Routine prescribers? No thanks

Interview with Mark Nelson

"I think we need to start thinking about novel ways of treating patients. I think what is going on is that we have all become rather routine prescribers just writing out our favorite prescription for the majority of patients- says in a very passionate way Mark Nelson, Director for the HIV Directorate and Deputy Director of Research, Chelsea and Westminster Hospital:- so we need to think about the necessity to individualize per patient, that doesn't mean patients must receive a treatment without HAART, that doesn't mean the patients need to receive treatment without nucleosides, it means that we need to consider the pros and cons for the individual patient".
Who is the candidate for a HAART without nukes? What type of patient may be the type of patient where we think about it? Well, first of all, there are individuals who have multiple resistance to nucleosides but we have kind of just thrown the nucleosides in: the viral load is undetectable, but they may now be experiencing toxicities to those drugs. Potentially, we are aware of a possible association of abacavir with heart disease, tenofovir with kidney and bone disease, as we get older we are more likely to get those: so people may feel safer off the nucleosides, particularly if they are not adding any power to the regimen. There may be individuals who have those toxicities who would prefer to come off and their physician would prefer them to come off those nucleosides. And at the end, there is the issue of cost, of course. You know, it's much cheaper potentially to give a single drug as long as that works as well. So, there are many factors, both patient factors, physician factors, but also population and social problems due to the fact that we are all facing hard times.

We can try to define three big main categories of patients that could take advantage of such simplification, starting from the naïve patients.

Sure. We need to think about several different groups of patients and where the idea of a nucleoside-sparing regimen may actually fit in. It is impor-

tant to explain what is a nucleoside-sparing regimens. We are talking about mostly protease inhibitor-based therapy, either a protease inhibitor alone or a protease inhibitor with another class of drugs. So, if we think firstly about the naïve patient, protease inhibitor monotherapy doesn't work. Two studies, the Monark study and a study of ritonavir and darunavir show that even in patients with low viral loads that start below 100.000, so called easy-to-treat patients, they didn't do as well as triple therapy. So, it doesn't seem to be a role of PI monotherapy alone, but there is increasing amount of data on the role of protease inhibitors and non-nucleosides, protease inhibitors and a CCR5 antagonist and protease inhibitors and an integrase inhibitor. The problem: is there really an advantage for the patient there? They are having to take often treatments twice a day because the only integrase inhibitor is raltegravir, they have the issues of protease inhibitor toxicity, so the drugs may actually work just as well as triple therapy in this dual therapy sparing the nucleosides, but is there an advantage? Probably not and there do appear to be some disadvantages. Now, I think there is an interesting study, the NEAT 001 study which is examining Truvada, ritonavir/darunavir vs. ritonavir/darunavir and raltegravir. I think it's' not only about virological success: virological success is likely to be equal, but the issues which are coming out to the patient of twice-daily treatment with raltegravir are: what happens if you fail an integrase-inhibitor containing regimen, etcetera, etcetera. I think there are a lot of issues other than virological success which we need do look at in these large studies.

And for patients that are in a failing regime?

In patients who are virologically failing in resource-rich world, in Europe, I think most people who would start in two nucleosides and a non-nucleoside will go to two nucleosides and a protease inhibitor. But people who are failing, in the resource-poor world the overall situation is different: viral load is not generally available, therefore virological failure is actually found out very late and it tends to be based on drops in CD4 count, clinical progression. So it's actually quite like they have been on that failing regimen for relatively long time, they have multiple nucleoside resistance. So, I think it's going to be much more used in failing patients in the resource-poor world and clearly it gets rid of the idea of needing a resistance test. If you are on two nucleosides and a non-nucleoside and you move to two new classes of drugs, no need to do resistance testing, so it may really be something which is very effective in the resource-poor world, but is clearly also something which could be made available in richer parts of this planet.

For patients that are controlled and I want to make an easier option?

I think the big place that we are going to be looking at nucleoside-sparing regimens in the future is switch patients. I think if you go to a clinic, most clinics would look at success rates of 90, even 95%, one clinic in the UK is reporting 99% of patients with an undetectable viral load. Therefore we can treat the virus, now we need to treat the patient. If the patient is going to be on treatment in the long term, it is likely that the biggest issues are going to be adherence, it's boring taking treatment, and the toxicities, particularly the long-term toxicities. So we need to think about simplifying their regimens. There is an increasing amount of data on the strategy of protease inhibitor monotherapy: just taking a single drug where there is a low rate of failure slightly higher than with triple therapy but not associated with resistance. Clearly if you take a single drug there is likely to be less toxicity and is going to be a great deal cheaper. Now, I don't think we need to go too much about cost, but it's going to be increasingly important for the clinics in order to give the excellent care that they give to the patient, however that is really going to be an important issue I think of protease inhibitor monotherapy. About the protease inhibitor monotherapy, I think there are physicians who love it, there are physicians who hate it and really we need to actually come together and make a good strategy of when it should be used, how it should be used and in what patients.

In your talk today you said that monotherapy is a strategy. What do you mean with strategy?

If you look at protease inhibitor monotherapy, if you take patients who are doing very well on treatment and who have full virological suppression, you randomize them to actually take PI monotherapy or to continue their triple therapy, there are more failures with PI monotherapy. So, that doesn't look good, but because there is no resistance or the risk of developing resistance is extremely low and certainly not higher than patients failing triple therapy. What we can do is if the patient, if the PI isn't strong enough by itself, is adding the nucleosides back again. So, it's the strategy of PI monotherapy with adding in nucleosides if they fail, rather than the treatment that means it's all finished with.

It is also an option for people that are aging older because it could be reduced polypharmacy?

Yes, I think that PI monotherapy is something that the people who are taking multiple drugs may like. There are clearly other strategies as well. It's about the individual patient: if someone is taking 20 tablets three times a day, reducing their HIV tablets by two or three makes no difference, but for some individuals who are struggling to take all their drugs it may be an advantage. This advantage, of course, is that would mean taking ritonavir, ritonavir does have a lot of drug interactions, it's very important again, but it's a balanced

approach and we don't just jump in without thinking.

To plan a therapy for a chronic condition in other therapeutic areas it is used an approach called induction and maintenance. Is it feasible in HIV field?

I think that the idea of induction/maintenance is something which has been explored several times within HIV and will be explored further in the future. I think what's happening as regards simplification and PI monotherapy is that at the moment it's a very reactive approach, so it's an approach if something is happening to that individual as regards toxicity or adherence. It's not something that in clinic we are thinking about doing something routinely. Induction/maintenance will only come to the fore if we get clinical research backing it up as approach and secondly if we are much more proactive of thinking about simplification of therapy. A patient who is on triple therapy and doing well with no side effects is unlikely to change to monotherapy, we find in clinical practice, because he says "Look, I am doing well, why would I want to switch?" and so it's a big discussion that has to go on about the possible advantages and disadvantages of such an approach.

You said it's a big discussion: it means that listen to the patient is the key anyway?

I think it's about explaining to the patient, I think… It's like many things that doctors can do.Iit's really about saying to the patient look, we don't know what is the right approach, this is a moving field, we know what a wrong approach is, but what is the correct approach, this is the advantages of such an approach, these are the disadvantages of such approach…. The problem is within the clinic there are more and more patients because they are doing well, they want to get out of that clinic and it has become a consultation of "your CD4 count is normal, your viral load is undetectable, see you in six months". I think we need to take a step back and look at the long-term effects of these drugs, the long-term effects of HIV and continue to rationalize different treatments for different people. ■

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