Session 2
Recent developments in antiretroviral therapy

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Changing times...

The search for increasingly potent antiretroviral regimens that lead to the development of combination HAART has lead to sustained clinical benefit in HIV-positive patients. The advance is not without cost, however, and issues of toxicity and safety are now recognized as key to driving adherence and efficacy. In the future such considerations should dominate the choice of early regimens; at the other end of the scale, the question of how to treat patients who have experienced virological failure as a result of mounting resistance to antiretrovirals, is being hotly debated.

In the session "Recent developments in antiretroviral therapy", Dr Antonella Castagna reviewed 24-week data from the MaxCmin1 trial, the first to compare the safety and efficacy of boosted PIs head-to-head, and called for further meaningful comparisons to be made in the clinic. Professor Schlomo Staszewski presented data indicating that boosted double PI regimens are emerging as a potential option for patients who are not able to take NNRTIs or NRTIs due to resistance or toxicity. Finally, Dr Nicholas Hellmann talked on the important implications for all patients on the management of viral fitness, mooting the idea that, for patients with limited future therapy options, continuing to take antiretroviral therapy despite the emergence of resistance and virological failure may offer clinical benefit.

Saquinavir/ritonavir 1000/100 mg bid – highly efficacious and tolerable

Protease inhibitor boosting is a method now widely used for improving the efficacy and convenience of standard PI regimens. "How can we compare the efficacy of boosted PIs?", was the key question Dr. Antonella Castagna asked in the introduction to her presentation "Saquinavir/ritonavir 1000/100 mg bid randomised clinical trials". Until now there has been no clinical evidence to support the efficacy or tolerability of one boosted PI regimen over another. The MaxCmin1 trial, for which 24 week data are now available, is the first ever comparative study of two boosted PIs.

The ideal PI, Dr Castagna said, is one that reaches "high concentrations without compromising tolerability". There are currently four different boosted PI regimens in clinical trials, and a number of different doses of these drugs have been analyzed. "We really need randomised clinical trials to evaluate the efficacy and safety of the different boosted PIs" Dr Castagna said. Presenting interim data from MaxCmin1, she showed that saquinavir/r 1000/100 mg bid is highly efficacious, and has a favourable tolerability profile compared with indinavir/r.

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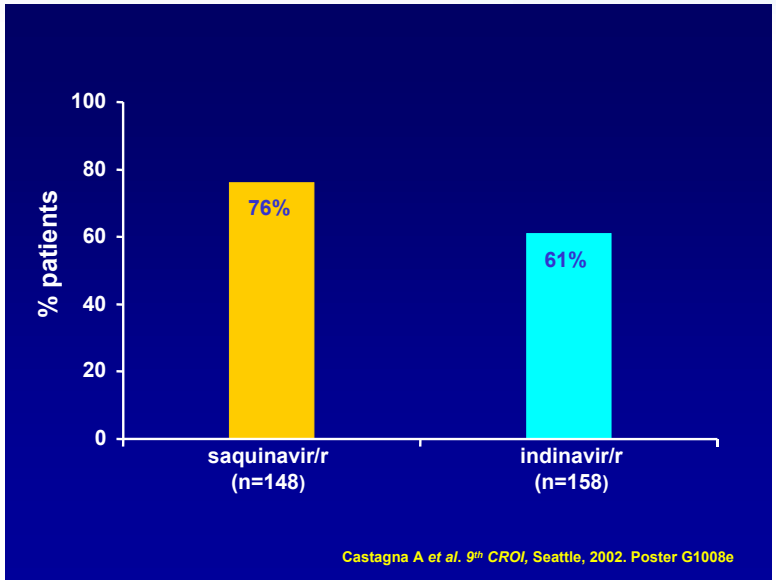

Figure 1: Percentage of patients with HIV RNA < 400 copies/ml on indinavir/r (800/100 mg bid) or saquinavir/r (1000/100 mg bid) at 24 weeks. Intent-to-treat analysis including all patients who received randomised medication.

The rationale of the MaxCmin1 trial is to evaluate the efficacy and safety of saquinavir/r (1000/100 mg bid) versus indinavir/r (800/100 mg bid) in matched cohorts of patients. A large proportion of the 306 individuals recruited to the trial were in the advanced stages of HIV, and 61% of the patients had previously taken a PI-based regimen.

- At 24 weeks, the efficacy of saquinavir/r (1000/100 mg bid) was superior to that of indinavir/r (800/100 mg bid) when patients who actually started taking the trial medication were considered.
- "The percentage of patients with HIV RNA lower than 400 copies is higher in the saquinavir group [76%] compared with the indinavir group [61%]", Dr Castagna said (Figure 1).

Only 2 patients on each arm discontinued the study drug due to virological failure. Statistical analyses were not presented for the planned 24-week interim analysis. A formal statistical analysis will be conducted when the full cohort of patients has reached 48 weeks of therapy.

Reviewing the safety of the two regimens, Dr Castagna highlighted the fact that the total number of grade 3 or 4 adverse events experienced by patients differed between the treatment arms.

- For patients remaining on therapy both drugs provided potent suppression of HIV.
- However, more patients discontinued therapy on the indinavir/r arm of the study due to adverse events.
- The main reason for the difference was that ten patients experienced a renal event while taking indinavir/r, compared with no patients taking saquinavir/r.
- Additionally, "the spectrum of reasons for discontinuation was wider in the indinavir group", Dr Castagna noted (Figure 2).

It is likely that the superior tolerability profile of saquinavir/r (1000/100 mg bid) drives the potency of this agent in comparison to indinavir/r. The interim results of MaxCmin1 therefore indicate that saquinavir/r (1000/100 mg bid) shows very good efficacy, and seems to be more tolerable than indinavir/r (800/100 mg bid). These results support the assertion that tolerability is indeed more important than pill count in driving adherence (Table 1). The final results of MaxCmin1 are expected later this year.

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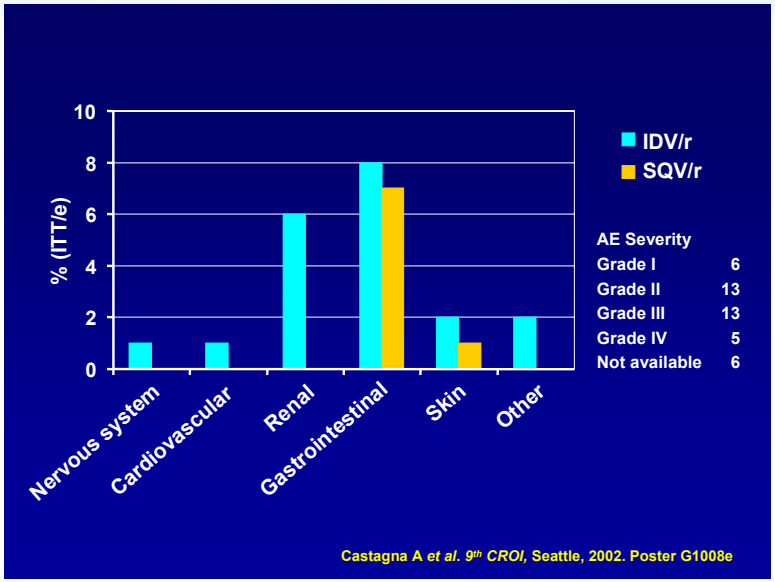

Figure 2: Clinical non-fatal adverse events leading to permanent discontinuation of randomised therapy in the MaxCmin1 study.

	SQV/r	IDV/r
Discontinuation (AE)	8%	20%
ITT * HIV-RNA <400 c/ml	76%	61%
ITT * HIV-RNA <100 c/ml	68%	56%

*analysis includes all patients who received randomised medication; discontinuation of randomised therapy = failure

Adapted from Castagna A *et al. 9th CROI*, Seattle, 2002. Poster G1008e

Table 1: MaxCmin1 summary of key results.

A large number of patients are currently taking saquinavir/ritonavir (400/400 mg bid) as part of their combination therapy. A key question is whether a switch to saquinavir/r 1000/100 mg bid offers improved tolerability. Dr Castagna therefore went on to present the results of a dose modification study, where patients taking saquinavir/ritonavir (400/400 mg bid) were switched to saquinavir/r (1000/100 mg bid).

Lower doses of ritonavir have been associated with decreases in cholesterol and triglyceride levels. In support of these findings:

- A trend towards a reduction in triglyceride levels was seen in patients switched to saquinavir/r (1000/100 mg bid), while efficacy of the two regimens was comparable.

Unusually for a boosted PI, Dr Castagna noted that switching to a 1000/100 saquinavir/r regimen “could be useful in eliminating the lipid profile without compromising the efficacy”.

Summing up, Dr Castagna predicted that head-to-head comparisons will be increasingly important in assessing different boosted PI regimens: the results of MaxCmin2, a trial directly comparing saquinavir/r (1000/100 mg bid) with lopinavir/r (400/100 mg bid) are expected later this year.

Double PI boosting treatments without NRTIs – a new treatment trend for the future?

"We've had a lot of success with our standard of care…but we face some serious limitations", Professor Schlomo Staszewski said in the introduction to his talk "Double PI boosting treatments to avoid NRTI toxicity". Citing systemic toxicities and the metabolic changes caused by antiretrovirals as major drawbacks to therapy, he went on to say that historically held views on the contribution of different classes of antiretrovirals to these problems are now changing in the light of new clinical evidence.

Prof. Staszewski presented evidence from the key PILLR trial, which questions the concept that PIs rather than NNRTIs are responsible for lipodystrophy. In this study, patients who had experienced lipodystrophy were switched from PI-based to PI-sparing regimens. In addition, he discussed findings from the M96-462 trial, which provides evidence that lipodystrophy occurs less frequently in patients taking saquinavir/ritonavir (400/400 mg bid) in the absence of NRTIs.

Key outcomes of the two studies are:

- On switching to a PI-sparing regimen, patients in the PILLR trial did not show an improvement in lipodystrophy; switching may even worsen lipodystrophy.
- Peripheral atrophy worsened in the PI-sparing cohort of the PILLR trial, lean body mass decreased and insulin resistance persisted.
- In the M96-462 trial, fat depletion was worse in a cohort of patients taking an NRTI-intensified regimen compared with saquinavir/ritonavir (Figure 3).

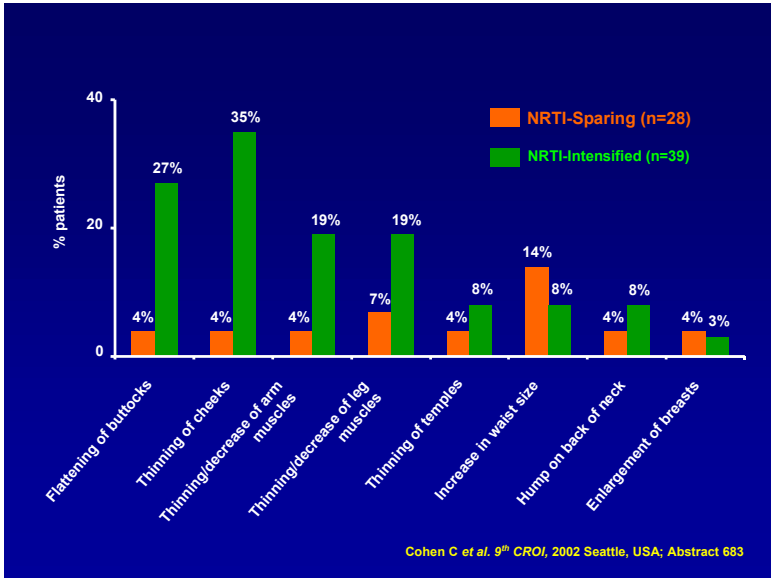

Figure 3: Changes in body composition (based on self reported changes, and confirmed by physical exam), in patients taking an NRTI-sparing and an NRTI-intensified regimen for 5 years (study M96-462).

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- The activity of the PI only regimen in the M96-462 trial was very good. After 5 years, 90% of patients on therapy had < 200 copies, which was comparable to the patients whose regimen was intensified.

Nucleoside antiretrovirals have been associated with a range of toxicities, most of which stem from interference with the mitochondria. "Some studies give evidence that lipodystrophy syndrome is caused by…the combination of these two groups of drugs", Prof. Staszewski said, referring to the PIs and NNRTIs. "The PI regimen may be less toxic than the divergent regimen, and may be as effective", he commented.

Given these results, boosted dual PI regimens without NRTIs have therefore been tested, to maximize further the efficacy of double PI regimens, while maintaining safety. For example the LOPSAQ trial, conducted by Prof. Staszewski, shows that ritonavir can indeed be used to boost two PIs concomitantly, in a safe and effective manner. Patients with limited NRTI treatment options due to resistance or toxicity were treated with saquinavir plus lopinavir/r (1000/400/100 mg bid). The trial found that:

- The double boosted regimen is very powerful. " We see a very nice decrease of the viral load in patients on the combination of saquinavir plus lopinavir/r without NRTIs by 3 log", Prof. Staszewski said. (see Figure 4)
- The regimen is effective even in patients who had previously failed all three classes of antiretrovirals.

In this group of patients, who are difficult to treat, the response to the dual boosted PI was "similar to what we see in a naive patient treated with a triple combination". By 15 weeks, 81% of patients had achieved HIV RNA levels < 400 copies/ml (Table 2).

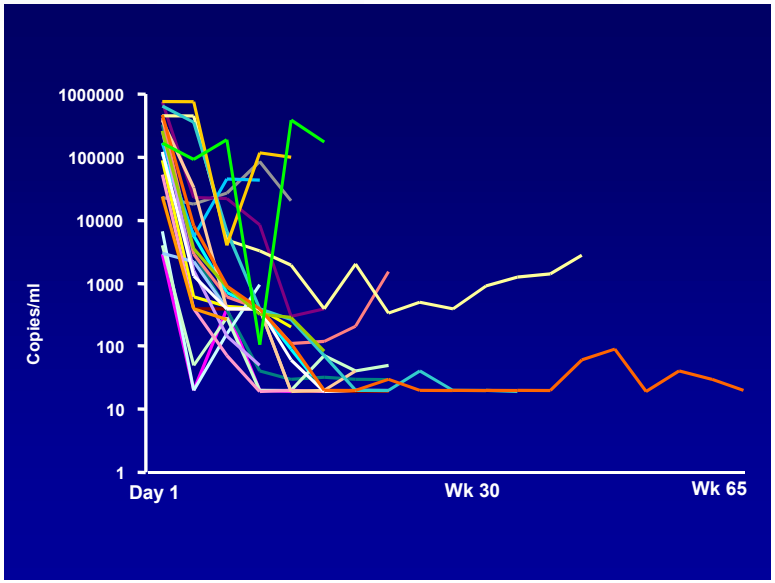

Figure 4: HIV RNA of 23 patients with viral load > 1000 copies/ml at baseline, who took saquinavir/lopinavir/r (1000/400/100 mg bid) over a median of 21 weeks. (LOPSAQ study).

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- The double boosted regimen was found to be well tolerated.

Addressing concerns over lipotoxicity of double PI regimens, Prof. Staszewski presented an analysis of the lipid levels of patients in the LOPSAQ trial. “Most of the patients only had a very modest increase [in cholesterol levels]”, he said, and similarly reported a “modest, modest” increase in triglyceride levels.

Boosted double PI regimens are therefore emerging as a potential option for patients who are not able to take NNRTIs or NRTIs due to resistance or toxicity. In conclusion, Prof. Staszewski said, “I think that there is a need for further investigation of this kind of regimen; what is very important…is to see if we can investigate this concept for first-line therapy”.

	VL at nadir (N, %)	Median time to VL nadir
>2 log reduction:	78% (21/27)	14 weeks
<400 copies/ml:	81% (22/27)	15 weeks
<50 copies/ml:	55% 15/27	17 weeks

Note: 2 patients had VL of 20 copies/ml for 8 and 12 months respectively before reaching <20 copies/ml

Table 2: Viral load reduction, from baseline to nadir, of patients on saquinavir/lopinavir/r without NRTIs (LOPSAQ study)

"Replicative fitness: the Achilles' heel of viral resistance?"

Dr Nicholas Hellmann

The issue of viral fitness is, as Dr Nicholas Hellmann put it, "a new and exciting area of HIV, which does have important implications for patient management". The aim of his presentation was to dissect the link between drug resistance and the ability of the HIV virus to replicate in patients.

The main message of Dr Hellmann's talk was that, while resistance to antiretrovirals should be avoided, "the presence of resistance to HIV often leads to a decrease in the ability of the virus to replicate, which may actually be a good thing".

To demonstrate this point, Dr Hellmann presented data from the UK and USA showing that, since the introduction of HAART:

- The number of deaths from AIDS has decreased, but the number of cases of AIDS continues to increase.
- There is a high prevalence of HIV drug resistance and treatment failure in the HIV-positive population (Figure 5).

However, Dr Hellmann noted, "despite the increasing prevalence of AIDS and drug resistance, there is still a declining number of deaths". This suggests that "there's some benefit to HAART that is independent to its pure antiviral effects".

The problem, Dr Hellmann said, is that the correlations between genotype and phenotype are not completely defined. Each patient is infected with a unique virus, and hundreds of resistance mutation are known. "Unfortunately, that leads to a very complex spectrum of phenotypes and unique interactions amongst these mutations", he said.

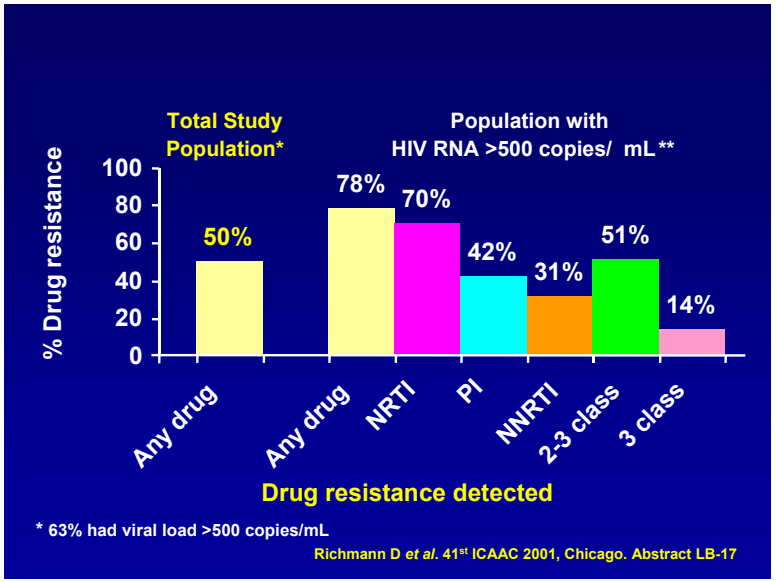

Figure 5: Prevalence of drug resistance in a cohort of US patients, representative of 209,000 individuals in medical care (HCSUS study).

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For example:

- 40% of viruses analyzed with the saquinavir-associated mutation, L90M, have phenotypic susceptibility to the drug (Figure 6).

Citing reasons for this anomaly, Dr Hellmann detailed “additional factors” that come into play, viral replicative capacity, for example:

- Viruses with reduced susceptibility to one or more drug commonly have a reduced capacity to replicate.
- With continued evolution, a virus does not retain it’s replicative capacity – this concept challenges the dogma that secondary mutations increase viral fitness.

This finding may explain why HAART appears to have benefits beyond it’s antiviral effects, since continued pressure on the mutant virus will prevent reversion to wild type, and keep viral load at a lower level. The effect is specific to particular mutations, especially those associated with PI-resistance, however, and Dr Hellmann illustrated that:

- The D30N mutation connected with Viracept failure is associated with “unfit virus that has a very low replication capacity”.
- As additional mutations accrue in virus containing the saquinavir-associated mutation L90M (which alone does not confer significant resistance to saquinavir), resistance increases but replicative capacity correspondingly decreases.

Dr Hellmann also said that “mounting evidence suggests that a mutant with a decreased replication capacity is associated with a slower viral load decrease, and slower immune destruction”.

In conclusion, in patients with limited future treatment options, “Continuing HAART therapy despite treatment failure, to maintain unfit virus, may actually provide some significant clinical benefits”.

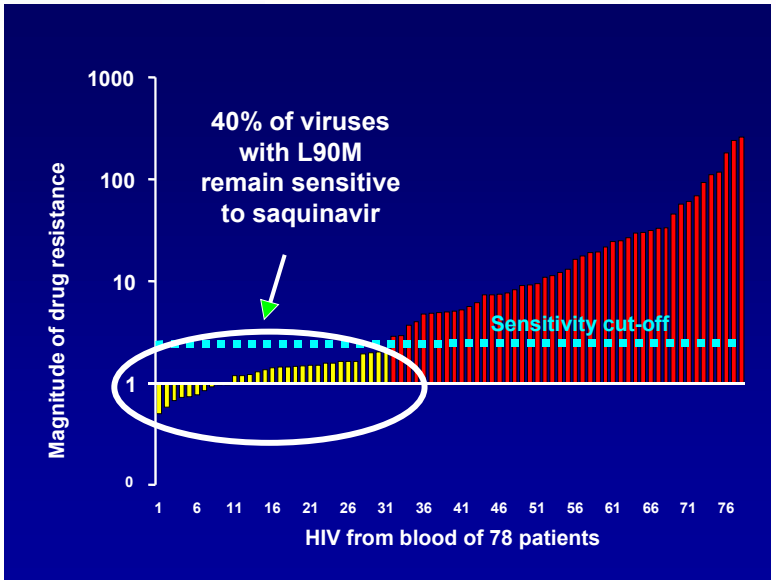

Figure 6: Phenotypic susceptibility of HIV-1 isolates harbouring the L90M mutation, to the antiretroviral agent saquinavir.