The old and the new: lessons learned for the future

Interview with Mark Weinberg

Sometime old words hide new concepts. It happends when in a changed environment arrive new opportunities. Its seems to me it is the case of terms like "monotherapy" or "dual therapy". Being involved in HIV field since the beginning of the story, about these topics I looked for an expert opinion of another old guy, Mark Weinberg, who is in seek the Director of the McGill University AIDS Centre at the Montreal Jewish General Hospital and Professor of Medicine and of Microbiology at McGill University.

"I think a lot of the ideas that we had previously dismissed may come back and I don't think we are going to be using monotherapy very much in the future, even an excellent drug like darunavir, boosted darunavir which some people have suggested could be used as a kind of monotherapy. I don't think is going to be sustainable, I don't think it's a good idea. I think that over the long term it will lead to a lot of treatment failure and resistance against all of the PI drugs, so I would not be in favor of this. I think I might be willing to give more of a chance to dual therapy with some of the newer agents coming forward. I think that some of them are really very very encouraging and, you know, the one new drug class that we have, notably the integrase inhibitors, are very much underexploited and we really need to fully consider how the integrase inhibitor class of drugs may make a real difference in regard perhaps to paving the road toward dual therapy and, you know, we may be in for some very pleasant surprises, we need to do the clinical trials but we have to be optimistic.

We have a lot of toxicity now on the floor, we have kidney, bone, muscle, mitochondrial myopathy, co-infection, we have to plan a long-term therapy, a chronic therapy. How can we deal with this toxicity?

Toxicity is part of the problem in regard to developing any really good triple strategy. There is no question that we learn more and more about toxicity as time goes by. We should be positive and remember though that we have at least four drugs that don't seem to have any major toxicities at all, maybe five drugs. One of them is certainly raltegravir, it's a very clean safe drug, another is 3TC, a third

drug is FTC and I think a fourth drug that is approved that falls into the same category is maraviroc. None of these drugs really shows any kind of long-term toxicity, in contrast probably with all of the others that are associated with some form of side effect. The newest drug that is now in clinical trials, dolutegravir, from what we see so far is also a very clean drug in terms of its toxicity profiles. So, again, I think we have to be optimistic.

So many drugs, but we haven't still resolved the first step: when we start?

Oh, I think we have resolved the first step of when we start. I think there is a growing consensus that we should start as soon as somebody is diagnosed as being HIV positive. Now, this is not always possible, we sometimes wait way too long before making a diagnosis of HIV positivity, but as far as I am concerned, and I think as far as other key opinion leaders like Stefano Vella are concerned, we really should start the moment somebody receives an HIV diagnosis, assuming, of course, that the person is going to be willing to take their drugs in a fully adherent way and that we will be using good drugs on this person. You know, there is so much evidence that allowing the virus to continue to replicate has the potential to do irreparable damage to the immune system. Why would anybody want to let that happen?

How to plan a chronic therapy, simplifying the puzzle?

I think we have to be willing to try some new approaches such as reducing viral load to undetectable levels by using three excellent drugs that should I believe include maraviroc, which I think is an excellent drug and one that is very much underutilized in the current spectrum of antiretroviral therapy. Once we do succeed in reducing viral load to undetectable levels, perhaps then simplification strategy could be contemplated in which we use drugs that are virtually non-toxic in a context of perhaps reducing the numbers of drugs sometimes and look forward to long-term success. Again, patients have to be fully adherent: we don't have that many drugs

that really have a fantastic safety profile, so we want to, therefore, and we need to preserve the drugs that have a fantastic safety profile for as long a period of time as possible. Patients need to understand this, so that they don't wind up being non-adherent and therefore develop resistance to some of these compounds which will then wind up only compromising their future therapy, and will result in them needing to take drugs perhaps that won't have as clean profiles in regard to toxicity as some of the other choices that might be available.

In your opinion, is possible to use an approach like induction and maintenance in chronic therapy for HIV infection?

Yes, I think induction/maintenance could be a very positive strategy, there is some clinical trials now underway to evaluate this hypothesis. You know, one of the worries, of course, that we would have is whether or not removing a drug as part of the simplification strategy could sometimes perhaps lead to more immune activation, so even if you don't immediately wind up with more viral load, are you going to wind up with more immune activation or are you going to wind up potentially causing long-term problems. I think this is a very important issue that needs to be evaluated very seriously.

Another aspect related to immune activation is aging: aging because we have patients that are getting older with HIV/AIDS and aging because there is an immune senescence caused by the replication and inflammation of HIV.

Yes, I completely agree, aging is a problem and I think that there is no question that some of the side effects that we associate with drugs are now showing up in the aging population, so it makes it very important to really think about using drugs that have the cleanest possible profiles as part of an antiretroviral regimen. If we assume that a cure is very far off, eradication is very far off and even the type of minimal cure that we would hope for whereby perhaps we would be able to never completely eradicate but still not have viral replication come back. Even for that kind of situation I think we would want to have a drug regimen that is as clean as possible and right now what we are seeing is that some of the very good drugs that are currently being prescribed as part of triple therapy do seem to be having side effects in the aging population, perhaps because people have been treated over such a long period of time and it's taking a lot of years for some of these side effects to show up. We have to be cognizant of this, absolutely.

The last aspect I actually want to cover together is the central nervous system problems. It's related to premature aging in some way and is related to the immune activation caused by the virus?

Well, of course, central nervous system aspects are extremely important. We know that some people who are HIV-positive who respond well to antiretroviral drugs may nonetheless wind up having problems of dementia. In some cases we think that it may be attributable to the fact that not all of the drugs that they may be on penetrate into brain tissue and central nervous system tissue as well as might happen for other drugs and there is apparently considerable inter-patient variability in regard to ability of drugs to penetrate the blood brain barrier. It's still on ongoing area of investigation, it needs more attention and hopefully we may be able to rely at some point on genomics. Certain genetic tests that may be able to tell us who can be safely treated with drugs that ostensibly don't seem to relate well to penetration of the blood brain barrier, some people may be able to get away with these drugs and other people may not. Its' an ongoing area of research. ■

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