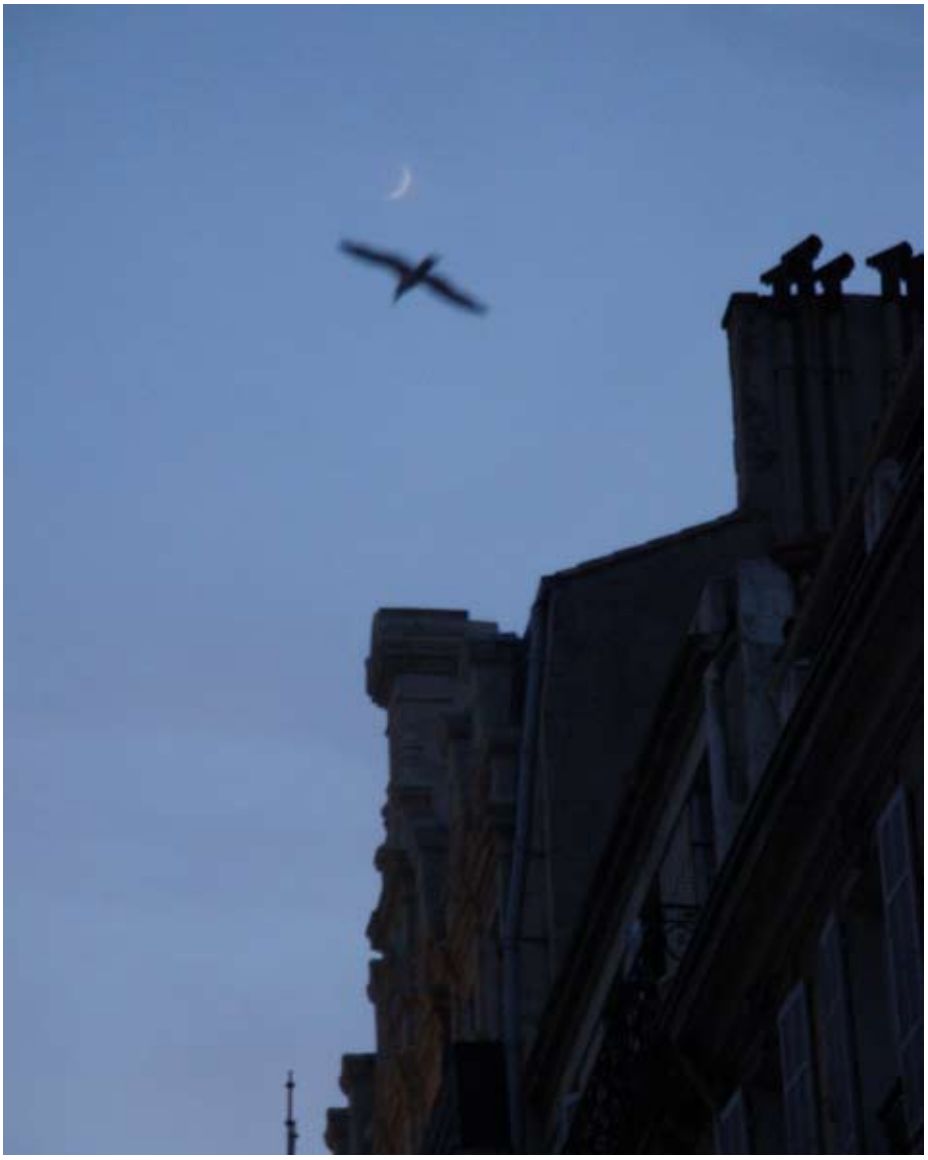
Opulence vs. austerity: how to deal with innovation?

Interview with Josè Gatell

In HIV field we have so many drug and different classes of drugs that could potentially change paradigms of established way of thinking about therapy of HIV infection. I'm referring to dual or to mono therapy, -for instance- but we are experiencing increasing warning on costs. How to deal with innovation and simplification in this our hard time? The question is for Josè Gatell, Senior Consultant & Head of Infectious Diseases & AIDS Units at the Hospital Clinic and Professor of Medicine at the University of Barcelona.

"I have two considerations on that: first of all, you point that every time some new drugs or new families are introduced, almost everything changes- say to me "That has been true for a number of years but now a new theme that will have to be introduced is the economic problem, is the cost of the drugs and so for a new drug to be considered in the initial therapy they will have to demonstrate a big and a very evident advantage over the old regimes unless the company prices these drugs at the same level of the old drugs, so that the issues of cost and cost efficacy is going to be strongly considered in the year 2012 and in the forthcoming years when we decide what to start with. That is one point and the second point in terms of a strategy. I think for the moment the only attempt that has been made to use monotherapy as initial therapy it failed, so that I don't think monotherapy is going to be considered for initial therapy. Conversely, the issue of combination of two drugs, like a protease inhibitor plus an integrase inhibitor, this may well work and may have some advantages. However, again, this type of therapy for the moment is substantially more expensive than, for example, a triple and they will have to show a really big advantage to be considered in practice for initial therapy.

Tolerance could be one of the key issues in this landscape?
Well, tolerance can be one of the key issues and when we talk about tolerance or side effects I think we need to differentiate between what we may call short-term or acute side effects and long-term side effects. Of course, if one drug is very clearly associated with long-term side



effects, that is going to be deleted from our armamentarium and this is what happened in the past for example with d4T or with AZT that is no longer in use. In terms of the acute toxicity…I mean it's true that this is important, however we need to take into account that short-term or acute toxicity for the drugs we are now using, this kind of toxicities are never very severe. People who pay for antiretroviral regimes they may say that well, you can start with the less costly regimes and if your patient develops some kind of toxicity, don't worry: just feel free to change. But they may not allow us to start with more expensive antiretroviral regimes simply because there is a little bit less short-term toxicity, mostly if this short-term toxicity is not a very severe one and it is something that you can solve simply by changing the regime.

The therapy of HIV infection is now, is a chronic therapy, that means that we have to plan for the future. Do you think that an approach like induction and maintenance could work?

Theoretically, it could and this is what in fact what we are doing with all of our simplification trials. The problem is that all the two or three trials along the history that have addressed the issue of induction simplification, they have failed. They have failed probably because the period of time of undetectable viral load was too short, so the simplification trials they work because we recruit or include patients that had been undetectable for a number of years and the longer you have been undetectable, the higher the likelihood of succeeding in a simplification trial. Conversely, the induction and maintenance trials, in general you go to the maintenance regime, to the less or to the most simple maintenance regimen very quickly after the patients reach undetectable viral load and probably this may be the explanation why some of these trials they have failed in the past.

What kind of strategies now we have available to simplification?

Well, I am going to address this issue in a symposium one hour from now. I mean, there are several strategies addressed to simplification and all these strategies in general they are focusing on trying to solve or in trying to overcome one issue. For example, you may wish not to have a patient long-life on a boosted protease inhibitor, so you may address the question of whether you can replace a boosted protease inhibitor with a non-nucleoside or with raltegravir, for example, or maybe in the future with elvitegravir or with dolutegravir. You may try to focus on how to address the question, to focus on the question of long-term potential kidney and bone toxicity of tenofovir and then you may try to jump to a simplification regime free of nucleosides, and this may mean monotherapy with boosted PI or PI plus raltegravir: So, I think there are a number of strategies that have proved to be successful and the strategy you may use for simplification is going to be depending on what is the problem or the hurdle you would like to overcome.

One problem that we try to overcome is aging and that it is related together to long-term strategy of therapy.

I think to overcome the problem of aging, we need to pray and ask God to bless us (laughing).

At a lower level, I am referring how to deal with the drugs.

Having said that, we may try to help God a little bit. Well, I think the issue of accelerated aging is not associated particularly to any type of drug or combination, is probably more associated with residual inflammation or with chronic inflammation and also with chronic immune activation.This is something that for the moment it happens or is a problem associated with any of the antiretroviral regimes we are using at that moment. So, in this regard, trying to address this problem, probably what we are going to need is to explore the possibility of whether residual viral replication can be shut down by intensifying antiretroviral treatment, or by using some drugs that have a better access to the GALT or to the lymphatic tissue and, at the end of the day, also trying to focus on the possibility of a functional cure or of an eradication of the HIV. But this is for the moment a domain of the research, not a domain of the clinical arena: I mean it's probably nothing that we are going to be able to solve in the next couple of years.

But we can address the problem of polypharmacy in this kind of patient.

Yes and no. No, I am saying yes and no, I mean… We can try to address and we have been successful and I am sure we'll be even more successful in the future in addressing the issue of antiretroviral therapy, of compressing the antiretroviral therapy in a few number of pills and, even better, in a single pill. The problem is that the more the patients are getting older, antiretroviral therapy is simply one of the components of the treatment our patients are receiving. I mean, our patients are receiving salicylate or statins for primary cardiovascular prevention, our patients are receiving drugs to help them sleeping better, they are receiving anti-inflammatory drugs for hip or for knee arthrosis, they are maybe receiving painkillers for whatever and so we are not going to be able to put all of that in a single pill. Just saying that we are treating our HIV patient in a single pill it's true and it's not true, it's true in terms of antiretroviral therapy but it's not true in the terms of the whole treatment these patients are receiving.

One aspect related to immune activation is also the CNS problem.

Well, despite many years of research on antiretroviral

therapy, the issue of CNS is not totally solved. First of all, the vast majority of our patients who have an undetectable viral load in plasma, they also have an undetectable viral load in the CSF. If we are able to achieve an undetectable viral load in the CSF, it's hard to think about what else can we do in these patients in terms of antiretroviral therapy. It's true that a small percentage of patients, despite having an undetectable viral load in the plasma, they still may have a detectable viral load in the CSF and in that case, I mean in that case we may try to change the antiretroviral therapy or to intensify the antiretroviral therapy or to choose drugs with a better CSF penetration and this may improve the situation. The problem is how to detect that, because this would mean that we may need to do a CSF extraction: we may need to obtain CSF in all our patients who are undetectable and that is something that is not yet in the routine clinical. I am not sure that I have to do a lumbar tap in all my patients just to check whether or not the viral load in the CSF is undetectable, but it may well be a recommendation in the near future. If you think about, for example, some kinds of leukemias, they get a lumbar tap just to check whether the leukemic cells have been cleared from the CSF and so that is something that is not today a formal recommendation but it may well be a recommendation in the near future saying that, well, if you have a patient that has been undetectable for more than one year or for more than two years and is doing well, just at least once in your life make sure that the virus has also been cleared at least from the CSF.

There is an increased also use of neuroimaging in order to determine if there are some lesions in the brain…

The neuroimaging technology is something that is fascinating, and it may help to differentiate between what it is normal and what is not normal. However many of this technologies are not able to translate in a meaningful clinical interpretation so quite often: I don't think that a neuroimaging procedure may help us to discriminate between what patients need a lumbar tap, as opposed to those patients who don't need it. If someone would find a correlation in one of these non-traumatic neuroimaging technologies, it can be used as a screening procedure to avoid a lumbar tap, that would be welcomed. ■

Andrea Tomasini