
UFRJ – Brazil

ISSN: 0103-0465
DST – *J bras Doenças Sex Transm* 13(1): 35-39, 2001

I would like to thank the Conference Organizers for giving me the honor and privilege of presenting this talk to such a distinguished audience.

Slide

Since the Geneva Conference, data have accumulated to indicate that eradication is unlikely with presently available drugs; virologic failures are more common in practice than in trials; the CD4 cell counts at which opportunistic infections occur in patients on therapy and patients who are not on therapy are similar; that, although many patients do not achieve full immune recovery, a large proportion achieve a "safe" level of immune competence; and that antiretroviral therapy is associated with potencially serious side effects, some of which may be time-dependent.

Slide

These newly accumulated data, in turn have led to a renewed debate on: the optimum time to treat; the choice of initial drug regimen; when to change and how to sequence regimens; how to simplify existing regimens; the role of new drugs and of pharmacologic enhancement in extending treatment benefits; and on the management and prevention of opportunistic infections.

During my presentation I will review recent data on each of these topics. I will finish by trying to predict, in light of the data reviewed, how the history of HIV treatment may unfold in the coming years.

Slide

Over the past several months, the optimal time to iniciate therapy has been hotly debated, particularly in reference to the threshold values of viral load and CD4. With regards to viral load, two separate reports published in JID have demonstrated a direct association between the slope of the increase of plasma viral load in the first few years after seroconversion and the probability of progressing to Aids. In the MACS study, as shown in these four panels, the rapidity of progression was found to be proportional to the slope of the increase of viral load. On the upper leftpanel are represented those who progressed in less than 3 years, on the upper right in 3 to 7 years, on the bottom left in more than seven and on the bottom right those who remained Aids-free for at least nine years.

Slide

It was also shown that, for those who progressed to Aids, the slope of viral load increase in the three years preceding progression to Aids was similar, regardless of prior Aids-free time. On the upper leftpanel are represented those who progressed in less than 3 years, on the upper right in 3 to 7 years, on the bottom left in more than seven and on the bottom right those who remained Aids-free for at least nine years. These observations argue against a blanket concept of a fixed set point. They also suggest that it may be more appropriate to measure viral load in a serial fashion, rather than relying on one or two measurements in order to make therapeutic decisions.

Slide

Julio Montaner will report in a late breaker session on a population based cohort analysis of antiretroviral naïve adult patients who started HAART between 08/96 and 09/00 in British Columbia. There were over 1,200 eligible participants and data were censored on January 31, 2000. Results showed that the effectiveness of therapy was dependent on baseline CD4 count, but not on age, gender, viral load, prior Aids diag-

nosis, or PI use. Furthermore, few patients with baseline CD4 > 200 cells/mm³ experienced clinical progression and progression rates were similar for patients with CD4 counts 200-350 or 350-500 cells/mm³.

Slide

These results suggest that it is probably OK to postpone treatment initiation, provided therapy is started while immune recovery to "safe" levels is still possible. The question of how to precisely define this moment remains unanswered.

Slide

Once the decision has been made to start therapy, the optimal initial regimen has also been a matter of debate. At the recent Retrovirus meeting, John Bartlett presented data on a re-analyzes of 22 different trials of triple drug therapy in naïve patients. These authors showed that when the same methodology and definitions are used virologic success rates are quite similar, regardless of the regimen used, as shown in the slide.

Slide

In the same study, these authors have also shown that, at 48 weeks, the proportion of participants with plasma viral load below 50 copies/ml or the median CD4 increase (as shown in the two columns in the far right) were very similar for patients who started triple regimens containing a protease inhibitor, a non-nuke or triple nukes.

Slide

In fact, as represented in this graph, they also showed that, regardless of the regimen, i.e, PI-containing, NNRTI-containing or triple nukes, there was a significant association between pill burden and virologic success, further reinforcing existing data on the relationship between adherence and virologic success.

Slide

Once treatmen is instituted, several groups have reported that virologic failure rates are much higher in clinical practice than in clinical trials. For example, at the Johns Hopkins HIV clinic, fewer than 40% of patients had a viral load below 500 copies/ml after 7-14 months on therapy, as shown on the right hand side of this slide.

Slide

On the other hand, immunologic failure may be less common. Several groups have reported on the so-called "discordant response". For example: Steve Deeks has recently reported in JID results on 380 patients on HAART. It was shown that, after 96 weeks of follow-up, gains in CD4 counts (shown in the upper panel) were almost identical for patients who experienced complete virologic success (i.e, remained undetectable throughout the follow-up period, represented in green in the graph) or who experienced a transient response (those who reached an undetectable level followed by viral rebound, represented in white in the graph). In addition, even patients with a partial response (those whose viral load fell but never became undetectable, purple in the graph), also experienced sustained increases in CD4 counts. These authors showed that the degree of viral suppression (the difference between the pre-treatment levels and the level achieved 12 weeks after virologic failure, termed "delta viral load" by the authors) is a stronger predictor of immunologic success than the absolute viral load achieved.

Slide

The relationship between sustained immunologic and clinical benefit despite virologic failure was demonstrated in a large prospective observational study (the Swiss Cohort Study). In this study, after 30 months of follow-up, after controlling for baseline CD4 and age, patients with transient virologic responses (the red curve in the middle panel) had clinical progression rates that were similar to that seen in patients who maintained an undetectable viral load (the red curve on the left panel).

Slide

It is worth mentioning that this phenomenon (immunologic and clinical benefit despite virologic failure) also occurs in patients receiving dual RT-therapy. For instance, this slide shows the results of a study conducted in Rio de Janeiro, involving 80 patients sequentially seen in an outpatient clinic and who started dual RT therapy in 1996/97 according to the guidelines of that time (being asymptomatic and having a CD4 > 200). After 2 years of follow-up, despite virologic failure in almost all (shown in the bottom panel), none had experienced disease progression and CD4 counts had risen on average by almost 200 cells (shown in the upper panel). This observation may be of particular importance for resource-limited settings, especially after the recently announced initiative by several pharmaceutical companies that may greatly reduce the cost of antiretrovirals, RTs in particular.

Slide

As previously discussed, regardless of the regimen chosen, a considerable proportion of patients eventually fail on their initial therapy. Thus, many patients will eventually use several antiretroviral regimens. For instance, according to Mike Saag, in the period 1996-99, at the University of Alabama, the median time on a single regimen was 4 months. Thus, for many (if not most) patients, the ultimate success of antiretroviral therapy will likely depend on the aggregate effectiveness of

sequential therapies, not solely on the potency of a particular regimen used as initial therapy. Nonetheless, there are limited data on the clinical impact of sequential therapies, particularly for patients at the earlier stages of HIV disease.

Slide

For this reason, we have developed a mathematical model which was published in AIDS last year. This model, to which we applied data from published studies, was used to compare expected clinical outcomes using three different therapeutic strategies, using PI and non-PI containing regimens as initial therapy and PI or dual PI-containing regimens after the first virologic failure. Two different scenarios (optimistic and pessimistic, according to the proportion of patients who maintained virologic control) were also used. After 5 years of follow-up, predicted clinical outcomes were virtually identical regardless of the initial regimen used, as can be seen by the almost overlapping lines in the graph. These results suggest that, with presently available data, it is not possible to predict which strategy for inicial therapy is best. Thus, it is likely that we will only be able to make firm recommendations after the results of trials that compare treatment strategies, such as INITIO and ACTG 384, are in, which may take a few years.

Slide

In the meantime, and since virologic failures are common, strategies to enhance compliance, reduce toxicity and prevent resistance are being developed, and include: the development of more user-friendly regimens; pharmacologic enhancement ("PI-boost"); development of new drugs in existing classes that are designed to select for novel mutation sites; development of new classes of drugs; and the evaluation of structured treatment interruptions.

Slide

The use of the combination of abacavir, AZT, and 3TC, which in the near future will involve only two pills a day, is an example of a simple regimen using existing drugs. In clinical trials, such as the one shown on this slide, results obtained with this regimen are comparable, in terms of viral load and CD4 response, to those obtained with a standard PI containing regimen, in this case AZT, 3TC, and Indinavir.

Slide

Regimens with single daily doses, which may even allow for directly observed therapy in some settings, are also being developed. For instance, ddI and efavirenz are already licensed for once-daily use. Studies are in progress involving other drugs, including lamivudine, FTC, nevirapine, tenofovir and combinations of PIs. In addition, a PI for once daily dosing (BMS-232632) is at an advanced stage of development.

Slide

The soon-to-be licensed drug formerly known as ABT-378 is an example of a new drug in an existing class that requires a higher genetic barrier for resistance to develop (ie, a larger number of mutations is necessary for the development of high level resistance). It is also an example of the pharmacologic boost that can be obtained with the concomitant use of small doses of ritonavir, often called "PI boost", as illustrated in this slide.

Slide

Additionally, several drugs in the existing classes are in advanced stages of development and can be expected to be licensed in the coming years. T-20 deserves special mention, since it is the first drug of a new class (fusion inhibitors) that should be entering phase III trials in the near future. In addition, T-1249 is another drug of this class entering clinical trials.

Slide

Another subject being hotly debated is the so-called "Strategic treatment interruptions". Here, two situations must be differentiated. The first involves patients failing therapy with multiply resistant HIV, which I prefer to call a "drug holiday". The second involves patients on therapy with full viral suppression, for whom temporary interruptions of treatment are being evaluated.

Slide

At the Retrovirus Conference early this year, Steve Deeks presented data to show that for patients failing therapy with multiply resistant HIV, the interruption of therapy is associated with an abrupt switch to a sensitive phenotype, which is simultaneous for all drugs, as shown for three different patients in this slide. Some cautionary notes, however, should be made. In that same presentation, convincing data was shown to indicate that this phenotypic change is associated with an abrupt drop in CD4 counts and a steep increase in viral load. In addition, once therapy is re-introduced, viruses with resistant phenotypes promptly re-emerge. These data suggest that, until more data are available, drug holidays as a therapeutic strategy should be viewed with extreme caution.

Slide

For patients on therapy and with full viral suppression, the rational for temporarily interrupting therapy is the hope that viral rebound may restore some HIV specific response (an "endogenous vaccination"), which, in turn, could lead to immunologic and clinical benefit. Studies involving such patients are being conduced by several groups. In general, as Dr. Fauci showed, it has so far been shown that decreases in CD4 counts precede

increases in viral load and that, upon resumption of HAART, viral load returns to < 50 copies/ml in nearly all individuals and the CD4 count returns to the levels prior to interrupting therapy. Notably, it has been reported that no genotypic or phenotypic resistance develops. Given these preliminary results, studies are under way to evaluate intermitent HAART as a means of controlling HIV replication while sparing patients the toxicity, inconvenience and cost of continuous HAART.

Slide

As has been reported from all countries that can afford the high price of antiretrovirals, the introduction of PIs into clinical practice was soon followed by a steep decline in mortality rates among patients with advanced HIV disease, as shown in this slide that most if not all of you have seen countless times. Nonetheless, several published reports have documented that impressive declines in mortality, rates actually preceded the availability of HAART by several years.

Slide

For instance, in British Columbia, mortality rates among patients with < 100 CD4 (in yellow in the graph) fell by approximately 70% between 1994 and 1996.

Slide

Similary, in Chicago, despite the continuous increase in the number of prevalent Aids cases (as shown in white in the larger graph), HIV-related deaths (as shown in the insert), decreased by over 60% in the same period.

Slide

In Europe, mortality rates among patients with CD4 counts below 200 and who were not on antiretroviral therapy (shown in the second column on the left) fell by 45% between 1995 and 1997. Clearly, other factors, besides HAART have influenced these declines in mortality rates.

Slide

According to data recently published in the NEJM, the incidence of opportunistic infections in the US declined markedly in the years that preceded the availability of HAART. It is thus quite possible that, in addition to the availability of potent antiretrovirals, better treatment and prophylaxis of opportunistic infections may have played an important role in the decline of mortality.

Slide

If this is the case, then the adequate use of available interventions to prevent opportunistic infections may remain very important. I would like to single out two infections, tuberculosis and pneumococcal infections, since both can cause significant morbidity and mortality in developing as well as developed countries and both may occur in patients with a relatively preserved immune system. In addition, both are potentially preventable with relatively cheap interventions.

Slide

A paper by Jones and collaborators that will be published in the next few months in the International Journal of Tuberculosis and Lung Diseases demonstrates that among patients with < 500 CD4 cells, TB incidence in the US has been steadily falling since the early 90's, irrespective of antiretroviral therapy in use, this fall being more marked amongst patients on HAART.

Slide

Several years ago, Bill Pappe showed in Haiti that, in a population without access to antiretroviral therapy, primary prophylaxis with INH was capable of reducing mortality. In a poster presented at this conference, Dr. Santoro-Lopes in my group reports the results of a prospective study involving 306 HIV+, PPD+ patients, with a median follow-up of 4 years. In Brazil, antiretroviral therapy, including protease inhibitors, is available free of charge to all HIV infected individuals. In this study, after adjustment for antiretroviral therapy, prophylaxis was shown not only to reduce the risk of TB by 84%, but also, as shown in the graph, to reduce the risk of death by almost 60% (patients who did not receive prophylasis shown in yellow, whereas those who received prophylaxis are represented in white in these survival curves). These results firmly indicate that even in areas or for populations with high prevalence rates of *M. tuberculosis infection,* primary prophylaxis remains very important even when HAART is available.

Slide

In 1999 Osmond reported in CID the results of a large observational study conducted in the US to evaluate pulmonary complications associated with HIV infection. In that study it was shown that the development of bacterial pneumonia (in white in the graph) was associated with significantly worse subsequent HIV disease course, when compared to CD4 matched controls (yellow in the graph). These data seem to reinforce the recommendation that pneumococcal vaccination should be considered as standard of care.

Slide

Nevertheless, in a recent issue of the Lancet, a team of investigators led by Charles Gilks reported the results of the first large trial to evaluate the efficacy of pneumococcal vacci-

nation. This study, conducted in Uganda, involved approximately 1,400 participants randomized to receive a 23-valent pneumococcal vaccine or placebo. Surprisingly, it was shown that both invasive pneumococcal disease and all cause pneumonia were more common in vaccinees (white in the graph) than in placebo recipients (represented in yellow in the graph). These unexpected findings raise several questions, including that recommendations from industrialised countries need to be evaluated in resource-poor settings and that policy should be evidence based, before any intervention becomes standard of care.

Slide

In summary, considering all the data that I have just reviewed, as well as other pieces of information that time constraints did not permit me to present, I will take the liberty of making some predictions as to what I think may happen between now and when we reconvene in Barcelona in two years: The pendulum will swing back towards later treatment; the definition of failure in clinical trials will be revisited; greater emphasis will be placed on "delta viral load"; CD4 count as a guide to therapy will undergo a renaissance; and simpler drug regimens will become available.

Slide

I also predict that there will be renewed interest in the prevention of opportunistic infections, which, in turn, will take into consideration local epidemiologic conditions; there will be a re-evaluation of the role of "less potent" regimens, particularly their cost-effectiveness in resource-limited settings; STI will be discussed as a means of making treatment less toxic and more affordable; and pressure on industry and Governments will increase to ensure equal and universal access to antiretroviral therapy.

These are only predictions. If they will pan out, only time will tell, since, as one American philosopher once said...

Slide

"All predictions are difficult, particularly when they involve the future".

Slide

Finally, I would like to sincerely thank all my friends and colleagues who shared with me their data, slides and wisdom in order to make this presentation possible.

Thank you.