Session 1
Selecting and optimizing first-line therapy

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Changing times...

The significant clinical benefits afforded by highly active antiretroviral therapy (HAART) have had an overwhelming impact on the life expectancy of individuals infected with HIV. As the number of people living with HIV as a long-term disease increases, so the issues relating to its management are changing.

With increasing survival of HIV-infected individuals taking HAART, there is a growing realization that antiretroviral drugs must be used strategically from the start of treatment for HIV infection, to maximize the benefits from as many drugs within each class of agents as possible. Given the changing face of HIV medicine, which factors should now govern the choice of antiretroviral regimens?

In the session:
"Selecting and optimizing first-line therapy"

- Professor David Back, Professor of Pharmacology at the University of Liverpool, Liverpool, UK, presented pharmacokinetic data showing that there is considerable interpatient variability in drug concentrations achieved with standard doses of both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Co-administering Viracept with food is a natural way of boosting nelfinavir concentrations, ensuring that they are within the therapeutic window in almost all patients.
- Viracept's efficacy, safety and tolerability were discussed by Dr Sharon Walmsley, Assistant Director of the Immunodeficiency Clinic at Toronto General Hospital, Toronto, Canada. Reviewing the data, she concluded that Viracept is a valuable option for the first-line treatment of HIV infection.
- Finally, Dr Mike Youle, Director of AIDS Research at the Royal Free Hospital, London, UK, presented resistance data on Viracept which show that this agent allows the future use of NNRTIs and other PIs, and is therefore a key drug to be used early in the strategic sequencing of antiretrovirals.

Drug levels: getting it right first time

"I really have one message that I want to try to get across to you… we try to ensure, as far as possible, that we have adequate drug concentrations on board with the regimens that we use – that is the challenge that we face," Professor David Back said, kicking off his presentation "Optimizing first protease inhibitor therapy". Describing a number of reasons why drug concentrations may be sub-optimal, including poor adherence, sub-optimal dosage, drug interactions, poor absorption and concomitant disease, Professor Back emphasized that, whatever the cause, the result is often virological failure.

The plasma concentration of a drug should ideally fall within its "therapeutic window", which lies between the threshold concentrations for tolerability and efficacy of an individual antiretroviral agent (Figure 1). "If we go too high, the drug concentrations can result in toxicity, but if we go too low, clearly we're going to have a lack of efficacy…it's a balance between efficacy and safety," he said.

Professor Back went on to stress the importance of defining this therapeutic window for all of the drugs that are used. However, pharmacokinetic data indicate that, even when standard dosages are used, there are significant interpatient differences in the drug levels achieved.

"This is true for all the protease inhibitors and non-nucleoside reverse transcriptase inhibitors," Professor Back said. However, he revealed that there are different issues for different drugs.

The majority of patients taking Viracept have optimal drug concentrations; however, in a proportion of individuals the trough levels are below the efficacy threshold. "The issue with nelfinavir is ensuring we have adequate concentrations," he said, adding that, "there are other issues with other drugs…with indinavir, it's toxicity."

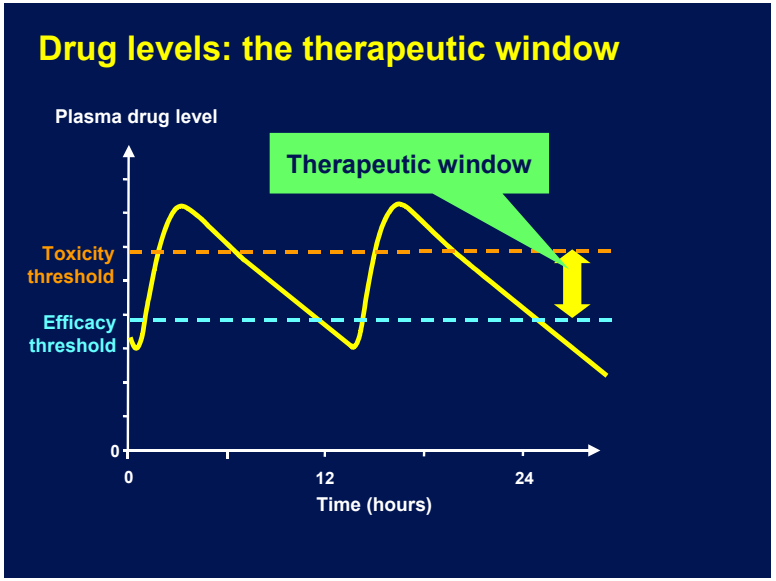

Figure 1. The therapeutic window of an individual antiretroviral agent lies between the threshold concentrations for tolerability and efficacy.

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So why do people differ? This, Professor Back explained, could be attributed to a range of host genetic factors, differences in renal and hepatic function, the presence or absence of co-morbidities, and age, all of which may interact and affect drug levels in complex ways.

The next question addressed was, "what are we doing to maximize the amount of drug we have in the system?" Boosting the plasma concentration of a therapeutic PI by administration of ritonavir at a sub-therapeutic dosage is now an accepted practice; however, with different drugs, as Professor Back put it:

- *"It's not always the same effect…there are some problems relating to boosting."*

Data from BEST, the BID Efficacy and Safety Trial, show clearly that the incidence of adverse events increased significantly when indinavir was boosted with ritonavir.

An emerging approach to optimizing antiretroviral therapy is therapeutic drug monitoring (TDM). Professor Back described how TDM was used to manage the indinavir toxicity issue in his clinic; patients who had very high indinavir levels had the option of either switching to another regimen, or having the dosage of indinavir/r altered. TDM can also be used to assess the impact of drug–drug interactions, for example, when lopinavir is co-administered with amprenavir or an NNRTI.

For some PIs, the pharmacokinetic profile can only be optimized by the addition of low-dose ritonavir. With nelfinavir, however, boosting can be achieved naturally with food (Figure 2), and Professor Back described how nelfinavir plasma concentrations could be boosted significantly and consistently even with a light snack. Natural boosting may avoid some of the problems associated with ritonavir boosting, such as toxicity and the potential for drug–drug interactions.

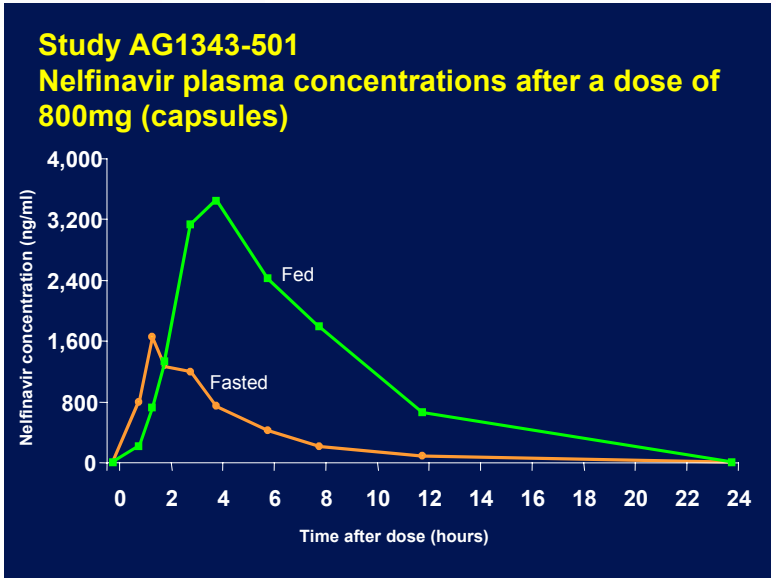

Figure 2. Nelfinavir plasma concentrations can be boosted naturally by taking the agent with food.

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Data from the ATHENA study provide evidence that TDM, combined with natural (food) boosting of Viracept, can achieve clinically significant improvements in virological response. In this study, patients receiving Viracept, or indinavir with or without ritonavir, were randomized to receive TDM or no TDM, and outcomes were assessed after 1 year. Patients in the Viracept group who were randomized to receive TDM were given advice to take their medication with food, if TDM showed that their trough nelfinavir concentration was below the expected value. Commenting upon this, Professor Back said that:

- "50% of those patients were then above the target level at the second measurement, after ensuring that the patients took the drug with food."

After 1 year, 81% of patients in the Viracept-TDM arm of the trial had achieved a viral load of < 500 copies/ml, compared with 59% of patients in the control (no TDM) arm. However, it is important to note that TDM itself was not the intervention that improved the outcome, but rather the action that was subsequently taken by patients – taking Viracept with food.

By identifying patients with potentially toxic or sub-therapeutic drug concentrations, TDM has the potential to improve the outcome of PI-based therapy. Summing up the different issues associated with the different PIs: "nelfinavir is a drug that has good bioavailability… but we can optimize it," Professor Back said.

Safety first: choosing PI therapy

In the opening remarks of her presentation "Viracept – an ongoing success story built on the strengths of its efficacy, safety and tolerability," Sharon Walmsley referred to the "huge shopping list" of various antiretroviral drugs that are now available to choose from when selecting medication for a particular patient. She asked, "how do we choose between them?"

- Efficacy was the first factor to be considered.

Comparing data from pivotal trials of a range of antiretroviral regimens, Dr Walmsley noted that "the bottom line is that most of these [regimens] perform much the same." For example, there are now several years" data to show that Viracept, as part of combination antiretroviral therapy, is effective in suppressing HIV RNA to undetectable levels in plasma long term. So, given that different HAART regimens are comparably effective, which factors should govern the choice of regimen for individual patients? Referring to data from the ICONA cohort study, where the reason for discontinuation of HAART in 862 antiretroviral-naive patients was prospectively analysed, she concluded that:

- *"Toxicity is the major reason why patients have to stop their first combination of drugs."* (Figure 3).

This conclusion prompted another question: how do you compare drugs in terms of their safety record when "you cannot find an antiretroviral drug that does not have toxicity?" The answer, she said, is to choose agents with side effects that are less disturbing for patients, or that have fewer implications for quality of life. Dr Walmsley then used the examples of hepatotoxicity, rash, safety in women, and lipid disorders, to illustrate the good tolerability and safety profiles of Viracept.

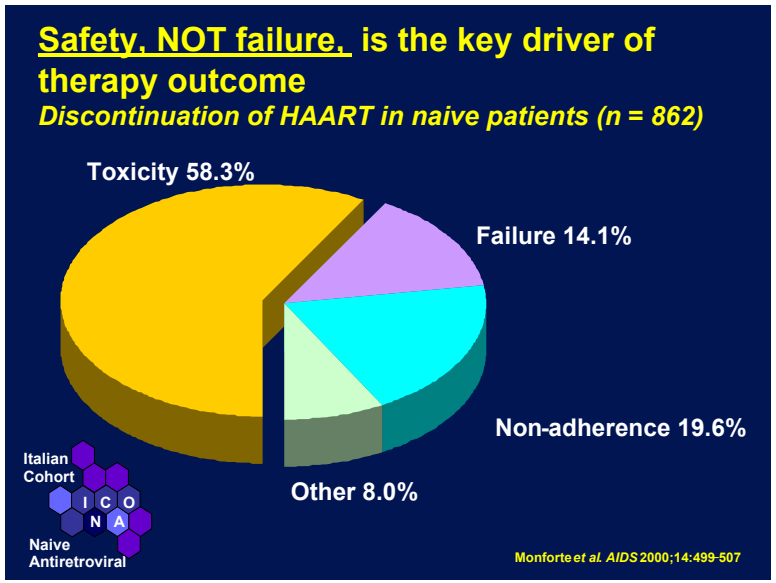

Figure 3. Reasons for treatment discontinuation at 45 weeks in the Italian Cohort Antiretroviral Naive (ICONA) study.

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- Hepatotoxicity is becoming an increasingly important consideration in the treatment of HIV-infected individuals, due to the high incidence of HIV-HCV co-infection, particularly among intravenous drug users.

Figure 4 details the results of a retrospective review of the incidence of hepatotoxicity in 553 HIV-HCV co-infected patients, who had taken a variety of different PI-based regimens.

- *"This suggests that nelfinavir does have a good safety margin for treating patients with HIV-HCV co-infection,"* Dr Walmsley noted.

"When patients [develop] rash on one of their antiretroviral drugs, the tendency is to stop it alone…but continue the other two," which increases the risk of resistance evolving to the remaining drugs in the regimen, she went on to say.

- Rash is most commonly associated with the NNRTI class of antiretrovirals.
- Nelfinavir is associated with low rash rates (≤ 3%), and, *"is a safe drug in that regard,"* Dr Walmsley said.

An increasing proportion of HIV-infected individuals are women of child-bearing potential – so the safety of antiretroviral agents in this population is paramount. The clinical data regarding safety of antiretrovirals during pregnancy are, at present, insufficient to draw solid conclusions, but data suggest that there may be differences in the risk associated with the use of different antiretroviral agents.

- As CDC category B agents, there is "no evidence of a teratogenic risk" with Viracept, saquinavir or ritonavir use during pregnancy.
- Viracept has not been associated with an increased risk of birth defects in comparison with the background population (2.8 *vs* 3.1 birth defects per 100 live births). The rate for efavirenz, a category C agent, has been calculated at 5.8 per 100 live births.

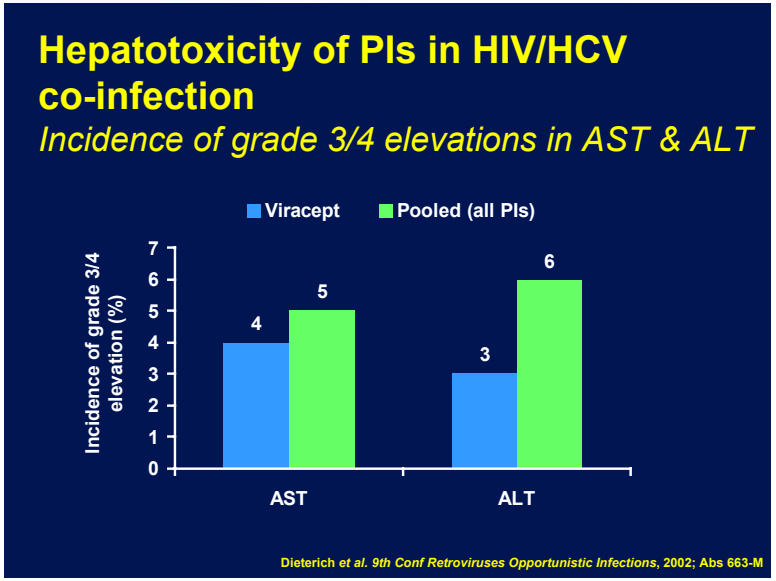

Figure 4. Incidence of hepatotoxicity in a cohort of HIV–HCV co-infected individuals treated with protease inhibitors.

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In summary, Viracept has a good safety record. Many patients, however, might be more concerned with clinical adverse effects that affect their day-to-day lives. Commenting on this, Dr Walmsley went on to say that the most common adverse effect associated with Viracept, namely diarrhoea:

- Occurs at “virtually the same” incidence as with other PIs.
- Is mild, self-limiting, easy to manage, and not associated with nausea or vomiting, for the majority of patients.

Dr Walmsley then revisited her earlier conclusion that toxicity is emerging as the most important determinant of treatment discontinuation at 1 year. Given the favourable toxicity profile of Viracept, it might be expected that patients remain on it for longer than with other antiretrovirals. Data from a large cohort trial comparing the risk factors for modification of HAART found that this is indeed the case:

- Patients taking Viracept were ‘less likely to discontinue their therapy”, or modify their treatment regimen, than the cohort as a whole.

Finally, Dr Walmsley showed data from a study in which patients had switched to Viracept from an NNRTI-based regimen. She concluded that patients who have either experienced failure or toxicity on an NNRTI ‘can be managed on nelfinavir”: switching to Viracept was associated with a decrease in viral load of 0.98 $\log_{10}$ copies/ml. In addition, following this switch, “the duration of time on nelfinavir was more than twice that they had spent on the original NNRTI,” Dr Walmsley said.

Concluding her presentation, she stated: “Nelfinavir does continue to be an important option for us to consider when initiating antiretroviral therapy.”

Planning ahead, thinking strategically

"Many patients are looking to stay on treatment long-term …what happens if a patient's viral load does break through?" Dr Mike Youle asked, as he began his presentation 'Strategic sequencing: making the most of protease inhibitors".

The issue is rooted in the problem of cross-resistance, where viral species that emerge with mutations conferring resistance to one agent in a given class may also be resistant to all other drugs in that class. In clinical terms, this concept is illustrated in data from the ACTG 398 study, which show response rates to treatment declining with increasing treatment experience.

- This scenario can be prevented if we "plan ahead and think strategically" when choosing therapy for an individual, suggesting that:
- If we use HAART carefully from the outset, we can ensure that future treatment options will work when the first or subsequent regimen(s) fail.

So, how does resistance to antiretrovirals arise? Taking the PI class of agents, "You may have an accumulation of different mutations, and it's the combination of those mutations that produces resistant variants and rebound of virus, and that varies differently for different drugs." There was, Dr Youle continued, "some argument that nelfinavir avoids the problem of cross-resistance."

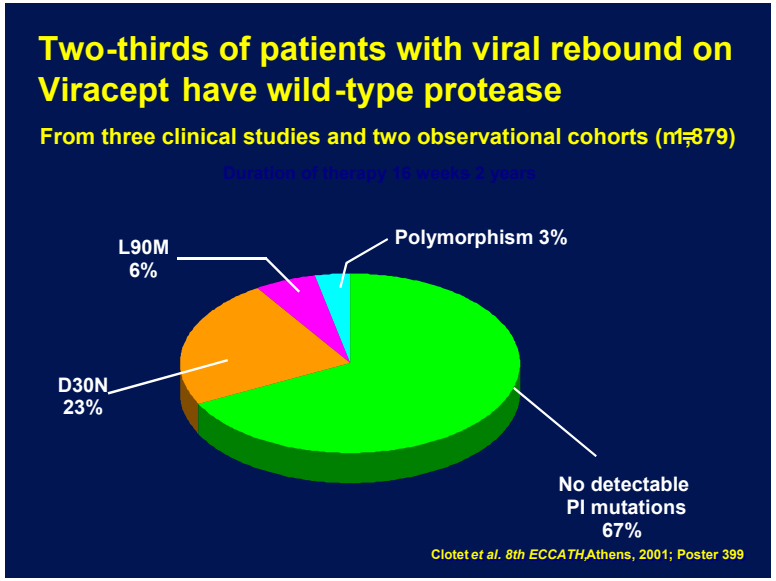

Figure 5. Genotypic analysis of HIV from patients (n = 184) experiencing either viral rebound or non-response after between 16 weeks and 2 years of Viracept-based antiretroviral therapy.

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In 184 patients, from three clinical studies and two observational cohorts, "two-thirds of the patients with high viral load on nelfinavir [had] no resistance mutations in protease," Dr Youle stated (see Figure 5). Moreover, of those patients who did have a protease mutation, the majority (70%) had acquired a change that does not confer cross-resistance to other antiretrovirals, namely the D30N mutation. "Overall, around 90% of patients who had some rebound on nelfinavir had a good chance of success with another protease inhibitor," he said.

- Summing up, Dr Youle said that, *"virological failure on nelfinavir is not usually associated with mutations in protease."*

Dr Youle then went on to illustrate that the favourable resistance profile of Viracept does translate into a clinically meaningful benefit to the patient. The GART study provided evidence that the D30N mutation associated with Viracept has a positive impact on the next round of HAART therapy. The findings from this genotypic study are complemented by phenotypic data from CCTG 575, which found that patients with viral rebound on Viracept have HIV that remains susceptible to other PIs.

Dr Youle also presented clinical evidence that the response of nelfinavir-experienced patients to subsequent PI-based regimens is durable (Figure 6). Additionally, in the C-BIG study, 55% of patients (who had previously experienced virological failure during Viracept-based HAART) achieved viral loads of ≤ 500 copies/ml after 52 weeks of saquinavir/ritonavir plus one new nucleoside reverse transcriptase inhibitor (NRTI) or NNRTI (as-treated population).

- Importantly, patients who had acquired the D30N mutation after experiencing virological failure on Viracept were also seen to respond to the new PI-based regimen.

In summary, Dr Youle said that strategic sequencing of antiretrovirals is key to the long-term management of HIV infection. Viracept appears to have an important role in this regard, as there is a growing body of clinical evidence indicating, he said, that "nelfinavir helps preserve future treatment options".

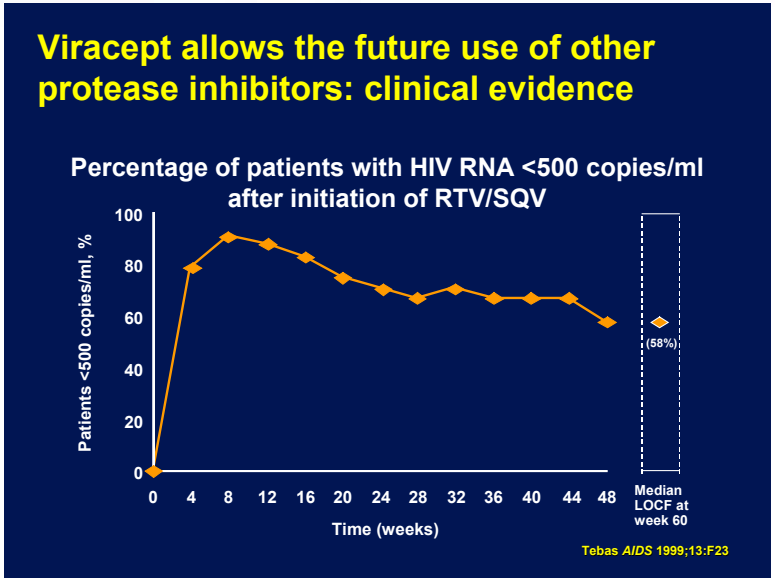

Figure 6. Virological response to a HAART regimen containing saquinavir/ritonavir in patients with prior virological rebound on Viracept-containing therapy.